Association between glycated haemoglobin levels and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease: a secondary analysis of the TECOS randomized clinical trial

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Aims

Whether glycaemic control is associated with cardiovascular outcomes in patients with type 2 diabetes (T2D) is unclear. Consequently, we assessed the relationship between glycated haemoglobin (HbA_{1c}) and cardiovascular outcomes in a placebo-controlled randomized trial which demonstrated no cardiovascular effect of sitagliptin in patients with T2D and atherosclerotic vascular disease.

Methods and results

Secondary analysis of 14 656 TECOS participants with time to event analyses using multivariable Cox proportional hazard models. During a median 3.0 (interquartile range 2.3–3.8) year follow-up, 456 (3.1% of 14 656) patients had first hospitalization for heart failure (HF), 1084 (11.5%) died, 1406 (9.6%) died or were hospitalized for HF, and 1689 (11.5%) had a non-HF cardiovascular event (cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, or hospitalization for unstable angina). Associations between baseline or time-varying HbA_{1c} and cardiovascular outcomes were U-shaped, with the lowest risk when HbA_{1c} was around 7%. Each one-unit increase in the time-varying HbA_{1c} above 7% was associated with an adjusted hazard ratio (HR) of 1.21 [95% confidence interval (CI) 1.11–1.33] for first HF hospitalization, 1.11 (1.03–1.21) for all-cause death, 1.18 (1.09–1.26) for death or HF hospitalization, and 1.10 (1.02–1.17) for non-HF cardiovascular events. Each one-unit decrease in the time-varying HbA_{1c} below 7% was associated with an adjusted HR of 1.35 (95% CI 1.12–1.64) for first HF hospitalization, 1.37 (1.16–1.61) for death, 1.42 (1.23–1.64) for death or HF hospitalization, and 1.22 (1.06–1.41) for non-HF cardiovascular events.

Conclusion

Glycated haemogobin exhibits a U-shaped association with cardiovascular outcomes in patients with T2D and atherosclerotic vascular disease, with nadir around 7%.
Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT00790205.

Keywords Diabetes mellitus • Heart failure • Glycaemic control • Outcomes

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Introduction

Heart failure (HF) is one of the most common complications of type 2 diabetes (T2D) due to the interplay of macrovascular and microvascular disease, the frequent coexistence of kidney disease, and the effect of insulin resistance on cardiac myocytes. However, HF events are infrequently included in primary efficacy analyses for T2D outcome trials.[1,2] Moreover, although patients with both T2D and HF exhibit more than a twofold higher mortality risk and nearly a fivefold higher risk of HF hospitalizations (HFH) compared to those without either condition,[3] less than 15% of participants in T2D cardiovascular outcome trials have HF at baseline.[2] An analysis of 12 cardiovascular outcome trials in T2D found no correlation between the degree of glycated haemoglobin (HbA_{1c}) reduction and the risk of HF events (Spearman correlation coefficient 0.26, $P = 0.40$),[2] and a meta-analysis of 30 trials reported no overall effect on the risk of HF with glucose-lowering interventions [risk ratio 0.98, 95% confidence interval (CI) 0.90–1.08], but with substantial heterogeneity between drug classes and an association between weight loss and lower HF risk.[4] While observational studies have suggested that the relationship between HbA_{1c} levels and mortality in individuals with T2D may be U-shaped,[5–8] the influence of lower target HbA_{1c} levels on the occurrence of cardiovascular events, particularly HF, is uncertain.[4,9]

As the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS)[10] found no association between sitagliptin use and HF outcomes [3.1% vs. 3.1% for HFH; hazard ratio (HR) 1.00, 95% CI 0.83–1.19][11] or all cardiovascular events (11.4% vs. 11.6%; HR 0.98, 95% CI 0.89–1.08),[10] we designed this study to examine whether outcomes varied by baseline or average achieved HbA_{1c} in TECOS participants. We examined whether HF or non-HF cardiovascular events varied by HbA_{1c} levels and whether any observed associations differed in patients with HF vs. without HF at baseline (18.0% of TECOS participants had a history of HF at baseline).

Methods

Study cohort

The design and main results of TECOS have been previously published.[10] In brief, it was a double-blind randomized trial of sitagliptin vs. placebo in patients aged ≥50 years with T2D and atherosclerotic cardiovascular disease. All patients had follow-up, including laboratory testing, at 4, 8, 12, 18, 24, 30, 36, 42, and 48 months and local investigators were allowed to use open-label glucose-lowering medications (other than dipeptidyl peptidase-4 inhibitors) as they saw fit – no targets were specified for HbA_{1c} levels and the additional glycaemic drugs used are listed in the main TECOS paper supplement (of note, no patients received sodium–glucose co-transporter 2 inhibitors). The ethics committees associated with all participating trial sites approved the protocol, and all participants provided written informed consent. We combined both arms of the trial for the present analyses since TECOS demonstrated no between-group differences in rates of major adverse cardiovascular events or HFH.

Endpoints

We examined several pre-defined outcomes in TECOS which were centrally adjudicated using standardized criteria: (i) frequency and time to first HFH, (ii) frequency and time to all-cause death, (iii) frequency and time to either HFH or all-cause death, (iv) frequency and time to cardiovascular death, (v) frequency and time to first event of a composite non-HF cardiovascular outcomes (cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, or hospitalization for unstable angina), (vi) frequency and time to worsening kidney function [defined for those with baseline estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 as a decrease in eGFR ≥50% or development of end-stage renal disease requiring dialysis or transplantation, and for those with baseline eGFR ≥90 mL/min/1.73 m^2 as development of end-stage renal disease or a decrease in eGFR of ≥30%], or (vii) frequency and time to severe hypoglycaemic events (a pre-specified and adjudicated endpoint in TECOS defined as an episode in which glucose was <3.9 mmol/L and the patient was sufficiently disoriented or incapacitated as to require third-party assistance from another individual or from healthcare personnel).

Statistical analysis

Baseline characteristics are reported based on baseline HbA_{1c} stratified into five categories commonly used in the literature: <6.5%, 6.5–6.9%, 7.0–7.4%, 7.5–8.0%, and >8.0%. Categorical variables are summarized as number (percentage) of participants, and continuous variables are presented as mean (standard deviation) or median (25th and 75th percentiles). Trends across the five categories were assessed using Cochran–Mantel–Haenszel (CMH) row mean scores for categorical variables and CMH correlation tests for continuous variables for the trend. Observed event rates were also reported according to the five HbA_{1c} categories, and a chi-square was used to test any differences among categories.

Unadjusted Kaplan–Meier curves were plotted to examine the associations between baseline HbA_{1c} categories and the endpoints of interest. Relationships between baseline HbA_{1c} as a continuous variable and outcomes were evaluated using multivariable adjusted Cox proportional hazards models stratified by region. For first HFH, the cause-specific Cox proportional hazards model was used by treating death as competing event. The proportional hazards assumption was evaluated graphically using standardized score process and found to be appropriately met. In the multivariable models, the following characteristics were included: sex, age, race, body mass index at randomization, history of coronary heart disease, history of peripheral artery disease, history of chronic obstructive pulmonary disease, history of atrial fibrillation/flutter, baseline eGFR, baseline systolic blood pressure, baseline urinary albumin to creatinine ratio, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, smoking status, concomitant medicine use at baseline (metformin, sulfonylurea, insulin, thiazolidinedione, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aspirin, and statin), and randomized study treatment. Restricted cubic spline methods with four knots were used to examine the linearity assumption, and predicted event rates were plotted according to baseline HbA_{1c} as a continuous measure. When the linearity assumption test for baseline HbA_{1c} was significant, HbA_{1c} was approximated using a piecewise linear spline. The cut point in the piecewise linear regression was determined with clinical input and visual inspection of the shape of the adjusted association between HbA_{1c} and endpoint of interest. The associations between achieved HbA_{1c} as a time-varying variable and the

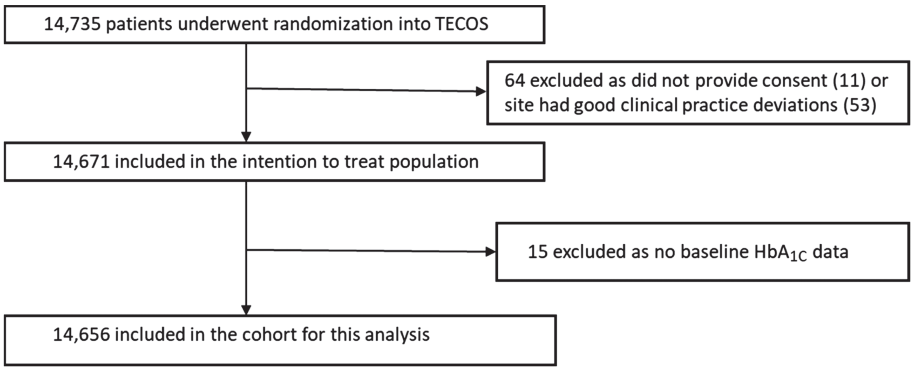

Figure 1 Study cohort derivation. HbA_{1c}, glycated haemoglobin.

outcomes of interest were also examined by using all HbA_{1c} measurements obtained during follow-up study visits and with the same covariates used for adjustment as detailed above. For this time-varying Cox regression analysis, timing of events was aligned with time of HbA_{1c} measurements and the updated HbA_{1c} was used only if it occurred prior to an event of interest.

To examine whether HF at baseline was associated with time-updated HbA_{1c} during the trial, the relationship between history of HF and HbA_{1c} values collected at different time points was modeled using repeated measures in a mixed model that included randomized study treatment and region. No imputation for missing HbA_{1c} at different times was performed for this analysis. Mean and standard deviation were plotted according to baseline HF status and follow-up time up to 48 months.

To evaluate whether prior HF modified the results, the interaction between time-updated HbA_{1c} and HF at baseline was tested in a Cox proportional hazard model. The interaction between time-updated HbA_{1c} and age (>70 years or ≤70 years) was also tested using the same procedure.

Missing data for baseline characteristics utilized in multivariable modeling were imputed using multiple imputation (the fully conditional specification method), and missing HbA_{1c} measurements during follow-up were imputed using the last observation carried forward for measurements obtained no more than 1 year prior to the missing observation in the time-varying Cox regression analysis. Missing HbA_{1c} values at baseline were not imputed since any such patients were excluded from this analysis. The only baseline variable with >1% missing data was urinary albumin to creatinine ratio.

All statistical tests were two-sided and were considered statistically significant when $P < 0.05$. Analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

Results

Of the 14 671 TECOS participants, we analysed the 14 656 who had baseline HbA_{1c} data available (*Figure 1*): mean age was 65.5 years, 29.3% were female, mean duration of diabetes was 11.6 years, 74.1% had known cardiovascular disease, 18.0% had a history of HF at baseline (*Table 1*), and median follow-up was 3.0 (interquartile range 2.3–3.8) years. Although there were small differences in comorbidity profiles across baseline HbA_{1c} strata, the key findings were that those with higher baseline HbA_{1c} values had longer durations of diabetes, were more likely to be current smokers, and were more likely to have diabetic neuropathy and/or exhibit features of diabetic nephropathy (with greater albuminuria levels) (*Table 1*). Concomitant medication use is listed in *Table 1* but it is worth emphasizing that only 2.7% of individuals were taking thiazolidinedione at baseline (rosiglitazone use was actively discouraged) and none were on a sodium–glucose co-transporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. During the 3 years of followup, 267 (1.8%) TECOS participants had a thiazolidinedione added to their therapy, 87 (0.6%) were started on a glucagon-like peptide-1 receptor agonist, and none had a sodium–glucose co-transporter 2 inhibitor added.[10]

Patients with HbA_{1c} 7.0–7.4% at baseline exhibited the lowest rates of HFH (online supplementary *Figure S1A*), all-cause death (online supplementary *Figure S1B*), death or HFH (*Figure 2*), and non-HF cardiovascular outcomes (*Table 2*). When baseline HbA_{1c} was examined as a continuous variable, multivariable adjustment revealed that the associations between HbA_{1c} and HFH or all-cause death were U-shaped with the nadir at an HbA_{1c} of 7% (*Figure 3*). This association did not differ by age (P for interaction = 0.36) and was similar for both endpoints separately (online supplementary *Figure S2*).

Each one-unit increase in time-varying HbA_{1c} above 7% was associated with an adjusted HR of 1.21 (95% CI 1.11–1.33) for HFH, 1.11 (1.03–1.21) for all-cause death, 1.18 (1.09–1.26) for death or HFH, and 1.10 (1.02–1.17) for non-HF cardiovascular events (*Table 3*). Each one-unit decrease in the time-varying HbA_{1c} below 7% was associated with an adjusted HR of 1.35 (95% CI 1.12–1.64) for HFH, 1.37 (1.16–1.61) for all-cause death, 1.42 (1.23–1.64) for death or HFH, and 1.22 (95% CI 1.06–1.41) for non-HF cardiovascular events (*Table 3*).

Statistically significant interactions were observed between history of HF and the magnitude of harm (expressed as HFH or all-cause death) as time-varying HbA_{1c} decreased below 7% (greater harm in those without a prior history of HF) and between age and the magnitude of harm as time-varying HbA_{1c} increased above 7% (greater harm in those ≥70 years) (online supplementary *Table S1*). However, there was no evidence of a statistical

Table 1 **Selected baseline characteristics, stratified by baseline glycated haemoglobin**

	All patients ($n = 14\,656$)	HbA_{1c} <6.5% ($n = 785$)	HbA_{1c} 6.5–6.9% ($n = 4329$)	HbA_{1c} 7.0–7.4% ($n = 4921$)	HbA_{1c} 7.5–8.0% ($n = 3710$)	HbA_{1c} >8% ($n = 911$)	*P*-value for trend
Age[a], years	65.5 (8.0)	66.2 (8.1)	66.0 (7.9)	65.6 (8.0)	64.7 (7.9)	64.9 (8.1)	<0.001
Female sex	4293 (29.3)	222 (28.3)	1218 (28.1)	1456 (29.6)	1146 (30.9)	251 (27.6)	0.09
Race/ethnicity							<0.001
White	9945 (67.9)	568 (72.4)	3161 (73.0)	3296 (67.0)	2329 (62.8)	591 (64.9)	
Black	447 (3.0)	33 (4.2)	128 (3.0)	169 (3.4)	93 (2.5)	24 (2.6)	
Asian	3264 (22.3)	96 (12.2)	781 (18.0)	1133 (23.0)	1042 (28.1)	212 (23.3)	
Other	1000 (6.8)	88 (11.2)	259 (6.0)	323 (6.6)	246 (6.6)	84 (9.2)	
Hispanic or Latino	1797 (12.3)	196 (25.0)	479 (11.1)	573 (11.6)	403 (10.9)	146 (16.0)	
Region							<0.001
Asia Pacific and other	4562 (31.1)	163 (20.8)	1159 (26.8)	1605 (32.6)	1333 (35.9)	302 (33.2)	
Eastern Europe	3962 (27.0)	201 (25.6)	1267 (29.3)	1213 (24.6)	1108 (29.9)	173 (19.0)	
Latin America	1470 (10.0)	190 (24.2)	389 (9.0)	442 (9.0)	315 (8.5)	134 (14.7)	
North America	2588 (17.7)	133 (16.9)	833 (19.2)	940 (19.1)	501 (13.5)	181 (19.9)	
Western Europe	2074 (14.2)	98 (12.5)	681 (15.7)	721 (14.7)	453 (12.2)	121 (13.3)	
Duration of diabetes[b] (years)	11.6 (8.1)	9.7 (7.7)	10.4 (7.7)	11.8 (8.2)	12.7 (8.2)	13.8 (8.7)	<0.001
BMI (kg/m^2)	30.2 (5.6)	29.7 (5.1)	30.3 (5.7)	30.2 (5.6)	30.1 (5.6)	30.8 (6.4)	0.001
Systolic blood pressure (mmHg)	135.0 (17.0)	135.8 (17.7)	134.5 (16.9)	134.8 (17.2)	135.8 (16.6)	134.9 (17.5)	0.004
Diastolic blood pressure (mmHg)	77.2 (10.5)	77.8 (10.4)	76.9 (10.4)	76.7 (10.6)	77.9 (10.3)	77.6 (10.5)	<0.001
eGFR, mL/min/1.73 m^2	74.9 (21.1)	74.3 (20.2)	75.2 (21.1)	74.5 (20.6)	75.1 (21.5)	75.3 (22.3)	0.43
eGFR <50 mL/min/1.73 m^2	1370 (9.4)	71 (9.1)	383 (8.9)	470 (9.6)	353 (9.6)	93 (10.3)	0.17
Urinary albumin to creatinine ratio[c], median (Q1, Q3), mg/g	10.6 (3.5, 35.5)	8.8 (2.0, 29.9)	9.0 (3.4, 28.4)	11.2 (3.7, 38.0)	12.4 (3.7, 50.4)	15.0 (5.3, 39.2)	<0.001
Total cholesterol (mg/dL)	165.8 (45.3)	166.9 (46.2)	164.2 (43.4)	164.2 (46.3)	168.5 (46.2)	168.9 (43.8)	<0.001
LDL cholesterol (mg/dL)	91.0 (57.9)	93.1 (42.2)	89.6 (36.1)	91.1 (85.1)	91.7 (36.8)	91.9 (36.1)	0.52
HDL cholesterol (mg/dL)	43.5 (12.5)	44.3 (12.3)	44.1 (12.3)	43.4 (13.0)	42.9 (12.1)	42.6 (12.5)	<0.001
Triglycerides (mg/dL)	165.4 (99.9)	158.2 (92.3)	157.9 (91.1)	165.4 (102.3)	172.9 (106.6)	176.5 (102.0)	<0.001
Prior CV disease	10 853 (74.1)	544 (69.3)	3261 (75.3)	3685 (74.9)	2674 (72.1)	689 (75.6)	0.64
Myocardial infarction	6248 (42.6)	325 (41.4)	1888 (43.6)	2127 (43.2)	1527 (41.2)	381 (41.8)	0.12
≥50% coronary stenosis	7680 (52.4)	381 (48.5)	2271 (52.5)	2656 (54.0)	1876 (50.6)	496 (54.4)	0.65
Prior PCI	5708 (39.5)	299 (38.6)	1684 (39.5)	1991 (41.0)	1369 (37.3)	365 (40.5)	0.42
CABG	3661 (25.0)	183 (23.3)	1119 (25.8)	1238 (25.2)	888 (23.9)	233 (25.6)	0.46
Prior cerebrovascular disease	3585 (24.5)	217 (27.6)	1076 (24.9)	1164 (23.7)	915 (24.7)	213 (23.4)	0.13
Prior peripheral artery disease	2429 (16.6)	142 (18.1)	641 (14.8)	832 (16.9)	653 (17.6)	161 (17.7)	0.01
Prior heart failure	2641 (18.0)	129 (16.4)	867 (20.0)	842 (17.1)	673 (18.1)	130 (14.3)	0.007
NYHA class ≥III	372 (14.1)	17 (13.2)	109 (12.6)	111 (13.2)	116 (17.2)	19 (14.6)	0.03
Prior COPD	1114 (7.6)	60 (7.6)	364 (8.4)	383 (7.8)	246 (6.6)	61 (6.7)	0.006
Prior hypertension	12 635 (86.2)	677 (86.2)	3771 (87.1)	4205 (85.5)	3197 (86.2)	785 (86.2)	0.32
Prior atrial fibrillation/flutter	1166 (8.0)	56 (7.1)	399 (9.2)	402 (8.2)	245 (6.6)	64 (7.0)	<0.001
Cigarette smoking							<0.001
Current smoker	1673 (11.4)	77 (9.8)	491 (11.3)	564 (11.5)	418 (11.3)	123 (13.5)	
Prior smoker	5837 (39.8)	350 (44.6)	1809 (41.8)	1959 (39.8)	1362 (36.7)	357 (39.2)	
Never smoked	7146 (48.8)	358 (45.6)	2029 (46.9)	2398 (48.7)	1930 (52.0)	431 (47.3)	
Diabetic neuropathy	3351 (22.9)	153 (19.5)	853 (19.7)	1118 (22.7)	973 (26.2)	254 (27.9)	<0.001
Medications							
Metformin	11 955 (81.6)	657 (83.7)	3597 (83.1)	4028 (81.9)	2974 (80.2)	699 (76.7)	<0.001
Sulfonylurea	6642 (45.3)	320 (40.8)	1802 (41.6)	2236 (45.4)	1833 (49.4)	451 (49.5)	<0.001
Thiazolidinedione	394 (2.7)	17 (2.2)	142 (3.3)	141 (2.9)	78 (2.1)	16 (1.8)	0.004
Insulin	3406 (23.2)	115 (14.6)	701 (16.2)	1153 (23.4)	1097 (29.6)	340 (37.3)	<0.001
Beta-blocker	9314 (63.6)	476 (60.6)	2834 (65.5)	3127 (63.5)	2320 (62.5)	557 (61.1)	0.04
ACE inhibitor or ARB	11 545 (78.8)	626 (79.7)	3412 (78.8)	3848 (78.2)	2935 (79.1)	724 (79.5)	0.87
Calcium channel blocker	4958 (33.8)	252 (32.1)	1485 (34.3)	1722 (35.0)	1214 (32.7)	285 (31.3)	0.16
Diuretic	6014 (41.0)	323 (41.1)	1809 (41.8)	2003 (40.7)	1507 (40.6)	372 (40.8)	0.37
Thiazide	3460 (57.5)	207 (64.1)	1011 (55.9)	1158 (57.8)	867 (57.5)	217 (58.3)	0.86
Aspirin	11 509 (78.5)	601 (76.6)	3400 (78.5)	3907 (79.4)	2878 (77.6)	723 (79.4)	0.84
Other antiplatelet	3184 (21.7)	161 (20.5)	897 (20.7)	1061 (21.6)	860 (23.2)	205 (22.5)	0.009
Statin	11 709 (79.9)	607 (77.3)	3505 (81.0)	3969 (80.7)	2911 (78.5)	717 (78.7)	0.100
Ezetimibe	760 (5.2)	41 (5.2)	215 (5.0)	293 (6.0)	160 (4.3)	51 (5.6)	0.55
Nitrates	2811 (19.2)	147 (18.7)	840 (19.4)	960 (19.5)	700 (18.9)	164 (18.0)	0.46

Results for continuous variables are mean (standard deviation), except where indicated, and categorical variables are *n* (%).

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NYHA, New York Heart Association; PCI, percutaneous coronary intervention, Q1, 25th percentile; Q3, 75th percentile.

SI conversion factors: urine albumin to creatinine ratio (mg/g to g/mol), multiply by 0.1131; total cholesterol, LDL-cholesterol, and HDL-cholesterol (mg/dL to mmol/L), multiply by 0.0259; triglycerides (mg/dL to mmol/L), multiply by 0.0113.

[a]Age missing among patients in Lithuania as birth date could not be provided.

[b]Duration = (year of randomization − year of diagnosis) + 1.

[c]Urinary albumin to creatinine ratio data available for only 5148 patients.

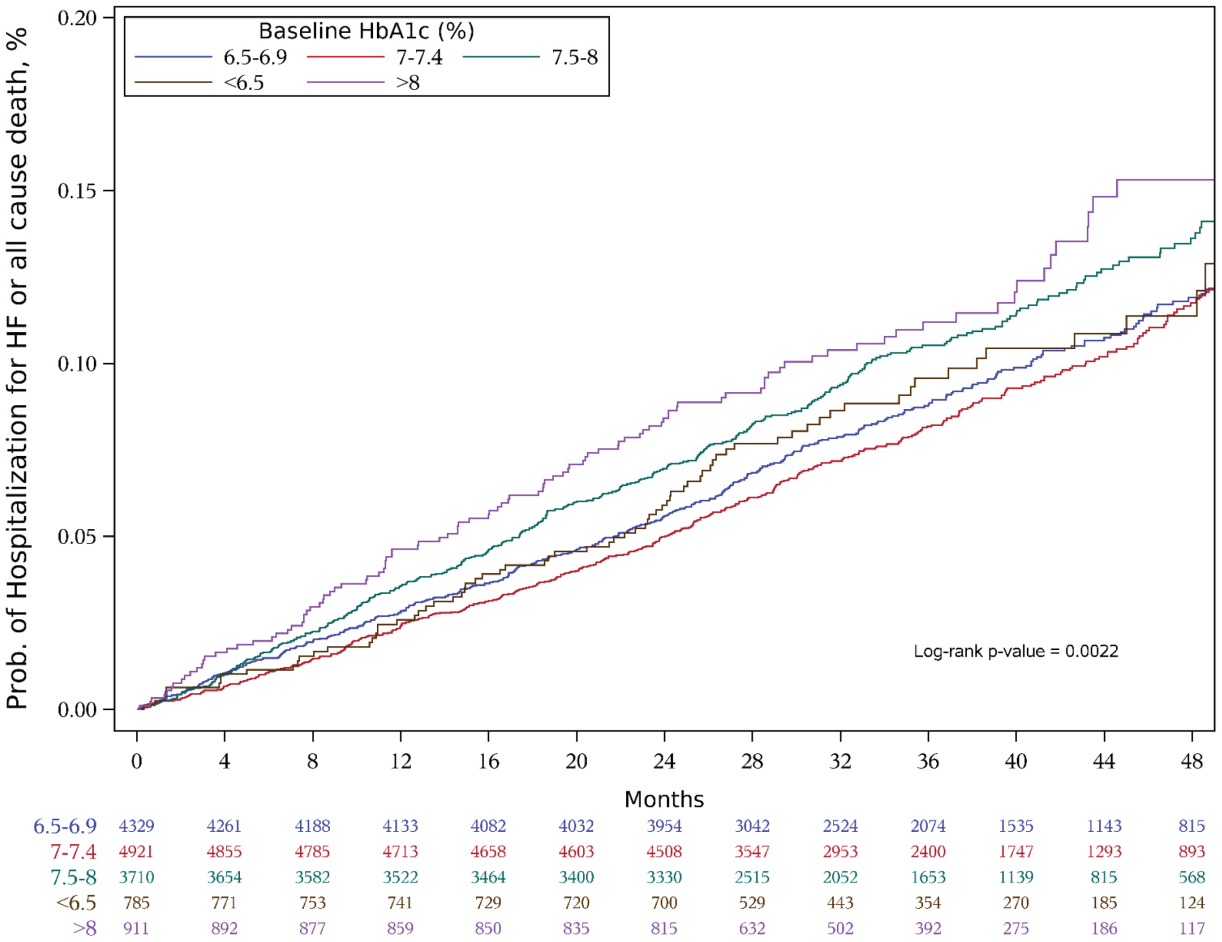

Figure 2 Kaplan–Meier estimated cumulative incidence of heart failure (HF) hospitalization or all-cause death according to baseline glycated haemoglobin (HbA_{1c}).

Table 2 **Clinical outcomes, stratified by baseline glycated haemoglobin**

	All patients (*n* = 14 656)	**HbA_{1c} <6.5% (*n* = 785)**	**HbA_{1c} 6.5–6.9% (*n* = 4329)**	**HbA_{1c} 7.0–7.4% (*n* = 4921)**	**HbA_{1c} 7.5–8.0% (*n* = 3710)**	**HbA_{1c} >8.0% (*n* = 911)**	***P*-value**
Hospitalization for HF	456 (3.1)	19 (2.4)	146 (3.4)	133 (2.7)	120 (3.2)	38 (4.2)	0.07
All-cause mortality	1084 (7.4)	60 (7.6)	299 (6.9)	339 (6.9)	305 (8.2)	81 (8.9)	0.04
Composite of hospitalization for HF or all-cause mortality	1406 (9.6)	73 (9.3)	401 (9.3)	435 (8.8)	391 (10.5)	106 (11.6)	0.02
Hospitalization for HF or CV death	1096 (7.5)	54 (6.9)	312 (7.2)	328 (6.7)	313 (8.4)	89 (9.8)	0.002
CV death	746 (5.1)	39 (5.0)	204 (4.7)	222 (4.5)	220 (5.9)	61 (6.7)	0.005
TECOS composite non-HF CV endpoint (CV death, non-fatal stroke, non-fatal MI, or hospitalization for unstable angina)	1689 (11.5)	69 (8.8)	463 (10.7)	575 (11.7)	458 (12.3)	124 (13.6)	<0.001
Worsening kidney function[a]	802 (5.5)	47 (6.0)	222 (5.1)	263 (5.3)	196 (5.3)	74 (8.1)	0.007
Severe hypoglycaemia	303 (2.1)	13 (1.7)	77 (1.8)	115 (2.3)	77 (2.1)	21 (2.3)	0.35

Data are *n* (%). *P*-values are chi-square tests.

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HF, heart failure; MI, myocardial infarction; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

[a]Defined for those with baseline eGFR <90 mL/min/1.73 m^2 as a decrease in eGFR ≥50% or development of end-stage renal disease requiring dialysis or transplantation, or for those with baseline eGFR >90 mL/min/1.73 m^2 as development of end-stage renal disease or a decrease in eGFR of ≥30%.

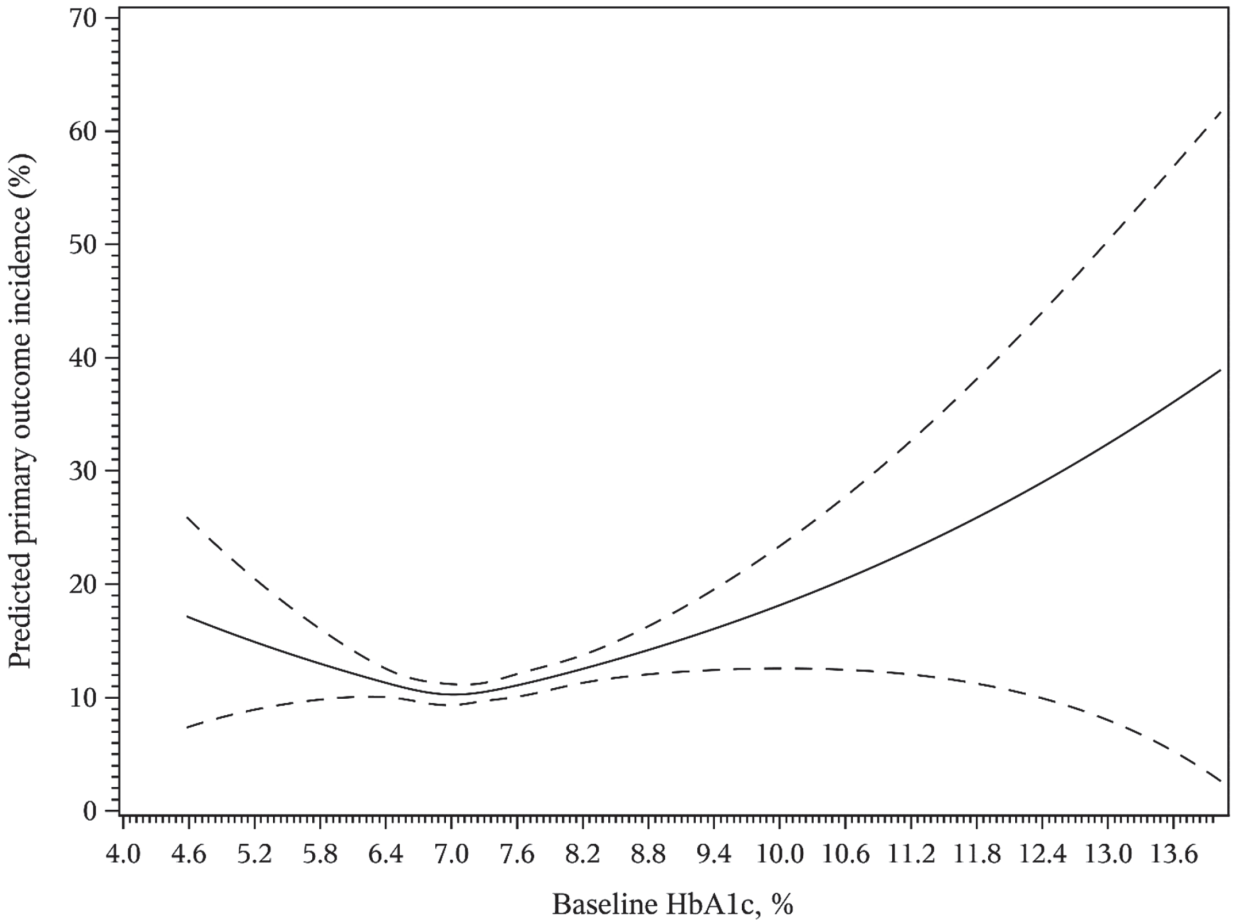

Figure 3 Multivariable adjusted incidence of heart failure hospitalization or all-cause death at 48 months by baseline glycated haemoglobin (HbA_{1c}). Adjusted for sex, age, race, body mass index at randomization, history of coronary disease, history of peripheral artery disease, history of chronic obstructive pulmonary disease, history of atrial fibrillation/flutter, baseline estimated glomerular filtration rate, baseline urinary albumin to creatinine ratio, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, smoking status, concomitant medication use (metformin, sulfonylurea, thiazolidinedione, insulin, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aspirin, and statin), and randomized treatment.

interaction between the magnitude of harm and history of HF as the HbA_{1c} increased above 7% or between age and harm as the HbA_{1c} decreased below 7% (online supplementary *Table S1*). Moreover, we still observed U-shaped associations for time-varying HbA_{1c} and outcomes in patients with vs. without HF (online supplementary *Figure S3*) or in patients older vs. younger than 70 years; the interactions only meant that the slopes of the increasing lines on each side of the nadir in the U differed between subgroups.

The incidence of severe hypoglycaemic events was approximately 2% regardless of baseline HbA_{1c} and did not exhibit a statistically significant risk gradient as HbA_{1c} deviated in either direction from 7% (*Tables 2* and *3*). However, the risk of worsening kidney function increased by 10% (adjusted HR 1.11, 95% CI 1.01–1.22) for each one-unit HbA_{1c} increase ≥7% (*Table 3*), and was highest in those with baseline HbA_{1c} >8% (online supplementary *Figure S4*).

Median HbA_{1c} values for trial participants decreased slightly over time (from 7.2% at baseline to 7.0% at 12 months, and 7.1% at 36 months). The rate of change in HbA_{1c} did not differ between participants with vs. without a history of HF at baseline (online supplementary *Figure S5*).

Discussion

We found a U-shaped association (with a nadir at 7%) between both baseline HbA_{1c} and time-varying HbA_{1c} with HFH, all-cause death, and the composite of HFH or death in patients aged ≥50 years with T2D and atherosclerotic cardiovascular disease. We also found U-shaped associations (of smaller magnitude) between HbA_{1c} and non-HF cardiovascular outcomes. While the risk of severe hypoglycaemic events did not differ according to baseline HbA_{1c} (admittedly within the restricted 6.5% to 8.0% range of HbA_{1c} enrolled in TECOS), the risk of worsening kidney function did increase

Table 3 Association between time-varying glycated haemoglobin during the trial and endpoints

Endpoint	HbA_{1c} <7.0% per one-unit decrease				HbA_{1c} ≥7.0% per one-unit increase			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Hospitalization for HF	1.27 (1.05–1.53)	0.013	1.35 (1.12–1.64)	0.002	1.14 (1.04–1.24)	0.004	1.21 (1.11–1.33)	<0.001
All-cause mortality	1.35 (1.14–1.59)	<0.001	1.37 (1.16–1.61)	<0.001	1.12 (1.03–1.21)	0.005	1.11 (1.03–1.21)	0.01
Composite of hospitalization for HF or all-cause mortality	1.39 (1.20–1.61)	<0.001	1.42 (1.23–1.64)	<0.001	1.18 (1.10–1.26)	<0.001	1.18 (1.09–1.26)	<0.001
Hospitalization for HF or CV death	1.33 (1.12–1.59)	0.001	1.38 (1.16–1.63)	<0.001	1.20 (1.12–1.30)	<0.001	1.19 (1.10–1.29)	<0.001
CV death	1.33 (1.09–1.61)	0.006	1.35 (1.10–1.65)	0.004	1.16 (1.06–1.26)	0.002	1.14 (1.04–1.25)	0.007
TECOS composite non-HF CV endpoint (CV death, non-fatal stroke, non-fatal MI, or hospitalization for unstable angina)	1.19 (1.03–1.37)	0.01	1.22 (1.06–1.41)	0.006	1.11 (1.04–1.18)	0.002	1.10 (1.02–1.17)	0.009
Worsening kidney function	1.20 (0.98–1.46)	0.07	1.27 (1.04–1.55)	0.02	1.14 (1.05–1.25)	0.003	1.11 (1.01–1.22)	0.03
Severe hypoglycaemia	1.03 (0.70–1.52)	0.88	1.27 (0.87–1.85)	0.22	1.07 (0.90–1.27)	0.47	0.96 (0.79–1.16)	0.67

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin.
[a]Adjusted for sex, age, race, region, body mass index at randomization, history of coronary disease, history of peripheral artery disease, history of chronic obstructive pulmonary disease, history of atrial fibrillation/flutter, baseline estimated glomerular filtration rate, baseline systolic blood pressure, baseline urinary albumin to creatinine ratio, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, smoking status, concomitant medication use (metformin, sulfonylurea, thiazolidinedione, insulin, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aspirin, and statin), and randomized treatment.

as HbA_{1c} deviated from 7% (consistent with a meta-analysis[12] of data from other randomized trials). It is important to note that the association between HbA_{1c} levels and outcomes that we observed is not due to use of glucose-lowering therapies known to modify HF risk independent of glycaemic effects: less than 2.4% of TECOS participants were taking a thiazolidinedione or a glucagon-like peptide-1 receptor agonist, and none a sodium– glucose co-transporter 2 inhibitor.[4,13,14]

While the meta-analysis of 12 cardiovascular outcome trials in T2D discussed in our Introduction reported no correlation between HbA_{1c} values and risk of HF events,[2] none of those trials specifically targeted HbA_{1c} reduction. For at least some of the agents with demonstrated cardiovascular efficacy in T2D, their impacts appear to be independent of their glucose-lowering effects.[14] While TECOS also did not target a specific HbA_{1c} level, it was robustly negative for any differences in cardiovascular outcomes with sitagliptin therapy vs. placebo,[10,11] and as such we were able to treat it as a cohort study and examine the associations between glycaemic levels and outcomes in patients with T2D with higher quality data than usually available in observational analyses since there was central adjudication of all endpoints using standardized criteria and blinded to baseline data. While our findings confirm earlier studies suggesting that the relationship between HbA_{1c} values and mortality[5–8] or macrovascular non-HF cardiovascular outcomes[5,6] appears to be U-shaped with a nadir between 6.5% and 7.5%, our study demonstrates that the same U-shaped association exists for HFH in T2D patients with atherosclerotic vascular disease as well as for all cardiovascular outcomes in patients with HF and T2D.

Although there is legitimate concern about the potential risks (and adverse effects) of hypoglycaemia if individuals with T2D are overtreated,[15–17] we did not find any difference in the rates of severe hypoglycaemic episodes across the gradient of HbA_{1c} values for patients recruited into TECOS. This finding is also consistent with an earlier TECOS report showing that severe hypoglycaemic events were not increased with sitagliptin therapy compared with placebo.[16] While mechanistic studies have documented improvements in left ventricular systolic function parameters with lowering of HbA_{1c} in individuals with diabetes,[18] achieving too low an HbA_{1c} may impair cardiac muscle energetics and adversely affect haemodynamics with increased peripheral vascular resistance (afterload) due to sympatho-adrenal system activation. It should also be recognized that trial participants tend to be on the healthier end of the spectrum and frailer patients are likely to exhibit a higher risk for hypoglycaemic events with more intensive treatment targets.[19]

Although TECOS includes data from nearly 45 000 patient-years of observation with central adjudication of all endpoints using standardized criteria and blinded to baseline data, and thus of higher quality than possible with many retrospective observational studies in real-world settings, there are some limitations to the present analyses. First, TECOS did not randomize patients to different intensities of glycaemic treatment and these analyses are post-hoc and observational — comparing different target HbA_{1c} levels was not an *a priori* hypothesis of TECOS, and despite rigorous multivariable adjustment, there may still be some residual confounding. Second, to be eligible for TECOS, participants had to have established atherosclerotic vascular disease, and thus these analyses illuminate the relationship between HbA_{1c} and

cardiovascular events in a secondary cardiovascular risk population, with uncertain generalizability to primary prevention patients. Third, due to trial eligibility criteria, TECOS participants had relatively well controlled HbA_{1c} levels at the time of enrolment, and these results may therefore not be generalizable to patients with poorer glycaemic control. In fact, the association between HbA_{1c} values and adverse cardiovascular outcomes may be even more pronounced in patients with more extreme HbA_{1c} levels excluded by the TECOS eligibility criteria. However, clinicians do not face clinical equipoise when HbA_{1c} levels are markedly elevated or low but do when HbA_{1c} is in the TECOS eligibility range. In the same vein, TECOS excluded patients with severe kidney dysfunction and thus our data cannot be extrapolated to patients with end-stage renal disease. Fourth, TECOS did not objectively measure left ventricular ejection fractions (LVEF) and thus we cannot distinguish between those patients with HF with reduced or preserved ejection fraction. While patients with lower LVEF had a worse prognosis independently of HbA_{1c} levels in T2D patients with recent acute coronary syndrome in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, LVEF did not modify the relationship between HbA_{1c} and clinical outcomes in their analyses.[20] In fact, although the ELIXA participants had slightly higher event rates than TECOS (not surprising since recent acute coronary syndrome was an inclusion criterion for ELIXA but present in less than half of TECOS participants), the association they found between each 1% increase in HbA_{1c} and the risk of HFH or cardiovascular death is very similar to what we found in TECOS: crude HR 1.20 (1.11–1.30) and adjusted HR 1.11 (1.01–1.21) in ELIXA[20] vs. 1.20 (1.12–1.30) and 1.19 (1.10–1.29) in TECOS. Fifth, as control of other cardiovascular risk factors was better in TECOS participants than usually seen in clinical practice,[21–23] this could have served to lower event rates, making it more difficult to tease out the association between HbA_{1c} levels and clinical outcomes. Sixth, although some may argue that the outcome differences may have been driven by differences in concomitant medication use, we adjusted for use of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statin, and glucose-lowering therapies in our multivariate models, <2.5% of patients were on thiazolidinediones or glucagon-like peptide-1 receptor agonists during the trial, none were taking a sodium–glucose co-transporter 2 inhibitor, and up-titration of glycaemic therapies largely occurred in patients with marked hyperglycaemia during follow-up (the mean HbA_{1c} when agents were added was 8.5%).[13] Thus, it would not alter our finding of a HbA_{1c} nadir of 7% but may have underestimated the magnitude of excess risk for patients with markedly elevated HbA_{1c}. In the same vein, given a prior TECOS sub-study demonstrated a U-shaped association between baseline blood pressure assessments and cardiovascular outcomes,[24] we adjusted for systolic blood pressure in our multivariable analyses. Similarily, given the known relationship between body weight and outcomes,[25] we adjusted for body mass index in our multivariable analyses. Finally, although there is emerging evidence that glycaemic variability may be an additional gluco-metabolic risk factor in individuals with diabetes,[26] we did not examine that in this trial, as to do so would require excluding early events (during the time period used to define HbA_{1c} variability) and thus both shorten duration of follow-up for events and introduce survivor bias. However, this is a rich topic for future research in this area, as is the prognostic value of HbA_{1c} in HF patients without diabetes.[27]

In conclusion, given the U-shaped association between average achieved HbA_{1c} during the TECOS trial and cardiovascular outcomes, we believe that targeting HbA_{1c} of 7% may help optimize outcomes in patients with T2D and atherosclerotic vascular disease. Whether a similar target should be pursued for the prevention of HF in patients with T2D but without existing vascular disease is an important open question[1,28,29] and future studies (ideally randomized trials) should compare different target HbA_{1c} levels for the primary prevention of HF in patients with T2D.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Data sharing

Requests to access the data for this study from qualified researchers trained in human subject confidentiality protocols may be submitted at dcri.org/data-sharing.

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