The outcomes of intravascular ultrasound-guided drug-eluting stent implantation among patients with complex coronary lesions: a comprehensive meta-analysis of 15 clinical trials and 8,084 patients

Zhong-Guo Fan[1], Xiao-Fei Gao[1,2], Xiao-Bo Li[1,2], Ming-Xue Shao[1,2], Ya-Li Gao[1], Shao-Liang Chen[1,2], Nai-Liang Tian[1,2]

[1]Department of Cardiology, Nanjing First Hospital, Nanjing Medical University; Nanjing-*People's Republic of China*
[2]Department of Cardiology, Nanjing Heart Center; Nanjing-*People's Republic of China*

Abstract

Objective: The effects of intravascular ultrasound (IVUS)-guided drug-eluting stent (DES) implantation in patients with complex coronary artery lesions remains to be controversial. This study sought to evaluate the outcomes of IVUS guidance in these patients.
Methods: The EMBASE, Medline, and other internet sources were searched for relevant articles. The primary endpoint was major adverse cardiac events (MACE), including all-cause mortality, myocardial infarction (MI), and target-vessel revascularization (TVR). The incidence of definite/probable stent thrombosis (ST) was analyzed as the safety endpoint.
Results: Fifteen clinical trials involving 8.084 patients were analyzed. MACE risk was significantly decreased following IVUS-guided DES implantation compared with coronary angiography (CAG) guidance (odds ratio [OR] 0.63, 95% confidence intervals [CI]: 0.53–0.73, p<0.001), which might mainly result from the lower all-cause mortality risk (OR 0.52, 95% CI: 0.40–0.67, p<0.001), MI (OR 0.70, 95% CI: 0.56–0.86, p=0.001), and TVR (OR 0.53, 95% CI: 0.40–0.70, p<0.001). The subgroup analyses indicated better outcomes of IVUS guidance in DES implantation for these patients with left main disease or bifurcation lesions.
Conclusion: IVUS guidance in DES implantation is associated with a significant reduction in MACE risk in patients with complex lesions, particularly those with left main disease or bifurcation lesions. More large and powerful randomized trials are still warranted to guide stenting decision making. *(Anatol J Cardiol 2017; 17: 258-68)*
Keywords: intravascular ultrasound, drug-eluting stent, complex lesions, meta-analysis

Introduction

In the new era of drug-eluting stents (DES), the improved stenting outcomes that have been reported mainly appear as decreased incidence of repeat revascularization compared to the bare-metal stents (1). To our knowledge, the successful procedure of stent implantation is considered to strengthen these beneficial effects, which are usually assessed according to the expansion and apposition of implanted stents.

Intravascular ultrasound (IVUS) guidance in DES implantation is an essential technique for prevention of stent malapposition because of its high resolution of evaluating lesion severity, optimizing stent implantation (2, 3). In recent years, several large observational clinical trials (Obs) (4, 5) have indicated the benefits of IVUS guidance in terms of a lower rate of major adverse cardiac events (MACE) than angiography guidance, as well as these recent comprehensive meta-analyses (6–8). However, a study by Park et al. (9) analyzing the data from the EXCELLENT trial (the Efficacy of Xience/Promus versus Cypher in rEducing Late Loss after stENTing) indicated no significant advantages of IVUS guidance, and another one recent observational trial (10) also showed doubt about the efficacy of IVUS guidance in DES implantation. In addition, the efficacy of IVUS guidance in patients with complex coronary lesions undergoing DES implantation still remains controversial. A large randomized controlled trial (RCT) conducted by Kim et al. (11) showed only limited or no benefits of IVUS guidance on prevention of MACE in patients with long coronary artery stenosis, whereas another one recent large RCT (12) indicated contrasting results. These conflicting data from several other recent RCTs (13, 14) and Obs (15–17) focusing on different coronary lesions have also raised questions regarding the usage of IVUS guidance. Moreover, only one meta-analysis recently published by Zhang et al. (18) pointed out that IVUS guidance would mostly benefit patients with complex

Address for correspondence: Nai-Liang Tian, Department of Cardiology, Nanjing First Hospital Nanjing Medical University; No. 68 Changle Road, 210006 Nanjing-*People's Republic of China*
Phone-Fax: +86-25-52208048 E-mail: tiannailiang@163.com
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coronary lesions or acute coronary syndromes (ACS) receiving DES implantation, although in which most of the enrolled clinical trials were retrospective or small scale. Furthermore, the absence of more precise subgroups depending on different coronary lesions would not allow them to identify specific patient populations. Therefore, we performed this comprehensive meta-analysis involving as many related clinical trials as possible to represent the largest analysis comparing efficacy and safety between IVUS guidance and angiography guidance in DES implantation for patients with complex coronary artery lesions and tried to identify the specific patient populations who would truly benefit from the technique.

Methods

Literature search

The EMBASE, Medline, and the Cochrane Controlled Trials Registry, as well as several other internet sources were searched for clinical trials comparing outcomes following IVUS guidance with coronary angiography guidance (described as the CAG group) in patients with complex coronary artery lesions [defined as long coronary artery lesions, chronic total occlusion (CTO) lesions, unprotected left main (LM) lesions, bifurcation lesions, multiple overlapping stents, or the composite of all these abovementioned lesions] receiving DES implantation from their date of inception until March 2016. The combinations of several relevant key words were used to make sure all relevant studies were included, including "intravascular ultrasound," "IVUS," "IVUS-guided," "angiography," "angiography-guided," "chronic total occlusion," "left main," "bifurcation," "long lesions," "drug-eluting stent," or "DES." All potentially relevant citations and references from published reviews or meta-analyses were subsequently screened for eligibility.

Inclusion and exclusion criteria

All included studies fulfilled the following criteria: (1) adult patients (age 18–90 years) undergoing percutaneous coronary intervention (PCI) with DES for complex coronary artery lesions as defined previously; and (2) clinical trials comparing the IVUS guidance and CAG guidance groups. The exclusion criteria were as follows: (1) non-human or ongoing studies; (2) non-English language studies; (3) duplicated studies, or different studies using the same sample; and (4) patients implanted with both of bare-metal stents and DES, whereas the relevant data of DES were not provided.

Data extraction, synthesis, and quality assessment

Two independent investigators (FZG and GXF) reviewed all relevant articles for assessing their eligibility, using standardized data-abstraction forms. The third investigator (LXB) resolved disagreements. The following data were extracted from each included study: the name or the first author of the trial, publication year, baseline demographics, characteristics of lesions, details of PCI procedure, and clinical outcomes during follow-up. All the included studies were divided into five subgroups according to the different types of coronary artery lesions, described as follows: long lesion, CTO, unprotected left main, bifurcation, and complex lesions subgroups (specific type of complex coronary lesions could not be distinguished from original study). On the other hand, we also performed a further analysis of propensity-matched and randomized studies. The quality of all retrieved studies were assessed in according to the Newcastle–Ottawa Scale (NOS) (19) and the Jadad score (20) for the cohorts and randomized studies respectively.

Study endpoints

The primary endpoint of this study was incidence of MACE, including all-cause mortality [cardiac death instead in four trials (12, 14, 21, 22)], myocardial infarction (MI; included both of Q-wave MI and non-Q-wave MI), and target-vessel revascularization (TVR). The safety endpoint was definite/probable stent thrombosis (ST), according to the definition of the Academic Research Consortium (23). The definitions of the clinical endpoints varied slightly among these included trials, but the studies generally followed standardized definitions.

Statistical analysis

We performed the present meta-analysis in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statements (24). All statistical analyses were performed with STATA 12.0 (StataCorp LP, College Station, TX, USA). All endpoints were treated as dichotomous variables, expressed with odds ratios (ORs) and 95% confidence intervals (CIs). Statistical heterogeneity among the included studies was measured using the Cochrane's Q test and the I^2 statistic. When the p value of Q test was <0.10 and/or the I^2 was ≥50%, significant heterogeneity was considered and a random-effects model would be selected. If not, the fixed-effects model with the Mantel–Haenszel method was used instead. We examined publication bias via the Egger's test (p<0.1 for significant asymmetry) (25). The sensitivity analyses (exclude one study at a time) were performed to assess the stability of the overall treatment effects. All p values were two-tailed, and p values <0.05 were considered statistically significant.

Results

Eligible studies and patient characteristics

After screening 456 initial articles using the electronic databases and another 10 articles through several other internet sources, 15 clinical trials were finally identified, including six RCTs (11–14, 26, 27) and nine Obs (15–17, 21, 22, 28–31; Fig. 1). In the 15 enrolled articles, there were two for long lesions (11, 12), three for CTO lesions (13, 15, 27), four for unprotected LM disease (16, 22, 28, 31), three for bifurcation lesions (17, 29, 30), and three for combined complex lesions (14, 21, 26). In addition, seven clini-

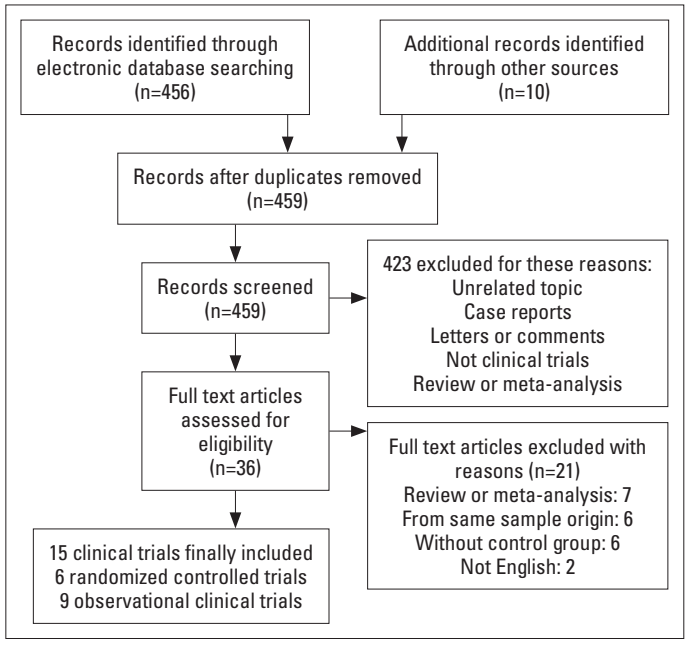

Figure 1. A flow chart of depicting the selection of the studies included in this meta-analysis

cal trials performed sub-analysis following the propensity score matching (15–17, 22, 29–31). The baseline characteristics and lesion or procedural characteristics of the included studies were summarized in Tables 1–3. The follow-up time of included studies ranged 1–4 years, and the qualities of these studies were good.

MACE

As depicted in Figure 2, the significant reduction in the overall MACE risk was observed related to IVUS guidance (OR 0.63, 95% CI: 0.53–0.73, p<0.001; I^2=11.6%, p=0.326; Fig. 2a), which was mainly because of the decreased risk from the subgroups of long lesions (OR 0.51, 95% CI: 0.33–0.80, p=0.003; I^2=0.0%, p=0.631) and unprotected LM (OR 0.57, 95% CI: 0.45–0.72, p<0.001; I^2=9.1%, p=0.347). The Egger's test did not suggest publication bias (p=0.464), and the sensitivity analysis demonstrated that the beneficial efficacy of IVUS guidance in DES implantation was always observed by omitting a single study at a time.

All-cause mortality

A significant lower incidence of all-cause mortality rate was observed in the IVUS guidance group than in the CAG guidance group (OR 0.52, 95% CI: 0.40–0.67, p<0.001; I^2=0.0%, p=0.768; Fig. 2b), as well as in the unprotected left main subgroup (OR 0.46, 95% CI: 0.32–0.65, p<0.001; I^2=0.0%, p=0.405) and the bifurcation lesions subgroup (OR 0.44, 95% CI: 0.24–0.81, p=0.008; I^2=0.0%, p=0.403). No publication bias was found examined by the Egger's test (p=0.281) and the stability of results were proved by the sensitivity analysis.

MI

The impact of IVUS guidance on the reduction in MI risk differed significantly from angiography guidance (OR 0.70, 95% CI: 0.56–0.86, p=0.001; I^2=10.2%, p=0.343; Fig. 2c); this difference can probably be attributed to the subgroups of unprotected LM disease (OR 0.67, 95% CI: 0.50–0.89, p=0.006; I^2=0.0%, p=0.726) and bifurcation lesions (OR 0.46, 95% CI: 0.25–0.81, p=0.008; I^2=0.0%, p=0.548). No publication bias was observed (p=0.204). The sensitivity analysis demonstrated these superior effects of IVUS guidance.

TVR and target-lesion revascularization

As shown in Figure 2d, TVR incidence was lower in the IVUS guidance group than in the CAG group (OR 0.53, 95% CI: 0.40–0.70, p<0.001; I^2=11.2%, p=0.343); a similar result of decreased TLR risk could also be acquired (OR 0.69, 95% CI: 0.50–0.94, p=0.019; I^2=52.3%, p=0.017, Fig. 2e). In addition, the results from analyses of different subroups also showed decreased TVR risk related to IVUS guidance in patients with CTO (OR 0.49, 95% CI: 0.26–0.91, p=0.025; I^2=0.0%, p=0.625) and bifurcation lesions (OR 0.62, 95% CI: 0.39–1.00, p=0.049), as well as found in the subgroup of long lesions (OR 0.50, 95% CI: 0.28–0.91, p=0.024) with respect to the lower TLR risk. Egger's test indicated no publication bias (p=0.575, 0.147, for TVR and TLR respectively). The sensitivity analysis confirmed the stability of results.

Definite/probable ST

IVUS guidance was associated with the lower incidence of definite/probable ST (OR 0.31, 95% CI: 0.20–0.50, p<0.001, Fig. 2f) without any heterogeneity (I^2=0.0%, p=0.787), and a decreased risk of ST pertaining to IVUS guidance was also observed in the subgroups of CTO (OR 0.26, 95% CI: 0.08–0.80, p=0.019; I^2=0.0%, p=0.679), unprotected LM disease (OR 0.25, 95% CI: 0.09–0.65, p=0.019; I^2=0.0%, p=0.839), and bifurcation lesions (OR 0.21, 95% CI: 0.09–0.48, p<0.001; I^2=0.0%, p=0.807). No evidence of publication bias was found determined by the Egger's test (p=0.424).

Outcomes of propensity-matched and randomized trials

Seven propensity-matched studies and six RCTs enrolling 6.573 patients were repeatedly analyzed and subgroup analyses indicated different results as follows: (1) IVUS-guided DES implantation was associated with decreased MACE risk in patients with long lesions (OR 0.51, 95% CI: 0.33–0.80, p=0.003, Fig. 3a) and unprotected LM disease (OR 0.65, 95% CI: 0.51–0.82, p<0.001); (2) all-cause mortality rates were found among patients with unprotected LM disease (OR 0.48, 95% CI: 0.33–0.69, p<0.001, Fig. 3b) and bifurcation lesions (OR 0.35, 95% CI: 0.16–0.75, p=0.007); (3) IVUS guidance was associated with a lower incidence of MI in patents with bifurcation lesions (OR 0.31, 95% CI: 0.13–0.75, p=0.009, Fig. 3c); (4) significant reduction in TVR risk was observed in patients with CTO lesions (OR 0.49, 95% CI: 0.26–0.92, p=0.025, Fig. 3d), whereas no significant difference was observed pertaining to TLR (TLR: OR 0.79, 95% CI: 0.61–1.01, p=0.058, Fig. 3e); (5) decreased ST incidence was observed in patients with CTO (OR 0.25, 95% CI: 0.08–0.76, p=0.015, Fig. 3f), LM disease (OR 0.22, 95% CI: 0.08–0.67, p=0.008), and bifurcation lesions (OR 0.22, 95% CI: 0.07–0.63, p=0.005).

Table 1. The baseline characteristics of the included trials

Study	Design	Enrolled patients	Patients (N) IVUS/Control	Age, years IVUS/Control	Male, n IVUS/Control	LVEF, % IVUS/Control	Follow-up	Study quality
RESET trial (2013)	RCT	Patients with long lesions	269/274	62.8/64.3	177/150	55.3/54.0	1 year	5*
IVUS-XPL trial (2016)	RCT	Patients with long lesions	700/700	64/64	483/481	62.9/62.4	1 year	5*
CTO-IVUS trial (2015)	RCT	Patients with CTO	201/201	61.0/61.4	162/162	56.9/56.7	1 year	5*
Tian et al. (2015)	RCT	Patients with CTO	115/115	67/66	102/92	55/56	2 years	4*
Hong et al. (2014)	Observational	Patients with CTO	206/328	62/63	159/234	NA	2 years	9
Agostoni et al. (2005)	Observational	Patients with unprotected LM	24/34	62/64	15/25	52/44	14 months	7
Hernandez et al. (2014)	Observational	Patients with unprotected LM	505/505	66.1/66.9	404/397	54.9/55.3	3 years	8
Park et al. (2009)	Observational	Patients with unprotected LM	145/145	64.21/64.99	102/102	60.18/61.17	3 years	9
Gao et al. (2014)	Observational	Patients with unprotected LM	337/679	66.0/67.1	274/526	58.7/56.7	1 year	9
Kim et al. (2010)	Observational	Patients with bifurcation	308/112	~59/60	~73%/72%	~60/59	4 years	8
Kim et al. (2011)	Observational	Patients with bifurcation	487/487	62.0/61.8	324/326	60.1/58.8	3 years	9
Chen et al. (2013)	Observational	Patients with bifurcation	324/304	63.4/64.5	261/227	60.9/59.8	1 year	8
Jakabcin et al. (2010)	RCT	Patients with complex lesions	105/105	59.4/60.2	77/75	NA	18 months	4*
AVIO trial (2013)	RCT	Patients with complex lesions	142/142	63.9/63.6	117/109	55.3/55.9	2 years	4*
Ahn et al. (2013)	Observational	Patients with complex lesions	49/36	65/65	30/22	54/56	2 years	7

CTO - chronic total occlusion; IVUS - intravascular ultrasound; LM - left main disease; LVEF - left ventricular ejection fraction; NA - not available; RCT - randomized controlled trials. Notes-The qualities of observational trials were assessed by the Newcastle–Ottawa Scale and the max score = 9; *-The qualities of included randomized trials were assessed by the Jadad score

Table 2. The characteristics of the past medical histories among the included trials

Study	Hypertension, n IVUS/Control	Diabetes, n IVUS/Control	Dyslipidemia, n IVUS/Control	Smoker, n IVUS/Control	Prior MI, n IVUS/Control	Prior PCI, n IVUS/Control
RESET trial (2013)	NA	85/82	165/165	58/47	3/8	NA
IVUS-XPL trial (2016)	454/444	250/256	471/458	155/181	34/29	76/69
CTO-IVUS trial (2015)	126/128	70/68	NA	71/69	16/16	31/32
Tian et al. (2015)	86/81	34/31	25/32	45/45	24/35	NA
Hong et al. (2014)	118/224	62/124	89/116	58/93	24/29	44/62
Agostoni et al. (2005)	14/20	9/10	15/23	4/7	9/17	12/7
Hernandez et al. (2014)	342/325	183/175	314/284	148/161	122/130	111/107
Park et al. (2009)	86/85	49/49	42/44	28/30	10/11	38/38
Gao et al. (2014)	244/489	109/232	228/487	111/230	60/123	60/119
Kim et al. (2010)	~43%/46%	~20%/22%	~28%/35%	~36%/36%	NA	~10%/7%
Kim et al. (2011)	292/284	155/162	168/170	106/111	42/39	NA
Chen et al. (2013)	216/185	60/54	108/107	147/154	50/35	57/51
Jakabcin et al. (2010)	70/75	44/47	66/69	42/37	39/34	18/15
AVIO trial (2013)	100/95	34/38	100/109	49/44	NA	NA
Ahn et al. (2013)	25/20	13/11	14/9	16/14	2/2	1/3

IVUS - intravascular ultrasound; MI - myocardial infarction; NA - not available; PCI - percutaneous coronary intervention

Table 3. Angiographic and procedural characteristics

Study	LM, n	LAD, n	LCX, n	RCA, n	#Lesion length, mm	#Stent length, mm	#Stent number, n	#Stent diameter, mm	Types of DES
RESET trial (2013)	0/0	167/185	41/35	61/54	29.6/30.6	32.4/32.3	NA	NA	Zotarolimus/Everolimus
IVUS-XPL trial (2016)	0/0	455/419	96/108	149/173	34.7/35.2	39.3/39.2	1.3/1.3	NA	Everolimus
CTO-IVUS trial (2015)	0/0	84/94	29/32	88/75	36.3/35.5	43.6/41.5	NA	2.91/2.85	Zotarolimus/Nobori Biolimus
Tian et al. (2015)	0/3	51/42	24/17	40/53	29.0/30.59	55/52	1.6/1.5	3.05/2.86	First and second-generation
Hong et al. (2014)	6/4	91/123	34/75	NA	26.6/27.0	44.6/36.9	1.70/1.42	2.96/2.83	Zotarolimus/Everolimus
Agostoni et al. (2005)	24/34	0/0	0/0	0/0	7.47/7.33	27/23	1.5/1.4	3.2/3.2	Sirolimus
Hernandez et al. (2014)	505/505	NA	NA	NA	NA	16.0/16.8	NA	3.8/3.65	NA
Park et al. (2009)	145/145	NA	NA	75/80	NA	35.16/35.63	1.23/1.24	NA	Sirolimus/Paclitaxel
Gao et al. (2014)	337/679	224/479	125/324	146/369	NA	35.4/33.3	1.5/1.4	3.5/3.4	Sirolimus
Kim et al. (2010)	NA	NA	NA	NA	~25/21	~34/26	~1.4/1.2	NA	Sirolimus/Paclitaxel
Kim et al. (2011)	17/19	404/402	63/63	20/22	NA	NA	1.3/1.2	NA	Sirolimus/Paclitaxel
Chen et al. (2013)	137/83	129/186	44/26	14/9	24.83/23.98	32.67/30.53	1.26/1.20	3.25/3.16	NA
Jakabcin et al. (2010)	3/4	59/57	NA	30/25	18.1/17.6	23.6/22.1	1.3/1.3	NA	Taxus/Cypher
AVIO trial (2013)	NA	NA	NA	NA	27.4/25.5	23.9/23.2	NA	2.95/2.86	NA
Ahn et al. (2013)	0/0	29/16	6/2	14/18	68/60	74/66	2.8/2.2	3.00/2.87	Sirolimus/Paclitaxel/Everolimus /Zotarolimus

DES - drug-eluting stent; LAD - left anterior descending artery; LCX - left circumflex artery; LM - left main coronary artery; mm - millimeters; RCA - right coronary artery; NA - not available; #: these data are mean values

Discussion

The major finding of this comprehensive meta-analysis was that IVUS guidance in DES implantation was associated with a 37% reduction in MACE risk and a 48% reduction in all-cause mortality risk compared with CAG guidance. In addition, IVUS guidance could also decrease the incidence of MI, TVR, TLR, and ST. The data from RCTs and the propensity-matched subgroups were repeatedly analyzed, which demonstrated broadly similar clinical outcomes; however, no statistically significant difference was observed pertaining to TLR risk. The subgroup analyses indicated that IVUS-guided DES implantation seemed to have more beneficial effects on patients with left main disease or bifurcation lesions.

IVUS plays a key role in the procedure of stent implantation, because not only much more accurate details of the PCI procedure could be provided to evaluate lesion severity and to optimize stent implantation, but also being helpful to detect these complications following the procedure earlier. These positive effects were thought to improve the clinical outcomes among patients undergoing stent implantation in the DES era, which were evaluated by several recent observational trials (4, 5) and meta-analyses (6–8). In contrast, another one large observational trial (9) indicated modest or no benefits of IVUS guidance in terms of the increased MACE risk (5.5% vs. 3.9%, p=0.148, for IVUS guidance vs. angiography guidance). In addition, Singh et al. (10) cautiously pointed out that IVUS guidance was associated with lower in-hospital mortality risk at the cost of expensive care fee and increased incidence of vascular complications (10). Who could benefit mostly from IVUS guidance after costing a large number of treatment fee? It is such an important question which can not be ignored, especially in these developping countries. As a result, identifying such specific patient populations is absolutely necessary. The large randomized IVUS-XPL (IVUS-Xience Prime stent for long coronary lesions) trial (12) had reported lower MACE risk with respect to IVUS guidance during DES implantation for patients with long artery lesions than angiography guidance (2.9% vs. 5.8%, p=0.007), whereas another one large randomized trial called the RESET trial (Real Safety and Efficacy Trial) (11) indicated a contrast result (4.5% vs. 7.3%, p=0.16, for IVUS guidance vs. angiography guidance). Several other cohort studies (15–17) enrolling large numbers of patients with different complex coronary artery lesions were also conducted to determine if some special patients can benefit mostly from the technique; however, final results were controversial, which called the usage of IVUS guidance in DES implantation for such patients into question. There were few meta-analyses except for one pubished by Zhang et al. (18) focused on this topic. However, most of the included data in this meta-analysis were based on observational trials, and there were no enough precise subgroups according to the various coronary artery lesions. So far, there had been no sufficient evidence to support the benefits of IVUS guidance in patients with complex coronary artery lesions.

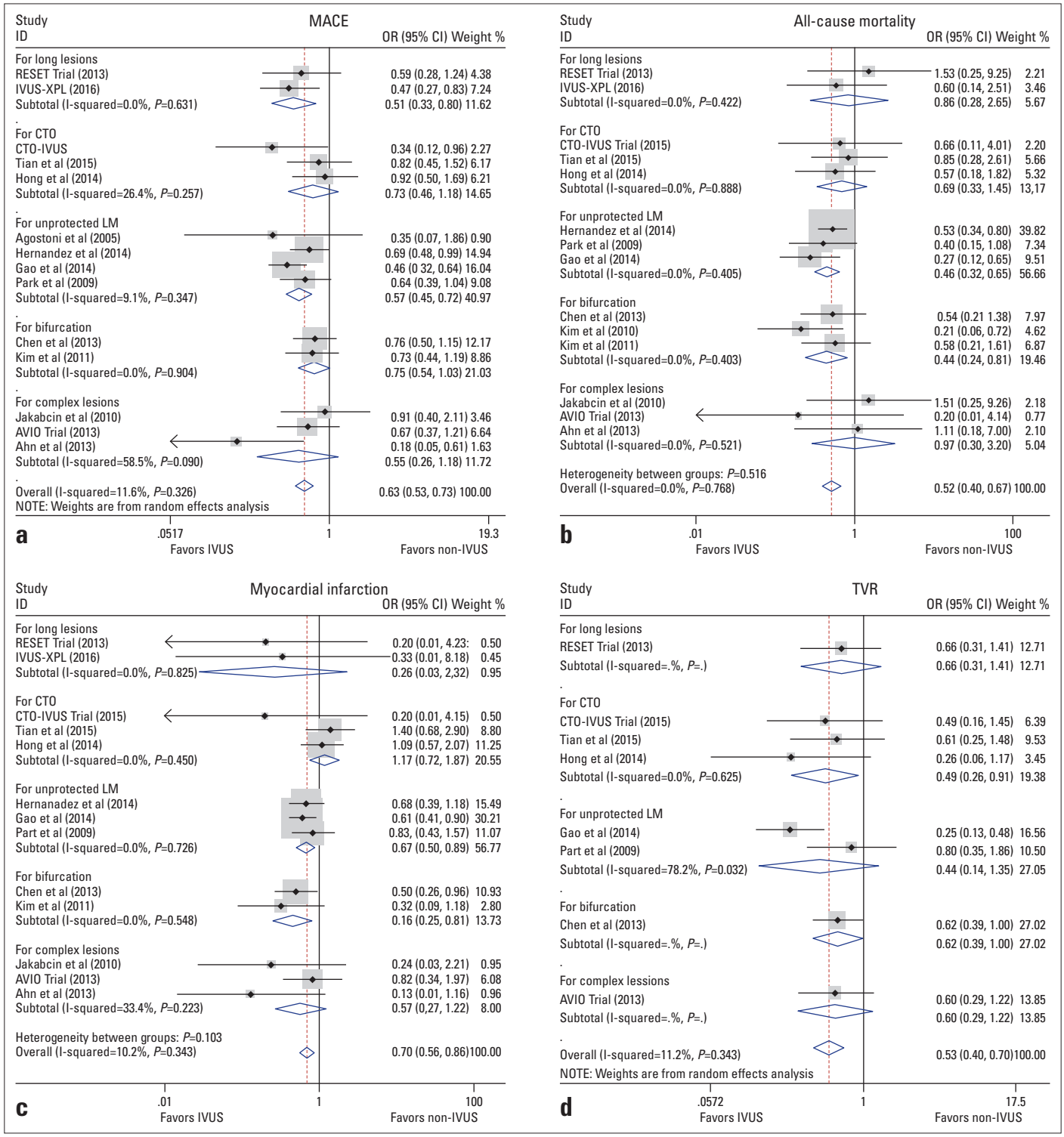

Figure 2. Forest plots of the efficacy endpoints of the included trials. The odds ratios of MACE (a), all-cause mortality (b), myocardial infarction (c), target-vessel revascularization (d), target-lesion revascularization (e), and stent thrombosis (f) associated with IVUS guidance compared with angiography guidance

Notably, most adverse events related to the procedure were potentially considered to be because of the underexpansion and malapposition of implanted stents, which might influence the clinical outcomes. The optimal stent deployment were considered if the following criteria were met: good apposition (all stent struts posited to the vessel wall), optimal stent expansion (minimal area of stents ≥5 mm^2) or cross-sectional area (CSA) >90% of distal reference lumen CSA for small vessel/and no edge dissection (5-mm margins proximal and distal to the stent). IVUS guidance had a beneficial effect on decreasing strut malapposi-

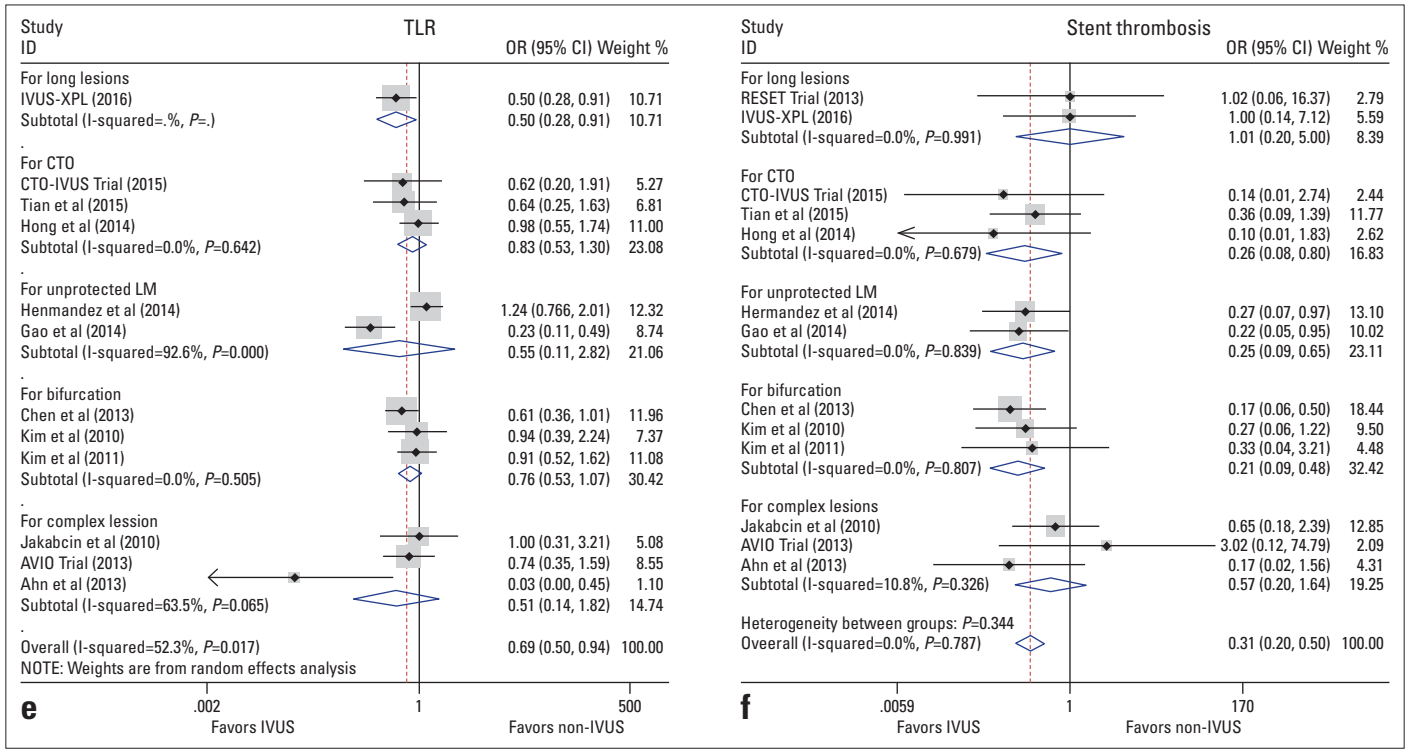

Figure 2. Forest plots of the efficacy endpoints of the included trials. The odds ratios of MACE (a), all-cause mortality (b), myocardial infarction (c), target-vessel revascularization (d), target-lesion revascularization (e), and stent thrombosis (f) associated with IVUS guidance compared with angiography guidance

tion risk and resulted in larger minimum luminal diameter (MLD), (14) which were thought to be more useful for the complex coronary artery lesions. The study from Park et al. (31) pointed out that IVUS-guided DES implantation might decrease the long-term mortality rate for unprotected LM coronary artery stenosis (4.7% vs. 16.0%, for IVUS guidance vs. angiography guidance) after analyzing the data of 145 matched pairs of patients. A recent large pooled analysis of four registries reported by Hernandez et al. (16) indicated an association of IVUS guidance during DES implantation with better 1-year outcomes in patients with LM disease, mainly derived from the lower incidence of all-cause mortality (7.4% vs. 13.0%, p=0.01) and ST (0.6% vs. 2.2%, p=0.04). On the other hand, Gao et al. (22) performed another one large cohort and stated several possible reasons to support the usage of IVUS guidance in patients with LM disease, including more accurate quantification of stent diameter or length as well as less late loss. Similarly, we found lower incidence of MACE composited of all-cause mortality, MI, and TVR pertaining to IVUS guidance, especially in patients with LM disease. These results might mostly benefit from IVUS guidance derived minimal area and fractional flow reserve, which facilitated detection of significant hemodynamically in this specific lesion subset of coronary disease (32). Indeed, these results from the over-mentioned registries were unavoidably affected by the unbalanced baseline characteristics and lesion or procedural details of the included patients. However, the repeated analyses of data from RCTs and propensity-matched subgroups in Obs were performed to decrease possible sources of bias, from which the results might confirm the beneficial efficacy of IVUS guidance partly. Thus, the recommendations for percutaneous revascularization of LM disease had been granted to a Class IIb level (33).

Since the "double kissing crush (DK Crush) with two stents" technique for bifurcation lesions was first reported by Chen et al. (34), the improved clinical outcomes had been observed mainly appeared as significant reduction in TLR and TVR risks. It should be noted that thrombosis might be thought as possible reason leading to repeat revascularization. There were many factors considered to be associated with incidence of ST, including the characteristics of lesions (anatomical), device, or techniques, resulting in more common usage of IVUS in this specific lesion subset (35, 36). One large observational trial conducted by Chen et al. (29) reported comparable very-late ST risk between the IVUS guidance group and the angiography guidance group in patients with bifurcation lesions (0.6% vs. 4.3%, p=0.003, for IVUS guidance and angiography guidance respectively); similar results were also reported by Kim et al. (30) In addition, bifurcation lesions are always a varied and complicated subset of coronary artery disease, meaning that they would be more possible to get advantages from imaging modality such as IVUS according to the clinical benefits described previously. The present meta-analysis indicated a lower incidence of ST following IVUS guidance, as well as other MACE involving all-cause mortality and MI, being similar as outcomes of these over-mentioned large observational tri-

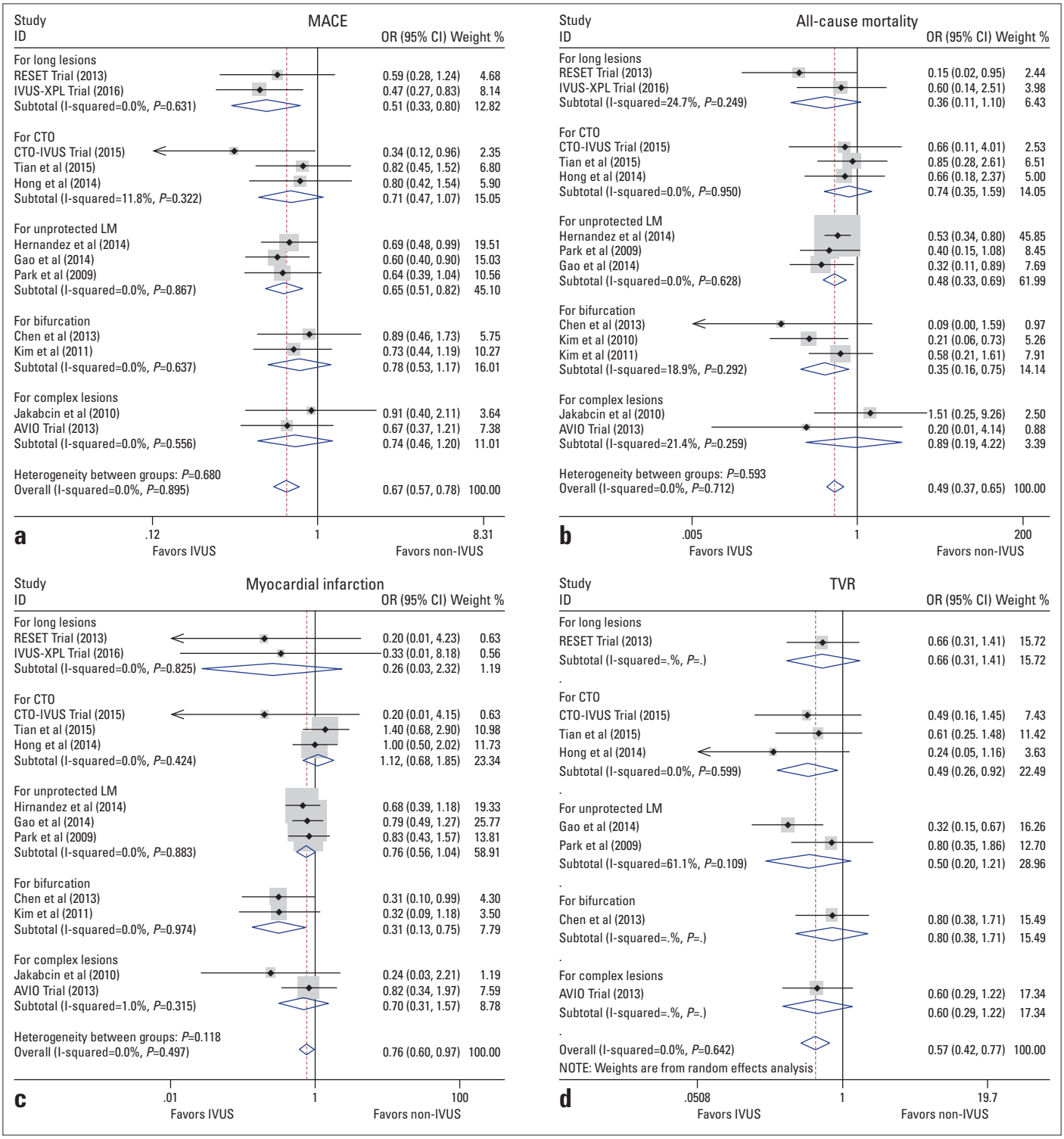

Figure 3. Forest plots of the efficacy endpoints of the propensity-matched and randomized trials. The odds ratios of MACE (a), all-cause mortality (b), myocardial infarction (c), target-vessel revascularization (d), target-lesion revascularization (e), and stent thrombosis (f) associated with IVUS guidance compared with angiography guidance

als. The repeated analyses of propensity-matched groups were also performed with the goal of decreasing bias and proving the final results, which might be the significant favorable evidence of IVUS guidance on improving clinical outcomes in this subset of patient populations.

In fact, the other different complex coronary artery lesions such as CTO lesions, long lesions, or combined of all-over-mentioned might just benefit partly from the IVUS guidance. A randomized trial conducted by Tian et al. (27) indicated that IVUS-guided stenting for the CTO lesions was associated with

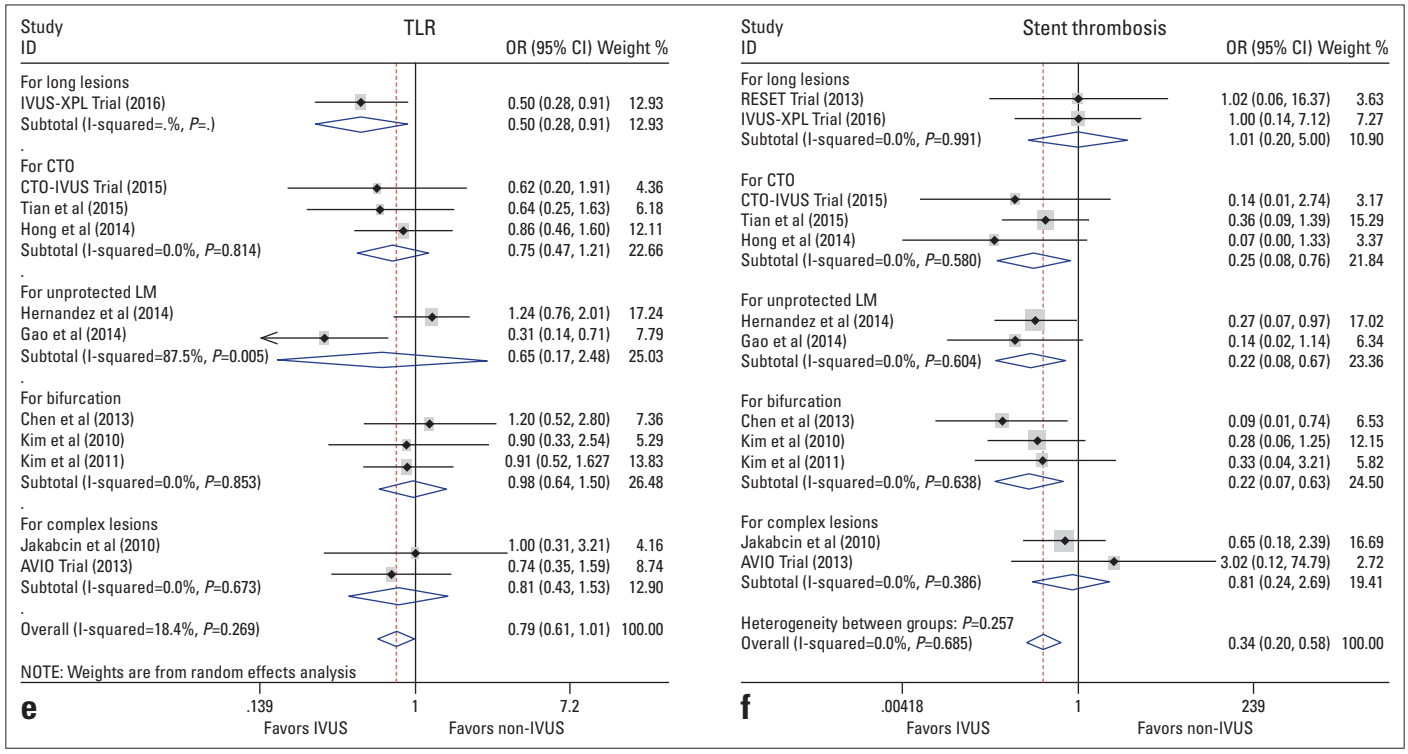

Figure 3. Forest plots of the efficacy endpoints of the propensity-matched and randomized trials. The odds ratios of MACE (a), all-cause mortality (b), myocardial infarction (c), target-vessel revascularization (d), target-lesion revascularization (e), and stent thrombosis (f) associated with IVUS guidance compared with angiography guidance

less late lumen loss and lower incidence of "in-true-lumen" stent restenosis, which might result from the advantages of IVUS guidance in optimizing stent expansion, edge dissection, and minimal stent area for such lesion subsets. However, these offered modest or no benefits in terms of decreasing the MACE incidence, there were more risk factors pertaining to the occurence of this lesion compared to other different lesions might be the possible reasons, such as more current smokers, high incidence of diabetes or poor compliance for antiplatelet treatment. On the other hand, Hong et al. (12) conducted the IVUS-XPL trial to evaluate the effects of IVUS guidance in patients with long coronary artery diseases. The largest randomized trial enrolled of 1,400 patients who were randomly assigned to two groups at a 1:1 ratio and demonstrated that IVUS guidance was associated with a significantly lower rate of the composite of MACE at 1 year (2.9% vs. 5.8%, p=0.07, for IVUS guidance vs. angiography guidance). In addition, Chieffo et al. (14) conducted one RCT focusing on combined complex lesions described the superiority of IVUS-guided DES implantation, whereas another RCT (26) reported a contrasting result, which is only small scale without enough powerty. Results from this present meta-analysis just indicated some limited benefits pertaining to IVUS guidance in DES implantation in these patients as well. As a result, possible reasons might be summarized as unbalanced baseline characteristics, uniform stenting procedure or different standards of decision making, and satisfaction for IVUS usage.

Several questions remained unsolved. First, there were not enough data to assess the efficacy of IVUS-guided PCI using different generations of DES because of varying drug coats or structures of implanted stents might lead to unsimilar outcomes. A second dilemma was considered as the absence of a cost-effectiveness analysis of IVUS just described by Zhang et al. (18), although these specific patient populations with left main disease or bifurcation lesions seemed to be associated with more feasible benefits.

Study limitations

This study has several limitations. First, this meta-analysis was performed without individual patient data, and the small sample size of several included RCTs also made the evaluation of IVUS guidance's efficacy easily influenced. Second, the unavoidable involvement of several potential confounding factors, such as the time of procedure and details of DES implantation, including types of DES, techniques, and the choice of sheath with different sizes, did not allow us to explore the true effects of IVUS guidance on patients with complex coronary artery lesions, despite the repeated analyses of data from matched and randomized trials. Third, the insufficient analyses of these data from Quantitative Coronary Analysis among each included trial limited us studying specific benefits on stenting procedure. In addition, this meta-analysis was performed mainly focused on evaluating the effects of IVUS applied for different types of

coronary artery lesions instead of heart diseases; therefore, the subgroup analysis of high-risk patients with ACS should not be conducted. At last but not least, there was no strict duration of dual-antiplatelet treatment for these included patients though it was commonly thought as lasting for ≥12 months.

Conclusion

IVUS-guided DES implantaion was seemed to improve the clinical outcomes in patients with complex coronary artery disease, particulaly in patients with left main disease or bifurcation lesions. However, powerful randomized clinical trials comparing IVUS guidance to angiography guidance in such patients with more precise subgroups focusing on different coronary lesions and types of implanted DES are still warranted to guide stenting decision making in the catheterization room.

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