EDITORIAL COMMENT

Clinical Benefit of IVUS Guidance for Coronary Stenting

The ULTIMATE Step Toward Definitive Evidence?*

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It has been more than 40 years since the first balloon angioplasty and 30 years since the first stent implantation. Technical advances in devices and procedural techniques, along with advances in adjunctive antiplatelet treatments and an overall better understanding of the physiology of ischemic heart disease, have led to substantial improvement in outcomes. Consequently, percutaneous coronary interventions (PCI) have been widely adopted. The journey of intracoronary imaging is strikingly different. Intravascular ultrasound (IVUS), an imaging modality that can visualize native as well as stented coronary vessels much better than angiography, was introduced almost 30 years ago. Despite this, IVUS is far from having become a routine tool in everyday clinical practice with a penetration in single-digit or low-teens figures in Europe and the United States. Some cardiologists blame an insufficiently compelling evidence of clinical benefit, but this does not explain why IVUS has already made a real breakthrough in Japan and Korea (1).

Historically, IVUS gained widespread attention soon after its introduction when Colombo et al. (2) and others showed that an angiographically good stent result frequently conceals poorly expanded struts with nasty edge dissections that inevitably increase the risk of acute complications. Initial efforts by many investigators on both sides of the Atlantic to show improved outcomes failed when IVUS was used to optimize bare-metal stent implantation (3,4). In the drug-eluting stent (DES) era, multiple observational and randomized clinical trials (RCTs) (5,6) showed promising results, overall pointing to the potential of IVUS guidance to further improve PCI outcomes (7) despite the low thrombosis and restenosis rates of current newer-generation DES (approximately 0.5% to 1% and 4% to 6%, respectively).

In this issue of the *Journal*, Zhang et al. (8) report the results of the ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions) trial, a randomized study conducted in 8 Chinese centers including 1,448 all-comer patients and comparing IVUS versus angiographic guidance for DES implantation. At 12 months, a 47% reduction in the primary outcome of target vessel failure (a composite of cardiac death, myocardial infarction, or target vessel revascularization) was observed (from 5.4% using IVUS to 2.9% with angiography alone; p = 0.019). Although all components of the composite endpoint were numerically lower in the IVUS-guided group, the reduction in target vessel failure was driven mainly by a reduction in target vessel revascularization (2.9% vs. 1.5%; p = 0.07). The Society for Cardiovascular Angiography and Interventions criteria were adopted for periprocedural myocardial infarction, and it is somewhat surprising that an IVUS strategy potentially leading to larger and longer stents more often postdilated at higher pressure reduced creatine kinase-MB release in the absence of differences with respect to acute stent thrombosis.

Against a background of previous RCTs showing a clinical benefit of IVUS guidance in selected lesion subsets (i.e., long [5] or chronically occluded [6] lesions), the authors categorize the ULTIMATE trial as an all-comers study. Still, they enrolled mainly a complex stable coronary artery disease (CAD) population with 30% of patients with either a left main coronary artery lesion, chronic total occlusion, or bifurcation treated with 2 stents. Notably, the average lesion (35 ± 22 mm) and stent length (66 ± 46 mm) in the ULTIMATE trial and in the previous IVUS-XPL (Impact of IntraVascular UltraSound Guidance on Outcomes of Xience Prime Stents in Long Lesions) trial [5], focused on >28-mm long lesions were almost identical. Still, benefit was not limited to the most complex lesions. The absolute reduction of events with IVUS was greater in the American College of Cardiology/American Heart Association class A/B1 than in class B2/C lesion types (2.8% vs. 2.3%, respectively).
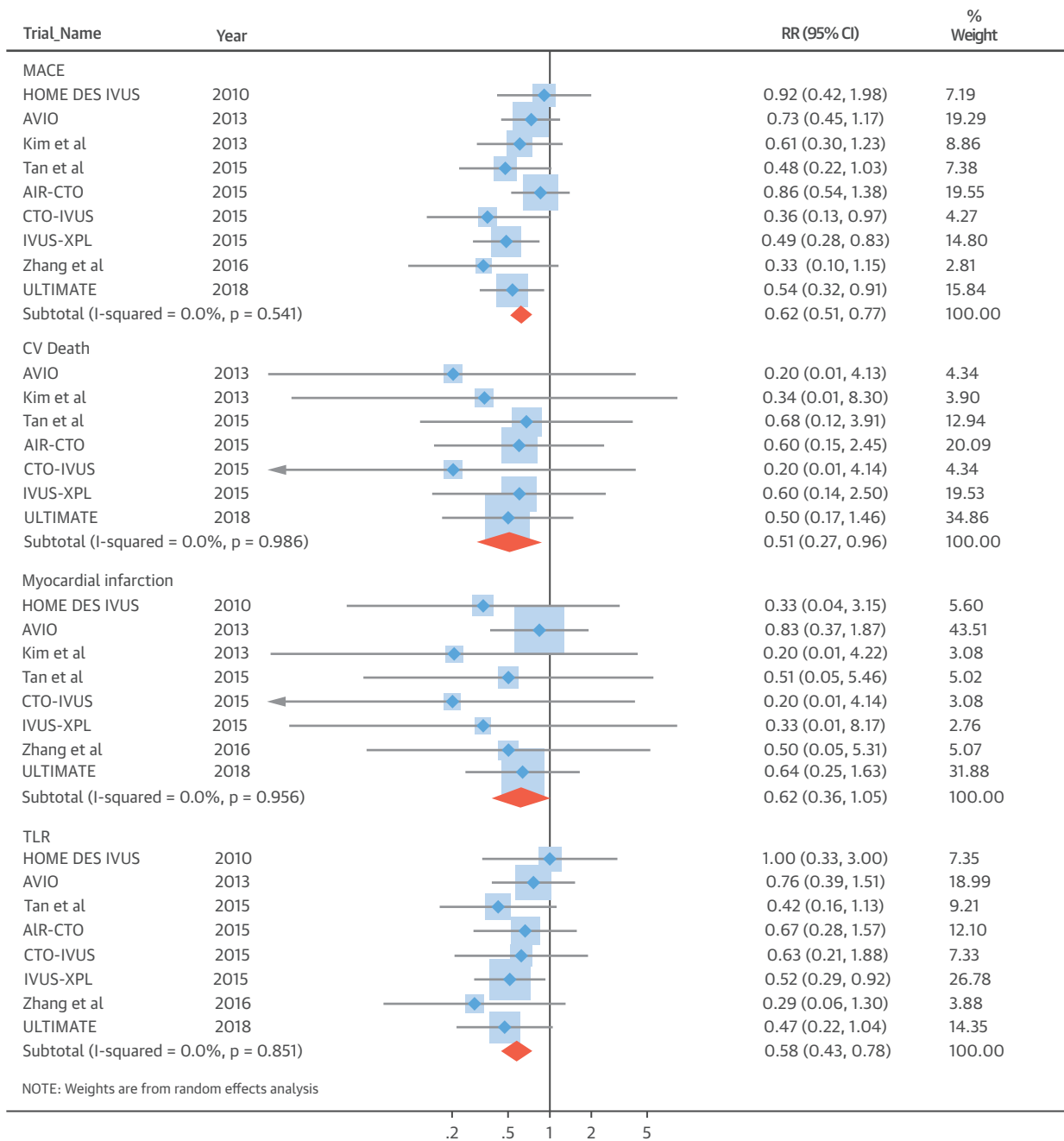
The benefit of IVUS guidance was also greater among patients who met all 3 criteria for optimal IVUS-guided PCI (53% of patients)—a finding supporting the relevance of these criteria. The criteria proposed in the ULTIMATE trial include stent expansion, plaque burden at the stent edge, and absence of large edge dissections. These criteria were met in only 53%. Stent expansion was defined in a very conservative manner (i.e., a minimal lumen area >90% of the distal reference lumen [RLA]), and accordingly, it was achieved in most lesions. This is at variance to results in trials using more aggressive criteria (e.g., minimal stent area > distal RLA, minimal stent area >80% or even >90% of the average RLA) with poor success in meeting these cutoffs (40% to 90%) [9]. The second criterion, a <50% plaque burden in the reference segment, was the most common cause of failure of the IVUS strategy. Adequate lesion coverage requires careful planning based on a pre-procedural IVUS pullback, ideally with the use of coregistration between IVUS and angiography. How often pre-stenting IVUS was applied and whether coregistration was used is not specified in the paper, but the quite modest difference in stent length between groups (∼3 mm) suggests an infrequent adoption of such a strategy. Nevertheless, every operator performing imaging-guided complex PCI must acknowledge that avoidance of residual plaque burden >50% may not be readily possible unless a full-metal jacket strategy is pursued. In such situations, it appears important to at least avoid residual disease burden in the presence of lipid-rich plaques because they seem to be essential triggers of edge restenosis [9].

How much do the results of the ULTIMATE trial add to the existing evidence, and what are the potential clinical implications? A European Association of Percutaneous Cardiovascular Interventions consensus document appraising the clinical role of intracoronary imaging recently reported a pooled analysis of available RCTs comparing IVUS-guided versus angiography-guided DES implantation [9]. Following up on that report, we performed an updated meta-analysis that incorporates the ULTIMATE trial data. The meta-analysis includes 9 RCTs and 4,724 patients and confirms the superiority of IVUS guidance in the reduction in major adverse cardiac events (relative risk [RR]: 0.62; 95% confidence interval [CI]: 0.51 to 0.77) and target lesion revascularization (RR: 0.58; 95% CI: 0.43 to 0.78) (Figure 1). Two aspects are novel. First, compared with the pre-ULTIMATE data, there is now for the first time a statistically significant, robust 49% relative risk reduction in cardiac mortality (RR: 0.51; 95% CI: 0.27 to 0.96) with all individual point estimates going in the same direction. Second, and of relevance for future recommendations, 2 large RCTs with >1,000 patients each consistently showed a reduction in major adverse cardiac events with IVUS guidance [5,8].

The Class IIb recommendation for the use of IVUS (or optical coherence tomography) to guide PCI in earlier clinical practice guidelines were upgraded to Class IIa indication in the most recent European guidelines on myocardial revascularization [10]. The question arises: after a positive, large, "all-comers" trial, are we now ready to recommend routine IVUS guidance in all patients, or should this still be restricted to selected patient and lesion subsets—and if so, to which groups? A closer look at the characteristics of patients included in the ULTIMATE trial is essential to address this critical question, and as mentioned earlier in the text, the included patients mainly belong to a complex stable CAD category rather than to an all-comers population by current standards. The impact of the ULTIMATE trial results on future recommendations remains to be determined, also in anticipation of 2 largescale optical coherence tomography guidance studies currently underway.

Are there downsides to a broader use of IVUS in clinical practice against the obvious benefits using IVUS? High cost, lack of availability, and prolongation of the procedure are often cited as reasons (or excuses) to justify the reluctance to move beyond angiography-oriented routine. The cost of the IVUS approach was not assessed in this paper, but previous analyses already showed that an IVUS-guided strategy is cost-effective. The safety of IVUS guidance did

FIGURE 1   Forrest Plot Comparing IVUS-Guided With Angiography-Guided PCI With DES

Trial_Name	Year	RR (95% CI)	% Weight
MACE			
HOME DES IVUS	2010	0.92 (0.42, 1.98)	7.19
AVIO	2013	0.73 (0.45, 1.17)	19.29
Kim et al	2013	0.61 (0.30, 1.23)	8.86
Tan et al	2015	0.48 (0.22, 1.03)	7.38
AIR-CTO	2015	0.86 (0.54, 1.38)	19.55
CTO-IVUS	2015	0.36 (0.13, 0.97)	4.27
IVUS-XPL	2015	0.49 (0.28, 0.83)	14.80
Zhang et al	2016	0.33 (0.10, 1.15)	2.81
ULTIMATE	2018	0.54 (0.32, 0.91)	15.84
Subtotal (I-squared = 0.0%, p = 0.541)		0.62 (0.51, 0.77)	100.00
CV Death			
AVIO	2013	0.20 (0.01, 4.13)	4.34
Kim et al	2013	0.34 (0.01, 8.30)	3.90
Tan et al	2015	0.68 (0.12, 3.91)	12.94
AIR-CTO	2015	0.60 (0.15, 2.45)	20.09
CTO-IVUS	2015	0.20 (0.01, 4.14)	4.34
IVUS-XPL	2015	0.60 (0.14, 2.50)	19.53
ULTIMATE	2018	0.50 (0.17, 1.46)	34.86
Subtotal (I-squared = 0.0%, p = 0.986)		0.51 (0.27, 0.96)	100.00
Myocardial infarction			
HOME DES IVUS	2010	0.33 (0.04, 3.15)	5.60
AVIO	2013	0.83 (0.37, 1.87)	43.51
Kim et al	2013	0.20 (0.01, 4.22)	3.08
Tan et al	2015	0.51 (0.05, 5.46)	5.02
CTO-IVUS	2015	0.20 (0.01, 4.14)	3.08
IVUS-XPL	2015	0.33 (0.01, 8.17)	2.76
Zhang et al	2016	0.50 (0.05, 5.31)	5.07
ULTIMATE	2018	0.64 (0.25, 1.63)	31.88
Subtotal (I-squared = 0.0%, p = 0.956)		0.62 (0.36, 1.05)	100.00
TLR			
HOME DES IVUS	2010	1.00 (0.33, 3.00)	7.35
AVIO	2013	0.76 (0.39, 1.51)	18.99
Tan et al	2015	0.42 (0.16, 1.13)	9.21
AIR-CTO	2015	0.67 (0.28, 1.57)	12.10
CTO-IVUS	2015	0.63 (0.21, 1.88)	7.33
IVUS-XPL	2015	0.52 (0.29, 0.92)	26.78
Zhang et al	2016	0.29 (0.06, 1.30)	3.88
ULTIMATE	2018	0.47 (0.22, 1.04)	14.35
Subtotal (I-squared = 0.0%, p = 0.851)		0.58 (0.43, 0.78)	100.00

NOTE: Weights are from random effects analysis

.2   .5   1   2   5

The Forrest plot summarizes the effects on cardiovascular outcomes of IVUS-guided as compared with angiography-guided PCI with DES. AIR-CTO = Study Comparing Angiography- vs. IVUS-Guided Stent Implantation for Chronic Total Occlusion in Coronary Artery trial; AVIO = Angiography Vs. IVUS Optimization trial; CI = confidence interval; CV = cardiovascular; DES = drug-eluting stents; IVUS = intravascular ultrasound; IVUS-XPL = Impact of IntraVascular UltraSound Guidance on Outcomes of Xience Prime Stents in Long Lesions trial; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; RR = relative risk; TLR = target lesion revascularization; ULTIMATE = Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions trial.

not emerge as a concern in previous studies (7), as well as in the ULTIMATE trial. The increase in procedural time of 15 min is acceptable in view of the CAD complexity. The 17-ml increase in contrast use in the IVUS group (8) is probably connected to the study protocol, and in clinical practice, IVUS even allows minimal-contrast procedures. The ease of use of imaging represents an ongoing issue, which may be resolved in the future by better software.

The ULTIMATE trial is an important addition to the body of evidence investigating the role of IVUS in optimizing PCI. The investigators should be commended for accepting—and eventually overcoming—the challenge to prove superiority of IVUS in patients with mainly (but not exclusively) complex CAD. Collectively, and particularly in view of the totality of RCT evidence, there is no question that the use of IVUS guidance to optimize PCI does improve patient prognosis. Against this background, there is no scientific justification for the observed inertia in integrating an imaging-guided strategy more broadly in clinical practice.

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