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ORIGINAL RESEARCH

Outcomes of Percutaneous Coronary Intervention for In-Stent Restenosis Versus De Novo Lesions: A Meta-Analysis

Ayman Elbadawi, MD; Alexander T. Dang, MD; Ingy Mahana, MD; Mohammed Elzeneini, MD; Fernando Alonso, MD; Subhash Banerjee, MD; Dharam J. Kumbhani, MD SM; Islam Y. Elgendy, MD; Gary S. Mintz, MD

BACKGROUND: In-stent restenosis (ISR) is commonly encountered even in the era of contemporary percutaneous coronary intervention (PCI). There is a paucity of data on the comparative outcomes of PCI for ISR lesions versus de novo lesions.

METHODS AND RESULTS: An electronic search was conducted for MEDLINE, Cochrane, and Embase through August 2022 for studies comparing the clinical outcomes after PCI for ISR versus de novo lesions. The primary outcome was major adverse cardiac events. Data were pooled using a random-effects model. The final analysis included 12 studies, with a total of 708 391 patients, of whom 71 353 (10.3%) underwent PCI for ISR. The weighted follow-up duration was 29.1 months. Compared with de novo lesions, PCI for ISR was associated with a higher incidence of major adverse cardiac events (odds ratio [OR], 1.31 [95% CI, 1.18–1.46]). There was no difference on a subgroup analysis of chronic total occlusion lesions versus none ($P_{interaction}$=0.69). PCI for ISR was associated with a higher incidence of all-cause mortality (OR, 1.03 [95% CI, 1.02–1.04]), myocardial infarction (OR, 1.20 [95% CI, 1.11–1.29]), target vessel revascularization (OR, 1.42 [95% CI, 1.29–1.55]), and stent thrombosis (OR, 1.44 [95% CI, 1.11–1.87]), but no difference in cardiovascular mortality (OR, 1.04 [95% CI, 0.90–1.20]).

CONCLUSIONS: PCI for ISR is associated with higher incidence of adverse cardiac events compared with PCI for de novo lesions. Future efforts should be directed toward prevention of ISR and exploring novel treatment strategies for ISR lesions.

Key Words: de novo lesions ■ in-stent restenosis ■ percutaneous coronary intervention

Percutaneous coronary intervention (PCI) remains the cornerstone in the management of patients with acute coronary syndrome and those with chronic coronary syndrome refractory to medical management.[1] The use of metallic coronary stents (ie, drug eluting and bare metal) has revolutionized this space during the past 2 decades.[2] However, metallic coronary stents have introduced another disease (ie, in-stent restenosis [ISR]).[3] ISR could present clinically with either chronic coronary syndrome or acute coronary syndrome.[2] Although the rates of ISR have decreased considerably with the more widespread use of drug-eluting stents (DES), especially second–generation, ISR remains a challenge even with DES, and the incidence is up to 5% to 15% after 5 years.[4,5] Despite the large number of PCIs performed annually in the United States and worldwide, data evaluating the long-term outcomes with PCI for ISR are limited. Moreover, comparative data on the outcomes associated with PCI with DES for ISR versus de novo lesions are limited. In that context, we aimed to perform a comprehensive meta-analysis investigating the comparative long-term outcomes with PCI for ISR versus de novo lesions.

Correspondence to: Islam Elgendy, MD, FACC, FAHA, FSCAI, FSVM, FESC, FACP, Gill Heart Institute, University of Kentucky, 900 S. Limestone Street, Lexington, KY 40536. Email: iyelgendy@gmail.com

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CLINICAL PERSPECTIVE

What Is New?

- Percutaneous coronary intervention (PCI) for in-stent restenosis was associated with a higher incidence of risk-adjusted major adverse cardiac events compared with PCI for de novo lesions at a median of ≈30 months.
- PCI for in-stent restenosis was associated with higher incidences of all-cause mortality, myocardial infarction, target vessel revascularization, and stent thrombosis.
- There was no evidence of interaction for the outcomes for chronic total occlusion versus non-chronic total occlusion.

What Are the Clinical Implications?

- In-stent restenosis is not a benign entity, and major efforts should be directed toward optimizing index PCI procedures.
- Further research is warranted to evaluate the outcomes of PCI of in-stent restenosis compared with de novo lesions using state-of-the-art PCI techniques, including routine intravascular imaging, transradial access, and advanced modalities such as laser atherectomy, brachytherapy, and drug-coated balloons.

Nonstandard Abbreviations and Acronyms

CTO	chronic total occlusion
DES	drug-eluting stent
ISR	in-stent restenosis
MACE	major adverse cardiac events
TVR	target vessel revascularization

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Data Sources and Search Strategy

We conducted a digital search of the following databases: MEDLINE, Cochrane, and Embase, through July 2022, using the terms "in-stent restenosis," "de novo stenosis," "revascularization," and "percutaneous coronary intervention" separately and in combination to identify studies that evaluated the outcomes with PCI for ISR versus de novo coronary artery lesions. We also conducted a simultaneous search of the abstracts presented at major societal meetings (American College of Cardiology, European Society of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions meetings) using similar keywords through August 2022. We searched the bibliographies of the retrieved studies, as well as ClinicalTrials.gov, to capture eligible studies that were not obtained through the initial search. This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Table S1).[6] A protocol for this meta-analysis was prospectively registered at PROSPERO (CRD42022364832). This study was deemed exempt from institutional review board evaluation, because it is a study-level meta-analysis.

Selection Criteria

We included studies that compared the clinical outcomes with PCI for ISR versus de novo coronary lesions. We included randomized or observational studies. In studies with multiple reports, we used data from the longest follow-up. We excluded studies that only reported outcomes after PCI for ISR without a comparator group of de novo PCI. Two investigators (I.M. and M.E.) conducted an independent screening, and discrepancies among investigators were resolved by consensus.

Data Extraction

Two independent investigators (I.M. and M.E.) extracted the following data: the study design, baseline characteristics, intervention strategies, and clinical outcomes. In case of discrepancies among investigators, this was resolved by consensus.

Outcomes

The primary outcome of the study was the composite of major adverse cardiovascular events (MACE). The secondary outcomes included all-cause mortality, cardiovascular mortality, myocardial infarction (MI), repeat ischemia-driven target vessel revascularization (TVR), and stent thrombosis. Definitions of outcomes were adopted as per each study.

Assessment of the Quality of the Included Studies

Because all of the included studies were observational, we assessed the quality of the included studies using the Newcastle-Ottawa quality assessment scale. Accordingly, the quality of the studies was classified as very good, good, satisfactory, or unsatisfactory corresponding to a score of 9 to 10, 7 to 8, 5 to 6, or 0 to 4 points, respectively.[7]

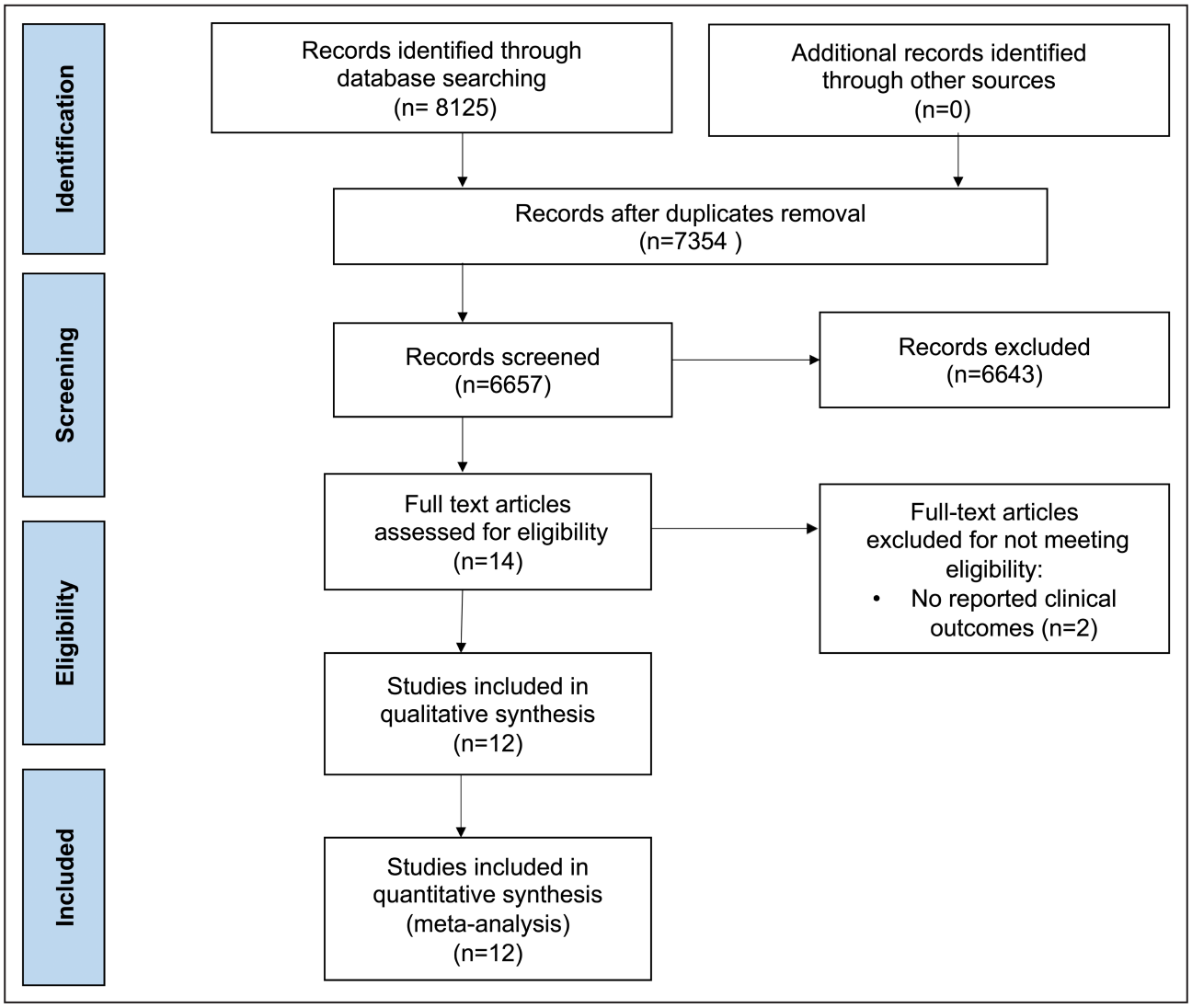

Figure 1. Study flowchart.

Statistical Analysis

Interrater agreement between the 2 researchers conducting study selection and data extraction was evaluated using κ coefficient. A random-effects model was used, and data were pooled using the DerSimonian-Laird inverse variance method. A random-effects model provides more conservative results than a fixed-effects model and assumes that each sample comes from a different population, and that the effects in these populations may also differ. Meta-analysis was conducted using pooled effect sizes from the included studies using risk-adjusted data when available. Statistical heterogeneity among the included studies was evaluated using I^2 statistics and Cochran *Q* test. I^2 statistic values <25%, 25% to 50%, and >50% corresponded to low, moderate, and high degree of heterogeneity, respectively.[8,9] Publication bias was assessed using the Egger test.[10] A prespecified subgroup analysis was conducted for the primary outcome according to chronic total occlusion (CTO) versus non-CTO coronary lesions. Sensitivity analysis for the primary outcome was conducted after excluding studies without risk-adjusted outcomes and studies with less than good quality based on the Newcastle-Ottawa scale. In the prespecified study protocol, we planned to report summary estimates using risk ratios. After conclusion of the study search, the studies meeting the selection criteria were mainly observational studies, and there were no available randomized clinical trials. As such, we decided to report summary estimates using odds ratios (ORs).[11] *P* values were considered statistically significant if ≤0.05. Statistical analyses were conducted using RevMan 5.0 software (Cochrane Collaboration, Oxford, UK).

Table 1. Characteristics of Included Studies

Study	Year	Study design	No.	PCI with stents %	DES %	Use of IVUS	Use of OCT	Focal ISR %	Diffuse ISR %	Occlusive ISR %	Follow-up
Abdelwahab et al[18]	2011	Prospective multicenter	872/4272	97.7/97.9	100/100	NA	NA	NA	NA	4.9	12.4 mo
Richardt et al[23]	2013	Prospective multicenter	281/3194	100/100	100/100	NA	NA	NA	NA	NA	2y
Gao et al[22]	2013	Retrospective single center	1300/27 211	100/100	100/100	4.1/3.5	NA	NA	NA	NA	17 mo
Shimonaga et al[15]	2015	Prospective single center	34/87	NA	NA	NA	NA	53	47	0	In-hospital
Redfors et al[19]	2017	Prospective multicenter	840/7742	100/100	100/100	42.3/38.8	NA	NA	NA	6	2y
Buchanan et al[17]	2018	Retrospective single center	472/1888	46.6/95.7	81.7/93.2	54/61	NA	NA	NA	NA	12 mo
Lee et al[16]	2020	Retrospective multicenter	164/1208	89.1/93.3	100/100	NA	NA	NA	NA	100	5y
Takeuchi et al[20]	2021	Retrospective single center	280/1258	49.3/87.9	100/100	79.6/91.6	27.9/11.1	NA	NA	NA	2y
Tamez et al[14]	2021	Retrospective multicenter	66 718/586 586	80.6/93	91.1/77.2	NA	NA	NA	NA	NA	4y
Tang et al[12]	2021	Prospective single center	69/357	48.4/79.4	100/100	17.9/15	NA	NA	NA	100	2y
Wang et al[13]	2021	Retrospective single center	212/2447	75.5/73.9	NA	6.8/6.8	NA	NA	NA	100	5y
Azzalini et al[21]	2017	Prospective multicenter	111/788	100/100	97.9/87.9	9.9/13.3	NA	NA	NA	100	15.7 mo

DES indicates drug-eluting stent; ISR, in-stent restenosis; IVUS, intravascular ultrasound; NA, not applicable; OCT, optical coherence tomography and PCI, percutaneous coronary intervention.

Table 2. Baseline Characteristics of Included Patients

Study	Age, y, mean±SD	Men %	Tobacco use %	HTN %	Diabetes %	Prior MI %	GFR	FH of CAD %	HLD %	ACS %
Abdelwahab et al[18]	66.2±10.4/65±10.5	75.9/74.4	16.2/23.5	86.9/83.3	28.8/32.2	49.8/26.2	NA	39.5/35.5	84.5/79.6	22/27.3
Richardt et al[23]	65.3±10.5/63.6±11.1	77.6/77.4	14.6/25.8	79.0/68.0	31.0/27.9	53.9/25.3	NA	36.2/32.0	81.1/62.4	47.3/56.0
Gao et al[22]	57.31±10.94/57.75±10.73	83.2/78.6	42.1/31.7	47.2/40.3	21.3/15.0	33.2/24.4	NA	4.2/3.4	34.5/26.3	63.4/60.2
Shimonaga et al[15]	71.1±9.8/70.8±8.4	64.7/80.5	55.9/69	82.4/90.8	67.6/58.6	47.1/18.4	NA	NA	73.5/73.6	0/0
Redfors et al[19]	63.6±10.9/63.6±10.9	76.5/73.8	19.9/22.9	90.2/78.5	37.0/31.9	48.2/22.7	92.8±38.4/94.2±37.7	NA	89.4/72.7	47.9/52.1
Buchanan et al[17]	65±11/66±11	68/64	16/16	96/97	47/45	53/52	NA	NA	95/96	67/59
Lee et al[16]	59.1±10.3/62.2±10.9	69.5/77.6	22/31.5	53.7/62.8	30.5/41.4	42.7/16.2	68.3±33.2/68.4±37.2	NA	49.4/49.3	40.9/31.7
Takeuchi et al[20]	69.4±10.0/67.9±11.2	83.9/80.0	16.4/21.7	83.9/70.0	54.7/39.2	NA	64.6±27.5/70.9±25.8	28.6/27.3	86.1/72.4	11.8/28.2
Tamez et al[14]	74.2±6.8/74.6±7.0	65.7/62.7	12.6/13.7	92.5/85.8	43.1 /36.1	50.4 /24.7	NA	21.2 /19.1	92.7/79.8	63.9/64.7
Tang et al[12]	64.8±9.8/63.1±11.6	82.6/83.8	39.1/44.8	69.6/70.3	50.7/46.5	58.0/17.9	93.3±27.2 /94.9±27.4	NA	71.0/61.3	56.5/56.3
Wang et al[13]	56.80±10.26/57.23±10.52	81.1/83.6	36.8/41.7	59.4/65.3	33.0/31.4	59.0/40.2	NA	NA	87.3/84.0	NA
Azzalini et al[21]	65.1±10.3/65.1±10.8	82.9/87.1	21.6/23.3	79.4/74.3	41.3/37.3	70.4/45.1	82.7±26.5/83.6±28.5	NA	85.0/79.8	18.2/18.3

ACS indicates acute coronary syndrome; CAD, coronary artery disease; FH, family history; GFR, glomerular filtration rate; HLD, hyperlipidemia HTN, hypertension; MI, myocardial infarction and NA, not applicable.

RESULTS

Included Studies

The study selection process is outlined in Figure 1. The final analysis included 12 studies published between 2011 to 2021, with a total of 708391 patients: 71353 patients underwent PCI for ISR, and 637038 patients underwent PCI for de novo lesions.[12-23] There was good interrater agreement between the 2 researchers performing study selection (κ=0.79; standard error=0.09) and data extraction (κ=0.81; standard error=0.06). The weighted follow-up duration was 29.8 months. The study characteristics are outlined in Table 1. Six studies were retrospective studies, and the remaining 6 studies were prospective studies. Four of the included studies exclusively evaluated patients with PCI for CTO.[12,13,16,21] PCI with stenting was used in the ISR group in 46% to 49% of patients in 3 studies,[12,17,20] 75% to 89% in 3 studies,[13,14,16] and 97% to 100% in the remaining studies. Stents used during PCI procedures were exclusively DES in 7 studies,[12,16,18,19,20,22,23] predominantly DES in 3 other studies,[14,17,21] and in 2 studies the types of stents were not reported.[13,15] Baseline characteristics of included patients and procedural characteristics appear in Table 2 and Table 3. The weighted mean age was 64.3 years and included predominantly men.

The quality of included studies is outlined in Table S2. Based on the Newcastle-Ottawa scale, all studies were considered to be of very good quality, except for 1 study, which was considered as good quality.[13]

Outcomes

MACE was reported in 11 studies (Table S3). Adjusted data were pooled from 9 studies as outlined in Table S4. Compared with de novo PCI, PCI with ISR was associated with a higher incidence of MACE (OR, 1.31 [95% CI, 1.18–1.46]; I^2=92%; Q=127.61, P<0.001) (Figure 2). Funnel plot inspection showed no publication bias (P=0.16) (Figure S1). Subgroup analysis showed no significant interaction according to CTO versus non-CTO lesions ($P_{interaction}$=0.69). Sensitivity analyses excluding studies not reporting risk-adjusted estimates (ie, Richardt et al[23] and Wang et al[13]) (OR, 1.34 [95% CI, 1.20–1.50]) showed similar results (Figure S2).

All-cause mortality was reported in 7 studies. There was a higher incidence of all-cause mortality among the ISR versus the de novo group (OR, 1.03 [95% CI, 1.02–1.04]; I^2=0%; Q=4.86, P=0.56). Subgroup analysis showed no significant interaction according to CTO versus non-CTO lesions ($P_{interaction}$=0.91) (Figure 3).

Cardiovascular mortality was reported in 5 studies.[2,3,5,8] There was no difference in cardiovascular mortality between the ISR and de novo groups (OR, 1.04 [95% CI, 0.90–1.20]; I^2=0%; Q=1.88, P=0.76). MI was reported in 11 studies (definition of MI according

Table 3. Procedure Characteristics

Study	Lesion length, mm, mean±SD or median (IQR)	LM disease >50%	Px LAD disease %	Any LAD disease %	RCA disease %	LCX disease %	SVG disease %	Radial access %	Rotational atherectomy %	Laser atherectomy %	Scoring/ cutting balloon %	Contrast volume , mL	Procedural duration , min	No. of stents , mean±SD or %	Average stent length mm	Average stent diameter
Abdelwahab et al[18]	18 (12–23)/15 (10–20)	1.3/1.3	NA	45.1/50.4	31.2/25.7	22.5/20.7	5.6/4.8	NA	NA	NA	NA	NA	NA	NA	20 (16–28)/18 (13–24)	3 (2.8–3)/3 (2.8–3)
Richardt et al[23]	18.0±12.9/16.6±10.1	1.6/1.9	NA	36.7/43.9	34.6/28.7	22.9/24.0	3.6/1.4	NA	NA	NA	NA	NA	NA	NA	22.1±6.4/20.9±6.6	3.2±0.5/3.1±0.5
Gao et al[22]	23.79±15.57/25.32±16.28	3.7/3.6	NA	40.5/43.1	34.0/30.8	20.5/22.3	1.3/0.3	70.1/80.6	NA	NA	3.8/1.2	NA	NA	2.04±1.09/1.90±1.04 (stents per patient)	29.95±17.71/ 30.73±17.77	3.02±0.43/ 3.06±0.47
Shimonaga et al[15]	14.6±7.0/22.0±11.7	NA	NA	44.1/55.2	32.4/24.1	23.5/20.7	NA	NA	NA	NA	NA	NA	NA	0/1.3±0.5	0/27.5±14.6	0/3.09±0.49
Redfors et al[19]	27.3±20.7/27.1±20.0	3.3/3.8	NA	41.8/46.5	44.3/36.3	29.8/31.1	9.4/4.5	5.2/4.3	NA	NA	NA	NA	NA	1.71±1.03/1.70±1.00	33.1±23.5/ 32.4±22.2	NA
Buchanan et al[17]	NA	1.8/3	NA	21/36	33/32	20/28	23/0	NA	1.0/4.9	1.6/0.3	19.0/5.4	NA	NA	1.17±0.87/1.29±0.95	19±6.4/19±6.7	NA
Lee et al[16]	16.4±11.1/19.6±14.1	NA	NA	43.3/38.3	38.4/40.8	18.3/20.9	NA	NA	NA	NA	NA	190.3±89.2/ 216.2±123.6	Fluoroscopic time 40.1±64.4/ 25.5±26.1	1.8±0.5/1.84±0.6	30.2±14.9/ 30.2±17.1	2.94±0.4/3.08±0.9
Takeuchi et al[20]	21.8±12.2/21.5±11.9	NA	NA	40.4/52.0	36.8/27.8	18.2/16.4	0.4/0.5	NA	3.6/6.4	NA	69.6/40.9	NA	NA	49.3/87.9	NA	NA
Tamez et al[14]	18.46±11.22/18.40±10.57	NA	NA	NA	NA	NA	NA	NA	0.9/1.6	0.5/0.1	17.3/3.8	NA	NA	DES G1/G2 76939 (90.7%), 640432 (77.7%); and BMS G1/G2 7876 (9.3%), 184142 (22.3%)	19.20±7.55 18.53±7.06	2.99±0.50 .96±0.52
Tang et al[12]	NA	1.4/5.9	NA	39.1/44.8	50.7/46.8	26.1/26.6	NA	77.5/81.5	NA	NA	NA	239 (180, 280)/250 (200, 300)	NA	NA	NA	NA
Wang et al[13]	24.2±17.3/16.9±11.5							83.5/84.9	NA	NA	NA	NA	51.09±30.72/ 56.90±37.91	75.4/73.9	26.19±5.28/ 26.10±5.25	3.00±0.41/2.91±0.40
Azzalini et al[21]	Lesion length >20mm: 68.5%/42.5%	NA	NA	27.0/28.6	55.0/51.8	18.0/19.6	NA	34.2/42.7	NA	NA	NA	302±134/ 332±137	115±75/128±69 (min)	2.34±1.31/2.20±1.27 (stents per patient)	77.3±49.7/ 69.1±40.7	NA

BMS indicates bare-metal stent; DES, drug-eluting stent; IQR, interquartile range; LAD, left anterior descending artery; LM, left main coronary artery; NA, not applicable; Px, proximal; RCA, right coronary artery and SVG, saphenous vein graft.

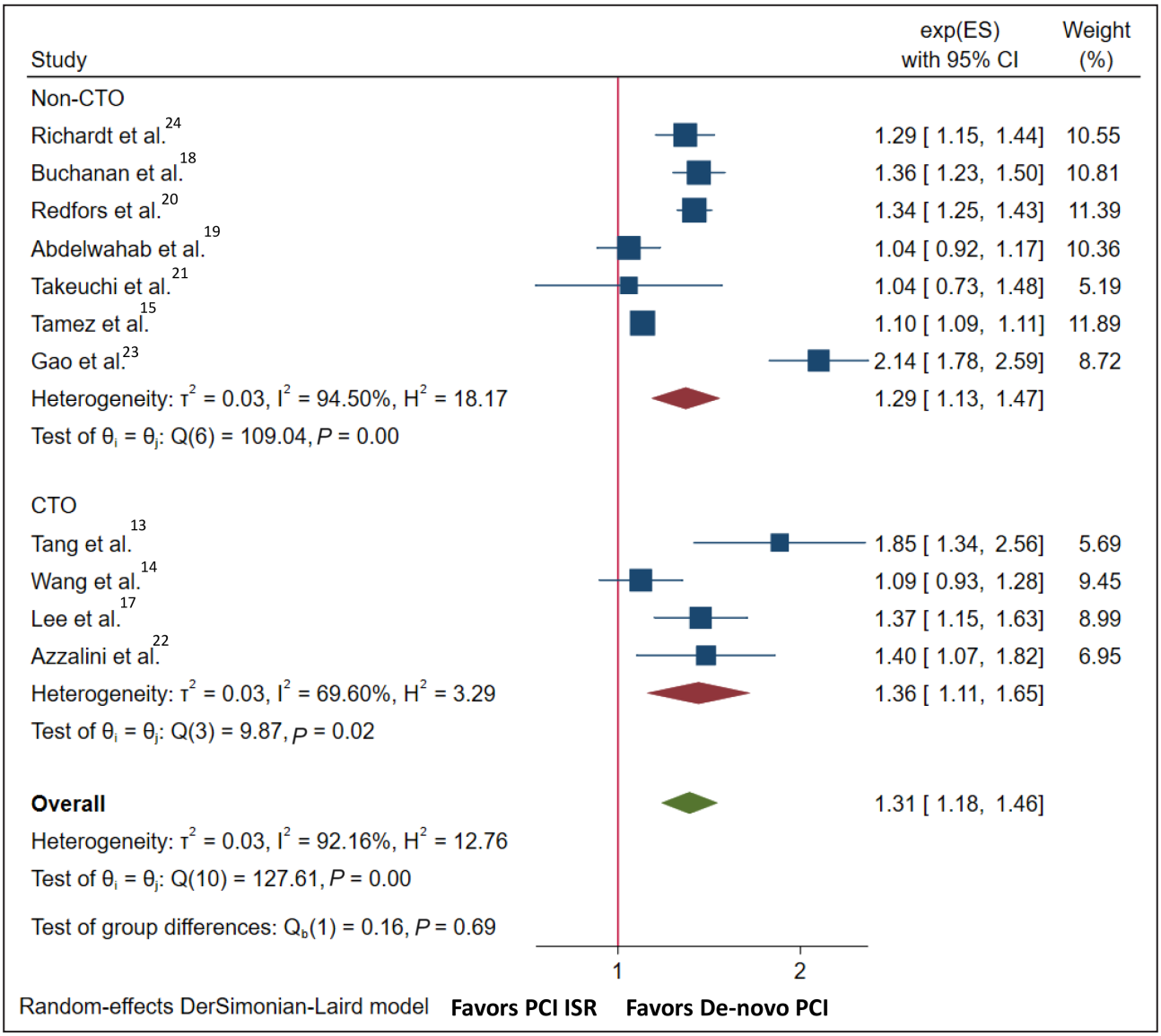

Figure 2. Forrest plot for long-term major adverse cardiovascular events after PCI of ISR vs de novo lesions.
CTO indicates chronic total occlusion; exp(ES), Exponentiated log effect-size; ISR, in-stent restenosis; and PCI, percutaneous coronary intervention.

to each study is reported in Table S5). There was a higher incidence of MI among the ISR versus de novo groups (OR, 1.20 [95% CI, 1.11–1.29]; I^2=38%; Q=16.10, P=0.10). Subgroup analysis showed no significant interaction according to CTO versus non-CTO lesions ($P_{interaction}$=0.73). TVR was reported in 9 studies.[1–5,9] Compared with de novo lesions, the ISR group had a higher incidence of TVR (OR, 1.42 [95% CI, 1.29–1.55]; I^2=86%; Q=57.00, P<0.001). Subgroup analysis showed no significant interaction according to CTO versus non-CTO lesions ($P_{interaction}$=0.86). Stent thrombosis was reported in 5 studies.[3–5,9] Analysis showed a higher incidence of stent thrombosis with PCI for ISR versus de novo lesions (OR, 1.44 [95% CI, 1.11–1.87]; I^2=84%; Q=26.43, P<0.001) (Figure 3).

DISCUSSION

In this meta-analysis of 12 studies including 708 391 patients, we evaluated the outcomes of PCI of ISR versus de novo lesions. The salient findings were: (1) PCI for ISR was associated with a higher incidence of risk-adjusted MACE compared with PCI for de novo lesions at a median of ≈30 months. (2) This was driven by a higher incidence of all-cause mortality, MI, TVR, and stent thrombosis in the ISR group. (3) There was no evidence of interaction for the outcomes in the CTO versus non-CTO subgroups (Figure 4).

ISR PCI represents about 10% of all PCI in the contemporary DES era.[24] Patients with ISR present in the form of acute coronary syndrome in more than

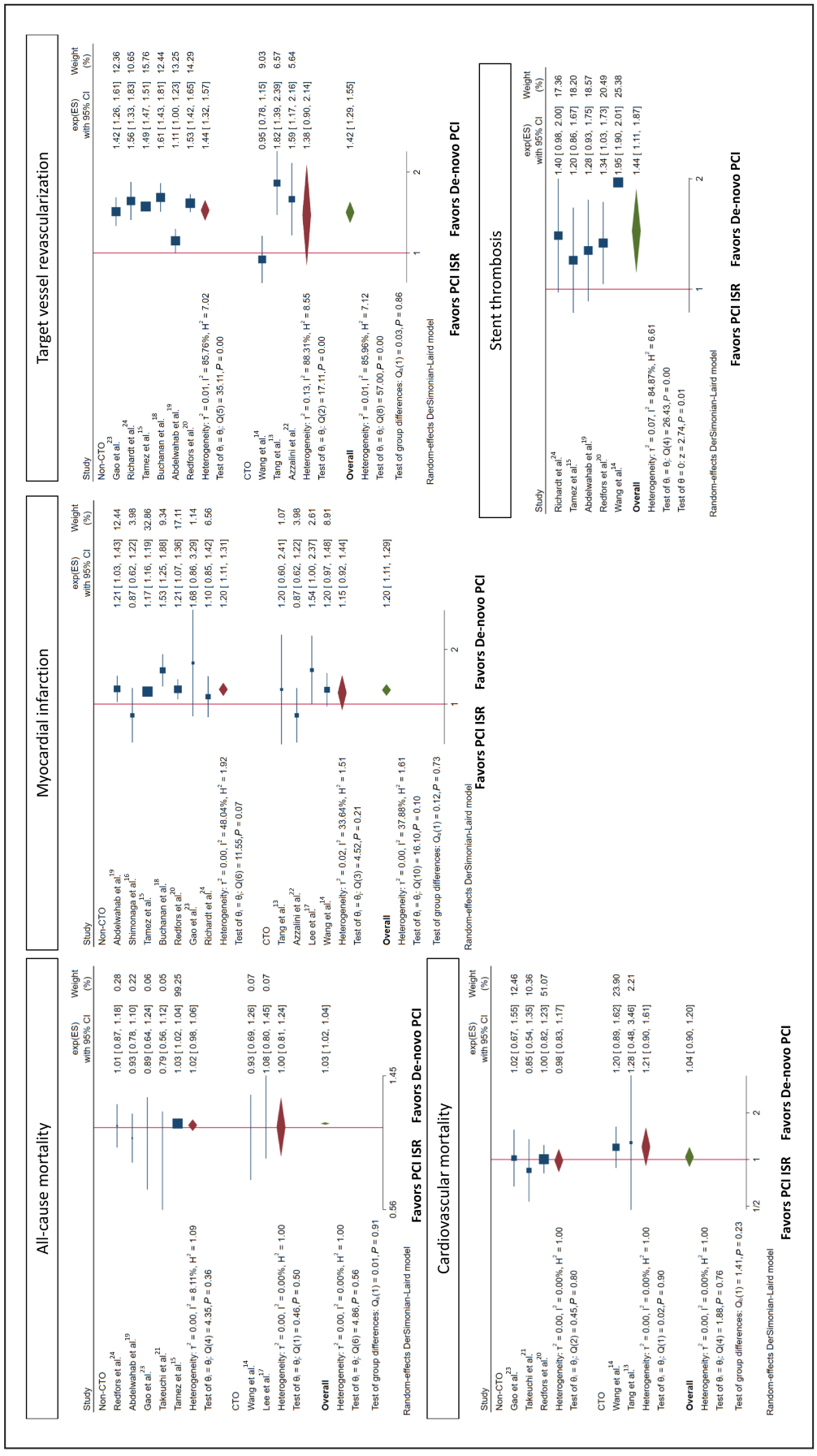

Figure 3. Forrest plot for secondary outcomes after PCI of ISR vs de novo lesions.
CTO indicates chronic total occlusion; exp(ES), Exponentiated log effect-size; ISR, in-stent restenosis; and PCI, percutaneous coronary intervention.

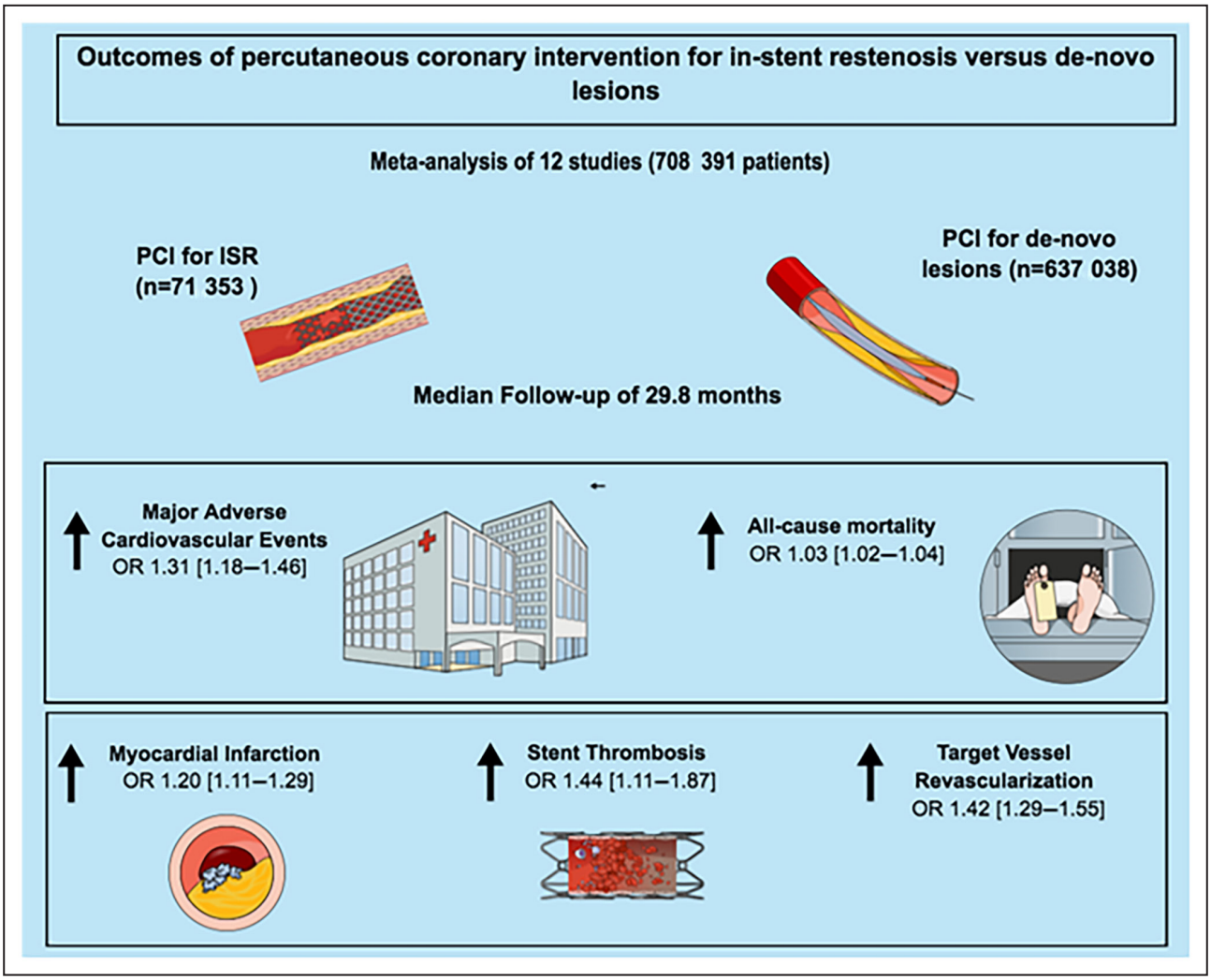

Figure 4. Summary of the outcomes with PCI for ISR vs de novo lesions.
ISR indicates in-stent restenosis; OR, odds ratio; and PCI, percutaneous coronary intervention.

two-thirds of patients and tend to present more often with unstable angina and less often with MI than de novo coronary lesions.[17,25] Clinicians have attempted to stratify different classes of ISR, either angiographically or by mechanism.[26,27] Focal patterns, which were predominantly treated with angioplasty and stenting, were associated with better clinical outcomes compared with more diffuse lesion patterns or CTOs.[26]

In this study, we pooled the totality of available data for the outcomes of PCI for ISR, compared with PCI for de novo lesions. This analysis is the largest to date, and showed a higher incidence of adverse clinical events, including all-cause mortality, after PCI for ISR versus de novo lesions. These findings are line with results of individual studies. The higher risk of adverse events with PCI for ISR is probably related to the unique pathophysiology of ISR lesions as well as the challenging nature of interventions for ISR lesions. ISR lesions have a distinctive pathophysiology, which is characterized by neointimal hyperplasia and neoatherosclerosis,[28] as opposed to the atherosclerotic plaque formation with fibro-fatty calcified core in de novo coronary artery disease. Optical coherence tomography studies have demonstrated the neointimal changes that occur with time inside DES. These include increased neointimal thickness and transformation from a homogenous to heterogenous or lipid-laden intima, with formation of cholesterol-rich plaques and thin-cap atheromas.[29,30] These neoatherosclerotic changes occur more frequently and earlier in DES than bare-metal stents and play a role in DES ISR.[31,32] Lipid-laden neointima also plays a role in the increased risk of late stent thrombosis with DES, in addition to delayed neointimal coverage of stent struts.[33,34] Although new-generation everolimus-eluting stents demonstrate better vessel healing and neointimal stent coverage than first-generation sirolimus- and paclitaxel-eluting stents, they have a similar prevalence of neoatherosclerosis.[35]

In addition to vessel remodeling following DES, mechanical factors, such as stent under expansion due to underlying calcification and malposition, also play a role in ISR.[36] Patient-related factors such as diabetes and renal failure have also been reported to be independent risk factors for ISR.[37,38]

Given its unique pathophysiology and complex clinical presentation, intervening on ISR portends a challenging subset of PCI procedures. Different intervention techniques are used in clinical practice, which are mainly based on clinical presentation, type of ISR lesions (ie, focal versus diffuse), and mechanism of ISR lesions. A mechanism-driven approach should be always considered when selecting a strategy for treatment of ISR, including restenting, balloon angioplasty, cutting and scoring balloons, rotational atherectomy, brachytherapy, or using drug-coated balloons.[5] Even with the wide variety of interventions, 2 modalities are preferred, repeat PCI with DES or angioplasty with drug-coated balloons.[39,40] In the current meta-analysis, the proportion of PCI with stenting among the ISR group varied across different studies from 48.4% to 100%, mainly with DES. Comparatively, a national cohort study of >5 million patients observed that 23.5% of patients with ISR did not receive DES and were more likely to receive other treatments.[24] Restenting ISR with DES, specifically everolimus stents, was found to be superior in both angiographic and clinical outcomes compared with other PCI methods.[41,42] However, operators should be mindful of multilayered stenting, and recurrent DES implantations could exacerbate a cycle of restenosis. Drug-coated balloons, although providing less lumen gain than restenting, are also a viable option, because they do not add a stent layer and still provide favorable outcomes.[43,44] Coronary artery bypass graft should ultimately be considered in patients with diffuse, recurrent ISR with associated multivessel disease, but this approach may be limited due to poor target vessels.[45] The use of intracoronary imaging to guide PCI can optimize lesion preparation, stent deployment, and may assist with identifying the mechanism of stent failure, reducing the risk of MACE compared with angiography-guided PCI.[46] Limited data were reported in the current analysis on the use of intracoronary imaging during PCI for ISR. Further research is warranted to evaluate the outcomes of PCI of ISR compared with de novo lesions using the state-of-the-art PCI techniques, including routine intravascular imaging, transradial access, and using advanced modalities such as laser atherectomy, brachytherapy, and drug-coated balloons.

In this analysis, the higher risk of adverse events with PCI for ISR, was observed irrespective of ISR morphology (ie, CTO or non-CTO). CTO ISR lesions represent the extreme end of the spectrum of ISR lesions, and share similar morphological patterns, including neointimal hyperplasia, neoatherosclerosis, and stent under expansion in CTO ISR. PCI for CTO ISR lesions entails different technical considerations. At 1 side, the previously deployed stent acts as a roadmap of the target vessel and also doubles as a guard against coronary dissection during PCI of the CTO.[16] However, the previous stent may obstruct the path of the wire and lead to suboptimal reentry for PCI. Lee et al additionally observed that stenting of ISR in CTO was a risk factor for MI and TVR, possibly explained by an abnormal vessel reaction and thrombus formation attributed to multilayered stenting.[16]

The collective data in this study demonstrated that PCI for ISR is associated with worse outcomes compared with de novo lesions. This highlights the need for optimization of index PCI procedures to reduce the chances of future ISR by adopting best practices such as adequate lesion preparation and intracoronary image-guided interventions. Future directions should be directed toward increasing awareness for adoption of these best practices, and toward exploring novel/alternative approaches for PCI of ISR.

Limitations

The current analysis has certain limitations. First, due to the observational nature of included studies, there is an inherent risk for selection bias. In our analysis, we have pooled risk-adjusted effect sizes to minimize this risk. Nevertheless, residual confounding cannot be ruled out. Second, there was a considerable degree of statistical heterogeneity for some of the study outcomes. Also, there were some variabilities among the included studies in the definition of the primary outcome. Nevertheless, we have adopted a random-effects model to mitigate the effects of such heterogeneity. Third, some of the included studies only reported data for patients who underwent stent implantation, and data for unsuccessful PCIs were not reported. This might have introduced selection bias by not reporting data for patients with unsuccessful PCIs or ISR with anatomies not amenable to stenting. Fourth, patients with recurrent ISR may be treated with different approaches and management strategies, contributing to heterogeneity of outcomes. Insufficient patient-level data precluded further subgroup analyses. Finally, the use of intracoronary imaging and laser atherectomy were either not reported or extremely low in the included studies in our analysis. This could impact the external generalizability of the findings to contemporary practice, given the viable role of these modalities in contemporary management of ISR lesions.

CONCLUSIONS

Compared with de novo lesions, PCI of ISR was associated with a higher incidence of risk-adjusted MACE at

a weighted follow-up of 29.8 months. This was mainly driven by a higher incidence of all-cause mortality, MI, repeat revascularization, and stent thrombosis. This association was demonstrated regardless of the nature of ISR (ie, CTO versus non-CTO). These findings crystallize the notion that both ISR itself and PCI for ISR are not benign entities, and major efforts should be directed toward optimizing index PCI procedures.

ARTICLE INFORMATION

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Affiliations

Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX (A.E., S.B., D.J.K.); Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX (A.T.D.); Department of Medicine, MedStar Georgetown Washington Hospital Center, Washington, DC (I.M.); Division of Cardiology, University of Florida, Gainesville, FL (M.E.); Department of Cardiology, Hospital Universitario de La Princesa, IIS-IP, Universidad Autónoma de Madrid, CIBER-CV, Madrid, Spain (F.A.); Division of Cardiovascular Medicine, Gill Heart Institute, University of Kentucky, Lexington, KY (I.Y.E.); and Cardiovascular Research Foundation, New York, NY (G.S.M.).

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Disclosures

None.

Supplemental Material

Tables S1–S5
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title, Pg 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract, Pg 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Lines 6-14, Pg 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Lines 14-16, Pg 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	"Selection Criteria", Pg 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify thedate when each source was last searched or consulted.	“Methods” Lines 18-23, Pg 3 and Lines 1-10, Pg 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	“Methods” Lines 18-23, Pg 3 and Lines 1-10, Pg 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each recordand each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Lines 12-21, Pg 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in theprocess.	"Data Extraction", Pg 4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in eachstudy were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	"Outcomes", Line 23, Pg4 and Lines 1-4, Pg 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	"Outcomes", Line 23, Pg4 and Lines 1-4, Pg 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	"Assessment of the quality of the included studies", Pg 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	"Statistical Analysis”, Pg 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics andcomparing against the planned groups for each synthesis (item #5)).	“Assessment of the quality of the included studies”, Pg 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or dataconversions.	Not Applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Tables 1,2,3 and Supplemental Tables 2,3,4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe themodel(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	"StatisticalAnalysis", Pg 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Lines 12-18 of "Statistical Analysis" , Pg 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Lines 19-23 of "Statistical Analysis", Pg 5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	“Assessment of the quality of the included studies”, Pg 5

PRISMA 2020 Checklist

Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	"Assessment of the quality of the included studies", Pg 5

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included inthe review, ideally using a flow diagram.	Lines 4-6, Pg 6 and Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Not Applicable
Study characteristics	17	Cite each included study and present its characteristics.	Line 4-16, Pg 6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Lines 17-19, Pg 6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision(e.g. confidence/credible interval), ideally using structured tables or plots.	"Outcomes", Lines 20-22, Pg 6 and Lines 1-19, Pg 7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Lines 17-19, Pg 6 and Supplemental Table 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g.confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	"Outcomes", Lines 20-22, Pg 6 and Lines 1-19, Pg 7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	"Outcomes", Pg 6-7 and Lines 3-5, Pg 12
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Lines 3-4,Pg 7 and Lines 5-7, Pg 12
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Lines 17-19, Pg 6 and Supplemental Table 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Lines 17-19, Pg 6 and Supplemental Table 2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Lines 20-22, Pg 7 and Lines 1-4, Pg 8
	23b	Discuss any limitations of the evidence included in the review.	Lines 1-9, Pg 12
	23c	Discuss any limitations of the review processes used.	Lines 1-3, Pg 12
	23d	Discuss implications of the results for practice, policy, and future research.	"Conclusion" Lines 12-17, Pg 12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Lines 6-10, Pg 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Protocol not prepared. Lines 8-10, Pg 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Not applicable
Competing interests	26	Declare any competing interests of review authors.	Not applicable
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from includedstudies; data used for all analyses; analytic code; any other materials used in the review.	Data is availablewithin manuscript.

PRISMA 2020 Checklist

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From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table S2: Risk of bias among included studies using Newcastle Ottawa score

Study	Selection				Comparability:	Outcome:		Total score
	Representativeness of the sample	Selection of the control group	Ascertainment of the exposure (disease)	Non-respondents	The subjects in different outcome groups are comparable	Assessment of the outcome:	Statistical test:	
Abdelwahab et al.[19]	1	1	2	1	2	2	1	10
Buchanan et al.[18]	1	1	2	1	2	2	1	10
Lee et al.[17]	1	1	2	1	2	2	1	10
Redfors et al.[20]	1	1	2	1	2	2	1	10
Shimonaga et al.[16]	1	1	1	1	1	2	1	8
Takeuchi et al.[21]	1	1	2	1	1	2	1	9
Tamez et al.[15]	1	1	2	1	2	2	1	10
Tang et al.[13]	1	1	2	1	1	2	1	9
Wang et al.[14]	1	1	2	1	1	2	0	8
Richardt et al.[24]	1	1	2	1	1	2	1	9
Gao et al.[23]	1	1	2	1	2	2	1	10
Azzalini et al.[22]	1	1	2	1	2	2	1	10

Table S3: Definition of major adverse cardiac events

Study	MACE definition
Abdelwahab et al.[19]	Composite of all-cause mortality, MI and CVA
Buchanan et al.[18]	Composite of all-cause mortality, MI and ischemia-driven repeat revascularization
Lee et al.[17]	Composite of all-cause mortality, MI and ischemia-driven repeat revascularization
Redfors et al.[20]	Composite of cardiac mortality, MI and stent thrombosis
Shimonaga et al.[16]	NA
Tamez et al.[15]	Composite of all-cause mortality, MI, CVA and ischemia-driven repeat revascularization
Tang et al.[13]	Composite of cardiac mortality, MI and ischemia-driven repeat revascularization
Wang et al.[14]	Composite of all-cause mortality, MI and acute heart failure
Richardt et al.[24]	Composite of all-cause mortality, MI and ischemia-driven repeat revascularization
Gao et al.[23]	Composite of cardiac mortality, MI and ischemia-driven repeat revascularization
Azzalini et al.[22]	Composite of cardiac mortality, MI and ischemia-driven repeat revascularization

Table S4: Risk adjustment in the included studies

Study	Adjusted outcomes?	Variables adjusted for
Abdelwahab et al.[19]	Yes	Age (>75 years), diabetes, hypertension, smoking, hyperlipidaemia, positive family history of coronary artery disease, previous myocardial infarction, atrial fibrillation, STEMI, target vessel: left anterior descending, chronic total occlusion, long lesion (>15 mm), type C lesion, bifurcation lesion and stent type
Buchanan et al.[18]	Yes	Clinical presentation of MI
Lee et al.[17]	Yes	Age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, chronic renal failure on hemodialysis, history of myocardial infarction, history of coronary artery bypass grafting, history of peripheral artery disease, history of cerebrovascular accident, clinical presentation of index CTO PCI, and ejection fraction (EF).
Redfors et al. [20]	Yes	Age, sex, diabetes, smoking (current), renal insufficiency, clinical presentation, previous MI, previous coronary artery bypass grafting, anemia, PRU, left anterior descending coronary artery (LAD) as culprit vessel, multivessel disease, PCI against a graft vessel, bifurcation lesion, moderate or severe coronary calcification, total stent length, vessel diameter, and DES generation.
Takeuchi et al. [21]	Yes	Age, gender, CKD incidence, hemoglobin level, and hs-CRP level
Tamez et al.[15]	Yes	Age, sex, race, ethnicity, diabetes, chronic kidney disease stage, hypertension, dyslipidaemia, PCI indication, bifurcation lesion, lesion in graft, chronic total occlusion, stent type, total stent length, and minimum stent diameter
Tang et al.[13]	Yes	Adjusted for clinical, angiographic, and procedural variables
Wang et al.[14]	No	
Richardt et al.[24]	No	
Gao et al.[23]	Yes	Sex, age, prior MI, prior percutaneous coronary intervention, previous coronary artery bypass graft, diabetes mellitus, hypertension, unstable angina, left main lesion, number of stents, number of lesions, sirolimus DES treatment, stent diameter, stent length, postdilation angioplasty, use of intravascular ultrasound
Azzalini et al.[22]	Yes	Age, center, prior MI, Diabetes, prior CABG, eGFR, acute coronary syndrome presentation, number of diseased vessels, J-CTO score, PROGRESSCTO score, use of DES, procedural success, major procedural complications, and use of dissection/re-entry techniques.

Table S5: Definitions of Myocardial infarction in included studies

Study	MI definition
Abdelwahab et al.[19]	ST-elevation myocardial infarction (STEMI; ST-elevation at least 1 mm in two or more limb leads, or at least 2 mm in two or more contiguous precordial leads or development of new left bundle branch block on the ECG) or non-ST-elevation myocardial infarction (NSTEMI; pathological increase of cardiac specific enzymes with CK-MB >1.5 times of normal limits, Troponin T or I >99th percentile of normal value)
Buchanan et al.[18]	MI was characterized as either non–ST-segment elevation MI or ST-segment elevation myocardial infarction. Non–ST-segment elevation MI was defined by the presence of typical chest pain or angina-equivalent symptoms in association with elevated troponin cardiac marker. ST-segment elevation myocardial infarction was defined by the presence of typical chest pain or angina-equivalent symptoms in association with ST-segment elevation on presenting electrocardiogram or new left bundle-branch block. MI was further characterized by Q-wave myocardial infarction (QWMI) if new Q waves deeper than 1 mm occurred in the 2 contiguous leads; otherwise, non-QWMI was diagnosed.
Lee et al.[17]	nonfatal MI
Redfors et al.[20]	MI was defined according to the Acute Catheterization and Urgent Intervention Triage Strategy criteria. (A) MI diagnosis before angiography or in medically treated patients: (1) If the peak troponin or creatine kinase (CK)–MB (or CK) levels are elevated but the peak has not yet been reached: Recurrent chest pain or ischemic equivalent symptoms lasting ≥30 minutes, or new ECG changes consistent with MI and the next troponin or CK-MB (or CK) level measured approximately 8 to 12 hours after the event is elevated by at least 50% above the previous level. (2) If the elevated troponin or CK-MB (or CK) levels are falling or have returned to normal: Recurrent chest pain or ischemic equivalent symptoms lasting ≥30 minutes, and a new elevation of troponin or CK-MB (or CK) >upper limits of normal (ULN) if the troponin or CK-MB (or CK) level has returned to <ULN, or a rise above the previous nadir level if the troponin or CK-MB (or CK) level has not returned to <ULN. (B) MI diagnosis after PCI: (1) If the baseline CK-MB (or CK) levels are normal: A new elevation of troponin or CK-MB >3× ULN (or CK >3× ULN) within 24 hours post-PCI. (2) If the baseline CK-MB (or CK) levels are elevated, but documented to be falling: recurrent chest pain or ischemic equivalent symptoms lasting ≥30 minutes, and an absolute rise of CK-MB >3× ULN (or an absolute rise in CK >2× ULN) above the previous nadir level within 24 hours post-PCI. (3) If the peak CK-MB (or CK) has not yet been reached before PCI: Recurrent chest pain or ischemic equivalent symptoms lasting ≥30 minutes, or new electrocardiographic changes consistent with a reinfarction and the next CK-MB (or CK) level measured approximately 8 to 12 hours after the event is elevated by at least 50% above the previous level or >3× ULN, whichever is greater. (C) MI diagnosis after coronary artery bypass surgery: Any CK-MB (or CK) ≥10 × ULN within 24 hours of operation and increased at least 50% over the most recent preoperation levels, or any CK-MB (or CK) ≥5× ULN within 24 hours of operation and increased at least 50% over the most recent preoperation levels and new significant (≥0.04 second) Q waves in ≥2 contiguous electrocardiographic leads. (D) Q-wave versus non–Q-wave MI: All reinfarctions will be adjudicated as being either Q wave (development of new pathologic Q waves in 2 or more contiguous leads) or non–Q wave.
Shimonaga et al.[16]	Periprocedural MI was defined as an increase in the troponin I levels greater than 0.15 ng/mL (3 times the ULN). Major PMI was defined as an increase in the troponin I levels greater than 0.75 ng/mL (15 times the ULN)
Tamez et al.[15]	Not avaialble
Tang et al.[13]	Not avaialble
Wang et al.[14]	Periprocedural MI was defined using the Society for Cardiovascular Angiography and Interventions (SCAI), Academic Research Consortium (ARC)-2, and fourth universal definitions.
Richardt et al.[24]	Myocardial infarction was defined according to an extended historical protocol definition and according to ARC definitions.1-2 A Q-wave myocardial infarction required, in th absence of cardiac enzyme data, a history of chest pain or other acute symptoms consistent with myocardial ischemia together with new pathological Q waves in two or more contiguous ECG leads as assessed by the core lab or clinical events committee. In the presence of elevated cardiac enzymes, new pathological Q waves in two or more contiguous ECG leads as assessed by the core lab or clinical events committee were sufficient to diagnose a Q-wave myocardial infarction. In the absence of an ECG, a Q-wave myocardial infarction could be adjudicated on the basis of the clinical scenario and appropriate cardiac enzyme data.
Gao et al.[23]	MI was diagnosed by electrocardiographic changes and/or a rise and fall of creatine kinase-myocardial band (CK-MB) fraction in the presence of ischemic symptoms. New development of pathological Q waves in 2 contiguous leads was defined as Q-wave MI; and in the absence of pathological Q waves, an elevation in CK-MB level >3 times the upper limit of normal was defined as non– Q-wave MI.
Azzalini et al.[22]	Periprocedural type 4a MI, target vessel MI (Q wave and non-Q wave MI) definition was not explicit

Figure S1: Funnel plot for publication bias

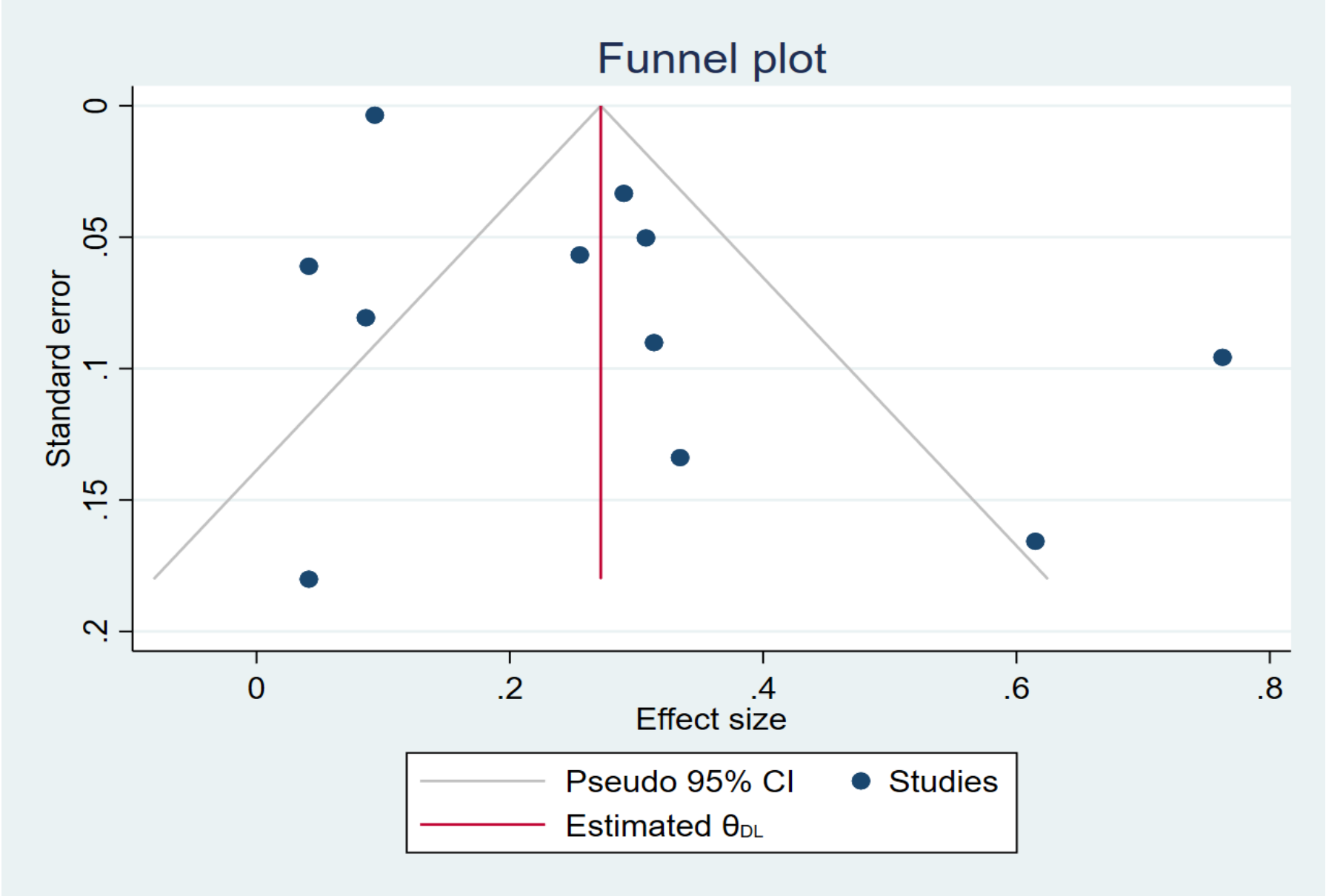

Figure S2: Sensitivity analysis for MACE excluding Richardt et al. and Wang et al.