Treatment effect of metformin combined with atorvastatin in reducing in-stent restenosis after percutaneous coronary intervention in coronary artery disease patients with type 2 diabetic patients

Mingli Chen, BS*, Fangfang Ma, BS*, Baohua Su, BS*, Caihong Wang, MM*, Qun Zheng, BS*, Yu Zhang, MM*, Meng Li, MM*, Shuai Liu, MM*, Shuzhi Zhang, MM*, Lansuo Yuan, MM*+ *

Abstract
To investigate the effectiveness of metformin and atorvastatin in preventing in-stent restenosis (ISR) on coronary patients with type 2 diabetes mellitus with percutaneous coronary intervention within 8 to 12 months after rapamycin-eluting stent implantation. A total of 1278 consecutive patients implanted with rapamycin-eluting stent from January 2012 to December 2019, who underwent coronary computed tomography or coronary angiography within 8 to 12 months. The patients were categorized into atorvastatin 20mg, or atorvastatin 20mg + metformin 1.5/d, or atorvastatin 40mg + metformin 1.5/d groups. The clinical characteristics of the 3 groups were compared. The correlation between variables and ISR was analyzed. A total of 701 patients participated in the study. The ratio of ISR/nonstenosis (P = .039) and fasting blood sugar (P = .001) differed significantly in the 3 groups. Logistic regression showed that d, L, different therapeutic agents, and dosage groups were independent risk factors of ISR. The longer L and smaller d may increase ISR incidence with 8 to 12 months after percutaneous coronary intervention. Both metformin and atorvastatin are beneficial in reducing stent restenosis by a dose-dependent manner. An increasing dose of atorvastatin and a combination of metformin decreases the incidence of ISR in patients.

Abbreviation: CT = computed tomography, ISR = in-stent restenosis, PCI = percutaneous coronary intervention, T2DM = type 2 diabetes mellitus.

Keywords: atorvastatin, coronary heart disease, in-stent restenosis, metformin, type 2 diabetes

1. Introduction
The rate of in-stent restenosis (ISR) in the bare metal stent era was about 40%, and which of the drug-eluting stent era was significantly reduced to about 10 to 15%. In coronary heart disease with diabetes, the rate of ISR after percutaneous coronary intervention (PCI) was still above average.[2] Studies have shown that diabetes is a predisposing factor for ISR after PCI in coronary heart disease. However, the mechanism remains unclear that the increased rate of ISR after PCI in coronary heart disease with type 2 diabetic mellitus (T2DM) patients. Speculate on the mechanism leading to ISR: elevated blood sugar, dyslipidemia, directly or indirectly, or other mechanisms such as endothelial damage or inflammatory effects? It was unclear yet. The traditional hypoglycemic drug metformin has curative and preventive effects on ISR.[3] However, there is no correlation between the blood glucose lowering index and ISR. To explore whether there are additional mechanisms against blood sugar control by metformin in preventing ISR? The lipid-lowering drug atorvastatin reduces the incidence of ISR. The present study aimed to investigate the preventive effect of metformin and different doses of atorvastatin on prevention of ISR after PCI in patients with coronary heart disease with T2DM.[3]

2. Methods
2.1. Research subjects
Inclusion criteria: 1278 coronary heart disease patients with T2DM who underwent coronary PCI in the Department of Cardiology, Harrison International Peace Hospital from January
of metformin 1.5/d and atorvastatin 20 mg (1/night), and 3
group of metformin (1.5/d) and atorvastatin 40 mg (1/night).

Calculation method of the total length of stent (L) and the
average diameter of the stent (d).

\[ L = \text{The total length obtained by adding the lengths of all stents, if there was more than one stents in patients. The total length of the stents} = \text{the sum of the lengths of all stents implanted by the patient: that is, the total length} \ (\text{mm}) = \text{the length of the stent 1} \ (\text{mm}) + \text{the length of the stent 2} \ (\text{mm}) + \ldots \ + \text{the length of the stent 3} \ (\text{mm}) \] + \ldots \ d = \text{Average diameter of all stents} \ (\text{mm/um/mm}). \text{The diameter of the stent} = \text{the average of the diameters of all stents implanted by the patient: that is: the diameter of the stent} \ (\text{mm}) = \text{(the diameter of the stent 1} + \text{the diameter of the stent 2} + \text{the diameter of the stent 3} \ldots) \text{(mm)} \] / \text{the number of stents.}

3.1. Coronary stenosis evaluation method

Coronary angiography was conducted using Judkin method. Each vascular area had ≥ 3 projection positions. The digital subtraction angiography image processing system (platform Medical System Workstation4.3) of vascular subtraction machine (US GE company PHILIPS, Fairfield, CT) conducts a quantitative analysis of stenosis. The angiographic results were judged by 2 interventional qualified cardiovascular interventionists, and the degree of coronary stenosis was evaluated as follows: the degree of coronary stenosis was stenosis with major coronary vascular stenosis ≥ 50%, and the main coronary vessels included the left main trunk, front descending branch, gyroscopic branch, and right crown.[6]

3.2. Coronary restenosis

Coronary stenosis refers to coronary angiography or coronary CT restenosis. Coronary angiography or coronary CT at 8 to 12 months after PCI shows target vessel showed ≥ 50% with or without clinical ischemic symptoms, and restenosis lesions within 5 mm of the diameter edge were also included in the whole scope of stents. If there is target lesion restenosis ≥ 50% by coronary angiography, 200 ug of nitroglycerin was administered to the corresponding coronary artery. Re-imaging was performed to assess the target lesions.[6]

3.3. Statistical analysis

Statistical analysis was performed using SPSS 17.0 software. The statistics of measurement data were analyzed by t test and analysis of variance (ANOVA). The count data were analyzed by Bangla, and the multivariate analysis was performed by logistic analysis. The difference was statistically significant at \( P < .05 \).

4. Results

4.1. Comparison of general data between the 3 groups of patients

A total of 701 cases (59.8 ± 10.2 years, 65.2% men) were enrolled in this study. No significant differences were detected in the gender, age, systolic blood pressure, diastolic blood pressure, fasting blood sugar, HbA1c, triacylglycerol, total cholesterol, and low-density lipoprotein in the 3 groups (all \( P > .05 \), Table 1).

Stenosis degree of coronary artery lesions were no significant differences in the group of atorvastatin 20 mg 1/night, metformin 1.5/d and atorvastatin 20mg 1/night and metformin 1.5/d, and atorvastatin 20 mg 1/night before PCI (\( P = .788 \), Table 2).

The number of coronary artery lesions were no significant differences in the group of atorvastatin 20mg 1/night, metformin 1.5/d and atorvastatin 20mg 1/night and metformin 1.5/d and atorvastatin 20 mg 1/night and metformin
1.5/d, and rosuvastatin 20mg 1/night before PCI \( (P = .995, \text{Table 3}) \).

No significant differences were detected in the mean length of the stents each patient and the mean diameter of implanted stents in the 3 groups \( (P > .05) \). Fasting blood glucose, HbA1c, dyslipidemia, and ISR were significantly lower in the metformin 1.5/d + atorvastatin 40 mg group than in the atorvastatin 20 mg/night group and metformin 1.5/d + atorvastatin 20 mg group for 8 to 12 months after PCI \( (P < .05, \text{Table 4}) \).

### 4.2. Analysis of influencing factors of stent restenosis

In-stent restenosis as a dependent variable \( \geq 50% = 1 \), in-stent stenosis \( < 50% \) or no ISR \( = 0 \), sex \( (\text{male} = 1, \text{female} = 0) \), body mass index \( < 24 \text{kg/m}^2 = 0, \geq 24 \text{kg/m}^2 = 1 \), age \( \geq 60 \text{years} = 1, < 60 \text{years} = 0 \), average diameter of implanted stents \( \geq 2.5 \text{mm} = 2, < 2.5 \text{mm} = 1 \), total stent length \( \geq 25 \text{mm} = 1, < 25 \text{mm} = 0 \), average diameter of the stent \( \geq 3.0 \text{mm} = 1, < 3.0 \text{mm} = 0 \), history of hypertension \( \text{diastolic blood pressure} \geq 90 \text{mm Hg} = 1, \text{systolic blood pressure} \geq 140 \text{mm Hg} = 1 \), history of diabetes \( \text{diabetes} = 1, \text{no diabetes} = 0 \), drug treatment group \( \text{metformin 1.5/d + atorvastatin 40 mg} = 2, \text{metformin 1.5/d + atorvastatin 20 mg} = 1, \text{atorvastatin 20 mg} = 0 \), etc as independent variables for multivariate regression analysis. Logistic regression showed the total length of the stent, the average diameter of the diameter and the different doses of drug groups were correlated with ISR \( (P < .05) \). Metformin 1.5/d + atorvastatin 20 mg/night was a protective factor for ISR \( \text{OR:} 0.557, \text{95\% CI} 0.412–0.753, P = 0.001, \text{Table 5} \).

### 5. Discussion

Coronary artery ISR is a major clinical problem after PCI. Some studies have shown that diabetes is an influencing factor for ISR after PCI, which may be attributed to hyperglycemia leading to endothelial injury, pro-inflammatory response, and increased ISR risk.\(^7\) The present study suggested that metformin application reduced the incidence of ISR. Further studies demonstrated

#### Table 1

| Group | Sex ratio | Age (yr) | SBP | DBP | FBG | HbAc (%) | TG | TC |
|-------|-----------|----------|-----|-----|-----|----------|----|----|
| 1     | 190/115   | 59.7 ± 10.107 | 137.5 ± 23.47 | 78.45 ± 13.47 | 6.84 ± 1.63 | 6.1 ± 4.2 | 1.53 ± 1.036 | 5.94 ± 0.779 |
| 2     | 170/72    | 59.65 ± 10.191 | 135.41 ± 22.55 | 77.92 ± 12.771 | 6.49 ± 1.534 | 6.4 ± 3.6 | 1.54 ± 1.099 | 5.90 ± 0.694 |
| 3     | 97/57     | 60.05 ± 10.215 | 135.84 ± 22.82 | 77.80 ± 11.903 | 6.45 ± 1.464 | 6.2 ± 5.6 | 1.65 ± 1.064 | 6.00 ± 0.789 |

F: 4.184 P: 0.1234

DBP = diastolic blood pressure, FBG = fasting blood sugar, SBP = systolic blood pressure, TC = total cholesterol, TG = triacylglycerol.

#### Table 2

| Group | d | L | ISR | FBG | TG | TC |
|-------|---|---|-----|-----|----|----|
| 1     | 3.22 ± 0.495 | 35.57 ± 19.882 | 44/261 | 5.56 ± 1.28 | 1.42 ± 0.89 | 4.96 ± 0.83 |
| 2     | 3.17 ± 0.486 | 35.76 ± 20.052 | 23/219 | 5.145 ± 0.498 | 1.27 ± 0.72 | 4.77 ± 1.02 |
| 3     | 3.19 ± 0.482 | 35.26 ± 19.124 | 11/143 | 5.01 ± 0.227 | 1.25 ± 0.70 | 4.24 ± 1.105 |

F: 0.803 P: 0.448

d = the mean diameter of implanted stents, FBG = fasting blood sugar, ISR = in-stent restenosis, L = the mean length of the stents, TC = total cholesterol, TG = triacylglycerol.

#### Table 3

| Variable | Coefficient | Std. error | P | Odds ratio | 95\% CI |
|----------|-------------|------------|---|------------|---------|
| Age      | 0.001554    | 0.01204    | .8973 | 1.0016 | 0.9782–1.0255 |
| BMI      | 0.004056    | 0.03005    | .8926 | 1.0041 | 0.9466–1.0650 |
| Sex      | −0.1727     | 0.246      | .4827 | 0.8414 | 0.5195–1.3627 |
| Dmean    | −1.5676     | 0.2698     | 6.296E-09 | 0.2085 | 0.1229–0.3539 |
| Ltotal   | 0.01483     | 0.006223   | .01717 | 1.0149 | 1.0026–1.0274 |
| Group    | −0.5851     | 0.1537     | .0001413 | 0.557 | 0.4121–0.7529 |
| DBPs     | −0.00792    | 0.007672   | .3019 | 1.008 | 0.9992–1.0232 |
| SBPs     | 0.002903    | 0.004603   | .5283 | 1.0029 | 0.9999–1.0120 |
| HDLs     | 0.2756      | 0.2678     | .3035 | 1.3173 | 0.7793–2.2286 |
| LDLs     | 0.004392    | 0.1859     | .9816 | 1.0043 | 0.6976–1.4459 |
| FBGs     | −0.002599   | 0.05319    | .961 | 0.9974 | 0.8987–1.1070 |
| TGs      | −0.006639   | 0.1106     | .9521 | 0.9934 | 0.7998–1.2338 |
| TCS      | −0.02653    | 0.1909     | .8895 | 0.9738 | 0.6699–1.4157 |

BMI = body mass index, DBP = diastolic blood pressure, FBG = fasting blood sugar, HDL = high-density lipoprotein, ISR = in-stent restenosis, LDL = low-density lipoprotein, L = the mean length of the stents, LDL = low-density lipoprotein, PCI = percutaneous coronary intervention, SBP = systolic blood pressure, TG = triacylglycerol, TC = total cholesterol.
The current study did not detect any gender-related differences in ISR, such as the increased probability of ISR in women. The data revealed that the males showed a significantly higher rate than females, which might be contrary to the epidemiological characteristics of the population. Thus, a large number of epidemiological sampling studies are needed.[11] The comparison of systolic blood pressure, diastolic blood pressure, fasting blood glucose, and blood lipids before and after the study showed a significant decrease, which suggests that the secondary prevention drug treatment after PCI was optimistic, which is in line with the decline in ISR. In addition, sexual trends did not meet the statistical difference criteria.[1,10,12]

Furthermore, this study belongs to a single-center study with a small sample size. The patient’s lesion’s syntax score, lesion calcification degree, noncompliant balloon post-dilation, stent balloon dilation pressure, and post-dilation pressure are not within the statistical range. In addition, patients with acute ST-segment elevation, emergency PCI, and patients with T2DM of fasting glycemic uncontrolment and type 1 diabetes patients were excluded from the study. The lack of intravascular ultrasound-related data for postoperative stent thrombosis, acute coronary syndrome, coronary heart disease death, all-cause death, and follow-up observations of multiple endpoints were not included in this study. Also, only patients who underwent coronary angiography or coronary CT were followed up and included in the estimation. The economic conditions of the patients were also considered fully. The current conclusions of this study need to be substantiated with a multicenter, larger sample, randomized, double-blind prospective observational study.

6. Conclusion
In summary, L, d, and the type and dose of metformin + atorvastatin in patients were predictors of ISR in patients 8 to 10 months after coronary PCI. The shorter stent length, larger mean diameter of the stents, the application of metformin 1.5/d + atorvastatin 40 mg/night were protective factors for low rates of ISR.
Author contributions
Mingli Chen and Lansuo Yuan contributed to the study’s conception and design. All authors collected the data and performed the data analysis. All authors contributed to the interpretation of the data and the completion of figures and tables. All authors contributed to the drafting of the article and the final approval of the submitted version.

Conceptualization: Mingli Chen.
Data curation: Baohua Su, Fangfang Ma, Lansuo Yuan, Meng Li, Mingli Chen, Shuai Liu, Shuzhi Zhang.
Formal analysis: Baohua Su, Caihong Wang, Fangfang Ma, Meng Li, Qun Zheng, Shuai Liu, Shuzhi Zhang.
Visualization: Yu Zhang.
Writing – original draft: Lansuo Yuan.

References
[1] Turak O, Canpolat U, Özcan F, et al. Usefulness of preprocedural serum uric acid level to predict restenosis of bare metal stents. Am J Cardiol. 2014;113:197–202.
[2] Quispe R, Manalac RJ, Faridi KF, et al. Relationship of the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio to the remainder of the lipid profile: the very large database of lipids-4 (VLDL-4) study. Atherosclerosis. 2015;242:243–50.
[3] Franzone A, Zaugg S, Piccolo R, et al. A randomized multicenter trial comparing the XIENCE everolimus eluting stent with the CYPHER sirolimus eluting stent in the treatment of female patients with de novo coronary artery lesions: the SPIRIT WOMEN study. PLoS One. 2017;12:e0182632.
[4] Haflane A, Genest J. High density lipoproteins: measurement techniques and potential biomarkers of cardiovascular risk. BBA Clin. 2015;3:175–88.
[5] Salazar MR, Carbajal HA, Espeche WG, et al. Use of the plasma triglyceride/high-density lipoprotein cholesterol ratio to identify cardiovascular disease in hypertensive subjects. J Am Soc Hypertens. 2014;8:724–31.
[6] Küp A, Toprak C, Bayam E, et al. Serum endocan levels predict drug-eluting stent restenosis in patients with stable angina pectoris. Acta Cardiol Sin. 2020;36:111–7.
[7] Cho JY. Identification of risk factors influencing in-stent restenosis with acute coronary syndrome presentation. Chonnam Med J. 2017;53:203–10.
[8] Abed AF, Jarrar YB, Al-Ameer HJ, et al. 2022. The protective effect of metformin against oxandrolone-induced infertility in male rats. Curr Pharm Des. 2022;28:324–30.
[9] Al Awaida W, Ahmed AA, Hamza AA, et al. Association of KDR rs1870377 genotype with clopidogrel resistance in patients with post percutaneous coronary intervention. Heliyon. 2021;7:e06251.
[10] Cui K, Lyu S, Song X, et al. Drug-eluting balloon versus bare-metal stent and drug-eluting stent for de novo coronary artery disease: a systematic review and meta-analysis of 14 randomized controlled trials. PLoS One. 2017;12:e0176365.
[11] Zeng WP, Zhang R, Li R, et al. Association of the endothelial nitric oxide synthase gene T786C polymorphism with in-stent restenosis in Chinese Han patients with coronary artery disease treated with drug-eluting stent. PLoS One. 2017;12:e0170964.
[12] Kundi H, Korkmaz A, Balun A, et al. Is in-stent restenosis after a successful coronary stent implantation due to stable angina associated with TG/HDL-C ratio? Angiology. 2017;68:816–22.