Intravascular Ultrasound-Guidance Is Associated With Lower Cardiovascular Mortality and Myocardial Infarction for Drug-Eluting Stent Implantation
— Insights From an Updated Meta-Analysis of Randomized Trials —

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Background: Randomized trials have been underpowered to determine an effect of intravascular ultrasound (IVUS) guidance on hard outcomes for drug-eluting stent (DES) implantation.

Methods and Results: Randomized trials that compared IVUS guidance vs. angiographic guidance for DES implantation were included; 10 trials with 5,060 patients. IVUS guidance was associated with a lower incidence of cardiovascular death (odds ratio [OR] 0.44, 95% CI 0.26–0.75), and myocardial infarction (OR 0.55, 95% CI 0.32–0.94).

Conclusions: IVUS-guidance is associated with a lower incidence of cardiovascular death and myocardial infarction in the era of DES. These findings should encourage operators to use IVUS more often.

Key Words: Drug-eluting stents; Intravascular ultrasound; Meta-analysis

Randomized trials have demonstrated that intravascular ultrasound (IVUS)-guidance for percutaneous coronary intervention (PCI) is associated with improved angiographic and composite clinical outcomes after drug-eluting stent (DES) implantation. A Bayesian meta-analysis of observational and randomized trials has shown that imaging guidance for PCI was associated with a reduction in the risk of death, but this effect was driven by observational studies. Further, the largest randomized trial of IVUS- vs. angiography-guided DES implantation (n=1,448) has been published since this network meta-analysis, and therefore we aimed to perform an updated meta-analysis of only randomized trials to examine the effect of IVUS-guidance on individual outcomes measures after DES implantation.

Methods
Details of our previous meta-analysis have been described. Briefly, we searched the major databases and conference proceedings from 2005 until February 2016 for randomized trials comparing IVUS-guided PCI vs. angiography-guided PCI for DES implantation. The primary outcome for this analysis was cardiovascular death. Because the incidences of the individual clinical outcomes were rare, summary estimates were constructed using a Peto model. Continuous outcomes were assessed by random effects standardized mean difference (SMD) meta-analysis. Funnel plots were used to assess publication bias. For the purpose of the current analysis, an updated search for these data sources was performed from February 2016 to March 2019.

Results
The updated search identified 3 new randomized trials. A total of 10 randomized trials with 5,060 patients (2,526 in the IVUS-guided group and 2,534 in the angiography-guided group) were included (Table). Most of the included trials evaluated the effect of IVUS on complex lesions (e.g., long lesions, chronic total occlusion, left main disease), except for the ULTIMATE trial, which enrolled all-comers. In the ULTIMATE trial, the mean lesion length was 34.5 mm, 66.9% were Type B2/C lesions, and 8.9% were chronic total occlusions.

The baseline diameter stenosis was similar in both groups (70% vs. 70%), as well as the baseline minimum lumen...
**Table. Baseline Characteristics of the Included Studies**

| Trial                  | Year | Patients, n | DES generation | Age, years* | Male, % | Follow-up, months | Lesion type                      |
|------------------------|------|-------------|----------------|-------------|---------|-------------------|----------------------------------|
| Liu et al⁶              | 2019 | 167/169     | Not reported   | 65/65       | 63/64   | 12                | Unprotected left main            |
| ULTIMATE⁵              | 2018 | 724/724     | 53% First, 47% Second | 65/66       | 74/73   | 12                | All-comers                       |
| Zhang et al⁷           | 2016 | 42/42       | Not reported   | 63/60       | 50/59   | 12                | Small vessel (2.25–2.75 mm)      |
| IVUS-XPL⁴              | 2015 | 700/700     | Second         | 64/64       | 69/69   | 12                | Long lesion (≥28 mm)             |
| CTO-IVUS⁴              | 2015 | 201/201     | Second         | 61/61       | 81/81   | 12                | CTO                             |
| AIR-CTO¹⁴              | 2015 | 115/115     | 74% First, 26% Second | 67/66       | 89/80   | 24                | CTO                             |
| Tan et al¹¹            | 2015 | 61/62       | First          | 77/76       | 62/69   | 24                | Unprotected left main            |
| Kim et al¹²            | 2013 | 269/274     | Second         | 63/64       | 66/55   | 12                | Long lesion (≥28 mm)             |
| AVIO¹³                 | 2013 | 142/142     | First          | 64/64       | 82/77   | 24                | Complex lesion**                 |
| HOME DES IVUS¹⁴        | 2010 | 105/105     | First          | 59/60       | 73/71   | 18                | Complex lesion***                |

Data are reported as intravascular ultrasound-guided/angiography-guided strategies. *Mean is reported. **Complex coronary lesion defined as long lesion (≥28 mm); chronic total occlusion; lesions involving a bifurcation; small vessels (≤2.5 mm) and patients requiring ≥4 stents. ***Complex coronary lesion defined as lesion Type B2/C according to the American Heart Association, proximal left anterior descending artery, left main disease, reference vessel diameter ≤2.5 mm, lesion length >20 mm, in-stent restenosis, insulin-dependent diabetes mellitus and acute coronary syndrome. CTO, chronic total occlusion; DES, drug-eluting stent.

**Figure 1.** Summary plot for cardiovascular mortality, myocardial infarction, target lesion revascularization, and stent thrombosis (see Table for study details). CI, confidence interval; IVUS, intravascular ultrasound; OR, odds ratio.
diameter (MLD; 0.86 vs. 0.85 mm). Post-dilation occurred more frequently in the IVUS-guided PCI group (74% vs. 63%, P<0.001). IVUS-guided PCI was also associated with a lower post-procedural diameter stenosis (SMD −0.15, 95% CI −0.28 to −0.03, P=0.02) and a larger post-intervention MLD (SMD 0.21, 95% CI 0.05–0.38, P<0.001).

The weighted mean follow-up time was 13.8±1.4 months. IVUS-guided PCI was associated with a lower incidence of cardiovascular death (0.3% vs. 1.1%; odds ratio [OR] 0.44, 95% CI 0.26–0.75, F=0%, P=0.003), myocardial infarction (MI; 0.2% vs. 0.9%; OR 0.55, 95% CI 0.32–0.94, F=0%, P=0.03), target lesion revascularization (TLR; 2.4% vs. 4.5%; OR 0.57, 95% CI 0.42–0.77, F=0%, P<0.001), and stent thrombosis (ST; 0.3% vs. 0.8%; OR 0.44, 95% CI 0.24–0.79, F=0%, P=0.006) (Figure 1). There was no evidence of publication bias for the primary outcome as evidenced in the funnel plot (Figure 2).

**Discussion**

In this updated meta-analysis of 10 randomized trials with 5,060 patients undergoing PCI with DES (i.e., 1st- or 2nd-generation) implantation for mostly complex lesions, IVUS-guidance was associated with a lower risk of cardiac death, MI, TLR, and ST at a mean of almost 14 months. We also noted no evidence of statistical heterogeneity for all the clinical outcomes. These findings extend our knowledge by suggesting the superiority of IVUS-guidance for DES implantation through a reduction of hard outcomes (i.e., cardiovascular death and MI), not only from observational studies but also as an aggregate of the available randomized trials supporting the individual (n=2,345) patient-level analysis of 3 randomized trials by Shin et al, which showed a reduction in MI with IVUS-guidance.15 Consistent with prior meta-analyses of randomized trials, we have demonstrated that IVUS-guidance was associated with a lower risk of adverse events driven by a lower risk of TLR as well as ST, both of which are directly related to stent optimization.14 A pooled analysis of 21 randomized trials showed that non-emergency, uncomplicated TLR is an independent predictor of death at 37 months,18 and numerous studies have shown that early ST is associated with an increased mortality rate.17

Despite the large body of evidence supporting the use of IVUS-guidance for DES implantation, IVUS is infrequently used. In 1 study of inpatient PCIs in the USA, IVUS was used in <10% of the procedures.19 The results of this current meta-analysis should encourage operators to use IVUS more often for complex lesions and convince the writers of guidelines to upgrade the recommendation for IVUS-guidance.20

Our study was limited by the lack of patient-level data, which might help to identify patient- and lesion-related characteristics associated with the most benefit from IVUS guidance. The individual trials examined different types of lesions, but we noted no evidence of statistical heterogeneity for all the outcomes. Further, the ULTIMATE trial, which included all-comer lesions, showed improved outcomes with IVUS-guidance.5 Finally, our findings were limited to lesions in which the IVUS catheter could be advanced across the lesions, as tight lesions that would not allow the advancement of the IVUS catheter were excluded from the trials; however, this mostly applies to pre-intervention IVUS imaging rather than to stent optimization, and newer IVUS catheters are addressing this technical issue.

**Disclosure**

Dr. Mintz receives honoraria from BostonScientific and Philips. The other authors have no conflicts of interest to disclose.

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