



Figure S1. Kaplan-Meier survival curves for all-cause mortality by HbA_{1c} and HbA_{1c} target categories. Cumulative survival by Kaplan-Meier analysis by HbA_{1c} categories (A), HbA_{1c} categories plus use of agents causing hypoglycaemia (B), HbA_{1c} target categories (C), and HbA_{1c} target categories plus use of agents causing hypoglycaemia (D). Number (percentage) of deaths or HRs (95% CI) for mortality are shown for each category. HbA_{1c} = haemoglobin A_{1c}; HR = hazard ratio; CI = confidence interval; C1 = HbA_{1c} < 6.5%; C2 = HbA_{1c} 6.5%-7.49%; C3 = HbA_{1c} 7.5%-8.49%; C4 = HbA_{1c} ≥ 8.5%; T1 = HbA_{1c} on-target (≤ 0.5% below or above personalized goal); T2 = HbA_{1c} below-target (> 0.5% below personalized goal); T3 = HbA_{1c} above-target (> 0.5% above personalized goal); hypo- = patients not on agents causing hypoglycaemia; hypo+ = patients on agents causing hypoglycaemia.

Table S1. Distribution of study participants according to personalized HbA_{1c} goals and target categories.

Personalized HbA _{1c} goals	Target categories			
	All	T1	T2	T3
All				
G0	3,859 (24.6)	1,401 (28.1)	674 (14.6)	1,784 (29.5)
G1	4,776 (30.5)	1,557 (31.1)	1,194 (25.8)	2,025 (33.5)
G2	4,508 (28.8)	1,392 (27.9)	1,553 (33.6)	1,563 (25.9)
G3	2,128 (13.6)	548 (11.0)	969 (21.0)	611 (10.1)
G4	385 (2.5)	91 (1.8)	231 (5.0)	63 (1.2)
Total	15,656	4,989 (31.9)	4,621 (29.5)	6,046 (38.6)
Hypo-				
G0	2,331 (40.0)	1,019 (47.3)	526 (25.5)	786 (48.9)
G1	1,871 (32.1)	666 (30.9)	709 (34.4)	496 (30.8)
G2	1,184 (20.3)	369 (17.1)	574 (27.8)	241 (15.0)
G3	383 (6.6)	93 (4.3)	213 (10.3)	77 (4.8)
G4	57 (1.0)	7 (0.3)	42 (2.0)	8 (0.5)
Total	5,826	2,154 (37.0)	2,064 (35.4)	1,608 (27.6)
Hypo+				
G0	1,528 (15.5)	382 (13.5)	148 (5.8)	998 (22.5)
G1	2,905 (29.6)	891 (31.4)	485 (19.0)	1,529 (34.5)
G2	3,324 (33.8)	1,023 (36.1)	979 (38.3)	1,322 (29.8)
G3	1,745 (17.8)	455 (16.0)	756 (29.6)	534 (12.0)
G4	328 (3.3)	84 (3.0)	189 (7.4)	55 (1.2)
Total	9,830	2,835 (28.8)	2,557 (26.0)	4,438 (45.2)

HbA_{1c} = haemoglobin A_{1c}; G0 = personalized HbA_{1c} goal <6.5%; G1 = personalized HbA_{1c} goal <7.0%; G2 = personalized HbA_{1c} goal <7.5%; G3 = personalized HbA_{1c} goal <8.0%; G4 = personalized HbA_{1c} goal <8.5%; T1 = HbA_{1c} on-target ($\leq 0.5\%$ below or above personalized goal); T2 = HbA_{1c} below-target ($> 0.5\%$ below personalized goal); T3 = HbA_{1c} above-target ($> 0.5\%$ above personalized goal); hypo- = patients not on agents causing hypoglycaemia; hypo+ = patients on agents causing hypoglycaemia.

Table S2. Baseline clinical features of study participants by HbA_{1c} categories plus use of agents causing hypoglycaemia.

Variables	Hypo-				Hypo+				P
	C1	C2	C3	C4	C1	C2	C3	C4	
N (%)	2,107 (13.5)	2,137 (13.6)	962 (6.1)	620 (4.0)	1,538 (9.8)	2,944 (18.8)	2,646 (16.9)	2,702 (17.3)	
Deaths, n (%)	248 (11.8%)	270 (12.6%)	161 (16.7%)	123 (19.8%)	489 (31.8%)	779 (26.5%)	697 (26.3%)	835 (30.9%)	<0.001
Age, years	63.5±10.1	65.0±9.8	64.9±10.3	64.2±11.4	68.6±10.4	68.6±9.7	68.0±10.0	66.8±10.6	<0.001
Male gender, n (%)	1,256 (59.6)	1,193 (55.8)	547 (56.9)	338 (54.5)	977 (63.5)	1,710 (58.1)	1,471 (55.6)	1,410 (52.2)	<0.001
Smoking, n (%)									0.01
Never	1,175 (55.8)	1,204 (56.3)	552 (57.4)	340 (54.8)	846 (55.0)	1,646 (55.9)	1,538 (58.1)	1,548 (57.3)	
Former	631 (29.9)	606 (28.4)	269 (28.0)	166 (26.8)	476 (30.9)	866 (29.4)	691 (26.1)	702 (26.0)	
Current	301 (14.3)	327 (15.3)	141 (14.7)	114 (18.4)	216 (14.0)	432 (14.7)	417 (15.8)	452 (16.7)	
Diabetes duration, years	6.5±7.2	9.2±9.0	12.8±9.8	12.9±11.3	12.5±9.8	14.8±9.9	16.8±10.0	16.8±9.8	<0.001
HbA _{1c} , % (mmol·mol ⁻¹)	5.93±0.44 (41.3±4.8)	6.93±0.28 (52.2±3.1)	7.89±0.27 (62.7±3.0)	9.85±1.49 (84.2±16.3)	5.94±0.48 (41.4±5.2)	7.01±0.28 (53.1±3.1)	7.95±0.29 (63.4±3.2)	9.76±1.26 (83.2±13.8)	<0.001
BMI, kg·m ⁻²	29.1±5.0	29.3±5.0	29.7±5.2	30.2±5.5	27.8±4.7	28.2±4.8	28.8±5.2	29.6±5.5	<0.001
Waist circumference, cm	102.9±10.1	103.2±10.1	104.1±10.6	105.0±11.3	100.3±9.7	100.9±9.7	102.2±10.6	103.8±11.0	<0.001
Triglycerides, mmol·L ⁻¹	1.48±0.94	1.53±0.89	1.61±0.91	1.93±1.43	1.42±0.95	1.45±0.82	1.54±0.88	1.83±1.24	<0.001
Total cholesterol, mmol·L ⁻¹	4.85±0.95	4.86±0.96	4.80±0.93	5.01±1.14	4.59±0.96	4.70±0.95	4.73±0.97	4.86±1.08	<0.001
HDL cholesterol, mmol·L ⁻¹	1.32±0.35	1.30±0.33	1.26±0.31	1.20±0.32	1.30±0.37	1.32±0.37	1.29±0.36	1.25±0.36	<0.001
LDL cholesterol, mmol·L ⁻¹	3.53±0.92	3.57±0.92	3.54±0.91	3.80±1.10	3.29±0.91	3.38±0.90	3.44±0.92	3.61±1.03	<0.001
Non-HDL cholesterol, mmol·L ⁻¹	2.87±0.84	2.87±0.83	2.82±0.81	2.95±0.90	2.66±0.83	2.73±0.82	2.74±0.83	2.80±0.90	<0.001
Systolic BP, mmHg	135.5±16.6	136.6±16.8	139.6±18.0	137.9±17.6	137.3±18.7	138.8±18.4	139.6±18.2	138.8±18.9	<0.001
Diastolic BP, mmHg	79.6±9.2	79.5±8.9	80.6±9.4	79.9±9.0	78.2±9.6	77.9±9.4	78.2±9.5	78.4±9.8	<0.001
Pulse pressure, mmHg	55.9±14.3	57.1±14.8	58.9±15.0	57.9±14.9	59.1±16.3	60.9±16.0	61.4±16.2	60.4±15.9	<0.001
Anti-hyperglycaemic treatment, n (%)									
Lifestyle	1,017 (48.3)	762 (35.7)	192 (20.0)	142 (22.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
Insulin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	440 (28.6)	913 (31.0)	1,062 (40.1)	1,509 (55.8)	<0.001
Non-insulin agents	1,090 (51.7)	1,375 (64.3)	770 (80.0)	478 (77.1)	1,098 (71.4)	2,031 (69.0)	1,584 (59.9)	1,193 (44.2)	<0.001
Metformin	1,063 (50.5)	1,346 (63.0)	746 (77.5)	447 (72.1)	683 (44.4)	1,494 (50.7)	1,460 (55.2)	1,406 (52.0)	<0.001
Pioglitazone	58 (2.8)	84 (3.9)	67 (7.0)	53 (8.5)	29 (1.9)	83 (2.8)	96 (3.6)	84 (3.1)	<0.001
Acarbose	15 (0.7)	16 (0.7)	21 (2.2)	20 (3.2)	21 (1.4)	27 (0.9)	26 (1.0)	24 (0.9)	<0.001
Sulfonylureas	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	820 (53.3)	1,677 (57.0)	1,472 (55.6)	1,281 (47.4)	<0.001
Repaglinide	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	335 (21.8)	537 (18.2)	371 (14.0)	282 (10.4)	<0.001
Lipid-lowering treatment, n (%)	901 (42.8)	1,007 (47.1)	419 (43.6)	263 (42.4)	671 (43.6)	1,382 (46.9)	1,309 (49.5)	1,286 (47.6)	<0.001
Anti-hypertensive treatment, n (%)	1,396 (66.3)	1,458 (68.2)	664 (69.0)	386 (62.3)	1,113 (72.4)	2,153 (73.1)	1,937 (73.2)	1,965 (72.7)	<0.001
Albuminuria, mg·day ⁻¹	33.8±148.1	46.8±392.8	41.6±165.7	52.3±217.5	81.1±298.6	84.7±357.4	86.4±371.1	106.0±307.0	<0.001
Serum creatinine, µmol·L ⁻¹	76.0±23.9	76.0±30.9	76.0±20.3	75.1±23.9	89.3±50.4	84.0±37.1	82.2±35.4	83.1±33.6	<0.001
eGFR, ml·min ⁻¹ ·1.73m ⁻²	85.6±18.6	84.3±17.8	84.1±18.0	85.2±20.5	76.1±22.8	77.3±21.1	78.3±21.2	77.8±22.8	<0.001
DKD phenotype, n (%)									
No DKD	1,649 (78.3)	1,600 (74.9)	679 (70.6)	391 (63.1)	905 (58.8)	1,785 (60.6)	1,590 (60.1)	1,385 (51.3)	
Albuminuric DKD with preserved eGFR	260 (12.3)	323 (15.1)	177 (18.4)	156 (25.2)	272 (17.7)	554 (18.8)	514 (19.4)	710 (26.3)	
Non-albuminuric DKD	127 (6.0)	149 (7.0)	73 (7.6)	43 (6.9)	194 (12.6)	316 (10.7)	287 (10.8)	287 (10.6)	
Albuminuric DKD with reduced eGFR	71 (3.4)	65 (3.0)	33 (3.4)	30 (4.8)	167 (10.9)	289 (9.8)	255 (9.6)	320 (11.8)	
DR, n (%)									<0.001
No DR	1,980 (94.0)	1,967 (92.0)	817 (84.9)	491 (79.2)	1,198 (77.9)	2,218 (75.3)	1,841 (69.6)	1,677 (62.1)	
Non-advanced DR	80 (3.8)	115 (5.4)	109 (11.3)	90 (14.5)	162 (10.5)	388 (13.2)	477 (18.0)	526 (19.5)	
Advanced DR	47 (2.2)	55 (2.6)	36 (3.7)	39 (6.3)	178 (11.6)	338 (11.5)	328 (12.4)	499 (18.5)	

CVD, n (%)								
Any	266 (12.6)	363 (17.0)	202 (21.0)	153 (24.7)	433 (28.2)	723 (24.6)	704 (26.6)	776 (28.7) <0.001
Myocardial infarction	138 (6.5)	156 (7.3)	83 (8.6)	63 (10.2)	216 (14.0)	358 (12.2)	362 (13.7)	366 (13.5) <0.001
Coronary revascularization	113 (5.4)	162 (7.6)	97 (10.1)	59 (9.5)	182 (11.8)	325 (11.0)	314 (11.9)	327 (12.1) <0.001
Stroke	45 (2.1)	41 (1.9)	25 (2.6)	11 (1.8)	81 (5.3)	102 (3.5)	93 (3.5)	115 (4.3) <0.001
Carotid revascularization	38 (1.8)	105 (4.9)	74 (7.7)	72 (11.6)	82 (5.3)	135 (4.6)	161 (6.1)	189 (7.0) <0.001
Ulcer/gangrene/amputation	21 (1.0)	31 (1.5)	15 (1.6)	15 (2.4)	71 (4.6)	136 (4.6)	116 (4.4)	151 (5.6) <0.001
Lower limb revascularization	18 (0.9)	38 (1.8)	29 (3.0)	26 (4.2)	47 (3.1)	97 (3.3)	92 (3.5)	103 (3.8) <0.001
Comorbidities n (%)								
Any	311 (14.8)	325 (15.2)	142 (14.8)	101 (16.3)	371 (24.1)	547 (18.6)	478 (18.1)	512 (18.9) <0.001
COPD	96 (4.6)	56 (2.6)	29 (3.0)	17 (2.7)	77 (5.0)	145 (4.9)	113 (4.3)	141 (5.2) <0.001
Chronic liver disease	120 (5.7)	177 (8.3)	86 (8.9)	69 (11.1)	179 (11.6)	238 (8.1)	240 (9.1)	252 (9.3) <0.001
Cancer	124 (5.9)	121 (5.7)	36 (3.7)	22 (3.5)	155 (10.1)	221 (7.5)	179 (6.8)	173 (6.4) <0.001

HbA_{1c} = haemoglobin A_{1c}; hypo- = patients not on agents causing hypoglycaemia; hypo+ = patients on agents causing hypoglycaemia; C1 = HbA_{1c} <6.5%; C2 = HbA_{1c} 6.5%-7.49%; C3 = HbA_{1c} 7.5%-8.49%; C4 = HbA_{1c} ≥8.5%; BMI = body mass index; BP = blood pressure; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; DKD = diabetic kidney disease; DR = diabetic retinopathy; = CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease.

Table S3. Baseline clinical features of study participants by HbA_{1c} target categories and use of agents causing hypoglycaemia.

Variables	Hypo-			Hypo+			<i>P</i>
	T1	T2	T3	T1	T2	T3	
N (%)	2,154 (11.5)	2,064 (17.2)	1,608 (12.5)	2,835 (26.2)	2,557 (38.2)	4,438 (24.3)	
Deaths, n (%)	247 (11.5%)	354 (17.2%)	201 (12.5%)	744 (26.2%)	976 (38.2%)	1,080 (24.3%)	<0.001
Age, years	64.0±9.6	66.5±10.4	61.9±10.2	68.7±9.7	71.7±9.1	65.2±10.2	<0.001
Male gender, n (%)	1,247 (57.9)	1,201 (58.2)	886 (55.1)	1,586 (55.9)	1,617 (63.2)	2,365 (53.3)	<0.001
Smoking, n (%)							<0.001
Never	1,204 (55.9)	1,179 (57.1)	888 (55.2)	1,633 (57.6)	1,402 (54.8)	2,543 (57.3)	
Former	645 (29.9)	621 (30.1)	406 (25.2)	790 (27.9)	834 (32.6)	1,111 (25.0)	
Current	305 (14.2)	264 (12.8)	314 (19.5)	412 (14.5)	321 (12.6)	784 (17.7)	
Diabetes duration, years	8.5±8.5	9.5±9.6	9.8±9.4	15.8±10.1	16.3±10.5	14.9±9.6	<0.001
HbA _{1c} , %	6.87±0.51	6.04±0.59	8.53±1.43	7.34±0.54	6.37±0.67	9.03±1.36	<0.001
(mmol·mol ⁻¹)	(51.6±5.6)	(42.5±6.4)	(69.7±15.6)	(56.7±5.9)	(46.1±7.3)	(75.2±14.9)	
BMI, kg·m ⁻²	29.4±5.0	28.8±4.9	30.2±5.5	28.3±4.9	27.8±4.6	29.5±5.5	<0.001
Waist circumference, cm	103.5±10.1	102.2±9.9	105.0±11.1	101.1±9.9	100.2±9.4	103.4±11.0	<0.001
Triglycerides, mmol·l ⁻¹	1.55±0.98	1.43±0.83	1.76±1.16	1.48±0.82	1.41±0.88	1.73±1.14	<0.001
Total cholesterol, mmol·l ⁻¹	4.88±0.93	4.79±0.95	4.94±1.05	4.70±0.95	4.61±0.96	4.84±1.03	<0.001
HDL cholesterol, mmol·l ⁻¹	1.29±0.33	1.33±0.36	1.23±0.32	1.31±0.36	1.32±0.37	1.26±0.36	<0.001
LDL cholesterol, mmol·l ⁻¹	3.58±0.91	3.46±0.91	3.71±1.02	3.39±0.89	3.29±0.92	3.57±0.99	<0.001
Non-HDL cholesterol, mmol·l ⁻¹	2.89±0.82	2.81±0.82	2.92±0.88	2.72±0.82	2.66±0.83	2.79±0.87	<0.001
Systolic BP, mmHg	136.6±16.7	136.7±17.0	137.3±17.6	139.7±18.6	138.3±18.6	138.6±18.4	<0.001
Diastolic BP, mmHg	79.8±8.8	79.4±9.2	80.3±9.3	78.4±9.4	77.5±9.7	78.4±9.6	<0.001
Pulse pressure, mmHg	56.8±14.6	57.3±14.7	57.0±14.8	61.3±16.1	60.8±16.4	60.1±15.9	<0.001
Anti-hyperglycaemic treatment, n (%)							
Lifestyle	810 (37.6)	927 (44.9)	376 (23.4)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
Insulin	0 (0.0)	0 (0.0)	0 (0.0)	972 (33.6)	860 (34.3)	2,092 (47.1)	<0.001
Non-insulin agents	1,344 (62.4)	1,137 (55.1)	1,232 (76.6)	1,863 (65.7)	1,697 (66.4)	2,346 (52.9)	<0.001
Metformin	1,310 (60.8)	1,111 (53.8)	1,181 (73.4)	1,474 (52.0)	1,084 (42.4)	2,485 (56.0)	<0.001
Pioglitazone	89 (4.1)	52 (2.5)	121 (7.5)	92 (3.2)	40 (1.6)	160 (3.6)	<0.001
Acarbose	17 (0.8)	21 (1.0)	34 (2.1)	32 (1.1)	26 (1.0)	40 (0.9)	<0.001
Sulfonylureas	0 (0.0)	0 (0.0)	0 (0.0)	1,610 (56.8)	1,314 (51.4)	2,326 (52.4)	<0.001
Repaglinide	0 (0.0)	0 (0.0)	0 (0.0)	461 (16.3)	510 (19.9)	554 (12.5)	<0.001
Lipid-lowering treatment, n (%)	948 (44.0)	972 (47.1)	670 (41.7)	1,366 (48.2)	1,176 (46.0)	2,106 (47.5)	<0.001
Anti-hypertensive treatment, n (%)	1,417 (65.8)	1,475 (71.5)	1,012 (62.9)	2,087 (73.6)	1,974 (77.2)	3,107 (70.0)	<0.001
Albuminuria, mg·day ⁻¹	31.8±114.0	53.8±413.8	39.9±176.4	88.7±363.5	101.7±343.1	85.0±320.9	<0.001
Serum creatinine, µmol·l ⁻¹	75.1±29.2	77.8±26.5	74.3±21.2	83.1±33.6	92.8±50.4	80.4±30.9	<0.001
eGFR, ml·min ⁻¹ ·1.73m ⁻²	85.5±17.0	82.3±19.3	87.1±18.6	77.5±20.9	71.9±22.3	80.8±21.6	<0.001
DKD phenotype, n (%)							<0.001
No DKD	1,656 (76.9)	1,520 (73.6)	1,143 (71.1)	1,692 (59.7)	1,339 (52.4)	2,634 (59.4)	
Albuminuric DKD with preserved eGFR	312 (14.5)	284 (13.8)	320 (19.9)	551 (19.4)	483 (18.9)	1,016 (22.9)	
Non-albuminuric DKD	140 (6.5)	161 (7.8)	91 (5.7)	321 (11.3)	362 (14.2)	401 (9.0)	

Albuminuric DKD with reduced eGFR	46 (2.1)	99 (4.8)	54 (3.4)	271 (9.6)	373 (14.6)	387 (8.7)	
DR, n (%)							<0.001
No DR	2,000 (92.9)	1,870 (90.6)	1,385 (86.1)	2,064 (72.8)	1,825 (71.4)	3,045 (68.6)	
Non-advanced DR	117 (5.4)	109 (5.3)	168 (10.4)	412 (14.5)	335 (13.1)	806 (18.2)	
Advanced DR	37 (1.7)	85 (4.1)	55 (3.4)	359 (12.7)	397 (15.5)	587 (13.2)	
CVD, n (%)							
Any	291 (13.5)	478 (23.2)	215 (13.4)	713 (25.1)	979 (38.3)	944 (21.3)	<0.001
Myocardial infarction	125 (5.8)	221 (10.7)	94 (5.8)	355 (12.5)	482 (18.9)	465 (10.5)	<0.001
Coronary revascularization	134 (6.2)	208 (10.1)	89 (5.5)	313 (11.0)	409 (16.0)	426 (9.6)	<0.001
Stroke	35 (1.6)	67 (3.2)	20 (1.2)	102 (3.6)	164 (6.4)	125 (2.8)	<0.001
Carotid revascularization	88 (4.1)	114 (5.5)	87 (5.4)	162 (5.7)	194 (7.6)	211 (4.8)	<0.001
Ulcer/gangrene/amputation	23 (1.1)	41 (2.0)	18 (1.1)	135 (4.8)	176 (6.9)	163 (3.7)	<0.001
Lower limb revascularization	33 (1.5)	46 (2.2)	32 (2.0)	89 (3.1)	125 (4.9)	125 (2.8)	<0.001
Comorbidities n (%)							
Any	239 (11.1)	479 (23.2)	161 (10.0)	517 (18.2)	782 (30.6)	609 (13.7)	<0.001
COPD	41 (1.9)	132 (6.4)	25 (1.6)	126 (4.4)	190 (7.4)	160 (3.6)	<0.001
Chronic liver disease	135 (6.3)	212 (10.3)	105 (6.5)	250 (8.8)	358 (14.0)	301 (6.8)	<0.001
Cancer	75 (3.5)	187 (9.1)	41 (2.5)	201 (7.1)	317 (12.4)	210 (4.7)	<0.001

HbA_{1c} = haemoglobin A_{1c}; hypo- = patients not on agents causing hypoglycaemia; hypo+ = patients on agents causing hypoglycaemia; T1 = HbA_{1c} on-target ($\leq 0.5\%$ below or above personalized goal); T2 = HbA_{1c} below-target ($>0.5\%$ below personalized goal); T3 = HbA_{1c} above-target ($>0.5\%$ above personalized goal); BMI = body mass index; BP = blood pressure; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; DKD = diabetic kidney disease; DR = diabetic retinopathy; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease.

The RIACE Study Group

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