Time in Range in Relation to All-Cause and Cardiovascular Mortality in Patients With Type 2 Diabetes: A Prospective Cohort Study

Jingyi Lu,[1] Chunfang Wang,[2] Yun Shen,[1] Lei Chen,[2] Lei Zhang,[1] Jinghao Cai,[1] Wei Lu,[1] Wei Zhu,[1] Gang Hu,[3] Tian Xia,[2] and Jian Zhou[1]

Diabetes Care 2021;44:549–555 | https://doi.org/10.2337/dc20-1862

OBJECTIVE

There is growing evidence linking time in range (TIR), an emerging metric for assessing glycemic control, to diabetes-related outcomes. We aimed to investigate the association between TIR and mortality in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

A total of 6,225 adult patients with type 2 diabetes were included from January 2005 to December 2015 from a single center in Shanghai, China. TIR was measured with continuous glucose monitoring at baseline, and the participants were stratified into four groups by TIR: >85%, 71–85%, 51–70%, and ≤50%. Cox proportional hazards regression models were used to estimate the association between different levels of TIR and the risks of all-cause and cardiovascular disease (CVD) mortality.

RESULTS

The mean age of the participants was 61.7 years at baseline. During a median follow-up of 6.9 years, 838 deaths were identified, 287 of which were due to CVD. The multivariable-adjusted hazard ratios associated with different levels of TIR (>85% [reference group], 71–85%, 51–70%, and ≤50%) were 1.00, 1.23 (95% CI 0.98–1.55), 1.30 (95% CI 1.04–1.63), and 1.83 (95% CI 1.48–2.28) for all-cause mortality (*P* for trend <0.001) and 1.00, 1.35 (95% CI 0.90–2.04), 1.47 (95% CI 0.99–2.19), and 1.85 (95% CI 1.25–2.72) for CVD mortality (*P* for trend = 0.015), respectively.

CONCLUSIONS

The current study indicated an association of lower TIR with an increased risk of all-cause and CVD mortality among patients with type 2 diabetes, supporting the validity of TIR as a surrogate marker of long-term adverse clinical outcomes.

With the advances in technology, the utility of continuous glucose monitoring (CGM) has grown rapidly during recent years, and its beneficial effects on multiple indices of glycemic control have been reported in patients with both type 1 and type 2 diabetes (1–4). Meanwhile, with the wealth of information on glucose profile throughout the day produced by CGM, numerous metrics have been developed to better elucidate the characteristics of glucose control. Of them, time in range (TIR), which is most accurately measured with CGM, is an intuitive metric that refers to the time that a person spends within a desired range (usually 3.9–10.0 mmol/L). Since TIR can provide

[1]Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Clinical Center for Diabetes, Shanghai Key Clinical Center for Metabolic Disease, Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai, China
[2]Division of Vital Statistics, Institute of Health Information, Shanghai Municipal Center for Disease Control and Prevention, Shanghai, China
[3]Pennington Biomedical Research Center, Baton Rouge, LA

Corresponding author: Jian Zhou, zhoujian@sjtu.edu.cn, or Tian Xia, xiatian@scdc.sh.cn

Received 25 July 2020 and accepted 16 September 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.12980045.

J.L., C.W., and Y.S. contributed equally to this work.

This article is featured in a podcast available at https://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

See accompanying article, p. 319.

valuable information that is not captured by hemoglobin A_{1c} (HbA_{1c}), it has been advocated as a key metric of glycemic control (5) and is regarded by patients with diabetes to be a crucial measure in diabetes management (6).

To date, evidence linking TIR to diabetes-related outcomes is beginning to emerge. In our previous cross-sectional study with a large sample of patients with type 2 diabetes, TIR was found to be negatively associated with the prevalence of diabetic retinopathy and carotid intima-media thickness (7). In a post hoc analysis from the Diabetes Control and Complications Trial (DCCT), Beck et al. (8) calculated TIR with seven-point fingerstick glucose values and demonstrated significant associations of TIR with the development of diabetic retinopathy and microalbuminuria. Moreover, in pregnant women with type 1 diabetes, TIR was observed to be significantly linked to large-for-gestational-age and adverse neonatal outcomes (9). However, the relationship between TIR and mortality among patients with type 2 diabetes has not been previously investigated.

The INDices of contInuous Glucose monitoring and adverse Outcomes of diabetes (INDIGO) study was designed to longitudinally examine the effects of quality of glucose control as assessed by CGM on the hard outcomes, including microvascular and macrovascular events and mortality in patients with type 2 diabetes. In this study, we report the principal findings regarding the association between TIR and all-cause mortality among patients with type 2 diabetes. In addition, mortality associated with cardiovascular diseases (CVD) in relation to TIR was also examined.

RESEARCH DESIGN AND METHODS

Study Population

In this prospective cohort study, we recruited inpatients admitted to the Department of Endocrinology and Metabolism of Shanghai Jiao Tong University Affiliated Sixth People's Hospital from January 2005 to December 2015. Patients who met the following criteria were included in the current study: *1*) aged ≥18 years with the diagnosis of type 2 diabetes; *2*) a stable glucose-lowering regimen for the previous 3 months; *3*) with available data on TIR; and *4*) a citizen of Shanghai, China. We excluded those with other types of diabetes (e.g., gestational diabetes mellitus or type 1 diabetes) and those who had experienced severe and recurrent hypoglycemic events within the previous 3 months. All patients provided written informed consent. The study protocol was approved by the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital and complied with the principles of the Helsinki Declaration.

Measurements

Patients' information on date of birth, sex, age of diabetes diagnosis, smoking status (current smoking or not), history of cancer and CVD (angina, coronary heart disease, or stroke), and medication prescriptions such as antihypertensive drugs, glucose-lowering drugs, and lipid-lowering drugs was collected through a standardized electronic inpatient medical record data collection form. At admission, trained doctors measured height, weight, and blood pressure using a standard protocol. Height and weight were measured to the nearest 0.1 cm using a stadiometer with light clothing and without shoes. BMI was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured three times using a standard mercury sphygmomanometer after 5 min of sitting, and the measurements were averaged. Blood samples were drawn in the next morning after hospital admission with at least 10-h fasting. Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were analyzed using an autoanalyzer (7600-120; Hitachi, Tokyo, Japan). HbA_{1c} was measured using the HLC-723G8 analyzer in standard mode (Tosoh G8; Tosoh Corporation).

Assessment of TIR

A CGM system (CGMS Gold; Medtronic Inc., Northridge, CA) was used for subcutaneous interstitial glucose monitoring, as previously described (10). In brief, the sensor of the CGM system was inserted on the first day during hospital admission (day 0) and removed after 72 h, generating a daily record of 288 continuous sensor values. At least four capillary blood glucose readings per day were measured by a SureStep blood glucose meter (LifeScan, Milpitas, CA) to calibrate the CGM system. TIR was defined as the percentage of time in the target glucose range of 3.9–10.0 mmol/L during a 24-h period. In addition, mean glucose and glucose coefficient of variation were calculated. During the 3-day CGM period, all participants adhered to a standard diet designed to ensure a total daily caloric intake of 25 kcal/kg/day, with 55% of calories coming from carbohydrates, 17% from proteins, and 28% from fats, as previously reported (10).

Prospective Follow-up

Causes and time of death were obtained from the database of the Shanghai Municipal Center for Disease Control and Prevention and were linked with study data through the personal identification number. The death causes were identified with the use of the codes in the ICD-10. ICD codes I00 through I99 were classified as CVD deaths. The rate of missing death events in Shanghai was proved to be 0.7‰ (T.X., J.Z., personal communication). We used chart review to evaluate the confirmation of death (COD) via the Shanghai adaptation of the Medical Record Audit Form. Trained physicians have reviewed the medical records of a death event and reassigned the COD, which provided a gold standard to measure the quality of routine COD data. The death events identified by Shanghai Civil Registration and Vital Statistics routine monitoring were thus reported with high sensitivity and specificity of 85.7% and 90.0%, respectively. In the current study, the major outcomes were all-cause and CVD mortality. All patients were followed up until a death event occurred or until 31 December 2018, whichever occurred first.

Statistical Analysis

Differences in risk factors among patients with different levels of TIR were tested using Pearson χ^2 for categorical variables. For continuous variables with normal or skewed distributions, ANOVA or Mann-Whitney *U* test was conducted. The correlations among glucose metrics were evaluated by Spearman correlation coefficients. The Cox proportional hazards model was used to estimate the association of TIR with the risks of total and CVD mortality. TIR was evaluated in the following two ways: as four categories (≤50%, 51–70%, 71–85%, and >85%) and as a continuous variable. We used these three cut points because they were close to the 25th, 50th, and 75th percentiles of the study population. The

Table 1—Characteristics of participants by different levels of TIR

		TIR				
	Total	≤50%	51–70%	71–85%	>85%	*P* value
Number of participants	6,225	1,662	1,637	1,480	1,446	
Age, years	61.7 ± 11.9	62.9 ± 12.1	62.2 ± 11.6	61.6 ± 11.8	59.7 ± 11.9	<0.001
Men, *n* (%)	3,404 (54.7)	862 (51.9)	899 (54.9)	835 (56.4)	808 (55.9)	0.046
BMI, kg/m^2	24.9 ± 3.5	24.8 ± 3.6	24.5 ± 3.4	25.0 ± 3.5	25.3 ± 3.6	<0.001
Diabetes duration, years	9.7 ± 7.4	11.0 ± 7.6	10.1 ± 7.5	9.4 ± 7.2	7.8 ± 6.7	<0.001
Systolic blood pressure, mmHg	133 ± 17	134 ± 18	133 ± 17	132 ± 16	131 ± 17	<0.001
Diastolic blood pressure, mmHg	80 ± 9	80 ± 9	80 ± 9	80 ± 10	80 ± 9	0.981
Total cholesterol, mmol/L	4.74 ± 1.19	4.93 ±1.42	4.78 ± 1.17	4.65 ± 1.06	4.57 ± 0.99	<0.001
Triglycerides, mmol/L	1.78 ± 1.8	2.09 ± 2.54	1.68 ± 1.51	1.67 ± 1.29	1.67 ± 1.44	<0.001
HDL cholesterol, mmol/L	1.12 ± 0.31	1.10 ± 0.32	1.14 ± 0.31	1.12 ± 0.31	1.12 ± 0.29	0.002
LDL cholesterol, mmol/L	2.96 ± 0.95	3.01 ± 0.98	3.01 ± 1.01	2.93 ± 0.9	2.86 ± 0.86	<0.001
HbA_{1c}, %	8.9 ± 2.2	10.1 ± 2.0	9.4 ± 2.1	8.5 ± 2.0	7.4 ± 1.7	<0.001
HbA_{1c}, mmol/mol	74.0 ± 24.0	87.0 ± 21.9	79.0 ± 23.0	69.0 ± 21.9	57.0 ± 18.6	<0.001
Mean glucose, mmol/L	9.2 ± 1.9	11.6 ± 1.4	9.4 ± 0.8	8.2 ± 0.8	7.2 ± 0.8	<0.001
Glucose coefficient of variation, %	25.7 ± 8.4	25.4 ± 8.5	29.4 ± 8.7	27.5 ± 7.1	20.3 ± 5.8	<0.001
TIR, %	64.6 ± 24.3	31.7 ± 13.6	60.7 ± 5.7	78.0 ± 4.2	93.0 ± 4.6	<0.001
History of CVD, *n* (%)	1,323 (21.3)	397 (23.9)	357 (21.8)	298 (20.1)	271 (18.7)	0.003
History of cancer, *n* (%)	285 (4.6)	75 (4.5)	76 (4.6)	69 (4.7)	65 (4.5)	0.994
Current smoker, *n* (%)	1,478 (23.7)	384 (23.1)	407 (24.9)	357 (24.1)	330 (22.8)	0.512
Use of insulin, *n* (%)	4,164 (66.9)	1,425 (85.7)	1,277 (78.0)	934 (63.1)	528 (36.5)	<0.001
Use of antihypertensive drugs, *n* (%)	3,382 (54.3)	954 (57.4)	855 (52.2)	820 (55.4)	753 (52.1)	0.005
Use of aspirin, *n* (%)	2,935 (47.1)	826 (49.7)	784 (47.9)	678 (45.8)	647 (44.7)	0.028
Use of statins, *n* (%)	2,397 (38.5)	664 (40.0)	668 (40.8)	544 (36.8)	521 (36.0)	0.013

Data are mean ± SD unless otherwise indicated.

analyses were first carried out after adjustment for age and sex (model 1) and then further for smoking, diabetes duration, BMI, systolic blood pressure, triglycerides, HDL cholesterol, LDL cholesterol, history of cancer, history of CVD, and use of antihypertensive drugs, aspirin, and statins (model 2). The restricted cubic spline nested in time-dependent Cox models was conducted to test whether there was a dose-response or nonlinear association of TIR as a continuous variable with the risks of all-cause and CVD mortality. A P value of <0.05 (two-tailed) was considered statistically significant. Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL).

RESULTS

The study cohort consisted of 6,225 participants with type 2 diabetes. At baseline, the mean age was 61.7 years, 54.7% were men, the mean duration of diabetes was 9.7 years, and the mean HbA_{1c} was 8.9% (74.0 mmol/mol). The 25th, 50th, and 75th percentiles of TIR were 48.5%, 68.5%, and 84.0%, respectively. General characteristics of the study population are presented in Table 1. Age, diabetes duration, systolic blood pressure, total and LDL cholesterol, triglycerides, HbA_{1c}, history of CVD, and use of insulin, antihypertensive medications, aspirin, and statins were inversely and BMI was positively associated with baseline TIR levels. The correlation coefficients were 0.53 for HbA_{1c} and mean glucose ($P < 0.001$) and -0.53 for HbA_{1c} and TIR ($P < 0.001$).

During a median follow-up of 6.9 years, 838 deaths were identified, 287 of which were due to CVD.

The multivariable-adjusted (age, sex, smoking, diabetes duration, BMI, systolic blood pressure, triglycerides, HDL cholesterol, LDL cholesterol, history of cancer, history of CVD, and use of antihypertensive drugs, aspirin, and statins: model 2) hazard ratios (HRs) associated with different levels of TIR (>85% [reference group], 71–85%, 50–70%, and ≤50%) were 1.00, 1.23 (95% CI 0.98–1.55), 1.30 (95% CI 1.04–1.63), and 1.83 (95% CI 1.48–2.28) for all-cause mortality (P for trend <0.001) and 1.00, 1.35 (95% CI 0.90–2.04), 1.47 (95% CI 0.99–2.19), and 1.85 (95% CI 1.25–2.72) for CVD mortality (P for trend $= 0.015$), respectively (Table 2 and Fig. 1).

When TIR was examined as a continuous variable by using restricted cubic splines, an inverse association of TIR with the risk of all-cause mortality was observed (Fig. 2), and the multivariable-adjusted (model 2) HRs for each 10% decrease in TIR were 1.08 (95% CI 1.05–1.12) for all-cause mortality and 1.05 (95% CI 1.00–1.11) for CVD mortality (Table 2).

When stratified by age, sex, history of CVD or cancer, use of insulin, and use of antihypertensive drugs, this inverse association between TIR and the risk of all-cause mortality was still present in all subgroups except for women (Table 3). There were no significant interactions of TIR and age, history of CVD or cancer, use of insulin, and use of antihypertensive drugs on the risk of all-cause mortality. Significant interactions of TIR and sex (P for interaction <0.05) with the risk of all-cause mortality were observed.

Overall, there was a J-shaped association of baseline HbA_{1c} with the risk of all-cause and CVD mortality among patients with type 2 diabetes after adjustment for confounding factors (Supplementary

Table 2—HRs for all-cause and cardiovascular mortality according to different levels of TIR

	TIR >85%	TIR 71–85%	TIR 51–70%	TIR ≤50%	*P* for trend	TIR as a continuous variable (each 10% decrease)
All-cause mortality						
Number of participants	1,446	1,480	1,637	1,662		
Number of deaths	126	185	219	308		
Person-years	10,704.8	10,708.6	11,493.0	11,300.4		
Adjusted HRs (95% CIs)						
Model 1	1.00	1.26 (1.01–1.59)	1.39 (1.12–1.74)	1.98 (1.60–2.44)	<0.001	1.10 (1.07–1.13)
Model 2	1.00	1.23 (0.98–1.55)	1.30 (1.04–1.63)	1.83 (1.48–2.28)	<0.001	1.08 (1.05–1.12)
Cardiovascular mortality						
Number of deaths	37	64	81	105		
Adjusted HRs (95% CIs)						
Model 1	1.00	1.43 (0.95–2.14)	1.66 (1.12–2.45)	2.15 (1.47–3.13)	<0.001	1.08 (1.03–1.13)
Model 2	1.00	1.35 (0.90–2.04)	1.47 (0.99–2.19)	1.85 (1.25–2.72)	0.015	1.05 (1.00–1.11)

Model 1 adjusted for age and sex; model 2 adjusted for age, sex, smoking, diabetes duration, BMI, systolic blood pressure, triglycerides, HDL cholesterol, LDL cholesterol, history of cancer, history of CVD, and use of antihypertensive drugs, aspirin, and statins.

Table 1), with increased risks of all-cause and CVD mortality observed among patients with HbA_{1c} <6% and ≥8% compared with those with HbA_{1c} of 6.0–6.9%.

CONCLUSIONS

This large prospective cohort study has found that TIR as assessed by CGM during hospitalization was inversely associated with long-term risks of all-cause and CVD mortality in patients with type 2 diabetes. These results support the validity of TIR as a surrogate marker of long-term adverse clinical outcomes and an end point in future clinical trials.

Since the landmark DCCT study (11), HbA_{1c} has been regarded as the "gold standard" for the assessment of glycemic control. However, several caveats of HbA_{1c} when evaluating individual glycemic control should be recognized (12). Certain medical conditions, such as anemia, hemoglobinopathies, kidney diseases, and pregnancy, may cause falsely low or high readings of HbA_{1c}. Besides, the intersubject variability in hemoglobin glycation may lead to discordance between a measured HbA_{1c} and the true mean glucose in a substantial portion of individuals (13). Moreover, HbA_{1c} does not capture information on hypoglycemia, hyperglycemia, and glycemic variability, which are critical for decision-making. Instead, TIR can complement HbA_{1c} and inform on optimal diabetes management. Recently, several lines of evidence have come to light linking TIR to diabetes-related outcomes. TIR has been reported to be associated with microvascular complications in

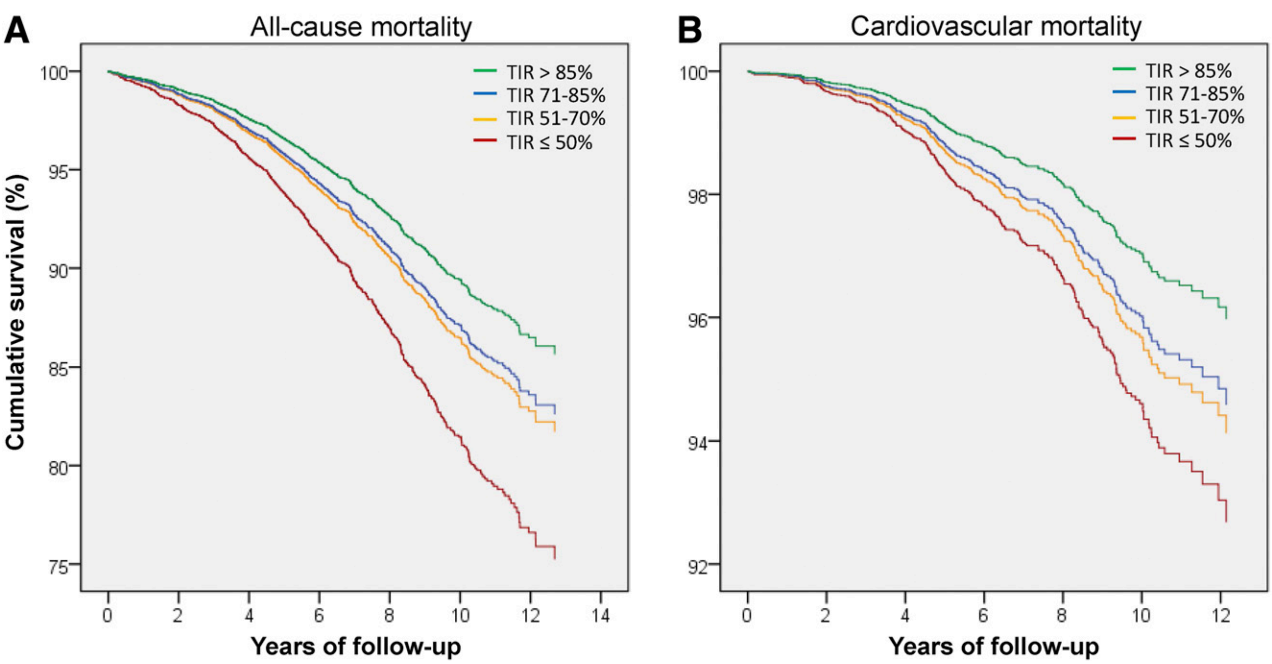

Figure 1—Multivariate-adjusted cumulative survival curves of all-cause (*A*) and cardiovascular (*B*) mortality by different levels of TIR. Adjusted for age, sex, BMI, diabetes duration, systolic blood pressure, triglyceride, HDL cholesterol, LDL cholesterol, smoking status, history of cancer and CVD, and use of antihypertensive drugs, aspirin, and statins.

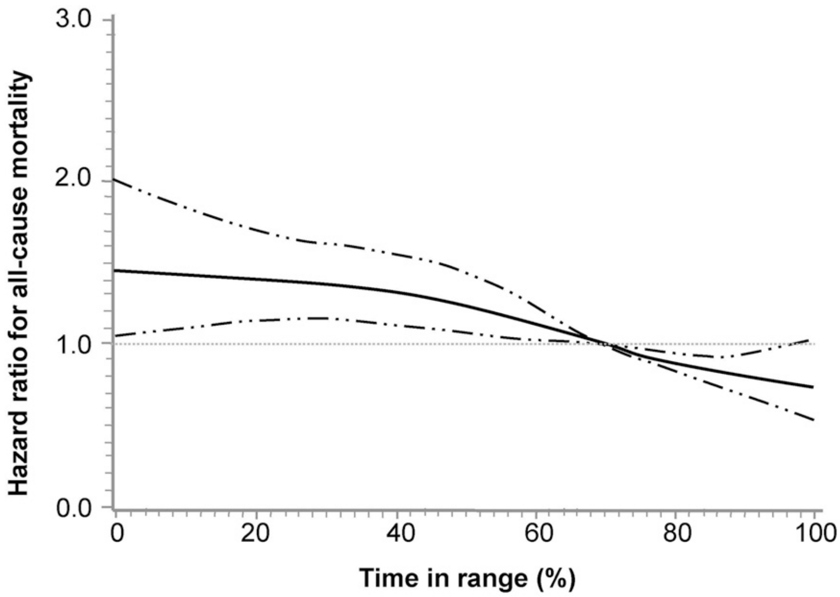

Figure 2—HRs of all-cause mortality by different levels of TIR. TIR of 70% was set as the reference. Adjusted for age, sex, BMI, diabetes duration, systolic blood pressure, triglyceride, HDL cholesterol, LDL cholesterol, smoking status, history of cancer and CVD, and use of antihypertensive drugs, aspirin, and statins.

both type 1 (8) and type 2 diabetes (10,14,15). In pregnant women with type 1 diabetes, TIR in the second and third trimester was tied to neonatal health outcomes (9). However, no prospective studies have assessed the association of TIR with the long-term risk of mortality among patients with type 2 diabetes. In contrast, there is ample evidence on the association between HbA_{1c} assessment and the risk of all-cause mortality in the general population (16,17) and people with diabetes (18–21). The present prospective study is the first one to find that TIR as assessed by CGM during hospitalization was inversely associated with long-term risks of all-cause and CVD mortality in patients with type 2 diabetes. In addition, we found that this inverse association between TIR and the risks of all-cause and CVD mortality was present in men, patients with different ages, and patients using or not using insulin and antihypertensive drugs.

It is noteworthy that moderate to strong correlations between TIR and HbA_{1c} were observed in two studies (22,23), in which a TIR of 70% was equivalent to HbA_{1c} of ~7% and an increment in TIR of 10% corresponded to a decrease in HbA_{1c} of 0.5–0.8%. Given these correlations, the relationship between TIR and mortality is to some extent expected. However, TIR provides different information than HbA_{1c}, which is most evident in the context of hypoglycemia and great glycemic variability. Moreover, there is evidence that TIR varies significantly at a given mean glucose or HbA_{1c} (24,25). Therefore, the association with all-cause mortality may be different between TIR and HbA_{1c}. Specifically, a U-shaped or J-shaped association of HbA_{1c} with all-cause mortality was apparent in numerous relevant studies, with the highest mortality risk observed in the low and high range of HbA_{1c} (18–20,26). A meta-analysis of 46 observational studies reported that patients with diabetes with HbA_{1c} ranging from 6.0% to 8.0% had the lowest all-cause and CVD mortality (27). Consistent with previous findings, the current study found a J-shaped association of HbA_{1c} with mortality among patients with type 2 diabetes. Although the mechanism behind the relationship between low HbA_{1c} and heightened mortality risk remains not fully understood, these observations, together with the results from certain randomized clinical trials (28–30), have led to a target HbA_{1c} of ~6.5–7.0% in most guidelines to date. On the contrary, the interpretation of TIR seems more straightforward. An increment in TIR means less time spent in hyperglycemia and/or hypoglycemia, and presumably improved diabetes-related outcomes, which is supported by the monotonical association between TIR categories and all-cause mortality in our study. Importantly, the distribution of time outside the target range is asymmetrical (31). One previous study using CGM data from type 1 diabetes showed that TIR was strongly correlated with measures of hyperglycemia, implying that TIR is largely a hyperglycemia metric. This observation is likely to be even more evident in type 2 diabetes, which is associated with a lower risk of hypoglycemia than type 1 diabetes. Therefore, by exploiting the information from CGM, a major goal of optimal glycemic control is to maximize TIR while minimizing the risk of hypoglycemia.

A recent international consensus (5) recommended that 14 days of CGM with at least 70% of data available are needed for accurate and meaningful interpretation, given that 14 days of monitoring provide a good estimation of overall glycemic control for the last 3 months (32,33). However, only 3 days of CGM were conducted in our study with a less accurate former-generation glucose sensor. Furthermore, the participants in the current study received a standard diet during CGM, as we intended to minimize the impact of interindividual variations in dietary intake, and the resulting CGM metrics may presumably be more closely related to the intrinsic dysfunction in glucose homeostasis and be more stable over time. Consequently, the glucose profiles captured in the current study may not fully represent the patients' glucose control in the real life. Indeed, the correlations of HbA_{1c} with mean glucose ($r_s = 0.53$) and TIR ($r_s = -0.53$) were lower in our study than those reported by Beck et al. (22) in 545 adults with type 1 diabetes (mean glucose: $r_s = 0.71$; TIR: $r_s = -0.67$), and the measured TIR seemed to deviate from the predicted TIR by HbA_{1c} according to two previous studies (22,23). Nevertheless, the consistent associations of TIR with mortality across multiple subpopulations supported the robustness of our findings. It is therefore reasonable to postulate that, when using a longer period of CGM with more accurate glucose sensors, the association of TIR with mortality may be even stronger, which warrants further investigations.

There are several strengths in our study, including the large sample size and long follow-up time, which allowed for high statistical power and the ability to perform stratified analyses. This is the

Table 3—HRs for all-cause mortality according to different levels of TIR among subpopulations

	TIR					
	>85%	71–85%	51–70%	≤50%	*P* for trend	*P* for interaction
Age, years						>0.05
<50	1.00	0.75 (0.20–2.85)	1.29 (0.38–4.45)	4.33 (1.46–12.8)	0.005	
≥50	1.00	1.36 (1.08–1.72)	1.41 (1.12–1.78)	1.97 (1.58–2.46)	<0.001	
Sex						<0.05
Men	1.00	1.52 (1.13–2.05)	1.41 (1.04–1.91)	2.34 (1.76–3.12)	<0.001	
Women	1.00	0.90 (0.62–1.29)	1.17 (0.84–1.64)	1.24 (0.89–1.72)	0.203	
History of CVD or cancer						>0.1
Yes	1.00	1.31 (0.90–1.89)	1.29 (0.90–1.84)	1.70 (1.20–2.41)	<0.001	
No	1.00	1.20 (0.89–1.61)	1.32 (0.99–1.77)	1.95 (1.48–2.57)	<0.001	
Use of insulin						>0.1
Yes	1.00	0.96 (0.72–1.29)	0.94 (0.71–1.26)	1.33 (1.01–1.74)	0.001	
No	1.00	1.29 (0.88–1.90)	1.52 (1.00–2.31)	2.06 (1.29–3.29)	0.018	
Use of antihypertensive drugs						>0.1
Yes	1.00	1.08 (0.82–1.43)	1.06 (0.81–1.39)	1.55 (1.20–2.00)	<0.001	
No	1.00	1.61 (1.05–2.47)	2.12 (1.40–3.20)	2.76 (1.84–4.14)	<0.001	

Adjusted for age, sex, smoking, diabetes duration, BMI, systolic blood pressure, triglycerides, HDL cholesterol, LDL cholesterol, history of cancer, history of CVD, and use of antihypertensive drugs, aspirin, and statins, other than the variable for stratification.

first cohort study to investigate the association between TIR assessed by CGM and the risk of mortality in patients with type 2 diabetes. There are also several limitations in this study. First, due to the observational design of the study, the causality between TIR and mortality can only be inferred and the presence of residual confounding remains a possibility. Second, as we discussed above, the glucose profiles observed in the study may not necessarily reflect the historical glycemic control of the enrolled subjects, and the study design precluded the exploration of the association between mortality and TIR as a time-dependent variable or the updated mean TIR, which might have underestimated the strength of the association. Third, the data on the smoking status, history of CVD, and cancer were collected by self-report, which may have introduced some misclassifications into the study. In addition, socioeconomic and lifestyle data were not available in the current study. Finally, the subjects included in the analysis were hospitalized patients with type 2 diabetes. Thus, the results of the study may not be generalizable to other populations with diabetes.

In conclusion, we found a strong and graded inverse relationship between TIR and the risks of all-cause and CVD mortality among patients with type 2 diabetes. Our findings suggest that patients with diabetes should be encouraged to aim for an achievable higher TIR to reduce the risk of adverse clinical outcomes, although the goal should be individualized. TIR, as an intuitive and valid measure of glycemic control, should be more widely accepted in both clinical practice and clinical studies.

Acknowledgments. The authors thank all of the involved clinicians, nurses, and technicians of the Shanghai Clinical Center for Diabetes for dedicating time and skill to the completion of this study.

Funding. This work was funded by the National Key R&D Program of China (2018YFC2001004), the National Natural Science Foundation of China (31971485), the Shanghai Municipal Education Commission Gaofeng Clinical Medicine Grant Support (20161430), and Shanghai Municipal Key Clinical Specialty.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. G.H., T.X., and J.Z. conceived of and designed the study. J.L., C.W., and Y.S. contributed to data collection, data analysis, and writing the manuscript. C.W., L.C., L.Z., J.C., W.L., and W.Z. contributed to data collection and analysis. W.L. and W.Z. contributed to conduction of the study and data collection. T.X. and J.Z. contributed to interpretation of data and revision of the manuscript. G.H. contributed to revision of the manuscript. J.Z. and T.X. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Battelino T, Conget I, Olsen B, et al.; SWITCH Study Group. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia 2012;55:3155–3162
2. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 2016;388:2254–2263
3. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Use of flash glucose-sensing technology for 12 months as a replacement for blood glucose monitoring in insulin-treated type 2 diabetes. Diabetes Ther 2017;8:573–586
4. Maiorino MI, Signoriello S, Maio A, et al. Effects of continuous glucose monitoring on metrics of glycemic control in diabetes: a systematic review with meta-analysis of randomized controlled trials. Diabetes Care 2020;43:1146–1156
5. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019;42:1593–1603
6. Runge AS, Kennedy L, Brown AS, et al. Does time-in-range matter? Perspectives from people with diabetes on the success of current therapies and the drivers of improved outcomes. Clin Diabetes 2018;36:112–119
7. Lu J, Home PD, Zhou J. Comparison of multiple cut points for time in range in relation to risk of abnormal carotid intima-media thickness and diabetic retinopathy. Diabetes Care 2020;43:e99–e101
8. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. Diabetes Care 2019;42:400–405
9. Kristensen K, Ögge LE, Sengpiel V, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. Diabetologia 2019;62:1143–1153
10. Lu J, Ma X, Zhou J, et al. Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. Diabetes Care 2018;41:2370–2376
11. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression

of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
12. Hirsch IB, Sherr JL, Hood KK. Connecting the dots: validation of time in range metrics with microvascular outcomes. Diabetes Care 2019;42: 345–348
13. Shrom D, Sarwat S, Ilag L, Bloomgarden ZT. Does A1c consistently reflect mean plasma glucose? J Diabetes 2010;2:92–96
14. Guo Q, Zang P, Xu S, et al. Time in range, as a novel metric of glycemic control, is reversely associated with presence of diabetic cardiovascular autonomic neuropathy independent of HbA1c in Chinese type 2 diabetes. J Diabetes Res 2020;2020:5817074
15. Mayeda L, Katz R, Ahmad I, et al. Glucose time in range and peripheral neuropathy in type 2 diabetes mellitus and chronic kidney disease. BMJ Open Diabetes Res Care 2020;8:e000991
16. Mongraw-Chaffin M, Bertoni AG, Golden SH, et al. Association of low fasting glucose and HbA1c with cardiovascular disease and mortality: the MESA Study. J Endocr Soc 2019;3:892–901
17. Paprott R, Schaffrath Rosario A, Busch MA, et al. Association between hemoglobin A1c and all-cause mortality: results of the mortality follow-up of the German National Health Interview and Examination Survey 1998. Diabetes Care 2015;38:249–256
18. Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481–489
19. Forbes A, Murrells T, Mulnier H, Sinclair AJ. Mean HbA_{1c}, HbA_{1c} variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. Lancet Diabetes Endocrinol 2018;6:476–486
20. Li FR, Zhang XR, Zhong WF, et al. Glycated hemoglobin and all-cause and cause-specific mortality among adults with and without diabetes. J Clin Endocrinol Metab 2019;104:3345–3354
21. Riddle MC, Ambrosius WT, Brillon DJ, et al.; Action to Control Cardiovascular Risk in Diabetes Investigators. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care 2010; 33:983–990
22. Beck RW, Bergenstal RM, Cheng P, et al. The relationships between time in range, hyperglycemia metrics, and HbA1c. J Diabetes Sci Technol 2019;13:614–626
23. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. Diabetes Technol Ther 2019;21: 81–85
24. Lu J, Ma X, Zhang L, et al. Glycemic variability modifies the relationship between time in range and hemoglobin A1c estimated from continuous glucose monitoring: a preliminary study. Diabetes Res Clin Pract 2020;161:108032
25. Rodbard D. Glucose time in range, time above range, and time below range depend on mean or median glucose or HbA1c, glucose coefficient of variation, and shape of the glucose distribution. Diabetes Technol Ther 2020;22: 492–500
26. Li W, Katzmarzyk PT, Horswell R, Wang Y, Johnson J, Hu G. HbA1c and all-cause mortality risk among patients with type 2 diabetes. Int J Cardiol 2016;202:490–496
27. Cavero-Redondo I, Peleteiro B, Álvarez-Bueno C, Rodriguez-Artalejo F, Martínez-Vizcaíno V. Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis. BMJ Open 2017;7:e015949
28. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
29. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358: 2545–2559
30. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358:2560–2572
31. Kovatchev BP. Metrics for glycaemic control - from HbA_{1c} to continuous glucose monitoring. Nat Rev Endocrinol 2017;13:425–436
32. Riddlesworth TD, Beck RW, Gal RL, et al. Optimal sampling duration for continuous glucose monitoring to determine long-term glycemic control. Diabetes Technol Ther 2018;20:314–316
33. Xing D, Kollman C, Beck RW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Optimal sampling intervals to assess long-term glycemic control using continuous glucose monitoring. Diabetes Technol Ther 2011;13:351–358