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ORIGINAL ARTICLE

Cause-specific risk of major adverse cardiovascular outcomes and hypoglycemic in patients with type 2 diabetes: a multicenter prospective cohort study

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Abstract

Purpose Glycated hemoglobin $A1_c$ ($HbA1_c$) and fasting plasma glucose (FPG) was identified to account for the risk of cardiovascular diseases in type 2 diabetic patients, but no study evaluated the risk based on both $HbA1_c$ and FPG levels. We described the risk of major adverse cardiovascular events (MACE) and hypoglycemic in type 2 diabetic patients according to both $HbA1_c$ and FPG levels.

Methods With the usage of databases of Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE), 1815 patients from 61 centers in China was identified and grouped according to the criterion value of $HbA1_c$ and FPG: Good glycemic control ($HbA1_c < 6.5\%$, FPG < 6.1 mmol/L); Insufficient glycemic control ($HbA1_c < 6.5\%$, FPG ≥ 6.1 mmol/L or $HbA1_c \geq 6.5\%$, FPG < 6.1 mmol/L); Poor glycemic control ($HbA1_c \geq 6.5\%$, FPG ≥ 6.1 mmol/L). Time-varying multivariable Cox proportional hazards models were employed.

Results Average age was 64.8 ± 5.8 years, with a median of 4.8 years of follow-up. Overall, the incidence rates of MACE were 20.6 per 1000-person-years in Good glycemic control compared with 45.9 per 1000-person-years in Insufficient glycemic control (adjusted hazard ratio (aHR): 1.99; 95% CI 1.11–3.56; $p = 0.02$) and 54.7 per 1000-person-years in Poor glycemic control (aHR: 2.46; 95% CI 1.38–4.40; $p = 0.002$), respectively. The risk of hypoglycemic was highest in Insufficient glycemic control; 67.3 per 1000-person-years compared with 46.3 per 1000-person-years in Good glycemic control (aHR: 1.62; 95% CI 1.03–2.56; $p = 0.04$). Apart from this, we also observed that both MACE (aHR:1.41; 95% CI 1.13–1.77; $p = 0.003$) and hypoglycemic episodes (aHR: 1.82; 95% CI 1.48–2.24; $p < 0.001$) were sufficiently more frequent in the insulin-exposed group than the non-exposed group. In a post-hoc analysis, the risk of MACE (aHR:1.43; 95% CI 1.09–1.86; $p = 0.01$) and hypoglycemic (aHR: 1.99; 95% CI 1.46–2.69; $p < 0.001$) were more pronounced in Insufficient glycemic control with insulin exposure.

Conclusions We observed a significant association of cause-specific risk of MACE and hypoglycemic with Insufficient glycemic control, particularly with insulin exposure.

Keywords Type 2 diabetes · Major adverse cardiovascular events · Good glycemic control · Insufficient glycemic control · Poor glycemic control

Abbreviations

$HbA1_c$	Glycated hemoglobin $A1_c$
FPG	fasting plasma glucose

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MACE	major adverse cardiovascular events
ADVANCE	Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation
aHR	adjusted hazard ratio
IQR	Interquartile range
BMI	body mass index
ACCORD	Action to Control Cardiovascular Risk in Diabetes
VADT	Veterans Affairs Diabetes Trail.

Introduction

As one of the most common chronic diseases, diabetes mellitus is key contributor to global disease burden, affecting 425 million people worldwide in 2017 [1]. Currently, Chinese adults account for around 10.9% of the population with diabetes worldwide [2]. Compared with those without diabetes, individuals with diabetes mellitus are at elevated risk for cardiovascular diseases and have at least twofold higher risk for cardiovascular death [3, 4]. Several previous clinical trials have shown that intensive glucose control attenuated the progression of microvascular disease, but the relationship between macrovascular complications and glycemic control remained uncertain [5, 6]. Remarkably, the other randomized trials reported a controversial association between glycemic control and cardiovascular diseases in patients with diabetes [7–10].

FPG was identified as diagnostic criteria for diabetes by World Health Organization in 1999. Compelling evidence revealed that FPG levels in not only diabetic persons but also nondiabetic persons have been related to a great risk for cardiovascular disease [11, 12], suggesting an association between FPG levels and cardiovascular risk. $HbA1_c$, reflecting long-term glycemic levels, was more accurate and stable than FPG [13]. American Diabetes Association advocated $HbA1_c$ as one of diagnostic criteria for diabetes in 2003. As with FPG, $HbA1_c$ was strongly associated with risk of cardiovascular diseases and diabetes [14]. Meta-analysis also suggested that an increased risk for cardiovascular events was associated with chronic hyperglycemia in people with diabetes [15]. Another study considered $HbA1_c$ was significantly associated with mortality in the onset of diabetic population [16]. Although $HbA1_c$ and FPG were highly consistent in diagnosing diabetes mellitus, they were not in predicting intermediate hyperglycemia [17]. The ADVANCE Collaborative Group suggested that intensive glucose control that lowered $HbA1_c$ to 6.5% reduced the incidence of vascular outcomes [18]. However, there was no evidence that intensive glucose control led to long-term benefits with respect to macrovascular events or mortality during the ADVANCE factorial trial [19]. Consequently, investigating the risk of cardiovascular events based on levels of both $HbA1_c$ and FPG may contribute to explaining the controversial association between glycemic control and cardiovascular diseases.

Considering the inconsistency of the previous research focusing on the link between the control of FPG or $HbA1_c$ levels and the risk of cardiovascular events, we thus evaluated the cause-specific risk of MACE and hypoglycemic on the basis of levels of both FPG and $HbA1_c$ and explored the relationship between the cause-specific risk and main drug exposure in post-hoc analyses.

Subjects and methods

Study design and participants

We analyzed data from the linkable databases of ADVANCE, a factorial randomized and controlled trial at 61 centers in China. The study was approved by the local ethics committee and was in accordance with the declaration of Helsinki on ethical principles for medical research involving human subjects. All patients provided written informed consent (registration number NCT00145925). Previous studies have described detailed rationale, follow-up schedule, design and endpoints of the trial [20, 21].

In brief, it was a 2×2 factorial randomized controlled trial. Participants who were treated for 6 weeks as run-in period with combination of perindopril and indapamide were randomly assigned (1:1) to receive modified-release gliclazide based intensive or standard therapy for glycemic control, and perindopril-indapamide or matching placebo for blood pressure control. The intensive glucose control received gliclazide modified-release-based regimen, other oral agents and insulin to achieve for a $HbA1_c$ value of 6.5% or lower. The local standard therapy received usual glucose control regimens except the use of gliclazide. According to the criteria of FPG and HbA1c levels set by World Health Organization in 1999 and American Diabetes Association in 2013, we defined Good glycemic control as the condition in which HbA1c (%) < 6.5% and FPG < 6.1 mmol/L, Insufficient glycemic control as the condition in which HbA1c(%) < 6.5% and FPG ≥ 6.1 mmol/L (or HbA1c(%) ≥ 6.5 and FPG < 6.1 mmol/L), and Poor glycemic control as the condition in which HbA1c(%) ≥ 6.5% and FPG ≥ 6.1 mmol/L. This method also had been recommended for participant management in the intensive group by ADVANCE Collaborative Group [18].

Eligible patients with type 2 diabetes were at least 55 years old (Interquartile range (IQR): 60–69) at the time of study entry, and had a history of major macrovascular or microvascular diseases. Further details of these patients had been described previously [22].

Glycemic exposure

Exposure to glycemia was measured firstly at baseline as FPG and HbA1c concentration, and subsequently over time as an updated mean of annual measurements of FPG and HbA1c concentration calculated for each individual from baseline to the final follow-up visit.

Clinical outcomes

MACE was identified as occurrence of any of an episode of major macrovascular events and major microvascular events. The major macrovascular events included death from cardiovascular causes, non-fatal stroke or non-fatal myocardial infarction. The microvascular events comprised of new or worsening nephropathy or retinopathy. Hypoglycemia were recorded systematically as prespecified events of clinical interest and reviewed proactively with patients. All the adverse cardiovascular events were described and defined by previous study [20]. Drug exposure measures were generated from prescription data at 61 centers in China. Diabetes duration was time from first diagnosis of diabetes to the date of first follow-up visit.

All these clinical outcomes were adjudicated by an independent End Point Adjudication Committee without awareness of the group assignments.

Statistical analysis

Standardized differences in continuous variables during the follow-up period were analyzed with the use of linear mixed models, appropriately. MACE and hypoglycemic risk were tested using Multiple Cox proportional hazards models from the index date to the date of an outcome event. The inclusion of age, gender, body mass index (BMI), diabetes duration, baseline high and low-density lipoprotein cholesterol, triglyceride, albumin-to-creatinine ratio, history of major macrovascular diseases, history of major microvascular diseases and smoking status as potential confounding risk covariates was chosen for the full adjustment.

Sensitivity analyses for MACE and hypoglycemic were carried out due to concern about the differences in risk factors in the post-hoc analyses. All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, NC). A $p < 0.05$ was considered statistically significant.

Results

Subjects and baseline characteristics

A total of 1898 participants were enrolled in ADVANCE trial at 61 hospitals in China (Supplementary Fig. 1). Complete case analyses were performed for 1815 patients (83 missing values were excluded). Approximately 52% of the entire cohort of patients were men. The baseline characteristics of the 1815 patients with a median diabetes

Table 1 Baseline patient characteristics

Baseline variable	Cohort		
	Good glycemic control ($n = 118$)	Insufficient glycemic control ($n = 774$)	Poor glycemic control ($n = 923$)
Demographics			
Age (years), mean (SD)	65.1 (5.4)	65.2 (5.9)	64.5 (5.8)
Gender, *n* (%)			
Male	60 (50.8)	406 (52.5)	472 (51.1)
Female	58 (49.2)	368 (47.5)	451 (48.9)
Clinical parameters mean (SD)			
$HbA1_c$ (%)	5.9 (0.7)	6.5 (0.9)	7.7 (1.4)
FPG (mmol/L)	5.8 (1.2)	6.9 (2.1)	8.6 (2.8)
BMI (kg/m^2)	24.8 (3.2)	25.2 (3.2)	25.3 (3.1)
SBP (mm Hg)	132.6 (18.5)	133.5 (18.2)	137.0 (19.2)
DBP (mm Hg)	74.0 (10.1)	74.6 (9.9)	76.8 (10.1)
TC (mmol/L)	5.1 (1.3)	5.0 (1.1)	5.2 (1.1)
TG (mmol/L)	1.9 (2.8)	1.8 (1.2)	2.1 (1.5)
HDL (mmol/L)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)
LDL (mmol/L)	3.2 (5.2)	3.0 (2.2)	3.1 (1.0)
Diabetes duration (years)	4.9 (5.2)	7.2 (5.8)	8.5 (6.0)
Current smokers, *n* (%)	25 (21.2)	182 (23.5)	223 (24.2)
Albumin-to-creatinine ratio (mg/mmol), median (IQR)	2.4 (1.1–6.7)	2.6 (1.1–8.0)	2.5 (1.1–7.6)
BMI categories, *n* (%)			
$< 30\ kg/m^2$	103 (87.3)	659 (85.1‘)	784 (84.9)
$\geq 30\ kg/m^2$	15 (12.7)	115 (14.9)	139 (15.1)
Previous cardiovascular disease			
History of major macrovascular disease, *n* (%)	22 (18.6)	147 (19.0)	185 (20.0)
History of major microvascular disease, *n* (%)	7 (5.9)	55 (7.1)	80 (8.7)
Main exposed medications, *n* (%)			
Insulin	32 (27.1)	362 (46.8)	517 (56.0)
Metformin	84 (71.2)	699 (90.3)	859 (93.1)
CCBs	77 (65.3)	477 (61.6)	539 (58.4)
Thiazolidinediones	18 (15.3)	143 (18.5)	157 (17.0)
α-glucosidase inhibitors	51 (44.1))	444 (60.9)	545 (61.6)
Gliclazide	82 (69.5)	538 (69.5)	310 (33.6)

duration of 7 years (IQR: 3–11) are described in Table 1. According to the updated mean of $HbA1_c$ and FPG, 118 (6.5%), 774 (42.6%) and 923 (50.9%) patients were assigned to Good glycemic control, Insufficient glycemic control and Poor glycemic control, respectively. The proportion of the above control group was also figured out in intensive glycemic control and standard glycemic control (Fig. 1). There were 27 (22.9%) patients in Good glycemic control, 254 (32.8%) in Insufficient glycemic control, and 242 (26.2%) in Poor glycemic control experiencing an episode of hypoglycemic. Among the main drug exposure, 32 (27.1%), 362 (46.8%) and 517 (56.0%) patients were exposed with insulin in Good glycemic, Insufficient glycemic, and Poor glycemic control, respectively.

Associations of high-risk of clinical outcomes with Insufficient glycemic control

The number of recorded events for different glycemic control are listed in Table 2. To summarize, 12 patients (20.6 per 1000-person-years) had MACE and 27 patients (46.3 per 1000-person-years) experienced hypoglycemic episodes in Good glycemic control, whereas 173 (45.9 per 1000-person-years) patients had MACE and 254 (67.3 per 1000-person-years) patients experienced hypoglycemic episodes in Insufficient glycemic control, 245 (54.7 per 1000-person-years) patients had MACE and 242 (54.1 per 1000-person-years) patients experienced hypoglycemic episodes in Poor glycemic control. For the main analyses, Good glycemic control was selected as the reference regimen. After adjustment for selected covariates, there was a higher risk of MACE in Insufficient glycemic control (aHR: 1.99; 95% CI 1.11–3.56; $p = 0.02$) and Poor glycemic control (aHR: 2.46; 95% CI 1.38–4.40; $p = 0.002$) compared with Good glycemic control. For hypoglycemic, there were increased aHR for Insufficient glycemic control (aHR: 1.62; 95% CI 1.03–2.56; $p = 0.04$) and Poor glycemic control (aHR: 1.16; 95% CI 0.73–1.83; $p = 0.54$).

Association between clinical outcomes with Insufficient glycemic control under insulin exposure

The number of MACE, hypoglycemic episodes, and the main drug exposure are provided in Supplementary Table 1.

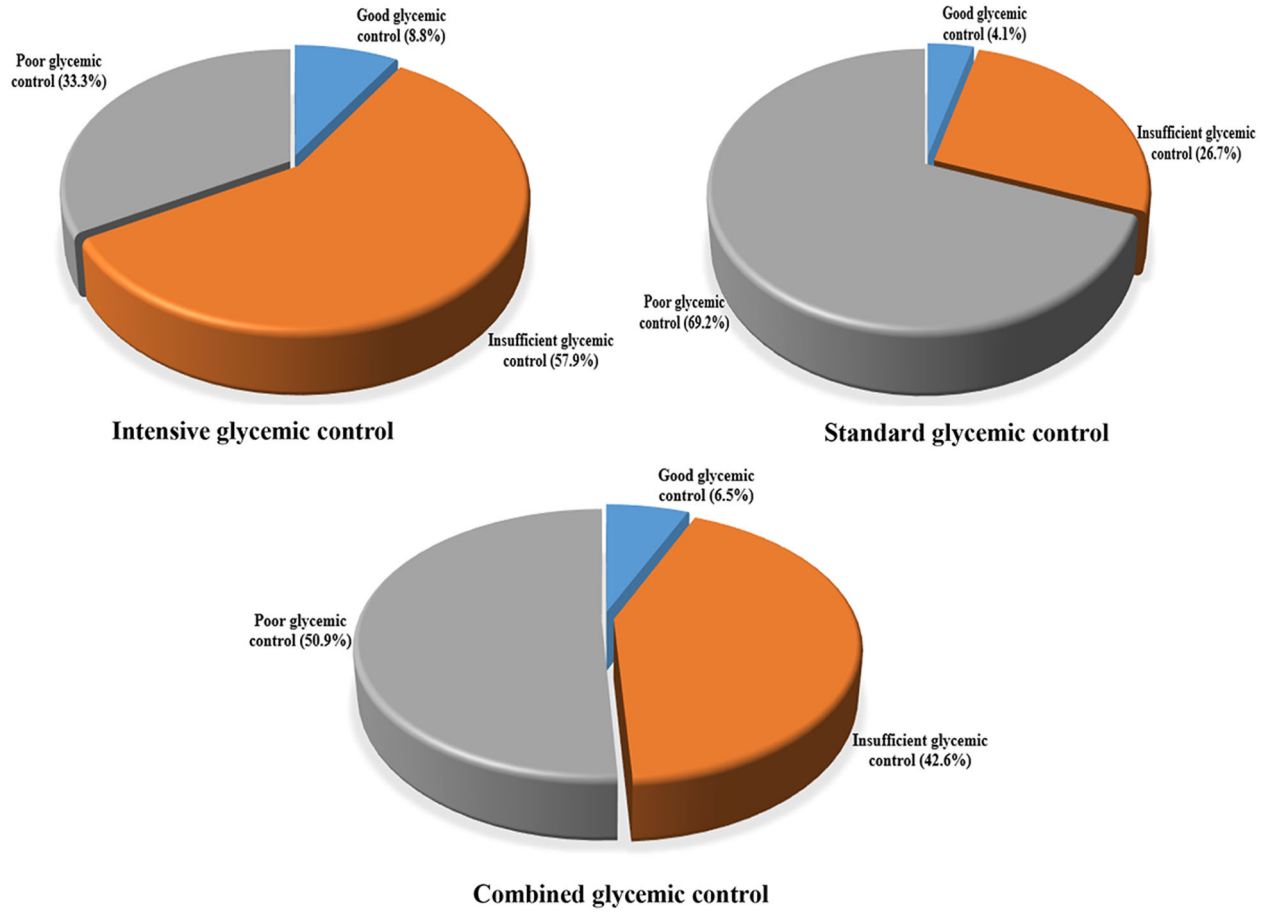

Fig. 1 The proportion of Good glycemic control, Insufficient glycemic control, and Poor glycemic control

Table 2 Comparison of number of events and adjust hazard ratios (aHR) between glycemic control groups

Group	MACE, *n* (%)[a]	aHR (95% CI)[b]	*p*-value	Hypoglycemic episodes, *n* (%)	aHR (95% CI)[b]	*p*-value
Good glycemic control	12 (10.2)	Reference		27 (22.9)	Reference	
Insufficient glycemic control	173 (22.4)	1.99 (1.11–3.56)	0.02	254 (32.8)	1.62 (1.03–2.56)	0.04
Poor glycemic control	245 (26.5)	2.46 (1.38–4.40)	0.002	242 (26.2)	1.16 (0.73–1.83)	0.54

MACE major adverse cardiovascular disease

[a]MACE included combined macro- and microvascular events, primary macrovascular and microvascular events

[b]Adjusted for age, gender, BMI, diabetes duration, baseline high and low-density lipoprotein cholesterol, triglyceride, albumin-to-creatinine ratio, history of major macrovascular diseases, history of major microvascular diseases and smoking status

Table 3 Comparison of number of events and adjust hazard ratios (aHR) between glycemic control with/ without insulin exposure

Group	Insulin exposure	MACE, *n* (%)[a]	aHR (95% CI)[b]	*p*-value	Hypoglycemic episodes, *n* (%)	aHR (95% CI)[b]	*p*-value
Good glycemic control	No	5 (41.7)	1 (reference)		11 (40.7)	1 (reference)	
	Yes	7 (58.3)	1.07 (0.47–2.45)	0.88	16 (59.3)	1.20 (0.45-3.20)	0.72
Insufficient glycemic control	No	57 (32.9)	1 (reference)		106 (41.7)	1 (reference)	
	Yes	116 (67.1)	1.43 (1.09–1.86)	0.01	148 (58.3)	1.99 (1.46–2.69)	< 0.001
Poor glycemic control	No	118 (48.2)	1 (reference)		80 (33.1)	1 (reference)	
	Yes	127 (51.8)	1.30 (0.95-1.78)	0.10	162 (66.9)	1.86 (1.37–2.54)	< 0.001

MACE major adverse cardiovascular disease

[a]MACE included combined macro- and microvascular events, primary macrovascular, and microvascular events

[b]Adjusted for age, gender, BMI, diabetes duration, baseline high and low-density lipoprotein cholesterol, triglyceride, albumin-to-creatinine ratio, history of major macrovascular diseases, history of major microvascular diseases and smoking status

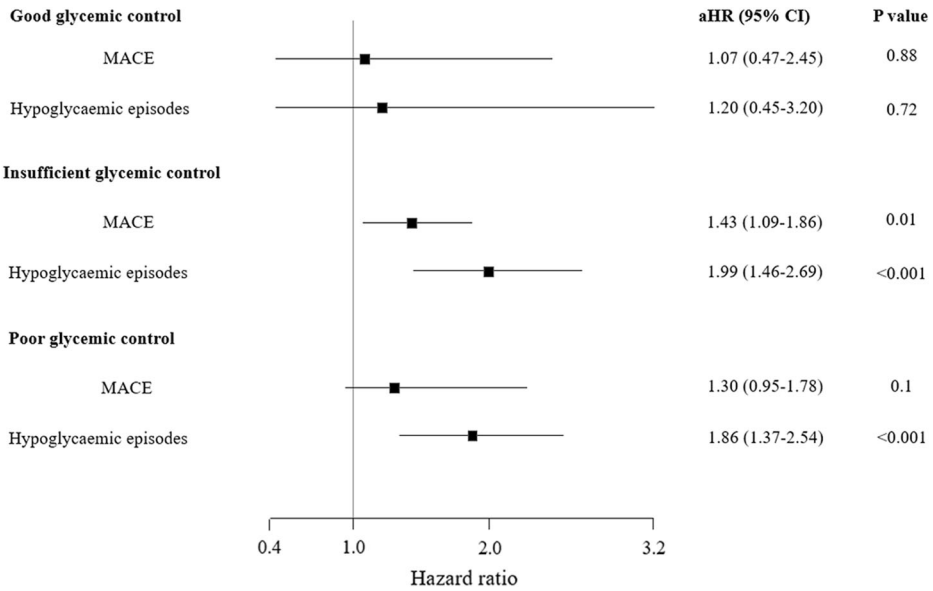

Fig. 2 Adjusted HR with 95% CI for the risk of MACE and hypoglycemic episodes in different glycemic control with insulin exposure

Under insulin exposure, there were 262 (57.2%) MACE and 318 (60.8%) hypoglycemic episodes in the entire cohort. The risk of both MACE (aHR: 1.41; 95% CI 1.13–1.77; $p = 0.003$) and hypoglycemic episodes (aHR: 1.82; 95% CI 1.48–2.24; $p < 0.001$) in patients with insulin exposure were greater than those without insulin exposure.

In post-hoc analyses, 7 (58.3%) MACE and 16 (59.3%) hypoglycemic episodes occurred in Good glycemic control with insulin exposure; 116 (67.1%) MACE and 148 (59.3%) hypoglycemic episodes occurred in Insufficient glycemic control with insulin exposure; 127 (51.8%) MACE and 162 (66.9%) hypoglycemic episodes occurred in Poor glycemic control with insulin exposure (Table 3).

No significant difference was observed between insulin-exposed group and non-insulin-exposed group in Good glycemic control. However, an increased risk of MACE

(aHR: 1.43; 95% CI 1.09–1.86; $p = 0.01$) and hypoglycemic episodes (aHR: 1.99; 95% CI 1.46–2.69; $p < 0.001$) was observed in Insufficient glycemic control with insulin exposure. The adjusted HR for hypoglycemic episodes was 1.86 (95% CI 1.37–2.54; $p < 0.001$) in Poor glycemic control with insulin exposure, but no difference for MACE was observed. Results from sensitivity analyses are also consistent with our primary findings (Fig. 2)

Discussion

This was the first population-based prospective study to compare the risk of MACE and hypoglycemic in Chinese patients with type 2 diabetes on the basis of levels of both $HbA1_c$ and FPG. Our findings demonstrated a statistically significant increase in risk of MACE and hypoglycemic in Insufficient glycemic control. There was also an obvious increase in risk of MACE in Poor glycemic control, but no consistent trend was observed for the risk of hypoglycemic. Furthermore, we also found a higher risk of MACE and hypoglycemic in patients with insulin exposure than those without. Notably, these differences were particularly pronounced in Insufficient glycemic control.

Prior epidemiologic studies evaluated that the relationship between glycemic control and cardiovascular events had not been consistent [9, 23, 24]. In parallel, some short-term trials considered either benefit or adverse effects [7, 8]. Almost all of previous studies used $HbA1_c$ or FPG as a single indicator. For example, ADVANCE [18], Action to Control Cardiovascular Risk in Diabetes (ACCORD) [25] and Veterans Affairs Diabetes Trail (VADT) [26] were designed to achieve normal $HbA1_c$, assessing the effect of intensive glycemic treatment on cardiovascular events. Furthermore, there was no evidence that intensive glucose control led to long-term benefits with respect to macrovascular events or mortality during the ADVANCE factorial trial [19]. Given that, our study was supposed to explain the controversial association between glycemic control and cardiovascular events. Equally, our prospective study cohort was a part of ADVANCE trial, but we assigned the patients to Good glycemic control, Insufficient glycemic control and Poor glycemic control using the update mean value of both $HbA1_c$ and FPG. Strikingly, 57.9% patients belonged to Insufficient glycemic control in intensive glycemic control, but only 26.7% patients belonged to Insufficient glycemic control in standard glycemic control (Fig. 1), which might explain, to some extent, no significant decrease in cardiovascular events with intensive glucose control. For the entire cohort, 50.9% and 42.6% patients were in Poor glycemic control and Insufficient glycemic control, respectively. This most likely meant that intensive and standard glycemic control might not the best treatment for patients with advanced type 2 diabetes. Presently, increasing views supported that glycemic goals should be individualized in diabetic patients [27–29].

Current studies reported that higher day-to-day fasting glycemic variability was associated with increased risk of severe hypoglycemic and cardiovascular outcomes [30, 31]. The study defined day-to-day fasting glycemic variability based on the standard measurement of the pre-breakfast self-measured blood glucose with Insulin Degludec or Insulin Glargine, finding a significant link of fluctuant blood glucose with severe hypoglycemic and cardiovascular outcomes. Recently, Cardoso et al. [32] found that long-term visit-to-visit glycemic variability was a better parameter than mean $HbA1_c$ levels for evaluating the risk of future development of cardiovascular complications in patients with type 2 diabetes. They also supported that FPG variability seemed a stronger risk predictor than $HbA1_c$ variability. In our study, the variability of blood glucose might be fluctuant in Insufficient glycemic control, which needed to be validated in the further investigation.

The strength of this study is the initially to compare the risk of cardiovascular events in Chinese population using the updated mean of both $HbA1_c$ and FPG, as well as its well-documented cohort with annual clinical outcomes evaluation over a long follow-up. Nevertheless, our study has some limitations. As a part of the ADVANCE trial with complex drug use, residual confounding due to unknown or unmeasured factors can not be ruled out. The major limitation of the study was that the drugs used in the study were conventional type 2 diabetes agents such as insulin, metformin, α-glucosidase inhibitors, and thiazolidinediones. Those drugs in randomized controlled trials not only failed to show consistent beneficial effects on MACE, but also increased hypoglycemic episodes [5, 18, 19, 25, 33]. In our study, there were many patients in intensive glycemic control who belonged to Insufficient glycemic control, which might be associated with the use of insulin and sulfonylurea. Thus, with the different benefit-harm profiles from traditional medication, new antihyperglycemic agents, such as pioglitazone, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 agonist, and sodium-glucose cotransporter-2 inhibitor, which were reported to reduce cardiovascular events and be less prone to hypoglycemic [34–36], were warranted for clinicians to reduce the MACE rate in patients with type 2 diabetes. In addition, the mainly enrolled individuals were elder with long-standing type 2 diabetes and chronic complications. Hence, our findings might not be generalized to younger with recent onset type 2 diabetes. Although our research, to some extent, explained the controversial association between glycemic control and cardiovascular events, elaborated mechanism of cardiovascular complications remained unclear in Insufficient glycemic control. Further studies specifically designed are

warranted to explore cause-and-effect relations and mechanism of cardiovascular events and Insufficient glycemic control.

In conclusion, this prospective cohort study with a long follow-up provided evidence that the cause-specific risk of MACE and hypoglycemic were significantly increased in Insufficient glycemic control, particularly with insulin exposure. In addition, clinical strategies targeting Insufficient glycemic control may provide therapeutic methods to reduce the cardiovascular complications in patients with type 2 diabetes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The study was approved by the local ethics committee and was in accordance with the 1964 Helsinki declaration and its later amendments.

Informed consent All patients provide written informed consent.

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