

# Visit-to-Visit Glycemic Variability is Associated with In-Stent Restenosis in Patients with Type 2 Diabetes after Percutaneous Coronary Intervention

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## Original investigation

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# Abstract

## Background:

Patients with type 2 diabetes are under substantially higher risk of in-stent restenosis (ISR) after coronary stent implantation. We sought to investigate whether visit-to-visit glycemic variability is a potential predictor of ISR in diabetic patients after stent implantation.

## Methods:

Type 2 diabetic patients underwent elective percutaneous coronary intervention were consecutively enrolled and 1-year follow-up coronary angiography was performed. The incidence of ISR and its relationship with visit-to-visit HbA<sub>1c</sub> variability, expressed as coefficient of variation (CV), standard deviation (SD) and variability independent of the mean (VIM), were studied. Multivariable Cox proportional hazards models were constructed to analyze the predictive value of glycemic variability for ISR.

## Results:

From September 2014 to July 2018 in Ruijin Hospital, a total of 420 diabetic patients (688 lesions) after stent implantation were included in the final analysis. During a mean follow-up of  $12.8 \pm 1.3$  months, the incidence of ISR was 8.6%, which was significantly increased in patients with higher CV of HbA<sub>1c</sub> ( $P = 0.001$ ). The mean diameter stenosis (DS), net luminal loss and net luminal gain were  $22.9 \pm 16.8\%$ ,  $0.42 \pm 0.88$  mm and  $1.66 \pm 0.83$  mm, respectively. Greater DS was observed in subjects with higher tertiles of CV of HbA<sub>1c</sub> ( $P < 0.001$ ), and this trend was more prominent in patients with optimal glycemic control (HbA<sub>1c</sub>  $\leq 7\%$ ). In multivariate analysis, HbA<sub>1c</sub> variability was independently associated with incidence of ISR after adjustment for traditional risk factors and mean HbA<sub>1c</sub> (HR: 3.00 [95% CI: 1.14 ~ 7.92] for highest vs. lowest tertile). Inclusion of CV of HbA<sub>1c</sub> led to a better risk stratification accuracy. Assessing glycemic variability by SD or VIM yielded similar findings.

## Conclusions:

This study suggests that visit-to-visit HbA<sub>1c</sub> variability is an independent predictor of incidence of ISR in patients with type 2 diabetes after stent implantation.

## Background

Patients with type 2 diabetes are under substantially increased risk of rapid-progressive and diffuse atherosclerosis[1, 2], myocardial infarction[3] and poor coronary collateralization[4]. After percutaneous coronary intervention (PCI) and deployment of stents, diabetic patients are predisposed to exaggerated neointimal hyperplasia and the development of in-stent restenosis (ISR)[5]. In the era of drug-eluting stents (DES), although restenosis rate has significantly declined, diabetic patients still suffer from higher risk of ISR than non-diabetic patients[6, 7]. The prognosis of diabetic patients after DES implantation is also more dismal than that of non-diabetic patients, with increased rates of cardiac death, myocardial infarction, target lesion failure and target vessel revascularization[8].

Hyperglycemia is a critical contributory factor to the development of restenosis[9], partly attributed to endothelial dysfunction[10], excessive production of reactive oxygen species [11] and formation of advanced glycation end-

production[12]. Pre-procedural optimal glycemic control was shown to be associated with lower rate of stent failure in comparison with suboptimal control patients[9]. A retrospective study analyzing glycemic control based on sequential HbA<sub>1c</sub> measurements from preprocedural to 6-month follow-up also suggested that sustained glycemic control is associated with better clinical outcomes in diabetic patients after PCI[13].

On the other hand, emerging evidence suggests that glycemic variability confers an additional risk to diabetic complications, which is predicted by mean glucose levels alone and may, to some extent, underlie the pathogenesis of micro- and macro-vascular diabetic complications. A retrospective study analyzing data from Diabetes Control and Complications Trial (DCCT) demonstrated that HbA<sub>1c</sub> variability adds to mean HbA<sub>1c</sub> in predicting the development of retinopathy and nephropathy in type 1 diabetes[14]. A prospective study of cohort of type 2 diabetes from Renal Insufficiency and Cardiovascular Events (RIACE) revealed that HbA<sub>1c</sub> variability affects chronic kidney disease more than average HbA<sub>1c</sub>[15]. Recently, two independent groups showed that long-term glycemic variability, either estimated by serial measurements of fasting plasma glucose or by HbA<sub>1c</sub>, was a strong predictor of all-cause mortality[16]. However, the relationship between glycemic variability and ISR is still unclear. Therefore, in the present study, we sought to investigate whether visit-to-visit HbA<sub>1c</sub> variability is a potential predictor of ISR in patients with type 2 diabetes after DES implantation.

## Methods

### Study population

A total of 920 consecutive patients with type 2 diabetes and coronary artery disease (CAD) were screened, who received follow-up coronary angiography ~ 12 months after DES-based PCI of *de novo* lesions in native coronary arteries between September 2014 and July 2018 from the database of Advanced Glycation Endproducts and Development of CAD Program (AGENDA) in Ruijin Hospital, Shanghai. ISR was defined as recurrence of luminal diameter stenosis (DS) of > 50% within the stent or in the 5-mm proximal or distal segments adjacent to the stent at follow-up angiography.

For the purpose of this study and to avoid confounding serum data, patients who had acute coronary syndrome (n = 86) during initial angiography and PCI, familial hypercholesterolemia (n = 5), malignant tumor (n = 13), or renal failure requiring hemodialysis (n = 8) were excluded. Another 36 subjects with no hematological and biochemical indices at admission were further excluded. During follow-up, 5 patients died and 68 patients were lost to follow-up. For calculation of glycemic variability, subjects (n = 279) without at least three HbA<sub>1c</sub> measurements during follow-up ( $\geq 3$  months apart) were also excluded. The remaining 420 subjects constituted the study population (Fig. 1). The diagnosis of type 2 diabetes was made according to the criteria of American Diabetes Association. Hypertension was diagnosed according to seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7). The estimated glomerular filtration rate (eGFR) was computed using the Chronic Kidney Disease Epidemiology Collaboration equation.

This study complies with the Declaration of Helsinki. The study protocol was approved by the local hospital ethics committee, and written informed consent was obtained from all participants.

### Angiographic Analysis

Coronary angiography was performed using standard Judkins technique through radial or femoral approach. For each patient, multiple matched angiographic views were obtained after intracoronary administration of nitrate. Quantitative coronary analysis of all angiographic data before and after procedure and during follow-up was performed (TERRA, GE, USA) by two experienced interventional cardiologists, who were unaware of clinical information of the patients. Using the outer diameter of the contrast-filled catheter as the calibration, the minimal lumen diameter (MLD) and reference diameter (RD) in diastole before intervention was determined from multiple projections by interpolated method. Lesion length was measured as the distance (in millimeters) from the proximal to distal shoulder in the projection with the least amount of foreshortening. The lesion was stented using a normal-to-normal technique, usually including 5-mm-long, angiographically normal segments proximal and distal to the lesion. Net luminal loss was defined as the difference between the MLD immediately after the procedure and that measured during follow-up. Net luminal gain was defined as the difference between the MLD before the procedure and that measured during follow-up. A value of 0 mm was assigned for MLD in the case of total occlusion at baseline. For patients who underwent multi-lesion coronary angioplasty, the most severe restenotic lesion at follow-up was entered into the analysis.

## Glycemic Variability Determinations

HbA<sub>1c</sub> was measured in the baseline and during follow-up period for at least three times in 3-month intervals. Then the mean and variability of HbA<sub>1c</sub> were calculated. Three measures of glycemic variability were employed for the analysis. Intraindividual variability of HbA<sub>1c</sub> was primarily defined as intraindividual coefficient of variation (CV) of HbA<sub>1c</sub> across visits. The alternative variability of HbA<sub>1c</sub> includes: 1) standard deviation (SD) and 2) the variability independent of the mean (VIM), which is calculated by the equation as previously reported[16]:  $VIM = 100 \times SD / \text{mean}^\beta$ , where  $\beta$  is the regression coefficient based on natural logarithm of SD on natural logarithm of mean of the study population. There is no significant correlation between VIM and mean HbA<sub>1c</sub> levels (Pearson's  $r = 0.070$ ,  $P = 0.169$ ).

## Statistical analysis

Continuous variables were presented as median (interquartile range) or mean  $\pm$  SD, and categorical data were summarized as frequencies (percentages). Normal distribution of continuous variables was evaluated by Shapiro-Wilk test. For normally distributed variables, differences in tertiles of glycemic variability and subgroup analysis were performed by one-way or two-way analysis of variance (ANOVA) followed by post hoc t-test with Bonferroni correction. For non-normally distributed continuous variables, differences were analyzed by Mann-Whitney U test or Kruskal-Wallis test. Differences in categorical variables were analyzed by  $\chi^2$  test. The association between measures of glycemic variability and the incidence of ISR was assessed by Cox regression from which hazard ratios (HR) and 95% confidence interval (CI) were calculated. The assumption of proportionality of the Cox model covariates was tested by plotting Schoenfeld residuals. Four models were constructed for each measure of glycemic variability and binary angiographic restenosis ( $DS \geq 50\%$ ) was employed as the dependent variable. In model 1, sex and age were adjusted. In model 2, we further adjusted admission systolic and diastolic blood pressure, body mass index (BMI), non-high-density lipoprotein (HDL) cholesterol and eGFR. In model 3, additional adjustment was performed with the post-PCI RD of target vessel, total stented length and medication use including oral hypoglycemic agent and insulin. In model 4, we further adjusted for the mean level of HbA<sub>1c</sub> during follow-up. Net reclassification improvements (NRI) and integrated discrimination improvements (IDI) were

analyzed to assess the improvement in clinical utility of the prediction model by considering glycemic variability. All statistical analyses were performed using the R statistical package v.3.6.3 (R Project for Statistical Computing, Vienna, Austria). A 2-tailed  $< 0.05$  was considered statistically significant.

## Results

### Baseline characteristics of the study population

A total of 420 subjects with 688 lesions, with a mean follow-up period of  $12.8 \pm 1.3$  months, were included in the analysis. The male-to-female ratio was 74:26 and the mean age was  $64.5 \pm 9.0$  years. Among these subjects, 73.8% were with hypertension and 77.6% of the subjects were with multivessel disease. The mean HbA<sub>1c</sub> during follow-up was  $7.4 \pm 1.2\%$ , and CV, SD, VIM of HbA<sub>1c</sub> during follow-up were 0.061 [IQR 0.038 ~ 0.107], 0.402 [IQR 0.252 ~ 0.839] and 0.209 [IQR 0.127 ~ 0.297], respectively. To analyze the effect of glycemic variability on ISR, we divided the population based on tertiles of CV of HbA<sub>1c</sub> (Table 1). There was no significant difference in age, sex, history of hypertension, admission blood pressure, smoking status and duration of diabetes between the three tertiles. At admission, subjects with the highest tertile of CV of HbA<sub>1c</sub> had higher levels of HbA<sub>1c</sub>, fasting and 2 h postprandial glucose, but lower 2 h postprandial insulin level than those with the lowest tertile. Fasting insulin level was similar between the three groups. Meanwhile, HDL cholesterol was lower, whereas serum creatine and high-sensitivity C-reactive protein were higher in subjects with the highest tertile. Oral hypoglycemic agent (OHA) and insulin were more frequently used in subjects with higher CV of HbA<sub>1c</sub>.

Table 1  
Baseline Characteristics.

<b>Teriles of CV of HbA<sub>1c</sub></b>	<b>T1 (0.005 ~ 0.045)</b>	<b>T2 (0.045 ~ 0.086)</b>	<b>T3 (0.086 ~ 0.397)</b>	<b>P</b>
n	141	139	140	
Demographic characteristics & clinical measures				
Male sex	102 (72.3)	110 (79.1)	97 (69.3)	0.161
Age, years	64.79 ± 8.80	63.99 ± 8.87	64.74 ± 9.33	0.705
BMI, kg/m <sup>2</sup>	25.61 ± 3.47	25.14 ± 2.83	25.59 ± 3.14	0.375
Systolic BP, mmHg	139.34 ± 20.09	137.43 ± 19.68	137.24 ± 23.39	0.657
Diastolic BP, mmHg	78.42 ± 13.57	75.96 ± 11.71	75.41 ± 11.18	0.091
Medical history				
Hypertension	101 (71.6)	105 (75.5)	104 (74.3)	0.749
Duration of diabetes, years	11.8 ± 9.8	8.9 ± 5.7	11.1 ± 8.0	0.078
Current smoker	59 (41.8)	76 (54.7)	60 (42.9)	0.058
Laboratory values				
HbA <sub>1c</sub> , %	7.0 ± 1.6	7.1 ± 1.0	8.4 ± 1.5	< 0.001
Fasting glucose, mmol/L	6.97 ± 2.61	6.85 ± 2.31	9.17 ± 3.86	< 0.001
Postparandial glucose (2 h), mmol/L	12.05 ± 3.87	12.57 ± 4.41	14.98 ± 5.04	< 0.001
Fasting insulin, µU/mL	11.03 (8.26 ~ 16.99)	9.97 (6.66 ~ 16.05)	11.04 (7.39 ~ 18.85)	0.451
Postparandial insulin (2 h), µU/mL	46.53 (35.88 ~ 75.78)	44.50 (26.59 ~ 83.72)	37.61 (24.18 ~ 63.65)	0.009
HOMA-IR	3.28 (2.18 ~ 5.57)	3.18 (1.73 ~ 5.16)	4.62 (2.29 ~ 6.68)	0.005
Triglyceride, mmol/L	1.50 (1.15 ~ 2.35)	1.28 (0.98 ~ 2.04)	1.70 (1.15 ~ 2.13)	0.008
Total cholesterol, mmol/L	4.20 ± 1.17	3.96 ± 1.08	4.10 ± 1.27	0.243
HDL cholesterol, mmol/L	1.06 ± 0.24	1.08 ± 0.28	0.98 ± 0.20	0.002
LDL cholesterol, mmol/L	2.44 ± 0.92	2.30 ± 0.88	2.46 ± 0.93	0.295

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium-channel blocker; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction.

<b>Tertiles of CV of HbA<sub>1c</sub></b>	<b>T1 (0.005 ~ 0.045)</b>	<b>T2 (0.045 ~ 0.086)</b>	<b>T3 (0.086 ~ 0.397)</b>	<b>P</b>
Non-HDL cholesterol, mmol/L	3.14 ± 1.16	2.88 ± 1.04	3.11 ± 1.24	0.119
sdLDL cholesterol, mmol/L	0.56 ± 0.27	0.53 ± 0.16	0.59 ± 0.32	0.509
Alanine aminotransferase, IU/L	26.97 ± 16.97	27.03 ± 17.47	28.76 ± 20.16	0.647
Serum creatinine, µmol/L	80.57 ± 18.76	87.34 ± 40.13	103.68 ± 100.37	0.008
Blood urea nitrogen, mmol/L	5.69 ± 1.74	5.66 ± 2.37	6.29 ± 3.05	0.052
eGFR, mL/min/1.73 m <sup>2</sup>	81.80 ± 16.73	82.19 ± 17.54	80.66 ± 20.46	0.775
hsCRP, mg/L	1.21 (0.55 ~ 4.24)	1.19 (0.42 ~ 4.09)	1.96 (0.91 ~ 8.55)	0.009
<b>Cardiac function</b>				
LVEF, %	63.3 ± 8.6	62.6 ± 8.8	62.2 ± 9.7	0.619
<b>Medication use</b>				
Aspirin	136 (96.5)	129 (92.8)	132 (94.3)	0.402
P2Y <sub>12</sub> inhibitor	129 (91.5)	129 (92.8)	128 (91.4)	0.893
Beta blocker	113 (80.1)	108 (77.7)	100 (71.4)	0.207
ACEI	49 (34.8)	42 (30.2)	56 (40.0)	0.230
ARB	47 (33.3)	65 (46.8)	57 (40.7)	0.072
CCB	45 (31.9)	53 (38.1)	39 (27.9)	0.183
Statin	136 (96.5)	133 (95.7)	136 (97.1)	0.806
OHA	66 (46.8)	57 (41.0)	79 (56.4)	0.034
Biguanides	30 (21.3)	30 (21.6)	42 (30.0)	0.155
Sulfonylureas	22 (15.6)	28 (20.1)	36 (25.7)	0.109
Meglitinides	4 (2.8)	6 (4.3)	8 (5.7)	0.492
Thiazolidinediones	2 (1.4)	2 (1.4)	8 (5.7)	0.046

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium-channel blocker; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction.

<b>Tertiles of CV of HbA<sub>1c</sub></b>	<b>T1</b> <b>(0.005 ~ 0.045)</b>	<b>T2</b> <b>(0.045 ~ 0.086)</b>	<b>T3</b> <b>(0.086 ~ 0.397)</b>	<b>P</b>
Insulin	23 (16.3)	21 (15.1)	46 (32.9)	< 0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium-channel blocker; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction.

## Angiographic Findings

There were no significant differences in the target vessels, stent counts, stented length, angiographic pre-and post-PCI RD, DS and MLD between the three groups (Table 2). In the overall population, follow-up coronary angiography showed the prevalence of binary angiographic ISR, defined as  $\geq 50\%$  DS, was 8.6%. The mean DS was  $22.9 \pm 16.8\%$ , and the mean net luminal loss and net luminal gain was  $0.42 \pm 0.88$  mm and  $1.66 \pm 0.83$  mm, respectively.

Table 2  
Lesion and Procedural Characteristics.

<b>Tertiles of CV of HbA<sub>1c</sub></b>	<b>T1</b> <b>(0.005 ~ 0.045)</b>	<b>T2</b> <b>(0.045 ~ 0.086)</b>	<b>T3</b> <b>(0.086 ~ 0.397)</b>	<b>P</b>
Left mainstem lesion	4 (1.82)	4 (1.73)	8 (3.38)	0.363
Left anterior descending lesion	104 (47.27)	96 (41.56)	92 (38.82)	
Circumflex lesion	65 (29.55)	65 (28.14)	71 (29.96)	
Right coronary lesion	47 (21.36)	66 (28.57)	66 (27.85)	
RD, pre-PCI, mm	$2.96 \pm 0.51$	$2.91 \pm 0.43$	$2.88 \pm 0.44$	0.176
%DS pre-PCI	$81.82 \pm 18.21$	$78.66 \pm 24.75$	$81.52 \pm 24.79$	0.278
MLD pre-PCI, mm	$0.54 \pm 0.55$	$0.62 \pm 0.72$	$0.55 \pm 0.77$	0.385
RD, post-PCI, mm	$3.17 \pm 0.81$	$3.14 \pm 0.94$	$3.13 \pm 0.91$	0.858
%DS post-PCI	$12.89 \pm 13.27$	$14.69 \pm 13.44$	$13.42 \pm 15.06$	0.370
MLD post-PCI, mm	$2.78 \pm 0.87$	$2.70 \pm 0.98$	$2.73 \pm 0.98$	0.696
Stent count	$1.45 \pm 0.64$	$1.53 \pm 0.71$	$1.48 \pm 0.72$	0.409
Stented length, mm	$36.76 \pm 17.88$	$38.24 \pm 20.72$	$37.11 \pm 18.98$	0.692

CV, coefficient of variation; DS, diameter stenosis; MLD, minimal luminal diameter; RD, reference diameter; PCI, percutaneous coronary intervention.

There was a significant increase in DS across tertiles of CV of HbA<sub>1c</sub> (Fig. 2A,  $P = 0.001$ ). Compared with subjects with the lowest tertile, a higher percentage of DS was found in the highest tertile ( $26.63 \pm 19.08$  vs.  $19.29 \pm$

14.47%,  $P < 0.001$ ). Accordingly, net luminal gain ( $P < 0.001$ ) was step-wisely decreased in subjects with higher glycemic variability as grouped by all the three measures (Fig. 2B). Although there was no difference in net luminal loss between tertiles of CV (Fig. 2C;  $P = 0.124$ ), it differed significantly between subjects with different tertiles of SD ( $P = 0.023$ ) or VIM ( $P = 0.014$ ) of HbA<sub>1c</sub> (**Supplementary figure I and II**). In addition, comparison of glycemic variability between subjects with and without ISR also showed significantly higher glycemic variability in ISR patients as analyzed by all the three measures (**Supplementary figure III**).

The rate of binary angiographic restenosis was substantially elevated with increasing tertiles of CV of HbA<sub>1c</sub> (lowest tertile: 5.0%, intermediate tertile: 6.5%, highest tertile: 14.3%;  $P = 0.011$ ). Similar findings were observed when grouping the population based on other measures of glycemic variability. Meanwhile, increased ISR rate was also observed in patients with higher pre-procedural (baseline HbA<sub>1c</sub> > 7%: 10.20% vs. HbA<sub>1c</sub> ≤ 7%: 6.86%,  $P < 0.001$ ) and post-procedural (mean HbA<sub>1c</sub> > 7%: 11.50% vs. HbA<sub>1c</sub> ≤ 7%: 4.52%,  $P < 0.001$ ) HbA<sub>1c</sub> levels.

The impact of glycemic variability on ISR was analyzed across subgroups of sex, age, dichotomized baseline BMI, eGFR and HbA<sub>1c</sub> (Fig. 3). Since the rate of binary ISR was relatively low, DS at follow-up angiography was compared between subgroups. We found DS was increased across tertiles of CV of HbA<sub>1c</sub> in male but not female subjects. A trend towards higher percentage of DS across the tertiles was more prominent in subjects with higher BMI and poorer renal function, and was similar between two age groups. Interestingly, compared with subjects with higher HbA<sub>1c</sub> at the time of PCI (HbA<sub>1c</sub> > 7%), those with lower HbA<sub>1c</sub> (≤ 7%) appeared to have more severe restenosis when having higher CV of HbA<sub>1c</sub>. There was no significant interaction term between tertiles of CV of HbA<sub>1c</sub> and these grouping variables, with the solo exception of basal HbA<sub>1c</sub> level ( $P = 0.010$ ). Dividing subjects by tertiles of SD or VIM yielded similar findings with a little variation (**Supplementary figure IV and V**).

## Multivariate Analysis

Multivariate analysis was performed to analyze the association between the incidence of ISR and different measures of glycemic variability (Table 3). The age- and sex- adjusted HR for ISR in subjects with the highest tertile versus the lowest tertile was 3.26 [95% CI 1.37 ~ 7.76]. After multivariate adjustment (model 3), the highest tertile conferred a higher risk of ISR as compared to the lowest tertile (2.92 [95% CI 1.18 ~ 7.20]). After additional adjustment for mean HbA<sub>1c</sub> during follow-up (model 4), the corresponding HR for ISR in the highest tertile versus the lowest tertile remained significant (3.00 [95% CI 1.14 ~ 7.92]). Similar findings were observed by inclusion of other measures of glycemic variability into these models. In the full adjustment model (model 4), the highest tertile of SD and VIM were significantly associated with 3.69- and 2.82-fold increased risk (all  $P < 0.05$ ) of ISR compared with the lowest tertile, respectively.

Table 3  
Multivariate Analysis.

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
<b>Tertiles of CV</b>		0.004*		0.008*		0.015*		0.023*
T1 (0.005 ~ 0.045)	reference	-	reference	-	reference	-	reference	-
T2 (0.045 ~ 0.086)	1.22 (0.45 ~ 3.27)	0.698	1.03 (0.38 ~ 2.80)	0.958	0.96 (0.34 ~ 2.74)	0.946	0.97 (0.34 ~ 2.75)	0.950
T3 (0.086 ~ 0.397)	3.26 (1.37 ~ 7.76)	0.008	3.06 (1.26 ~ 7.45)	0.014	2.91 (1.18 ~ 7.20)	0.020	3.00 (1.14 ~ 7.92)	0.026
<b>Tertiles of SD</b>		0.002*		0.004*		0.008*		0.013*
T1 (0.058 ~ 0.321)	reference	-	reference	-	reference	-	reference	-
T2 (0.321 ~ 0.665)	1.60 (0.58 ~ 4.40)	0.364	1.27 (0.45 ~ 3.59)	0.648	1.11 (0.39 ~ 3.20)	0.848	1.16 (0.40 ~ 3.37)	0.792
T3 (0.665 ~ 3.169)	3.88 (1.54 ~ 9.77)	0.004	3.53 (1.38 ~ 9.06)	0.009	3.28 (1.25 ~ 8.65)	0.016	3.69 (1.23 ~ 11.05)	0.020
<b>Tertiles of VIM</b>		0.020*		0.042*		0.029*		0.032*
T1 (0.08 ~ 0.156)	reference	-	reference	-	reference	-	reference	-

Model 1, includes adjustment for age and sex; Model 2: additional adjustment for systolic and diastolic blood pressure, body mass index, non-HDL cholesterol and eGFR; Model 3, additional adjustment for the post-PCI reference diameter of target vessel, total stented length and medication use including oral hypoglycemic agent and insulin; Model 4, additional adjustment for mean level of HbA<sub>1c</sub> during follow-up. \* *P* for trend. CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>; HDL, high-density lipoprotein; HR, hazard ratios; PCI, percutaneous coronary intervention; SD, standard deviation; VIM, variability independent of the mean.

	Model 1		Model 2		Model 3		Model 4	
T2 (0.156 ~ 0.265)	1.85 (0.73 ~ 4.70)	0.196	1.78 (0.70 ~ 4.55)	0.230	1.74 (0.66 ~ 4.58)	0.265	1.67 (0.63 ~ 4.43)	0.304
T3 (0.265 ~ 1.262)	2.82 (1.16 ~ 6.85)	0.022	2.53 (1.02 ~ 6.27)	0.045	2.86 (1.11 ~ 7.38)	0.030	2.82 (1.09 ~ 7.29)	0.032
<p>Model 1, includes adjustment for age and sex; Model 2: additional adjustment for systolic and diastolic blood pressure, body mass index, non-HDL cholesterol and eGFR; Model 3, additional adjustment for the post-PCI reference diameter of target vessel, total stented length and medication use including oral hypoglycemic agent and insulin; Model 4, additional adjustment for mean level of HbA<sub>1c</sub> during follow-up. * <i>P</i> for trend. CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>; HDL, high-density lipoprotein; HR, hazard ratios; PCI, percutaneous coronary intervention; SD, standard deviation; VIM, variability independent of the mean.</p>								

Inclusion of glycemic variability led to better risk stratification accuracy. After entering tertiles of CV of HbA<sub>1c</sub> in the model, 29.4% of subjects with ISR were correctly reclassified to a higher risk category and none was reclassified to a lower category. In patients without ISR, 10.8% were correctly reclassified to a lower risk category and 9.4% were reclassified to a higher category (categories of restenosis: <10%, 10 ~ 20%, ≥ 20%). Accordingly, the categorical NRI was 30.76% ([95% CI 14.78 ~ 46.74%], *P* < 0.001), and IDI was 2.81% ([95% CI 0.81 ~ 4.82%], *P* = 0.006).

## Discussion

The major findings of the present study are that patients with type 2 diabetes and high post-procedure HbA<sub>1c</sub> variability tend to have greater neointimal hyperplasia and increased rate of ISR in comparison with those with low HbA<sub>1c</sub> variability. Evaluation of HbA<sub>1c</sub> variability by different measures exhibits consistent findings. Accounting for HbA<sub>1c</sub> variability leads to better risk stratification accuracy of ISR in patients with type 2 diabetes after stent implantation.

## Impact Of Glycemic Level And Stability On Isr

Compelling evidence has demonstrated a substantially increased rate of ISR in diabetic patients after coronary intervention irrespective of the specific treatment modalities including balloon angioplasty, bare-metal stents (BMS) and DES[6, 17, 18]. However, very few studies analyzed the association of glucose level and stability with the rate of ISR. Corpus et al found that optimal glucose control (HbA<sub>1c</sub> ≤ 7%) before catheterization was associated with a ~ 2-fold decrease in rate of target vessel revascularization compared to those with suboptimal glucose control (HbA<sub>1c</sub> > 7%)[9]. A single center prospective study showed that diabetic patients with poor glycemic control at time points both pre- and post-PCI had higher risk of major adverse cardiovascular events (MACE) than non-diabetic patients[13]. In contrast, a retrospective study showed that diabetic patients with good glycemic control (HbA<sub>1c</sub> ≤ 6.9%) only at the time of PCI, but not at follow-up, was associated with significantly lower incidence of MACE compared to those with poor glycemic control (HbA<sub>1c</sub> > 6.9%; 18.4% vs. 26.2%, *P* < 0.05)[19]. These studies

unanimously suggest that glycemic control at the time of PCI is of importance to prevent subsequent restenosis and adverse cardiovascular outcomes, but with conflicting findings on the effect of post-procedural glycemic control. Actually, glycemic control in these studies was defined according to the cut-off level of HbA<sub>1c</sub> at certain time points without consideration of glycemic variability. A substantial proportion of patients in these studies received coronary intervention based on BMS, which does not necessarily respond in the same way as that of DES in the process of restenosis under hyperglycemic conditions.

In the present study, all the enrolled patients received DES-based PCI, which reflects the predominant treatment modality in current clinical practice. In accordance with previous reports, we found diabetic patients with poor glycemic control at the time of PCI (HbA<sub>1c</sub> > 7%) had a 1.49-fold higher rate of ISR than those with good glycemic control (HbA<sub>1c</sub> ≤ 7%). By grouping patients based on mean HbA<sub>1c</sub> during follow-up instead, there was an even higher (2.54-fold) increased rate of ISR in subjects with good versus poor glycemic control. Importantly, we for the first time reported that the rate of ISR and angiographic DS were increased across tertiles of HbA<sub>1c</sub> variability parameters. There was also a trend towards greater net luminal loss and less net luminal gain in patients with higher variability of HbA<sub>1c</sub>. Therefore, previous reports and our findings suggest that both glycemic level and stability are important in the process of ISR after DES implantation in patients with type 2 diabetes. Interestingly, subgroup analysis showed that the impact of glycemic variability on DS was more prominent in subjects with good (HbA<sub>1c</sub> ≤ 7%) as compared to those with poor glycemic control (HbA<sub>1c</sub> > 7%) at the time of PCI, suggesting high glycemic variability is likely to be more influential on ISR in individuals with seemingly controlled glycemic level.

Currently, there is no universally accepted “gold standard” to quantify glycemic variability. In this study, we assessed HbA<sub>1c</sub> variability by three different measures. In addition to SD, CV and VIM were employed to adjust for mean HbA<sub>1c</sub> during follow-up. VIM was calculated based on logarithmic curve fitting to eliminate its correlation with mean HbA<sub>1c</sub>, and CV is relatively simple and more feasible in clinical practice. Analysis of glycemic variability by all of these three measures yielded similar findings. After adjusting for mean HbA<sub>1c</sub> level during follow-up, different measures of HbA<sub>1c</sub> variability remained significantly associated with the incidence of ISR. Inclusion of glycemic variability led to significantly increased risk prediction accuracy compared to the model that only includes conventional risk factors, lesion and procedure characteristics, and mean HbA<sub>1c</sub>. These findings support the notion that glycemic variability is independent of glycemic level in association with ISR. Actually, previous secondary analyses of data from DCCT[14] and Finnish Diabetic Nephropathy (FinnDiane) Study[20] revealed that HbA<sub>1c</sub> variability is an independent predictor of incident microalbuminuria, progression of renal disease and also incident cardiovascular events in patients with type 1 diabetes. A study analyzing 58,832 patients with type 2 diabetes in a large primary care database in England showed that HbA<sub>1c</sub> variability was strongly associated with overall mortality and emergency hospitalization and not explained by mean HbA<sub>1c</sub>[21]. A single center prospective study found that elevated admission glycemic variability appears even more important than admission glucose in predicting 1-year MACE in patients with acute myocardial infarction[22]. Therefore, although it is hard to tease out the relative effect of glycemic variability after accounting for glycemic level in the process of ISR, glycemic variability appears to function independently in various diabetic complications including ISR.

## Possible Mechanisms

It is unclear the specific mechanism by which glycemic variability affects the development of restenosis in diabetic patients. Based on previous clinical and basic science studies, potential mechanisms include: First, glycemic fluctuation was shown to stimulation production of reactive oxygen species and pro-inflammatory cytokines, which are essential players in the pathogenesis of restenosis[23]. Second, glycemic variability is strongly correlated with postprandial  $\beta$ -cell dysfunction in type 2 diabetic patients using OHA. Consistently, we found postprandial insulin level was lower and insulin resistance was higher in patients with the highest tertile of CV than those with the lowest tertile[24]. Given that insulin resistance is an established contributory factor in restenosis, the impact of glycemic variability on ISR may also be secondary to insulin resistance.

## Study Limitation

Our findings should be interpreted in the context of following limitations. First, this study is a retrospective analysis based on prospectively collected data, and all the enrolled patients were from a single center. Second, fluctuations in fasting plasma glucose (FPG) and HbA<sub>1c</sub> appear to function differentially in the process of diabetic complications[14, 25]. Variability of FPG was not analyzed in this study, which may have different features or function in different phases as compared to that of HbA<sub>1c</sub>. Third, this study was not designed to analyze the predictive value of glycemic variability for hard endpoint in diabetic patients underwent PCI. Although we found ISR rate was significantly elevated in patients with high variability of HbA<sub>1c</sub>, whether these patients suffer higher risk of cardiovascular mortality remains inconclusive.

## Conclusions

In conclusion, our findings suggest that greater visit-to-visit HbA<sub>1c</sub> variability is associated with higher incidence of ISR in patients with type 2 diabetes after stent implantation. Variability of HbA<sub>1c</sub> adds to mean level for risk prediction of ISR.

## Abbreviations

BMI: body mass index; BMS: bare-metal stents; CAD: coronary artery disease; CI: confidence interval; CV: coefficient of variation; DES: drug-eluting stent(s); DS: diameter stenosis; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; HDL: high-density lipoprotein; HR: hazard ratios; IDI: integrated discrimination improvements; ISR: in-stent restenosis; MACE: major adverse cardiovascular events; MLD: minimal lumen diameter; NRI: net reclassification improvements; OHA: oral hypoglycemic agent; PCI: percutaneous coronary intervention; RD: reference diameter; SD: standard deviation; VIM: variability independent of the mean.

## Declarations

### Ethics approval and consent to participate

The study was approved by the Hospital Ethics Committee, and written informed consent was obtained from all patients.

### Consent for publication

Not applicable

## Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

CY and XW performed study design, data analysis, data interpretation, and manuscript writing. CY, YS, LL, FD performed data collection. ZY, JH, RZ and WS performed manuscript revision. All authors read and approved the final manuscript.

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None.

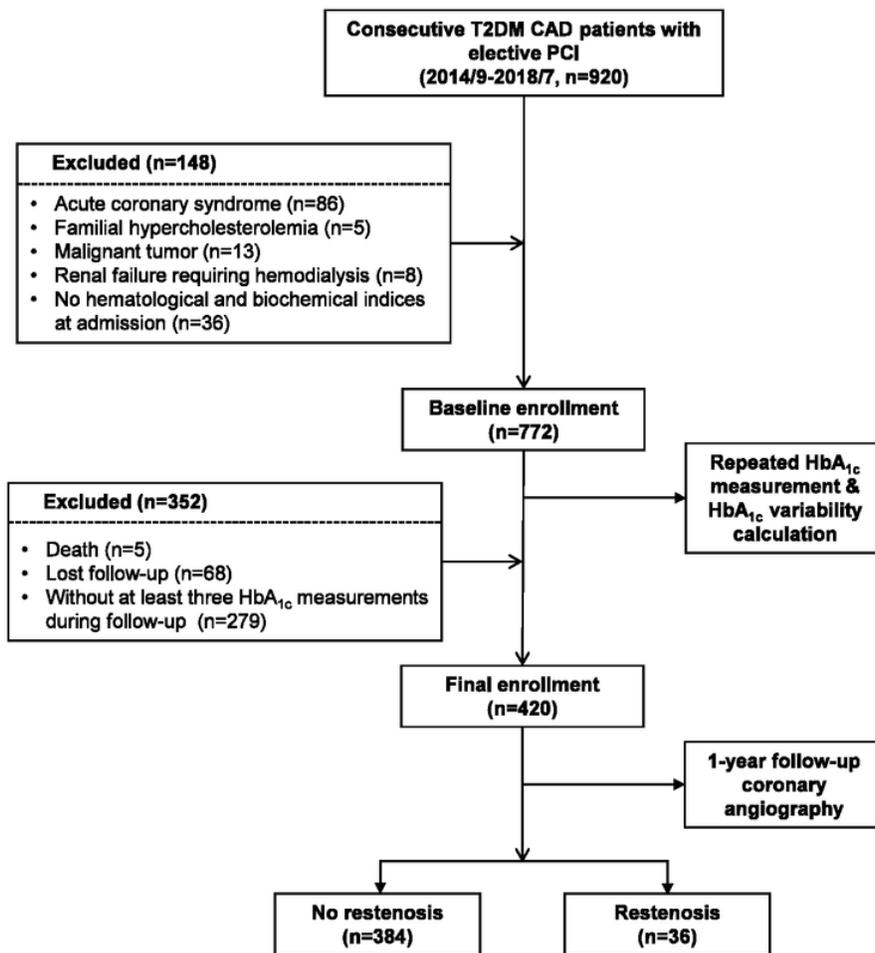
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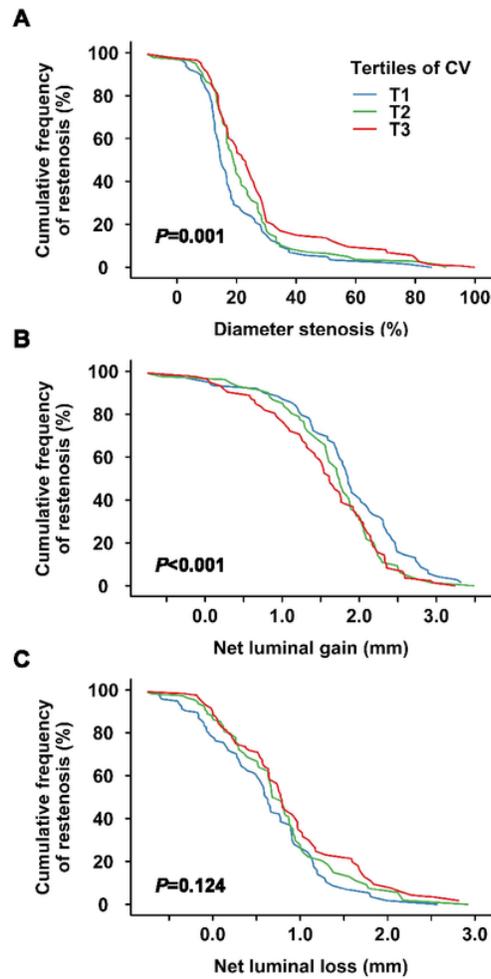
## Figures



**Figure 1. Flow chart of recruitment procedure.** T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; PCI, percutaneous coronary intervention; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>.

## Figure 1

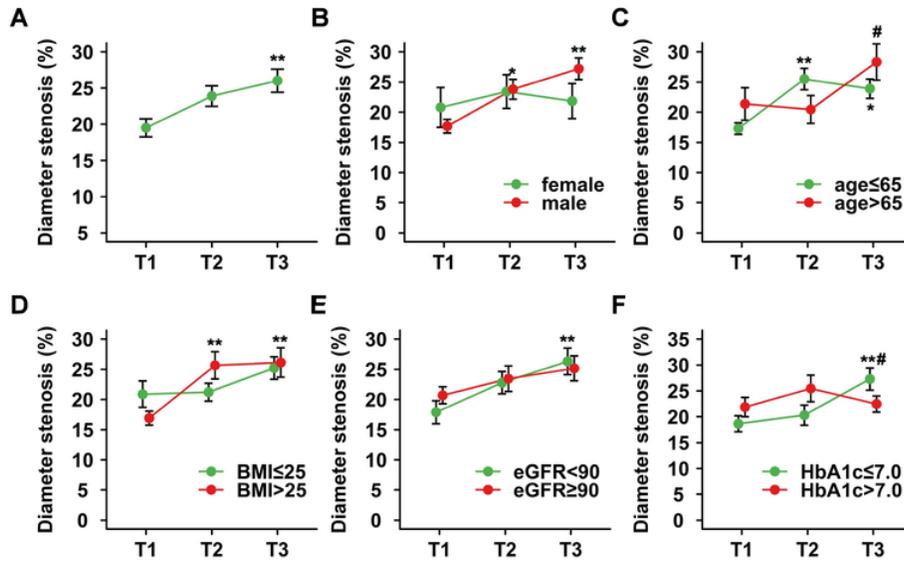
Flow chart of recruitment procedure. T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; PCI, percutaneous coronary intervention; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>.



**Figure 2. Cumulative frequency of restenosis according to tertiles of CV of HbA<sub>1c</sub>.** Cumulative frequency curves for diameter stenosis (A), net luminal gain (B) and net luminal loss (C) at follow-up angiography in subjects with different tertiles of CV of HbA<sub>1c</sub>. CV, coefficient of variation; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>.

## Figure 2

Cumulative frequency of restenosis according to tertiles of CV of HbA<sub>1c</sub>. Cumulative frequency curves for diameter stenosis (A), net luminal gain (B) and net luminal loss (C) at follow-up angiography in subjects with different tertiles of CV of HbA<sub>1c</sub>. CV, coefficient of variation; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>.



**Figure 3. The impact of glycemic variability on ISR across subgroups.** The impact of glycemic variability on ISR was analyzed in the overall population (A) and across subgroups of sex (B), age (C), dichotomized baseline BMI (D), dichotomized baseline eGFR (E) and dichotomized baseline HbA<sub>1c</sub> (F). ISR, in-stent restenosis; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>.

### Figure 3

The impact of glycemic variability on ISR across subgroups. The impact of glycemic variability on ISR was analyzed in the overall population (A) and across subgroups of sex (B), age (C), dichotomized baseline BMI (D), dichotomized baseline eGFR (E) and dichotomized baseline HbA<sub>1c</sub> (F). ISR, in-stent restenosis; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>.

## Supplementary Files

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