

**Title Page: Prediction of Complications and All-cause Mortality with Glycemic and Lipid
Variability in Diabetes Mellitus Using Machine Learning**

Sharen Lee * ¹, Jiandong Zhou * ², Wing Tak Wong PhD ³, Tong Liu MD PhD ⁴, William KK Wu
PhD FRCPath FRCP ⁵, Ian Chi Kei Wong PhD ^{6,7}, Qingpeng Zhang PhD # ², Gary Tse PhD FRCP
FFPH # ^{3,7}

¹ Cardiovascular Analytics Group, Laboratory of Cardiovascular Physiology, Li Ka Shing Institute of
Health Sciences, Hong Kong, China

² School of Data Science, City University of Hong Kong, Hong Kong, China

³ School of Life Sciences, Chinese University of Hong Kong, Hong Kong S.A.R., China

⁴ Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular disease, Department of
Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin
300211, China

⁵ Li Ka Shing Institute of Health Sciences, Faculty of Medicine, The Chinese University of Hong
Kong, Hong Kong, China

⁶ Department of Pharmacology and Pharmacy, University of Hong Kong, Pokfulam, Hong Kong,
China

Medicines Optimisation Research and Education (CMORE), UCL School of Pharmacy, London,
United Kingdom

⁷ Faculty of Health and Medical Sciences, University of Surrey, GU2 7AL, Guildford, United
Kingdom

Co-first authors

Correspondence to:

Dr. Qingpeng Zhang, PhD

School of Data Science, City University of Hong Kong,

Hong Kong SAR, China

Email: qingpeng.zhang@cityu.edu.hk

Dr. Gary Tse, PhD, FRCP, FFPH

*Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular disease, Department of
Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin
300211, China*

Faculty of Health and Medical Sciences, University of Surrey, GU2 7AL, Guildford, United Kingdom

Email: g.tse@surrey.ac.uk

Supplementary Details

Description of anti-diabetic drugs

The mean daily insulin dosage regimen of the cohort is 20.2 ± 12.6 units per day. Other classes of anti-diabetic agents prescribed include: 1) biguanide (n= 14 522, mean daily dose= 1682 ± 882 mg/day), 2) sulphonylurea (n= 10 459, mean daily dose= 191 ± 312 mg/day), 3) thiazolidinedione (n= 890, mean daily dose= 7.59 ± 9.03 mg/day), 4) alpha-glucosidase inhibitor (n= 751, mean daily dose= 138 ± 128 mg/day), 5) DPP4 inhibitor (n= 113, mean daily dose= 91.6 ± 27.5 mg), 6) GLP agonist (n= 13, mean daily dose= 11.9 ± 3.96 mg/day), 7) meglitinide (n= 9, mean daily dose= 1.17 ± 0.887 mg/day). The following classes of cardiovascular medications were prescribed: 1) ACEI/ ARB (n= 15 059, mean daily dose= 17.4 ± 37.0 mg/day), 2) CCB (n= 10 986, mean daily dose= 60.0 ± 50.6 mg/day), 3) lipid-lowering agents (n= 10 685, mean daily dose= 23.3 ± 68.4 mg/day), 4) aspirin (n= 9114, mean daily dose= 102 ± 54.1 mg/day), 5) diuretic (n= 7 349, mean daily dose= 40.3 ± 64.2 mg/day), 6) beta-adrenergic receptor blocker (n= 7 082, mean daily dose= 79.4 ± 81.6 mg/day).

Description of machine learning results

There may be slight difference between importance ranking and minimal depth sequence, although they both can be used to identify the highly predictive risk variables. Both importance ranking and minimal depth were used to uncover the most important variables for predicting time-to-event complication outcomes.

The results showed that age, CKD, baseline hemoglobin, biguanide, and AMI are the five most predictive risk variables to predict all-cause mortality. Moreover, age is the most important variable for renal complication prediction, followed by baseline hemoglobin, HF, AMI, and IHD. AMI, CKD, age, stroke and mean HbA1c are much predictive for PVD prediction. Age, biguanide, IHD, baseline hemoglobin shows great importance for neurological complication. IHD, biguanide, standard deviation of HbA1c, and mean triglyceride are the most five predictive risk factors to identify

ophthalmological complication. For predicting ischemic stroke, age, HF, HT, stroke, IHD are significantly predictive. Age, CKD, AMI, IHD, HF, and HT shows much informative for AF outcome prediction. While CKD, AMI, age, baseline hemoglobin and mean HDL were very useful to predict HF outcome. For ICH prediction, patient's age, baseline hemoglobin, CKD, HT, mean IDL are more predictive, while age, AMI, HF, baseline hemoglobin, and mean triglyceride are the most important for IHD outcome prediction. AMI, HF, age, CKD, and baseline hemoglobin are the most informative for AMI outcome prediction, while patient's age, gender, hypoglycemia, and mean HDL is useful for osteoporosis prediction.

Supplementary Table 1. ICD-9 of Outcome and Pre-existing Comorbidities

	ICD Code
Type 1 Diabetes Mellitus	250.01
Outcome	
Neurological Complications	250.6
Ophthalmological Complications	250.5
Renal Complications	250.4
Peripheral Vascular Disease	250.7
Ischemic Stroke and Transient Ischemic Attack	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.91, 436, 435
Intracranial Hemorrhage	430.00, 431.00, 432.00, 432.10, 432.90, 852.00-852.09, 852.20-852.29, 852.40-852.49, 853.00
Atrial Fibrillation	427.31, 429.4
Heart Failure	428.00-428.99
Ischemic Heart Disease	410.00-411.99, 413.00-414.99
Acute Myocardial Infarction	410.00-410.99
Osteoporosis	733.00
Dementia	290.00-290.99, 331.00, 294.10-294.29, 331.19
Pre-existing Comorbidity	
Chronic Renal Disease	585.00-585.99
Chronic Obstructive Pulmonary Disease	490.00-496.99
Heart Failure	398.91, 402.91, 428.00-428.99
Ischemic Heart Disease	411.00-411.99, 413.00-414.99
Hypertension	401.9
Chronic Liver Disease	570.00-573.99
Acute Myocardial Infarction	410.00-410.99, 412.00-412.99
Stroke	430.00-438.99

Supplementary Table 2. Extracted parameters of patient data

Category	Parameters
Demographic	Age Male Type 1 Diabetes Mellitus
Comorbidities	Hypertension Ophthalmological Complications Ischemic Heart Disease Ischemic Stroke and Transient Ischemic Attack Heart Failure Chronic Renal Disease Chronic Liver Disease Acute Myocardial Infarction Chronic Obstructive Pulmonary Disease
Anti-diabetic Medication	Biguanide Sulphonylurea Thiazolidinedione Alpha-Glucosidase Dipeptidyl Peptidase-4 Inhibitor Glucagon-Like Peptide-1 Receptor Agonist
Cardiovascular Medication	Angiotensinogen-Converting Enzyme Inhibitor/ Angiotensin-Receptor Blocker Calcium Channel Blocker Lipid-Lowering Agents Aspirin Diuretic Beta-Adrenergic Receptor Blocker
Urinalysis	Albumin/Creatinine Ratio (mg/mmol) Creatinine Clearance (ml/min) Spot Protein (g/d) Spot Albumin (mg/L) Spot Glucose (mmol/L) 24-hours Total Protein (g/d) 24-hours Total Albumin (mg/d)
Glycemic and Lipid Profile	Fasting Glucose (mmol/L) Random Glucose (mmol/L) HbA1c (%) Total Cholesterol (mmol/L) High Density Lipoprotein (HDL) Cholesterol (mmol/L) Calculated Low Density Lipoprotein (LDL) Cholesterol (mmol/L) Direct LDL Cholesterol (mmol/L) Triglyceride (mmol/L)
Renal and Liver Function Test	Creatinine (umol/L) Sodium (mmol/L) Potassium (mmol/L) Urate (umol/L) Urea (mmol/L) Albumin (g/L) Alanine Aminotransferase (ALT) (U/L) Alkaline Phosphatase (ALP) (U/L) Total Bilirubin (umol/L) Total Protein (g/L)
Complete Blood Count	Hemoglobin (g/dL)

Mean Corpuscular Hemoglobin (MCH) (pg)
Mean Corpuscular Hemoglobin Concentration (MCHC) (g/dL)
Mean Corpuscular Volume (MCV) (fL)
Hematocrit (L/L)
Basophil (x10⁹/L)
Eosinophil (x10⁹/L)
Lymphocyte (x10⁹/L)
Monocyte (x10⁹/L)
Neutrophil (x10⁹/L)
Platelet (x10⁹/L)
Red Blood Cell (x10¹²/L)
White Blood Cell (x10⁹/L)

Supplementary Table 3. Univariate Cox Regression for Adverse Outcomes

Predictor	Hazard Ratio (HR)	95% Confidence Interval (CI)	P-Value
<i>Neurological Complications</i>			
Age	1.01	[1.00, 1.01]	<0.001
Male	1.47	[1.34, 1.62]	<0.0001
Diabetes Duration	1.04	[1.03, 1.06]	<0.0001
HbA1c			
Baseline	0.999	[0.974, 1.02]	0.934
Mean	1.18	[1.14, 1.22]	<0.0001
Standard Deviation	1.13	[1.07, 1.19]	<0.0001
Coefficient of Variation	1.01	[1.00, 1.01]	0.014
Total Cholesterol			
Baseline	0.960	[0.917, 1.01]	0.081
Mean	1.06	[1.00, 1.12]	0.042
Standard Deviation	1.16	[1.06, 1.27]	0.001
Coefficient of Variation	1.01	[1.00, 1.02]	0.001
HDL Cholesterol			
Baseline	1.01	[0.891, 1.15]	0.863
Mean	0.634	[0.544, 0.741]	<0.0001
Standard Deviation	0.555	[0.323, 0.954]	0.033
Coefficient of Variation	1.00	[0.994, 1.01]	0.881
LDL Cholesterol			
Baseline	1.00	[0.946, 1.06]	0.964
Mean	1.03	[0.961, 1.11]	0.398
Standard Deviation	1.27	[1.11, 1.45]	<0.001
Coefficient of Variation	1.01	[1.00, 1.01]	0.001
Triglyceride			
Baseline	0.962	[0.928, 0.997]	0.035
Mean	1.07	[1.05, 1.10]	<0.0001
Standard Deviation	1.05	[1.02, 1.09]	0.002
Coefficient of Variation	1.00	[0.999, 1.00]	0.229
Baseline NLR	0.994	[0.981, 1.01]	0.357
Baseline Hemoglobin Count	0.945	[0.923, 0.968]	<0.0001
Baseline Anemia	1.17	[1.06, 1.29]	0.002
Hypoglycemia Frequency	1.01	[0.977, 1.04]	0.612
Anti-Diabetic Agent			
Sulphonylurea	0.936	[0.853, 1.03]	0.162
Biguanide	0.978	[0.892, 1.07]	0.629
DPP4 Inhibitor	0.923	[0.392, 1.73]	0.608
Thiazolidinedione	0.718	[0.539, 0.956]	0.023
Alpha-Glucosidase Inhibitor	1.05	[0.812, 1.37]	0.694
<i>Ophthalmological Complications</i>			
Age	0.999	[0.997, 1.00]	0.427
Male	1.01	[0.955, 1.07]	0.694
Diabetes Duration	1.11	[1.10, 1.12]	<0.0001
HbA1c			
Baseline	1.01	[0.997, 1.03]	0.109

Mean	1.25	[1.23, 1.28]	<0.0001
Standard Deviation	1.07	[1.04, 1.11]	<0.0001
Coefficient of Variation	0.999	[0.995, 1.00]	0.508
Total Cholesterol			
Baseline	0.996	[0.969, 1.03]	0.804
Mean	1.10	[1.06, 1.14]	<0.0001
Standard Deviation	1.06	[0.994, 1.13]	0.077
Coefficient of Variation	1.00	[0.997, 1.01]	0.760
HDL Cholesterol			
Baseline	0.993	[0.917, 1.08]	0.870
Mean	0.842	[0.768, 0.923]	<0.001
Standard Deviation	0.432	[0.305, 0.613]	<0.0001
Coefficient of Variation	0.990	[0.986, 0.995]	<0.0001
LDL Cholesterol			
Baseline	0.994	[0.959, 1.03]	0.720
Mean	1.05	[1.00, 1.10]	0.032
Standard Deviation	1.06	[0.974, 1.16]	0.170
Coefficient of Variation	1.00	[0.999, 1.00]	0.342
Triglyceride			
Baseline	1.01	[0.993, 1.03]	0.245
Mean	1.07	[1.05, 1.08]	<0.0001
Standard Deviation	1.05	[1.03, 1.07]	<0.0001
Coefficient of Variation	0.999	[0.997, 1.00]	0.287
Baseline NLR	0.986	[0.977, 0.995]	0.003
Baseline Hemoglobin Count	1.01	[0.993, 1.03]	0.265
Baseline Anemia	0.939	[0.881, 1.00]	0.051
Hypoglycemia Frequency	0.949	[0.926, 0.972]	<0.0001
Anti-Diabetic Agent			
Sulphonylurea	0.972	[0.918, 1.03]	0.344
Biguanide	1.41	[1.33, 1.50]	<0.0001
DPP4 Inhibitor	1.01	[0.660, 1.56]	0.954
Thiazolidinedione	1.09	[0.937, 1.26]	0.271
Alpha-Glucosidase Inhibitor	0.948	[0.798, 1.13]	0.540

Renal Complications

Age	1.02	[1.02, 1.02]	<0.0001
Male	1.12	[1.06, 1.18]	<0.0001
Diabetes Duration	1.05	[1.04, 1.06]	<0.0001
HbA1c			
Baseline	1.00	[0.987, 1.02]	0.813
Mean	1.13	[1.11, 1.15]	<0.0001
Standard Deviation	1.07	[1.04, 1.10]	<0.0001
Coefficient of Variation	1.00	[1.00, 1.01]	0.089
Total Cholesterol			
Baseline	0.999	[0.973, 1.03]	0.943
Mean	1.08	[1.05, 1.12]	<0.0001
Standard Deviation	1.18	[1.11, 1.24]	<0.0001
Coefficient of Variation	1.01	[1.01, 1.01]	<0.0001

HDL Cholesterol			
Baseline	1.00	[0.929, 1.08]	0.979
Mean	0.510	[0.464, 0.560]	< 0.0001
Standard Deviation	0.372	[0.268, 0.516]	< 0.0001
Coefficient of Variation	1.00	[0.996, 1.00]	0.906
LDL Cholesterol			
Baseline	1.00	[0.969, 1.04]	0.942
Mean	1.04	[0.998, 1.09]	0.062
Standard Deviation	1.27	[1.18, 1.38]	< 0.0001
Coefficient of Variation	1.01	[1.01, 1.01]	< 0.0001
Triglyceride			
Baseline	0.989	[0.970, 1.01]	0.231
Mean	1.10	[1.08, 1.11]	< 0.0001
Standard Deviation	1.06	[1.04, 1.08]	< 0.0001
Coefficient of Variation	1.00	[1.00, 1.00]	0.045
Baseline NLR	1.00	[0.994, 1.01]	0.821
Baseline Hemoglobin Count	0.908	[0.896, 0.921]	< 0.0001
Baseline Anemia	1.46	[1.38, 1.55]	< 0.0001
Hypoglycemia Frequency	1.00	[0.982, 1.02]	0.865
Anti-Diabetic Agent			
Sulphonylurea	1.29	[1.22, 1.36]	< 0.0001
Biguanide	0.970	[0.920, 1.02]	0.275
DPP4 Inhibitor	0.761	[0.485, 1.19]	0.234
Thiazolidinedione	1.00	[0.867, 1.16]	0.986
Alpha-Glucosidase Inhibitor	1.14	[0.986, 1.33]	0.075

Dementia

Age	1.08	[1.07, 1.08]	< 0.0001
Male	0.717	[0.630, 0.815]	< 0.0001
Diabetes Duration	0.981	[0.956, 1.01]	0.140
HbA1c			
Baseline	1.00	[0.968, 1.04]	0.891
Mean	1.00	[0.953, 1.05]	0.963
Standard Deviation	1.11	[1.03, 1.19]	0.005
Coefficient of Variation	1.01	[1.00, 1.02]	0.003
Total Cholesterol			
Baseline	0.984	[0.922, 1.05]	0.617
Mean	0.945	[0.871, 1.03]	0.181
Standard Deviation	1.01	[0.864, 1.17]	0.935
Coefficient of Variation	1.00	[0.995, 1.01]	0.411
HDL Cholesterol			
Baseline	1.02	[0.852, 1.23]	0.818
Mean	0.956	[0.779, 1.17]	0.664
Standard Deviation	1.35	[0.660, 2.74]	0.414
Coefficient of Variation	1.01	[0.995, 1.02]	0.342
LDL Cholesterol			
Baseline	1.05	[0.971, 1.14]	0.220
Mean	0.925	[0.835, 1.03]	0.140
Standard Deviation	1.17	[0.960, 1.42]	0.119

Coefficient of Variation	1.01	[1.00, 1.01]	0.013
Triglyceride			
Baseline	0.990	[0.946, 1.04]	0.643
Mean	1.00	[0.956, 1.05]	0.877
Standard Deviation	0.981	[0.917, 1.05]	0.569
Coefficient of Variation	0.999	[0.995, 1.00]	0.532
Baseline NLR	1.01	[0.993, 1.02]	0.302
Baseline Hemoglobin Count	0.927	[0.897, 0.957]	<0.0001
Baseline Anemia	1.43	[1.25, 1.64]	<0.0001
Hypoglycemia Frequency	1.01	[0.964, 1.05]	0.723
Anti-Diabetic Agent			
Sulphonylurea	1.22	[1.08, 1.39]	0.002
Biguanide	0.962	[0.846, 1.09]	0.548
DPP4 Inhibitor	0.459	[0.115, 1.84]	0.271
Thiazolidinedione	0.857	[0.592, 1.24]	0.414
Alpha-Glucosidase Inhibitor	0.729	[0.473, 1.12]	0.152

Osteoporosis

Age	1.06	[1.04, 1.07]	<0.0001
Male	0.249	[0.186, 0.335]	<0.0001
Diabetes Duration	1.01	[0.961, 1.06]	0.776
HbA1c			
Baseline	0.957	[0.893, 1.03]	0.205
Mean	1.00	[0.916, 1.10]	0.943
Standard Deviation	0.879	[0.747, 1.04]	0.123
Coefficient of Variation	0.985	[0.969, 1.00]	0.059
Total Cholesterol			
Baseline	0.997	[0.885, 1.12]	0.954
Mean	1.06	[0.918, 1.23]	0.411
Standard Deviation	0.966	[0.720, 1.30]	0.819
Coefficient of Variation	0.997	[0.981, 1.01]	0.757
HDL Cholesterol			
Baseline	1.01	[0.723, 1.41]	0.958
Mean	1.78	[1.29, 2.44]	<0.001
Standard Deviation	1.49	[0.412, 5.42]	0.542
Coefficient of Variation	0.987	[0.968, 1.01]	0.222
LDL Cholesterol			
Baseline	1.04	[0.902, 1.21]	0.566
Mean	1.03	[0.854, 1.24]	0.773
Standard Deviation	0.940	[0.639, 1.38]	0.752
Coefficient of Variation	0.996	[0.985, 1.01]	0.489
Triglyceride			
Baseline	1.04	[0.991, 1.09]	0.117
Mean	0.918	[0.818, 1.03]	0.145
Standard Deviation	0.855	[0.708, 1.03]	0.105
Coefficient of Variation	0.990	[0.981, 0.998]	0.020
Baseline NLR	0.986	[0.951, 1.02]	0.454
Baseline Hemoglobin Count	0.853	[0.803, 0.906]	<0.0001

Baseline Anemia	1.71	[1.32, 2.21]	<0.0001
Hypoglycemia Frequency	1.04	[0.969, 1.12]	0.263
Anti-Diabetic Agent			
Sulphonylurea	0.924	[0.726, 1.18]	0.522
Biguanide	1.21	[0.948, 1.54]	0.127
DPP4 Inhibitor	0.808	[0.113, 5.76]	0.831
Thiazolidinedione	0.608	[0.271, 1.37]	0.228
Alpha-Glucosidase Inhibitor	1.10	[0.567, 2.14]	0.775

Peripheral Vascular Disease

Age	1.02	[1.01, 1.02]	<0.0001
Male	1.36	[1.17, 1.58]	<0.0001
Diabetes Duration	0.968	[0.939, 0.998]	0.035
HbA1c			
Baseline	1.03	[0.987, 1.07]	0.195
Mean	1.20	[1.14, 1.26]	<0.0001
Standard Deviation	1.19	[1.11, 1.28]	<0.0001
Coefficient of Variation	1.01	[1.01, 1.02]	0.001
Total Cholesterol			
Baseline	0.938	[0.870, 1.01]	0.095
Mean	1.14	[1.05, 1.25]	0.003
Standard Deviation	1.34	[1.21, 1.50]	<0.0001
Coefficient of Variation	1.02	[1.01, 1.03]	<0.0001
HDL Cholesterol			
Baseline	1.10	[0.905, 1.35]	0.330
Mean	0.452	[0.346, 0.590]	<0.0001
Standard Deviation	1.82	[0.840, 3.93]	0.130
Coefficient of Variation	1.03	[1.02, 1.03]	<0.0001
LDL Cholesterol			
Baseline	0.937	[0.853, 1.03]	0.177
Mean	1.11	[0.994, 1.24]	0.065
Standard Deviation	1.54	[1.26, 1.88]	<0.0001
Coefficient of Variation	1.01	[1.01, 1.02]	<0.001
Triglyceride			
Baseline	1.00	[0.959, 1.05]	0.898
Mean	1.09	[1.06, 1.13]	<0.0001
Standard Deviation	1.09	[1.05, 1.13]	<0.0001
Coefficient of Variation	1.01	[1.00, 1.01]	<0.0001
Baseline NLR	1.02	[1.00, 1.03]	0.016
Baseline Hemoglobin Count	0.868	[0.836, 0.901]	<0.0001
Baseline Anemia	1.71	[1.46, 2.01]	<0.0001
Hypoglycemia Frequency	1.07	[1.03, 1.12]	0.001
Anti-Diabetic Agent			
Sulphonylurea	0.897	[0.772, 1.04]	0.159
Biguanide	0.768	[0.663, 0.889]	0.889
DPP4 Inhibitor	0.943	[0.304, 2.93]	0.919
Thiazolidinedione	0.952	[0.634, 1.43]	0.812
Alpha-Glucosidase Inhibitor	1.81	[1.30, 2.52]	<0.001

<i>Intracranial Hemorrhage</i>			
Age	1.03	[1.02, 1.03]	<0.0001
Male	1.20	[1.06, 1.35]	0.004
Diabetes Duration	0.966	[0.942, 0.990]	0.006
HbA1c			
Baseline	1.02	[0.988, 1.05]	0.218
Mean	0.991	[0.945, 1.04]	0.703
Standard Deviation	1.04	[0.970, 1.12]	0.265
Coefficient of Variation	1.01	[0.998, 1.01]	0.168
Total Cholesterol			
Baseline	0.950	[0.893, 1.01]	0.104
Mean	0.945	[0.875, 1.02]	0.155
Standard Deviation	1.13	[1.00, 1.29]	0.050
Coefficient of Variation	1.01	[1.00, 1.02]	0.026
HDL Cholesterol			
Baseline	0.980	[0.826, 1.16]	0.815
Mean	0.757	[0.619, 0.926]	0.007
Standard Deviation	1.17	[0.598, 2.30]	0.644
Coefficient of Variation	1.01	[1.00, 1.02]	0.020
LDL Cholesterol			
Baseline	0.975	[0.902, 1.05]	0.513
Mean	0.875	[0.794, 0.964]	0.007
Standard Deviation	1.15	[0.954, 1.38]	0.145
Coefficient of Variation	1.01	[1.00, 1.01]	0.008
Triglyceride			
Baseline	0.994	[0.955, 1.04]	0.776
Mean	1.07	[1.03, 1.10]	<0.001
Standard Deviation	1.05	[1.00, 1.10]	0.033
Coefficient of Variation	1.00	[0.998, 1.01]	0.462
Baseline NLR	1.00	[0.989, 1.02]	0.623
Baseline Hemoglobin Count	0.923	[0.894, 0.952]	<0.0001
Baseline Anemia	1.19	[1.05, 1.35]	0.008
Hypoglycemia Frequency	1.04	[0.997, 1.08]	0.075
Anti-Diabetic Agent			
Sulphonylurea	1.17	[1.04, 1.32]	0.012
Biguanide	0.875	[0.775, 0.988]	0.031
DPP4 Inhibitor	0.850	[0.318, 2.27]	0.746
Thiazolidinedione	1.05	[0.763, 1.45]	0.764
Alpha-Glucosidase Inhibitor	0.887	[0.610, 1.29]	0.533
<i>Ischemic Stroke and Transient Ischemic Attack/ Transient Ischemic Attack</i>			
Age	1.03	[1.03, 1.04]	<0.0001
Male	0.998	[0.897, 1.11]	0.964
Diabetes Duration	0.989	[0.968, 1.01]	0.327
HbA1c			
Baseline	0.984	[0.954, 1.01]	0.291
Mean	1.05	[1.01, 1.09]	0.024
Standard Deviation	0.994	[0.929, 1.06]	0.854
Coefficient of Variation	0.997	[0.990, 1.00]	0.350

Total Cholesterol			
Baseline	0.987	[0.935, 1.04]	0.637
Mean	1.03	[0.967, 1.11]	0.329
Standard Deviation	1.10	[0.977, 1.24]	0.114
Coefficient of Variation	1.01	[0.999, 1.01]	0.113
HDL Cholesterol			
Baseline	1.01	[0.872, 1.18]	0.868
Mean	0.800	[0.671, 0.954]	0.013
Standard Deviation	1.20	[0.660, 2.18]	0.551
Coefficient of Variation	1.01	[1.00, 1.02]	0.061
LDL Cholesterol			
Baseline	0.967	[0.903, 1.04]	0.335
Mean	1.00	[0.922, 1.09]	0.942
Standard Deviation	1.14	[0.962, 1.34]	0.133
Coefficient of Variation	1.00	[0.999, 1.01]	0.119
Triglyceride			
Baseline	0.981	[0.943, 1.02]	0.342
Mean	1.05	[1.02, 1.09]	0.003
Standard Deviation	1.03	[0.985, 1.08]	0.193
Coefficient of Variation	1.00	[0.997, 1.00]	0.995
Baseline NLR	1.01	[0.992, 1.02]	0.404
Baseline Hemoglobin Count	0.986	[0.958, 1.02]	0.337
Baseline Anemia	1.07	[0.956, 1.20]	0.232
Hypoglycemia Frequency	1.00	[0.963, 1.04]	0.963
Anti-Diabetic Agent			
Sulphonylurea	1.19	[1.07, 1.33]	0.001
Biguanide	1.18	[1.06, 1.32]	0.003
DPP4 Inhibitor	0.491	[0.158, 1.52]	0.218
Thiazolidinedione	0.765	[0.551, 1.06]	0.107
Alpha-Glucosidase Inhibitor	0.891	[0.640, 1.24]	0.496

Ischemic Heart Disease

Age	1.02	[1.02, 1.02]	<0.0001
Male	1.03	[0.975, 1.10]	0.266
Diabetes Duration	1.02	[1.01, 1.04]	<0.0001
HbA1c			
Baseline	0.996	[0.980, 1.01]	0.647
Mean	1.05	[1.03, 1.08]	<0.0001
Standard Deviation	0.987	[0.951, 1.02]	0.470
Coefficient of Variation	0.996	[0.993, 1.00]	0.046
Total Cholesterol			
Baseline	1.01	[0.978, 1.04]	0.634
Mean	1.25	[1.21, 1.30]	<0.0001
Standard Deviation	1.22	[1.16, 1.29]	<0.0001
Coefficient of Variation	1.01	[1.01, 1.01]	<0.0001
HDL Cholesterol			
Baseline	1.12	[1.03, 1.21]	0.006
Mean	0.642	[0.581, 0.710]	<0.0001

Standard Deviation	0.596	[0.421, 0.844]	0.004
Coefficient of Variation	1.00	[0.998, 1.01]	0.366
LDL Cholesterol			
Baseline	1.01	[0.972, 1.05]	0.675
Mean	1.27	[1.22, 1.33]	<0.0001
Standard Deviation	1.43	[1.32, 1.56]	<0.0001
Coefficient of Variation	1.01	[1.00, 1.01]	<0.0001
Triglyceride			
Baseline	0.981	[0.960, 1.00]	0.084
Mean	1.09	[1.07, 1.10]	<0.0001
Standard Deviation	1.05	[1.02, 1.07]	<0.0001
Coefficient of Variation	1.00	[0.999, 1.00]	0.313
Baseline NLR	1.00	[0.996, 1.01]	0.379
Baseline Hemoglobin Count	0.925	[0.911, 0.939]	<0.0001
Baseline Anemia	1.29	[1.21, 1.38]	<0.0001
Hypoglycemia Frequency	1.00	[0.979, 1.02]	0.983
Anti-Diabetic Agent			
Sulphonylurea	1.16	[1.09, 1.23]	<0.0001
Biguanide	1.10	[1.03, 1.16]	0.003
DPP4 Inhibitor	1.13	[0.752, 1.71]	0.553
Thiazolidinedione	1.13	[0.974, 1.31]	0.107
Alpha-Glucosidase Inhibitor	1.20	[1.03, 1.41]	0.023

Acute Myocardial Infarction

Age	1.03	[1.03, 1.03]	<0.0001
Male	0.80	[0.914, 1.05]	0.562
Diabetes Duration	0.989	[0.975, 1.00]	0.103
HbA1c			
Baseline	1.01	[0.986, 1.03]	0.603
Mean	1.07	[1.04, 1.10]	<0.0001
Standard Deviation	1.01	[0.966, 1.05]	0.726
Coefficient of Variation	0.998	[0.994, 1.00]	0.338
Total Cholesterol			
Baseline	0.990	[0.956, 1.03]	0.562
Mean	1.18	[1.13, 1.23]	<0.0001
Standard Deviation	1.22	[1.14, 1.30]	<0.0001
Coefficient of Variation	1.01	[1.01, 1.02]	<0.0001
HDL Cholesterol			
Baseline	0.992	[0.900, 1.09]	0.867
Mean	0.522	[0.462, 0.591]	<0.0001
Standard Deviation	0.680	[0.453, 1.02]	0.064
Coefficient of Variation	1.01	[1.00, 1.01]	0.005
LDL Cholesterol			
Baseline	0.982	[0.940, 1.03]	0.430
Mean	1.18	[1.12, 1.24]	<0.0001
Standard Deviation	1.41	[1.28, 1.56]	<0.0001
Coefficient of Variation	1.01	[1.00, 1.01]	<0.0001
Triglyceride			

Baseline	0.977	[0.952, 1.00]	0.076
Mean	1.09	[1.08, 1.11]	< 0.0001
Standard Deviation	1.06	[1.03, 1.08]	< 0.0001
Coefficient of Variation	1.00	[1.00, 1.00]	0.042
Baseline NLR	1.00	[0.993, 1.01]	0.601
Baseline Hemoglobin Count	0.895	[0.879, 0.911]	< 0.0001
Baseline Anemia	1.48	[1.38, 1.60]	< 0.0001
Hypoglycemia Frequency	1.01	[0.982, 1.03]	0.619
Anti-Diabetic Agent			
Sulphonylurea	1.22	[1.14, 1.31]	< 0.0001
Biguanide	0.961	[0.896, 1.03]	0.271
DPP4 Inhibitor	0.836	[0.474, 1.47]	0.535
Thiazolidinedione	0.868	[0.710, 1.06]	0.164
Alpha-Glucosidase Inhibitor	1.23	[1.02, 1.48]	0.032

Atrial Fibrillation

Age	1.04	[1.04, 1.05]	< 0.0001
Male	0.884	[0.807, 0.968]	0.008
Diabetes Duration	0.989	[0.975, 1.00]	0.103
HbA1c			
Baseline	1.00	[0.975, 1.03]	0.975
Mean	0.961	[0.926, 0.996]	0.029
Standard Deviation	1.05	[0.993, 1.11]	0.090
Coefficient of Variation	1.01	[1.00, 1.01]	0.024
Total Cholesterol			
Baseline	1.03	[0.990, 1.08]	0.134
Mean	0.889	[0.838, 0.943]	< 0.0001
Standard Deviation	1.12	[1.02, 1.23]	0.020
Coefficient of Variation	1.01	[1.01, 1.02]	< 0.001
HDL Cholesterol			
Baseline	1.02	[0.894, 1.15]	0.823
Mean	0.667	[0.572, 0.779]	< 0.0001
Standard Deviation	0.988	[0.590, 1.65]	0.962
Coefficient of Variation	1.01	[1.00, 1.02]	0.005
LDL Cholesterol			
Baseline	1.03	[0.969, 1.09]	0.389
Mean	0.832	[0.773, 0.895]	< 0.0001
Standard Deviation	1.20	[1.04, 1.37]	0.011
Coefficient of Variation	1.01	[1.01, 1.01]	< 0.0001
Triglyceride			
Baseline	0.982	[0.950, 1.01]	0.266
Mean	1.04	[1.01, 1.07]	0.019
Standard Deviation	0.998	[0.955, 1.04]	0.914
Coefficient of Variation	0.998	[0.995, 1.00]	0.147
Baseline NLR	1.00	[0.992, 1.02]	0.574
Baseline Hemoglobin Count	0.907	[0.886, 0.929]	< 0.0001
Baseline Anemia	1.41	[1.28, 1.56]	< 0.0001
Hypoglycemia Frequency	1.03	[1.00, 1.06]	0.030

Anti-Diabetic Agent			
Sulphonylurea	1.17	[1.07, 1.28]	0.001
Biguanide	0.933	[0.851, 1.02]	0.136
DPP4 Inhibitor	0.716	[0.321, 1.60]	0.413
Thiazolidinedione	0.965	[0.751, 1.24]	0.781
Alpha-Glucosidase Inhibitor	1.00	[0.765, 1.31]	0.997

Heart Failure

Age	1.03	[1.03, 1.04]	<0.0001
Male	1.27	[1.17, 1.39]	<0.0001
Diabetes Duration	0.937	[0.919, 0.955]	<0.0001
HbA1c			
Baseline	1.02	[0.993, 1.04]	0.170
Mean	1.05	[1.02, 1.09]	0.004
Standard Deviation	1.10	[1.04, 1.16]	<0.001
Coefficient of Variation	1.01	[1.00, 1.01]	0.001
Total Cholesterol			
Baseline	0.999	[0.954, 1.05]	0.961
Mean	1.06	[0.997, 1.12]	0.065
Standard Deviation	1.28	[1.19, 1.38]	<0.0001
Coefficient of Variation	1.02	[1.01, 1.03]	<0.0001
HDL Cholesterol			
Baseline	0.976	[0.857, 1.11]	0.709
Mean	0.417	[0.352, 0.494]	<0.0001
Standard Deviation	1.25	[0.754, 2.07]	0.387
Coefficient of Variation	1.02	[1.02, 1.03]	<0.0001
LDL Cholesterol			
Baseline	1.02	[0.962, 1.08]	0.517
Mean	1.06	[0.988, 1.14]	0.103
Standard Deviation	1.51	[1.33, 1.71]	<0.0001
Coefficient of Variation	1.01	[1.01, 1.02]	<0.0001
Triglyceride			
Baseline	1.00	[0.973, 1.03]	0.930
Mean	1.09	[1.07, 1.12]	<0.0001
Standard Deviation	1.06	[1.03, 1.09]	<0.001
Coefficient of Variation	1.00	[1.00, 1.01]	0.006
Baseline NLR	1.02	[1.01, 1.03]	<0.0001
Baseline Hemoglobin Count	0.835	[0.815, 0.854]	<0.0001
Baseline Anemia	1.85	[1.67, 2.04]	<0.0001
Hypoglycemia Frequency	1.08	[1.06, 1.11]	<0.0001
Anti-Diabetic Agent			
Sulphonylurea	1.30	[1.19, 1.43]	<0.0001
Biguanide	0.618	[0.563, 0.678]	<0.0001
DPP4 Inhibitor	0.608	[0.253, 1.46]	0.266
Thiazolidinedione	0.722	[0.540, 0.964]	0.027
Alpha-Glucosidase Inhibitor	1.17	[0.905, 1.50]	0.235

All-Cause Mortality

Age	1.06	[1.06, 1.06]	<0.0001
-----	------	--------------	-------------------

Male	1.14	[1.10, 1.18]	< 0.0001
Diabetes Duration	0.930	[0.923, 0.936]	< 0.0001
HbA1c			
Baseline	0.997	[0.988, 1.01]	0.549
Mean	0.964	[0.951, 0.977]	< 0.0001
Standard Deviation	1.11	[1.09, 1.14]	< 0.0001
Coefficient of Variation	1.01	[1.01, 1.01]	< 0.0001
Total Cholesterol			
Baseline	0.992	[0.976, 1.01]	0.340
Mean	0.965	[0.943, 0.988]	0.003
Standard Deviation	1.29	[1.25, 1.33]	< 0.0001
Coefficient of Variation	1.02	[1.02, 1.03]	< 0.0001
HDL Cholesterol			
Baseline	0.964	[0.921, 1.01]	0.114
Mean	0.571	[0.537, 0.607]	< 0.0001
Standard Deviation	3.11	[2.60, 3.72]	< 0.0001
Coefficient of Variation	0.970	[0.927, 1.02]	0.194
LDL Cholesterol			
Baseline	1.02	[0.995, 1.04]	0.131
Mean	0.919	[0.893, 0.946]	< 0.0001
Standard Deviation	1.56	[1.48, 1.64]	< 0.0001
Coefficient of Variation	1.02	[1.01, 1.02]	< 0.0001
Triglyceride			
Baseline	0.989	[0.978, 1.00]	0.0557
Mean	1.06	[1.05, 1.07]	< 0.0001
Standard Deviation	1.03	[1.02, 1.04]	< 0.0001
Coefficient of Variation	1.00	[1.00, 1.00]	0.002
Baseline NLR	1.03	[1.03, 1.04]	< 0.0001
Baseline Hemoglobin Count	0.794	[0.786, 0.801]	< 0.0001
Baseline Anemia	2.11	[2.04, 2.20]	< 0.0001
Hypoglycemia Frequency	1.08	[1.06, 1.09]	< 0.0001
Anti-Diabetic Agent			
Sulphonylurea	1.13	[1.09, 1.17]	< 0.0001
Biguanide	0.541	[0.522, 0.560]	< 0.0001
DPP4 Inhibitor	0.450	[0.324, 0.655]	< 0.0001
Thiazolidinedione	0.703	[0.632, 0.782]	< 0.0001
Alpha-Glucosidase Inhibitor	1.05	[0.953, 1.17]	0.305