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FOCUS ON CORONARY IMAGING AND PHYSIOLOGY

Clinical Outcomes Following Intravascular Imaging-Guided Versus Coronary Angiography–Guided Percutaneous Coronary Intervention With Stent Implantation

A Systematic Review and Bayesian Network Meta-Analysis of 31 Studies and 17,882 Patients

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ABSTRACT

OBJECTIVES The authors sought to explore the comparative clinical efficacy of different imaging modalities for guiding percutaneous coronary interventions (PCI).

BACKGROUND Coronary angiography (CA) is the standard imaging modality for intraprocedural guidance of PCI. Intracoronary imaging techniques, including intravascular ultrasound (IVUS) and optical coherence tomography (OCT), can overcome some limitations of CA.

METHODS Comprehensive hierarchical Bayesian network meta-analysis of randomized clinical trials and adjusted observational studies comparing clinical outcomes of PCI with stent implantation guided by CA, IVUS, or OCT.

RESULTS A total of 31 studies encompassing 17,882 patients were included. Compared with CA guidance, the risks of all-cause death (odds ratio [OR]: 0.74; 95% credible interval [CrI]: 0.58 to 0.98), myocardial infarction (OR: 0.72; 95% CrI: 0.52 to 0.93), target lesion revascularization (OR: 0.74, 95% CrI: 0.58 to 0.90) and stent thrombosis (OR: 0.42; 95% CrI: 0.20 to 0.72) were significantly reduced by IVUS guidance. PCI guidance using either IVUS or OCT was associated with a significant reduction of major adverse cardiovascular events (OR: 0.79; 95% CrI: 0.67 to 0.91 and OR: 0.68; 95% CrI: 0.49 to 0.97, respectively) and cardiovascular death (OR: 0.47; 95% CrI: 0.32 to 0.66 and OR: 0.31; 95% CrI: 0.13 to 0.66, respectively). No differences in terms of comparative clinical efficacy were found between IVUS and OCT for all the investigated outcomes. Pooled estimates were consistent across several sensitivity analyses. However, the treatment effect of IVUS on all-cause death was neutralized in the analysis restricted to randomized clinical trials (OR: 1.03; 95% CrI: 0.41 to 2.14).

CONCLUSIONS Compared with CA, the use of intravascular imaging techniques for PCI guidance reduces the risk of cardiovascular death and adverse events. (J Am Coll Cardiol Intv 2017;10:2488–98) © 2017 by the American College of Cardiology Foundation.

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Coronary angiography (CA) is the reference standard imaging modality for intraprocedural guidance of percutaneous coronary intervention (PCI), but its limitations are well known with respect to plaque characterization, assessment of vessel and lumen dimensions, evaluation of stent results, and intraobserver and interobserver variability (1). A suboptimal PCI increases the hazard for adverse events in both the early post-operative period and the long term.

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Intracoronary imaging, including intravascular ultrasound (IVUS) and optical coherence tomography (OCT), allows for detailed in vivo characterization of coronary lesions, anatomy, and stent results (2). By addressing the limitations of CA (3), it may be hypothesized that PCI guidance by means of IVUS or OCT is associated with improved clinical outcomes, but this assumption lacks a firm evidence base. A number of recent randomized controlled trials (RCTs) and observational registries have refueled the debate on the best invasive imaging modality for PCI guidance (4). Most of these studies focused on surrogate angiographic or composite endpoints and had limited statistical power to detect statistically significant differences at the clinical level. Also important, many studies have compared IVUS or OCT with CA, the historical reference standard, but few studies have compared OCT and IVUS directly.

In a multistrategy scenario such as the one described above, a network meta-analysis extends conventional pairwise meta-analyses by providing treatment-specific effect estimates alongside an informative ranking (5). In addition, indirect evidence from the network may provide useful information on the comparative effectiveness of treatments with a limited number of head-to-head comparisons. To date, no network meta-analysis has explored the comparative efficacy of PCI guided by different imaging modalities. To fill this gap, we sought to conduct a comprehensive hierarchical Bayesian network meta-analysis of studies exploring the outcomes of PCI procedures guided by CA, IVUS, or OCT.

METHODS

ELIGIBILITY CRITERIA AND LITERATURE SEARCH. We searched RCTs or observational studies comparing 2 or more invasive imaging modalities for guiding PCI with stent implantation. Studies of intravascular imaging to guide bailout stenting (i.e., stenting only in presence of flow-limiting dissections or significant residual stenosis after plain old balloon angioplasty) or "spot stenting" were excluded. To reduce the risk of bias arising from the inclusion of observational studies, we considered eligible only nonrandomized studies that used matching algorithms for statistical adjustment. Medline, EMBASE, and the Cochrane Library were screened using the combination of medical subject headings (MeSH) and text words for (["percutaneous coronary intervention" OR "PCI"] AND ["intravascular imaging" OR "intravascular ultrasound" OR "optical coherence tomography" OR "IVUS" OR "OCT" OR "optical frequency domain" OR "OFDI"]). We also explored major cardiology and congress websites for other relevant studies to be included. All searches were restricted to studies conducted in human subjects published from the date of databases' inception to March 6, 2017. There was no language restriction or use of additional filters. A cross-reference check of previously published reviews and/or meta-analyses on this topic was performed. The literature searches and all analyses were conducted following the PRISMA guidelines and the PRISMA statement for network meta-analyses (6,7).

OUTCOMES OF INTEREST. The primary endpoint of the meta-analysis was all-cause mortality. Secondary endpoints were the composite of major adverse cardiac events (MACE) based on the individual study definitions, cardiovascular death, myocardial infarction (MI), target lesion revascularization (TLR), and stent thrombosis (ST).

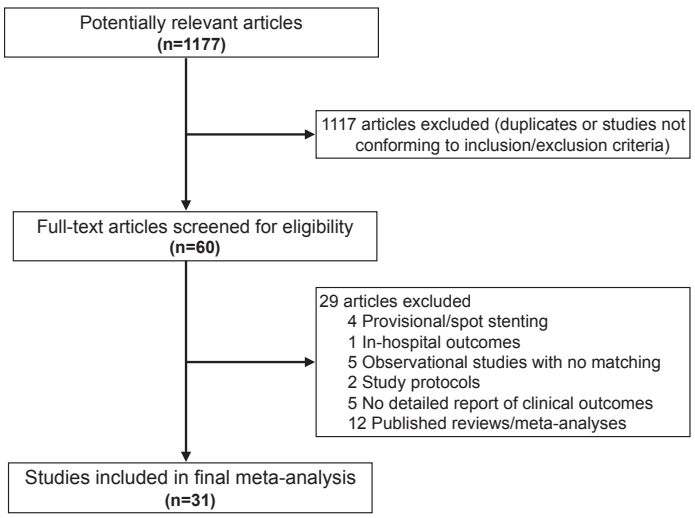
DATA EXTRACTION. Two investigators (S.R. and G.V.) independently determined study eligibility after carefully checking titles, abstracts, and full texts of studies identified by the literature search. Disagreements, if any, were resolved by consensus. Two investigators (G.F. and S.P.) extracted all data from the included studies and collected them into a dedicated electronic spreadsheet. A third author (S.B.) verified the congruity of extracted data against original source documents. Studies of OCT and optical frequency domain imaging were included as part of the same network node.

STATISTICAL ANALYSIS. A hierarchical Bayesian network meta-analysis was conducted to estimate the posterior mean effect (reported as odds ratio [OR] or mean difference, as appropriate) and 95% credible interval (CrI) for all outcomes of interest by using random effects consistency models. An estimated

ABBREVIATIONS AND ACRONYMS

CA = coronary angiography
CrI = credibility interval
CTO = chronic total occlusion
DES = drug-eluting stent(s)
IVUS = intravascular ultrasound
MACE = major adverse cardiac event(s)
MI = myocardial infarction
OCT = optical coherence tomography
OR = odds ratio
PCI = percutaneous coronary intervention
RCTs = randomized controlled trials
ST = stent thrombosis
TLR = target lesion revascularization

FIGURE 1 Flow Diagram of the Literature Search



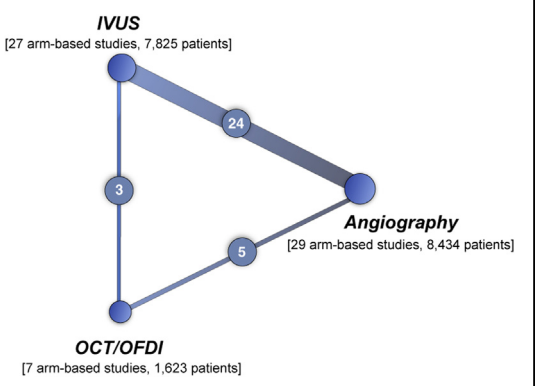
effect was considered significant when the upper or lower CrI did not include the unity. Models were computed with Markov chain Monte Carlo simulations, using 4 chains with overdispersed values and Gibbs sampling based on 100,000 iterations. A set of 50,000 tuning iterations and vague priors were used in all models. Convergence was checked using the Brooks-Gelman-Rubin diagnostic and by visual inspection of convergence plots. Pairwise OR and 95% CrI were summarized from the median of the posterior distribution. A relative effect estimate was considered significant if the 95% CrI did not cross the unity. The 3 investigated imaging strategies were ranked according to their comparative effectiveness. Inconsistency was evaluated by contrasting direct and indirect evidence of the network ("node split"). Heterogeneity was assessed by means of the I-square statistic (with an I-square value >50% being considered the result of severe heterogeneity). A random-effect meta-regression was performed to assess the impact of the varying length of follow-up on effect size measures across the included studies. All analyses were conducted with the R statistical software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) equipped with the "gemtc" package.

SENSITIVITY ANALYSES. Several sensitivity analyses were conducted to assess the consistency of the main results across studies with different design or baseline characteristics. First, because observational studies may carry the risk of residual bias despite statistical adjustment (i.e., due to unmeasured confounders), we down-weighted the information provided by these studies by applying a variance inflation ("power prior") to the likelihood. In weighted analyses, a weight of 0 completely excludes the study, whereas a value of 1 assigns full weight. As such, we selected a weighting factor of 0.7 for observational studies and 1 for RCTs. Additional sensitivity analyses, with the weighting factor for observational studies ranging from 0.6 to 0.8, were also performed. Moreover, we conducted separate analyses for RCTs and observational studies across all the investigated outcomes. Analyses were also restricted to studies in which at least 100 patients were enrolled in a treatment arm and to studies that did not adopt invasive intravascular imaging for complex anatomic settings (i.e., bifurcations and chronic total occlusions [CTOs]). Finally, we assessed the consistency of the results by restricting the network to studies that employed drug-eluting stents (DES) during PCI. The impact of second-generation DES use on the pooled estimates was also explored.

RESULTS

A flowchart summarizing the literature search flow is shown in Figure 1. After screening, 31 studies encompassing a total of 17,882 patients were deemed eligible and included in the final analysis (4,8-37). The characteristics of the network are shown in Figure 2. Briefly, the loops were fully closed within the network and the number of direct comparisons between CA and OCT (n = 5) and between OCT and IVUS (n = 3) was lower than the number of comparisons between CA and IVUS (n = 24).

FIGURE 2 Imaging Strategies Included in the Network



The width of connecting lines between different treatment nodes reflects the number of studies available for each comparison. The size of each circle reflects the number of studies considered in each treatment node. IVUS = intravascular ultrasound; OCT = optical coherence tomography; OFDI = optical frequency domain imaging.

The main characteristics of the studies included in the meta-analysis are shown in **Tables 1 and 2**. A total of 17 RCTs and 14 adjusted observational studies were included. Bare-metal stents were used in 10 older studies, whereas most of the contemporary studies used DES. Three studies included only patients undergoing PCI of a CTO, whereas 2 studies enrolled patients undergoing PCI at bifurcation sites. In 4 studies, intravascular imaging was used to guide PCI of the left main. The total number of studies for each specific outcome measure is reported in the Online Table S1. The length of follow-up between included studies varied from a minimum of 1 month to a maximum of 36 months. Definitions of intravascular imaging guidance and MACE across included studies are provided in the Online Table S2.

All models had adequate convergence. The results of the analysis regarding all-cause death are presented in **Figure 3**. Compared with CA, all-cause death was significantly reduced with IVUS use (OR: 0.74; 95% CrI: 0.58 to 0.98), whereas it trended toward a reduction with OCT (OR: 0.59; 95% CrI: 0.29 to 1.20). In rank probability analysis, CA was ranked as the worst strategy for PCI guidance.

Results for secondary clinical endpoints are shown in **Table 3**. PCI guidance using either IVUS or OCT was associated with a significant reduction in the odds of MACE (OR: 0.79; 95% CrI: 0.67 to 0.91 and OR: 0.68; 95% CrI: 0.49 to 0.97 for IVUS and OCT, respectively) and cardiovascular death (OR: 0.47; 95% CrI: 0.32 to 0.66 and OR: 0.31; 95% CrI: 0.13 to 0.66, respectively). The odds ratios for MI (OR: 0.72; 95% CrI: 0.52 to 0.93), TLR (OR: 0.74; 95% CrI: 0.58 to 0.90) and ST (OR: 0.42; 95% CrI: 0.20 to 0.72) were significantly reduced by IVUS compared with CA, whereas no significant differences emerged between OCT and CA, and between IVUS and OCT. Rank probability analyses for secondary outcomes are presented in **Figure 4**. CA was consistently rated as the worst strategy for all the investigated outcomes.

No significant relationship between varying length of follow-up and the effect size measures was identified in meta-regression analyses for all outcomes of interest (Online Table S3). The results of the network node-split analysis are shown in **Figure 5**. There was no evidence of inconsistency in the network for all the outcomes of interest (all Bayesian p values > 0.05). Heterogeneity across included studies is presented in Online Table S4. There was no evidence of significant heterogeneity for all the investigated outcomes.

SENSITIVITY ANALYSES. Sensitivity analyses, including weighted analyses that account for different study design, separate analyses for RCTs and observational studies, and analyses restricted to studies with >100 patients and noncomplex anatomic settings, are shown in Online Tables S5 to S9. The results of these sensitivity analyses were largely consistent with those of the main analysis.

TABLE 1 Characteristics of Studies Included in the Meta-Analysis

Study/First Author (Ref. #)	Year of Publication	Number of Patients	Study Design	Type of Stent	Follow-Up Duration (Months)
Angiography vs. IVUS					
RESIST (8)	1998	76/79	Randomized	BMS	6
CRUISE (9)	2000	229/270	Randomized	BMS	9
OPTICUS (10)	2001	275/273	Randomized	BMS	12
Gaster et al. (11)	2003	54/54	Randomized	BMS	30
TULIP (12)	2003	76/74	Randomized	BMS	6–12
DIPOL (13)	2007	80/83	Randomized	BMS	6
AVID (14)	2009	406/394	Randomized	BMS	12
HOME DES IVUS (15)	2010	105/105	Randomized	DES	18
Kim et al. (16)	2013	274/269	Randomized	DES	12
AVIO (17)	2013	142/142	Randomized	DES	24
CTO-IVUS (18)	2015	201/201	Randomized	DES	12
AIR-CTO (19)	2015	115/115	Randomized	DES	24
IVUS-XPL (20)	2015	700/700	Randomized	DES	12
Tan et al. (21)	2015	62/61	Randomized	DES	24
Roy et al. (22)	2008	884/884	Observational, PSM	DES	12
MAIN-COMPARE (23)	2009	201/201	Observational, PSM	BMS/DES	36
MATRIX (24)	2011	548/548	Observational, PSM	DES	24
Kim et al. (25)	2011	487/487	Observational, PSM	DES	36
Chen et al. (26)	2012	123/123	Observational, PSM	DES	12
Wakabayashi et al. (27)	2012	637/637	Observational, PSM	BMS/DES	12
EXCELLENT (28)	2013	463/463	Observational, PSM	DES	12
De la Torre Hernandez et al. (29)	2014	505/505	Observational, PSM	DES	36
Gao et al. (30)	2014	291/291	Observational, PSM	DES	12
Hong et al. (31)	2014	201/201	Observational, PSM	DES	24
Angiography vs. OCT					
DOCTORS (32)	2016	120/120	Randomized	BMS or DES	6
CLI-OPCI (33)	2012	335/335	Observational, Matched	BMS/DES	12
Sheth et al. (34)	2016	428/214	Observational, PSM	BMS/DES	12
Iannaccone et al. (35)	2016	270/270	Observational, PSM	NA	23
IVUS vs. OCT					
Kim et al. (36)	2016	114/114	Observational, PSM	DES	12
OPINION (37)	2016	405/412	Randomized	DES	12
Angiography vs. IVUS vs. OCT					
ILUMIEN III (4)	2016	146/146/158	Randomized	DES	1

BMS = bare-metal stent(s); DES = drug-eluting stent(s); IVUS = intravascular ultrasound; NA = not available; OCT = optical coherence tomography; PSM = propensity score matched.

TABLE 2 Clinical Characteristics of Patients Across Studies Included in the Meta-Analysis

Study/First Author (Ref. #)	Age (yrs)	DM (%)	ACS (%)	HTN (%)	Men (%)	LVEF (%)	LM (%)	LAD (%)	LCX (%)	RCA (%)
Angiography vs. IVUS										
RESIST (8)	56/57	11/11	0/0	34/30	93/86	53/51	NA	47/48	11/11	42/41
CRUISE (9)	61/60	18/23	NA	59/52	72/69	54/55	0/0	46/43	18/24	36/33
OPTICUS (10)	61.5/60.1	17/17	32/36	52/48	78/77	57.7/56.5	0/0	50/51	14/18	35/30
Gaster et al. (11)	57/57	11/4	0/0	24/20	100/100	69/65	NA	46/48	26/24	28/28
TULIP (12)	63/61	21/16	0/0	30/27	72/71	NA	0/0	38/39	21/10	41/51
DIPOL (13)	54/56	11/10	0/0	NA	73/71	48/52	0/0	46.3/41.0	23.8/26.5	30.0/32.5
AVID (14)	63/62	17/15	NA	45/46	68/73	55/53	0.5/0.8	37/40	18/15	32/35
HOME DES IVUS (15)	60.2/59.4	45/42	60/72	71/67	71/73	NA	4/3	54/56	15/11	24/29
Kim et al. (16)	64.3/62.8	29.9/31.6	48.5/46.8	65.8/61.3	54.7/65.8	54.0/55.3	0/0	57.5/50.0	18.4/20.7	24.1/29.3
AVIO (17)	63.6/63.9	26.8/23.9	26.1/26.9	66.9/70.4	76.8/82.4	55.9/55.3	NA	48.6/53.3	NA	NA
CTO-IVUS (18)	61.4/61.0	33.8/34.8	0/0	63.7/62.7	80.6/80.6	56.7/56.9	0/0	46.8/41.8	15.9/14.4	37.3/43.8
AIR-CTO (19)	66/67	27.0/29.6	24.4/28.7	70.4/74.8	80.0/88.7	56/55	2.6/0	36.5/44.3	14.8/20.9	46.1/34.8
IVUS-XPL (20)	64/64	37/36	49/49	63/65	69/69	62.4/62.9	NA	60/65	15/14	25/21
Tan et al. (21)	75.9/76.5	29.5/34.4	66.1/70.5	46.8/41.0	69.4/62.3	53.3/55.3	100/100	NA	NA	NA
Roy et al. (22)	65.6/66.0	34.4/35.9	60.9/62.1	81.6/81.8	70.0/69.3	48/47	2.3/2	33.0/32.9	23.2/24.7	34.3/34.4
MAIN-COMPARE (23)	64.3/65.3	31.3/34.8	61.7/60.7	51.7/57.7	72.6/69.2	61.4/61.5	100/100	NA	NA	64.3/37.8
MATRIX (24)	64.4/64.8	31.0/31.6	36.0/33.4	80.7/81.5	73.9/73.7	NA	3.3/3.3	50.9/51.1	38.3/37.8	28.3/28.5
Kim et al. (25)	61.8/62.0	33.3/31.8	56.5/53.2	58.3/60.0	66.9/66.5	58.8/60.1	3.9/3.5	82.5/83.0	12.9/12.9	4.5/4.1
Chen et al. (26)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wakabayashi et al. (27)	67.0/66.7	39.9/41.9	56.4/57.6	89.8/91.5	68.9/67.8	NA	3.8/4.3	24.9/25.7	23.2/23	31.7/32.5
EXCELLENT (28)	62.8/62.5	37.8/37.4	51.6/50.5	74.5/72.8	63.3/65.7	NA	0/0	23.5/53.6	23.5/19.7	27/26.8
De la Torre Hernandez et al. (29)	66.9/66.1	34.6/36.2	61/59	64.3/67.7	78.7/80	55.3/54.9	100/100	NA	NA	NA
Gao et al. (30)	NA	NA	9.6/8.9 (STEMI)	NA	NA	56.9/57.3	100/100	13.4/9.6	7.9/6.5	10.3/7.2
Hong et al. (31)	62/62	31/30	42/39	60/58	77/77	NA	1/1	34/44	25/16	NA
Angiography vs. OCT										
DOCTORS (32)	60.2/60.8	15.8/21.7	100/100	41.7/55.8	75.8/79.2	NA	0/0	50.0/46.7	23.3/21.7	26.7/31.6
CLI-OPCI (33)	67.0/64.8	29.0/24.2	62.1/59.1	73.8/75.5	75.5/78.2	52.8/53.8	2.4/6.6	53.4/60.9	NA	NA
Sheth et al. (34)	61.2/60.9	18.5/17.8	100/100	NA	82.7/78	NA	0/0	45.8/44.8	7.7/8.9	48.6/49.5
Iannaccone et al. (35)	61/60	18/17	100/100	59/56	79/79	NA	4.6/4.2	55/59	27/26	31/35
IVUS vs. OCT										
Kim et al. (36)	61.7/61.5	18.4/8.4	66.7/68.4	44.7/43.9	78.1/73.7	56.2/57.0	0/0	61.4/71.1	11.4/6.1	27.2/22.8
OPINION (37)	68/69	40.7/41.0	13.1/11.7	73.8/76.5	79.5/76.5	NA	0/0	48.6/54.1	21.5/20.4	28.9/24.8
Angiography vs. IVUS vs. OCT										
ILUMIEN III (4)	67/66/66	29/38/33	34/36/36	75/77/77	73/73/69	NA	0/0/0	57/47/51	21/29/27	22/25/22

Values refer to corresponding treatment arms from original studies.

ACS = acute coronary syndrome(s); DM = diabetes mellitus; HTN = hypertension; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; LVEF = left ventricular ejection fraction; NA = not available; RCA = right coronary artery; other abbreviations as in Table 1.

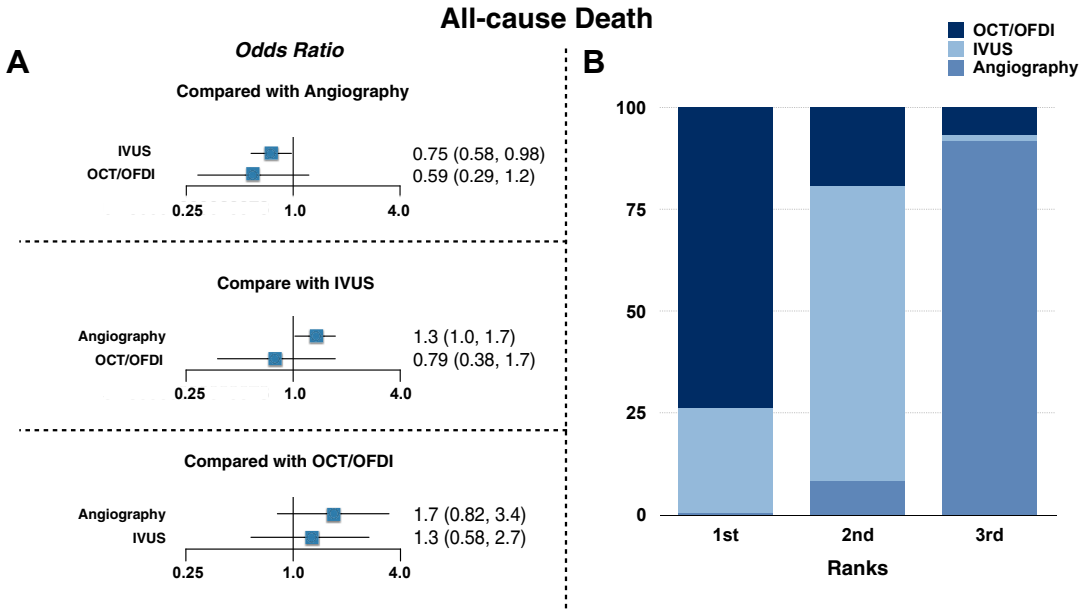
The results of separate analyses for RCTs and observational studies across all the investigated outcomes are presented in Online Tables S10 and S11 and graphically displayed in **Figure 6**. Pooled estimates were substantially consistent between RCTs and observational studies. However, the treatment effect of IVUS versus CA on all-cause death was neutralized when the analysis was restricted to randomized clinical trials (OR: 1.03; 95% CrI: 0.41 to 2.14). Similarly, observational studies were responsible for most of the treatment effect on all-cause death in the comparison between OCT and CA. Cardiovascular death was consistently reduced in analyses of IVUS versus CA in both RCTs and observational studies.

Sensitivity analyses assessing the impact of intravascular imaging guidance with DES are shown in Online Tables S12 and S13. The pooled estimates were largely consistent with the main analysis.

DISCUSSION

Over decades, the number of PCI procedures has increased significantly (38). Stent implantation has become part of standard PCI procedures as a strategy to prevent acute vessel recoil and counteract the potential negative consequences of endothelial barotrauma after balloon dilation (i.e., intimal dissection, increased thrombogenicity). Iteration of stent device technology has extended the use of PCI in more complex anatomic settings such as bifurcations, left main, and CTO interventions (39). In both simple and complex anatomic scenarios,

FIGURE 3 Network Summary Statistics for All-Cause Death



A shows forest plots for the comparisons among treatments included in the network. **B** shows the results of rank probability analysis. Abbreviations as in Figure 2.

optimization of stent implantation using invasive imaging has been advocated as a strategy to reduce the rate of adverse events following PCI (40).

Our updated Bayesian network meta-analysis, encompassing a total of 17,882 patients and recent results of the ILUMIEN III (Observational Study of Optical Coherence Tomography in Patients Undergoing Fractional Flow Reserve and Percutaneous Coronary Intervention Stage III) and OPINION (OPtical Frequency Domain Imaging Versus INtravascular Ultrasound in Percutaneous Coronary InterventiON) trials, showed that: 1) IVUS significantly reduces all-cause death compared with CA, but the treatment effect on mortality disappears when the analysis is restricted to RCTs; 2) PCI guidance using either IVUS or OCT was associated with a significant and consistent reduction of MACE and cardiovascular mortality; 3) benefits of IVUS use were also statistically significant for MI, ST, and repeat revascularization; 4) CA was rated as the worst strategy in rank probability analysis; and 5) no differences emerged in terms of comparative efficacy between IVUS and OCT. Importantly, the summary estimates of these treatment effects were consistent across multiple sensitivity analyses.

Limitations of CA-guided PCI, potentially resulting in unfavorable clinical outcomes, are well known (41).

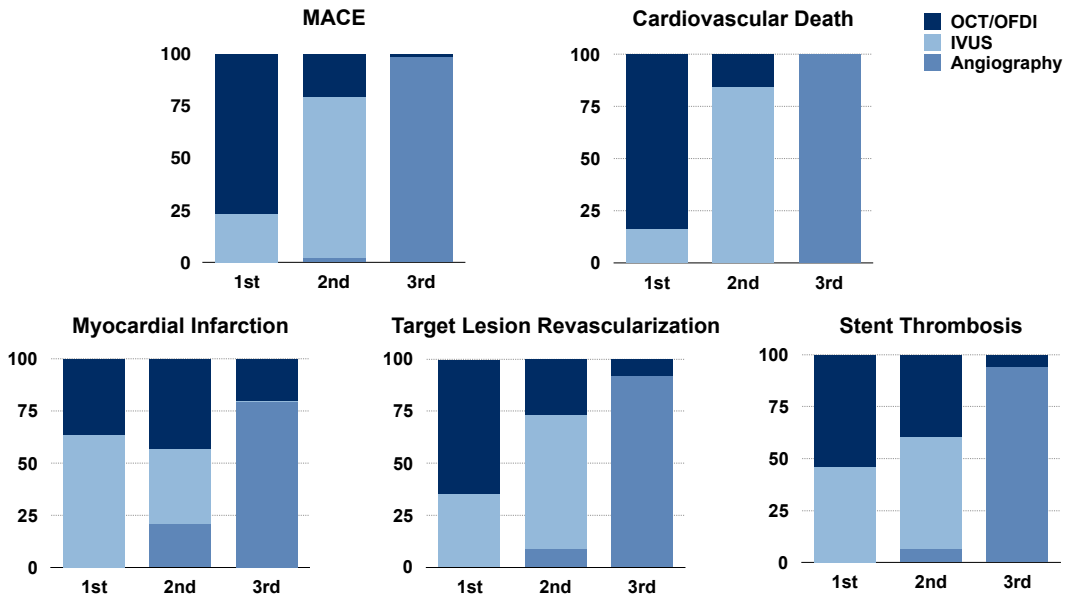
TABLE 3 Main Analysis for Secondary Endpoints

	Angiography	IVUS	OCT/OFDI
MACE			
Angiography	–	0.79 (0.67–0.91)	0.68 (0.49–0.97)
IVUS	1.30 (1.10–1.50)	–	0.87 (0.61–1.30)
OCT/OFDI	1.50 (1.00–2.00)	1.10 (0.78–1.60)	–
Cardiovascular death			
Angiography	–	0.47 (0.32–0.66)	0.31 (0.13–0.66)
IVUS	2.10 (1.50–3.10)	–	0.66 (0.27–1.50)
OCT/OFDI	3.20 (1.50–7.60)	1.50 (0.66–3.70)	–
Myocardial infarction			
Angiography	–	0.72 (0.52–0.93)	0.79 (0.44–1.40)
IVUS	1.40 (1.10–1.90)	–	1.10 (0.60–2.10)
OCT/OFDI	1.30 (0.72–2.30)	0.90 (0.47–1.70)	–
Target lesion revascularization			
Angiography	–	0.74 (0.58–0.90)	0.66 (0.35–1.20)
IVUS	1.40 (1.10–1.70)	–	0.88 (0.47–1.60)
OCT/OFDI	1.50 (0.83–2.90)	1.10 (0.61–2.10)	–
Stent thrombosis			
Angiography	–	0.42 (0.20–0.72)	0.39 (0.10–1.20)
IVUS	2.40 (1.40–5.10)	–	0.93 (0.24–3.40)
OCT/OFDI	2.60 (0.80–10.0)	1.10 (0.29–4.20)	–

Orange cells indicate a significant increased risk for the outcome of interest, whereas **blue cells** indicate a significant reduction in the risk of experiencing an adverse event.

MACE = major adverse cardiac event(s); other abbreviations as in Figure 1.

FIGURE 4 Treatment Rank Probabilities for Secondary Clinical Outcomes



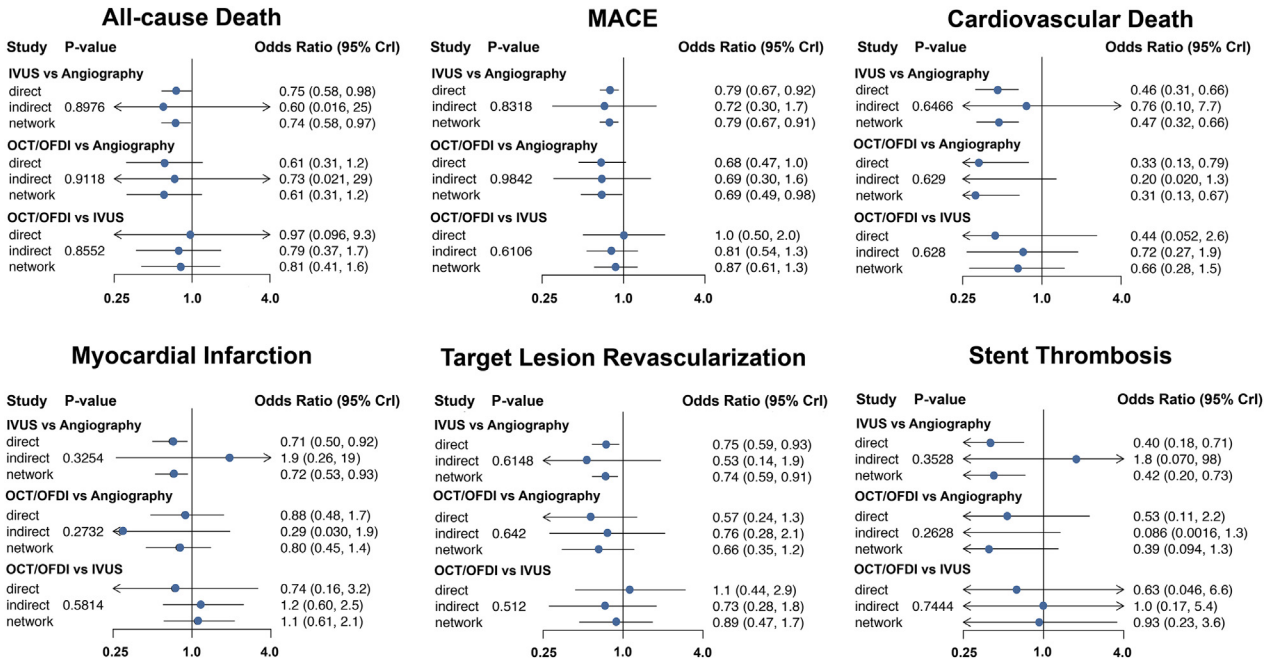
Secondary clinical outcomes include MACE, cardiovascular death, myocardial infarction, target lesion revascularization, and stent thrombosis. MACE = major adverse cardiac event(s); other abbreviations as in Figure 2.

Previously published meta-analyses have explored the impact of IVUS use as an invasive imaging modality for guiding PCI (42). Most of these studies differed in terms of inclusion criteria and design of included studies, but the principal findings were consistent with our results showing substantial benefits of IVUS use leading to a significant reduction in the risk of MACE and hard clinical endpoints such as death, cardiovascular death, MI, and ST. In our meta-analysis, all-cause death was the primary outcome of interest because its definition is unequivocal and consistent across all studies. Although IVUS was found to reduce all-cause death compared with CA, this result should be cautiously interpreted because it was driven by adjusted observational studies that may entail some residual confounding. Conversely, cardiovascular death was significantly and consistently reduced by IVUS in both RCTs and observational studies, whereas the results of the comparison between OCT and CA are more uncertain due to the smaller number of studies and large confidence intervals. This likely reflects a residual power issue because the estimate pointed toward a suggested benefit. Indeed, there were only 2 RCTs comparing OCT with angiography (DOCTORS [Does Optical Coherence Tomography Optimize Results of Stenting] and ILUMIEN III trials), and therefore, the total number of randomized patients to OCT-guided PCI in the published reports is currently limited.

Benefits in terms of cardiovascular mortality following intravascular imaging use are expected to accrue with reduced risks of MI, TLR, and ST. Interestingly, the magnitude of treatment effect in reducing cardiac mortality with intravascular imaging in our analysis was even larger than for these single endpoints. Because MI, TLR, and ST all have some degree of prognostic implication, a synergistic survival benefit can be hypothesized when its risk is simultaneously tempered. Moreover, by potentially reducing the burden of myocardial ischemia in the long term, improved PCI results could exert additional prognostic benefits by tempering the risk of secondary events associated with cardiac death but not directly related to PCI (i.e., reduced rates of cardiac arrhythmias or heart failure).

The current meta-analysis adds to previous findings in the published reports by comparing, in a comprehensive network of treatments, all different imaging modalities currently used in daily practice. In particular, the comparative efficacy of IVUS and OCT is a relevant aspect of our analysis because only a few studies have investigated the differential clinical impact of PCI guidance using these techniques in a head-to-head manner. Interestingly, despite intrinsic

FIGURE 5 Results of Network Node-Split

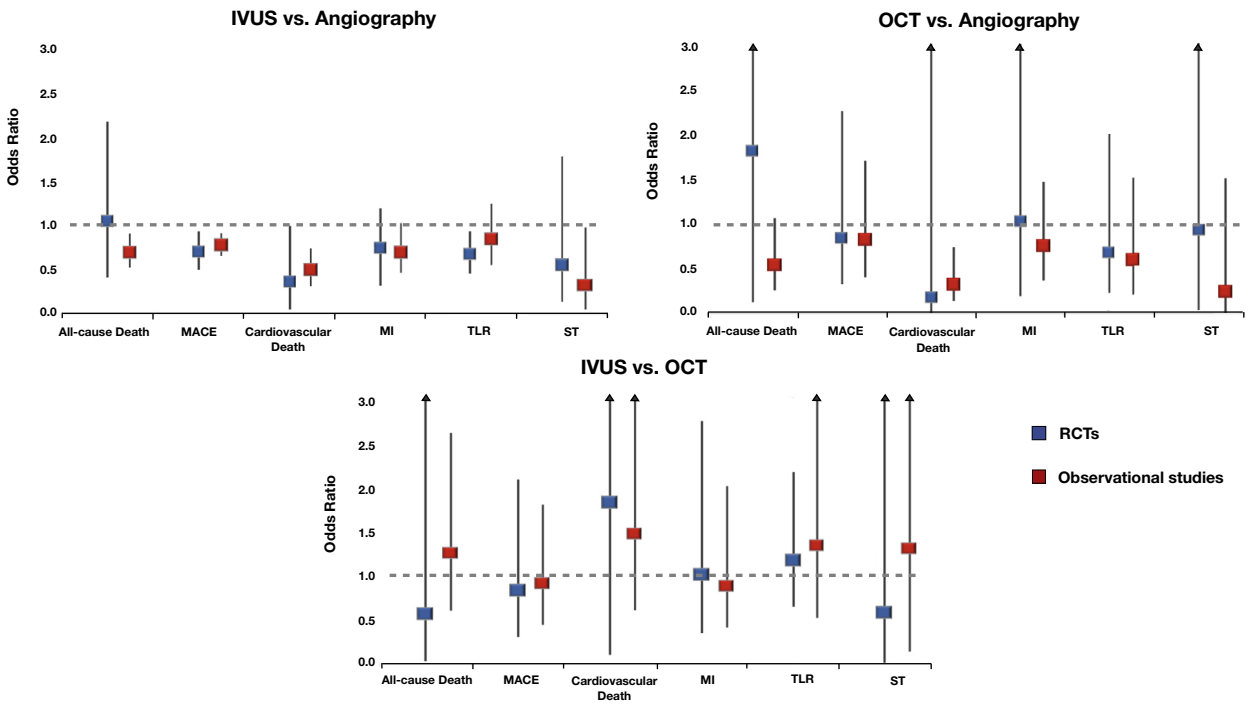


Node-split analyses for all-cause death, MACE, cardiovascular death, myocardial infarction, target lesion revascularization, and stent thrombosis. Abbreviations as in Figures 2 and 3.

technical differences between IVUS and OCT leading to specific profiles of potential advantages and limitations for each technique (3), similar clinical outcomes were identified for the 2 strategies, consistent with recent results from the ILUMIEN III and OPINION trials. Indeed, a tradeoff between spatial resolution and intimal characterization currently exists between the 2 techniques, with IVUS allowing for an easier visualization of the entire vessel structure, particularly when extensive circumferential calcification or attenuated plaques are not encountered, and OCT providing a more detailed intimal definition that confers greater sensitivity for detection of intimal dissections, stent malapposition, thrombus, and plaque protrusion. Previous studies have shown that such technical differences may have an impact on PCI results with the use of larger stents and increased post-stent vessel dimensions when IVUS is used (43), and reduced number of dissections left untreated or tissue prolapse with OCT (4). Being that post-stenting vessel dimensions are an important determinant of clinical outcomes, some concerns have been raised for PCI optimization using OCT due to potential underestimation of proper stent/vessel size. Our meta-analysis, specifically conducted in a large sample of PCI patients with more statistical power to detect differences even in low-frequency events, does not support that concept. Moreover, recent findings from the ILUMIEN III study showed that when a specific OCT implantation protocol (e.g., stent selection guided by measurements at the external elastic lamina in the proximal and distal reference segments) is used, minimum stent area achieved with OCT is noninferior to IVUS guidance. The large multicenter ILUMIEN IV trial has been planned to investigate differences in clinical outcomes between IVUS and OCT.

STUDY STRENGTHS AND LIMITATIONS. As noted in the preceding text, different aspects of this meta-analysis are novel and of potential clinical interest with respect to the existing published reports. Indeed, to the best of our knowledge, no meta-analysis has previously comprehensively explored the results of OCT studies for PCI guidance. Moreover, invasive and conventional imaging strategies for guiding PCI have never been evaluated and compared in the context of a network meta-analysis. Several advantages of this statistical approach may be relevant in this context. A network of treatments allows for the inclusion of studies that use different imaging modalities in their treatment arms and, by pooling direct and indirect evidence, can strengthen the amount of evidence for

FIGURE 6 Results of Stratified Analyses for RCTs and Observational Studies



Results of stratified analyses for randomized clinical trials (RCTs) and observational studies across all the investigated outcomes. Abbreviations as in Figure 2.

comparisons that have been infrequently performed in the literature (i.e., IVUS vs. OCT).

On the other hand, a number of limitations of our analysis should also be acknowledged. First, the comparative efficacy among different imaging techniques is currently limited to selected lesions that can be favorably evaluated using intravascular imaging. Second, the number of studies in the network was unbalanced between the IVUS and OCT nodes, and only 2 RCTs compared IVUS and OCT directly (namely, the OPINION and ILUMIEN III trials) leading to wide CrIs, particularly when the analyses were restricted to RCTs. Third, the definition of MACE varied substantially among included studies. Fourth, the inclusion of observational studies may have potentially biased our pooled estimates due to residual confounding that can be present even after statistical adjustment. However, we sought to extensively address the risk of potential bias by avoiding the inclusion of unadjusted cohorts and down-weighting/excluding observational studies in multiple sensitivity analyses. Finally, we did not have access to individual patient data, and therefore, our findings should be interpreted cautiously in view of the inability to perform specific types of analysis with study-level data. For example, although meta-regressions suggested no significant relationship between time of follow-up and effect size in our meta-analysis, an increased effect size with longer time of follow-up was observed in some of the trials and registries included. Patient-level data would be necessary to fully explore this issue by plotting pooled Kaplan-Meier curves and performing landmark analyses.

CONCLUSIONS

Compared with standard CA, the use of intravascular imaging techniques during PCI reduces the risk of cardiovascular death and major adverse cardiovascular events. No differences in terms of comparative clinical efficacy were found between IVUS and OCT for all the investigated outcomes.

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PERSPECTIVES

WHAT IS KNOWN? CA has inherent limitations with respect to the assessment of proper vessel dimensions and evaluation of procedural results. Intracoronary imaging, including IVUS and OCT, can overcome some drawbacks of CA, allowing for detailed in vivo characterization of coronary lesions, anatomy, and stent results.

WHAT IS NEW? This network meta-analysis, encompassing a total of 17,882 patients and recent results from the ILUMIEN III and OPINION trials, identified a significant reduction in the risk of major adverse cardiac events and cardiovascular death with IVUS and OCT guidance during PCI. No differences with regard to the comparative efficacy of IVUS and OCT emerged for all investigated outcomes.

WHAT IS NEXT? Further studies are needed to confirm the clinical equipoise between IVUS and OCT when used as imaging modalities for PCI guidance. Potential advantages following future or current iterations of intravascular imaging technology (i.e., better spatial resolution for IVUS and OCT) and the combined use of imaging techniques alongside the functional identification of lesions associated with ischemia should be investigated.

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KEY WORDS clinical outcomes, coronary angiography, intravascular ultrasound, optical coherence tomography, percutaneous coronary intervention

APPENDIX For supplemental tables, please see the online version of this paper.