

# Immunosuppressive Therapy for Restenosis Prevention after Coronary Bare-Metal Stent Implantation -A Meta-Analysis

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## Research article

**Keywords:** immunosuppressive therapy, restenosis, bare-metal stents , meta-analysis

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# Abstract

**Background:** Previous studies revealed controversial results regarding the prevention of in-stent restenosis after coronary bare-metal stents (BMS) placement with systemic administration of immunosuppressive drugs. We therefore conducted a meta-analysis to investigate the role played by immunosuppressive therapy (IST) in reducing both in-stent restenosis and adverse clinical events after BMS implantation.

**Methods:** We searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases for randomized, controlled studies that investigated the therapeutic effects of IST after BMS insertions. Endpoints assessed were: (1) angiographic restenosis by the end of at least 6 months of follow-up; (2) target vessel revascularization (TVR); and (3) risk of major adverse cardiovascular events (MACE). MACE was defined as death, myocardial infarction and TVR.

**Results:** Nine randomized, controlled trials including 1576 patients (mean age 62 years; follow-up of 6-12 months) were included in this analysis. Meta-analysis showed periprocedural IST + BMS significantly reduced in-stent restenosis as compared to BMS alone (RR: 0.59 [0.39-0.90],  $P = 0.01$ ). In particular, IST reduced restenosis in high-risk patients (defined as patients with mean reference diameter  $< 3.0$  mm or high periprocedural C-reactive protein level) (RR: 0.34 [0.15,0.74],  $P = 0.006$ ) rather than in low-risk patients ( $P$  for interaction = 0.06). Similarly, IST also reduced the risk of MACE (RR: 0.63 [0.50-0.80],  $P < 0.01$ ) and TVR (RR: 0.57 [0.33-0.97],  $P = 0.04$ ).

**Conclusions:** Periprocedural IST reduces the risk of angiographic restenosis, TVR and MACE in patients with BMS implantation. The advantage of IST is driven mainly by a lower risk of in-stent restenosis in high-risk patients. Key words: immunosuppressive therapy, restenosis, bare-metal stents , meta-analysis

## Background

In-stent restenosis after stent insertions remains a challenge of contemporary percutaneous coronary intervention (PCI) [1]. The introduction of drug-eluting stents (DES) has significantly reduced restenosis by comparison with bare-metal stents (BMS) [2]. Nonetheless, DES use has been linked to a high bleeding risk because of prolonged dual antiplatelet therapy, stent thrombosis, and also socioeconomic considerations in developing countries [3]. Furthermore, stenting with the new-generation DES offers a similar risk of adverse events at long-term follow-up as compared to BMS [4]. Thus, there is still a considerable proportion of patients receiving BMS implantation in Europe [5] and US [6].

Some human studies have verified the benefits of immunosuppressive therapy (IST) when used systemically in the prevention of restenosis after BMS implantation [7–13]. However, several others indicated no effects on reducing restenosis or clinical outcomes [14–16]. Sardar et al. [17] conducted a meta-analysis in 2012 including 5 studies which investigated the effect of steroids on restenosis in patients undergoing percutaneous coronary angioplasty or BMS implantation, which demonstrated steroids use was associated with a risk reduction in restenosis, mortality and target vessel

revascularization (TVR). Cassese et al. [18] performed a meta-analysis by including 7 studies to evaluate the impact of oral IST on target lesion revascularization (TLR) and death/myocardial infarction (MI), which also reported the merits associated with IST in terms of lowering risk of TLR, but failed to demonstrate a reduction in death/ MI. However, the former study included only 3 trials focusing on steroids and did not perform intention-to-treatment analysis; the latter investigated the endpoints not originally focused on by the majority of the studies included. Furthermore, new trials [15, 16] were conducted after the previous meta-analyses. Hence, we aimed to conduct a meta-analysis to confirm the value of IST for the prevention of restenosis detected by angiography surveillance after BMS implantation.

## Methods

We conducted our meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines[19].

### Search strategy and selection criteria

We searched PubMed, Web of Science, Cochrane Central Register of Controlled Trials, and [ClinicalTrials.gov](http://ClinicalTrials.gov) databases for relevant studies up to August 2018. The search terms included “glucocorticoid(s)”, “prednisolone” / “prednisone” / “cortisone”, “sirolimus” / “rapamycin”, “immunosuppressive” / “immunosuppression” combined with “restenosis”, “percutaneous coronary intervention”. Reference lists of obtained articles were reviewed. Selection criteria included: (1) randomized controlled trials; (2) comparisons were conducted between IST+BMS group(s) and BMS alone group; (3) intention-to-treat analysis; (4) endpoints could be counted by patient and (5)  $\geq 6$ -month follow-up after stenting.

Two of the authors (Y. L. Dai and J. Zhou) made the same contribution for the searching, screening and selecting the eligible studies. Conflicts were discussed with a third investigator (Y. M. He).

### Data extraction and quality assessment

We extracted study data as follows: first author; year of publication; design details; number of participants; protocol of IST; events of restenosis; TVR; and major adverse cardiovascular events (MACE), as well as useful data such as patient demographics and the duration of follow-up.

We performed the assessment of bias using the Cochrane Collaboration tools based on methodological items, including randomization, allocation concealment, blinding, incomplete reporting of outcomes, selective presentation of outcomes, and other biases[20].

### Outcomes assessment

The primary endpoint was in-stent restenosis detected by routine angiographic surveillance after stenting during follow-up of at least 6 months. Secondary endpoints were TVR (defined as any repeat revascularization of the target vessel) and MACE (defined as death, MI and TVR). Definitions of other endpoints are shown in supplemental table 2.

## Statistical analysis

Intention-to-treat analysis was used for outcome analysis. For the meta-analysis, relative risks (RRs) and 95% confidence intervals (CIs) for each study were calculated. Pooled RRs and CIs were estimated either by a fixed-effect model (Mantel-Haenszel method) or, in the presence of heterogeneity (defined as  $I^2$  value >50%), by random-effect model (DerSimonian-Laird method). We investigated publication bias via drawing Begg's funnel plot and performing Harbord test. To help explain heterogeneity, subgroup analyses and Monte-Carlo permutation tests for meta-regression were performed by grouping studies according to sample sizes, features of patients (patients with mean reference diameter <3.0 mm or elevated C-reactive protein after PCI were considered as high-risk patients, otherwise defined as low-risk patients), therapies and publication year. Sensitivity analyses were conducted using the "1-study removed" method to determine the impact of any single study on main findings. Interaction between subgroup and treatment was assessed by permutation test at the  $P < 0.10$  level of significance. All analyses were carried out using STATA version 14.0 (Stata Corp, College Station, TX).  $P$  value less than 0.05 was considered statistically significant, except where otherwise specified.

## Results

### Literature search and selection

The final search on September 10, 2018, resulted in 1137 articles. The majority of the articles were precluded because of duplicates, reviews, commentary articles, unrelated topic and animal studies. Twenty-eight full-text articles were read, of which 19 were excluded, including 5 studies without randomized designs, 6 reviews and 8 irrelevant studies. Hence, 9 studies [7, 8, 10–16] were included in this meta-analysis, including 1576 patients, of whom 848 (54%) received IST. The review process is shown in Fig. 1.

### Study characteristics and study quality

The supplemental table 1 presents an overview of the included studies. Patients with indications for revascularization were randomized to IST + BMS versus BMS alone. The IST consisted of steroids or sirolimus in all cases and was administered by oral route except in two studies. In five trials, sirolimus dose varied between 2 and 3 mg per day for a duration of 7–30 days after index PCI [8, 10–12]. Oral steroids were given to patients with a duration of 28–45 days in three studies [7, 13, 16]. In studies using non-oral steroids, IST was administered once or twice in total [14, 15]. Per protocol endpoints including

angiographic and clinical endpoints and their definitions were listed in supplemental table 1 and table 2. Few key differences were found among these studies with respect to definition of restenosis, TVR, TLR, death, and MACE. Quality assessments of included studies were shown in supplemental table 3.

Study and patient characteristics were available for all studies (Table 1). The sample sizes ranged between 80 and 315, whereas three studies only included equal to or less than 100 cases. The average age of patients enrolled ranged from 58 (10) to 65 (9) years, and male patients dominated all of studies. Over half of the patients were diagnosed with acute coronary syndrome (ACS) at admission in 6 trials, and reference diameter (RD) before PCI ranged between 2.59 mm and 3.41 mm. Angiographic surveillance were made in majority of patients in 8 studies. Mean clinical follow-up duration varied from 6 to 12 months.

## Primary endpoint

The primary endpoint (in-stent restenosis) was presented in 7 of 9 studies after precluding 2 trials [11, 13], among which one didn't perform routine angiographic surveillance and another reported events not counted by patient. In total, 273 of 1218 (22.4%) patients met the restenosis criteria detected by angiographic surveillance after 6–9 months. A random-effect model was used to estimate the combined RRs and 95% CIs according to  $I^2$  which showed that periprocedural IST+BMS significantly reduced the risk of restenosis as compared to BMS alone (18.7% versus 27.0%, RR: 0.59 [0.39–0.90],  $P = 0.01$ ;  $I^2 = 64.2%$ ,  $P$  for heterogeneity = 0.01) (Fig. 2A).

## Secondary endpoints

Event rates were low for death (1%), MI (1%) and TLR (4 studies reported the incidence), thus combining estimated RRs was performed for TVR and MACE. Eight studies reported the incidence of MACE, including 748 patients in IST+BMS group and 628 in BMS alone group. A significant reduction in MACE was observed among those assigned to IST+BMS group (14.3% versus 21.2%, RR: 0.63 [0.50–0.80],  $P < 0.01$ ;  $I^2 = 32.0%$ ,  $P$  for heterogeneity = 0.17) (Fig. 2B). The risk of TVR, reported in 6 studies, were also reduced with IST (12.4% versus 18.6%, RR: 0.57 [0.33–0.97],  $P = 0.04$ ;  $I^2 = 61.2%$ ,  $P$  for heterogeneity = 0.02) (Fig. 2C).

## Subgroup analysis on the primary endpoint

Subgroup analyses were conducted to explore potential sources of heterogeneity across studies by dividing these studies into several groups according to sample sizes, features of patients, different therapies and publication year.

Subgroup analyses based on sample sizes and features of patients consistently revealed significant between-group heterogeneity ( $P$  for interaction = 0.02 and 0.06, respectively). In the subgroup with small

sample sizes, IST lowered the risk of restenosis (RR: 0.23 [0.13,0.42],  $P < 0.001$ ;  $I^2 = 0\%$ ,  $P$  for heterogeneity = 0.69) as compared to BMS alone. Similarly, the combined results of 3 trials with high-risk patients showed IST reduced restenosis (RR: 0.34 [0.15,0.74],  $P = 0.006$ ;  $I^2 = 71\%$ ,  $P$  for heterogeneity = 0.02) (Fig. 3A). However, the benefit was observed neither in the subgroup with large sample sizes, nor in the subgroup with low-risk patients.

Next, in the subgroup analysis based on different drug use, difference occurred between sirolimus subgroup (RR: 0.37 [0.15,0.91],  $P = 0.03$ ) and steroid subgroup (RR: 0.79 [0.50,1.25],  $P = 0.31$ ). Nonetheless, between-group heterogeneity test did not reach statistical significance ( $P$  for interaction = 0.20) (Fig. 3A). Final subgroup analysis was performed according to publication year. The combined results of trials published before 2010 revealed pronounced IST effect on restenosis (RR: 0.53 [0.31,0.92],  $P = 0.03$ ). However, interaction test did not show between-group heterogeneity ( $P$  for interaction = 0.64) (Fig. 3A).

## Subgroup analysis on the secondary endpoints

In the subgroup analyses, sample size was the only factor influencing the effect of IST on the risk of MACE according to Monte Carlo permutation result ( $P$  for interaction = 0.02). In the subgroup with smaller sample sizes, IST+BMS versus BMS reduced the risk of MACE (RR: 0.32 [0.19,0.54],  $P < 0.001$ ;  $I^2 = 0\%$ ,  $P$  for heterogeneity = 0.58), while another subgroup with larger sample sizes showed a similar risk of MACE. (Fig. 3B).

Similarly, sample size was also the main source of heterogeneity across studies regarding the effects of IST on the risk of TVR ( $P$  for interaction = 0.03). Whereas subgroup analysis according to features of patients, different therapies and publication year revealed generally consistent results (Fig. 3C).

## Sensitivity analysis and publication bias

Sensitivity analysis for the primary endpoint was performed to investigate whether the lack of each study will alter the pooled RRs (Fig. 4B). No results changed materially after an individual study was omitted. A Begg's funnel plot for the primary endpoint rate showed the studies were equally distributed on the two sides (Fig. 4A). Moreover, Harbord test was performed to further identify the underlying heterogeneity and its results indicated the absence of bias ( $P = 0.15$ ).

## Discussion

In the present meta-analysis of 9 unique studies including 1576 patients with a follow-up of 6–12 months, we demonstrate that IST + BMS reduced the risk of restenosis, MACE, and TVR as compared to BMS alone. Patients with high-risk features responded favorably to the IST.

As a main finding, IST + BMS versus BMS alone decreases restenosis. However, this finding should be interpreted with caution as an obvious heterogeneity was observed in this analysis. Thus, subgroup analyses were carried out. Subgroup analysis according to the features of patients showed IST could only reduce restenosis in high-risk patients, which was further confirmed by interaction test with meta-regression ( $P$  for interaction = 0.06). Surprisingly, all patients included in 3 trials with small sample sizes had high-risk features in the subgroup analysis by sample sizes, which may explain why IST reduced the risk of restenosis only after combining studies with small sample sizes. Finally, subgroup analyses based on different therapies and publication year both showed some degree of heterogeneity, although  $P$  value for interaction didn't reach statistical significance.

As illustrated by experimental studies, the inflammatory reaction plays an essential role in the process of neointimal proliferation [21]. Inhibition of cell proliferation and migration by releasing immunosuppressive drugs in situ is the intrinsic feature of DES [22]. Whether systemic administration of these drugs, focusing on steroids and sirolimus in previous studies, could reduce restenosis as DES did has attracted attention for a long period [23].

Our meta-analysis revealed the favorable effect of IST on restenosis. Notably, the analysis showed high-risk patients would benefit more from IST, suggesting patients with high-risk features (mean reference diameter <3.0mm [24], elevated C-reactive protein after PCI [25]) may have more remarkable inflammation reactions in situ and be more likely to experiencing restenosis after BMS implantation as compared to those without these features. Furthermore, higher dose intensity for a longer period might be needed to reduce restenosis as illustrated by comparing SSTARs study [16] and IMPRESS-LD study [26] with IMPRESS(2) [7, 9] studies. Although permute tests didn't show significant heterogeneity between steroid subgroup and sirolimus subgroup, different effects may exist.

BMS+IST versus BMS alone reduced the risk of MACE and TVR at mid-term follow-up. These results merit cautious discussion since the duration of follow-up differs and we can not calculate hazard ratios (HRs) due to lack of individual patient data.

Unlike immunosuppressive drugs acting within a limited vessel in DES, systemic use of IST may bring about unsought adverse reactions. However, in the included studies only a small number of patients experienced major side effects and discontinued IST. Moreover, the studies with longer follow-up didn't reveal higher incidence of diabetes, malignancies, and other major adverse effects in IST groups in comparison with control arms[27, 28].

Our study has several limitations. First, the sample sizes in some studies were relatively small, with a sample size less than or equal to 100. Second, several estimated effects (e.g. 1 trial did not report the results of clinical endpoints) could not be obtained in some trials. Third, we are unable to calculate HRs, which have better validities in the occurrence of different follow-up durations, and can not control for traditional risk factors due to having no access to all raw datasets.

## Conclusion

The present meta-analysis demonstrates that IST reduces the risk of restenosis, TVR and MACE as compared with BMS alone. The benefits of the IST are mainly driven by a lower risk of restenosis in high-risk patients.

## Abbreviations

ACS: acute coronary syndrome; BMS: bare-metal stent(s); CIs: confidence intervals; DES: drug-eluting stent(s); HRs: hazard ratios; IST: immunosuppressive therapy; MACE: major adverse cardiovascular event(s); MI: myocardial infarction; PCI: percutaneous coronary intervention; RD: reference diameter; RRs: relative risks; TLR: target vessel revascularization; TVR: target vessel revascularization

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of data and material

All data are presented within the manuscript. Raw data can be available by corresponding author per request.

### Competing interests

The author declare that they have no competing interests.

### Funding

No funding was received for this study.

### Authors' contributions

Y-M He and Y-L Dai designed this study. Y-L Dai and JZ made substantial contributions to literature searching, eligible studies selecting and data extracting. Y-L Dai, JZ, Y-F Jiang and S-D Hu were involved

in data analysis. Y-M He, Y-L Dai and JZ wrote the manuscript. All author approved the final version of the manuscript.

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## Tables

**Table 1.** Characteristics of patients included in the meta-analysis stratified by trial.

Trial	N	Age, years	Males (%)	ACS (%)	LAD (%)	RD pre, mm	IST method	Surveillance angiography (%)	Mean follow up time, months
Lee <i>et al.</i> <sup>14</sup>	140	58(9)	66	61	46	3.41(0.38)	before PCI: 1g methylprednisolone i.v.	91	10.3
IMPRESS <sup>7</sup>	83	64(9)	83	11	52	3.10(0.05)	72h to 45 days after PCI: prednisone oral	98	12
OSIRIS <sup>8</sup>	300	65(9)	78	0	49	2.59(0.52)	48h prior to 7 days after PCI: sirolimus oral	86	12
ORAR II <sup>10</sup>	100	65(9)	91	65	47	2.94(0.56)	2.7h prior to 14 days after PCI: sirolimus oral	87	12
Stojkovic <i>et al.</i> <sup>12</sup>	80	58(10)	70	54	41	2.59(0.44)	post-procedure to 30 days: sirolimus oral	90	6.8
Cemigliaro <i>et al.</i> <sup>11</sup>	108	63(11)	84	68	76	2.93(0.72)	post-procedure to 30 days: sirolimus oral	96	12
Namdari <i>et al.</i> <sup>15</sup>	200	60(7)	56	N/A	N/A	N/A	two doses at 2-week interval: prednisolone i.m.	100	N/A
CEREA-DES <sup>13</sup>	250	64(9)	84	61	62	3.15(0.53)	post-procedure to 40 days: prednisone oral	N/A	12
SSTARS <sup>16</sup>	315	60	85	58	N/A	3.18(0.42)	6h prior to 28 days after PCI: prednisolone oral	91	6

Data are mean (SD), unless otherwise indicated. # variables counted by patient.

ACS: acute coronary syndrome; IST: immunosuppressive therapy; i.v.: intravenous; i.m.: intramuscular; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; RD pre: reference diameter before intervention; N/A: not applicable. Trial acronyms: IMPRESS: Immunosuppressive Therapy for the Prevention of Restenosis After Coronary Artery Stent Implantation; OSIRIS: Oral Sirolimus to Inhibit Recurrent In-stent Stenosis; ORAR: Oral Rapamycin in Argentina; CEREA-DES: Cortisone plus BMS or DES versus BMS alone to eliminate restenosis; SSTARS: STeroids and Stents Against Re-Stenosis.

# Figures

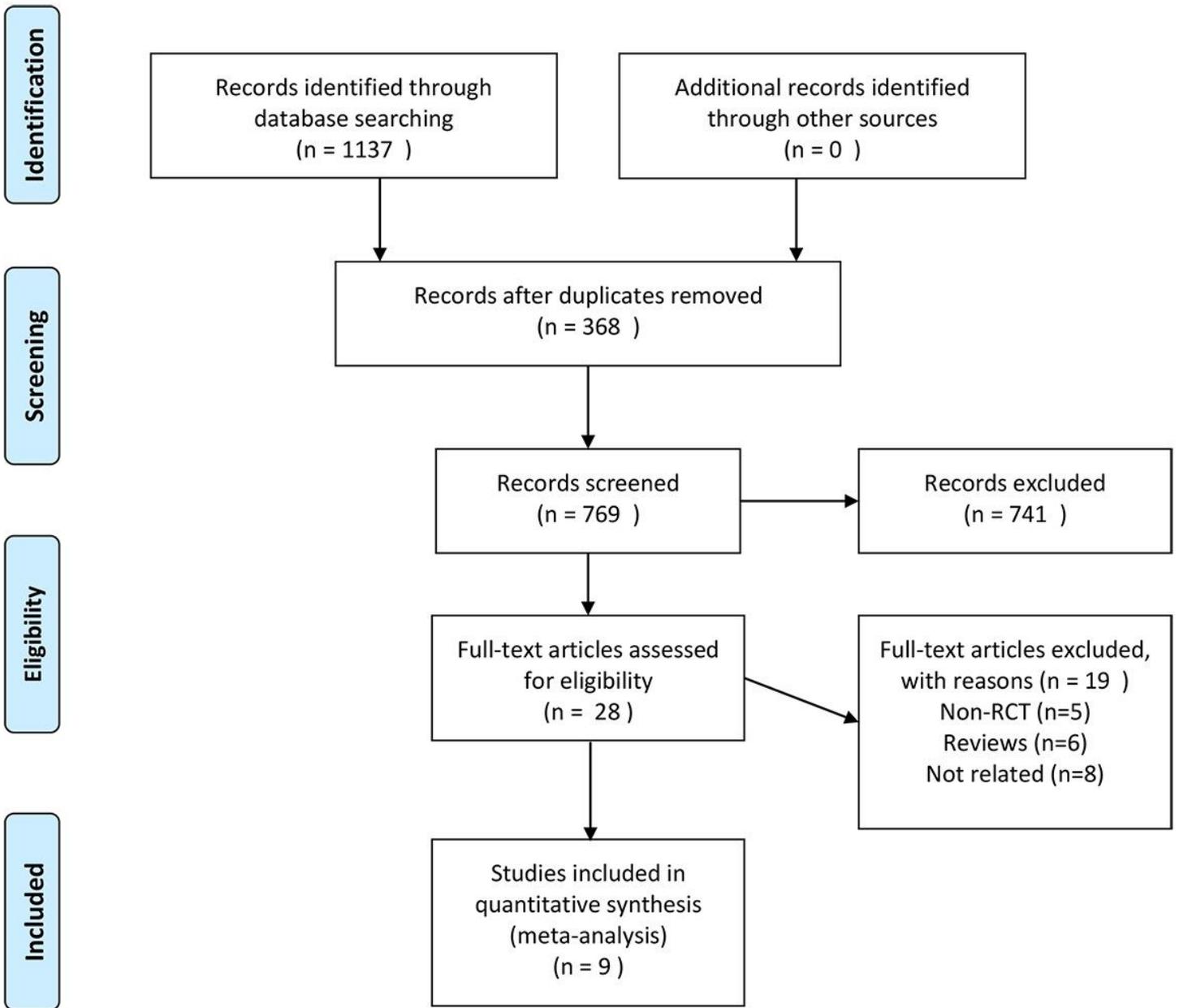
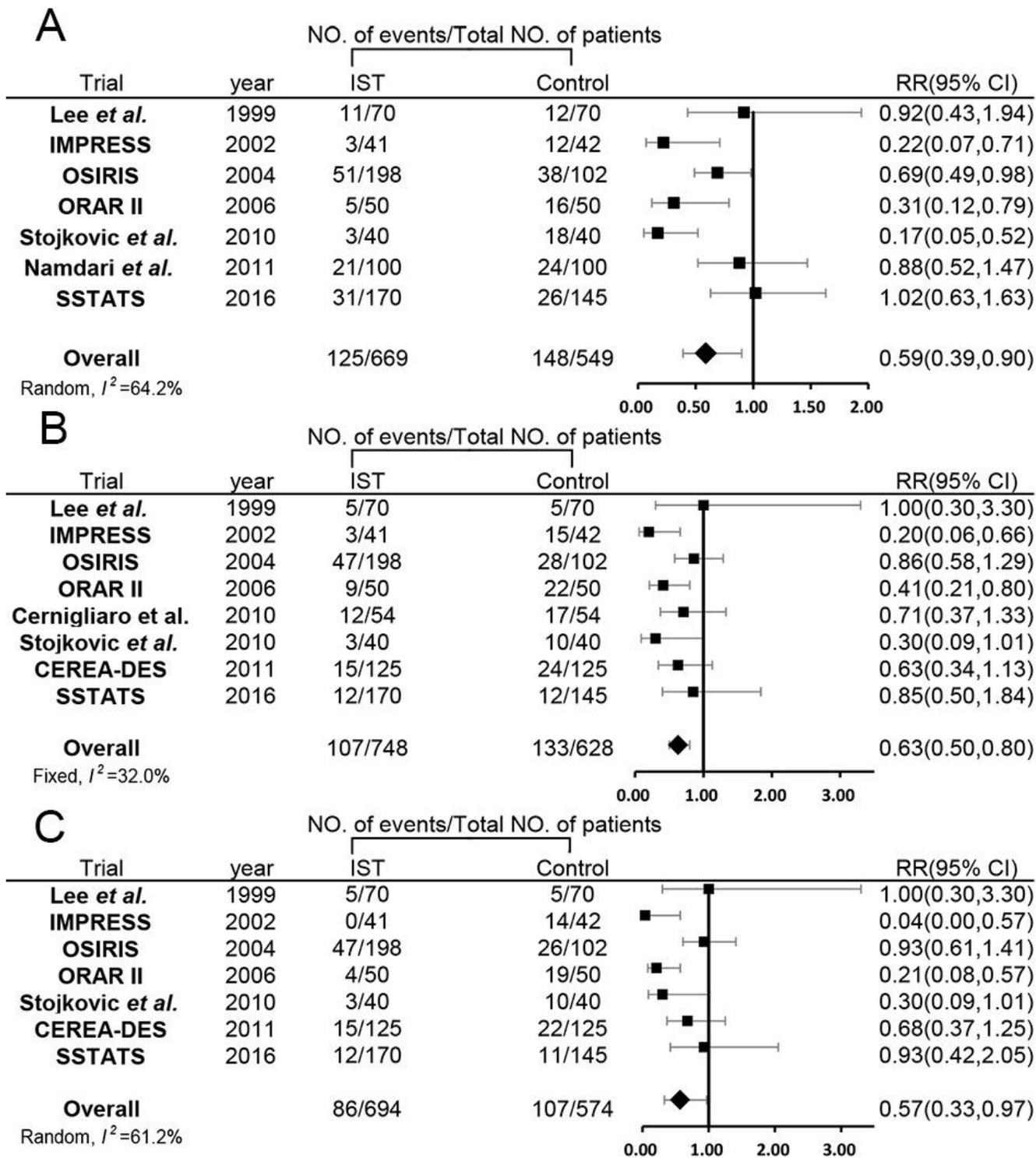


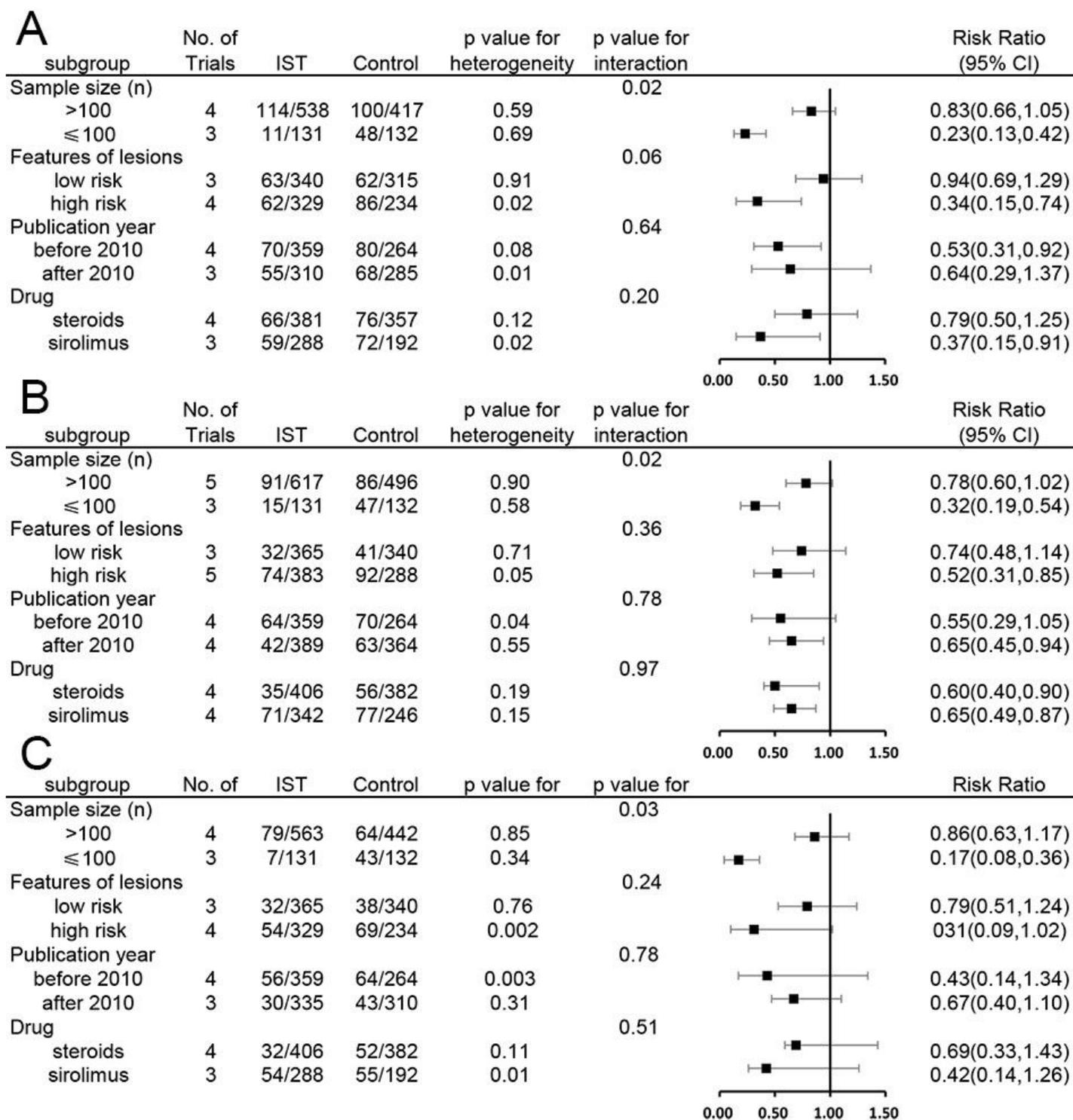
Figure 1

The complete procedure of the study selection and exclusion. Nine studies were finally included.



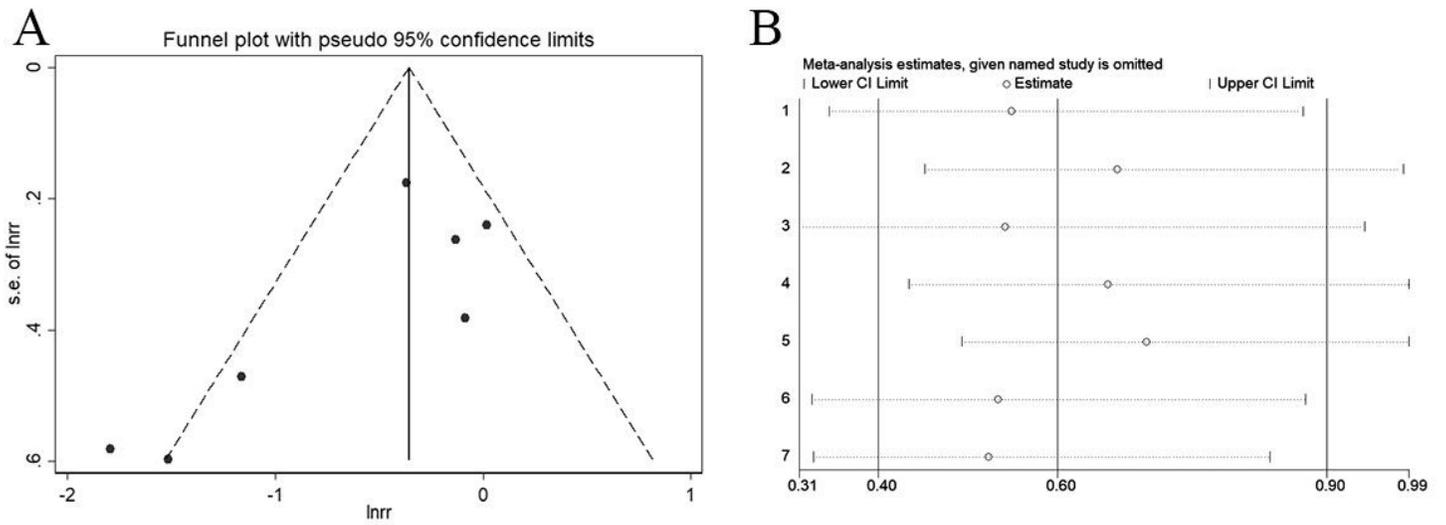
**Figure 2**

Risk estimates of primary and secondary outcomes for IST + BMS versus BMS alone. Forest plots show results for rates of restenosis (A), rates of target vessel revascularization (B), and risk of major adverse cardiovascular events (C). IST: immunosuppressive therapy. CI: confidence interval. Trial acronyms are as in the table 1.



**Figure 3**

Subgroup analyses for the effects of IST + BMS versus BMS alone on rates of restenosis (A), rates of target vessel revascularization (B), and risk of major adverse cardiovascular events (C). Abbreviations are as in Fig.2.



**Figure 4**

Begg's funnel plot with pseudo 95% confidence limits is drawn (A). Meta-analysis random-effects estimates are computed omitting one study at time (B). Rates of restenosis was extracted for analysis. lnrr: logarithm of risk ratio. Other abbreviations are as in Fig.2.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementarydata.docx](#)
- [prismacheklist1.0.doc](#)