# Risk Factors of Coronary In–Stent Restenosis in Drug-Eluting Stent: A Systematic Review and Meta-Analysis

# Hotmauli Siahaan<sup>1\*</sup>, Hari Basuki Notobroto<sup>2</sup>, Yudi Her Oktaviono<sup>3</sup>, Paulus Parholong Siahaan<sup>4</sup>, David Setyo Budi<sup>4</sup>, Rizky Novita Anjaswanti<sup>5</sup>

<sup>1</sup>Doctoral Program of Public Health, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia. <sup>2</sup>Department of Epidemiology, Biostatistics, Population Studies and Health Promotion, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia.

<sup>3</sup>Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

<sup>4</sup>Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

<sup>5</sup>Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia.

#### \*Corresponding Author:

Hotmauli Siahaan, MD. Faculty of Public Health, Universitas Airlangga, Campus C, Mulyorejo, Surabaya 60115, Indonesia. Email: <u>hotmauli.siahaan-2023@fkm.unair.ac.id</u>

### ABSTRACT

**Background:** In-stent restenosis (ISR) is an event of coronary atherosclerosis re-budling following the stent implantation in percutaneous coronary intervention. The events of ISR have been significantly reduced since the introduction of drug-eluting stents. However, ISR could still occur, and factors affecting the incident have not yet been discovered. This study aims to evaluate the risk factors of coronary in-stent restenosis in drug-eluting stents. Methods: Studies on the factors and risks of ISR in patients with drug-eluting stents were systematically searched in databases (PubMed, ScienceDirect, Springer, Google Scholar, and ProQuest) on September 20th, 2023. The odds ratio (OR) and mean difference (MD) were analyzed using Review Manager 5.4. **Results:** Diabetes mellitus (OR 1.73 [95%CI 1.56, 1.91] p < 0.00001) and smoking (OR 1.24 [95%CI 1.13, 1.36] p < 0.0001) are the patients' clinical characteristics that are associated with ISR in DES. It is closely related to the contribution of diabetes mellitus in promoting platelet adhesion and smoking in enhancing intimal hyperplasia. As in the angiography characteristics, stent lesion at LAD (OR 1.20 [95%CI 1.07, 1.35] p = 0.002) and stent length (MD 3.61 [95%CI 1.81, 5.42] p < 0.0001) are correlated with the events of ISR. Every millimeter excess of stent length significantly increases the risk of ISR. Therefore, reducing the excess stent length may contribute to the reduced risk of ISR in DES. Conclusion: The identification of risk factors contributing to ISR in DES may help cardiologists modify the attributable factors and prevent the occurrence of ISR.

Keywords: Drug-eluting stents, Meta-analysis, Risk factor ISR, Systematic review.

## INTRODUCTION

Percutaneous coronary intervention (PCI) has become one of the effective methods for the treatment of coronary heart disease (CHD). However, it is easy to have in-stent restenosis (ISR), even cardiovascular events after PCI, which affects the therapeutic effects. In-stent restenosis is a corollary of the improved durability of modern-day coronary inter. After performing percutaneous coronary intervention (PCI), patients are still at risk of developing new stenosis, such as intra-stent restenosis (ISR).<sup>1</sup> The widespread application of new anticoagulants and drug-eluting stents has significantly decreased the incidence of coronary ISR. Nevertheless, large-scale clinical trials have confirmed that a 5% probability of restenosis exists despite the use of drug-eluting stents.<sup>2</sup>

The first and especially second-generation drug-eluting stents (DES) were specifically designed to reduce hyperproliferation within stents as a mechanism to overcome the high rate of ISR.<sup>3</sup> Nevertheless, the prevalence of ISR is estimated to vary from 3 to 20% in the current DES era, depending on coronary anatomy, and patient- and procedure-related factors.<sup>3</sup> This suggests that the type of stent is only one factor to consider when searching for additional promoters of ISR. The results of previous research concluded that the factors associated with ISR after PCI have not been clearly defined. In previous studies, several risk factors for ISR have been found, but not much research data on risk factors for ISR in drug-eluting stents (DES). For this reason, we systematically review the latest evidence to detect the risk factors of instent restenosis with drug-eluting stents (DES).

# **METHODS**

This meta-analysis is conducted based on PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) 2020 guidelines. This study had been registered on the PROSPERO database (CRD42023465249).

# **Eligibility Criteria**

Studies were selected based on inclusion criteria, which are: (1) observational study with human subjects, (2) investigated the association between risk factors and ISR after stent implantation (DES), (3) ISR was defined as  $\geq$ 50% diameter stenosis of the culprit lesion by quantitative coronary analysis. The exclusion criteria were: (1) CAD without implantation stent, (2) RCT study. Two independent reviewers screened for the included studies (PS and PBTS). Our senior reviewer (HS) made the final decision when there were differences in the screening results.

# Search Strategy and Selection of Studied

Electronic databases include PubMed, ScienceDirect, Springer, Google Scholar, and Proquest. The search terms have diabetes mellitus, ISR, in-stent restenosis, PCI, risk factor, and drug-eluting stent. Databases were searched using terms (('risk factors')) AND (('drug eluting stent')) AND (('in stent restenosis')) on September 20th, 2023. Newcastle-Ottawa Scale was used to evaluate the risk of bias for each study independently, with each bias assessment consisting of the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest, with the assessment of good, fair, and low quality of a study.

### **Data Extraction**

The following data: age, patient's status of hypertension, diabetes mellitus, smoking, dyslipidemia, and family history of CAD, and the paramount data of lesion at LAD, lesion at LCX, lesion at RCA, stent diameter, and stent length, each representing ISR and Non-ISR patients were collected and recorded in a formatted table.

### **Statistical Analysis**

The software Review Manager 5.4 was used to conduct statistical analyses, dichotomous data (risk ratio and odds ratio) used Mantel-Haenszel statistical method for hypertension, diabetes mellitus, smoking, dyslipidemia, and family history of CAD, and the paramount data of lesion at LAD, lesion at LCX, lesion at RCA, and continuous data (mean difference) used inverse variance statistical method for stent length and diameter. Heterogeneity was analyzed using the DerSimonian and Laird random-effect model.

Sensitivity analysis should also be done, by using the leave-one-out approach to detect study outliers and changes in heterogeneity (I2), with I2 values of 0-50% representing low heterogeneity, 50-75% representing moderate heterogeneity, and 76-100% representing substantial heterogeneity. The data analysis employed either the fixed or the random effect model. All statistical analysis with a p-value < 0.05 was considered statistically significant. Leave-one-out sensitivity analysis was conducted to find the source of statistical heterogeneity and demonstrate how each study affected the overall result.



Figure 1. The study selection process in the PRISMA diagram

### RESULTS

### **Characteristics of Studies**

Among 12,526 studies gathered from databases, 28 articles were included.<sup>4-31</sup> The risk of bias from 26 articles was assessed to be good, while the other 2 studies were fair. This study involved a total of 12.559 patients, where 2.701 patients developed ISR and the rest 9.858 were

non-ISR patients as controls. Most of the studies originated from China, while there was one study from Turkiye, one study from Japan, and the rest one study was from Italy. Data were collected from patients from 2004 to 2020. Moreover, the quality of the included studies was assessed using the Newcastle-Ottawa Scale and summarized in Supplementary Materials (**Table S2**).

Table 1. Characteristics of subjects.

No	Outcomes	No of Studies	Type of TE	TE (95% CI)	Р	<b>1</b> <sup>2</sup>	P for I <sup>2</sup>
1.	Hypertension	26	OR	1.23 (1.03, 1.47)	0.02	61%	< 0.0001
2.	Diabetes Mellitus	25	OR	1.73 (1.56, 1.91)	< 0.00001	43%	0.01
3.	Smoking	27	OR	1.24 (1.13, 1.36)	< 0.0001	33%	0.05
4.	Family history of CAD	10	OR	1.27 (1.02, 1.58)	0.03	0%	0.77
5.	Dyslipidemia	19	OR	1.12 (0.89, 1.41)	0.33	71%	<0.00001

26 articles discuss hypertension and the incidence of ISR. The results of the study stated that hypertension showed a significant relationship with the incidence of ISR (OR 1.23; CI 95% 1.03-1.47; I2 61%; p < 0.0001). However, the prevalence of hypertension between ISR and non-ISR was 2402 versus 9922, which shows an increased rate of restenosis in hypertension. In the diabetes mellitus variable, 25 articles discuss the relationship between diabetes mellitus and ISR incidence. This study found a significant correlation between diabetes mellitus and ISR events (OR 1.73; 95% CI 1.56-1.91; I2 43%;

p<0.00001). The research we have conducted from 27 articles states that there is a significant correlation between smoking and the incidence of ISR (OR 1.24; 95% CI 1.13-1.36; I2 33%; p <0.0001). Research conducted on 10 research articles found a significant relationship between ISR and family history of CHD (OR 1.27; CI 95% 1.02-1.58; I2 0%; p= 0.03). Meanwhile, research between ISR and dyslipidemia stated that there was no significant relationship between the two (OR 1.12; CI 95% 0.89-1.41; I2 71%; p= 0.33) (**Figure 2**).

Hypertension							
	ISR		Non I	SR		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Canbolat 2019	50	99	128	220	4.8%	0.73 [0.46, 1.18]	-+-
Chen 2022	16	30	128	227	3.2%	0.88 [0.41, 1.90]	
Cheng 2019	61	93	592	1039	5.0%	1.44 [0.92, 2.25]	+
Feng 2022	17	20	146	215	1.6%	2.68 [0.76, 9.44]	
Gabbasov 2016	49	53	70	73	1.2%	0.53 [0.11, 2.45]	
Jiang 2022	182	279	706	1222	6.2%	1.37 [1.05, 1.80]	-
Li 2018	38	72	169	344	4.6%	1.16 [0.70, 1.92]	_ <del></del>
Li 2022	37	62	178	279	4.3%	0.84 [0.48, 1.47]	
Luo 2022	108	192	234	476	5.8%	1.33 [0.95, 1.86]	+
Nakamura 2021	124	146	137	165	4.0%	1.15 [0.63, 2.12]	_ <b>_</b>
Nan 2020	20	24	144	190	1.9%	1.60 [0.52, 4.91]	
Qian 2018	89	118	97	143	4.4%	1.46 [0.84, 2.51]	+
Qin 2017	84	132	764	1074	5.5%	0.71 [0.49, 1.04]	
Song 2021	31	38	119	176	2.7%	2.12 [0.88, 5.11]	
Tocci 2016	275	354	355	442	5.8%	0.85 [0.61, 1.20]	
Wang 2018	48	74	192	294	4.4%	0.98 [0.57, 1.67]	-+-
Wang 2020	43	64	55	145	3.9%	3.35 [1.80, 6.23]	
Wu 2018	64	81	97	133	3.7%	1.40 [0.72, 2.70]	- <del></del>
Xi 2023	43	57	215	357	3.8%	2.03 [1.07, 3.84]	
Zeng 2021	32	43	154	203	3.2%	0.93 [0.43, 1.97]	
Zhang 2021	9	18	56	96	2.2%	0.71 [0.26, 1.96]	
Zhao 2015	31	45	164	427	3.7%	3.55 [1.83, 6.87]	
Zhao 2019	24	42	239	316	3.7%	0.43 [0.22, 0.83]	_ <b></b>
Zhao 2020	33	37	248	361	2.1%	3.76 [1.30, 10.86]	
Zhou 2022	23	30	139	185	2.6%	1.09 [0.44, 2.70]	
Zhu 2022	142	199	717	1120	5.8%	1.40 [1.01, 1.95]	-
Total (95% CI)		2402		9922	100.0%	1.23 [1.03, 1.47]	<b>◆</b>
Total events	1673		6243				
Heterogeneity: Tau <sup>2</sup> =	0.12; Chi	<sup>2</sup> = 64.1	79, df = 2	5 (P < (	0.0001); P	²= 61%	
Test for overall effect:	Z = 2.24 (	(P = 0.0	12)				0.01 0.1 1 10 100 Non ISR ISR

	ISR		Non I	SR		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Canbolat 2019	29	99	63	220	5.0%	1.03 [0.61, 1.74]	_ <b>+</b> _
Chen 2022	13	30	48	227	1.1%	2.85 [1.30, 6.28]	
Cheng 2019	42	93	308	1039	5.0%	1.95 [1.27, 3.00]	
Feng 2022	10	20	54	215	0.8%	2.98 [1.18, 7.55]	
Gabbasov 2016	30	53	25	73	1.6%	2.50 [1.21, 5.18]	
Jiang 2022	171	279	433	1222	11.2%	2.89 [2.21, 3.77]	-
Jing 2015	15	50	12	50	1.5%	1.36 [0.56, 3.30]	_ <b>_</b>
Li 2018	27	72	86	344	3.4%	1.80 [1.05, 3.08]	<b></b>
Li 2022	28	62	109	279	3.9%	1.28 [0.74, 2.24]	_ <del></del>
Luo 2022	47	192	91	476	7.1%	1.37 [0.92, 2.05]	+
Nakamura 2021	86	146	91	165	6.3%	1.17 [0.74, 1.83]	_ <b>+</b>
Nan 2020	11	24	91	190	2.0%	0.92 [0.39, 2.16]	
Qian 2018	51	118	43	143	4.0%	1.77 [1.06, 2.95]	<b>⊢</b> •−
3ong 2021	20	38	43	176	1.3%	3.44 [1.67, 7.09]	——
Tocci 2016	141	354	155	442	15.0%	1.23 [0.92, 1.64]	
Wang 2020	36	64	59	145	2.9%	1.87 [1.03, 3.40]	
Wu 2018	29	81	30	133	2.6%	1.91 [1.04, 3.52]	
Xi 2023	22	57	87	357	2.7%	1.95 [1.09, 3.50]	
Zeng 2021	24	43	105	203	2.9%	1.18 [0.61, 2.29]	_ <del></del>
Zhang 2021	8	18	34	96	1.1%	1.46 [0.53, 4.04]	
Zhao 2015	17	45	63	247	2.2%	1.77 [0.91, 3.46]	
Zhao 2019	17	42	79	316	2.0%	2.04 [1.05, 3.97]	
Zhao 2020	14	37	89	361	1.9%	1.86 [0.92, 3.77]	
Zhou 2022	9	30	52	185	1.8%	1.10 [0.47, 2.55]	<b>_</b>
Zhu 2022	97	199	379	1120	10.6%	1.86 [1.37, 2.52]	
Total (95% CI)		2246		8424	100.0%	1.73 [1.56, 1.91]	•
Total events	994		2629				
-leterogeneity: Chi <sup>2</sup> =	41.97, df	= 24 (F	= 0.01);	I <sup>2</sup> = 439	%		
Fest for overall effect:	Z = 10.61	(P < 0.	.00001)				0.01 0.1 1 10 10

# Smoking

	ISR		Non I	SR		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Canbolat 2019	62	99	108	220	3.3%	1.74 [1.07, 2.82]	
Chen 2022	20	30	72	227	0.7%	4.31 [1.92, 9.67]	
Cheng 2019	35	93	332	1039	4.5%	1.29 [0.83, 1.99]	+
Feng 2022	7	20	55	215	0.8%	1.57 [0.59, 4.13]	
Gabbasov 2015	28	53	34	73	1.8%	1.28 [0.63, 2.61]	_ <del></del>
Jiang 2022	118	279	413	1222	11.8%	1.44 [1.10, 1.87]	
Jing 2015	26	50	23	50	1.5%	1.27 [0.58, 2.79]	_ <del></del>
Li 2018	39	72	136	344	2.9%	1.81 [1.08, 3.01]	
Li 2022	10	62	57	279	2.3%	0.75 [0.36, 1.56]	
Luo 2022	96	192	187	476	7.2%	1.55 [1.10, 2.17]	
Nakamura 2021	67	146	76	165	5.1%	0.99 [0.64, 1.55]	-+
Nan 2020	14	24	76	190	0.9%	2.10 [0.89, 4.97]	+
Qian 2018	38	118	43	143	3.5%	1.10 [0.65, 1.87]	_ <b>+</b>
Qin 2017	44	132	440	1074	8.6%	0.72 [0.49, 1.06]	
Song 2021	12	38	43	176	1.4%	1.43 [0.66, 3.07]	
Tocci 2016	124	354	145	442	11.2%	1.10 [0.82, 1.48]	<b>+</b> -
Wang 2018	26	74	128	294	4.5%	0.70 [0.41, 1.19]	
Wang 2020	22	64	49	145	2.6%	1.03 [0.55, 1.91]	
Wu 2018	30	81	46	133	2.9%	1.11 [0.63, 1.98]	_ <del></del> _
Xi 2023	24	57	123	357	2.6%	1.38 [0.78, 2.44]	+
Zeng 2021	22	43	70	203	1.6%	1.99 [1.02, 3.87]	
Zhang 2021	13	18	65	96	0.8%	1.24 [0.41, 3.79]	
Zhao 2015	19	45	77	247	1.8%	1.61 [0.84, 3.09]	+
Zhao 2019	21	42	157	316	2.5%	1.01 [0.53, 1.93]	
Zhao 2020	14	37	98	361	1.5%	1.63 [0.81, 3.30]	+
Zhou 2022	11	30	74	185	1.7%	0.87 [0.39, 1.93]	
Zhu 2022	74	199	392	1120	9.9%	1.10 [0.80, 1.50]	+
Total (95% CI)		2452		9792	100.0%	1.24 [1.13, 1.36]	•
Total events	1016		3519				
Heterogeneity: Chi² = Test for overall effect:	38.91, df Z = 4.39 (	= 26 (P (P < 0.0	? = 0.05); 1001)	l² = 33'	%		0.01 0.1 1 10 100 Non ISR ISR

Family history	of CAI	D													
	ISR Non ISR Odds Ratio Odds Ratio														
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl							
Chen 2022	9	30	38	227	4.5%	2.13 [0.91, 5.01]									
Cheng 2019	10	93	84	1039	8.8%	1.37 [0.69, 2.74]									
Feng 2022	7	20	55	215	4.4%	1.57 [0.59, 4.13]									
Qin 2017	28	132	168	1074	20.8%	1.45 [0.93, 2.27]		+							
Song 2021	12	38	34	176	5.9%	1.93 [0.88, 4.20]									
Wang 2018	14	74	54	294	12.6%	1.04 [0.54, 1.99]		<b>_</b> _							
Wu 2018	16	81	23	133	10.0%	1.18 [0.58, 2.39]									
Zeng 2021	12	43	64	203	11.6%	0.84 [0.41, 1.74]									
Zhao 2015	23	45	131	247	14.2%	0.93 [0.49, 1.75]									
Zhao 2020	9	37	72	361	7.3%	1.29 [0.58, 2.85]									
Total (95% CI)		593		3969	100.0%	1.27 [1.02, 1.58]		◆							
Total events	140		723												
Heterogeneity: Chi <sup>2</sup> =	5.67, df=	9 (P =	0.77); l² =	= 0%					100						
Test for overall effect: .	Z = 2.17 (	(P = 0.0	)3)				0.01	Non ISR ISR	100						

### Hyperlipidemia

	ISR		Non I	SR		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Canbolat 2019	55	99	161	220	6.1%	0.46 [0.28, 0.75]	
Cheng 2019	39	93	326	1039	6.6%	1.58 [1.03, 2.43]	<b>⊢</b> •−
Feng 2022	17	20	123	215	2.4%	4.24 [1.21, 14.89]	
Gabbasov 2015	53	53	70	73	0.6%	5.31 [0.27, 105.05]	
Jiang 2022	115	279	379	1222	7.7%	1.56 [1.19, 2.04]	
Li 2018	40	72	178	344	6.0%	1.17 [0.70, 1.94]	_ <del></del>
Li 2022	14	62	68	279	5.1%	0.91 [0.47, 1.74]	
Nakamura 2021	97	146	119	165	6.2%	0.77 [0.47, 1.24]	
Qin 2017	56	132	528	1074	7.1%	0.76 [0.53, 1.10]	
Song 2021	31	38	104	176	3.8%	3.07 [1.28, 7.34]	│ <del>──</del>
Tocci 2016	220	354	324	442	7.5%	0.60 [0.44, 0.81]	
Wang 2018	40	74	152	294	6.0%	1.10 [0.66, 1.83]	+-
Wu 2018	54	81	73	133	5.6%	1.64 [0.93, 2.92]	
Xi 2023	10	57	27	357	4.3%	2.60 [1.18, 5.71]	<b>_</b>
Zhang 2021	14	18	62	96	2.6%	1.92 [0.59, 6.29]	
Zhao 2015	23	45	131	247	5.2%	0.93 [0.49, 1.75]	<b>_</b>
Zhao 2019	14	42	93	316	4.9%	1.20 [0.60, 2.38]	<del></del>
Zhao 2020	19	37	212	361	4.9%	0.74 [0.38, 1.46]	
Zhu 2022	77	199	437	1120	7.5%	0.99 [0.72, 1.34]	+
Total (95% CI)		1901		8173	100.0%	1.12 [0.89, 1.41]	•
Total events	988		3567				
Heterogeneity: Tau <sup>2</sup> =	0.16; Chi	<b>=</b> 62.9	51, df = 1	8 (P < 0	).00001);	I² = 71%	
Test for overall effect:	Z=0.97 (	P = 0.3	3)				Non ISR ISR

Figure 2. Forest plot of the relationship between patient characteristics and ISR incidence

No	Outcomes	No of Studies	Type of TE	TE (95% CI)	Р	<b> </b> <sup>2</sup>	P for l <sup>2</sup>
1.	Lesion at LAD	21	OR	1.20 (1.07, 1.35)	0.002	39%	0.04
2.	Lesion at LCX	19	OR	1.17 (1.02, 1.34)	0.02	47%	0.01
3.	Lesion at RCA	21	OR	1.17 (1.04, 1.31)	0.008	31%	0.09
4.	Stent Diameter	13	MD	-0.12 (-0.22, -0.03)	0.009	94%	<0.00001
5.	Stent Length	13	MD	3.61 (1.81, 5.42)	<0.0001	93%	<0.00001

#### Table 2. Angiography characteristics

LAD is a lesion location that shows a significant correlation with the incidence of ISR (OR 1.20; 95% 1.07-1.35; I2 39%; p= 0.002). Apart from that, lesions located in the LCX also

have a significant relationship with the incidence of ISR (OR 1.17; 95% 1.02-1.34, I2 47%; p = 0.02). Lesions in the RCA were significantly correlated with the incidence of ISR (OR 1.17; 95% 1.04-1.31; I2 31%; p = 0.008). On the other hand, we have found that ISR is more likely to occur in patients with small stent diameters. The research we conducted on 13 articles stated that there was a significant relationship between stent diameter and ISR (MD -0.12; 95% CI -0.22, -0.03; I2 94%; p 0.009). The research we have conducted in 13 articles states that there is a significant relationship between stent length and the incidence of ISR (MD 3.61; 95% CI 1.81-5.42; I2 93%; p <0.0001) (Figure 3).

LCOIOII UT LAD							
	ISR		Non IS	R		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Canbolat 2019	44	99	88	220	5.6%	1.20 [0.74, 1.94]	
Chen 2022	24	30	170	227	1.5%	1.34 [0.52, 3.45]	
Cheng 2019	53	93	509	1039	6.7%	1.38 [0.90, 2.12]	<b></b>
Feng 2022	13	20	124	215	1.4%	1.36 [0.52, 3.55]	
Gabbasov 2015	36	53	41	73	2.1%	1.65 [0.79, 3.46]	<u> </u>
Li 2018	31	72	144	344	5.3%	1.05 [0.63, 1.75]	_ <b>_</b>
Nakamura 2021	76	146	78	165	6.5%	1.21 [0.78, 1.89]	
Nan 2020	10	24	88	190	2.1%	0.83 [0.35, 1.96]	
Qin 2017	100	132	636	1074	6.3%	2.15 [1.42, 3.26]	
Song 2021	24	38	104	176	2.5%	1.19 [0.58, 2.45]	
Tocci 2016	146	354	212	442	20.6%	0.76 [0.57, 1.01]	
Wang 2018	52	74	172	294	3.8%	1.68 [0.97, 2.91]	
Wang 2020	36	64	54	145	2.7%	2.17 [1.19, 3.94]	
Wu 2018	42	81	78	133	5.3%	0.76 [0.44, 1.32]	
Zeng 2021	14	43	49	203	2.1%	1.52 [0.74, 3.10]	
Zhang 2021	18	18	85	96	0.1%	4.98 [0.28, 88.27]	
Zhao 2015	25	45	160	247	4.1%	0.68 [0.36, 1.29]	
Zhao 2019 Zhao 2020	24	42	179	316	3.3%	1.02 [0.53, 1.96]	
Zhao 2020 Zhau 2020	23	37	199	301	2.6%	1.34 [0.67, 2.68]	
Zhou 2022	15	30	84	185	2.2%	1.20 [0.56, 2.60]	
Znu 2022	123	199	620	1120	13.3%	1.31 [0.96, 1.78]	-
Total (95% CI)		1694		7265	100.0%	1.20 [1.07, 1.35]	+
Total events	929		3874				
Heterogeneity: Chi <sup>2</sup> = 3	32.53, df=	= 20 (P	= 0.04);1	<sup>2</sup> = 399	6		
Test for overall effect: J	Z = 3.17 (ł	<sup>o</sup> = 0.00	02)				0.01 0.1 I 10 100 Non ISR ISR
							Non lore lore
Lesion at LCX							
	ISF		Nonl	<b>CD</b>			
Study or Subgroup		•	NUT	SK		Odds Ratio	Odds Ratio
Chen 2022	Events	Total	Events	SK Total	Weight	Odds Ratio M-H, Fixed, 95% Cl	Odds Ratio M-H, Fixed, 95% Cl
	Events 15	Total 30	Events 87	Total 227	Weight 2.6%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45]	Odds Ratio M-H, Fixed, 95% Cl
Cheng 2019	Events 15 16	<b>Total</b> 30 93	Events 87 156	Total 227 1039	Weight 2.6% 5.4%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07]	Odds Ratio M-H, Fixed, 95% Cl
Cheng 2019 Feng 2022	Events 15 16 12	Total 30 93 20	Events 87 156 75	Total 227 1039 215	Weight 2.6% 5.4% 1.3%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15]	Odds Ratio M-H, Fixed, 95% Cl
Cheng 2019 Feng 2022 Li 2018	Events 15 16 12 14	Total 30 93 20 72	Events 87 156 75 76	Total 227 1039 215 344	Weight 2.6% 5.4% 1.3% 5.4%	Odds Ratio M-H, Fixed, 95% Cl 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61]	Odds Ratio M-H, Fixed, 95% Cl
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021	Events 15 16 12 14 23	Total 30 93 20 72 146	Events 87 156 75 76 31	Total 227 1039 215 344 165	Weight 2.6% 5.4% 1.3% 5.4% 6.3%	Odds Ratio M-H, Fixed, 95% Cl 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46]	Odds Ratio M-H, Fixed, 95% Cl
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020	Events 15 16 12 14 23 7	Total 30 93 20 72 146 24	Events 87 156 75 76 31 39	5K <u>Total</u> 227 1039 215 344 165 190	Weight 2.6% 5.4% 1.3% 5.4% 6.3% 1.6%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11]	Odds Ratio M-H, Fixed, 95% Cl
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017	Events 15 16 12 14 23 7 52	Total 30 93 20 72 146 24 132	Events 87 156 75 76 31 39 344	5K Total 227 1039 215 344 165 190 1074	Weight 2.6% 5.4% 1.3% 5.4% 6.3% 1.6% 11.6%	Odds Ratio M-H, Fixed, 95% Cl 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00]	Odds Ratio M-H, Fixed, 95% Cl
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021	Events 15 16 12 14 23 7 52 21	Total 30 93 20 72 146 24 132 38	Events 87 156 75 76 31 39 344 61	Total 227 1039 215 344 165 190 1074 176	Weight 2.6% 5.4% 1.3% 6.3% 1.6% 11.6% 2.5%	Odds Ratio M-H, Fixed, 95% Cl 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74]	Odds Ratio M-H, Fixed, 95% Cl
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016	Events 15 16 12 14 23 7 52 21 91	Total 30 93 20 72 146 24 132 38 354	Events 87 156 75 76 31 39 344 61 79	Total 227 1039 215 344 165 190 1074 176 442	Weight 2.6% 5.4% 1.3% 6.3% 1.6% 11.6% 2.5% 13.3%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.50 [1.22]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018	Events 15 16 12 14 23 7 52 21 91 34	Total 30 93 20 72 146 24 132 38 354 74	Events 87 156 75 76 31 39 344 61 79 114	Total 227 1039 215 344 165 190 1074 176 442 294	Weight 2.6% 5.4% 1.3% 6.3% 1.6% 11.6% 2.5% 13.3% 6.3%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 2.50 [2.00]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020	Events 15 16 12 14 23 7 52 21 91 34 8	Total 30 93 20 72 146 24 132 38 354 74 64	Events 87 156 75 76 31 39 344 61 79 114 32	Total 227 1039 215 344 165 190 1074 176 442 294 145	Weight 2.6% 5.4% 1.3% 6.3% 1.6% 2.5% 13.3% 6.3% 4.4%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 2.051 [0.25, 1.17]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018	Events 15 16 12 14 23 7 52 21 91 34 8 25 25	Total 30 93 20 72 146 24 132 38 354 74 64 81	Events 87 156 76 31 39 344 61 79 114 32 55	Total 227 1039 215 344 165 190 1074 176 442 294 145 133	Weight 2.6% 5.4% 1.3% 5.4% 1.6% 11.6% 2.5% 13.3% 6.3% 4.4% 7.3%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 2.020 2.000 2.000	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018 Zeng 2021	Events 15 16 12 14 23 7 52 21 91 34 8 25 0 0	Total 30 93 20 72 146 24 132 38 354 74 64 81 43	Events 87 156 76 31 39 344 61 79 114 32 55 29	Total 227 1039 215 344 165 190 1074 176 442 294 145 133 203	Weight 2.6% 5.4% 1.3% 5.4% 6.3% 1.6% 11.6% 2.5% 13.3% 6.3% 4.4% 7.3% 2.6%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 0.07 [0.00, 1.13] 4.041 0.041 5.02]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018 Zeng 2021 Zhang 2021	Events 15 16 12 14 23 7 52 21 91 34 8 25 0 13	Total 30 93 20 72 146 24 132 38 354 74 64 81 43 15 43 15 43 15 43 15 43 43 43 43 45 45 45 45 45 45 45 45 45 45	Events 87 156 75 31 39 344 61 79 114 32 55 29 55	Total 227 1039 215 344 165 190 1074 176 442 294 145 133 203 203	Weight 2.6% 5.4% 1.3% 5.4% 1.6% 1.6% 2.5% 13.3% 6.3% 4.4% 7.3% 2.6% 1.2%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 0.07 [0.00, 1.13] 1.94 [0.64, 5.87] 1.44 [0.67, 2.42]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018 Zeng 2021 Zhang 2021 Zhao 2015 Zhao 2010	Events 15 16 12 14 23 7 52 21 91 34 8 25 0 13 34 8 25 0 13 16	Total 30 93 20 72 146 24 132 38 354 74 64 81 43 18 43	Events 87 156 76 31 39 344 61 79 114 32 55 29 55 82	Total 227 1039 215 344 165 190 1074 176 442 294 145 133 203 96 247	Weight 2.6% 5.4% 1.3% 5.4% 6.4% 1.6% 1.6% 1.6% 1.3% 6.3% 4.4% 7.3% 2.6% 1.2% 4.2%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 0.07 [0.00, 1.13] 1.94 [0.64, 5.87] 1.11 [0.57, 2.16] 0.24 [0.90, 4.44]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018 Zeng 2021 Zhang 2021 Zhao 2015 Zhao 2019 Zhao 2020	Events 15 16 12 14 23 7 52 21 91 34 8 25 0 13 34 8 25 0 13 16 2 2 12 0	Total 30 93 20 72 146 24 132 38 354 74 64 81 43 18 45 22 22 22	Events 87 156 76 31 39 344 61 79 114 32 55 29 55 82 41	Total 227 1039 215 344 190 1074 176 442 294 145 133 203 96 247 316	Weight 2.6% 5.4% 1.3% 5.4% 6.3% 1.6% 11.6% 2.5% 13.3% 6.3% 4.4% 7.3% 2.6% 1.2% 4.2% 2.3%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 0.07 [0.00, 1.13] 1.94 [0.64, 5.87] 1.11 [0.57, 2.16] 0.34 [0.08, 1.44] 1.97 [4.09, 2.02]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018 Zeng 2021 Zhang 2021 Zhao 2015 Zhao 2019 Zhao 2020 Zhao 2020	Events 15 16 12 14 23 7 52 21 91 34 8 25 0 13 34 8 25 0 13 16 2 19	Total 30 93 20 72 146 24 132 38 354 74 64 81 43 18 45 42 37 20	Events 87 156 75 76 31 39 344 61 79 114 32 55 29 55 29 55 82 41 126 20 20	Total 227 1039 215 344 190 1074 176 442 294 145 133 203 96 247 316 361	Weight 2.6% 5.4% 1.3% 5.4% 6.3% 1.6% 11.6% 2.5% 13.3% 6.3% 4.4% 7.3% 2.6% 1.2% 4.2% 2.3% 2.3% 2.9%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 0.07 [0.00, 1.13] 1.94 [0.64, 5.87] 1.11 [0.57, 2.16] 0.34 [0.08, 1.44] 1.97 [1.00, 3.89] 0.79 [0.26, 2.441] 1.97 [1.00, 3.89]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018 Zeng 2021 Zhang 2021 Zhao 2015 Zhao 2019 Zhao 2020 Zhou 2022 Zhu 2022	Events 15 16 12 14 23 7 52 21 91 34 8 25 0 13 34 8 25 0 13 16 2 19 4 5 4	Total 30 93 20 72 146 24 132 38 354 74 64 81 43 18 45 42 37 30 200	Events 875 156 75 76 31 39 344 61 79 114 32 55 29 55 29 55 82 41 126 30 302 41 302 55 29 55 82 41 126 30 30 30 30 30 30 30 30 30 30	Total 227 1039 215 344 160 1074 176 442 294 145 133 203 96 247 316 361 1820	Weight 2.6% 5.4% 1.3% 5.4% 6.3% 1.6% 11.6% 2.5% 13.3% 6.3% 4.4% 7.3% 2.6% 1.2% 4.2% 2.3% 2.9% 1.8% 1.8%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.39 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 0.07 [0.00, 1.13] 1.94 [0.64, 5.87] 1.11 [0.57, 2.16] 0.34 [0.08, 1.44] 1.97 [1.00, 3.89] 0.79 [0.26, 2.44] 1.01 [0.72, 2.14]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018 Zeng 2021 Zhang 2021 Zhao 2015 Zhao 2019 Zhao 2020 Zhou 2022	Events 15 16 12 14 23 7 52 21 91 34 8 25 0 13 16 2 19 4 54	Total 30 93 20 72 146 24 132 38 354 64 81 43 18 45 42 37 30 199	Events 87 156 75 76 31 39 344 61 79 114 32 55 29 55 82 41 126 30 302	Total 227 1039 215 344 190 1074 176 442 294 145 133 203 96 247 316 361 185 1120	Weight 2.6% 5.4% 1.3% 5.4% 1.6% 11.6% 2.5% 13.3% 6.3% 4.4% 7.3% 2.6% 1.2% 4.2% 2.3% 2.9% 1.8% 16.9%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 0.07 [0.00, 1.13] 1.94 [0.64, 5.87] 1.11 [0.57, 2.16] 0.34 [0.08, 1.44] 1.97 [1.00, 3.89] 0.79 [0.26, 2.44] 1.01 [0.72, 1.42]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018 Zeng 2021 Zhang 2021 Zhao 2015 Zhao 2015 Zhao 2019 Zhao 2020 Zhou 2022 Zhu 2022	Events 15 16 12 14 23 7 52 21 91 34 8 25 0 13 34 8 25 0 13 16 2 19 9 4 54	Total 303 20 72 146 24 132 38 354 74 64 81 43 18 45 45 45 45 37 30 199 <b>1542</b>	Events   87   156   76   31   39   344   61   79   114   32   55   29   55   82   41   126   300	Total 227 1039 215 344 165 190 1074 176 442 294 145 133 203 96 247 316 361 185 1120 <b>6972</b>	Weight 2.6% 5.4% 1.3% 5.4% 1.6% 2.5% 13.3% 6.3% 4.4% 7.3% 2.6% 1.2% 4.2% 2.3% 1.2% 4.2% 2.3% 1.8% 16.9%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 0.07 [0.00, 1.13] 1.94 [0.64, 5.87] 1.11 [0.57, 2.16] 0.34 [0.08, 1.44] 1.97 [1.00, 3.89] 0.79 [0.26, 2.44] 1.01 [0.72, 1.42] 1.17 [1.02, 1.34]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018 Zeng 2021 Zhang 2021 Zhao 2015 Zhao 2019 Zhao 2020 Zhou 2022 Zhu 2022 <b>Total (95% CI)</b> Total events	Events 15 16 12 14 23 7 52 21 91 34 8 25 0 13 16 2 19 4 54 54 426	Total 30 93 20 72 146 24 132 38 354 74 64 81 43 18 45 45 37 30 199 1542	Events   87   156   76   31   39   344   61   79   114   32   55   29   55   82   41   126   300   302   1814	Total 227 1039 215 344 165 190 1074 176 442 294 145 133 203 96 247 316 3161 185 1120 6972	Weight 2.6% 5.4% 1.3% 5.4% 1.6% 11.6% 2.5% 13.3% 6.3% 4.4% 7.3% 2.6% 1.2% 4.2% 2.3% 2.9% 1.8% 16.9%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 0.07 [0.00, 1.13] 1.94 [0.64, 5.87] 1.11 [0.57, 2.16] 0.34 [0.08, 1.44] 1.97 [1.00, 3.89] 0.79 [0.26, 2.44] 1.01 [0.72, 1.42] 1.17 [1.02, 1.34]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018 Zeng 2021 Zhang 2021 Zhao 2015 Zhao 2015 Zhao 2019 Zhao 2020 Zhou 2022 Zhu 2022 Total (95% CI) Total events Heterogeneity: Chi <sup>=</sup> =	Events 15 16 12 14 23 52 21 91 34 8 25 0 13 16 2 19 4 54 54 54 54 54 54 54 54 54	Total   30   93   20   72   146   24   132   38   354   64   81   43   18   45   42   37   30   199   1542	Events   87   156   75   76   31   39   344   61   79   114   32   55   29   55   82   41   126   302   1814   2	Total   227   1039   215   344   165   190   1074   176   442   294   145   133   203   96   247   3161   185   1120   6972	Weight 2.6% 5.4% 1.3% 5.4% 1.6% 11.6% 2.5% 13.3% 6.3% 4.4% 7.3% 2.6% 1.2% 4.2% 2.3% 2.3% 2.8% 1.2% 4.2% 1.8% 16.9%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 0.07 [0.00, 1.13] 1.94 [0.64, 5.87] 1.11 [0.57, 2.16] 0.34 [0.08, 1.44] 1.97 [1.00, 3.89] 0.79 [0.26, 2.44] 1.01 [0.72, 1.42] 1.17 [1.02, 1.34]	Odds Ratio M-H, Fixed, 95% CI
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018 Zeng 2021 Zhao 2015 Zhao 2019 Zhao 2019 Zhao 2020 Zhou 2022 Zhu 2022 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect	Events 15 16 12 14 23 7 52 21 91 34 8 25 0 13 16 2 19 4 54 54 54 54 54 54 54 54 54	Total 30 93 20 72 146 24 132 38 354 74 64 81 43 18 45 42 37 30 199 1542 <sup>7</sup> = 18 (f (P = 0.1)	Events   87   156   75   76   31   39   344   61   79   114   255   29   55   82   41   126   302   1814   2   1814   2   201);	Total   227   1039   215   344   165   190   1074   176   442   294   145   133   203   96   247   361   185   1120   6972	Weight 2.6% 5.4% 1.3% 5.4% 1.6% 11.6% 2.5% 13.3% 6.3% 4.4% 7.3% 2.6% 1.2% 4.2% 2.3% 2.9% 16.9% 16.9%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 0.07 [0.00, 1.13] 1.94 [0.64, 5.87] 1.11 [0.57, 2.16] 0.34 [0.08, 1.44] 1.97 [1.00, 3.89] 0.79 [0.26, 2.44] 1.01 [0.72, 1.42] 1.17 [1.02, 1.34]	Odds Ratio M-H, Fixed, 95% Cl
Cheng 2019 Feng 2022 Li 2018 Nakamura 2021 Nan 2020 Qin 2017 Song 2021 Tocci 2016 Wang 2018 Wang 2020 Wu 2018 Zeng 2021 Zhang 2021 Zhao 2015 Zhao 2015 Zhao 2019 Zhao 2020 Zhou 2022 Zhu 2022 Total (95% CI) Total events Heterogeneity: Chi <sup>#</sup> = Test for overall effect	Events 15 16 12 14 23 7 52 21 91 34 8 25 0 13 16 2 19 4 54 54 54 54 54 54 55 55 55	Total 30 93 20 72 146 24 132 38 354 64 81 43 18 45 42 37 30 199 <b>1542</b> <sup>7</sup> = 18 (f (P = 0.1	Events   87   156   75   76   31   39   344   61   79   114   32   55   29   55   29   55   302   1814   2   1814   2   52)	Total   227   1039   215   344   165   190   1074   176   442   294   145   133   203   96   247   3161   185   1120   6972	Weight 2.6% 5.4% 1.3% 5.4% 1.6% 11.6% 2.5% 13.3% 6.3% 4.4% 7.3% 2.6% 1.2% 4.2% 2.9% 1.8% 16.9%	Odds Ratio M-H, Fixed, 95% CI 1.61 [0.75, 3.45] 1.18 [0.67, 2.07] 2.80 [1.10, 7.15] 0.85 [0.45, 1.61] 0.81 [0.45, 1.46] 1.59 [0.62, 4.11] 1.38 [0.95, 2.00] 2.33 [1.14, 4.74] 1.59 [1.13, 2.24] 1.34 [0.80, 2.24] 0.50 [0.22, 1.17] 0.63 [0.35, 1.14] 0.07 [0.00, 1.13] 1.94 [0.64, 5.87] 1.11 [0.57, 2.16] 0.34 [0.08, 1.44] 1.97 [1.00, 3.89] 0.79 [0.26, 2.44] 1.01 [0.72, 1.42] 1.17 [1.02, 1.34]	Odds Ratio M-H, Fixed, 95% CI

	ISR		Non I	SR		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Canbolat 2019	36	99	71	220	5.3%	1.20 [0.73, 1.97]	-+
Chen 2022	13	30	92	227	2.3%	1.12 [0.52, 2.42]	
Cheng 2019	24	93	374	1039	8.6%	0.62 [0.38, 1.00]	
Feng 2022	7	20	85	215	1.8%	0.82 [0.32, 2.15]	
Gabbasov 2015	25	53	31	73	2.6%	1.21 [0.59, 2.46]	
Li 2018	27	72	124	344	5.1%	1.06 [0.63, 1.80]	_ <b>_</b>
Nakamura 2021	48	146	57	165	6.8%	0.93 [0.58, 1.49]	<b>_</b> _
Nan 2020	7	24	63	190	1.9%	0.83 [0.33, 2.11]	
Qin 2017	64	132	412	1074	8.8%	1.51 [1.05, 2.17]	
Song 2021	14	38	67	176	2.9%	0.95 [0.46, 1.96]	
Tocci 2016	354	138	442	15.9%	1.02 [0.75, 1.38]	+	
Wang 2018 40 74			120	294	4.2%	1.71 [1.02, 2.85]	
Wang 2020	20	64	59	145	4.7%	0.66 [0.36, 1.24]	
Wu 2018	33	81	42	133	3.6%	1.49 [0.84, 2.65]	+
Zeng 2021	6	43	39	203	2.2%	0.68 [0.27, 1.73]	
Zhang 2021	16	18	61	96	0.4%	4.59 [1.00, 21.15]	
Zhao 2015	22	45	88	247	2.6%	1.73 [0.91, 3.28]	
Zhao 2019	16	42	87	316	2.4%	1.62 [0.83, 3.17]	
Zhao 2020	13	37	142	361	3.2%	0.84 [0.41, 1.69]	
Zhou 2022	14	30	68	185	1.9%	1.51 [0.69, 3.27]	
Zhu 2022	100	199	444	1120	12.6%	1.54 [1.14, 2.08]	
Total (95% CI)		7265	100.0%	1.17 [1.04, 1.31]	*		
Total events	657		2664				
Heterogeneity: Chi <sup>2</sup> =	28.96, df	= 20 (F	e = 0.09);	I <sup>2</sup> = 319	%		
Test for overall effect:	Z = 2.66 (	(P = 0.0	)08)				0.01 0.1 1 10 100 Non ISR ISR
Stent Diameter	•						

		ISR		N	on ISR			Mean Difference	Mean Difference
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Canbolat 2019	2.9	0.4	99	2.9	0.4	220	7.9%	0.00 [-0.09, 0.09]	
Chen 2022	2.96	0.07	30	3.36	0.28	227	8.4%	-0.40 [-0.44, -0.36]	
Cheng 2019	2.96	0.26	93	3.13	0.25	1039	8.3%	-0.17 [-0.22, -0.12]	
Jiang 2022	2.7	0.3	279	3	0.4	1222	8.4%	-0.30 [-0.34, -0.26]	
Jing 2015	2.88	0.48	50	2.86	0.5	50	6.3%	0.02 [-0.17, 0.21]	<del></del>
Li 2018	2.78	0.45	72	3.08	0.5	344	7.6%	-0.30 [-0.42, -0.18]	_ <b></b>
Li 2022	2.99	0.6	62	2.98	0.42	279	6.9%	0.01 [-0.15, 0.17]	
Nakamura 2021	2.98	0.41	146	2.95	0.4	165	7.9%	0.03 [-0.06, 0.12]	-+
Qin 2017	2.93	0.61	132	2.9	0.62	1074	7.6%	0.03 [-0.08, 0.14]	_ <del></del>
Tocci 2016	2.91	0.39	354	2.96	0.38	442	8.3%	-0.05 [-0.10, 0.00]	
Wang 2018	2.81	0.41	74	2.83	0.45	294	7.7%	-0.02 [-0.13, 0.09]	
Zhao 2015	2.93	0.41	45	3.06	0.33	247	7.4%	-0.13 [-0.26, -0.00]	
Zhou 2022	2.73	0.34	30	2.99	0.4	185	7.3%	-0.26 [-0.39, -0.13]	
Total (95% CI)			1466			5788	100.0%	-0.12 [-0.22, -0.03]	◆
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0.03; C Z = 2.61	hi² = 2 (P = 0	17.79, ).009)	df=12(	(P < 0.1	00001)	; I² = 94%		-0.5 -0.25 0 0.25 0.5 Non ISR ISR

# Stent Length

		ISR		No	on ISR			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Canbolat 2019	20.4	6	99	19.9	6	220	8.6%	0.50 [-0.92, 1.92]	+-
Chen 2022	64.77	5.3	30	57.2	2.27	227	8.3%	7.57 [5.65, 9.49]	
Cheng 2019	26.43	3.4	93	24.01	3.26	1039	9.0%	2.42 [1.70, 3.14]	-
Jiang 2022	59.7	27.4	279	43	21.6	1222	6.9%	16.70 [13.26, 20.14]	
Jing 2015	21.38	6.76	50	18.34	5.06	50	7.9%	3.04 [0.70, 5.38]	
Li 2018	48.6	12.8	72	37.3	8.4	344	7.2%	11.30 [8.21, 14.39]	
Li 2022	25.32	8.48	62	26.48	7.48	279	8.0%	-1.16 [-3.45, 1.13]	
Nakamura 2021	30.7	15.1	146	30.9	18.3	165	6.6%	-0.20 [-3.91, 3.51]	
Qin 2017	22.72	5.51	132	22.76	8.35	1074	8.8%	-0.04 [-1.10, 1.02]	+
Tocci 2016	24.3	15.6	354	21.7	13.9	442	8.1%	2.60 [0.52, 4.68]	
Wang 2018	22.41	4.37	74	21.32	5.62	294	8.8%	1.09 [-0.09, 2.27]	<u>+</u>
Zhao 2015	19.21	6.38	45	17.38	5.92	247	8.2%	1.83 [-0.17, 3.83]	
Zhou 2022	43.1	18.7	30	38.2	20.8	185	3.6%	4.90 [-2.43, 12.23]	
Total (95% CI)			1466			5788	100.0%	3.61 [1.81, 5.42]	◆
Heterogeneity: Tau <sup>2</sup> =	9.29; C	hi <b>²</b> = 1∣	69.28, (	df = 12 (	P < 0.	00001)	; I <b>²</b> = 93%		
Test for overall effect:	Z = 3.92	? (P < 0	).0001)						-20 -10 0 10 20 Non ISR ISR
Figure 3 Forest	nlot of t	he re	lation	shin he	otwee	n and	ioaranh	v characteristics an	d ISR incidence

Figure 3. Forest plot of the relationship between angiography characteristics and ISR incidence

### **Blood Parameters**

No	Outcomes	No of Studies	Type of TE	TE (95% CI)	Р	<b> </b> <sup>2</sup>	P for I <sup>2</sup>
1.	Platelet Count	8	MD	-6.07 (-25.52, 13.38)	0,54	97%	<0.00001
2.	NLR	4	MD	0.46 (-0.51, 1.44)	0.35	96%	<0.00001
3.	RDW	6	MD	0.48 (0.09, 0.87)	0.02	91%	<0.00001
4.	Creatinine	8	MD	0.20 (-0.12, 0.52)	0.22	78%	<0.0001

#### Table 3. Blood parameters

Based on research that has been conducted from 8 articles, it is stated that there is no significant relationship between platelet count and the incidence of ISR (MD -6.07; CI 95% -25.52-13.38; I2 97%; p=0.54). In addition, research conducted on the Neutrophil Lymphocyte Ratio stated that there was no significant relationship with the incidence of ISR (MD 0.46; CI 95% -0.51-1.44; I2 96%; p=0.35). Meanwhile, research on red cell distribution width (RDW) stated that there was a significant relationship with the incidence of ISR (MD 0.48; CI 95% 0.09-0.87; I2 91%; p=0.02). Creatinine did not have a significant relationship with the incidence of ISR (MD 0.20; CI 95% -0.12-0.52; I2 78%; p=0.22) (Figure 4).



Creatinine													
	ISR			Non ISR				Mean Difference	Mean Difference				
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI			
Cheng 2019	78.23	11.37	93	76.39	10.23	1039	1.7%	1.84 [-0.55, 4.23]				-	
Luo 2022	74.13	23.32	192	69	17.7	476	0.8%	5.13 [1.47, 8.79]			-		
Qian 2018	94.57	88.55	118	84.18	56.32	143	0.0%	10.39 [-8.06, 28.84]	•				
Qin 2017	78.54	20.26	132	74.24	19.04	1074	0.8%	4.30 [0.66, 7.94]					
Song 2021	88.1	18.2	38	81.5	14.8	176	0.3%	6.60 [0.41, 12.79]					
Tanindi 2015	1.1	0.3	32	0.9	0.3	283	47.2%	0.20 [0.09, 0.31]					
Wu 2018	79.17	16.94	81	81.76	16.55	133	0.5%	-2.59 [-7.23, 2.05]	←		+	—	
Zhao 2015	0.85	0.22	45	0.86	0.23	247	48.8%	-0.01 [-0.08, 0.06]			•		
Total (95% CI)			731			3571	100.0%	0.20 [-0.12, 0.52]			◆		
Heterogeneity: Tau² = 0.05; Chi² = 31.49, df = 7 (P < 0.0001); l² = 78%										- <u> </u>	<u> </u>	<u> </u>	<u> </u>
Test for overall effect: Z = 1.23 (P = 0.22)												2	4

Figure 4. Forest plot of the relationship between blood parameters and ISR incidence

### DISCUSSION

Hypertension is a predisposing factor for coronary artery disease. High or fluctuating blood pressure causes acceleration of blood shear force on the vessel wall, therefore damaging the endothelial cells lining and stimulating restenosis.<sup>15,32</sup> So, patients who underwent PCI are advised to strictly control their blood pressure to avoid restenosis. Both hypertension and diabetes mellitus complicate vascular lesions and unstable endothelial function.<sup>33</sup> During PCI intervention, coronary intimal tear or dissection tends to occur and promotes platelet adhesion.<sup>34</sup> Additionally, blood glucose may directly disrupt coronary endothelial cells, thus promoting ISR occurrence.35 Unstable glucose metabolism activates an inflammation cascade in the endothelial wall, which is a predisposing factor for plaque formation. Inadequate blood glucose control following the PCI procedure will aggravate protein glycosylation and oxidation processes, thus stimulating ISR.<sup>36</sup> Moreover, cigarette smoking is closely related to the development and progression of coronary arterial disease. Our study reported a significant correlation between (OR 1.24; 95% CI 1.13-1.36; I2 33%; p < 0.0001). This result is coherent with the study by Huang et al., which reported a microstructural change of the coronary artery after stenting in smoking vs non-smoking patients. Patients with persistent smoking demonstrated increased neointimal coverage, while smoking cessation retarded neointimal hyperplasia process.<sup>37</sup> This phenomenon is expected due to the nature of nicotine in cigarettes, which has been proven to stimulate proliferation and migration of endothelial cells, therefore accelerating intimal hyperplasia.<sup>38,39</sup> Family history may provoke ISR due to differences in immune response and genetic factors.<sup>40</sup> This study states that a family history of CAD has a significant effect on the incidence of ISR. This is in contrast to research conducted by Cheng *et al*, which stated that family history of CAD was not significantly related to the incidence of ISR (p>0.05).<sup>5</sup> Dyslipidemia may also predispose to ISR, because, in particular, high LDL-C stimulates inflammation, damages endothelial cells, and promotes deposition of cholesterol in the blood vessel wall.<sup>40</sup>

LAD is the lesion location that demonstrated significant correlation with ISR incidence (OR 1.20; 95% 1.07-1.35; I2 39%; p= 0.002). This result is similar to the previous studies, which also imply that the most common site of restenosis is the lesion in the LAD.<sup>41,42</sup> Originally, bypass grafting was determined as superior compared to PCI in the LAD stenosis, because a significantly higher incidence of restenosis and revascularization was found in PCI compared to grafting.<sup>43-45</sup> However, the start of DES has dramatically reduced the incidence of restenosis in LAD.<sup>46</sup> But still, with the treatment of PCI using DES, the ISR event was found to occur mostly in LAD lesions. In a study conducted by,<sup>9</sup> stated that the incidence of ISR in ACS patients after successful PCI during angiographic followup of more than 2 years. The average time from stent placement to the occurrence of ISR was 32.8 months, and ISR tended to occur in LAD and LCX. Several other studies have shown that stent length is an important determinant of ISR. Our study found a significant correlation between stent length and ISR incidence (MD 3.61; 95% CI 1.81-5.42; I2 93%; p < 0.0001). It shows that patients with longer stent lengths are more likely to experience ISR. Previous studies have shown similar results, where stent length is described as an important risk factor for ISR.47 Research conducted by Hong et al. found that stent length (>40 mm) was an independent predictor of the development of ISR.48 Mauri et al.49 stated that each 10 mm increase of stent length was associated with an absolute increase of 7.7% stenosis diameter (p<0.0001).49 On the other hand, we found that ISR was more likely to occur in patients with small stent diameter, however, this correlation is not significant (MD -0.12; 95% CI -0.22, -0.03; I2 94%; p= 0.009). HORIZONS-AMI study reported that vascular caliber  $\leq 3 \text{ mm}$ increased ISR significantly.50

The NLR (neutrophil count divided by lymphocyte count) is a potential biomarker of inflammation. Neutrophils play a major role in endothelial injury and platelet aggregation in acute coronary events. Lymphocytes represent the immunomodulatory response. Moreover, low lymphocyte counts in patients with CAD reflect the physiological stress of cortisol and correlate with a worse prognosis.<sup>51</sup> NLR is an effective biomarker of systemic inflammation and is considered a predictor for the prognosis of different cardiovascular diseases, especially for CAD. CHD patients with high NLR have the potential for unstable plaque and inflammatory conditions.52 In a recent study, NLR was independently associated with early ISR after stent implantation in patients with femoropopliteal CTO.53 The study conducted by Turak et al investigated the relationship of NLR before PCI and found that the NLR value predicted a higher incidence of ISR in ACS patients 54

Red blood cell distribution width (RDW) is a parameter that reflects the size of red blood cells. An increase in RDW indicates a greater heterogeneity of red blood cells in the peripheral blood.<sup>55</sup> Red cell distribution width is a measurement of the variability and size of erythrocytes. By deforming the red cell membrane, Inflammation may induce changes in red blood cell maturation, leading to increased

RDW.<sup>56</sup> In a recent study, an increased RDW predicted BMS restenosis, suggesting potential as a useful screening tool to stratify patients by higher or lower risk of ISR.<sup>57</sup> The mechanisms underlying the relationship between RDW restenosis and DES remain unclear. In this study, it was stated that RDW had a significant relationship with the incidence of ISR. This is different from research conducted by which stated that although RDW was higher in the ISR group, it did not show significance in multivariate analysis.<sup>31</sup>

Creatinine is a product of the hydrolysis reaction of phosphocreatine that occurs in muscles, which occurs with a fairly constant rhythm. A large amount of creatinine contained in the blood circulation will be filtered out with the urine, and not reabsorbed into the blood. Research conducted has found that serum creatinine in the ISR group was higher than in the non-ISR group, indicating that serum creatinine may be correlated with the occurrence of PCHD.<sup>26</sup> Creatinine is considered an indicator that can reflect kidney function. Research by Okada<sup>58</sup> found that serum creatinine was closely related to ISR in CHD patients.

### Limitation the Study

Finally, this systematic review and metaanalysis have several limitations. First, the included studies were predominantly observational. Second, the small sample size makes the trial underpowered to detect small differences in some risk factors, such as hyperlipidemia, platelet count, and NLR. At last, further well-powered studies with more extensive adjustment of confounders are warranted to address some limitations of our current meta-analysis.

### CONCLUSION

From our study, we found that diabetes mellitus and smoking are associated with the incidence of ISR in DES. In addition, as the angiography characteristics, stent lesion at LAD, RCA, and stent length may contribute to ISR in DES. By identifying the risk factors of ISR in DES, cardiologists may modify the attributable factors. Thus, ISR in DES could be prevented. Further studies need to be conducted to explain the mechanism behind each risk factor in contributing to the event of ISR.

# **CONFLICTS OF INTEREST**

The authors have no conflicts of interest to declare.

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