Observational Study

Medicine

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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

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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 20 mg, or atorvastatin 20 mg + metformin 1.5/d, or atorvastatin 40 mg + 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.[1] 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.[2]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

The study was supported by the ACG Institute for Clinical Research and Education (No 15003).

The authors have no conflicts of interest to disclose.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article [and its supplementary information files].

This study was approved by the ethics committee of the Harrison International Peace Hospital Affiliated to Hebei Medical University.

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How to cite this article: Chen M, Ma F, Su B, Wang C, Zheng Q, Zhang Y, Li M, Liu S, Zhang S, Yuan L. 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. Medicine 2022;101:41(e31107).

Received: 14 April 2022 / Received in final form: 8 September 2022 / Accepted: 13 September 2022

http://dx.doi.org/10.1097/MD.0000000000031107

2012 to December 2016 were enrolled in this study. The age of the cohort was ≥ 18 years or/and ≤ 85 years. According to the initial estimation of ISR rate of 10 to 20%, the sample size of each group was about 114 to 228 cases. All patients voluntarily participated in this study and signed the informed consent in person, which was approved by the Medical Ethics Committee of Hengshui Harixun International Peace Hospital (Hengshui Harixun International Peace Hospital Ethics Committee 2012-1-0120 [Provincial and municipal level]).

Exclusion criteria: Patients with type 1 diabetes, acute PCI for acute myocardial infarction, and patients with severe renal insufficiency who were contraindicated for coronary angiography, those who do not receive atorvastatin or metformin for various reasons or were allergic to the 2 drugs, patients who did not complete coronary angiography or coronary computed tomography (CT) assessment for 12 months, and other factors were not suitable for enrollment in this study.

2.2. Diagnostic criteria and related definitions

2.2.1. Diagnostic criteria for type 2 diabetes. Fasting venous blood glucose ≥ 7.0 mmol/L and/or 2 hours postprandial blood sugar level ≥ 11.1 mmol/L or a clear history of type 2 diabetes.[4] The diagnostic criteria for dyslipidemia are those who meet any of the following criteria: total cholesterol ≥ 5.7, triacylglycerol ≥ 1.7, low-density lipoprotein ≥ 3.4, high-density lipoprotein cholesterol < 1.0mmol/L, or those who are taking lipid-lowering drugs. Coronary heart disease was defined as follows: clinical ischemic symptoms, coronary angiography results in at least one stenosis of coronary vessels ≥ 50%. Coronary stent placement criteria: at least one coronary artery vessel ≥ 70% and at least one implanted stent. The immediate residual stenosis of the implanted stent should be < 10%, thrombolysis in myocardial infarction blood flow level 3, and no adverse cardiac events, such as death, angina, and myocardial infarction.[5]

3. Methods

Preoperative load of aspirin 300 mg, clopidogrel (300 mg within 6 h before PCI or 600 mg 2 h before PCI), or Ticagrelor 180 mg, followed by aspirin 100 mg (1/d), clopidogrel 75 mg (1/d), or Ticagrelor 90 mg (2/d); Patients with type 2 diabetes were treated with subcutaneous injections of insulin aspart and insulin detemir. PCI access is adopted PCI approach was adopted in the right radial artery or the right femoral artery by Seldinger method. Bolus of unfractional heparin 3000 IU was placed into by the 6 F arterial sheath. Subsequently, coronary angiography was performed using the Judkins method, and 100 IU/kg of unfractionated heparin was added before PCI. The main stenosis of the main coronary vessels (left main, anterior descending, circumflexed, and right coronary) ≥ 70% is the standard stenosis of the stent. Accompanying the chest pain symptoms of patients with coronary heart disease, such as acute ischemia and hypoxia caused by severe coronary stenosis, the clinical symptoms of myocardial cell damage, mainly compressive chest pain, lasts about a few minutes each time. The seizures are often induced by overwork or emotional agitation, last for a few minutes each time or relieved by nitrates, and/or dynamic changes in the ECG such as ECG downslope or T wave inversion appear in 2 leads. Stent corresponds to the location of the stenotic lesions on coronary angiography. The residual stenosis diameter of the implant is < 10%, and the distal blood flow of the target vessel is thrombolysis in myocardial infarction 3. No adverse cardiac events (death, myocardial infarction, emergency coronary artery bypass grafting, and emergency PCI) were observed. Postoperative application of aspirin 100 mg (1/d), clopidogrel 75 mg (1/d), or ticagrelor 90 mg (2/d). Then, the patients were randomly divided into 1 group of atorvastatin 20 mg (1/night), 2 group 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 = 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 = the sum of the lengths of all stents implanted by the patient: that is, the total length (mm) = the length of the stent 1 (mm) + the length of the stent 2 (mm) + the length of the stent 3 (mm) +…. d = Average diameter of all stents (mm) (unit:mm). The diameter of the stent = the average of the diameters of all stents implanted by the patient: that is: the diameter of the stent (mm) = (the diameter of the stent 1 + the diameter of the stent 2 + the diameter of the stent 3 +...) (mm)/ 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 interventionalists, 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 atorvastoratin 20mg 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 rosuvastatin 20mg 1/night before PCI (P = .995, 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, Table 4).

4.2. Analysis of influencing factors of stent restenosis

In-stent restenosis as a dependent variable (at least one in-stent stenosis ≥ 50% = 1, in-stent stenosis < 50% or no ISR = 0), gender (male = 1, female = 0)), body mass index (< 24 kg/m^2 = 0, ≥ 24 kg/m^2 = 1), age (age ≥ 60 years = 1, age < 60 years = 0), average diameter of implanted stents (average diameter ≤ 2.5 mm = 2, 2.5 mm < average diameter ≤ 3.0 mm = 1, average diameter > 3.0 mm = 0), total stent length (total stent length ≤ 15mm = 2, 15mm < total stent length ≤ 25mm = 1, total stent length > 25mm = 0), history of hypertension (no controlled hypertension: systolic blood pressure ≥ 140 mm Hg and/ or diastolic blood pressure ≥ 90 mm Hg = 1, controlled hypertension:systolic blood pressure < 140 mm Hg and/or diastolic blood pressure < 90mm Hg = 0), dyslipidemia (dyslipidemia = 1, no dyslipidemia = 0), history of diabetes (history of diabetes = 1, no history of diabetes = 0), drug treatment group (metformin 1.5/d + atorvastatin 40 mg group = 2, metformin 1.5/d + atorvastatin 20 mg group = 1, atorvastatin 20 mg group = 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 (OR: 0.557, 95% CI 0. 412–0. 753, P = 0. 001, 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

Comparison of general data between the 2 groups of patients.

Group	Sex ratio	Age (yr)	SBP	DBP	FBG	HbAc (%)	TG	TC
1	190/115	59.7 ± 10.107	137.5 ± 23.47	78.45 ± 13.473	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 value	4.184	0.126	0.615	0.198	0.075	0.468	0.974	1.236
P value	0.1234	0.882	0.541	0.82	0.928	0.185	0.378	0.291

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

Table 2

Post-FBG, dyslipidemia, and ISR incidence.

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 ± 1.05
	F:0.803	F:0.044	F:6.474	F:34.064	F:3.892	F:39.85
	P:0.448	P:0.957	0.039	0.001	0.021	0.001

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

Correlation and correlation coefficients of logistic regression indicators for ISR.

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	0.9929–1.0232
SBPs	0.002903	0.004603	.5283	1.0029	0.9939–1.0120
HDLs	0.2756	0.2678	.3035	1.3173	0.7793–2.2266
LDLs	0.004292	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.

Table 4

Comparison of basic and characteristic parameters in the 3 groups of patients with 8 to 12 months after PCI.

Group	d	L	ISR (%)	FBG	HbA1c (%)	TG	TC	LDL
Atorvastatin 20 mg 1/night	3.22 ± 0.50	35.57 ± 19.88	52/218(0.19)	5.56 ± 1.28	6.0 ± 3.9	1.42 ± 0.89	4.96 ± 0.83	2.99 ± 0.72
Metformin 1.5/d and Rosuvastatin 10 mg 1/night	3.17 ± 0.49	35.76 ± 20.05	39/231(0.14)	5.15 ± 0.50	5.7 ± 4.2	1.27 ± 0.72	4.77 ± 1.02	2.86 ± 0.71
Metformin 1.5/d and Atorvastatin 40 mg 1/night	3.19 ± 0.48	35.26 ± 19.12	30/240(0.11)	5.01 ± 0.23	5.7 ± 4.6	1.25 ± 0.70	4.24 ± 1.05	2.78 ± 0.70
F value	0.803	0.044	7.131	34.064	21.321	3.892	39.85	6.404
P	P:0.448	P:0.957	0.028	0.001	0.001	0.021	0.001	0.002

d = the mean diameter of implanted stents, DBP = diastolic blood pressure, FBG = fasting blood sugar, ISR = in-stent restenosis, L = the mean length of the stents, LDL = low-density lipoprotein, PCI = percutaneous coronary intervention, SBP = systolic blood pressure, TC = total cholesterol, TG = triacylglycerol.

Table 5

Logistic regression analysis of influencing factors of in-stent restenosis.

Variable	Coefficient	Std. error	*P* value	Odds ratio	95% CI
Age	0.002	0.012	.897	1.002	0.978–1.026
BMI	0.004	0.030	.893	1.004	0.947–1.065
Sex	–0.173	0.246	.483	0.841	0.520–1.363
Mean diameter of stents	–1.568	0.270	.006	0.209	0.123–0.354
Total length of stents	0.015	0.006	.017	1.015	1.003–1.027
Category of drug group	–0.585	0.154	.001	0.557	0.412–0.753
History of hypertension	0.003	0.005	.528	1.003	0.994–1.012
Dyslipidemia	0.004	0.186	.982	1.004	0.698–1.446
History of T2DM	–0.003	0.053	.961	0.997	0.899–1.107

BMI = body mass index, T2DM = type 2 diabetes mellitus.

that the fasting blood sugar level in groups of metformin 1.5/d + atorvastatin 20 mg/night and metformin 1.5/d + atorvastatin 40 mg/night was significantly lower than in that of atorvastatin 20 mg (1/night) ($P < .05$); however, the correlation between the blood glucose drop and ISR was not observed ($P > .05$). It was speculated that metformin reduced incidence of ISR with other unclear mechanisms than glycemic drop factors. Furthermore, in terms of humoral factors: oxandrolone is an androgen and steroid hormone-like substance, and the increased concentration in the body leads to endothelial damage and the formation of atherosclerotic plaques, and the incidence of coronary heart disease increases. Metformin can inhibit the level of oxandrolone, thereby improving and reducing the occurrence of in-stent restenosis.[8]The lipid-lowering drug atorvastatin has a marked effect on improving blood lipids. Atorvastatin can ameliorate the consequences of genetic variants by lowering low-density lipoprotein, KDR rs1870377 SNP is strongly associated (Chi-square, P value < 0.05) with CR under dominant, codominant, and recessive models, which allele leads to clopidogrel resistance and elevated low-density lipoprotein.[9] The study also suggested that atorvastatin prevents and treats ISR in a dose-dependent manner. With increasing doses, atorvastatin is beneficial to strengthen the preventive effect. This study suggested that metformin 1.5/d + atorvastatin 40 mg/night had a more significant effect on the reduction rate of ISR ($P < .05$), which was consistent with previous studies, but no significant correlation was established between decreased blood lipid levels and ISR, which may remind us to explore mechanisms other than lipid lowering by atorvastatin in reducing ISR. In addition, the length of the stent and the diameter of the stent were significantly correlated with ISR. The longer length of the stent, the smaller diameter of the stent are negatively correlated with the rate of ISR ($P < .05$).[3,10]

The current clinical study reported that the incidence of ISR increases in an age-dependent manner, which was not statistically significant ($P > .05$). Thus, which trend will further observe by increasing the sample size in future studies. Also, it is a single-center study. The average age of the cohort was about 60 years in total participants, which might not represent the entire adult population with coronary heart disease.

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.

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