Observational Study

Medicine®

OPEN

The number of stents was an independent risk of stent restenosis in patients undergoing percutaneous coronary intervention

Long Tang, MD[a], Qian-Wei Cui, MD[b], Dan-Ping Liu, MD[a], Ying-Ying Fu, MD[a,*]

Abstract

Percutaneous coronary intervention (PCI) is one of the most effective therapies for coronary artery disease, but stent restenosis remains an important clinical challenge. The studies about the independent effect of the number of stents on stent restenosis were limited.

The purpose was to identify the independent effect of the number of stents on stent restenosis.

A retrospective cohort study of data reuse.

From July 2009 to August 2011, a total of 2338 cases met the inclusion and exclusion criteria.

The univariate analysis showed that the number of stents was a risk of stent restenosis, the OR value was 1.30 (95% CI:1.15 to 1.47, $P < .001$). The multi-factor regression analysis also showed that the number of stents was an independent risk of stent restenosis, the adjusted OR value was 1.38 (95% CI: 1.15 to 1.66, $P < .001$).Compared with 1–2 stents, the adjusted OR values of 3–5 stents and more than 6 stents were respectively 2.20 (95% CI: 1.24 to 3.90, $P = .007$) and 5.33 (95% CI: 1.89 to 15.08, $P = .002$), and the trend adjusted OR values was 2.26 (95% CI: 1.43 to 3.59, $P < .001$).The subgroup analysis of multi-factor regression analysis showed that when patients with the following conditions: 50 < Age, female, non-DES or SES, the risk of stent restenosis increased obviously.

The number of stents was an independent risk of stent restenosis in patients undergoing PCI, especially for patients with the following conditions: 2<the number of stents, 50 < age, female, Non-DES (Drug-eluting stents) or SES (sirolimus-eluting stent).

Abbreviations: BMS = bare metal stents, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, CTO = chronic total occlusion, DES = Drug-eluting stents, DM = diabetes mellitus, LAD = left anterior descending artery, LCX = left circumflex artery, LM = left main stem, PCI = percutaneous coronary intervention, RCA = right coronary artery, SES = sirolimus-eluting stent, STEMI = ST-elevation myocardial infarction.

Keywords: number of stents, percutaneous coronary intervention (PCI), stent restenosis

1. Introduction

Coronary artery disease (CAD) has been a major cause of death in the world.[1] PCI is one of the most effective therapies for coronary artery disease.[2] In recent years, the development of the stent materials and related techniques had obviously decreased the complication rate.[3] The frequency of stent restenosis at 6 months after stenting is approximately 25% for bare metal stents and less than 10% for drug-eluting stents. Although intracoronary stent restenosis is much less common with the use of DES than with BMS,[4] the number of stents being implanted in interventional practice means that the stent restenosis remains an important clinical challenge.[5] Until now, there were some small sample studies showed that the number of stents was one possible risk of stent restenosis in patients undergoing PCI.[6–8] At the same time, these studies were about the incidence of stent restenosis at 6 months to 1 year and without adjusting the potential confounders. So, the independent effect of the number of stents on stent restenosis, especially to the delayed stent restenosis, was still unknown. The objective of the present study was to identify the independent effect of the number of stents on stent restenosis, especially to the delayed stent restenosis.

2. Methods

2.1. Study design

A retrospective cohort study of data reuse.

2.2. Objection

The purpose was to identify the independent effect of the number of stents on stent restenosis.

Editor: Ovidiu Constantin Baltatu.

The authors have no funding and conflicts of interest to disclose.

[a] Department of Emergency, [b] Department of Cardiovascular, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi, China.

[*] Correspondence: Ying-Ying Fu, Department of Emergency, Shaanxi Provincial People's Hospital, No. 256 You Yi Xi Road, Xi'an, Shaanxi 710068, China (e-mail: sxxafyy@163.com).

How to cite this article: Tang L, Cui Qw, Liu Dp, Fu Yy. The number of stents was an independent risk of stent restenosis in patients undergoing percutaneous coronary intervention. Medicine 2019;98:50(e18312).

Received: 12 July 2019 / Received in final form: 26 September 2019 / Accepted: 5 November 2019

http://dx.doi.org/10.1097/MD.0000000000018312

2.3. Data source

The data was provided by Tong-Wen Sun, which was stored in the dryad database (https://datadryad.org/resource/doi:10.5061/dryad.13d31).[9]

2.4. Inclusion criteria

Patients who underwent PCI between July 2009 and August 2011, A hospital in the Henan province, China, between 2009 and 2011.

2.5. Exclusion criteria

1) Patients were with prior PCI;
2) Patients were with prior CABG (Coronary Artery Bypass Grafting);
3) missing value of number or type of sent.

2.6. Patient and public involvement

New ethics approval was not applicable, because the original author had obtained the ethical approval when conducting this study.

2.7. Participants

The study was carried out on consecutively enrolled patients who underwent PCI between July 2009 and August 2011, at a single high-volume PCI center, a total of 2338 cases met the inclusion and exclusion criteria.

2.8. The main outcome

The main outcome was stent restenosis which was detected by follow-up angiography. The follow-up angiography only performed on the symptoms and the examination abnormalities.

2.9. The protocol of PCI

All patients were treated with loading doses of aspirin (300 mg) and clopidogrel (300 mg) before coronary intervention, unless antiplatelet medication had been given to them. The treatment strategy including stenting techniques, the selection of stent type, and the use of glycoprotein IIb/IIIa receptor inhibitors or intravascular ultrasound was all charged by the surgeon's discretion. All patients were prescribed to take aspirin 100 mg per day indefinitely, and take clopidogrel 75 mg per day for at least 1 year after PCI.

Patients were divided into the following 4 groups according to their clinical presentation and timing of PCI:

1) patients with ST-elevation myocardial infarction (STEMI) treated with urgent PCI (urgent PCI);
2) patients with STEMI treated with delayed PCI (delayed PCI);
3) patients with stable angina (SA);
4) patients with non-ST elevation ACS (NSTE-ACS) including patients with non-ST elevation myocardial infarction (MI) and patients with unstable angina.

2.10. Clinical outcomes and data collection

The prospective data were entered into a database that contained demographic, clinical, angiographic and procedural information. The median follow-up time of these patients was 29.8 months (quartiles, 25.6–34 months). After reading a lot of literature, we finally determined the variables that might be related to stent restenosis as follows: age sex hypertension stroke atrial fibrillation COPD (chronic obstructive pulmonary disease) OMI (old myocardial infarction) DM (diabetes mellitus) smoking statin aspirin clopidogrel LDL-C TC presentation stable angina type of stent 1-vessel two-vessel multi-vessel LM (left main stem) LAD (left anterior descending artery) LCX (left circumflex artery) RCA (right coronary artery) occlusion CTO (chronic total occlusion) ostial lesions and bifurcation lesion.

2.11. Statistical analysis

1) Statistical description: Mean ± standard deviation ($x \pm s$) was used for continuous variables of baseline data in the 2 groups, and counts data were shown by numerical values and percentages.
2) Univariate analysis was carried out to detect the possible risk that may be associated with stent restenosis.
3) In multi-factor analysis, we adjusted the possible variables that may be related to stent restenosis to determine the relationship between the number of stents and stent restenosis.
4) Subgroup analysis of multi-factor regression analysis was carried out respectively based on age sex presentation and type of stent to further detect the relationship between the number of stents and stent restenosis.
5) Finally, we used forest to show the results of multivariate and subgroup analysis. All the statistical analyses were performed by EmpowerStats (version numbers: 2018-12-16, Copyright 2009 X&Y Solutions, Inc) and R software. $P < .05$ was considered as a statistical difference.

3. Results

3.1. Characteristics of the study groups

From July 2009 to August 2011, a total of 2338 cases met the inclusion and exclusion criteria. The clinical characteristics of patients were shown in Table 1 and Figure 1.

3.2. The results of univariate analysis

The univariate analysis found that the stroke Non-DES bifurcation lesion and number of stents were associated with stent restenosis. The OR value of them were respectively 2.00 (95% CI: 1.12 to 3.58, $P = .019$), 2.13 (95% CI: 1.42 to 3.20, $P < .001$), 1.53 (95% CI: 1.03 to 2.27, $P = .04$) and 1.21 (95% CI: 1.08 to 1.37, $P = .001$). (Table 2)

3.3. The results of multi-factor regression analysis

In multi-factor regression analysis, we adjusted the possible confounding factors that might be related to stent restenosis as follows: age sex hypertension stroke atrial fibrillation COPD OMI DM smoking statin aspirin clopidogrel LDL-C TC presentation stable angina type of stent 1-vessel two-vessel multi-vessel LM LAD LCX RCA occlusion CTO (chronic total occlusion) ostial lesions and bifurcation lesion to identify the independent effect of the number of stents on stent restenosis. We found that as the number of stents every increased by 1, the risk of stent restenosis increased by 38%, the adjusted OR value of it

Table 1

Baseline characteristics of the study population.

Number of stents	1 stent (n = 896)	2–3 stents (n = 1096)	4–5 stents (n = 300)	>=6 stents (n = 46)	*P* value
Age	58.31 ± 11.50	60.72 ± 10.75	61.17 ± 10.62	59.30 ± 10.51	<.001
Sex	605 (67.52%)	726 (66.24%)	224 (74.67%)	26 (56.52%)	.016
Hypertension	399 (44.58%)	563 (51.37%)	173 (57.67%)	24 (52.17%)	<.001
Stroke	40 (4.46%)	55 (5.02%)	19 (6.33%)	3 (6.52%)	.596
Atrial fibrillation	20 (2.23%)	19 (1.73%)	6 (2.00%)	0 (0.00%)	.666
COPD	7 (0.78%)	9 (0.82%)	5 (1.67%)	0 (0.00%)	.454
OMI	59 (6.58%)	91 (8.30%)	34 (11.33%)	7 (15.22%)	.018
DM	135 (15.08%)	241 (21.99%)	87 (29.00%)	11 (23.91%)	<.001
Smoking	288 (32.14%)	340 (31.02%)	116 (38.67%)	11 (23.91%)	.049
Statin	800 (89.29%)	1000 (91.24%)	282 (94.00%)	43 (93.48%)	.078
Aspirin	882 (98.55%)	1080 (98.63%)	296 (98.67%)	46 (100.00%)	.876
Clopidogrel	863 (96.53%)	1051 (95.98%)	286 (95.33%)	43 (93.48%)	.621
LDL-C	2.66 ± 0.92	2.71 ± 0.93	2.66 ± 0.99	2.86 ± 0.92	.348
TC	4.22 ± 1.03	4.32 ± 1.07	4.22 ± 1.10	4.55 ± 1.09	.063
Presentation					.071
Urgent PCI	47 (5.25%)	39 (3.56%)	6 (2.00%)	4 (8.70%)	
Delayed PCI	179 (19.98%)	247 (22.54%)	73 (24.33%)	8 (17.39%)	
NSTE-ACS	537 (59.93%)	634 (57.85%)	164 (54.67%)	26 (56.52%)	
Stable angina	133 (14.84%)	176 (16.06%)	57 (19.00%)	8 (17.39%)	
type of stent					<.001
SES	643 (71.76%)	696 (63.56%)	154 (51.33%)	20 (43.48%)	
PES	253 (28.24%)	169 (15.43%)	37 (12.33%)	6 (13.04%)	
Non-DES	0 (0.00%)	230 (21.00%)	109 (36.33%)	20 (43.48%)	
1-vessel	648 (72.32%)	249 (22.72%)	10 (3.33%)	0 (0.00%)	<.001
Two-vessel	184 (20.54%)	566 (51.64%)	106 (35.33%)	7 (15.22%)	<.001
Multi-vessel	61 (6.81%)	281 (25.64%)	183 (61.00%)	38 (82.61%)	<.001
LM	18 (2.01%)	42 (3.83%)	11 (3.67%)	5 (10.87%)	.003
LAD	687 (76.67%)	941 (85.86%)	280 (93.33%)	45 (97.83%)	<.001
LCX	223 (24.89%)	624 (56.93%)	243 (81.00%)	43 (93.48%)	<.001
RCA	257 (28.68%)	610 (55.66%)	242 (80.67%)	44 (95.65%)	<.001
Occlusion	84 (9.38%)	159 (14.51%)	62 (20.67%)	8 (17.39%)	<.001
CTO	39 (4.35%)	109 (9.95%)	50 (16.67%)	8 (17.39%)	<.001
Ostial lesion	82 (9.15%)	133 (12.14%)	35 (11.67%)	9 (19.57%)	.044
Bifurcation lesion	115 (12.83%)	211 (19.25%)	81 (27.00%)	11 (23.91%)	<.001

was 1.38 (95% CI: 1.15 to 1.66, $P < .001$). When comparing with 1 stent, the 2-3 stents 4–5 stents and >=6 stents were with higher risk of stent restenosis, the adjusted OR value of them were respectively 1.59 (95% CI: 0.88 to 2.86, $P = .122$),2.07 (95% CI: 0.91 to 4.71, $P = .081$) and 5.12 (95% CI: 1.68 to 15.57, $P = .004$) and the adjusted trend OR value was 1.59 (95% CI: 1.13 to 2.23, $P = .007$). When comparing with 1–2 stents, the adjusted OR value of 3–5 stents and >=6 stents were also with higher risk of stent restenosis, the adjusted OR value of them were respectively 2.20 (95% CI: 1.24 to 3.90, $P = .007$) and 5.33 (95% CI: 1.89 to 15.08, $P = .002$) and the adjusted trend OR value was 2.26 (95% CI: 1.43 to 3.59, $P < .001$). (see Table 3 and Fig. 2)

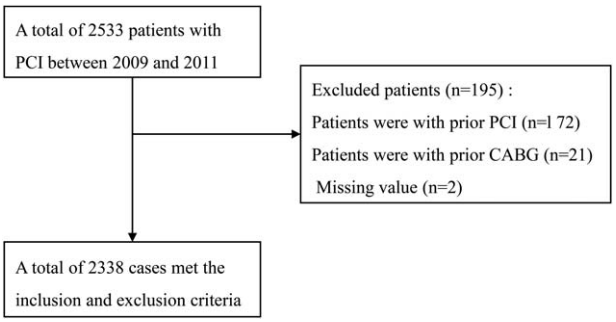

Figure 1. A flow chait of the inclusion and exclusion of patients.

3.4. The results of subgroup analysis of multi-factor regression analysis to further detect the relationship between the number of stents and stent restenosis

In subgroup multi-factor regression analysis, we adjusted the variables which were adjusted in multi-factor regression analysis, except itself of the subgroup variables. We found that patients with 50<Age ≤ 70 70 < Age female delayed PCI stable angina, NSTE-ACS , SES, and Non-DES, as the number of stents increased, the risk of stent restenosis increased obviously. Due to the small sample size of urgent PCI, the subgroup analysis of multi-factor analysis failed to get the results of subgroup after adjusting the related variables. While, patients with PES, as the number of stents increased, the risk of stent restenosis did not increase. (see Table 4 and Fig. 3)

4. Discussion

In our study, we found that the number of stents was an independent risk of stent restenosis in patients undergoing PCI, especially for patients with any of the following conditions: 2 < the number of stents, 50 < Age, female, non-DES, or SES.

Table 2

Univariate analysis.

Variables	Statistics	Restenosis, *P* value
Age	59.95+11.08	0.99 (0.97, 1.00), .143
Sex (M/F)	1724/808	1.39 (0.95, 2.04), .09
COPD	22 (0.87%)	2.63 (0.77, 9.01), .123
OMI	235 (9.28%)	0.79 (0.42, 1.49), .471
DM	521 (20.58%)	1.24 (0.84, 1.84), .277
Hypertension	1246 (49.21%)	1.15 (0.82, 1.60), .427
Stroke	135 (5.33%)	2.00 (1.12, 3.58), .019
Atrial fibrillation	50 (1.97%)	1.44 (0.51, 4.07), .487
Smoking	815 (32.18%)	1.15 (0.81, 1.64), .427
LDL-C	2.67+0.94	0.97 (0.80, 1.18), .784
TC	4.26+1.06	1.04 (0.88, 1.23), .627
Statin	2303 (90.92%)	0.86 (0.49, 1.49), .586
Aspirin	2498 (98.70%)	1.96 (0.27, 14.39), .509
Clopidogrel	2430 (96.05%)	0.80 (0.36, 1.76), .578
Presentation		
Urgent PCI	99 (3.91%)	Reference
Delayed PCI	521 (20.57%)	0.63 (0.23, 1.76), .382
NSTE-ACS	1495 (59.02%)	1.32 (0.52, 3.32), .557
Stable angina	418 (16.50%)	1.20 (0.45, 3.21), .722
Type of stent		
SES	1650 (65.17%)	Reference
PES	504 (19.91%)	1.15 (0.74, 1.80), .525
Non-DES	378 (14.93%)	2.13 (1.42, 3.20), <.001
One-vessel	993 (39.20%)	0.92 (0.65, 1.29), .618
Two-vessel	929 (36.68%)	0.87 (0.61, 1.25), .458
Multi-vessel	606 (23.92%)	1.32 (0.91, 1.91), .144
LM	86 (3.40%)	1.99 (0.97, 4.05), .059
LAD	2092 (82.59%)	1.34 (0.82, 2.17), .238
LCX	1224 (48.32%)	1.12 (0.80, 1.57), .501
RCA	1257 (49.62%)	1.06 (0.76, 1.48), .727
Occlusion	330 (13.03%)	0.88 (0.52, 1.48), .631
CTO	226 (8.92%)	1.29 (0.75, 2.20), .359
Ostial lesion	275 (10.86%)	1.02 (0.60, 1.74), .944
Bifurcation lesion	447 (17.65%)	1.53 (1.03, 2.27), .036
Number of stents	2.16+1.26	1.21 (1.08, 1.37), .001

Table 3

Multivariate logistic regression.

Exposure	Non-adjusted OR	Adjusted OR, *P* value
Number of stents	1.30 (1.15, 1.47), *P*<.0001	1.38 (1.15, 1.66), <.001
Number of stents		
1 stent	reference	reference
2–3 stents	1.27 (0.83, 1.97), *P*=.2737	1.59 (0.88, 2.86), .122
4–5 stents	1.95 (1.12, 3.37), *P*=.0176	2.07 (0.91, 4.71), .081
>=6 stents	4.42 (1.84, 10.57), *P*=.0009	5.12 (1.68, 15.57), .004
number of stent (trend)	1.49 (1.18, 1.89), *P*=.0008	1.59 (1.13, 2.23), .008
Number of stents		
1–2 stents	reference	reference
3–5 stents	1.81 (1.23, 2.66), *P*=.0027	2.20 (1.24, 3.90), .007
>=6 stents	4.39 (1.89, 10.21), *P*=.0006	5.33 (1.89, 15.08), .002
number of stents (trend)	1.92 (1.40, 2.64), *P* < .0001	2.26 (1.43, 3.59), <.001

Adjusted: Sex; type of stent; Presentation; Age; COPD; OMI; smoking; DM; LDL-C; TC; aspirin; 1-vessel; two-vessel; multi-vessel; LM; LAD; LCX; RCA; occlusion; CTO; ostial lesion; bifurcation lesion; statin; clopidogrel; hypertension; stroke; atrial fibrillation.

There were some studies showed that the number of stents was one possible risk of stent restenosis in patients undergoing PCI. A total of 189 patients with 318 stents underwent invasive coronary angiography were enrolled in Yung-Liang Wan's study, they found that the number of stents was significantly related to stent restenosis.[6] In Volpe M's study which included 796 patients previously treated with PCI, they found that patients with stent restenosis received higher stent number (1.40±0.74) than patients without stent restenosis (1.24±0.51), $P < .001$.[7] In a retrospective study involving a total of 261 patients with coronary heart disease from Dongfeng General Hospital implanted with a coronary DES, number of stents was associated with stent restenosis.[8] However, these studies did not adjust the possible confounding factors only, so they could only show that the number of stents was one possible risk of stent restenosis in patients undergoing PCI. In our study, we not only found that the number of stents was associated with stent restenosis, but also

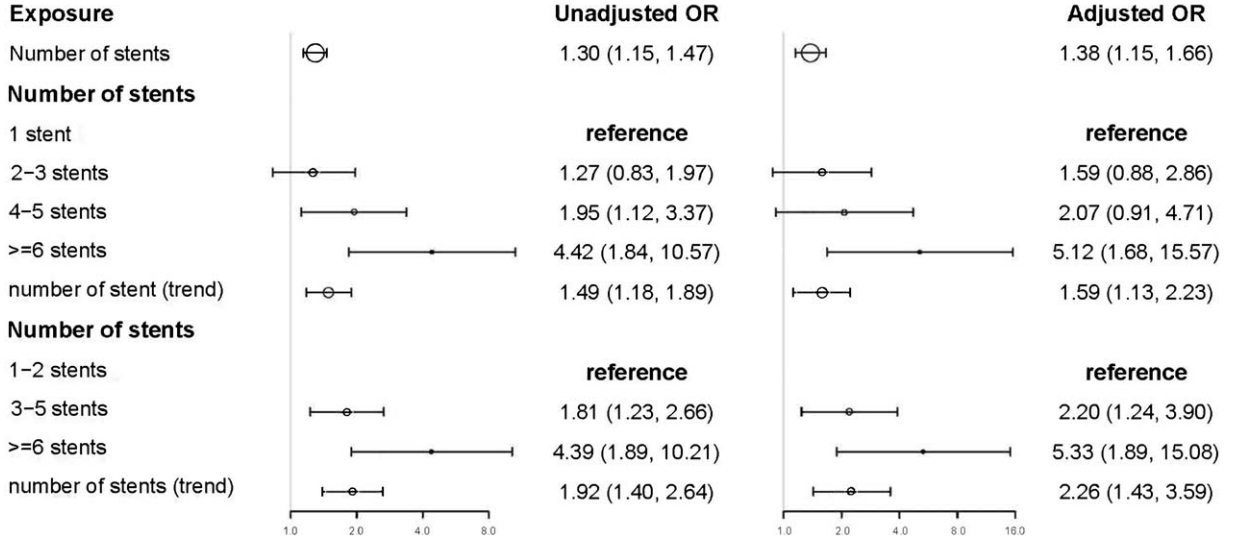

Figure 2. The multivariate logistic regression.

Table 4

Subgroup analysis of multivariate logistic regression to further detect the relationship between the number of stents and stent restenosis.

Exposure	Non-adjusted OR	Adjusted OR, *P* value
Age		
Age≤50	1.26 (0.98, 1.61) 0.0723	1.50 (0.96, 2.34), .073
50<Age≤70	1.21 (1.03, 1.44) 0.0240	1.36 (1.06, 1.74), .016
70<Age	1.95 (1.40, 2.71) <0.0001	2.12 (1.07, 4.22), .032
Sex		
Female	1.57 (1.26, 1.96) <0.0001	1.97 (1.37, 2.83), < .001
Man	1.20 (1.02, 1.40) 0.0231	1.20 (0.95, 1.52), .133
Presentation		
Stable angina	1.16 (0.84, 1.60) 0.3747	2.21 (1.01, 4.80), .046
Urgent PCI	1.76 (1.14, 2.72) 0.0103	-
Delayed PCI	1.34 (0.95, 1.90) 0.0998	2.09 (1.02, 4.28), .043
NSTE-ACS	1.28 (1.09, 1.51) 0.0021	1.27 (1.00, 1.60), .047
Type of stent		
SES	1.20 (0.99, 1.46) 0.0569	1.51 (1.13, 2.01), .005
PES	1.24 (0.91, 1.69) 0.1728	1.35 (0.84, 2.17), .211
Non-DES	1.28 (0.98, 1.68) 0.0749	1.46 (1.01, 2.13), .046
Total	1.23 (1.07, 1.41) 0.0035	1.38 (1.15, 1.66), <.001

The adjusted variables including sex; type of stent; presentation; age; COPD; OMI; smoking; DM; LDL-C; TC; aspirin; 1-vessel; two-vessel; multi-vessel; LM; LAD; LCX; RCA; occlusion; CTO; ostial lesion; bifurcation lesion; statin; clopidogrel; hypertension; stroke; atrial fibrillation in each subgroup analysis, except itself of the subgroup variables.

verified that the number of stents was an independent risk of stent restenosis in patients undergoing PCI, after we adjusted the possible confounding factors that might be related to stent restenosis as follows: age sex hypertension stroke atrial fibrillation COPD OMI DM smoking statin aspirin clopidogrel LDL-C TC presentation stable angina type of stent 1-vessel two-vessel multi-vessel LM LAD LCX RCA occlusion CTO ostial lesions and bifurcation lesion.

After adjusting for other factors that may lead to restenosis of cardiac stents, we found that the risk of restenosis of 2–3 stents was not increased compared with that of 1 stent, but the further studies found that the risk of restenosis of 3–5 stents was 2.2 times of 1–2 stents. Therefore, when the number of stents was greater than 2, the risk of restenosis would increase significantly. Although the drug eluting stent can reduce the risk of early stent thrombosis, it can increase the risk of delayed stent thrombosis.[10–13] The more stents, the higher the risk of stent thrombosis,[13,14] and the thrombus organization would lead to stent restenosis.[15–17] At the same time, the more stents, the greater the damage to blood vessels caused by the stent itself.[18,19] The inflammation reaction that caused by endothelial damage and the activation of platelets, fibrin and neutrophils, promotes proliferation of fibroblasts and smooth muscle cells, finally resulting in stent restenosis.[20–24] In addition, drug-eluting stents can cause structural and functional damage to endothelial cells, which can cause damage to vascular endothelial repair, and promote new atherosclerosis. New atherosclerosis may be also a possible reason for stent restenosis.[25–27]

Our study showed that when the age was over 50 years old, the risk of stent restenosis increased by 36% for every additional stent, and when the age was over 70 years old, the risk of stent restenosis increased by 112% for each additional stent. The possible reason was that with the increase of age, hypertension, coronary heart disease, diabetes, cerebrovascular accident and other diseases were more likely to occur, and the risk of vascular injury and thrombosis was higher.[28] In addition, as a foreign body, the stent itself had a high risk of stent restenosis with the increase of the number of stents.[6–8] Therefore, when combining age >50 and more stents, the risk of restenosis will increase more obviously.

This study found that with the increase in the number of stents, the risk of stent stenosis in female patients was significantly higher than that in male patients. For every stent added, the risk of stent stenosis in female patients increased by 97%. The reasons may be as follows:

1) estrogen levels in the body decreased significantly after menopause with women, while estrogen could increase endothelial cell-mediated dilation and delay the formation of arteriosclerosis;[29,30]
2) at the same time, the diameter of coronary artery in women is smaller than that in men,[31] so the stent placement would be relatively more damaging to blood vessels.

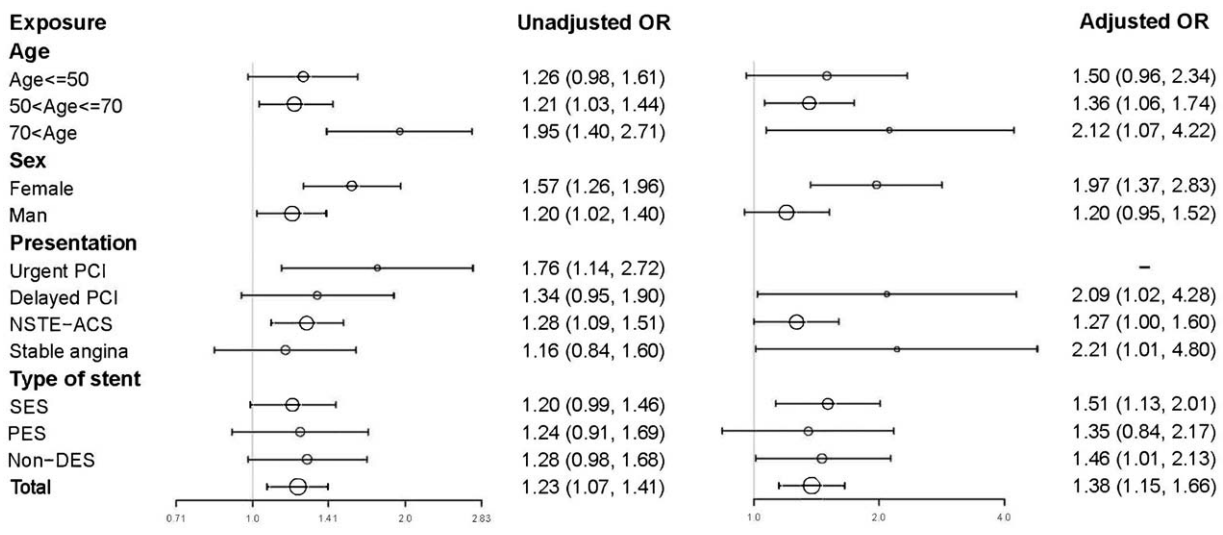

Figure 3. The subgroup analysis.

Our study found that the risk of restenosis increased by 109%, 27%, and 121% for each additional stent of delayed PCI, NSTE-ACS and Stable angina. Due to the small sample size of urgent PCI, the subgroup analysis of multi-factor analysis failed to get the results of subgroup after adjusting the related variables. However, univariate analysis found that the risk of stent restenosis was increased by 76% for every stent added during urgent PCI. So, patients with NSTE-ACS had significantly lower risk of restenosis than other types of presentation as the number of stents increased. The reason may be that the vascular lesion of NSTE-ACS was generally more serious than other types of ACS,[32] and its thrombus was mainly white thrombus,[33] which the main component was platelet. As a result of that, the blood vessel opening mainly depends on stent placement, but thrombolysis therapy was not effective. That means that stent placement was the most critical and important treatment.[31] However, the stent placement in other types of ACS sometimes might be ineffective and unnecessary which would cause side effects obviously.

This study found that PES stents had a lower risk of restenosis than SES and non-DES stents. At present, there were consistent research conclusions that the restenosis rate of drug-eluting stents was lower than that of non-drug-eluting stents. However, the incidence of restenosis of PES and SES stents is still controversial. A randomized controlled trial involving 1012 cases followed up for 10 years found that the stent restenosis rate of PES was 33.8%, while that of SES was 33.7%. There was no significant difference between the two ($P = .72$).[34] In another retrospective study that included 1845 patients, it was found that drug-eluting stent types were the stronger predictors of restenosis. Compared with PES, SES was associated with adjusted OR of 0.60 (95% CI, 0.44 to 0.81) for angiographic restenosis.[35] Our research got a different conclusion, which may be due to the relatively large sample size of this research, while we adjust the mixed variables, so our research conclusion has certain reliability. However, since our study is a retrospective study, further study is needed.

When compared with the previous studies, our study has the following characteristics:

1) our study was with a much larger sample size which would make the results more reliable;
2) we adjusted the possible confounding factors that might be related to stent restenosis to achieve the independent effect of the number of stents on stent restenosis;
3) we found that the number of stents ≤ 2 would significantly decrease the risk of stent restenosis, which has not been reported before;
4) we also found that $50 <$ Age and female as the number of stents increased, the risk of stent restenosis would increase obviously, which also hasn't been reported before;
5) at the same time, we also newly found that patients with PES (paclitaxel-eluting stent), as the number of stents increased, the risk of stent restenosis did not increase.

4.1. Generalizability

1) We adjusted the possible confounding factors that might be related to stent restenosis to achieve the independent effect of the number of stents on stent restenosis;
2) we found that the number of stents ≤ 2 would significantly decrease the risk of stent restenosis, which has not been reported before;
3) we also found that $50 <$ Age and female as the number of stents increased, the risk of stent restenosis would increase obviously, which also has not been reported before.

4.2. Limitations of this study

1) This is an observational single-center registry and may have an inherent bias common to this type of study.
2) The follow-up angiography was only performed on the symptoms and the examination abnormalities, so only 23.8% of patients, which might lead the rate of in-stent restenosis to be underestimated.

5. Conclusion

The number of stents was an independent risk of stent restenosis in patients undergoing PCI, especially for patients with the following conditions: $2 <$ the number of stents, $50 <$ age, female, non-urgent PCI, Non-DES or SES.

Acknowledgments

Thank for Seung Tong-Wen Sun providing the data in the dryad database.

Author contributions

Data curation: Dan-Ping Liu.
Project administration: Ying-Ying Fu.
Software: Qian-Wei Cui, Dan-Ping Liu.
Supervision: Ying-Ying Fu.
Writing – original draft: Long Tang.

References

[1] Lekshmi KM, Che HL, Cho CS, et al. Drug- and gene-eluting stents for preventing coronary restenosis. Chonnam Med J 2017;53:14–27.
[2] Wang JL, Qin Z, Wang ZJ, et al. New predictors of in-stent restenosis in patients with diabetes mellitus undergoing percutaneous coronary intervention with drug-eluting stent. J Geriatr Cardiol 2018;15:137–45.
[3] van den Berg JC. In-stent restenosis management: The best is yet to come. J Cardiovasc Surg 2017;58:508–17.
[4] Berta B, Jambrik Z, Kohar K, et al. Efficacy of drug-eluting balloon in patients with bare-metal or drug-eluting stent restenosis. Hellenic J Cardiol 2014;55:369–77.
[5] Oh PC, Suh SY, Kang WC, et al. The efficacy and safety of drug-eluting balloons for the treatment of in-stent restenosis as compared with drug-eluting stents and with conventional balloon angioplasty. Korean J Intern Med 2016;31:501–6.
[6] Wan YL, Tsay PK, Chen CC, et al. Coronary in-stent restenosis: Predisposing clinical and stent-related factors, diagnostic performance and analyses of inaccuracies in 320-row computed tomography angiography. Int J Cardiovasc Imaging 2016;32(Suppl 1):105–15.
[7] Tocci G, Barbato E, Coluccia R, et al. Blood pressure levels at the time of percutaneous coronary revascularization and risk of coronary in-stent restenosis. Am J Hypertens 2016;29:509–18.
[8] Qian H, Luo Z, Xiao C, et al. Red cell distribution width in coronary heart disease: prediction of restenosis and its relationship with inflammatory markers and lipids. Postgrad Med J 2018;94:489–94.
[9] Yao H, Wan Y, Zhang X, et al. Long-term follow-up results in patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents: results from a single high-volume pci center. BMJ Open 2014;4: e004892.
[10] Kotani J, Nanto S, Ueda Y, et al. Angioscopic findings before and after thrombus-related drug-eluting stent failure. Cardiovasc Interv Ther 2015;30:198–208.
[11] Taniwaki M, Radu MD, Zaugg S, et al. Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. Circulation 2016;133:650–60.

[12] Partida RA, Yeh RW. Contemporary drug-eluting stent platforms: design, safety, and clinical efficacy. Interv Cardiol Clin V 5 2016;331–47.
[13] Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: Evidence from a comprehensive network meta-analysis. Lancet (London, England) 2012;379: 1393–402.
[14] Thayssen P, Jensen LO, Lassen JF, et al. The risk and prognostic impact of definite stent thrombosis or in-stent restenosis after coronary stent implantation. EuroIntervention 2012;8:591–8.
[15] Fujii K, Masutani M, Ohyanagi M. Contribution of organized thrombus to in-stent restenosis after sirolimus-eluting stent implantation: Optical coherence tomography findings. Eur Heart J 2008;29:1385.
[16] Miyake K, Tada T, Kadota K, et al. Incomplete stent apposition, multiple interstrut hollows and their related thrombus in in-stent restenosis lesions assessed with optical coherence tomography. Eur Heart J 2013;34:5433–15433.
[17] Bulum J, Ernst A, Strozzi M. The impact of successful manual thrombus aspiration on in-stent restenosis after primary pci: Angiographic and clinical follow-up. Coron Artery Dis 2012;23:487–91.
[18] Wang Y. Stents fabricated from a sheet with increased strength, modulus and fracture toughness. Free Patents Online 2010;US 2010/0244304A1.
[19] Lee JH, Kim ED, Jun EJ, et al. Analysis of trends and prospects regarding stents for human blood vessels. Biomater Res 2018;22:8–18.
[20] McDonald RA, Halliday CA, Miller AM, et al. Reducing in-stent restenosis: Therapeutic manipulation of mirna in vascular remodeling and inflammation. J Am Coll Cardiol 2015;65:2314–27.
[21] Wasser K, Schnaudigel S, Wohlfahrt J, et al. Inflammation and in-stent restenosis: The role of serum markers and stent characteristics in carotid artery stenting. PloS One 2011;6:e22683.
[22] Kucukseymen S. Inflammation effects on stent restenosis. Angiology 2017;68:741.
[23] Bae I-H, Jeong MH, Lim KS, et al. Novel polymer-free everolimus-eluting stent fabricated using femtosecond laser improves re-endothelialization and anti-inflammation. Sci Rep 2018;8:7383–17383.
[24] Kundi H. Association of novel inflammatory and oxidative stress biomarkers with in-stent restenosis. Angiology 2017;68:832.
[25] Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents: Importance of delayed healing. Arterioscler Thromb Vasc Biol 2007;27:1500–10.
[26] Hokimoto S, Tabata N, Yamanaga K, et al. Prevalence of coronary macro- and micro-vascular dysfunctions after drug-eluting stent implantation without in-stent restenosis. Int J Cardiol 2016;222:185–94.
[27] Nakata T, Fujii K, Fukunaga M, et al. Morphological, functional, and biological vascular healing response 6 months after drug-eluting stent implantation: a randomized comparison of three drug-eluting stents. Catheter Cardiovasc Interv 2016;88:350–7.
[28] Munoz Maniega S, Chappell FM, Valdes Hernandez MC, et al. Integrity of normal-appearing white matter: Influence of age, visible lesion burden and hypertension in patients with small-vessel disease. J Cerebr Blood Flow Metabol 2017;37:644–56.
[29] Takeda R, Ikeda M, Miyamori I, et al. Relationship of plasma levels of estradiol to the severity of coronary arteriosclerosis. Atherosclerosis 1987;68:175–6.
[30] Novella S, Heras M, Hermenegildo C, et al. Effects of estrogen on vascular inflammation: a matter of timing. Arterioscler Thromb Vasc Biol 2012;32:2035–42.
[31] Lo RC, Lu B, Fokkema MT, et al. Relative importance of aneurysm diameter and body size for predicting abdominal aortic aneurysm rupture in men and women. J Vasc Surg 2014;59:1209–16.
[32] Rodriguez F, Mahaffey KW. Management of patients with nste-acs: a comparison of the recent aha/acc and esc guidelines. J Am Coll Cardiol 2016;68:313–21.
[33] Viswanathan GN, Marshall SM, Balasubramaniam K, et al. Differences in thrombus structure and kinetics in patients with type 2 diabetes mellitus after non st elevation acute coronary syndrome. Thromb Res 2014;133:880–5.
[34] Yamaji K, Raber L, Zanchin T, et al. Ten-year clinical outcomes of first-generation drug-eluting stents: The sirolimus-eluting vs. Paclitaxel-eluting stents for coronary revascularization (sirtax) very late trial. Eur Heart J 2016;37:3386–95.
[35] Adnan K, Alban D, Julinda M, et al. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. Circulation 2006;113:2293–300.