Expedited Publication

Outcomes With Intravascular Ultrasound-Guided Stent Implantation

A Meta-Analysis of Randomized Trials in the Era of Drug-Eluting Stents

Islam Y. Elgendy, MD*; Ahmed N. Mahmoud, MD*; Akram Y. Elgendy, MD; Anthony A. Bavry, MD, MPH

Background—In the era of drug-eluting stents, it is unknown if intravascular ultrasound (IVUS) guidance for percutaneous coronary intervention should be routinely endorsed. This study aimed to determine if IVUS-guided stent implantation is associated with improved outcomes.

Methods and Results—Randomized trials that reported clinical outcomes and compared routine IVUS-guided stent implantation with an angiography-guided approach in the era of drug-eluting stents were included. Summary estimates were constructed primarily using the Peto model. Seven trials with 3192 patients were analyzed. The mean length of the coronary lesions was 32 mm. At a mean of 15 months, routine IVUS-guided percutaneous coronary intervention was associated with a reduction in the risk of major adverse cardiac events (6.5% versus 10.3%; odds ratio, 0.60; 95% confidence interval, 0.46–0.77; $P<0.0001$), mainly because of reduction in the risk of ischemia-driven target lesion revascularization (4.1% versus 6.6%; odds ratio, 0.60; 95% confidence interval, 0.43–0.84; $P=0.003$). The risk of cardiovascular mortality (0.5% versus 1.2%; odds ratio, 0.46; 95% confidence interval, 0.21–1.00; $P=0.05$), and stent thrombosis (0.6% versus 1.3%; odds ratio, 0.49; 95% confidence interval, 0.24–0.99; $P=0.04$) also appeared to be lower in the IVUS-guided group.

Conclusions—In the era of drug-eluting stents for diffuse coronary lesions, IVUS-guided percutaneous coronary intervention is superior to angiography-guided percutaneous coronary intervention in reducing the risk of major adverse cardiac events. This is primarily because of reduction in the risk of ischemia-driven target lesion revascularization. This analysis also suggests that risk of cardiovascular mortality and stent thrombosis might be lower with an IVUS-guided approach.
(*Circ Cardiovasc Interv*. 2016;9:e003700. DOI: 10.1161/CIRCINTERVENTIONS.116.003700.)

Key Words: coronary artery disease ■ drug-eluting stents ■ meta-analysis ■ percutaneous coronary intervention ■ ultrasonography, interventional

Intravascular ultrasound (IVUS) is a useful tool for optimization of stent implantation by insuring good stent expansion and apposition.[1–5] Despite this benefit, routine IVUS is limited by cost considerations and additional time that is needed to perform the procedure. It is also unknown which coronary lesion characteristics are best served by IVUS. A meta-analysis of randomized trials in the era of bare-metal stents concluded that IVUS guidance was associated with a reduction in major adverse cardiac events (MACE) and repeat revascularization with a neutral effect on death and myocardial infarction (MI).[6] Percutaneous coronary intervention (PCI) is currently performed with drug-eluting stents, which has significantly reduced the risk for restenosis, compared with bare-metal stents.[7] A large-scale network meta-analysis demonstrated that all drug-eluting stents (and in particular second generation drug-eluting stents) reduce adverse events compared with bare-metal stents.[8] Accordingly, in present day practice, there may be less need for a routine IVUS-guided PCI approach. Meta-analyses in the era of drug-eluting stents were influenced by including observational studies.[9–13] Furthermore, the results of additional multicenter randomized trials have become available.[14–16] Therefore, we aimed to conduct an updated comprehensive meta-analysis of randomized trials to evaluate clinical outcomes associated with IVUS-guided PCI compared with angiography-guided PCI in the era of drug-eluting stents.

Received February 8, 2016; accepted February 22, 2016.

From the Department of Medicine, University of Florida, Gainesville (I.Y.E., A.N.M., A.Y.E., A.A.B.); and North Florida/South Georgia Veterans Health System, Gainesville (A.A.B.)

*Drs IY Elgendy and Mahmoud contributed equally to this work.

The Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.116.003700/-/DC1.

Correspondence to Anthony A. Bavry, MD, MPH, Medical Service, Cardiology Section (111D), North Florida/South Georgia Veterans Health System (Malcom Randall Veterans Administration Medical Center), 1601 SW Archer Rd, Gainesville, FL 32608. E-mail anthony.bavry@va.gov

WHAT IS KNOWN

- Meta-analysis of randomized trials of bare-metal stents concluded that IVUS guidance was associated with a reduction in major adverse cardiac events (MACE) and repeat revascularization with a neutral effect on death and myocardial infarction but currently percutaneous coronary intervention (PCI) is performed with drug-eluting stents.
- Meta-analyses of IVUS in the era of drug-eluting stents were influenced by including observational studies.

WHAT THE STUDY ADDS

- This meta-analysis of randomized trials using drug-eluting stents demonstrated that IVUS-guided PCI is superior to angiography-guided PCI in reducing the risk of major adverse cardiac events. This is primarily because of reduction in the risk of ischemia-driven target lesion revascularization.

Methods

Data Sources

A computerized search of the Medline database without language restriction was performed from 2005 until February 2016 using the keywords and Medical Subject Heading: coronary, angiography and intravascular ultrasound, limited to clinical trial and human. In addition, the Web of Science, the Cochrane Register of Controlled Trials, major scientific sessions, and clinicaltrial.gov were also searched using the same keywords. The reference lists of the retrieved articles and prior meta-analyses were reviewed.[9–13] This meta-analysis was registered at the PROSPERO international prospective register of systematic reviews (CRD42015029621).

Selection Criteria and Data Extraction

Clinical trials that randomized patients with obstructive coronary artery disease to either IVUS-guided PCI versus angiography-guided PCI were included. We required that the patients were treated with drug-eluting stents. We preferentially reported the outcomes at the longest reported follow-up time. We communicated with the corresponding authors when further article clarification was necessary. The quality of the included trials was evaluated based on the adequate description of treatment allocation, blinded outcome assessment, and description of loss to follow-up.[17]

Two independent authors (A.N.M. and A.Y.E.) extracted data on study design, sample size, intervention strategies, outcomes, and other study characteristics from the included studies. Extracted data were verified by the first author (I.Y.E.). Discrepancies were resolved by consensus of the authors. For all clinical outcomes, the number of events that occurred in each arm of the trial was tabulated.

Outcomes and Definitions

The interventional angiographic outcomes assessed included postintervention minimum luminal diameter (MLD in millimeter), and postintervention percent diameter stenosis. The clinical outcomes evaluated were MACE as defined per the individual studies, all-cause mortality, cardiovascular mortality, spontaneous nonfatal myocardial infarction, ischemia-driven or clinically driven target lesion revascularization (TLR), ischemia-driven or clinically driven target vessel revascularization, and stent thrombosis. Stent thrombosis was defined as definite or probable according to the Academic Research Consortium.[18]

Table 1. Baseline Characteristics of the Included Studies

Characteristic	IVUS-XPL[14]	CTO-IVUS[15]	AIR-CTO[16]	Tan et al[26]	Kim et al[27]	AVIO[28]	HOME DES IVUS[29]
Year	2015	2015	2015	2015	2013	2013	2010
Patients, n	700/700	201/201	115/115	61/62	269/274	142/142	105/105
Drug-eluting stent type	Second generation	Second generation	First/second generation*	First generation	Second generation	First generation	First generation
Age, years, mean	64/64	61/61	67/66	77/76	63/64	64/64	59/60
Male, %	69/69	81/81	89/80	62/69	66/55	82/77	73/71
DM, %	36/37	35/34	30/27	34/30	32/30	24/27	42/45
Clinical presentation							
Stable angina, %	51/51	100/100	71/76	30/34	53/51	70/64	38/40
Unstable angina, %	35/32	0/0	9/10	70/66	38/39	30/26	43/39†
ST-elevation MI, %	14/17	0/0	20/15‡	0/0	9/10	0/0	29/21
LVEF, %	63/62	57/57	55/56	55/53	55/54	55/56	NR
Follow-up duration, mo	12	12	24	24	12	24	18

Data are reported as intravascular ultrasound-guided/angiography-guided strategies. AIR-CTO indicates Study Comparing Angiography- vs. IVUS-Guided Stent Implantation for Chronic Total Occlusion in Coronary Artery; AVIO, Angiography vs IVUS Optimisation; CTO IVUS, Impact of Intravascular Ultrasound-Guided Chronic Total Occlusion Intervention With Drug-Eluting Stents; DM, diabetes mellitus; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS-XPL, Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and NR, not reported.

*76% first generation, and 24% second generation.

†Non–ST-elevation acute coronary syndrome.

‡Acute myocardial infarction>24 hours.

Statistical Analysis

Outcomes were assessed using an intention-to-treat analysis. Standardized mean differences were used for continuous variables. Because we anticipated that some of clinical outcomes are rare; fixed effects summary odds ratios (OR) were performed primarily with a Peto model.[19,20] Summary risk ratios were also constructed with a DerSimonian and Laird[21] model as a secondary analysis. Statistical heterogeneity was studied using the I^2 statistic.[22] Egger et al[23] method was used to estimate publication bias. This meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[24] All *P* values were 2-tailed, with statistical significance set at 0.05, and confidence intervals (CI) were calculated at the 95% level for the overall estimates effect. All analyses were performed using STATA software version 14 (STATA Corporation; College Station, TX).

For the outcome of MACE, a sensitivity analysis was performed: (1) limited to multicenter trials, (2) excluding trials that had any losses to follow-up, (3) excluding trials that exclusively enrolled patients with chronic total occlusions (CTO), and (4) excluding trials that exclusively implanted first generation drug-eluting stents. Random effects meta-regression analyses were prespecified for the outcome of MACE in relation to baseline lesion length, diabetes mellitus, and publication year.[25]

Results

Included Studies

The electronic search yielded 241 articles that were screened by reviewing the title and abstract (Figure I in the Data Supplement). A total of 7 trials (n=3192) were included in the meta-analysis.[14–16,26–29] The measures of the study quality are summarized in Table I in the Data Supplement. All the included studies were conducted in multiple centers except for Tan et al[26] and Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance (HOME DES IVUS).[29] which were single center studies. Two trials enrolled patients with CTO,[15,16] 1 trial enrolled only patients with left main disease,[26] whereas one trial treated complex lesions.[28] The follow-up time ranged from 12 to 24 months. Overall, the weighted mean follow-up duration was 15 (±5) months. The baseline characteristics of the included studies are summarized in Table 1, whereas Table 2 reports the angiographic characteristics.

Overall, the mean lesion length was 32±5 mm. The baseline diameter stenosis was similar in the IVUS-guided PCI and the angiography-guided PCI (72% versus 73%). At baseline, the MLD was minimally larger in the IVUS-guided PCI group compared with the angiography-guided PCI group (0.92 versus 0.88 mm, $P<0.0001$ respectively). Postdilation occurred in 63% of the IVUS-guided PCI group versus 47% of the angiography-guided group ($P<0.0001$). Only 1 study reported postintervention minimal stent cross-sectional area, which was higher in the IVUS-guided PCI group (5.9 versus 4.4 mm).[16] IVUS-guided PCI versus angiography-guided PCI was associated with a larger postintervention MLD (standardized mean differences, 0.18; 95% CI, 0.05–0.36; $P=0.04$). IVUS-guided PCI was associated with a smaller postprocedure percent diameter stenosis (standardized mean differences, –0.17; 95% CI, –0.29 to –0.05; $P=0.005$) compared with angiography-guided PCI.

Table 2. Angiographic Characteristics

Characteristic	IVUS-XPL[14]	CTO-IVUS[15]	AIR-CTO[16]	Tan et al[26]	Kim et al[27]	AVIO[28]	HOME DES IVUS[29]
Coronary arteries							
LAD, %	65/60	42/47	44/37	NA*	62/68	53/49	56/54
LCX, %	14/15	14/16	21/15	NA*	15/13	NR	11/15
RCA, %	21/25	44/37	35/46	NA*	23/20	NR	29/24
Multivessel disease, %	67/70	NA	NA	NA*	41/38	NR	15/17
Bifurcating lesions, %	NR	NA	NA	NA*	0/0	23/27	NR
Chronic total occlusions, %	NR	100/100	100/100	NA*	0/0	14/18	NR
Reference vessel diameter, mm‡	2.9(0.5)/2.9(0.5)	2.7(0.4)/2.6(0.6)	2.7(0.4)/2.6(0.3)	NR	2.8/2.8†	2.7(0.5)/2.6(0.4)	3.2(0.6)/3.0(0.3)
Preintervention MLD, mm‡	0.8(0.4)/0.8(0.4)	NR	NR	1.9(0.2)/1.9(0.2)	1.0/0.9†	0.8(0.5)/0.7(0.5)	1.1(0.4)/1.0(0.4)
Preintervention diameter stenosis, %	71(14)/71(14)	NR	NR	NR	NR	72(16)/76(16)	82(8)/79(9)
Lesion length, mm‡	35(11)/35(11)	36(17)/36(17)	28(18)/29(19)	NR	30/30†	27(16)/26(15)	18(7)/18(7)
Total stented length, mm‡	39(13)/39(12)	44(19)/42(18)	55(23)/52(25)	21(6)/18(5)	33/31†	24(7)/23(7)	24/22
Post-dilation, %	76/57	51/41	NR	23/9	48/43	88/68	24/0

Data are reported as intravascular ultrasound-guided/angiography-guided strategies. AIR-CTO indicates Study Comparing Angiography- vs. IVUS- Guided Stent Implantation for Chronic Total Occlusion in Coronary Artery; AVIO, Angiography vs IVUS Optimisation; CTO IVUS, Impact of Intravascular Ultrasound-Guided Chronic Total Occlusion Intervention With Drug-Eluting Stents; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS-XPL, Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; LAD, left anterior descending artery; LCX, left circumflex artery; MLD, minimum luminal diameter; NR, not reported; RCA, right coronary artery; and SD, standard deviation.

*This trial evaluated left main lesions.

†Median is reported.

‡Mean and standard deviation is reported.

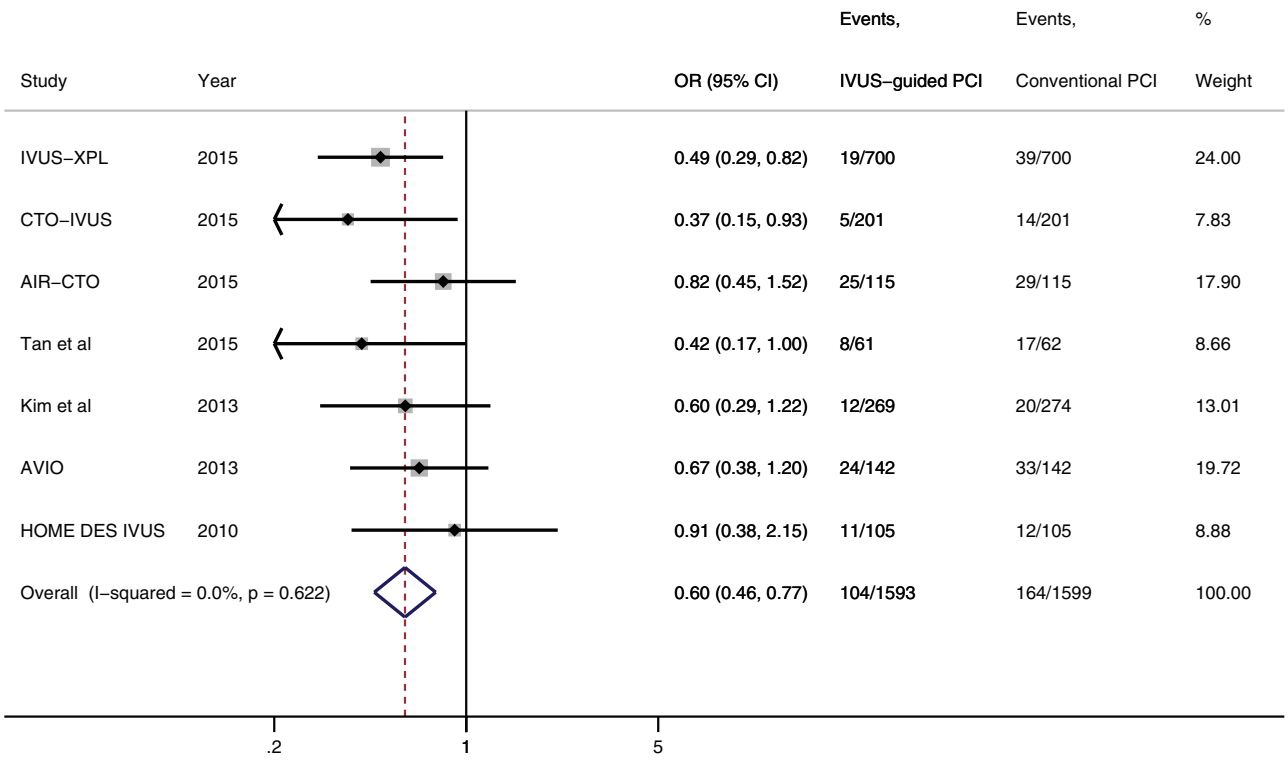

Figure 1. Summary plot for major adverse cardiac events.[14–16,26–29] The relative size of the data markers indicates the weight of the sample size from each study. AIR-CTO indicates Study Comparing Angiography- vs. IVUS- Guided Stent Implantation for Chronic Total Occlusion in Coronary Artery; AVIO, Angiography vs IVUS Optimisation; CI, confidence interval; CTO IVUS, Impact of Intravascular Ultrasound-Guided Chronic Total Occlusion Intervention With Drug-Eluting Stents; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS, intravascular ultrasound; IVUS-XPL, Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; MACE, major adverse cardiac events; OR, odds ratio; and PCI, percutaneous coronary intervention.

Major Adverse Cardiac Events

All the included studies reported the incidence of MACE. The definition of MACE per the individual studies is reported in Table II in the Data Supplement. Compared with angiography-guided PCI, IVUS-guided PCI strategy was associated with a lower risk of MACE (6.5% versus 10.3%; OR, 0.60; 95% CI, 0.46–0.77; $P<0.0001$; $I^2=0\%$; Figure 1). There was no evidence of publication bias with Egger test ($P=0.49$). The sensitivity analyses yielded similar results: (1) limited to multicenter trials (OR, 0.60; 95% CI, 0.45–0.79; $P<0.0001$; $I^2=0\%$), (2) excluding trials with any losses to follow-up (OR, 0.55; 95% CI, 0.36–0.84; $P=0.005$; $I^2=0\%$), (3) excluding trials that exclusively enrolled patients with CTO (OR, 0.58; 95% CI, 0.43–0.79; $P<0.0001$; $I^2=0\%$), and (4) excluding trials that exclusively implanted first generation drug-eluting stents (OR, 0.57; 95% CI, 0.41–0.79; $P=0.001$; $I^2=0\%$). To account for the possibility of a variable treatment effect with a longer follow-up time, we performed a subgroup analysis at 12 and 24 months, which demonstrated a similar effect ($OR_{12\ months}$, 0.56; 95% CI, 0.40–0.77; $P<0.0001$; $I^2=0\%$ and $OR_{24\ months}$, 0.67; 95% CI, 0.46–0.97; $P=0.03$; $I^2=0\%$, respectively). Meta-regression analyses did not identify a difference in treatment effect based on lesion length, diabetes mellitus, or publication year ($P=0.30$, 0.74, and 0.17, respectively).

Other Outcomes

IVUS-guided PCI was associated with a significant reduction in the risk of TLR (4.1% versus 6.6%; OR, 0.60; 95% CI, 0.43–0.84; $P=0.003$, $I^2=0\%$). IVUS-guided PCI appeared to be associated with a lower risk of cardiovascular mortality (0.5% versus 1.2%; OR, 0.46; 95% CI, 0.21–1.00; $P=0.05$; $I^2=0\%$), and stent thrombosis (0.6% versus 1.3%; OR, 0.49; 95% CI, 0.24–0.99; $P=0.04$; $I^2=0\%$). The risk of myocardial infarction was nonsignificantly lower with IVUS-guided PCI (0.8% versus 1.5%; OR, 0.52; 95% CI, 0.26–1.02; $P=0.06$; $I^2=0\%$). Figure 2 demonstrates the forest plot for cardiovascular mortality, myocardial infarction, TLR, and stent thrombosis, whereas Table 3 summarizes the summary estimates for the outcomes of interest using Peto and DerSimonain Laird methods.

Discussion

This meta-analysis of 7 randomized trials in the era of drug-eluting stents with 3192 patients demonstrated that IVUS-guided PCI was associated with a significantly larger postintervention MLD, as well as a greater reduction in the diameter stenosis. IVUS-guided PCI was associated with a reduction in the risk of MACE (number needed to treat=26), primarily because of a reduction in ischemia or clinically driven TLR (number needed to treat=40) at a mean follow-up of 15 months. IVUS-guided PCI also appeared to be associated with a borderline lower risk of stent thrombosis and cardiovascular mortality. Although improved stent apposition might be expected to decrease

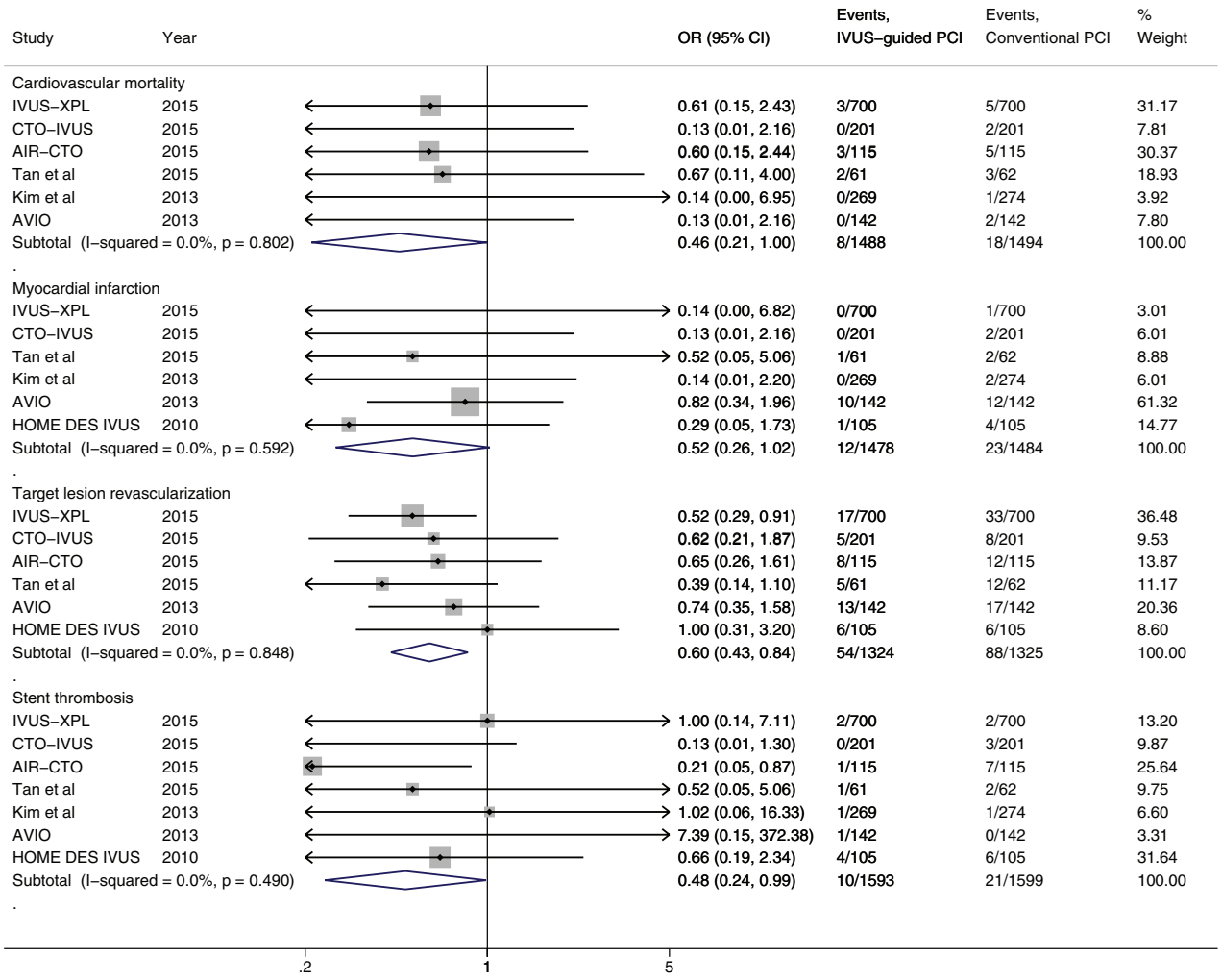

Figure 2. Summary plot for cardiovascular mortality, myocardial infarction, target lesion revascularization, and stent thrombosis. Trials were listed in the forest plot for the individual outcome only if the outcome was reported by the trial.[14–16,26–29] The relative size of the data markers indicates the weight of the sample size from each study. In IVUS-XPL, myocardial infarction was defined as target lesion myocardial infarction. AIR-CTO was excluded from the analysis for myocardial infarction because this study included periprocedural myocardial infarction as part of their definition for myocardial infarction. AIR-CTO indicates Study Comparing Angiography- vs. IVUS- Guided Stent Implantation for Chronic Total Occlusion in Coronary Artery; AVIO, Angiography vs IVUS Optimisation; CI, confidence interval; CTO IVUS, Impact of Intravascular Ultrasound-Guided Chronic Total Occlusion Intervention With Drug-Eluting Stents; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS, intravascular ultrasound; IVUS-XPL, Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; OR, odds ratio; and PCI, percutaneous coronary intervention.

both of these outcomes, these were secondary outcomes with limited number of events, which reduced the power to detect a difference.

Prior meta-analyses in the era of drug-eluting stents were limited by inclusion of observational studies.[9–13] The data analyzed from randomized trials in the earlier meta-analyses had failed to demonstrate the superiority of an IVUS-guided PCI approach because of limited number of randomized trials. By including the totality of data to date, this analysis showed the superiority of IVUS-guided PCI compared with angiography-guided PCI in the drug-eluting stent era. These results are applicable to the studied patient population, of which the most salient characteristic was diffuse coronary artery disease (mean lesion length of 32 mm).

One mechanism by which IVUS is beneficial is that IVUS guidance results in larger postintervention diameters mainly as a result of angiography-guided postdilatation. This was observed in the Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study. In that large study, IVUS-guided PCI resulted in additional optimization of the procedure that otherwise would not have been performed. The most common changes (in decreasing frequency) were selection of larger size stents/balloons, higher inflation pressures, longer stents, and additional postdilatation.[30] We observed this phenomenon in the present analysis where IVUS guidance resulted in more frequent postdilatation and a larger postintervention minimum lumen diameter. The later has been believed to be a major contributing factor for the prevention of restenosis after DES implantation.[31]

Table 3. Summary Estimates for the Outcomes of Interest

Outcome	Incidence IVUS-Guided, %/Angiography-Guided, %	Model	OR*	95% CI	*P* Value	I^2%
MACE	6.5/10.3	Peto	0.60	0.46–0.77	<0.0001	0
		DL	0.65	0.52–0.82	<0.0001	0
Cardiovascular mortality	0.5/1.2	Peto	0.46	0.21–1.00	0.05	0
		DL	0.51	0.24–1.12	0.09	0
MI	0.8/1.5	Peto	0.52	0.26–1.02	0.06	0
		DL	0.60	0.31–1.17	0.13	0
TLR	4.1/6.6	Peto	0.60	0.43–0.84	0.003	0
		DL	0.62	0.45–0.86	0.004	0
TVR	5.5/8.7	Peto	0.61	0.41–0.91	0.02	0
		DL	0.63	0.43–0.92	0.02	0
Stent thrombosis	0.6/1.3	Peto	0.49	0.24–0.99	0.04	0
		DL	0.57	0.26–1.23	0.15	0

CI indicates confidence interval; DL, DerSimonian and Laird; MACE, major adverse cardiac events; MI, myocardial infarction; OR, odds ratio; TLR, target lesion revascularization; and TVR, target vessel revascularization.

*Risk ratio was reported for DerSimonian and Laird method.

The American College of Cardiology/American Heart Association guideline gives a class IIb recommendation for IVUS utilization in left main coronary artery stenting and for assessment of nonleft main intermediate coronary stenosis.[32] An analysis from the National Cardiovascular Data Registry (NCDR) data showed that IVUS was used in ≈20% of total PCI procedures.[33] A potential explanation for infrequent use could be perceived lack of benefit from this technology because some operators may think that visual assessment of the coronary lesions is sufficient. However, it is well known that physician's assessment of the severity of coronary lesions is variable and poorly correlates with myocardial ischemia.[34,35] Alternatively, the cost of the equipment and lack of reimbursement are considerations for underutilisation.[36] However, a previous study had suggested that IVUS guidance was not only cost-effective, but may be cost-saving among patients who are at increased risk of restenosis (eg, diabetics, chronic kidney disease, and acute coronary syndromes).[37] The results of this analysis support the recommendation to expand the routine use of IVUS for revascularization of diffuse lesions (ie, >30 mm).

Although we demonstrated that an IVUS-guided approach was associated with a reduction in MACE, primarily because of reduction in ischemia or clinically driven TLR, the magnitude of the reduction was small (absolute risk reduction=2.5%). Most of the included studies demonstrated a reduction in TLR with an IVUS-guided approach except for HOME DES IVUS, which showed a neutral effect on TLR. One potential explanation is that this trial mainly treated focal lesions (mean, 18 mm).

This analysis has some limitations. First, the definition of MACE was different among the trials; however, there was a clear benefit from IVUS on the outcome of TLR. Furthermore, we observed no evidence of heterogeneity for the outcome of MACE. Second, lack of access to patient level data precluded a full evaluation to identify patient characteristics (ie, stable angina versus acute coronary syndromes) associated with the maximal clinical benefits. Third, because of the way individuals trials were designed, we were not able to assess the impact of IVUS guidance on postinterventional cross-sectional area. Most trials reported postinterventional MLD and percent diameter stenosis, which are crude measures to gauge final stent size. Moreover, preintervention MLD was only reported by 5 of the included studies. Fourth, 3 of the included studies did not have 100% follow-up. The losses to follow-up were small (ranged from 2% to 5%) and likely not a meaningful source of bias. However, we performed a sensitivity analysis excluding these 3 trials and demonstrated a similar treatment effect. Finally, the included studies cannot generalize IVUS usage for all lesions but is most applicable to diffuse lesions.

Conclusions

In the era of drug-eluting stents, IVUS-guided PCI is superior to angiography-guided PCI in reducing the risk of major adverse cardiac events. This is primarily because of reduction in the risk of ischemia-driven target vessel revascularization. The risk of stent thrombosis and cardiovascular mortality may also be reduced with an IVUS-guided approach. The routine use of IVUS for revascularization of diffuse coronary lesions should be considered.

Disclosures

Dr Anthony A. Bavry discloses the following relationship: Honorarium from American College of Cardiology. The other authors report no conflicts.

References

1. de Jaegere P, Mudra H, Figulla H, Almagor Y, Doucet S, Penn I, Colombo A, Hamm C, Bartorelli A, Rothman M, Nobuyoshi M, Yamaguchi T, Voudris V, DiMario C, Makovski S, Hausmann D, Rowe S, Rabinovich S,

Sunamura M, van Es GA. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC Study). *Eur Heart J*. 1998;19:1214–1223.
2. Fitzgerald PJ, Oshima A, Hayase M, Metz JA, Bailey SR, Baim DS, Cleman MW, Deutsch E, Diver DJ, Leon MB, Moses JW, Oesterle SN, Overlie PA, Pepine CJ, Safian RD, Shani J, Simonton CA, Smalling RW, Teirstein PS, Zidar JP, Yeung AC, Kuntz RE, Yock PG. Final results of the Can Routine Ultrasound Influence Stent Expansion (CRUISE) study. *Circulation*. 2000;102:523–530.
3. Nicholls SJ, Tuzcu EM, Sipahi I, Schoenhagen P, Nissen SE. Intravascular ultrasound in cardiovascular medicine. *Circulation*. 2006;114:e55–e59. doi: 10.1161/CIRCULATIONAHA.106.637942.
4. Hong MK, Mintz GS, Lee CW, Park DW, Choi BR, Park KH, Kim YH, Cheong SS, Song JK, Kim JJ, Park SW, Park SJ. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. *Eur Heart J*. 2006;27:1305–1310. doi: 10.1093/eurheartj/ehi882.
5. Fujii K, Carlier SG, Mintz GS, Yang YM, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW, Leon MB. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol*. 2005;45:995–998. doi: 10.1016/j.jacc.2004.12.066.
6. Parise H, Maehara A, Stone GW, Leon MB, Mintz GS. Meta-analysis of randomized studies comparing intravascular ultrasound versus angiographic guidance of percutaneous coronary intervention in pre-drug-eluting stent era. *Am J Cardiol*. 2011;107:374–382. doi: 10.1016/j.amjcard.2010.09.030.
7. Bavry AA, Bhatt DL. Appropriate use of drug-eluting stents: balancing the reduction in restenosis with the concern of late thrombosis [published correction appears in *Lancet*. 2008;372:536]. *Lancet*. 2008;371:2134–2143. doi: 10.1016/S0140-6736(08)60922-8.
8. Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, Vlachojannis GJ, Jensen LO, Christiansen EH, Berencsi K, Valgimigli M, Orlandi C, Petrou M, Rapezzi C, Stone GW. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol*. 2015;65:2496–2507. doi: 10.1016/j.jacc.2015.04.017.
9. Ahn JM, Kang SJ, Yoon SH, Park HW, Kang SM, Lee JY, Lee SW, Kim YH, Lee CW, Park SW, Mintz GS, Park SJ. 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;113:1338–1347. doi: 10.1016/j.amjcard.2013.12.043.
10. Zhang Y, Farooq V, Garcia-Garcia HM, Bourantas CV, Tian N, Dong S, Li M, Yang S, Serruys PW, Chen SL. Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. *EuroIntervention*. 2012;8:855–865. doi: 10.4244/EIJV8I7A129.
11. Jang JS, Song YJ, Kang W, Jin HY, Seo JS, Yang TH, Kim DK, Cho KI, Kim BH, Park YH, Je HG, Kim DS. Intravascular ultrasound-guided implantation of drug-eluting stents to improve outcome: a meta-analysis. *JACC Cardiovasc Interv*. 2014;7:233–243. doi: 10.1016/j.jcin.2013.09.013.
12. Klersy C, Ferlini M, Raisaro A, Scotti V, Balduini A, Curti M, Bramucci E, De Silvestri A. Use of IVUS guided coronary stenting with drug eluting stent: a systematic review and meta-analysis of randomized controlled clinical trials and high quality observational studies. *Int J Cardiol*. 2013;170:54–63.
13. Zhang YJ, Pang S, Chen XY, Bourantas CV, Pan DR, Dong SJ, Wu W, Ren XM, Zhu H, Shi SY, Iqbal J, Gogas BD, Xu B, Chen SL. Comparison of intravascular ultrasound guided versus angiography guided drug eluting stent implantation: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2015;15:153. doi: 10.1186/s12872-015-0144-8.
14. Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Kang WC, Her AY, Kim YH, Kim Y, Hur SH, Hong BK, Kwon H, Jang Y, Hong MK; IVUS-XPL Investigators. Effect of Intravascular Ultrasound-Guided vs Angiography-Guided Everolimus-Eluting Stent Implantation: The IVUS-XPL Randomized Clinical Trial. *JAMA*. 2015;314:2155–2163. doi: 10.1001/jama.2015.15454.
15. Kim BK, Shin DH, Hong MK, Park HS, Rha SW, Mintz GS, Kim JS, Kim JS, Lee SJ, Kim HY, Hong BK, Kang WC, Choi JH, Jang Y; CTO-IVUS Study Investigators. 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. doi: 10.1161/CIRCINTERVENTIONS.115.002592.
16. Tian NL, Gami SK, Ye F, Zhang JJ, Liu ZZ, Lin S, Ge Z, Shan SJ, You W, Chen L, Zhang YJ, Mintz G, Chen SL. 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;10:1409–1417. doi: 10.4244/EIJV10I12A245.
17. Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ*. 2001;323:42–46.
18. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med*. 2007;356:1020–1029. doi: 10.1056/NEJMoa067731.
19. O'Connor D, Green S, Higgins JP. 9.4.4.2. Peto odds ratio method. In: Higgins JP, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration; 2011. http://handbook.cochrane.org/chapter_9/9_4_4_2_peto_odds_ratio_method.htm. Accessed February 2, 2016.
20. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis*. 1985;27:335–371.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560. doi: 10.1136/bmj.327.7414.557.
23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
24. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
25. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med*. 2002;21:1559–1573. doi: 10.1002/sim.1187.
26. Tan Q, Wang Q, Liu D, Zhang S, Zhang Y, Li Y. Intravascular ultrasound-guided unprotected left main coronary artery stenting in the elderly. *Saudi Med J*. 2015;36:549–553. doi: 10.15537/smj.2015.5.11251.
27. Kim JS, Kang TS, Mintz GS, Park BE, Shin DH, Kim BK, Ko YG, Choi D, Jang Y, Hong MK. Randomized comparison of clinical outcomes between intravascular ultrasound and angiography-guided drug-eluting stent implantation for long coronary artery stenoses. *JACC Cardiovasc Interv*. 2013;6:369–376. doi: 10.1016/j.jcin.2012.11.009.
28. Chieffo A, Latib A, Caussin C, Presbitero P, Galli S, Menozzi A, Varbella F, Mauri F, Valgimigli M, Arampatzis C, Sabate M, Erglis A, Reimers B, Airoldi F, Laine M, Palop RL, Mikhail G, Maccarthy P, Romeo F, Colombo A. 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. doi: 10.1016/j.ahj.2012.09.017.
29. Jakabcin J, Spacek R, Bystron M, Kvasnák M, Jager J, Veselka J, Kala P, Cervinka P. 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;75:578–583. doi: 10.1002/ccd.22244.
30. Witzenbichler B, Maehara A, Weisz G, Neumann FJ, Rinaldi MJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Brodie BR, Stuckey TD, Mazzaferri EL Jr, Xu K, Parise H, Mehran R, Mintz GS, Stone GW. 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;129:463–470. doi: 10.1161/CIRCULATIONAHA.113.003942.
31. Kastrati A, Dibra A, Mehilli J, Mayer S, Pinieck S, Pache J, Dirschinger J, Schömig A. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. *Circulation*. 2006;113:2293–2300. doi: 10.1161/CIRCULATIONAHA.105.601823.
32. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58:e44–e122. doi: 10.1016/j.jacc.2011.08.007.
33. Dattilo PB, Prasad A, Honeycutt E, Wang TY, Messenger JC. Contemporary patterns of fractional flow reserve and intravascular ultrasound use among

patients undergoing percutaneous coronary intervention in the United States: insights from the National Cardiovascular Data Registry. *J Am Coll Cardiol*. 2012;60:2337–2339. doi: 10.1016/j.jacc.2012.08.990.

34. Nallamothu BK, Spertus JA, Lansky AJ, Cohen DJ, Jones PG, Kureshi F, Dehmer GJ, Drozda JP Jr, Walsh MN, Brush JE Jr, Koenig GC, Waites TF, Gantt DS, Kichura G, Chazal RA, O'Brien PK, Valentine CM, Rumsfeld JS, Reiber JH, Elmore JG, Krumholz RA, Weaver WD, Krumholz HM. Comparison of clinical interpretation with visual assessment and quantitative coronary angiography in patients undergoing percutaneous coronary intervention in contemporary practice: the Assessing Angiography (A2) project. *Circulation*. 2013;127:1793–1800. doi: 10.1161/CIRCULATIONAHA.113.001952.
35. Elgendy IY, Conti CR, Bavry AA. Fractional flow reserve: an updated review. *Clin Cardiol*. 2014;37:371–380. doi: 10.1002/clc.22273.
36. Elgendy IY, Choi C, Bavry AA. The Impact of Fractional Flow Reserve on Revascularization. *Cardiol Ther*. 2015;4:191–196. doi: 10.1007/s40119-015-0051-1.
37. Alberti A, Giudice P, Gelera A, Stefanini L, Priest V, Simmonds M, Lee C, Wasserman M. Understanding the economic impact of intravascular ultrasound (IVUS). *Eur J Health Econ*. 2016;17:185–193. doi: 10.1007/s10198-015-0670-4.