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

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There are conflicting data regarding the benefit of intravascular ultrasound (IVUS)–guided percutaneous coronary intervention (PCI) over angiography-guided PCI. Since the last meta-analysis was published, several new studies have been reported. We performed a comprehensive meta-analysis to evaluate the clinical impact of IVUS-guided PCI with drug-eluting stent compared with conventional angiography-guided PCI. This meta-analysis included 26,503 patients from 3 randomized and 14 observational studies; 12,499 patients underwent IVUS-guided PCI and 14,004 underwent angiography-guided PCI. Main outcome measures were total mortality, myocardial infarction (MI), stent thrombosis, and target lesion revascularization (TLR). IVUS-guided PCI was significantly associated with more stents, longer stents, and larger stents. Regarding clinical outcomes, IVUS-guided PCI was associated with a significantly lower risk of TLR (odds ratio [OR] 0.81, 95% confidence interval [CI] 0.66 to 1.00, $p = 0.046$). In addition, the risk of death (OR 0.61, 95% CI 0.48 to 0.79, $p < 0.001$), MI (OR 0.57, 95% CI 0.44 to 0.75, $p < 0.001$), and stent thrombosis (OR 0.59, 95% CI 0.47 to 0.75, $p < 0.001$) were also decreased. In conclusion, our meta-analysis demonstrated that IVUS-guided PCI was associated with lower risk of death, MI, TLR, and stent thrombosis after drug-eluting stent implantation. **(Am J Cardiol 2014;113:1338–1347)**

Intravascular ultrasound (IVUS) has provided valuable information on cross-sectional coronary vascular structure and has played a key role in contemporary stent-based percutaneous coronary interventions (PCIs) by accurately assessing coronary anatomy, assisting in selection of treatment strategy, and defining optimal stenting outcomes.[1–6] In the bare-metal stent era, randomized trials and meta-analysis demonstrated that IVUS-guided PCI was mainly associated with a lower risk of angiographic restenosis and target vessel revascularization (TVR).[7,8] In the drug-eluting stent (DES) era, a recent meta-analysis showed that the risk of death and stent thrombosis (ST) was reduced by IVUS-guided DES implantation.[9] Recently, 2 randomized trials and several observational studies have been reported since the last meta-analysis was published. Accordingly, we performed an updated comprehensive meta-analysis to evaluate the clinical impact of IVUS-guided PCI with DES implantation (compared with conventional angiography-guided PCI).

Methods

The literature was searched for studies that compared the clinical outcomes of IVUS-guided PCI with those of angiography-guided PCI and conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for conducting and reporting systematic reviews.[10] A computerized search was performed of MEDLINE, EMBASE, and Cochrane databases from January 1995 to May 2013. Combinations of the following terms were used in the search process: "ultrasound, intravascular," "IVUS," "IVUS-guided," "angiography-guided," "percutaneous coronary intervention," "PCI," "drug-eluting stent," and "stent." Additional data sources included conference proceedings from major meetings of the American Heart Association, American College of Cardiology, and Transcatheter Cardiovascular Therapeutics. Reference lists of selected reports were reviewed for other potentially relevant citations. In the case of duplicate reports from the same patients, the most complete data were retrieved from the studies for quantitative synthesis. Additional searches for potential studies included references of review reports and earlier meta-analyses. Two investigators (J-MA and S-HY) independently screened the titles and abstracts and eventually examined the full texts of the original

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See page 1346 for disclosure information.

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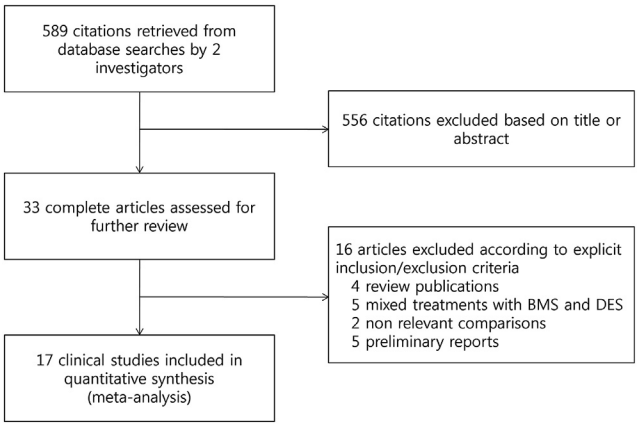


Figure 1. Flow diagram of the included studies. Diagram demonstrating inclusion and exclusion process for studies incorporated into the final analyses.

reports included in the study. Discrepancies were resolved by consensus.

Studies were included in the meta-analysis if they met the following prespecified criteria: (1) clinical studies published in peer-reviewed journals with fully available text, (2) studies comparing cohorts of IVUS-guided PCI with angiography-guided PCI with DES, (3) documentation of clinical outcomes of death, myocardial infarction (MI), repeat revascularization, or ST, separately or in combination, and (4) follow-up duration of $\geq$9 months. Reports of mixed treatment with bare-metal stent and DES implantation were excluded.

Patient characteristics, study design, and outcomes were systematically reviewed and recorded. The following outcomes were extracted: the number and length of implanted stents, minimal lumen diameter, mean stent diameter, and major adverse cardiac events (MACEs: defined as the composite of death, MI, and repeat revascularization) or individual outcomes of death, MI, target lesion revascularization (TLR), TVR, and ST. The quality of the retrieved studies was assessed to ensure minimization of bias, but no formal scoring system was used. Reviewers were not blinded to reports, publication sites, or author affiliations.

A random-effects meta-analysis was used to obtain the overall effect for the odds ratios (ORs) and the standardized mean difference for binary or continuous data. The DerSimonian and Laird model was used for the random-effects meta-analysis to account for excess variability (heterogeneity) across studies.[11] Statistical heterogeneity across studies was assessed with the I^2 statistic that is derived from Cochran's Q.[11] I^2 values >25%, >50%, and >75% were considered as evidence of low, moderate, and severe statistical heterogeneity, respectively.

To examine the possible sources of heterogeneities, a random-effects meta-regression was performed to test whether any covariate was associated with an observed effect size. Publication bias (i.e., the likelihood of a small yet nominally significant study being selectively published) was examined by visual inspection of constructed funnel plots that relate the effect size to the precision of the effect estimate. Presence of asymmetry suggested possible publication bias. Egger's test was employed to quantify the asymmetry.

A 2-tailed p value of <0.05 was considered statistically significant. All data analyses were performed with Comprehensive Meta-Analysis, version 2 (Biostat, Inc., New Jersey).

Results

The electronic search yielded 589 citations that were screened by reviewing the title or abstract. Of these, 33 publications were reviewed in full and 17 studies (26,503 patients) were included in the meta-analysis (Figure 1). Of these patients, 12,499 underwent IVUS-guided PCI and 14,004 underwent angiography-guided PCI. Three studies were prospective randomized controlled studies,[12–14] and the other 14 studies were prospective or retrospective observational studies.[15–28]

Baseline characteristics of the included studies, major enrollment criteria, and the definition of clinical outcomes are provided in Table 1. Two studies were dedicated to left main stenosis,[15,17] 3 studies to bifurcation,[18,20,22] 2 studies to long lesion,[14,26] and 5 studies to real-world PCI population with minimal exclusion criteria.[16,19,23,24,27] Overall, the average patient age was 63 years; 69% of patients were men, 31% had diabetes, and the average follow-up length was 29 months.

Ten studies reported minimal lumen diameter by quantitative coronary angiographic analysis, and 12 studies reported mean stent diameter. Compared with angiography-guided PCI, IVUS-guided PCI was associated with larger stents and a larger postprocedure angiographic minimal lumen diameter. The mean difference in stent size and in postprocedural minimal lumen diameter was 0.33 mm (95% confidence interval [CI] 0.22 to 0.44, p <0.001) and 0.34 mm (95% CI 0.27 to 0.40, p <0.001), respectively. IVUS guidance was also associated with more stents and longer stents as reported in 9 studies and 13 studies, respectively. The mean difference in the number and length of stents used was 0.27 (95% CI 0.11 to 0.43, p <0.001) and 0.18 mm (95% CI 0.08 to 0.27, p <0.001), respectively (Figure 2). Significant heterogeneity was observed across the studies regarding mean stent diameter, implanted stent number, and implanted stent length.

Periprocedural MI was reported in 6 studies. Of note, the risk of periprocedural MI did not significantly differ between IVUS-guided and angiography-guided DES implantation (OR 1.01, 95% CI 0.73 to 1.67, p = 0.65). However, severe heterogeneity was observed across the studies (I^2 = 81).

Long-term MACE was reported in 16 studies. IVUS-guided DES implantation was associated with a significant reduction of MACE (OR 0.74, 95% CI 0.64 to 0.85, p <0.001) with mild heterogeneity across the studies (I^2 = 46.2; Figure 3). Mortality was reported in 16 studies; IVUS-guided DES implantation resulted in a significant reduction of death (OR 0.61, 95% CI 0.48 to 0.79, p <0.001) with mild heterogeneity across the studies (I^2 = 42; Figure 3). MI was reported in 16 studies; IVUS-guided DES implantation led to a significant reduction of MI (OR 0.57, 95% CI 0.44 to 0.75, p <0.001) with mild heterogeneity across the studies (I^2 = 35; Figure 3). TVR was reported in 12 studies; the risk of TVR significantly reduced by IVUS-guided PCI (OR 0.82, 95% CI 0.70 to 0.97, p = 0.022) with mild heterogeneity across the studies (I^2 = 38.5; Figure 3). TLR was

Table 1
Baseline characteristics of included studies

Study	Publication Year	Enrollment Period	Patient Number	Design	Adjustment	Study Region	Follow-Up (Mo)	Age (yrs)	Men (%)†	Diabetes (%)	Hypertension (%)	Hyperlipidemia (%)	LVEF (%)	ACS (%)
Agostoni et al[15]	2005	2002−2003	24/34	Observational	—	EU	12	62/64	62/73	37/29	58/59	62/68	52/44	33/32
Roy et al[16]	2008	2003−2006	884/884	Observational	P	US	12	66/66	69/70	36/34	82/82	86/87	47/48	76/75
Park et al[17]	2009	2003−2006	145/145	Observational	P	Asia	36	64/65	70/70	34/34	59/59	29/30	61/63	63/61
Jakabcin et al[12]	2010	2004−2005	105/105	RCT	—	EU	18	60/59	71/73	45/42	71/67	66/63	—	60/62
Kim et al[18]	2010	2003−2006	303/112	Observational	C	Asia	48	60/61	73/72	23/21	47/55	22/24	59/59	48/51
Claessen et al[19]	2011	2004−2006	631/873	Observational	P	US/EU	24	65/64	74/74	32/31	82/81	84/82	—	33/36
Kim et al[20]	2011	2004−2006	487/487	Observational	P	Asia	36	62/62	67/67	32/33	60/58	35/35	61/59	53/56
Youn et al[21]	2011	2003−2008	125/216	Observational	—	Asia	36	60/61	74/63*	27/33	50/51	22/11*	45/48*	100/100
Park et al[24]	2012	—	619/802	Observational	P	Asia	12	62/63*	64/65	38/39	71/76*	76/76	—	49/54*
Ahn et al[26]	2013	2008−2009	49/36	Observational	—	Asia	24	65/65	61/61	27/30	51/56	29/25	54/56	47/47
Ahn et al[27]	2013	2008−2010	1,616/1,628	Observational	P	Asia	24	62/64*	69/64*	31/32	57/63*	40/34*	60/59	51/68*
Chen et al[22]	2013	2007−2010	324/304	Observational	P	Asia	12	63/65	81/75	19/18	67/61	33/35	61/60	87/79*
Chieffo et al[13]	2013	—	142/142	RCT		EU	24	64/64	82/77	24/27	70/67	70/77	55/56	30/26
Hur et al[23]	2013	2003−2006	2,765/1,816	Observational	C	Asia	36	60/63*	71/67*	26/27	47/51*	23/20*	58/55*	54/59*
Kim et al[14]	2013	—	269/274	RCT		Asia	12	63/64	66/55*	32/30	61/66	61/62	55/54	38/39
Yoon et al[28]	2013	—	662/912	Observational	C	Asia	12	61/63*	65/65	28/30	60/63	61/56	—	60/55
Witzenbichler et al[25]	2014	—	3,349/5,234	Observational	C	US/EU	12	63/64*	73/75	31/33	78/81*	68/78*	—	—

Data are presented as IVUS-guided PCI/angiography-guided PCI.

ACS = acute coronary syndrome; C = Cox proportional hazard model; EU = Europe; LVEF = left ventricular ejection fraction; P = propensity score method; RCT = randomized controlled trial; US = United States.

* $p < 0.05$.

† Percentage of total population.

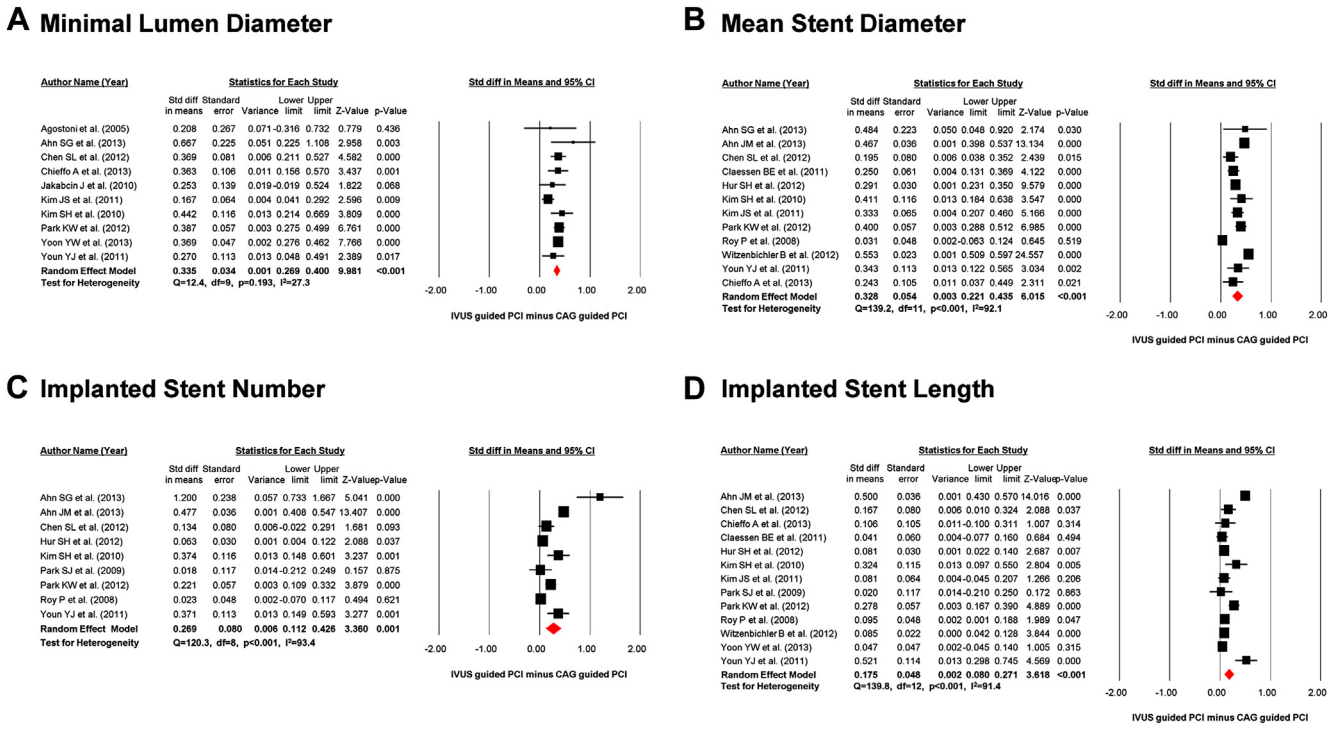


Figure 2. Forest plot of the mean difference of the minimal lumen diameter *(A)*, stent size *(B)*, implanted stent number *(C)*, and implanted stent length *(D)* in IVUS- versus angiography-guided PCI. *Squares* is the effect size of the individual studies; *diamonds*, the summarized effect size; *horizontal lines*, upper and lower border of 95% confidence interval. CAG = coronary angiography; df = degrees of freedom; diff = difference; Std = standardized.

reported in 12 studies; the risk of TLR was significantly reduced by IVUS-guided PCI (OR 0.81, 95% CI 0.66 to 1.00, p = 0.046) with mild heterogeneity across the studies (I^2 = 41; Figure 3). ST was reported in 16 studies; IVUS-guided DES implantation was associated with a significant reduction of ST (OR 0.59, 95% CI 0.47 to 0.75, p <0.001) with no heterogeneity across the studies (I^2 = 5; Figure 3).

Visual inspection of the funnel plots for MACE, death, MI, TVR, TLR, and ST did not reveal asymmetry, and no evidence of publication bias was observed based on Egger's regression tests (Figure 4).

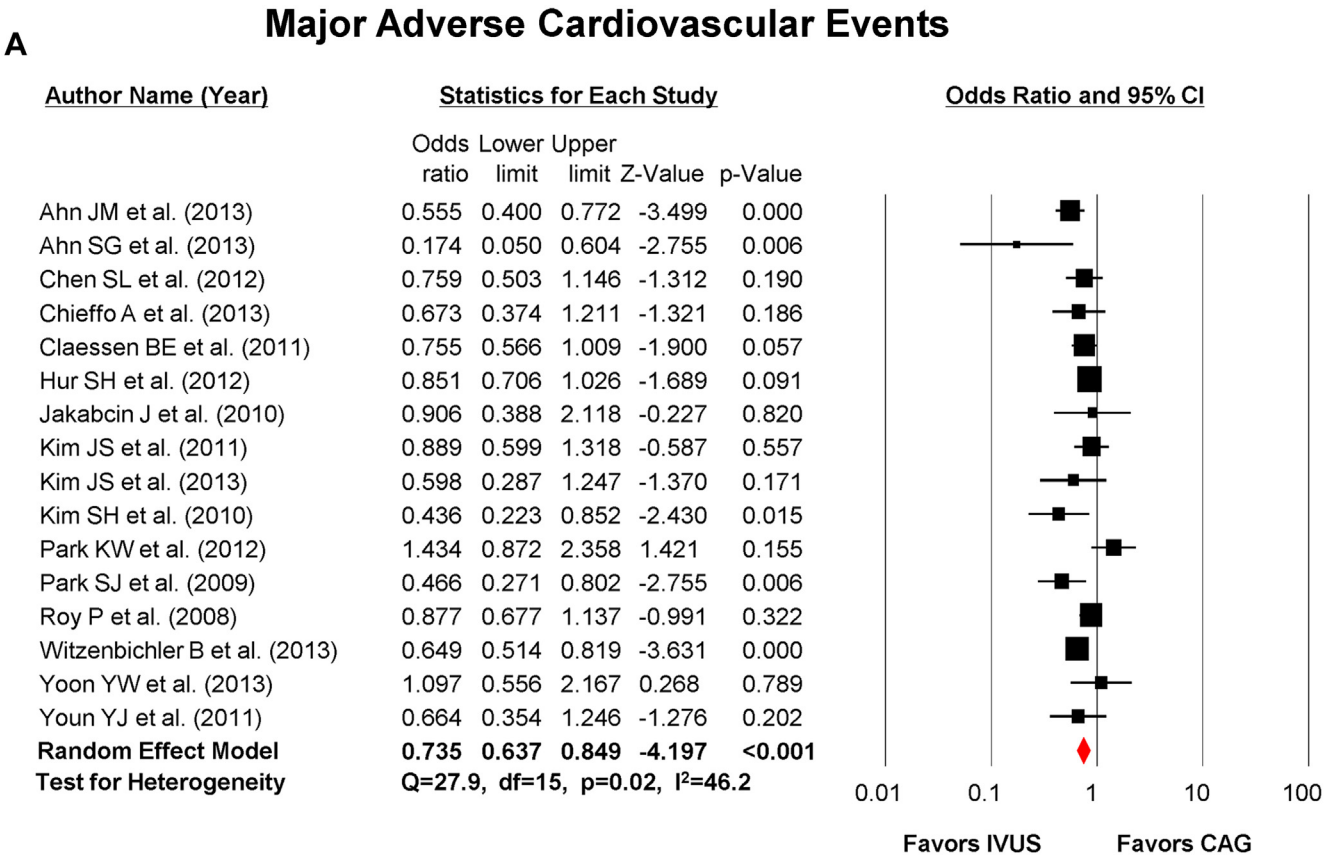
Discussion

The present updated meta-analysis showed that IVUS-guided PCI was associated with a significantly reduced risk of death, MI, ST, and TLR as well as a lower risk of the composite of death, MI, or repeated revascularization over a follow-up period of 12 months to 4 years.

An initial meta-analysis performed in the bare-metal stent era demonstrated that IVUS-guided stenting significantly lowered 6-month angiographic restenosis and TVR.[7] A subsequent meta-analysis including only the 7 randomized trials also showed that IVUS-guided bare-metal stent implantation reduced angiographic restenosis, repeat revascularization, and MACE, with a neutral effect on death and MI.[8]

A recent meta-analysis of IVUS-guided DES implantation reported a significant reduction in death, MACE, and ST compared with angiographic guidance.[9] Unlike the bare-metal stent era, a reduction in restenosis or repeat revascularization was not demonstrated; this could be explained by the very low rate of restenosis after DES implantation, relatively short follow-up periods, and unreported incidences of TLR or TVR in individual studies.

Notably, our present meta-analysis demonstrated a reduction in TLR after IVUS-guided DES implantation by 34% and MI by 56%, presumably because of the addition of new studies reporting event rates such as the IVUS-guided substudy from ADAPT-DES (Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents).[25] ADAPT-DES enrolled 8,583 patients (3,349 underwent IVUS-guided PCI and 5,234 angiography-guided PCI). IVUS guidance lead to the use of larger stents or balloons, more postdilation, additional stents, or higher pressures in about 75% of patients resulting in lower rates of ST, MI, and TLR. Another noteworthy study was the prespecified long lesion subset from the Real Safety and Efficacy of a 3-Month Dual Antiplatelet Therapy Following Zotarolimus-Eluting Stents Implantation (RESET) trial, the only randomized trial powered for clinical outcomes.[14] In the intention-to-treat analysis of RESET, IVUS-guided PCI was associated with only a trend toward reduction of MACE; however, because of a high rate of crossover (especially from the angiography-guided to the IVUS-guided group), the per-protocol analysis showed a reduction of MACE at 1 year in the group treated with actual IVUS-guided DES implantation. Adding to the decrease of TLR and MI reported in the meta-analysis by Zhang et al,[9] our meta-analysis also demonstrated a reduction of death, ST, or MACE by 39%, 41%, and 25%, respectively. Although further study is necessary to understand the exact mechanisms, the reduction of thrombotic complications including



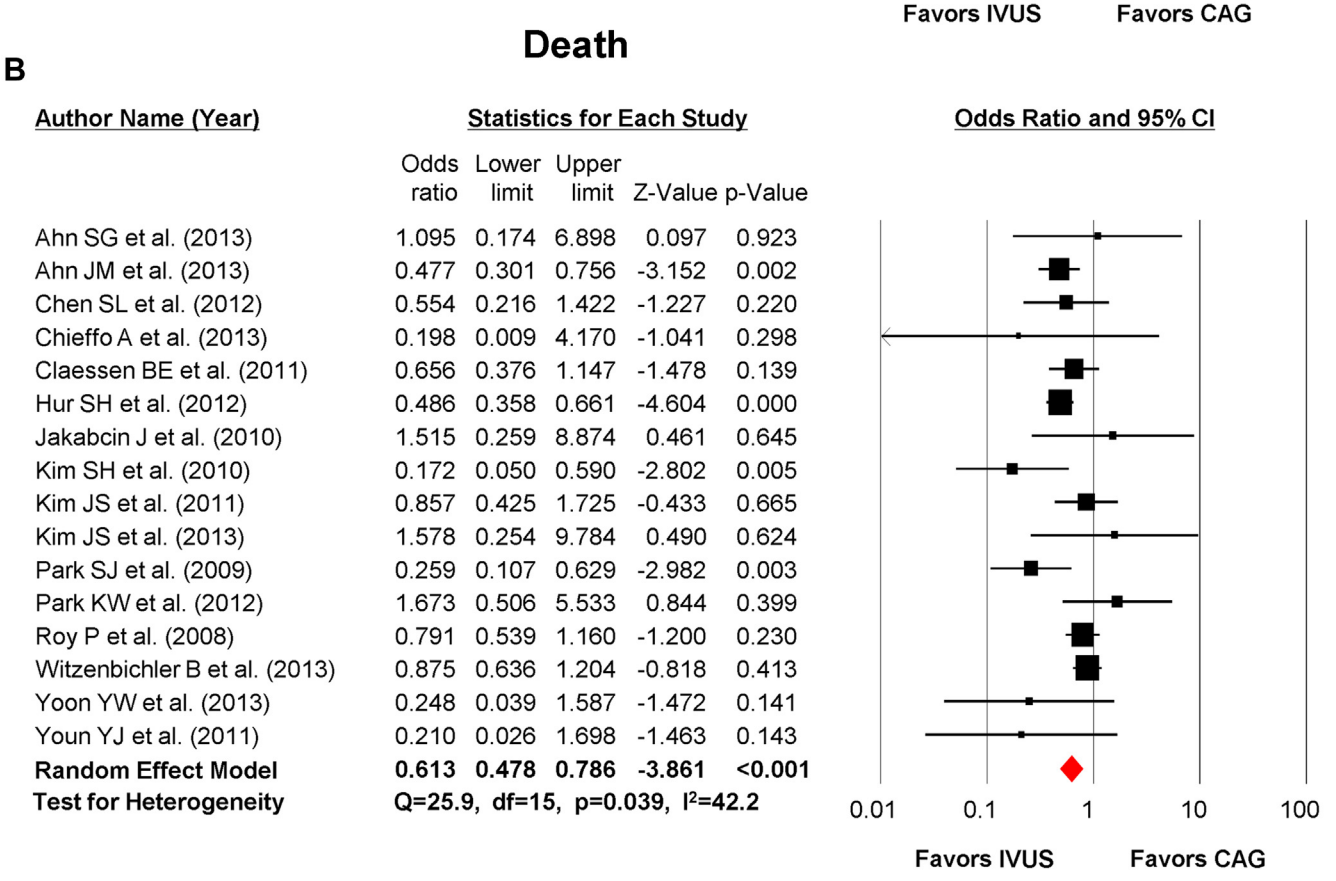
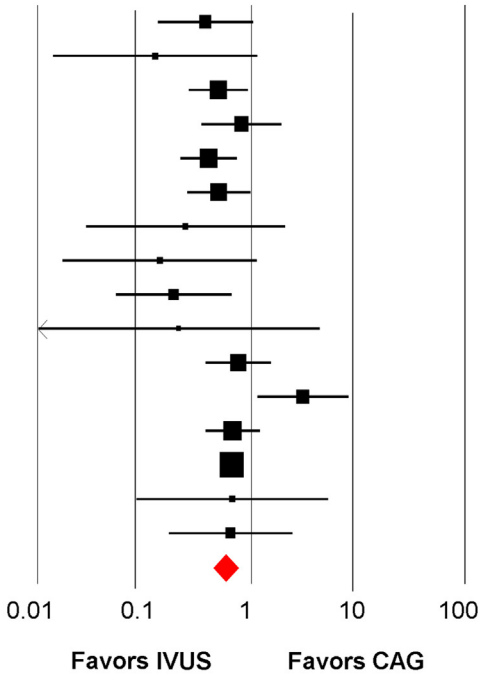


Figure 3. Forest plot of OR for MACEs *(A)*, death *(B)*, MI *(C)*, TVR *(D)*, TLR *(E)*, and ST *(F)* in IVUS- versus angiography-guided PCI. *Squares* is the effect size of the individual studies; *diamonds*, the summarized effect size; *horizontal lines*, upper and lower border of 95% confidence interval. CAG = coronary angiography; df = degrees of freedom.

C

Myocardial Infarction

Author Name (Year)	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ahn JM et al. (2013)	0.373	0.131	1.061	-1.849	0.064
Ahn SG et al. (2013)	0.126	0.014	1.154	-1.833	0.067
Chen SL et al. (2012)	0.494	0.257	0.948	-2.120	0.034
Chieffo A et al. (2013)	0.810	0.338	1.941	-0.472	0.637
Claessen BE et al. (2011)	0.399	0.214	0.744	-2.893	0.004
Hur SH et al. (2012)	0.497	0.247	1.004	-1.949	0.051
Jakabcin J et al. (2010)	0.242	0.028	2.094	-1.288	0.198
Kim SH et al. (2010)	0.139	0.017	1.150	-1.830	0.067
Kim JS et al. (2011)	0.189	0.054	0.665	-2.596	0.009
Kim JS et al. (2013)	0.209	0.010	4.414	-1.006	0.315
Park SJ et al. (2009)	0.757	0.369	1.550	-0.762	0.446
Park KW et al. (2012)	3.043	1.125	8.234	2.191	0.028
Roy P et al. (2008)	0.670	0.369	1.218	-1.313	0.189
Witzenbichler B et al. (2013)	0.660	0.508	0.858	-3.110	0.002
Yoon YW et al. (2013)	0.666	0.083	5.317	-0.383	0.701
Youn YJ et al. (2011)	0.640	0.167	2.458	-0.650	0.516
Random Effect Model	**0.571**	**0.435**	**0.751**	**-4.011**	**<0.001**
Test for Heterogeneity	**Q=22.9, df=15, p=0.086, I^2=34.5%**				



D

Target Vessel Revascularization

Author Name (Year)	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ahn JM et al. (2013)	0.703	0.455	1.086	-1.588	0.112
Chen SL et al. (2012)	0.728	0.447	1.185	-1.277	0.201
Chieffo A et al. (2013)	0.592	0.289	1.212	-1.434	0.152
Claessen BE et al. (2011)	0.851	0.619	1.169	-0.997	0.319
Hur SH et al. (2012)	1.135	0.895	1.438	1.046	0.296
Kim JS et al. (2013)	0.667	0.316	1.409	-1.062	0.288
Park SJ et al. (2009)	0.720	0.310	1.668	-0.767	0.443
Park KW et al. (2012)	0.929	0.491	1.758	-0.226	0.821
Roy P et al. (2008)	0.928	0.668	1.290	-0.445	0.656
Witzenbichler B et al. (2013)	0.590	0.455	0.766	-3.961	0.000
Yoon YW et al. (2013)	1.409	0.663	2.992	0.891	0.373
Youn YJ et al. (2011)	0.881	0.453	1.716	-0.372	0.710
Random Effect Model	**0.824**	**0.698**	**0.972**	**-2.297**	**0.022**
Test for Heterogeneity	**Q=17.9, df=11, p=0.08, I^2=38.5**				

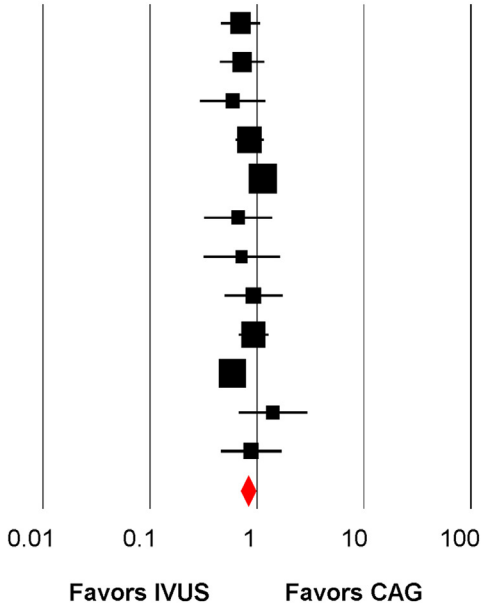
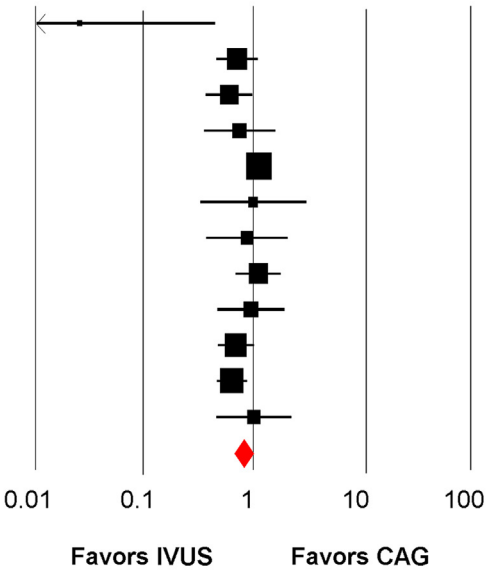


Figure 3. (*continued*).

E

Target Lesion Revascularization

Author Name (Year)	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ahn SG et al. (2013)	0.025	0.001	0.452	-2.501	0.012
Ahn JM et al. (2013)	0.708	0.449	1.118	-1.481	0.139
Chen SL et al. (2012)	0.603	0.362	1.003	-1.949	0.051
Chieffo A et al. (2013)	0.750	0.350	1.608	-0.739	0.460
Hur SH et al. (2012)	1.133	0.881	1.458	0.974	0.330
Jakabcin J et al. (2010)	1.000	0.320	3.124	0.000	1.000
Kim SH et al. (2010)	0.875	0.364	2.105	-0.298	0.765
Kim JS et al. (2011)	1.113	0.681	1.819	0.427	0.670
Park KW et al. (2012)	0.954	0.462	1.967	-0.129	0.898
Roy P et al. (2008)	0.693	0.467	1.027	-1.829	0.067
Witzenbichler B et al. (2013)	0.636	0.457	0.884	-2.696	0.007
Youn YJ et al. (2011)	1.014	0.449	2.287	0.033	0.974
Random Effect Model	**0.811**	**0.660**	**0.996**	**-1.998**	**0.046**
Test for Heterogeneity	**Q=18.7, df=11, p=0.067, I^2=41.2**				



F

Definite or Probable Stent Thrombosis

Author Name (Year)	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ahn SG et al. (2013)	0.163	0.017	1.557	-1.575	0.115
Ahn JM et al. (2013)	0.199	0.037	1.079	-1.872	0.061
Chen SL et al. (2012)	0.164	0.055	0.489	-3.240	0.001
Chieffo A et al. (2013)	3.009	0.121	74.609	0.672	0.501
Claessen BE et al. (2011)	0.553	0.149	2.051	-0.885	0.376
Hur SH et al. (2012)	0.855	0.558	1.308	-0.723	0.470
Jakabcin J et al. (2010)	0.653	0.184	2.314	-0.661	0.509
Kim SH et al. (2010)	0.263	0.059	1.179	-1.745	0.081
Kim JS et al. (2011)	0.332	0.033	3.300	-0.941	0.347
Kim JS et al. (2013)	1.000	0.070	14.371	0.000	1.000
Park SJ et al. (2009)	1.000	0.406	2.465	0.000	1.000
Park KW et al. (2012)	0.498	0.091	2.719	-0.804	0.421
Roy P et al. (2008)	0.583	0.392	0.867	-2.666	0.008
Witzenbichler B et al. (2013)	0.497	0.289	0.855	-2.529	0.011
Yoon YW et al. (2013)	1.000	0.106	9.393	0.000	1.000
Youn YJ et al. (2011)	0.854	0.210	3.468	-0.221	0.825
Random Effect Model	**0.592**	**0.468**	**0.750**	**-4.358**	**<0.001**
Test for Heterogeneity	**Q=15.7, df=15, p=0.40, I^2=4.63%**				

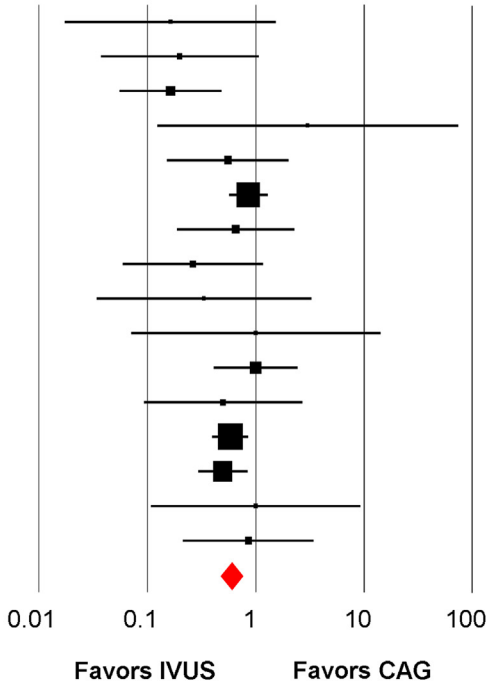


Figure 3. (*continued*).

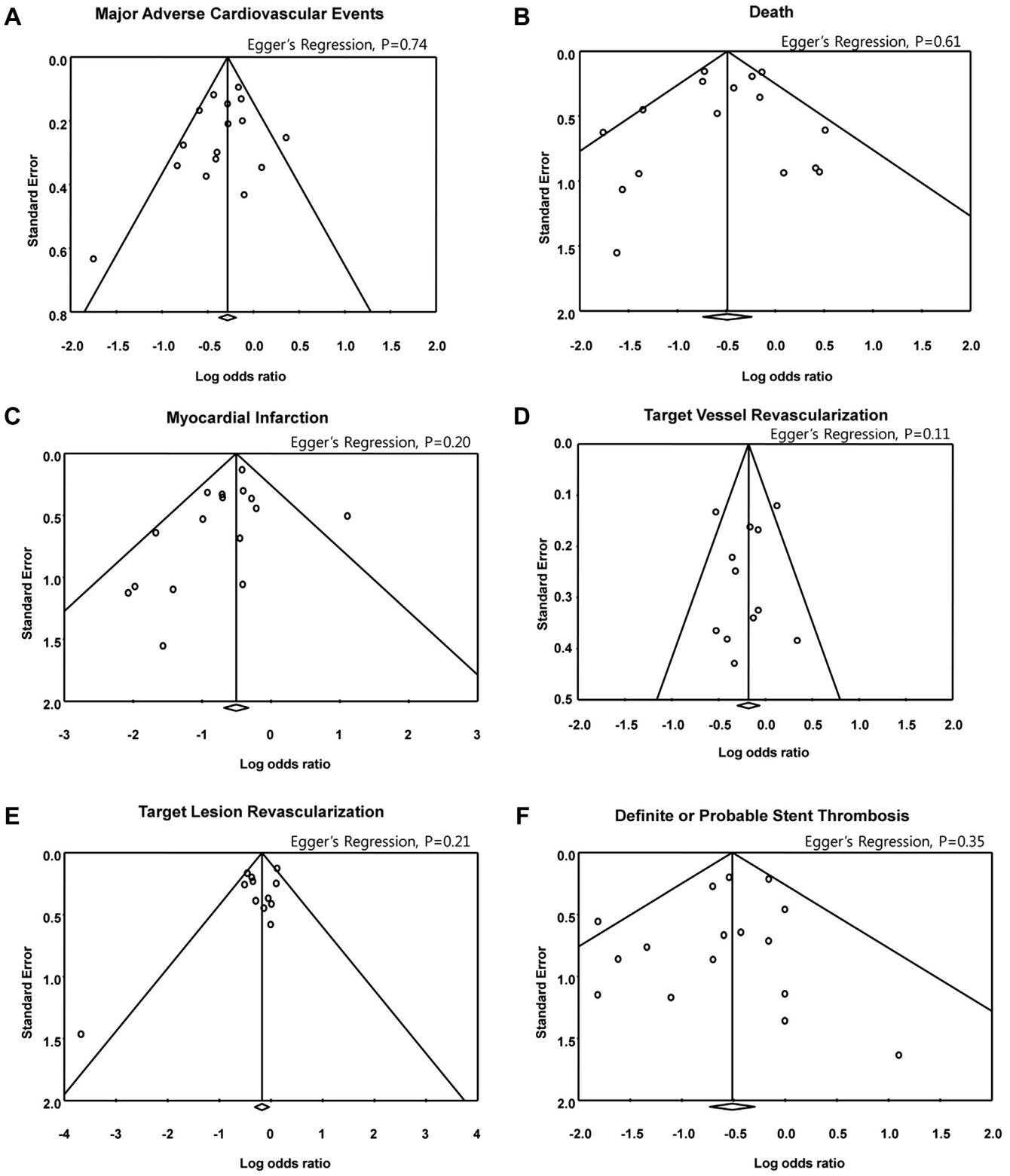


Figure 4. Funnel plot for MACEs *(A)*, death *(B)*, MI *(C)*, TVR *(D)*, TLR *(E)*, and ST *(F)* and Egger's linear regression analysis.

ST or MI could be an important contributing factor. DES is associated with delayed arterial healing and potential inflammation, which generates a propensity for stent-related thrombotic events, especially under suboptimal stent implantation including underexpansion, malapposition, inflow or outflow disease, dissection, and thrombus. ST events (and even some restenosis events) can cause death or MI rather than repeat revascularization. Therefore, earlier

detection of these factors may lead to the reduction of thrombotic complications and improved survival.[29]

The present results can be explained by an analysis of the procedural characteristics that showed that IVUS-guided PCI increased mean stent size and minimal lumen diameter by 0.33 and 0.34 mm, respectively, although longer stents and more stents were implanted in the IVUS-guided group. Although some investigators raised concerns about the increase in periprocedural MI associated with IVUS guidance, our analysis did not show any relation between IVUS guidance and periprocedural MI.[24]

This study has several limitations. First, despite the extensive literature search used in this study, only 3 randomized controlled studies were identified to be included in the meta-analysis. Second, some of the results of our meta-analysis had significant heterogeneities. Third, we were unable to create a database from individual patient data. Fourth, we cannot assess complications associated with IVUS evaluation, because complications were not reported in any of the 17 studies included in the present meta-analysis. However, the risk of periprocedural MI did not significantly differ between IVUS-guided and angiography-guided DES implantation (OR 1.01, $p = 0.65$). Finally, although a systematic literature search was performed, we may have missed publications.

Disclosures

Dr. Mintz is a consultant for Boston Scientific (Natick, Massachusetts), Volcano (San Diego, California), and InfraReDx (Burlington, Massachusetts), and his institution, the Cardiovascular Research Foundation (New York, New York), receives grant or fellowship support from these 3 companies. The other authors have no conflicts of interest to disclose.

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