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

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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 coronary artery lesions.

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
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 I² statistic. When the p value of Q test was <0.10 and/or the I² 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-
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; F=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; F=0.0%, p=0.726) and bifurcation lesions (OR 0.46, 95% CI: 0.25–0.81, p=0.008; F=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; F=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; F=52.3%, p=0.017, Fig. 2e). In addition, the results from analyses of different subgroups 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; F=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 (I²=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; F=0.0%, p=0.679), unprotected LM disease (OR 0.25, 95% CI: 0.09–0.65, p=0.019; F=0.0%, p=0.839), and bifurcation lesions (OR 0.21, 95% CI: 0.09–0.48, p<0.001; F=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 patients 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) | Age, years | Male, n | LVEF, % | 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 | 54/55.3 | 3 years | 8           |
| Park et al. (2009)     | Observational | Patients with unprotected LM | 145/145 | 64.21/64.9 | 102/102 | 60.1/61.17 | 3 years | 9           |
| Gao et al. (2014)      | Observational | Patients with unprotected LM | 337/679 | 67.4/67.1 | 274/526 | 58.7/56.7 | 1 year | 9           |
| Kim et al. (2010)      | Observational | Patients with bifurcation | 308/112 | 60/60 | 102/102 | 56.9/56.7 | 4 years | 8           |
| Kim et al. (2011)      | Observational | Patients with bifurcation | 487/487 | 60.1/61.8 | 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 | 59.4/59.2 | 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 | Diabetes, n | Dyslipidemia, n | Smoker, n | Prior MI, n | Prior PCI, n |
|------------------------|-----------------|-------------|-----------------|-----------|-------------|-------------|
| RESET trial (2013)     | NA              | 85/82       | 165/165         | 56/47     | 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)| 342/235         | 183/175     | 314/284         | 148/161   | 12/130      | 11/107      |
| 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.
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 developing 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 published 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.
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 mm²) 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 malapposition.

**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 had been granted to a Class IIb level (33).

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 (33). 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 to previous studies (34).

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. The recommendations for percutaneous revascularization of LM disease had been granted to a Class Ib level (33).

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.
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-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...
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 occurrence 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 stent thrombosis (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 power. 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. Second, the insufficient analyses of these data 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

| Study ID | TLR OR (95% CI) Weight % |
|----------|-------------------------|
| For long lesions | 0.50 (0.28, 0.91) 12.93 |
| Subtotal | 0.50 (0.28, 0.91) 12.93 |
| For CTO | 0.62 (0.20, 1.91) 4.36 |
| Tian et al (2015) | 0.64 (0.25, 1.63) 6.18 |
| Hong et al (2014) | 0.86 (0.46, 1.60) 12.11 |
| Subtotal | 0.75 (0.47, 1.21) 22.66 |
| For unprotected LM | 1.24 (0.76, 2.01) 17.24 |
| Gao et al (2014) | 0.31 (0.14, 0.71) 7.79 |
| Subtotal | 0.65 (0.17, 2.48) 25.03 |
| For bifurcation | 1.20 (0.52, 2.80) 7.36 |
| Chen et al (2013) | 0.90 (0.33, 2.54) 5.29 |
| Kim et al (2011) | 0.91 (0.52, 1.67) 13.83 |
| Subtotal | 0.98 (0.54, 1.76) 26.48 |
| For complex lesions | 1.00 (0.31, 3.21) 4.16 |
| Jakaboin et al (2010) | 0.74 (0.35, 1.59) 8.74 |
| Subtotal | 0.81 (0.43, 1.53) 12.90 |
| Overall (I-squared=18.4%, P=0.069) | 0.79 (0.61, 1.01) 100.00 |

NOTE: Weights are from random effects analysis

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 occurrence 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 stent thrombosis. 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 power. 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.

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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 implantation was seemed to improve the clinical outcomes in patients with complex coronary artery disease, particularly 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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**References**

1. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007; 356: 998-1008.
2. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130: 2354-94.
3. Windecker S, Kohl P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. EuroIntervention 2015; 10: 1024-96.
4. Wittenbach B, Maehara A, Weisz G, Neumann FJ, Rinaldi MJ, Metzger DC, et al. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. Circulation 2014; 129: 463-70.
5. Claessen BE, Mehran R, Mintz GS, Weisz G, Leon MB, Dogan O, et al. Impact of intravascular ultrasound imaging on early and late clinical outcomes following percutaneous coronary intervention with drug-eluting stents. JACC Cardiovasc Interv 2011; 4: 974-81.
6. Ahn JM, Kang SJ, Yoon SH, Park HW, Kang SM, Lee JY, et al. Meta-analysis of outcomes after intravascular ultrasound-guided versus angiography-guided drug-eluting stent implantation in 26,503 patients enrolled in three randomized trials and 14 observational studies. Am J Cardiol 2014; 113: 1388-47.
7. Jang JS, Song YJ, Kang W, Jin HY, Seo JS, Yang TH, et al. Intravascular ultrasound-guided implantation of drug-eluting stents to improve outcome: a meta-analysis. JACC Cardiovasc Interv 2014; 7: 233-43.
8. Klersy C, Ferlini M, Raisaro A, Scotti V, Balduini A, Curti M, et al. Use of IVUS guided coronary stenting with drug eluting stent. Int J Cardiol 2013; 170: 54-63.
9. Park KW, Kang SH, Yang HM, Lee HY, Kang HJ, Cho YS, et al. Impact of intravascular ultrasound guidance in routine percutaneous coronary intervention for conventional lesions: data from the EXCELLENT trial. Int J Cardiol 2013; 167: 721-6.
10. Singh V, Badheka AO, Arora S, Panaich SS, Patel NJ, Patel N, et al. Comparison of inhospital mortality, length of hospitalization, costs, and vascular complications of percutaneous coronary interventions guided by ultrasound versus angiography. Am J Cardiol 2015; 115: 1357-66.
11. Kim JS, Kang TS, Mintz GS, Park BE, Shin DH, Kim BK, et al. Randomized comparison of clinical outcomes between intravascular ultrasound and angiography-guided drug-eluting stent implantation for long coronary artery stenoses. JACC Cardiovasc Interv 2013; 6: 369-76.
12. Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, et al. Effect of Intravascular Ultrasound-Guided vs Angiography-Guided Everolimus-Eluting Stent Implantation: The IVUS-XPL Randomized Clinical Trial. JAMA 2015; 314: 2155-63.
13. Kim BK, Shin DH, Hong MK, Park HS, Rha SW, Mintz GS, et al. Clinical Impact of Intravascular Ultrasound-Guided Chronic Total Occlusion Intervention With Zotarolimus-Eluting Versus Biolimus-Eluting Stent Implantation: Randomized Study. Circ Cardiovasc Interv 2015; 8: e002592.
14. Chieffo A, Latib A, Caussin C, Presbitero P, Galli S, Menozzi A, et al. A prospective, randomized trial of intravascular-ultrasound guided compared to angiography guided stent implantation in complex coronary lesions: the AVIO trial. Am Heart J 2013; 165: 65-72.
15. Hong SJ, Kim BK, Shin DH, Kim JS, Hong MK, Gwon HC, et al. Usefulness of intravascular ultrasound guidance in percutaneous coronary intervention with second-generation drug-eluting stents for chronic total occlusions (from the Multicenter Korean-Chronic Total Occlusion Registry). Am J Cardiol 2014; 114: 534-40.
16. de la Torre Hernandez JM, Baz Alonso JA, Gomez Hospital JA, Alfonso Manterola F, Garcia Camarero T, Gimeno de Carlos F, et al. Clinical impact of intravascular ultrasound guidance in drug-eluting stent implantation for unprotected left main coronary disease: pooled analysis at the patient-level of 4 registries. JACC Cardiovasc Interv 2014; 7: 244-54.
17. Kim JS, Hong MK, Ko YG, Choi D, Yoon JH, Choi SH, et al. Impact of intravascular ultrasound guidance on long-term clinical outcomes in patients treated with drug-eluting stent for bifurcation lesions: data from a Korean multicenter bifurcation registry. Am Heart J 2011; 161: 180-7.
18. Zhang YJ, Pang S, Chen XY, Bourantas CV, Pan DR, Dong SJ, et al. Comparison of intravascular ultrasound guided versus angiography guided drug eluting stent implantation: a systematic review and meta-analysis. BMC Cardiovasc Disord 2015; 15: 129-139.

19. Biondi-Zoccai GG, Abbate A, Agostoni P, Testa L, Burzotta F, Lotriente M, et al. Long-term benefits of an early invasive management in acute coronary syndromes depend on intracoronary stenting and aggressive antiplatelet treatment: a metaregression. Am Heart J 2005; 149: 502-11.

20. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12.

21. Ahn SG, Yoon J, Sung JK, Lee JH, Lee JV, Yoon YJ, et al. Intra-vascular ultrasound-guided percutaneous coronary intervention improves the clinical outcome in patients undergoing multiple overlapping drug-eluting stents implantation. Korean Circ J 2013; 43: 231-8.

22. Gao XF, Kan J, Zhang YJ, Zhang JJ, Tian NL, Ye F, et al. Comparison of one-year clinical outcomes between intravascular ultrasound-guided versus angiography-guided implantation of drug-eluting stents for left main lesions: a single-center analysis of a 1,016-patient cohort. Patient Prefer Adherence 2014; 8: 321-309.

23. Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medical Devices Advisory Panel of the Food and Drug Administration Center for Devices and Radiologic Health, December 7-8, 2006. Circulation 2007; 115: 2352-7.

24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700.

25. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.

26. Jakabbin J, Spacek R, Bystron M, Kvasnak M, Jager J, Veselka J, et al. Long-term health outcome and mortality evaluation after invasive coronary treatment using drug eluting stents with or without the IVUS guidance. Randomized control trial. HOME DES IVUS. Catheter Cardiovasc Interv 2010; 75: 578-83.

27. Tian NL, Gami SK, Ye F, Zhang JJ, Liu ZZ, Lin S, et al. Angiographic and clinical comparisons of intravascular ultrasound- versus angiography-guided drug-eluting stent implantation for patients with chronic total occlusion lesions: two-year results from a randomised AIR-CTO study. EuroIntervention 2015; 10: 1409-17.

28. Agostoni P, Valgimigli M, Van Mieghem CA, Rodriguez-Granillo GA, Aoki J, Ong AT, et al. Comparison of early outcome of percutaneous coronary intervention for unprotected left main coronary artery disease in the drug-eluting stent era with versus without intravascular ultrasonic guidance. Am J Cardiol 2005; 95: 644-7.

29. Chen SL, Ye F, Zhang JJ, Tian NL, Liu ZZ, Santos T, et al. Intravascular ultrasound-guided systematic two-stent techniques for coronary bifurcation lesions and reduced late stent thrombosis. Catheter Cardiovasc Interv 2013; 81: 456-63.

30. Kim SH, Kim YH, Kang SJ, Park DW, Lee SW, Lee CW, et al. Long-term outcomes of intravascular ultrasound-guided stenting in coronary bifurcation lesions. Am J Cardiol 2010; 106: 612-8.

31. Park SJ, Kim YH, Park DW, Lee SW, Kim WJ, Suh J, et al. Investigators M-C. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. Circ Cardiovasc Interv 2008; 2: 167-77.

32. D’Ascenzo F, Barbero U, Cerrato E, Lipinski MJ, Omede P, Montefusco A, et al. Accuracy of intravascular ultrasound and optical coherence tomography in identifying functionally significant coronary stenosis according to vessel diameter: A meta-analysis of 2,581 patients and 2,807 lesions. Am Heart J 2015; 169: 663-73.

33. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Imaging and Interventions. Catheter Cardiovasc Interv 2012; 79: 453-95.

34. Chen SL, Santos T, Zhang JJ, Ye F, Xu YW, Fu Q, et al. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions: results from the DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) trial. J Am Coll Cardiol 2011; 57: 914-20.

35. Garcia-Garcia HM, Gomez-Lara J, Gonzalez N, Garg S, Shin ES, Goedhart D, et al. A comparison of the distribution of necrotic core in bifurcation and non-bifurcation coronary lesions: an in vivo assessment using intravascular ultrasound radiofrequency data analysis. EuroIntervention 2010; 6: 321-7.

36. Medina A, Martin P, Suarez de Lezo J, Novoa J, Melian F, Hernandez E, et al. Ultrasound study of the prevalence of plaque at the carina in lesions that affect the coronary bifurcation. Implications for treatment with provisional stent. Rev Esp Cardiol 2011; 64: 43-50.