**Supplementary Materials**

**Supplementary Table 1: Definition of measures of variability.**

represents the repeatedly measured variable for individual *i* at time *j*.

|  |  |  |
| --- | --- | --- |
| Measure |  |  |
| Mean | Cumulative Mean |  |
| Var, SD | Variance, Standard deviation | , |
| CV | Coefficient of variation |  |
| ARV | Average real variability |  |

**Supplementary Table 2. Baseline characteristics in ACCORD separated by primary outcome and two secondary outcomes, nephropathy and retinopathy.** Data are means and (SD) or number of individuals and (%).

BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CVD: Cardiovascular disease; CHF: Congestive heart failure; eGFR: estimated glomerular filtration rate from four variable Modification of Diet in Renal Disease Study (MDRD) equation· 1 Primary composite: end-stage renal disease (ESRD) or photocoagulation or vitrectomy; 2 Nephropathy: end-stage renal disease (ESRD) including requirement for dialysis or serum creatinine > 3·3 mg per deciliter (291·72 *μmol/L*); 3 Retinopathy: photocoagulation or vitrectomy·

†smoker: smoked more than 100 cigarettes during lifetime.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Primary Composite1** | | P-value | **Nephropathy2** | | P-value | **Retinopathy3** | | P-value |
| **No (*n =* 8914)** | **Yes (*n*=1106)** | **No (*n =* 9765)** | **Yes (n = 269)** | **No (*n =* 8918)** | **Yes (*n*=880)** |
| **Age (years)** | 62·7 (6·7) | 62·9 (6·2) | 0·58 | 62·8(6·6) | 32·2(6·5) | 0·15 | 62·7(6·7) | 62·9(6·1) |  |
| **Intensive glycemic treatment (% yes)** | 4470 (50·1) | 538 (48·6) | 0·36 | 4887 (50·0) | 128 (47·6) | 0·46 | 4451 (50·0) | 432 (49·1) | 0·65 |
| **Intensive BP treatment (% yes)** | 2042 (22·9) | 260 (23·5) | 0·68 | 2248 (23·0) | 56 (20·8) | 0·44 | 2033 (22·8) | 215 (24·4) | 0·30 |
| **Intensive lipids treatment (% yes)** | 2420 (27·1) | 281 (25·4) | 0·23 | 2627 (26·9) | 79 (29.4) | 0·41 | 2430 (27.3) | 213 (24.2) | 0·06 |
| **Female (yes %)** | 3415 (38·3) | 433 (39·2) | 0·61 | 3760 (38·5) | 93 (34·6) | 0·21 | 3395 (38·1) | 358 (40·7) | 0·14 |
| **Race (%)** |  |  | <0·01 |  |  | 0·41 |  |  | <0·01 |
| **Black** | 1651 (18·5) | 247 (22·3) |  | 1847 (18·9) | 57 (21·2) |  | 1625 (18·2) | 204 (23·2) |  |
| **Hispanic** | 620 (7·0) | 96 (8·7) |  | 694 (7·1) | 24 (8·9) |  | 617 (6·9) | 76 (8·6) |  |
| **White** | 5614 (63·0) | 645 (58·3) |  | 6102 (62·5) | 162 (60·2) |  | 5637 (63·3) | 504 (57·3) |  |
| **Other** | 1029 (11·5) | 118 (10·7) |  | 1122 (11·5) | 26 (9·7) |  | 1033 (11·6) | 96 (10·9) |  |
| **Diabetes duration (years)** | 10·3 (7·4) | 14·4 (7·9) | <0·01 | 10·8 (7·6) | 11·9 (7·9) | 0·02 | 10·31 (7·4) | 15·3 (7·6) | <0·01 |
| **CVD history (% yes)** | 3074 (34·5) | 430 (38·9) | <0·01 | 3409 (35·0) | 101 (37·5) | 0·42 | 3052 (34·3) | 347 (39·4) | <0·01 |
| **History of heart failure (% yes)** | 398 (4·5) | 77 (7·0) | <0·01 | 456 (4·7) | 20 (7·4) | 0·05 | 392 (4·4) | 61 (6·9) | <0·01 |
| **History of eye disease (% yes)** | 2515 (28·2) | 615 (55·6) | <0·01 | 3035 (31·1) | 102 (37·9) | 0·02 | 2514 (28·2) | 536 (60·9) | <0·01 |
| **Smoker† (% yes)** | 4030 (52·2) | 483 (48·1) | 0·01 | 4395 (51·7) | 123 (53·0) | 0·74 | 4036 (52·3) | 377 (46·5) | <0·01 |
| **Insulin (% yes)** | 5997 (67.5) | 478 (43.5) | <0.01 | 6326 (65.0) | 152 (57.1) | 0.01 | 6008 (67.6) | 342 (39.1) | <0·01 |
| **Fibrate (% yes)** | 8313 (93.7) | 1046 (95.1) | 0.07 | 9121 (93.8) | 251 (94.4) | 0.81 | 8305 (93.6) | 836 (95.3) | 0.06 |
| **ARB (% yes)** | 7422 (83.4) | 909 (82.6) | 0.48 | 8816 (83.3) | 225 (84.6) | 0.64 | 7422 (83.5) | 719 (81.9) | 0.24 |
| **ACEi (% yes)** | 4067 (45.7) | 470 (42.7) | 0.06 | 4437 (45.5) | 107 (40.2) | 0.10 | 4045 (45.5) | 382 (43.5) | 0.27 |
| **BMI (kg/m2)** | 32·2 (5·4) | 32·2 (5·5) | 0·63 | 32·2 (5·4) | 32·2 (5·4) | 0·83 | 32·2 (5·4) | 32·16 (5·5) | 0·72 |
| **DBP (mmHg)** | 75 (11) | 74 (11) | <0·01 | 75 (11) | 75 (10) | 0·89 | 75 (11) | 73 (11) | <0·01 |
| **SBP (mmHg)** | 136 (17) | 139 (18) | <0·01 | 136 (17) | 138 (19) | 0·07 | 136 (17) | 140 (18) | <0·01 |
| **HDL cholesterol (mg/dL)** | 42 (11) | 43 (12) | <0·01 | 42 (11) | 41 (12) | 0·33 | 42 (11) | 43 (13) | <0·01 |
| **LDL cholesterol (mg/dL)** | 105 (34) | 107 (34) | 0·07 | 105 (34) | 107 (36) | 0·25 | 105 (34) | 107 (34) | 0·03 |
| **Total cholesterol (mg/dL)** | 183 (42) | 185 (44) | 0·30 | 183 (42) | 188 (44) | 0·09 | 183 (41) | 185 (45) | 0·40 |
| **Triglycerides (mg/dL)** | 192 (150) | 181 (137) | 0·03 | 190 (149) | 205 (138) | 0·10 | 192 (151) | 172·5 (134) | <0·01 |
| **HbA1c (%)** | 8·3 (1·0) | 8·6 (1·1) | <0·01 | 8·3 (1·1) | 8·5 (1·2) | <0·01 | 8·3 (1·0) | 8·6 (1·1) | <0·01 |
| **Fasting glucose (mg/dL)** | 175 (55) | 178 (65) | 0·06 | 175 (56) | 181 (66) | 0·08 | 175 (55) | 178 (65) | 0·17 |
| **Urine albumin to creatinine ratio (mg/g)** | 84·3 (323·1) | 204·7 (553·9) | <0·01 | 91·7 (333·4) | 314·2 (833·3) | <0·01 | 83·7 (308·8) | 202·4 (551·5) | <0·01 |
| **eGFR (ml/min/1·73 m2)** | 91 (27·3) | 87 (26·1) | <0·01 | 91 (27·1) | 87 (27·7) | 0·03 | 92 (27·3) | 87 (25·7) | <0·01 |

**Supplementary Table 3. Baseline characteristics in the VADT separated by primary composite outcome and two secondary outcomes, nephropathy and retinopathy.** Data are means and (SD) or number of individuals and (%).

BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CVD: Cardiovascular disease; eGFR: estimated glomerular filtration rate from Modification of Diet in Renal Disease Study (MDRD) equation.

1Primary composite: Creatinine ≥ 3.3 mg per deciliter (291·72 *μmol* per liter) or eGFR < 30 *ml* per minute or photocoagulation or vitrectomy; 2 Nephropathy: serum creatinine ≥ 3·3 mg per deciliter (291·72 *μmol* per liter) or eGFR < 30 *ml* per minute; 3 Retinopathy: photocoagulation or vitrectomy. Subjects with at least two glucose measures were included.

†Pack-year is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Primary Composite1** | | P-value | **Nephropathy2** | | P-value | **Retinopathy 3** | | P-value |
|  | **No (*n*=1472)** | **Yes (*n*=186)** | **No (n = 1615)** | **Yes (n = 42)** | **No (n = 1323)** | **Yes (n = 154)** |
| **Age (years)** | 60·3 (8·6) | 60·5 (8·2) | 0·85 | 60·3 (8·6) | 61·0 (8·1) | 0·63 | 60·2 (8·7) | 60·6 (8·3) | 0·79 |
| **Intensive treatment (% yes)** | 741 (50·4) | 84 (45·2) | 0·21 | 806 (49·9) | 19 (45·2) | 0·66 | 654 (49·5) | 69 (44·8) | 0·31 |
| **Female (% yes)** | 40 (2·7) | 9 (4·8) | 0·17 | 48 (3·0) | 1 (2·4) | 1 | 34 (2·6) | 8 (5·2) | 0·11 |
| **Non-Hispanic White (% yes)** | 925 (62·8) | 106 (57·0) | 0·14 | 1004 (62·2) | 26 (61·9) | 1 | 852 (64·4) | 86 (55·8) | 0·05 |
| **Diabetes duration (years)** | 11·3 (7·4) | 13·4 (7·8) | <0·01 | 11·5 (7·4) | 13·1 (8·5) | 0·16 | 10·6 (7·0) | 13·7 (7·6) | <0·01 |
| **CVD history (% yes)** | 599 (40·7) | 77 (41·4) | 0·91 | 652 (40.4) | 23 (54·8) | 0·09 | 538 (40·7) | 61 (39·6) | 0·88 |
| **Adherent to Diet (% yes)** | 664 (45·2) | 76 (40·9) | 0·30 | 724 (44·9) | 15 (35·7) | 0·31 | 583 (44·2) | 69 (44·8) | 0·95 |
| **Smoking (% yes)** |  |  | 0·51 |  |  | 0·31 |  |  | 0·12 |
| **Current smoker** | 242 (16·5) | 29 (15·6) |  | 263 (16·3) | 8 (19·0) |  | 228 (16·9) | 22 (14·3) |  |
| **Previous smoker** | 837 (56·9) | 100 (53·8) |  | 909 (56·4) | 27 (64·3) |  | 744 (57·3) | 81 (52·6) |  |
| **Non-smoker** | 391 (26·6) | 57 (30·6) |  | 441 (27·3) | 7 (16·7) |  | 335 (25·8) | 51 (33·1) |  |
| **Insulin (% yes)** | 735 (50.1) | 100 (54.1) | 0.31 | 810 (50.3) | 24 (58.5) | 0.38 | 630 (47.8) | 84 (54.9) | 0.11 |
| **Fibrates (% yes)** | 234 (15.9) | 21 (11.3) | 0.13 | 247 (15.3) | 8 (19.0) | 0.65 | 218 (16.5) | 15 (9.7) | 0.04 |
| **ARB (% yes)** | 94 (6.4) | 15 (8.1) | 0.58 | 103 (6.4) | 6 (14.3) | 0.08 | 77 (5.8) | 12 (7.8) | 0.43 |
| **ACEi (% yes)** | 987 (67.1) | 129 (69.4) | 0.48 | 1088 (67.4) | 28 (66.7) | 1.00 | 879 (66.4) | 107 (69.5) | 0.50 |
| **Pack-cigarette years**† | 26·9 (33·5) | 21·3 (30·1) | 0·03 | 26·0 (32·7) | 29·9 (39·4) | 0·47 | 27·7 (33·8) | 19·4 (26·9) | <0·01 |
| **BMI (kg/m2)** | 31·3 (4·5) | 30·7 (4·2) | 0·08 | 31·3 (4·5) | 31·1 (4·8) | 0·75 | 31·3 (4·5) | 30·7 (4·20) | 0·11 |
| **SBP (mmHg)** | 131 (16) | 135 (19) | <0·01 | 131 (17) | 136 (17) | 0·10 | 131 (16) | 134 (19) | <0·01 |
| **DBP (mmHg)** | 76 (10) | 76 (11) | 0·70 | 76 (10) | 74 (11) | 0·21 | 76 (10) | 77 (11) | 0·26 |
| **HDL cholesterol (mg/dL)** | 36 (10) | 36 (10) | 0·91 | 36 (10) | 33 (8) | 0·04 | 36 (10) | 36 (11) | 0·33 |
| **LDL cholesterol (mg/dL)** | 110 (63) | 117 (79) | 0·19 | 111 (66) | 118 (39) | 0·53 | 111 (66) | 116 (85) | 0·40 |
| **Total cholesterol (mg/dL)** | 183 (47) | 190 (49) | 0·06 | 183 (48) | 199 (46) | 0·03 | 183 (49) | 187 (49) | 0·42 |
| **Triglycerides (mg/dL)** | 215 (296) | 217 (156) | 0·92 | 214 (286) | 256 (164) | 0·34 | 222 (312) | 209 (151) | 0·63 |
| **Glycated hemoglobin level (%)** | 9·4 (1·5) | 9·6 (1·6) | 0·15 | 9·4 (1·5) | 9·7 (1·4) | 0·14 | 9·4 (1·5) | 9·5 (1·6) | 0·42 |
| **Glucose (mg/dl)** | 203 (68) | 209 (69) | 0·29 | 203 (67) | 234 (86) | <0·01 | 204 (68) | 200 (62) | 0·49 |
| **Albumin to creatinine ratio (mg/g) (mg/g)** | 100·4 (316·7) | 208·7 (69·1) | <0·01 | 103·2 (315·9) | 536·1(740·0) | <0·01 | 95·6 (318·3) | 157·4 (321·1) | 0·03 |
| **eGFR (ml/min/1·73 m2)** | 82·5 (21·9) | 79·5 (20·9) | 0·08 | 82·6 (21·7) | 64·2 (16·9) | <0·01 | 82·7 (22·0) | 82·6 (20·3) | 0·94 |

**Supplementary Table 4: Baseline characteristics in ACCORD by a redefined nephropathy criterion.** Data are means and (SD) or number of individuals and (%).

1Primary Composite: nephropathy (defined as below) or photocoagulation or vitrectomy

2Nephropathy: two consecutive values of serum creatinine > 3·3 mg per deciliter (291·72 *μmol* per liter) or with consecutive values of glomerular filtration rate (GFR) < 30 *ml* per minute

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Primary Composite1** | | P-value | **Nephropathy2** | | P-value |
| **No (n =8838)** | **Yes (n=951)** | **No (n = 9954)** | **Yes (n = 99)** |
| **Age (years)** | 62·67 (6·66) | 63·17 (6·21) | 0·03 | 62·7 (6·6) | 64·4 (7·1) | 0·01 |
| **Intensive treatment (% yes)** | 4408 (49·9) | 473 (49·7) | 0·96 | 4971 (49·9) | 53 (53·5) | 0·54 |
| **Female (yes %)** | 2017 (22·8) | 230 (24·2) | 0·01 | 3803 (38·2) | 51 (51·5) | <0·01 |
| **Race (%)** |  |  | <0·01 |  |  |  |
| **Black** | 1615 (18·3) | 215 (22·6) |  | 1890 (19·0) | 18 (18·2) | 0·73 |
| **Hispanic** | 613 (6·9) | 80 (8·4) |  | 713 (7·2) | 5 (5·1) |  |
| **White** | 5588 (63·2) | 549 (57·7) |  | 6217 (62·5) | 62 (62·6) |  |
| **Other** | 1022 (11·6) | 107 (11·3) |  | 1134 (11·4) | 14 (14·1) |  |
| **Diabetes duration (years)** | 10·27 (7·39) | 15·32 (7·72) | <0·01 | 10·7 (7·6) | 15·0 (8·6) | <0·01 |
| **CVD history (% yes)** | 3015 (34·1) | 383 (40·3) | <0·01 | 3466 (34·8) | 52 (52·5) | <0·01 |
| **History of heart failure (% yes)** | 385 (4·4) | 68 (7·2) | <0·01 | 466 (4·7) | 9 (9·1) | 0·07 |
| **History of eye disease (% yes)** | 2478 (28·0) | 572 (60·1) | <0·01 | 3087 (31·0) | 53 (53·5) | <0·01 |
| **Smoker† (% yes)** | 4006 (52·3) | 406 (46·4) | <0·01 | 4493 (51·9) | 38 (42·7) | 0·11 |
| **Insulin (% yes)** | 5966 (67.7) | 381 (40.3) | <0·01 | 6436 (64.9) | 54 (54.5) | 0.04 |
| **Fibrates (% yes)** | 8238 (93.6) | 900 (95.0) | 0.10 | 9300 (93.8) | 91 (92.9) | 0.85 |
| **ARB (% yes)** | 7362 (83.5) | 776 (81.9) | 0.21 | 8279 (83.4) | 77 (78.6) | 0.26 |
| **ACEi (% yes)** | 4022 (45.6) | 406 (42.8) | 0.11 | 4518 (45.5) | 36 (36.7) | 0.10 |
| **BMI (kg/m2)** | 32·2 (5·4) | 32·2 (5·5) | 0·98 | 32·2 (5·4) | 33·24 (5·7) | 0·06 |
| **DBP (mmHg)** | 75 (11) | 3·47 (11) | <0·01 | 7 (11) | 74 (12) | 0·20 |
| **SBP (mmHg)** | 136 (19) | 140·43 (17·80) | <0·01 | 136 (17) | 144 (18) | <0·01 |
| **HDL cholesterol (mg/dL)** | 41·71 (11·39) | 43·14 (12·70) | <0·01 | 42 (12) | 39 (12) | 0·02 |
| **LDL cholesterol (mg/dL)** | 104·62 (33·84) | 106·69 (34·21) | 0·07 | 105 (34) | 106 (39) | 0·81 |
| **Total cholesterol (mg/dL)** | 183·19 (41·51) | 184·39 (44·60) | 0·40 | 183 (42) | 187 (46) | 0·37 |
| **Triglycerides (mg/dL)** | 192·13 (150·89) | 177·10 (134·54) | <0·03 | 190 (149) | 221 (119) | 0·04 |
| **HbA1c (%)** | 8·27 (1·04) | 8·57 (1·11) | <0·01 | 8·3 (1·05) | 8·60 (1·2) | <0·01 |
| **Fasting glucose (mg/dL)** | 174·96 (54·82) | 177·81 (66·10) | 0·14 | 175·2 (56·0) | 181·9 (73·5) | 0·24 |
| **Urine albumin to creatinine ratio (mg/g)** | 79·18 (295·28) | 229·67 (587·69) | <0·01 | 91·9 (343·7) | 676·8 (915·4) | <0·01 |
| **eGFR (ml/min/1·73 m2)** | 91·77 (27·13) | 85·04 (26·50) | <0·01 | 91·4 (27·0) | 61·07 (22·78) | <0·01 |

**Supplementary Table 5: Sensitivity analysis.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Model-1**  Age Adjustment + insulin | | **Model-2**  Multivariate Adjustment+ insulin | | **Model-3**  Model 2 + Cumulative HbA1c+ insulin | |
|  | HR (95% C.I.) | P-value | HR (95% C.I.) | P-value | HR (95% C.I.) | P-value |
| **(1) Excluded patients with baseline eye disease and macroalbuminuria** | | | | | | |
| **ACCORD** | | | | | | |
| **Primary Composite (n=483)** | | | | | | |
| Log(CV)-glucose | 1·35 (1·23-1·48) | **<0·001** | 1·19 (1·07-1·31) | **<0·001** | 1·17 (1·06-1·30) | **<0·001** |
| ARV-glucose | 1·30 (1·20-1·41) | **<0·001** | 1·16 (1·05-1·27) | **<0·001** | 1·14 (1·04-1·25) | **<0·001** |
| **VADT** | | | | | | |
| **Primary Composite (n=110)** | | | | | | |
| Log(CV)-glucose | 1·46(1·16-1·84) | **0·001** | 1·32(1·04-1·68) | **0.022** | 1·26 (1.00 -1·60) | 0.064 |
| ARV-glucose | 1·27(1·08-1·50) | **0·004** | 1·20(1·00-1·43) | 0.050 | 1.15 (0.95-1·38) | 0.147 |
| **(2) Adjusted for insulin use** | | | | | | |
| **ACCORD** | | | | | | |
| **Primary Composite (n=1106)** | | | | | | |
| Log(CV)-glucose | 1·27 (1·18-1·37) | **<0·001** | 1·16 (1·07-1·26) | **<0·001** | 1·15 (1·06-1·25) | **0·001** |
| ARV-glucose | 1·21 (1·14-1·29) | **<0·001** | 1·12 (1·04-1·21) | **0·002** | 1·12 (1·04-1·20) | **0·004** |
| **VADT** | | | | | | |
| **Primary Composite (n=178)** | | | | | | |
| Log(CV)-glucose | 1·58(1·31-1·90) | **<0·001** | 1·42(1·16-1·73) | **0.001** | 1·37 (1.11 -1·67) | **0.003** |
| ARV-glucose | 1·31(1·15-1·48) | **<0·001** | 1·19(1·03-1·37) | **0.018** | 1.15 (0.99-1·34) | 0.061 |
| **(3) Included participants with 5 glucose measurements** | | | | | | |
| **ACCORD** | | | | | | |
| **Primary Composite (n=508)** | | | | | | |
| Log(CV)-glucose | 1·44 (1·31-1·58) | **<0·001** | 1·27 (1·15-1·40) | **<0·001** | 1·25 (1·13-1·39) | **<0·001** |
| ARV-glucose | 1·30 (1·21-1·41) | **<0·001** | 1·17 (1·08-1·28) | **<0·001** | 1·16 (1·06-1·26) | **0·001** |
| **VADT** | | | | | | |
| **Primary Composite (n=183)** | | | | | | |
| Log(CV)-glucose | 1·56(1·22-2.00) | **<0·001** | 1·40(1·09-1·81) | **0.009** | 1·34 (1.18 -1·70) | **0.025** |
| ARV-glucose | 1·41(1·18-1·70) | **<0·001** | 1·31(1·08-1·60) | **0.006** | 1.27 (1.04-1·55) | **0.020** |
| **(4) Included glucose measurements until intensive treatment stopped** | | | | | | |
| **ACCORD** | | | | | | |
| **Primary Composite (n=1106)** | | | | | | |
| Log(CV)-glucose | 1·36(1·22-2.00) | **<0·001** | 1·20(1·11-1·13) | **<0·001** | 1·19 (1.09 -1·29) | **<0·001** |
| ARV-glucose | 1·29(1·21-1.37) | **<0·001** | 1·17(1·08-1·26) | **<0·001** | 1·15 (1.07 -1·24) | **<0·001** |

**Supplementary Table 6.** Estimated hazard ratios (95% Confidence Interval, CI) of glycemic variability for the primary composite outcome accounting for adherence to glucose lowering medications in three analyses in ACCORD: (1) adherence was adjusted as a time-varying covariate in the whole group sample; (2) adherence summarized as a binary indicator (high vs low adherence, see below for details) was adjusted as a time in-varying covariate in whole group sample; and (3) stratified analysis among adherence-high vs adherence-low groups. Note, among patients who developed a primary outcome, 43.5% had high adherence rates, while 67.5% had high adherence rate among patient did not develop primary outcome.

ACCORD study provided questionnaires which research staff used to document glycemic medication adherence. This medication log contains a variable indicating the percentage of the time that patients took the medication since the last visit as: 1. All or almost all (80-100%); 2. Some (1% - 79%); 3. None (0%); 4. > Prescribed (>100%). Adherence was then summarized for each patient as having high or low adherence if more than 90% (adherence-high) or less than 90% (adherence-low), respectively, of the visits indicated 80-100% adherence rate. And patients were classified into two groups to represent adherence-high and adherence-low. Overall, there were 47.4% patients who reported 80%-100% adherence throughout ≥ 90% of the visits. There were 215 (2%) participants with missing values for adherence.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 1. **Whole Group** | | 1. **Whole Group** | | 1. **Stratified Analysis** | | | |
| **Time-varying1** | | **High vs low adherence2** | | **High adherence** | | **Low adherence** | |
| **HR (95% CI)** | **P-value** | **HR (95% CI)** | **P-value** | **HR (95% CI)** | **P-value** | **HR (95% CI)** | **P-value** |
| LogCV | 1.18 (1.09 ,1.28) | <0.001 | 1.18 (1.08, 1.28) | <0.001 | 1.17 (1.04 ,1.31) | 0.005 | 1.18 (1.06 ,1.31) | 0.003 |
| ARV | 1.14 (1.05 ,1.23) | 0.001 | 1.14 (1.06, 1.23) | 0.001 | 1.13 (1.02 ,1.24) | 0.019 | 1.12 (1.01 ,1.23) | 0.026 |

**1 Time-varying: adherence was incorporated as a time varying covariate in the Cox proportional model.**

**2 High vs low adherence: a binary adherence indicator (summarized as above) was incorporated as an additional covariate.**

**Supplementary Figure 1: Mean profile plots for glucose from baseline to 84 months in ACCORD and VADT (Vertical bars represent standard errors).** FPG: Fasting plasma glucose.

|  |  |
| --- | --- |
| ACCORD | VADT |
| A close up of a map  Description automatically generated | A close up of a map  Description automatically generated |

**Supplementary Figure 2. Boxplot of glucose variability (left panel: coefficient of variability; right panel: absolute real variability) at each visit in ACCORD separated by glucose lowering treatment arms (upper panel) and insulin use (lower panel).**





**Supplementary Figure 3. Boxplot of glucose variability (left panels: coefficient of variability; right panels: absoluate real variability) at each visit in the VADT separated by treatment arms (upper panel) and insulin use status (lower panel).**





**Supplementary Figure 4. Hazard ratio (95% CI) per SD increase in log(CV) fasting glucose or ARV fasting glucose for risk of the composite primary outcome and the individual microvascular outcomes.**

A screenshot of a cell phone

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SCr: serum creatinine; UAlb: urine albuminuria; ESRD: end-stage renal disease. # Events: number of events in each analysis. Hazard ratios were estimated based on multivariate adjustment including cumulative HbA1c (i.e., Model 3 described in Table 2). Note that multivariate model (Model 3) leads to a decrease in sample size and the number of events.