Visit-to-Visit HbA1c Variability is Associated with In-Stent Restenosis in Patients with Type 2 Diabetes after Percutaneous Coronary Intervention

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Original investigation

Keywords: HbA1c variability; in-stent restenosis; type 2 diabetes; percutaneous coronary intervention; diameter stenosis.

DOI: https://doi.org/10.21203/rs.3.rs-30051/v2

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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 HbA$_1c$ variability is a potential predictor of ISR in diabetic patients after stent implantation.

**Methods:** We consecutively enrolled type 2 diabetic patients who underwent successful elective percutaneous coronary intervention and performed follow-up coronary angiography after around 12 months. The incidence of ISR and its relationship with visit-to-visit HbA$_1c$ 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 HbA$_1c$ 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±1.3 months, the incidence of ISR was 8.6%, which was significantly increased in patients with higher CV of HbA$_1c$ ($P=0.001$). The mean diameter stenosis (DS), net luminal loss and net luminal gain were 22.9±16.8%, 0.42±0.88 mm and 1.66±0.83 mm, respectively. Greater DS was observed in subjects with higher tertiles of CV of HbA$_1c$ ($P<0.001$), and this trend was more prominent in patients with optimal glycemic control (HbA$_1c$≤7%) in the baseline. In multivariate analysis, HbA$_1c$ variability was independently associated with incidence of ISR after adjustment for traditional risk factors and mean HbA$_1c$ (HR: 3.00 [95% CI:1.14~7.92] for highest vs. lowest tertile). Inclusion of CV of HbA$_1c$ led to a better risk stratification accuracy. Assessing HbA$_1c$ variability by SD or VIM yielded similar findings.

**Conclusions:** This study suggests that visit-to-visit HbA$_1c$ variability is an independent predictor of incidence of ISR in patients with type 2 diabetes after stent implantation.

**Trial registration:** Trials number, NCT02089360; registered on March 17,2014.

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, 6]. 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[7, 8]. 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[9].

Hyperglycemia is a critical contributory factor to the development of restenosis[10], partly attributed to endothelial dysfunction[11], excessive production of reactive oxygen species [12] and formation of advanced glycation end-production[13]. Pre-procedural optimal glycemic control was shown to be associated with lower rate of stent failure in comparison with suboptimal control patients[10]. A retrospective study analyzing glycemic control based on sequential HbA$_1c$ 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[14].

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. In the short-term, glycemic variability assessed by continuous glucose monitoring or serial glucose levels during hospitalization is associated with poor prognosis in patients with coronary artery disease (CAD)[15-18]. In the long-term, a retrospective study analyzing data from Diabetes Control and Complications Trial (DCCT) demonstrated that HbA$_1c$ variability adds to mean HbA$_1c$ in predicting the development of retinopathy and nephropathy in type 1 diabetes[19].
prospective study of cohort of type 2 diabetes from Renal Insufficiency and Cardiovascular Events (RIACE) revealed that HbA1c variability affects chronic kidney disease more than average HbA1c[20]. Recent studies further showed that long-term glycemic variability, either estimated by serial measurements of fasting plasma glucose or by HbA1c, is a strong predictor of all-cause mortality and cardiovascular events[21-23]. However, the relationship between glycemic variability and ISR is still unclear. Therefore, in the present study, we sought to investigate whether visit-to-visit HbA1c 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 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. Patients were referred to coronary angiography for the evaluation of established or suspected CAD due to typical chest pain, positive exercise stress test, or positive myocardial perfusion scan. 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. All these patients received a quarterly clinical evaluation, routine analyses and HbA1c measurements. Follow-up coronary angiography was performed after around 12 months and all the enrolled patients were reminded by telephone in advance. During follow-up, 5 patients died and 68 patients were lost to follow-up. For calculation of HbA1c variability, subjects (n=279) without at least three HbA1c measurements during follow-up (≥3 months apart) were also excluded. The remaining 420 subjects constituted the study population (Figure 1). The diagnosis of type 2 diabetes was made according to the criteria of American Diabetes Association (symptoms of diabetes with casual plasma glucose concentration ≥ 200 mg/dL [11.1 mmol/L] or fasting plasma glucose ≥ 126 mg/dL [7.0 mmol/L], 2 h postprandial glucose ≥ 200 mg/dL [11.1 mmol/L] during an oral glucose tolerance test, and currently or previously treated with insulin and/or oral hypoglycemic agents)[24]. Hypertension was diagnosed according to seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7).

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.

Baseline clinical and biochemical assessments

Blood samples were obtained at the day of angiography in all patients after an overnight fasting and collected in a quiet, air-conditioned room after at least 20 min supine rest. Serum glucose, insulin, blood urea nitrogen, creatinine, uric acid, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, apolipoprotein A-I and apolipoprotein B were assessed (HITACHI 912 Analyzer, Roche Diagnostics, Germany). The estimated glomerular filtration rate (eGFR) was computed using the Chronic Kidney Disease Epidemiology Collaboration equation[25]. Blood HbA1c concentration was measured using ion-exchange high performance liquid chromatography with Bio-rad Variant Hemoglobin Testing System (Bio-Rad Laboratories, USA). Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) was determined using a commercially available electrochemiluminescence immunoassay kit (Roche Diagnostics). Serum levels of high sensitive C-reactive protein (hsCRP) were determined by ELISA (Biocheck Laboratories, Toledo, OH, USA). The detailed information about medical history and lifestyles including smoking status was obtained using a standard questionnaire by trained physicians. Body mass index (BMI) was calculated using the formula of weight/height^2 (kilograms per square meter)[26]. Blood pressure was measured on the non-dominant arm in a seated position after a 10-min rest, using an electronic blood pressure monitor.
(OMRON Model HEM-752 FUZZY’ Omron Co., Dalian, China). Three measurements were taken at 1-min intervals, and the average was used for analysis.

**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 (QCA) of all angiographic data before and after procedure and during follow-up was performed (TERRA, GE, USA) by two experienced interventional cardiologists (FH Ding and XQ Wang), 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.

**HbA1c variability determinations**

HbA1c was measured in the baseline and during follow-up period for at least three times in 3-month interval. Then the mean and variability of HbA1c were calculated. Three measures of HbA1c variability were employed for the analysis. Intraindividual variability of HbA1c was primarily defined as intraindividual coefficient of variation (CV) of HbA1c across visits. The alternative variability of HbA1c includes: 1) standard deviation (SD) and 2) the variability independent of the mean (VIM), which is calculated by the equation as previously reported[27]: \( \text{VIM} = 100 \times \frac{\text{SD}}{\text{mean}} \), where \( \beta \) is the regression coefficient based on natural logarithm of SD on natural logarithm of mean of the study population.

**Statistical analysis**

Continuous variables were presented as median (interquartile range) or mean ± 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 HbA1c 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 HbA1c 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. Five models were constructed for each measure of HbA1c variability and binary angiographic restenosis (DS≥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, BMI, non-HDL-C 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 (OHA) and insulin. In model 4 and 5, we further adjusted for baseline HbA1c and the mean HbA1c level during follow-up, respectively. Net reclassification improvements (NRI) and integrated discrimination improvements (IDI) were analyzed to assess the improvement in clinical utility of the prediction model by considering HbA1c 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±1.3 months, were included in the analysis. The male-to-female ratio was 74:26 and the mean age was 64.5±9.0 years. Among these subjects, 73.8% were with hypertension and 77.6% of the subjects were with multivessel disease. The mean HbA1c during follow-up was 7.4±1.2%, and CV, SD, VIM of HbA1c 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. CV (Pearson's r = 0.325, P<0.001) and SD (Pearson's r = 0.445, P<0.001) were correlated to the mean HbA1c while there was no significant correlation between VIM and the mean HbA1c level (Pearson's r=0.070, P=0.169). To analyze the effect of HbA1c variability on ISR, we divided the population based on tertiles of CV of HbA1c (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 HbA1c had higher levels of HbA1c, 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-C was lower, whereas serum creatine and hsCRP were higher in subjects with the highest tertile. OHA and insulin were more frequently used in subjects with higher CV of HbA1c.

Table 1. Baseline Characteristics.
| 9tiles of CV of HbA1c | T1 | T2 | T3 | P |
|----------------------|----|----|----|---|
| n                    | 141| 139| 140|   |

**graphic characteristics & clinical measures**

| sex       | 102 (72.3) | 110 (79.1) | 97 (69.3) | 0.161 |
| years     | 64.79±8.80  | 63.99±8.87  | 64.74±9.33 | 0.705 |
| kg/m²     | 25.61±3.47  | 25.14±2.83  | 25.59±3.14 | 0.375 |
| sbp, mmHg | 139.34±20.09 | 137.43±19.68 | 137.24±23.39 | 0.657 |
| dbp, mmHg | 78.42±13.57 | 75.96±11.71 | 75.41±11.18 | 0.091 |

**al 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 |

**atory values**

| HbA1c, % | 7.0±1.6 | 7.1±1.0 | 8.4±1.5 | <0.001 |
| glucose, mmol/L | 6.97±2.61 | 6.85±2.31 | 9.17±3.86 | <0.001 |
| parandial glucose (2h), mmol/L | 12.05±3.87 | 12.57±4.41 | 14.98±5.04 | <0.001 |
| insulin, µU/mL | 11.03 (8.26~16.99) | 9.97 (6.66~16.05) | 11.04 (7.39~18.85) | 0.451 |
| parandial 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 |
| IA-IR | 3.28 (2.18~5.57) | 3.18 (1.73~5.16) | 4.62 (2.29~6.68) | 0.005 |
| globulin, g/L | 133.99±16.10 | 131.82±17.46 | 131.66±20.73 | 0.489 |
| aspartate aminotransferase, µmol/L | 1.50 (1.15~2.35) | 1.28 (0.98~2.04) | 1.70 (1.15~2.13) | 0.008 |
| l cholesterol, mmol/L | 4.20±1.17 | 3.96±1.08 | 4.10±1.27 | 0.243 |
| cholesterol, mmol/L | 1.06±0.24 | 1.08±0.28 | 0.98±0.20 | 0.002 |
| cholesterol, mmol/L | 2.44±0.92 | 2.30±0.88 | 2.46±0.93 | 0.295 |
| HDL cholesterol, mmol/L | 3.14±1.16 | 2.88±1.04 | 3.11±1.24 | 0.119 |
| reat creatinine, µmol/L | 26.97±16.97 | 27.03±17.47 | 28.76±20.16 | 0.647 |
| urea nitrogen, µmol/L | 80.57±18.76 | 87.34±40.13 | 103.68±100.37 | 0.008 |
| urea nitrogen, µmol/L | 5.69±1.74 | 5.66±2.37 | 6.29±3.05 | 0.052 |
| creatinine, µmol/L | 81.80±16.73 | 82.19±17.54 | 80.66±20.46 | 0.775 |
| fP, µmol/L | 1.21 (0.55~4.24) | 1.19 (0.42~4.09) | 1.96 (0.91~8.55) | 0.009 |

**al function**

| F, % | 63.3±8.6 | 62.6±8.8 | 62.2±9.7 | 0.619 |
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 ≥50% DS, was 8.6%. The mean DS was 22.9±16.8%, and the mean net luminal loss and net luminal gain was 0.42±0.88 mm and 1.66±0.83 mm, respectively.

Table 2. Lesion and Procedural Characteristics.
| Tertiles of CV of HbA1c | T1       | T2       | T3       | P       |
|-------------------------|----------|----------|----------|---------|
|                         | (0.005~0.045) | (0.045~0.086) | (0.086~0.397) |         |

| 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) |         |
| Multivessel disease     | 109 (77.3) | 103 (74.1) | 114 (81.4) | 0.338   |
| RD, pre-PCI, mm         | 2.96±0.51  | 2.91±0.43 | 2.88±0.44 | 0.176   |
| %DS pre-PCI             | 81.82±18.21 | 78.66±24.75 | 81.52±24.79 | 0.278   |
| MLD pre-PCI, mm         | 0.54±0.55  | 0.62±0.72 | 0.55±0.77 | 0.385   |
| RD, post-PCI, mm        | 3.17±0.81  | 3.14±0.94 | 3.13±0.91 | 0.858   |
| %DS post-PCI            | 12.89±13.27 | 14.69±13.44 | 13.42±15.06 | 0.370   |
| MLD post-PCI, mm        | 2.78±0.87  | 2.70±0.98 | 2.73±0.98 | 0.696   |
| Stent count             | 1.45±0.64  | 1.53±0.71 | 1.48±0.72 | 0.409   |
| Stented length, mm      | 36.76±17.88 | 38.24±20.72 | 37.11±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 HbA1c (Figure 2A, *P*=0.001). Compared with subjects with the lowest tertile, a higher percentage of DS was found in the highest tertile (26.63±19.08 vs. 19.29±14.47%, *P*<0.001). Accordingly, net luminal gain (*P*<0.001) was step-wisely decreased in subjects with higher HbA1c variability as grouped by all the three measures (Figure 2B). Although there was no difference in net luminal loss between tertiles of CV (Figure 2C, *P*=0.124), it differed significantly between subjects with different tertiles of SD (*P*=0.023) or VIM (*P*=0.014) of HbA1c (Supplementary figure I and II). In addition, comparison of HbA1c variability between subjects with and without ISR also showed significantly higher HbA1c 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 HbA1c (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 HbA1c variability. Meanwhile, increased ISR rate was also observed in patients with higher pre-procedural (baseline HbA1c>7%; 10.20% vs. HbA1c≤7%; 6.86%, *P*=0.001) and post-procedural (mean HbA1c>7%; 11.50% vs. HbA1c≤7%; 4.52%, *P*=0.001) HbA1c levels.

The impact of HbA1c variability on ISR was analyzed across subgroups of sex, age, dichotomized baseline BMI, eGFR and HbA1c (Figure 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 HbA1c 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 HbA1c at the time of PCI (HbA1c>7%), those with lower HbA1c (≤7%) appeared to have more severe restenosis when having higher CV of HbA1c. There was no significant interaction term between tertiles of CV of HbA1c and these grouping variables, with the sole exception of basal HbA1c 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 HbA1c 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 baseline HbA1c (model 4) or the mean HbA1c during
follow-up (model 5), the corresponding HR for ISR in the highest tertile versus the lowest tertile remained significant (model 4: 3.28 [95% CI 1.25~8.55]; model 5: 3.00 [95% CI 1.14~7.92]). Similar findings were observed by inclusion of other measures of HbA1c variability into these models. In the full adjustment model (model 5), 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.**

| Tertiles | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
|----------|---------|---------|---------|---------|---------|
|          | HR (95% CI) | $P$ | HR (95% CI) | $P$ | HR (95% CI) | $P$ | HR (95% CI) | $P$ | HR (95% CI) | $P$ |
| CV       | 0.004* | - | 0.008* | - | 0.015* | - | 0.013* | - | 0.023* | - |
| T1       | 1.22 | (0.45~3.27) | 0.698 | (0.38~2.79) | 0.958 | (0.34~2.74) | 0.946 | (0.35~2.86) | 1.00 | (0.34~2.75) | 0.97 | (0.34~2.75) |
| T2       | 3.26 | (1.37~7.76) | 0.008 | (1.26~7.45) | 0.014 | (1.18~7.20) | 0.020 | (1.25~8.55) | 3.28 | (1.14~7.92) | 3.00 | (1.14~7.92) |
| T3       | 3.88 | (1.54~9.77) | 0.004 | (1.38~9.06) | 0.009 | (1.25~8.65) | 3.28 | (1.39~11.61) | 4.02 | (1.23~11.05) | 3.00 | (1.23~11.05) |
| SD       | 0.002* | - | 0.004* | - | 0.008* | - | 0.006* | - | 0.013* | - |
| T1       | 1.60 | (0.58~4.40) | 0.364 | (0.45~3.59) | 1.27 | (0.38~3.20) | 0.648 | (0.41~3.55) | 1.11 | (0.40~3.37) | 0.848 | (0.40~3.37) |
| T2       | 3.88 | (1.54~9.77) | 0.004 | (1.38~9.06) | 3.53 | (1.25~8.65) | 0.009 | (1.39~11.61) | 3.28 | (1.23~11.05) | 3.28 | (1.23~11.05) |
| T3       | 2.82 | (1.16~6.85) | 0.022 | (1.02~6.26) | 2.53 | (1.11~7.38) | 0.045 | (1.10~7.42) | 2.86 | (1.09~7.29) | 2.86 | (1.09~7.29) |
| VIM      | 0.020* | - | 0.042* | - | 0.029* | - | 0.030* | - | 0.032* | - |
| T1       | 1.85 | (0.73~4.70) | 0.196 | (0.69~4.54) | 1.78 | (0.66~4.58) | 0.230 | (0.66~4.60) | 1.74 | (0.63~4.43) | 0.265 | (0.63~4.43) |
| T2       | 2.82 | (1.16~6.85) | 0.022 | (1.02~6.26) | 2.53 | (1.11~7.38) | 0.045 | (1.10~7.42) | 2.86 | (1.09~7.29) | 2.86 | (1.09~7.29) |

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, model 3 with additional adjustment for baseline HbA1c; Model 5, model 3 with additional adjustment for the mean HbA1c during follow-up. * $P$ for trend. CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; HR, hazard ratios; PCI, percutaneous coronary intervention; SD, standard deviation; VIM, variability independent of the mean.
Inclusion of HbA1c variability led to better risk stratification accuracy. After entering tertiles of CV of HbA1c 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 HbA1c variability tend to have greater neointimal hyperplasia and increased rate of ISR in comparison with those with low HbA1c variability. Evaluation of HbA1c variability by different measures exhibits consistent findings. Accounting for HbA1c 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**

Diabetic patients with obstructive and non-obstructive coronary stenosis generally had poor clinical outcomes, owning to diffuse distribution of atherosclerotic lesions, unstable plaques, microvascular dysfunction and higher incidence of in-stent restenosis (ISR)[28, 29]. 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[7, 30, 31]. 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 (HbA1c≤7%) before catheterization was associated with a ~2-fold decrease in rate of target vessel revascularization compared to those with suboptimal glucose control (HbA1c>7%)[10]. 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[14]. In contrast, a retrospective study showed that diabetic patients with good glycemic control (HbA1c≤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 (HbA1c>6.9%; 18.4% vs. 26.2%, P<0.05)[32]. 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 HbA1c 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 (HbA1c>7%) had a 1.49-fold higher rate of ISR than those with good glycemic control (HbA1c≤7%). By grouping patients based on mean HbA1c during follow-up instead, there was an even higher (2.54-fold) increased rate of ISR in subjects with poor versus good glycemic control. Importantly, we for the first time reported that the rate of ISR and angiographic DS were increased across tertiles of HbA1c variability parameters. There was also a trend towards greater net luminal loss and less net luminal gain in patients with higher variability of HbA1c. 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 HbA1c variability on DS was more prominent in subjects with poor (HbA1c≤7%) as compared to those with poor glycemic control (HbA1c>7%) at the time of PCI. This might be due to the reason that HbA1c reflects both fasting and postprandial glucose levels. In well-controlled diabetic patients (HbA1c<7.3%), postprandial glucose level is a predominant contributor to HbA1c, and this contribution decreases progressively with increasing level of HbA1c[33]. Hence, variability of postprandial glucose might be more important than fasting glucose in the development of ISR and this hypothesis awaits further investigation.

Currently, there is no universally accepted "gold standard" to quantify glycemic variability. In this study, we assessed HbA1c variability by three different measures. In addition to SD, CV and VIM were employed to adjust for mean HbA1c during follow-up.
VIM was calculated based on logarithmic curve fitting to eliminate its correlation with mean HbA1c, and CV is relatively simple and more feasible in clinical practice. Analysis of HbA1c variability by all of these three measures yielded similar findings. After adjusting for mean HbA1c level during follow-up, different measures of HbA1c variability remained significantly associated with the incidence of ISR. Inclusion of HbA1c variability led to significantly increased risk prediction accuracy compared to the model that only includes conventional risk factors, lesion and procedure characteristics, and mean HbA1c. These findings support the notion that HbA1c variability is independent of glycemic level in association with ISR. Actually, previous secondary analyses of data from DCCT[19] and Finnish Diabetic Nephropathy (FinnDiane) Study[34] revealed that HbA1c 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 HbA1c variability was strongly associated with overall mortality and emergency hospitalization and not explained by mean HbA1c[35]. 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[36]. Therefore, although it is hard to tease out the relative effect of HbA1c variability after accounting for HbA1c level in the process of ISR, HbA1c variability appears to function independently in various diabetic complications including ISR.

Possible mechanisms

It is unclear the specific mechanism by which HbA1c variability affects the development of restenosis in diabetic patients. Based on previous clinical and basic science studies, potential mechanisms include: First, hyperglycemia and glycemic fluctuation directly and indirectly stimulate the production of reactive oxygen species, inflammatory and metabolic cytokines, which are essential players in the development of adverse myocardial and vascular remodeling, and worse clinical outcomes both in patients with or without diagnosed diabetes[37-41]. Second, glycemic variability is strongly correlated with postprandial β-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[42]. Given that insulin resistance is an established contributory factor in restenosis, the impact of HbA1c variability on ISR may also be secondary to insulin resistance. Third, dysregulated glucose homeostasis is associated with endothelial dysfunction and higher risk of cardiovascular events[43, 44]. Mounting evidence suggests that endothelial dysfunction is an important predictor of restenosis after stent implantation[45, 46]. Hence, endothelial dysfunction and delayed reendothelialization may serve as an important underlying mechanism in the development of ISR in conditions of high glycemic variability.

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 HbA1c appear to function differentially in the process of diabetic complications[19, 47]. Variability of FPG was not analyzed in this study, which may have different features or function in different phases as compared to that of HbA1c. Moreover, conditions that affect erythrocyte turnover may also affect HbA1c level. Third, coronary lesions and restenosis were analyzed by QCA. Intravascular imaging techniques such as intravascular ultrasound would provide more accurate assessments. Fourth, this study was not designed to analyze the predictive value of HbA1c variability for hard endpoint in diabetic patients underwent PCI. Although we found ISR rate was significantly elevated in patients with high variability of HbA1c, whether these patients suffer higher risk of cardiovascular mortality remains inconclusive.

Conclusions

In conclusion, our findings suggest that greater visit-to-visit HbA1c variability is associated with higher incidence of ISR in patients with type 2 diabetes after stent implantation. Variability of HbA1c adds to mean level for risk prediction of ISR. Measures targeting both glycemic level and stability may provide favorable effects to reduce the incidence of ISR and improve clinical outcomes in patients with type 2 diabetes after PCI.
Abbreviations
BMI: body mass index; BMS: bare-metal stents; BSA: body surface area; 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-C: high-density lipoprotein cholesterol; HR: hazard ratios; hs-CRP: high sensitive C-reactive protein; IDI: integrated discrimination improvements; ISR: in-stent restenosis; LDL-C: low-density lipoprotein cholesterol; MACE: major adverse cardiovascular events; MLD: minimal lumen diameter; NRI: net reclassification improvements; NT-proBNP: N-terminal pro-B-type natriuretic peptide; OHA: oral hypoglycemic agent; PCI: percutaneous coronary intervention; QCA: quantitative coronary analysis; 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.

Funding
This study was supported by National Natural Science Foundation of China (Grant No. 81670451, 81470469, 81770430, 81870179), Shanghai Rising-Star Program (Grant No. 17QA1403000), Shanghai Municipal Commission of Health and Family Planning (Grant No. 2018YQ17, 2019Y0042), Ruijin Youth Training Program (Grant No. 2019QNPY01033), Shanghai Science and Technology Commission Natural Fund Project (17ZR1417200), Talent Young Investigators of Shanghai Jiao Tong University School of Medicine (17XJ11009), Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support (20181801).

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

Acknowledgements
None.

References
1. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB: Clinical Update: Cardiovascular Disease in Diabetes Mellitus: Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus - Mechanisms, Management, andClinical Considerations. Circulation 2016, 133(24):2459-2502.
2. Natali A, Vichi S, Landi R, Severi S, L'Abbate A, Ferrannini E: Coronary atherosclerosis in Type II diabetes: angiographic findings and clinical outcome. Diabetologia 2000, 43(5):632-641.
3. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998, 339(4):229-234.

4. Shen Y, Ding FH, Dai Y, Wang XQ, Zhang RY, Lu L, Shen WF. Reduced coronary collateralization in type 2 diabetic patients with chronic total occlusion. *Cardiovasc Diabetol* 2018, 17(1):26.

5. West NE, Ruygrok PN, Disco CM, Webster MW, Lindeboom WK, O'Neill WW, Mercado NF, Serruys PW. Clinical and angiographic predictors of restenosis after stent deployment in diabetic patients. *Circulation* 2004, 109(7):867-873.

6. Qin Z, Zhou K, Li YP, Wang JL, Cheng WJ, Hu CP, Shi C, He H, Zhou YJ. Remnant lipoproteins play an important role in instent restenosis in type 2 diabetes undergoing percutaneous coronary intervention: a single-centre observational cohort study. *Cardiovasc Diabetol* 2019, 18(1):11.

7. Fröbert O, Lagerqvist B, Carlsson J, Lindbäck J, Stenestrand U, James SK. Differences in Restenosis Rate With Different Drug-Eluting Stents in Patients With and Without Diabetes Mellitus. *A Report From the SCAAR (Swedish Angiography and Angioplasty Registry)* 2009, 53(18):1660-1667.

8. Gilbert J, Raboud J, Zinman B. Meta-analysis of the effect of diabetes on restenosis rates among patients receiving coronary angioplasty stenting. *Diabetes Care* 2004, 27(4):990-994.

9. Mathew V, Gersh BJ, Williams BA, Laskey WK, Willerson JT, Tilbury RT, Davis BR, Holmes DR, Jr. Outcomes in patients with diabetes mellitus undergoing percutaneous coronary intervention in the current era: a report from the Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial. *Circulation* 2004, 109(4):476-480.

10. Corpus RA, George PB, House JA, Dixon SR, Ajluni SC, Devlin WH, Timmis GC, Balasubramaniam M, O'Neill WW. Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated type II diabetic patients undergoing elective percutaneous coronary intervention. *J Am Coll Cardiol* 2004, 43(1):8-14.

11. Hink U, Li H, Mollnau H, Oelze M, Matheis E, Hartmann M, Skatchkov M, Thiass F, Stahl RA, Warnholtz A et al. Mechanisms underlying endothelial dysfunction in diabetes mellitus. *Circ Res* 2001, 88(2):E14-22.

12. Inoguchi T, Li P, Umeda F, Kakimoto M, Imamura M, Aoki T, Etoh T, Hashimoto T, Naruse M et al. High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C-dependent activation of NAD(P)H oxidase in cultured vascular cells. *Diabetes* 2000, 49(11):1939-1945.

13. Basta G, Schmidt AM, De Caterina R. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. *Cardiovasc Res* 2004, 63(4):582-592.

14. Kassaian SE, Goodarzynejad H, Boroumand MA, Salarifar M, Masoudkabir F, Mohajeri-Tehrani MR, Pourhoseini H, Sadeghian S, Ramezanpour N, Alidoosti M et al. Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting. *Cardiovasc Diabetol* 2012, 11:82.

15. Pu Z, Lai L, Yang X, Wang Y, Dong P, Wang D, Xie Y, Han Z. Acute glycemic variability on admission predicts the prognosis in hospitalized patients with coronary artery disease: a meta-analysis. *Endocrine* 2020, 67(3):526-534.

16. Gerbaut E, Darier R, Montaudon M, Beauvieux MC, Coffin-Boutreux C, Coste P, Douard H, Ouattara A, Catargi B. Glycemic Variability Is a Powerful Independent Predictive Factor of Midterm Major Adverse Cardiac Events in Patients With Diabetes With Acute Coronary Syndrome. *Diabetes Care* 2019, 42(4):674-681.

17. Takahashi H, Iwashashi N, Kirigaya J, Kataoka S, Minamimoto Y, Gohbara M, Abe T, Okada K, Matsuzawa Y, Konishi M et al. Glycemic variability determined with a continuous glucose monitoring system can predict prognosis after acute coronary syndrome. *Cardiovasc Diabetol* 2018, 17(1):116.

18. Besch G, Pili-Floury S, Morel C, Gilard M, Flicoteaux G, Salomon du Mont L, Perrotti A, Meneveau N, Chocron S, Schiele F et al. Impact of post-procedural glycemic variability on cardiovascular morbidity and mortality after transcatheter aortic valve implantation: a post hoc cohort analysis. *Cardiovasc Diabetol* 2019, 18(1):27.

19. Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. *Diabetes Care* 2008, 31(11):2198-2202.

20. Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, Morano S, Cavalot F, Lamacchia O, Laviola L. HbA1c variability as an independent correlate of nephropathy, but not retinopathy, in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicenter study. *Diabetes care* 2013, 36(8):2301-2310.
21. Hirakawa Y, Arima H, Zoungas S, Ninomiya T, Cooper M, Hamet P, Mancia G, Poulter N, Harrap S, Woodward M et al: Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: the ADVANCE trial. Diabetes Care 2014, 37(8):2359-2365.

22. Orsi E, Solini A, Bonora E, Fondelli C, Trevisan R, Vedovato M, Cavalot F, Gruden G, Morano S, Nicolucci A et al: Haemoglobin A1c variability is a strong, independent predictor of all-cause mortality in patients with type 2 diabetes. Diabetes Obes Metab 2018, 20(8):1885-1893.

23. Xia J, Xu J, Hu S, Hao H, Yin C, Xu D: Impact of glycemic variability on the occurrence of periprocedural myocardial infarction and major adverse cardiovascular events (MACE) after coronary intervention in patients with stable angina pectoris at 6 months follow-up. Clin Chim Acta 2017, 471:196-200.

24. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998, 15(7):539-553.

25. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T et al: A new equation to estimate glomerular filtration rate. Ann Intern Med 2009, 150(9):604-612.

26. Yang CD, Shen Y, Lu L, Ding FH, Yang ZK, Zhang RY, Shen WF, Jin W, Wang XQ: Insulin resistance and dysglycemia are associated with left ventricular remodeling after myocardial infarction in non-diabetic patients. Cardiovasc Diabetol 2019, 18(1):100.

27. Echouffo-Tcheugui JB, Zhao S, Brock G, Matsouaka RA, Kline D, Joseph JJ: Visit-to-Visit Glycemic Variability and Risks of Cardiovascular Events and All-Cause Mortality: The ALLHAT Study. Diabetes Care 2019, 42(3):486-493.

28. Marfella R, Sardu C, Calabrò P, Siniscalchi M, Minicucci F, Signoriello G, Balestrieri ML, Mauro C, Rizzo MR, Paolisso G et al: Non-ST-elevation myocardial infarction outcomes in patients with type 2 diabetes with non-obstructive coronary artery stenosis: Effects of incretin treatment. Diabetes Obes Metab 2018, 20(3):723-729.

29. Marfella R, Sardu C, Balestrieri ML, Siniscalchi M, Minicucci F, Signoriello G, Calabrò P, Mauro C, Pieretti G, Coppola A et al: Effects of incretin treatment on cardiovascular outcomes in diabetic STEMI-patients with culprit obstructive and multivessel non obstructive-coronary-stenosis. Diabetology & metabolic syndrome 2018, 10:1.

30. Elezi S, Kastrati A, Pache J, Wehinger A, Hadamitzky M, Dirschinger J, Neumann FJ, Schomig A: Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. J Am Coll Cardiol 1998, 32(7):1866-1873.

31. Gilbert J, Raboud J, Zinman B: Meta-analysis of the effect of diabetes on restenosis rates among patients receiving coronary angioplasty stenting. Diabetes Care 2004, 27(4):990-994.

32. Ike A, Nishikawa H, Shirai K, Mori K, Kuwano T, Fukuda Y, Takamiya Y, Yanagi D, Kubota K, Tsuchiya Y et al: Impact of glycemic control on the clinical outcome in diabetic patients with percutaneous coronary intervention—from the FU-registry. Circ J 2011, 75(4):791-799.

33. Monnier L, Colette C: Contributions of fasting and postprandial glucose to hemoglobin A1c. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2006, 12 Suppl 1:42-46.

34. Wadén J, Forsblom C, Thorn LM, Gordin D, Saraheimo M, Groop P-H: A1C variability predicts incident cardiovascular events, microalbuminuria, and overt diabetic nephropathy in patients with type 1 diabetes. Diabetes 2009, 58(11):2649-2655.

35. Critchley JA, Carey IM, Harris T, DeWilde S, Cook DG: Variability in Glycated Hemoglobin and Risk of Poor Outcomes Among People With Type 2 Diabetes in a Large Primary Care Cohort Study. Diabetes Care 2019, 42(12):2237-2246.

36. Su G, Mi SH, Tao H, Li Z, YangHX, Zheng H, Zhou Y, Tian L: Impact of admission glycemic variability, glucose, and glycosylated hemoglobin on major adverse cardiac events after acute myocardial infarction. Diabetes Care 2013, 36(4):1026-1032.

37. Sun J, Xu Y, Dai Z, Sun Y: Intermittent high glucose stimulate MCP-1, IL-18, and PAI-1, but inhibit adiponectin expression and secretion in adipocytes dependent of ROS. Cell Biochem Biophys 2009, 55(3):173-180.

38. Sardu C, Barbieri M, Balestrieri ML, Siniscalchi M, Paolisso P, Calabrò P, Minicucci F, Signoriello G, Portoghese M, Mone P et al: Thrombus aspiration in hyperglycemic ST-elevation myocardial infarction (STEMI) patients: clinical outcomes at 1-year follow-up. Cardiovasc Diabetol 2018, 17(1):152.
39. D’Onofrio N, Sardu C, Paolisso P, Minicucci F, Gragnano F, Ferraraccio F, Panarese I, Scisciola L, Mauro C, Rizzo MR et al.: MicroRNA-33 and SIRT1 influence the coronary thrombus burden in hyperglycemic STEMI patients. J Cell Physiol 2020, 235(2):1438-1452.

40. Marfella R, Rizzo MR, Siniscalchi M, Paolisso P, Barbieri M, Sardu C, Savinelli A, Angelico N, Del Gaudio S, Esposito N et al.: Peri-procedural tight glycemic control during early percutaneous coronary intervention up-regulates endothelial progenitor cell level and differentiation during acute ST-elevation myocardial infarction: effects on myocardial salvage. Int J Cardiol 2013, 168(4):3954-3962.

41. Sasso FC, Pafundi PC, Marfella R, Calabrò P, Piscione F, Furbatto F, Esposito G, Galiero R, Gragnano F, Rinaldi L et al.: Adiponectin and insulin resistance are related to restenosis and overall new PCI in subjects with normal glucose tolerance: the prospective AIRE Study. Cardiovasc Diabetol 2019, 18(1):24.

42. Kohnert KD, Augstein P, Zander E, Heinke P, Peterson K, Freyse EJ, Hovorka R, Salzsieder E: Glycemic variability correlates strongly with postprandial beta-cell dysfunction in a segment of type 2 diabetic patients using oral hypoglycemic agents. Diabetes Care 2009, 32(6):1058-1062.

43. Torimoto K, Okada Y, Mori H, Tanaka Y: Relationship between fluctuations in glucose levels measured by continuous glucose monitoring and vascular endothelial dysfunction in type 2 diabetes mellitus. Cardiovasc Diabetol 2013, 12(1).

44. Sardu C, Paolisso P, Sacra C, Mauro C, Minicucci F, Portoghese M, Rizzo MR, Barbieri M, Sasso FC, D’Onofrio N et al.: Effects of Metformin Therapy on Coronary Endothelial Dysfunction in Patients With Prediabetes With Stable Angina and Nonobstructive Coronary Artery Stenosis: The CODYCE Multicenter Prospective Study. Diabetes Care 2019, 42(10):1946-1955.

45. Kitta Y, Nakamura T, Kodama Y, Takano H, Umetani K, Fujioka D, Saito Y, Kawabata K, Obata JE, Ichigi Y et al.: Endothelial vasomotor dysfunction in the brachial artery is associated with late in-stent coronary restenosis. J Am Coll Cardiol 2005, 46(4):648-655.

46. Lafont A, Durand E, Samuel JL, Besse B, Addad F, Lévy BI, Desnos M, Guérot C, Boulanger CM: Endothelial dysfunction and collagen accumulation: two independent factors for restenosis and constrictive remodeling after experimental angioplasty. Circulation 1999, 100(10):1109-1115.

47. Kilpatrick ES, Rigby AS, Atkin SL: The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. Diabetes Care 2006, 29(7):1486-1490.

Figures
Figure 1. Flow chart of recruitment procedure. T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; PCI, percutaneous coronary intervention; HbA1c, glycated hemoglobin A1c.
Figure 2. Cumulative frequency of restenosis according to tertiles of CV of HbA1c. 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 HbA1c. CV, coefficient of variation; HbA1c, glycated hemoglobin A1c.

Figure 2

Cumulative frequency of restenosis according to tertiles of CV of HbA1c. 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 HbA1c. CV, coefficient of variation; HbA1c, glycated hemoglobin A1c.
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 HbA1c (F). ISR, in-stent restenosis; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c.

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