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Glycemic levels and cardiovascular events in type 2 diabetes: A cohort study of drugs with different hypoglycemic potentials

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Research indicates a U-shaped association between mortality and glycated hemoglobin (HbA1c) levels in patients receiving sulfonylurea or insulin. However, the relationship between glucose levels and cardiovascular events in patients on novel agents with a lower hypoglycemic potential remains unknown. This study was aimed to examine the association between cardiovascular events and HbA1c in patients with type 2 diabetes receiving drugs with different hypoglycemic potentials. This is an observational cohort study using a multicenter electronic medical record database. This study included patients who received a diagnosis of type 2 diabetes between 2009 and 2020 and received non-insulin antidiabetic drugs. These drugs were divided into drugs with a high-hypoglycemic-risk (sulfonylurea and meglitinides) and drugs with a low-hypoglycemic-risk (incretin mimetics, sodium-glucose cotransporter-2 inhibitors, thiazolidinediones, and acarbose). The events of interest were mortality and major adverse cardiovascular events (MACEs). A total of 6,789 patients were included, with 3,191 patients in low-hypoglycemic-risk drugs cohort and 3,598 patients in high-hypoglycemic-risk drugs cohort. Both cohorts exhibited a U-shaped association between HbA1c levels and the risk of mortality and MACEs. Among patients receiving low-hypoglycemic-risk drugs, HbA1c levels of 6.7% and 6.8% were associated with the lowest risk of mortality and MACEs, respectively. Similarly, in patients receiving high-hypoglycemic-risk drugs, the lowest risk of mortality and MACEs was observed at HbA1c levels of 6.8% and 7.2%, respectively. Both low and high HbA1c levels were associated with an increased risk of mortality and cardiovascular events, whereas intermediate levels were linked to the lowest risk. These findings support a U-shaped association between glycemic control and adverse outcomes in patients with type 2 diabetes receiving non-insulin-based therapies.

Keywords Diabetes, HbA1c, Mortality, Major adverse cardiovascular events

Abbreviations

BMI	Body mass index
DCSI	Diabetes Complications Severity Index
DPP-4	Dipeptidyl peptidase-4
GLP-1	Glucagon-like peptide-1

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HR	Hazard ratio
HbA1c	Glycated hemoglobin
ICD	International Classification of Diseases
MACE	Major adverse cardiovascular event
RCT	Randomized controlled trial
SGLT-2	Sodium-glucose cotransporter-2
TMUCRD	Taipei Medical University Clinical Research Database

Background

Diabetes is a major risk factor for both microvascular and macrovascular complications, and intensive glycemic control has long been hypothesized to reduce target organ damage and mortality. However, evidence from randomized controlled trials (RCTs) has challenged this assumption, with conflicting results regarding the cardiovascular benefits of near-normal glycemic targets.

For instance, the Action to Control Cardiovascular Risk in Diabetes trial found that intensive glycemic control (HbA1c < 6%) did not significantly reduce cardiovascular events in patients with type 2 diabetes compared to standard glycemic control (HbA1c 7–7.9%). Moreover, the trial reported an unexpected increase in mortality among patients in the intensive control group[1]. Similar findings were observe in the Veterans Affairs Diabetes Trial and the Action in Diabetes and Vascular Disease trial, where intensive glucose control was associated with a higher incidence of severe hypoglycemia[2,3]. Subsequent observational studies confirmed that severe hypoglycemia may contribute to an increased risk of mortality and cardiovascular events[4,5]. Notably, these RCTs primarily used metformin, sulfonylureas, and insulin as the cornerstone of glucose-lowering therapy.

Following these landmark trials, several novel antidiabetic agents have emerged, including dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. Unlike insulin and insulin secretagogues, these newer agents have a lower risk of hypoglycemia, raising questions about whether the U-shaped association between HbA1c and cardiovascular outcomes observed in earlier studies also applies to these newer therapies. Furthermore, it remains unclear whether achieving near-normal HbA1c levels with these novel agents offers greater cardiovascular benefits compared to older treatment approaches.

To address this gap, this study aims to examine the association between HbA1c levels and cardiovascular outcomes in patients with type 2 diabetes treated with antidiabetic agents of different hypoglycemic potentials, utilizing real-world clinical data.

Methods

Study design and data sources

In this observational population-based cohort study, data were obtained from the Taipei Medical University Clinical Research Database (TMUCRD), a multicenter electronic medical record database managed by three medical centers. The TMUCRD contains extensive data on patient demographics; outpatient, emergency, and inpatient visits; medication records; diagnostic codes; and laboratory and examination reports. The TMUCRD ensures data reliability by adhering to a standardized data framework, conducting regular quality assessments, and performing validation processes to maintain data integrity and consistency[6]. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Joint Institutional Review Board of Taipei Medical University (approval no. N202306045). Informed consent was waived by the Joint Institutional Review Board of Taipei Medical University due to the retrospective nature of this study.

Study cohort

The data period used in the study was from January 1, 2008 to December 31, 2021. Patients aged 30 years or above who received a diagnosis of diabetes and were first treated with non-insulin antidiabetic drugs between 2009 and 2020 were included in the study. A diagnosis of diabetes was established using *International Classification of Diseases*, *Ninth Edition* (*ICD-9*) code 250 or *International Classification of Diseases*, *Tenth Edition* (*ICD-10*) codes E08–E13. The date of the first prescription for a non-insulin antidiabetic drug was defined as the index date. Patients were classified into two cohorts based on the hypoglycemic risk of the medications they received. The high-hypoglycemic-risk drugs cohort included patients who received sulfonylureas or meglitinides, both of which stimulate insulin secretion irrespective of blood glucose levels, thereby increasing the risk of hypoglycemia. The low-hypoglycemic-risk drugs cohort included patients who received thiazolidinediones, acarbose, DPP-4 inhibitors, GLP-1 receptor agonists, or SGLT-2 inhibitors. These medications lower glucose levels without directly stimulating insulin secretion and do not increase the incidence of severe hypoglycemia, even when used in combination therapies[7–12]. Metformin was not included as an independent variable in our classification because many patients were already on metformin as background therapy (47.8% in the high-hypoglycemic-risk drugs cohort and 66.9% in the low-hypoglycemic-risk drugs cohort), making it non-discriminatory for stratification in our study.

Exclusion criteria

Patients meeting any of the following criteria were excluded from the study: (1) having type 1 diabetes; (2) having received non-insulin antidiabetic drugs for less than 180 days; (3) having received both high- and low-hypoglycemic-risk drugs simultaneously; (4) having received insulin; (5) dying before the index date or within 6 months after the index date; (6) having been hospitalized for MACEs or heart failure before the index date; (7) having incomplete laboratory data on HbA1c, triglyceride, low-density lipoprotein cholesterol, or creatinine

levels within 180 days before the index date; or (8) having no HbA1c records within 180 days after the index date. eFigure 1 depicts the patient selection process.

Glycemic levels

Glycemic levels were represented by HbA1c values measured after the initiation of antidiabetic therapy (i.e., following the index date). Post-index mean HbA1c was defined as a single time-fixed variable for each patient. This variable was calculated as the average of all measurements made during follow-up. A sensitivity analysis was conducted to assess individual changes in HbA1c levels over time, using time-varying HbA1c for each patient. Time-varying HbA1c was sorted based on the date of the blood test and the HbA1c value would be carried forward until the next blood test. In the main and sensitivity analyses, the HbA1c values were ranked and divided into five quintiles based on the single mean values or time-varying HbA1c values.

Study outcomes

The events of interest were all-cause mortality and MACEs. MACEs were defined as a composite of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. Mortality records were obtained from the national database of the Ministry of Health and Welfare. Other outcomes were identified using *ICD-9* or *ICD-10* codes (listed in eTable 1).

Follow-up

Patients were followed up from the index date until the events of interest occurred, they discontinued their drugs, they switched from high- to low-hypoglycemic-risk drugs or vice versa, or the end of the study period was reached (December 31, 2021), whichever occurred first.

Comorbidities and medications

The severity of diabetes was evaluated using the Diabetes Complications Severity Index (DCSI), a research tool that reliably predicts the rates of mortality and hospitalization for patients with diabetes[13]. Patients were evaluated in terms of the extent and severity of organ damage caused by diabetes. A higher score indicated more severe diabetes-associated complications, with a maximum attainable score of 13.

Additionally, since health deterioration may be reflected by HbA1c levels and may affect clinical outcomes, we evaluated the degree of frailty by using the Multimorbidity Frailty Index, a research tool developed using real-world data and based on a cumulative deficit model involving *ICD-9* and *ICD-10* codes[14,15]. This index has been used as a reliable indicator of mortality and adverse health outcomes in older Taiwanese populations.

The disease diagnostic codes for the baseline comorbidities and the Anatomical Therapeutic Chemical codes for medications are listed in the supplementary materials.

Statistical analysis

Based on the post-index mean HbA1c distribution, each cohort was divided into five quintiles, with the middle quintile serving as the reference group. The baseline characteristics were compared across quintiles by using chi-squared tests and analysis of variance. Cox proportional-hazards models were used to estimate the risk of clinical events associated with HbA1c and other baseline covariates. Significant covariates were included in multivariate models for adjustment. A sensitivity analysis was conducted using time-varying Cox models to evaluate the risk of events related to HbA1c variations.

To assess association between HbA1c and clinical events and identify potential treatment targets, a Cox proportional-hazards model with a B-spline basis and a truncated power function basis was used to explore the nonlinear association between continuous HbA1c levels and clinical events. In addition, subgroup analyses were conducted for age, body mass index (BMI), and frailty to explore potential variations in associations.

A two-sided p value of less than 0.05 was considered significant. All analyses were conducted using SAS/STAT software version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 6,789 patients were included in this study. These patients were divided into groups of 3,191 patients on low-hypoglycemic-risk drugs and 3,598 patients on high-hypoglycemic-risk drugs. The mean follow-up period was 3.2 years and 3.9 years in the low-hypoglycemic-risk and high-hypoglycemic-risk drugs cohorts, respectively. As the primary objective of this study was not to compare the outcomes between the low-hypoglycemic-risk and high-hypoglycemic-risk drugs cohorts, the difference in follow-up times between these two cohorts does not introduce bias.

Table 1 and eTable 2 present the baseline characteristics of patients for the mortality and MACEs outcome, respectively, stratified by post-index mean HbA1c levels. In both cohorts, patients in the lower HbA1c quintiles tended to be older, frailer, have higher DCSI scores, and more comorbidities.

The impact of baseline characteristics on mortality and cardiovascular events is illustrated in eTables 3 and 4. In the low-hypoglycemic-risk drugs cohort, univariable analysis showed that patients with older age, male sex, certain comorbidities (such as atrial fibrillation), higher diabetic complication severity, moderate and severe frailty, more advanced CKD staging were associated with a higher risk of all-cause mortality and MACEs (eTable 3). Similarly, in the high-hypoglycemic-risk drugs cohort, older age, greater comorbidity burden, higher DCSI scores, more advanced CKD staging, and increased frailty were associated with a higher risk of all-cause mortality and MACEs (eTable 4). These significant baseline characteristics were adjusted for in the following analysis of clinical outcomes to account for potential confounding effects.

		Users of low-hypoglycemic-risk drugs						Users of high-hypoglycemic-risk drugs					
		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
		N = 637	*N* = 639	*N* = 639	*N* = 638	*N* = 638	p value	*N* = 719	*N* = 723	*N* = 717	*N* = 720	*N* = 719	p value
Post-index HbA1c (%), mean (SD)		5.8 (0.6)	6.5 (0.1)	6.8 (0.1)	7.2 (0.1)	8.5 (1.7)	<0.001	6.0 (0.5)	6.8 (0.1)	7.2 (0.1)	7.7 (0.2)	9.4 (2.8)	<0.001
Age, years, mean (SD)		62 (13.4)	62.6 (11.7)	61 (11.5)	59.6 (11.4)	58.2 (13.3)	<0.001	60.4 (13.2)	58.4 (12.0)	57.5 (11.2)	56.1 (11.3)	55.3 (12.4)	<0.001
Male, n (%)		346 (54.3)	333 (52.1)	328 (51.3)	330 (51.7)	342 (53.6)	0.79	415 (57.7)	424 (58.6)	417 (58.2)	382 (53.1)	392 (54.5)	0.126
Comorbidity, n (%)													
	Coronary artery disease	151 (23.7)	155 (24.3)	160 (25.0)	138 (21.6)	137 (21.5)	0.46	101 (14.1)	88 (12.2)	81 (11.3)	70 (9.7)	65 (9.0)	0.022
	Congestive heart failure	34 (5.3)	25 (3.9)	14 (2.2)	28 (4.4)	31 (4.9)	0.051	23 (3.2)	15 (2.1)	23 (3.2)	14 (1.9)	15 (2.1)	0.30
	Atrial fibrillation	12 (1.9)	13 (2.0)	7 (1.1)	5 (0.8)	8 (1.3)	0.27	10*			3 (0.4)	2 (0.3)	0.50
	Peripheral vascular disease	7 (1.1)	8 (1.3)	5 (0.8)	9 (1.4)	3 (0.5)	0.45	8 (1.1)	4 (0.6)	3 (0.4)	9 (1.3)	5 (0.7)	0.33
	Cerebrovascular disease	50 (7.9)	41 (6.4)	26 (4.1)	28 (4.4)	44 (6.9)	0.016	63 (8.8)	34 (4.7)	41 (5.7)	28 (3.9)	44 (6.1)	0.001
	Hypertension	382 (60.0)	394 (61.7)	369 (57.8)	364 (57.1)	335 (52.5)	0.013	352 (49.0)	300 (41.5)	289 (40.3)	291 (40.4)	282 (39.2)	0.001
	Hyperlipidemia	311 (48.8)	369 (57.8)	370 (57.9)	360 (56.4)	288 (45.1)	<0.001	231 (32.1)	278 (38.5)	304 (42.4)	305 (42.4)	215 (29.9)	<0.001
	Chronic kidney disease	135 (21.2)	116 (18.2)	107 (16.7)	90 (14.1)	98 (15.4)	0.009	104 (14.5)	64 (8.9)	70 (9.8)	62 (8.6)	78 (10.9)	0.002
eGFR (mL/min/1.73 m^2), *n* (%)													
	≥60	488 (76.6)	554 (86.7)	563 (88.1)	576 (90.3)	570 (89.3)	<0.001	595 (82.8)	667 (92.3)	667 (93.0)	667 (92.6)	663 (92.2)	<0.001
	30–59	117 (18.4)	77 (12.1)	71 (11.1)	59 (9.2)	63 (9.9)		108 (15.0)	49 (6.8)	44 (6.1)	47 (6.5)	43 (6.0)	
	<30	32 (5.0)	8 (1.3)	5 (0.8)	3 (0.5)	5 (0.8)		16 (2.2)	7 (1.0)	6 (0.8)	6 (0.8)	13 (1.8)	
Charlson–Deyo Comorbidity Index, mean (SD)		1.7 (1.5)	1.5 (1.3)	1.5 (1.2)	1.4 (1.1)	1.4 (1.3)	<0.001	1.3 (1.2)	1.1 (1.0)	1.2 (1.1)	1.1 (1.0)	1.1 (1.2)	0.064
Diabetes Complications Severity Index, mean (SD)		1.2 (1.6)	1.1 (1.5)	0.8 (1.2)	0.8 (1.2)	0.8 (1.3)	<0.001	0.7 (1.2)	0.5 (0.9)	0.5 (1.1)	0.4 (1.0)	0.5 (1.0)	<0.001
Multimorbidity Frailty Index													
	Mean score (SD)	5.1 (4.5)	4.6 (4.0)	4.3 (3.8)	4.2 (3.8)	4.1 (4.1)	<0.001	3.7 (4.3)	2.8 (3.3)	2.8 (3.5)	2.5 (3.1)	2.5 (3.4)	<0.001
	Fit (0 to <5.25)	349 (54.8)	367 (57.4)	388 (60.7)	400 (62.7)	413 (64.7)	0.009	496 (69.0)	543 (75.1)	553 (77.1)	574 (79.7)	578 (80.4)	<0.001
	Mild frailty (5.25 to <10.5)	219 (34.4)	222 (34.7)	198 (31.0)	193 (30.3)	178 (27.9)		165 (23.0)	162 (22.4)	138 (19.3)	128 (17.8)	117 (16.3)	
	Moderate and severe frailty (≥10.5)	69 (10.8)	50 (7.8)	53 (8.3)	45 (7.1)	47 (7.4)		58 (8.1)	18 (2.5)	26 (3.6)	18 (2.5)	24 (3.3)	
Medications at baseline, *n* (%)													
	Diuretics	135 (21.2)	90 (14.1)	76 (11.9)	82 (12.9)	98 (15.4)	<0.001	100 (13.9)	66 (9.1)	84 (11.7)	66 (9.2)	83 (11.5)	0.019
	ACE inhibitors	28 (4.4)	22 (3.4)	28 (4.4)	27 (4.2)	28 (4.4)	0.90	32 (4.5)	30 (4.2)	29 (4.0)	26 (3.6)	24 (3.3)	0.83
	ARB	354 (55.6)	349 (54.6)	317 (49.6)	322 (50.5)	314 (49.2)	0.060	294 (40.9)	259 (35.8)	264 (36.8)	256 (35.6)	259 (36.0)	0.196
	Beta-blockers	248 (38.9)	239 (37.4)	218 (34.1)	217 (34.0)	206 (32.3)	0.081	215 (29.9)	153 (21.2)	182 (25.4)	171 (23.8)	167 (23.2)	0.002
	Calcium channel blockers	245 (38.5)	227 (35.5)	209 (32.7)	200 (31.4)	220 (34.5)	0.077	241 (33.5)	186 (25.7)	181 (25.2)	185 (25.7)	176 (24.5)	0.001
	Alpha-blockers	22 (3.5)	22 (3.4)	16 (2.5)	23 (3.6)	23 (3.6)	0.79	34 (4.7)	14 (1.9)	18 (2.5)	13 (1.8)	27 (3.8)	0.0031
	Statin	382 (60.0)	450 (70.4)	418 (65.4)	418 (65.5)	381 (59.7)	<0.001	343 (47.7)	366 (50.6)	394 (55.0)	390 (54.2)	313 (43.5)	<0.001
	Aspirin	164 (25.8)	185 (29.0)	162 (25.4)	149 (23.4)	158 (24.8)	0.22	164 (22.8)	143 (19.8)	136 (19.0)	138 (19.2)	133 (18.5)	0.25
	P2Y12 inhibitors	71 (11.2)	68 (10.6)	53 (8.3)	44 (6.9)	41 (6.4)	0.005	32 (4.5)	25 (3.5)	33 (4.6)	21 (2.9)	28 (3.9)	0.44

Continued

		Users of low-hypoglycemic-risk drugs						Users of high-hypoglycemic-risk drugs					
	Anticoagulants	19 (3.0)	18 (2.8)	10 (1.6)	12 (1.9)	12 (1.9)	0.32	4 (0.6)	8 (1.1)	4 (0.6)	2 (0.3)	5 (0.7)	0.39
Laboratory data at baseline, mean (SD)													
	HbA1c (%)	7.1 (1.9)	7.4 (2.0)	7.5 (1.1)	7.9 (1.4)	8.8 (2.0)	< 0.001	8.3 (2.4)	8.8 (2.6)	9.1 (2.4)	9.1 (2.0)	10.0 (2.3)	< 0.001
	Triglycerides (mg/dl)	166.1 (129.3)	162.2 (109.1)	166.7 (116.6)	167.9 (114.3)	205.9 (182.8)	< 0.001	211.3 (350.6)	182.9 (144.7)	217.7 (404.7)	213.7 (322.8)	237.5 (241.2)	0.020
	LDL-C (mg/dl)	109.9 (36.8)	105.7 (31.5)	107.5 (33.8)	109.1 (33.0)	116.9 (38.0)	< 0.001	118.3 (39.0)	116.1 (36.6)	121.9 (37.9)	122.2 (37.8)	123.3 (41.2)	0.001
	Creatinine (mg/dl)	1.6 (6.0)	1.1 (3.5)	1.3 (5.5)	1.4 (6.4)	1.2 (3.9)	0.40	1.1 (3.9)	1.2 (5.8)	1.5 (9.8)	1.0 (3.5)	0.9 (0.7)	0.32
SGLT2i or GLP-1 RA during follow-up period, *n* (%)		184 (28.9)	181 (28.3)	215 (33.7)	211 (33.1)	195 (30.6)	0.14	NA	NA	NA	NA	NA	NA

Table 1. Baseline characteristics of patients stratified by post-index mean HbA1c for all-cause mortality outcome. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; SGLT-2i, sodium-glucose cotransporter-2 inhibitors. Charlson–Deyo Comorbidity Index = myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, and acquired immunodeficiency syndrome. *According to the guidelines of the Health and Welfare Data Science Center, statistical data with fewer than three cases cannot be exported.

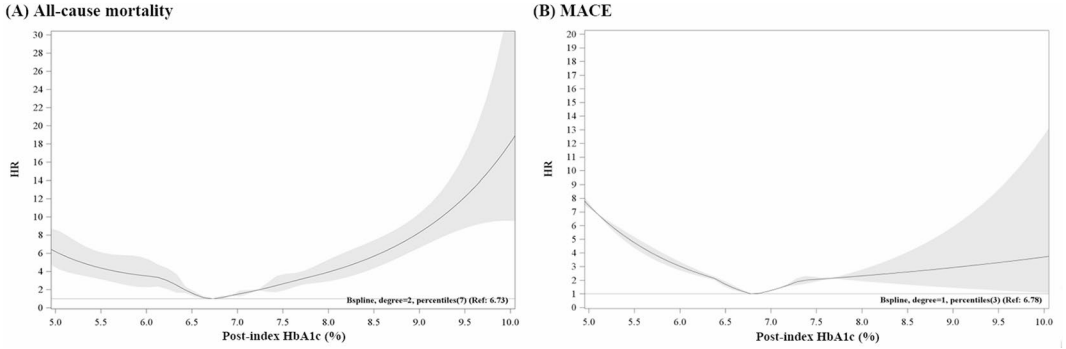

Fig. 1. Risk of cardiovascular events in relation to HbA1c in diabetic patients treated with low-hypoglycemic-risk drugs. In the low-hypoglycemic-risk drugs cohort, the relationship between post-index mean HbA1c and cardiovascular events displayed a U-shaped pattern. HbA1c levels of 6.73% and 6.78% were associated with the lowest risks of all-cause mortality (**A**) and MACEs (**B**), respectively.

Post-index HbA1c (%) during follow-up period, mean (SD)	Event number	Rate per 1000 person-year	Crude HR (95% CI)	Adjusted HR (95% CI)*
All-cause mortality				
Quintile 1: 5.8 (0.62)	24	11.39	6.12 (2.12–17.63)	4.03 (1.37–11.85)
Quintile 2: 6.5 (0.11)	8	3.63	1.89 (0.57–6.31)	1.81 (0.54–6.05)
Quintile 3: 6.8 (0.10)	4	1.85	1.0 [Reference]	1.0 [Reference]
Quintile 4: 7.2 (0.14)	7	3.44	1.89 (0.55–6.44)	2.22 (0.65–7.62)
Quintile 5: 8.5 (1.73)	19	11.43	6.34 (2.16–18.66)	7.22 (2.43–21.43)
MACE				
Quintile 1: 5.8 (0.60)	24	11.43	3.99 (1.27–12.56)	3.33 (1.03–10.78)
Quintile 2: 6.5 (0.13)	12	5.47	2.39 (0.76–7.54)	2.11 (0.66–6.70)
Quintile 3: 6.8 (0.10)	4	1.86	1.0 [Reference]	1.0 [Reference]
Quintile 4: 7.2 (0.25)	9	4.49	2.76 (0.84–9.01)	2.73 (0.83–8.96)
Quintile 5: 8.5 (1.75)	9	5.44	3.57 (1.08–11.79)	3.32 (0.98–11.20)

Table 2. Risk of events at different levels of post-index mean HbA1c in low-hypoglycemic-risk drugs cohort. CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; SD, standard deviation. *All-cause mortality model adjusted for age at index date, sex, comorbidities (congestive heart failure, atrial fibrillation, cerebrovascular disease), Charlson-Deyo index, diabetic complication severity index, Multimorbidity Frailty Index score, comedication (diuretics, ACE inhibitors, ARB, P2Y12 inhibitors), CKD stage. MACE model adjusted for age at index date, sex, comorbidities (atrial fibrillation), diabetic complication severity index, Multimorbidity Frailty Index score, comedication (P2Y12 inhibitors), lab data (HbA1C), CKD stage.

Risk of adverse events associated with HbA1c levels in patients on low-hypoglycemic-risk drugs

In patients on low-hypoglycemic-risk drugs, a U-shaped association was observed between HbA1c levels and the risk of all-cause mortality and MACEs. Figure 1 presents the results of a nonlinear model, indicating HbA1c levels of 6.7% and 6.8% were associated with the lowest risk of mortality and MACEs, respectively. The overall risk of mortality was low, with incidence rates ranging from 1.85 to 11.43 per 1,000 person-years. Compared with the reference quintile (quintile 3), the lowest and highest HbA1c quintiles were associated with a significantly higher risk of mortality, and the lowest HbA1c quintile was associated with a significantly higher risk of MACEs (Table 2). Sensitivity analysis using time-varying HbA1c revealed a similar U-shaped pattern for the two outcomes in patients on low-hypoglycemic-risk drugs (eTable 5). According to our subgroup analysis, this association between adverse events and HbA1c was consistent across all subgroups regardless of age, BMI, or degree of frailty (eTable 6).

Risk of adverse events associated with HbA1c levels in patients on high-hypoglycemic-risk drugs

In the patients on high-hypoglycemic-risk drugs, a similar U-shaped association was observed between HbA1c levels and the risk of adverse events (Fig. 2). In this cohort, HbA1c levels of 6.9% and 7.2% corresponded to the lowest risk of mortality and MACEs, respectively. These levels are slightly higher than those reported in patients on low-hypoglycemic-risk drugs. Compared with the reference quintile (quintile 3), higher (quintile

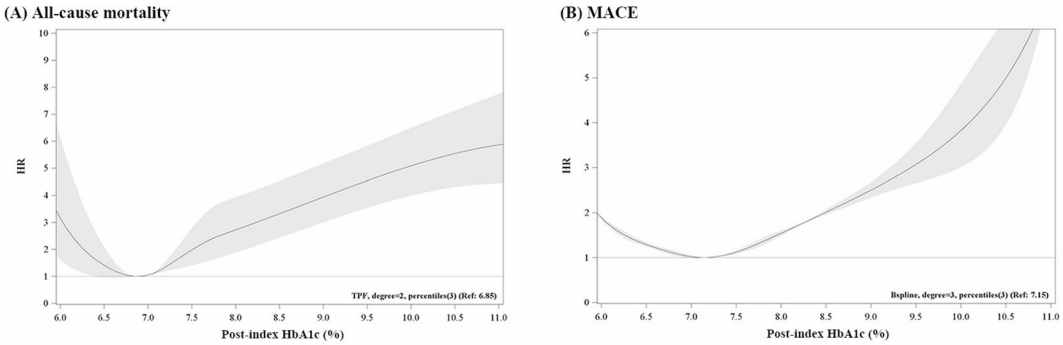

Fig. 2. Risk of cardiovascular events in relation to HbA1c in diabetic patients treated with high-hypoglycemic-risk drugs. In the high-hypoglycemic-risk drugs cohort, the relationship between post-index mean HbA1c and cardiovascular events displayed a U-shaped pattern. HbA1c levels of 6.85% and 7.15% were associated with the lowest risks of all-cause mortality (**A**) and MACEs (**B**), respectively.

Post-index HbA1c (%) during follow-up, mean (SD)	Event number	Rate per 1,000 person-years	Crude HR (95% CI)	Adjusted HR (95% CI)*
All-cause mortality				
Quintile 1: 6.0 (0.51)	37	12.26	3.41 (1.74–6.69)	2.12 (1.04–4.31)
Quintile 2: 6.8 (0.12)	6	1.95	0.54 (0.20–1.45)	0.49 (0.18–1.34)
Quintile 3: 7.2 (0.12)	11	3.61	1.0 [reference]	1.0 [reference]
Quintile 4: 7.7 (0.20)	9	3.27	0.92 (0.38–2.23)	1.23 (0.50–3.04)
Quintile 5: 9.4 (2.84)	15	6.95	2.04 (0.93–4.44)	2.28 (1.02–5.12)
MACEs				
Quintile 1: 6.1 (0.63)	25	8.43	2.83 (1.32–6.06)	2.12 (0.98–4.61)
Quintile 2: 6.8 (0.12)	14	4.61	1.55 (0.67–3.58)	1.47 (0.63–3.41)
Quintile 3: 7.2 (0.15)	9	2.98	1.0 [reference]	1.0 [reference]
Quintile 4: 7.7 (0.22)	11	4.01	1.36 (0.56–3.29)	1.83 (0.75–4.47)
Quintile 5: 9.3 (2.33)	19	8.95	3.13 (1.42–6.94)	3.84 (1.72–8.56)

Table 3. Risk of events at different levels of post-index mean HbA1c in patients receiving high-hypoglycemic-risk drugs. CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; SD, standard deviation. *All-cause mortality events were adjusted for age at the index date, comorbidities (coronary artery disease, cerebrovascular disease, hypertension, chronic kidney disease, and hyperlipidemia), Charlson–Deyo Comorbidity Index score, Diabetes Complications Severity Index score, Multimorbidity Frailty Index score, comedication (diuretics, ACE inhibitors, ARB, beta-blockers, calcium channel blockers, and alpha-blockers), laboratory data (HbA1c and LDL-C), and CKD stage. MACE events were adjusted for age at the index date, sex, comorbidities (coronary artery disease, peripheral vascular disease, and cerebrovascular disease), Charlson–Deyo Comorbidity Index score, Diabetes Complications Severity Index score, Multimorbidity Frailty Index score, comedication (diuretics, beta-blockers, calcium channel blockers, aspirin, and P2Y12 inhibitors), and CKD stage.

5) and lower (quintile 1) HbA1c quintiles were associated with a significantly higher risk of mortality, although the overall risk of mortality was low in this cohort (Table 3). Similarly, a higher (quintile 5) HbA1c quintile was associated with a significantly higher risk of MACEs compared with the reference quintile (quintile 3). When post-index HbA1c was used as a time-varying covariate, a U-shaped pattern was also observed for both mortality and MACE events (eTable 5). This U-shaped association was consistent across different subgroups, including those of older and younger patients and fit and nonfit patients (eTable 6).

Discussion

This study demonstrated a U-shaped association between HbA1c levels and the risk of mortality and MACEs in both low- and high-hypoglycemic-risk drugs cohorts. The lowest risk of mortality and MACEs was observed at HbA1c levels of 6.7% and 6.8% in the low-hypoglycemic-risk group, whereas in the high-hypoglycemic-risk group, the lowest risk was seen at HbA1c levels between 6.9% and 7.2%. These findings are consistent with prior studies that have reported nonlinear associations between glycemic control and cardiovascular risk, suggesting that both inadequate and excessive glucose lowering may be associated with adverse outcomes.

The U-shaped association between HbA1c and mortality has been widely reported in both RCTs and observational studies, reinforcing the complexity of glycemic control strategies[16–22]. Currie et al.[22] demonstrated

that, among patients receiving a combination of sulfonylurea and metformin, the lowest mortality risk was observed at an HbA1c level of 7.5%, while HbA1c levels approaching 6.5% were associated with increased mortality risk. Similarly, an early nested case-control study found that patients with HbA1c levels below 6% had a higher likelihood of experiencing cardiovascular events compared to those with HbA1c levels between 6% and 8%[21]. More recently, a prospective cohort study of community-dwelling patients with type 2 diabetes found a J-shaped association between baseline HbA1c levels and mortality risk, with the lowest risk observed at HbA1c levels between 6.5% and 7.0%[18]. These previous findings align with our study, which also demonstrated that both low and high HbA1c levels were associated with increased risks of mortality and cardiovascular events, with the lowest risk observed at intermediate HbA1c levels. This consistency supports the generalizability of the U-shaped association across diverse type 2 diabetes populations and treatment regimens.

Previous meta-regression analyses of RCTs on novel antidiabetic agents have reported a linear association between HbA1c reduction and lower cardiovascular risk, with most studies achieving an HbA1c level close to 7%[23]. However, our findings suggest that achieving near-normal HbA1c levels may not necessarily confer additional cardiovascular benefits, particularly among patients receiving low-hypoglycemic-risk drugs. This observation raises important questions about the optimal glycemic target in real-world settings, particularly in the context of modern antidiabetic therapies. Current clinical guidelines recommend an HbA1c target of $<7\%$ for most patients while emphasizing the importance of individualized glycemic goals based on patient characteristics[24]. Our findings underscore the complexity of glycemic management and highlight the need for more nuanced approaches in defining optimal targets. Glycemic control should be contextualized within the broader clinical picture, taking into account comorbidities, functional status, and nutritional condition, particularly in patients with low HbA1c levels. Rather than applying uniform targets, individualized treatment strategies may be more appropriate. Further prospective studies and clinical trials are needed to refine optimal HbA1c targets for different patient subgroups and treatment strategies.

The mechanism underlying the lack of additional cardiovascular benefit from intensive glycemic control remains unclear. One potential explanation is the impact of hypoglycemia, which has been shown to impair cardiac autonomic function, promote platelet aggregation, and trigger inflammatory responses, all of which contribute to an increased risk of cardiovascular events[25,26]. However, hypoglycemia alone may not fully explain the observed U-shaped relationship between HbA1c levels and health outcomes. Emerging evidence suggests that low HbA1c levels do not always indicate optimal health; instead, in certain contexts, they may serve as a marker of vulnerability. Findings from the Action in Diabetes and Vascular Disease trial provides compelling support for this hypothesis[27]. This large-scale study identified a significant association between severe hypoglycemia and an increased risks of both cardiovascular and non-cardiovascular adverse events, suggesting that hypoglycemia may be a marker of underlying frailty or comorbid conditions that heighten susceptibility to poor clinical outcomes. Moreover, hypoglycemia is recognized as a predictor of frailty. Abdelhafiz et al. highlighted that frailty, characterized by weight loss, diminished physiological reserves, and reduced insulin resistance, can lead to normoglycemia or even hypoglycemia[28]. Additionally, hypoglycemia itself can contribute to the development of frailty, creating a cyclical relationship that underscores the importance of individualized diabetes management in this population. To account for the confounding effect of frailty, our study utilized the Multimorbidity Frailty Index, providing a more nuanced understanding of the relationship between HbA1c, hypoglycemia, and adverse clinical outcomes.

Notably, our study identified that an HbA1c level of 6.9% was associated with the lowest risk of mortality in patients receiving high-hypoglycemic-risk drugs. This HbA1c level is lower than those reported in prior observational studies, where the optimal HbA1c range was typically between 7% and 8%, particularly in populations where sulfonylurea use was predominant[20,22]. Several factors may contribute to these differences, including the younger age (mean: 57 years), lower burden of comorbidities, and lower overall mortality rate in our cohort compared with prior studies. These findings align with current clinical guidelines, which recommend lower HbA1c targets for patients with a longer life expectancy and fewer comorbidities[24].

This study has several limitations. First, as an observational study, certain confounding factors could not be accounted for due to data availability, including BMI, smoking status, malnutrition, and anemia. Nutritional and smoking status data were unavailable in TMUCRD, and BMI and hemoglobin levels were not routinely measured for many participants. Malnutrition and certain nutrient deficiencies (e.g., iron and vitamin deficiency anemia) can reduce erythropoiesis and erythrocyte turnover, potentially leading to falsely elevated HbA1c levels[29,30]. Conversely, conditions such as protein-energy malnutrition, hemolytic anemia, and high red blood cell turnover can lower HbA1c levels, further complicating its interpretation[31,32]. Additionally, because TMUCRD is not a nationwide database, we could not determine the exact time from diabetes diagnosis to first medication use. To address this, we adjusted for baseline diabetes severity using the DCSI, which serves as a proxy for disease progression. Furthermore, as the use of DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones, and GLP-1 receptor agonists is regulated by strict insurance reimbursement criteria in Taiwan, patients within the same cohort were likely prescribed these medications at similar time points, minimizing differences in diabetes duration. Second, the relatively short follow-up duration may limit the ability to fully capture long-term outcomes. Third, there is a potential loss to follow-up for MACE events if patients sought care outside our affiliated institutions. However, more than 90% of participants visited our institutions at least quarterly, reducing the risk of missing MACE events. Furthermore, the MACE event rate in our study was comparable to those reported in previous literature, supporting the reliability of our findings[33,34]. Fourth, the variability in HbA1c measurement frequency could affect the accuracy of the calculated post-index mean HbA1c values. To address this concern, we conducted a sensitivity analysis using time-varying HbA1c, which yielded consistent results with the primary analysis, supporting the robustness of our findings. Fifth, in the low-hypoglycemic-risk cohort, more than 70% of patients were prescribed DPP-4 inhibitors (eTable 7). Future research is needed to explore whether HbA1c associations with mortality or MACE risk vary with drugs offering confirmed cardiovascular

benefits, such as SGLT-2 inhibitors or GLP-1 receptor agonists. Finally, our cohort, characterized by low event rates, represents a relatively low-risk population. Thus, findings may not fully generalize to higher-risk or more vulnerable groups. These limitations should be considered when interpreting the study findings.

Conclusions

In this cohort of patients with type 2 diabetes treated with non-insulin therapies, both elevated and low HbA1c levels were associated with increased risks of mortality and cardiovascular events, with the lowest risk observed at intermediate HbA1c levels. This U-shaped association between glycemic control and adverse outcomes underscores the complexity of glycemic management and highlights the need for future prospective studies to better define optimal HbA1c targets tailored to individual patient characteristics and treatment regimens.

Data availability

The data supporting the findings of this study are available from TMUCRD, but restrictions apply to the data availability as the data were used under license for this study and are therefore not publicly available. Data are however available from the authors upon reasonable request and with permission of Clinical Data Center, Office of Data Science, Taipei Medical University. Requests for data access can be directed to the corresponding author Chun-Yao Huang (email: cyhuang@tmu.edu.tw).

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Author contributions
Y.C.L, C.W.C, Y.H.S and C.Y.H were responsible for the conception and design of the study. Y.C.L, L.Y.H, Y.H.S and C.Y.H were responsible for acquisition, analysis, and interpretation of data. L.Y.H and Y.H.S were responsible for the statistical analyses. Y.C.L, B.L.C, Y.H.S and C.Y.H supervised and provided administrative support. Y.C.L drafted the manuscript. C.W.C, L.Y.H, B.L.C, Y.H.S and C.Y.H critically reviewed the manuscript. All authors have read and approved the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
This study was approved by the Joint Institutional Review Board of Taipei Medical University (approval no. N202306045). Informed consent was waived by the Joint Institutional Review Board of Taipei Medical University due to the retrospective nature of this study.

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