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ORIGINAL RESEARCH

Intravascular Imaging–Guided Versus Angiography-Guided Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis of Randomized Trials

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BACKGROUND: Despite the initial evidence supporting the utility of intravascular imaging to guide percutaneous coronary intervention (PCI), adoption remains low. Recent new trial data have become available. An updated study-level meta-analysis comparing intravascular imaging to angiography to guide PCI was performed. This study aimed to evaluate the clinical outcomes of intravascular imaging–guided PCI compared with angiography-guided PCI.

METHODS AND RESULTS: A random-effects meta-analysis was performed on the basis of the intention-to-treat principle. The primary outcomes were major adverse cardiac events, cardiac death, and all-cause death. Mixed-effects meta-regression was performed to investigate the impact of complex PCI on the primary outcomes. A total of 16 trials with 7814 patients were included. The weighted mean follow-up duration was 28.8 months. Intravascular imaging led to a lower risk of major adverse cardiac events (relative risk [RR], 0.67 [95% CI, 0.55–0.82]; $P<0.001$), cardiac death (RR, 0.49 [95% CI, 0.34–0.71]; $P<0.001$), stent thrombosis (RR, 0.63 [95% CI, 0.40–0.99]; $P=0.046$), target-lesion revascularization (RR, 0.67 [95% CI, 0.49–0.91]; $P=0.01$), and target-vessel revascularization (RR, 0.60 [95% CI, 0.45–0.80]; $P<0.001$). In complex lesion subsets, the point estimate for imaging-guided PCI compared with angiography-guided PCI for all-cause death was a RR of 0.75 (95% CI, 0.55–1.02; $P=0.07$).

CONCLUSIONS: In patients undergoing PCI, intravascular imaging is associated with reductions in major adverse cardiac events, cardiac death, stent thrombosis, target-lesion revascularization, and target-vessel revascularization. The magnitude of benefit is large and consistent across all included studies. There may also be benefits in all-cause death, particularly in complex lesion subsets. These results support the use of intravascular imaging as standard of care and updates of clinical guidelines.

Key Words: intravascular ultrasound ■ meta-analysis ■ optical coherence tomography ■ percutaneous coronary intervention

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are adjunctive tools for the guidance and optimization of percutaneous coronary intervention (PCI). These intravascular imaging modalities allow for assessment of plaque characteristics and accurate vessel sizing during PCI, thereby leading to the implantation of larger stents with increased minimal stent areas, preventing major malapposition,

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CLINICAL PERSPECTIVE

What Is New?

- In this contemporary updated meta-analysis of all randomized clinical trials, intravascular imaging–guided percutaneous coronary intervention (PCI) compared with angiography-guided PCI conferred a 33% reduction in major adverse cardiac events, 51% reduction in cardiac death, 37% reduction in stent thrombosis, 33% reduction in target-lesion revascularization, and 40% reduction in target-vessel revascularization.
- In complex lesion subsets, the point estimate for imaging-guided PCI compared with angiography-guided PCI for all-cause death was a relative risk of 0.75 (95% CI, 0.55–1.02; *P*=0.07).

What Are the Clinical Implications?

- Intravascular imaging guidance significantly improves clinical outcomes following PCI, and intravascular imaging should be considered for all PCIs, especially for complex lesion subsets.
- Currently ongoing and future clinical trials on intravascular imaging–guided PCI may add further evidence in terms of long-term outcomes and reductions in all-cause death and could lead to strengthening of clinical guideline recommendations.

Nonstandard Abbreviations and Acronyms

ILUMIEN IV	Optical Coherence Tomography (OCT) Guided Coronary Stent Implantation Compared to Angiography: A Multicenter Randomized Trial in PCI
IMPROVE	Impact on Revascularization Outcomes of Intravascular Ultrasound-Guided Treatment of Complex Lesions and Economic Impact Trial
MACEs	major adverse cardiac events
OCTOBER	European Trial on Optical Coherence Tomography Optimized Bifurcation Event Reduction
OPTIMAL	Optimization of Left Main PCI With Intravascular Ultrasound Trial
RENOVATE-COMPLEX-PCI	Randomized Controlled Trial of Intravascular Imaging Guided Versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention
TLR	target-lesion revascularization
TVR	target-vessel revascularization
ULTIMATE	Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions

identifying optimal landing zones for stents and allowing for correction of significant edge dissection.[1] These factors have translated into improved clinical outcomes in randomized controlled trials (RCTs), predominantly by reducing major adverse cardiac events (MACEs), target-vessel failure, and target-lesion revascularization (TLR).[2–5] European guidelines currently recommend IVUS as a class IIa (level of evidence B) recommendation in selected patients to optimize stent implantation and the treatment of unprotected left main lesions.[6] American guidelines similarly provide a class IIa (level of evidence B) recommendation that IVUS can be useful for procedural guidance, particularly in cases of left main or complex coronary stenting, and that OCT is a reasonable alternative to IVUS except in ostial left main disease.[7]

Despite this, adoption of intravascular imaging to guide PCI remains low.[8–10] This may in part reflect skepticism regarding the benefit of intravascular imaging on harder clinical end points such as death, and in part be a reflection of the modest endorsement from guidelines.[11] Other potential reasons for low adoption of intravascular imaging include lack of education and training for operators; perceived additional procedural time; additional procedural costs; and, depending on the specific health care systems, lack of linkage to reimbursement and perceived low reimbursement.

The majority of RCTs comparing intravascular imaging-guided PCI to angiography-guided PCI have a relatively small sample size and are therefore underpowered to detect differences in clinically important but low-frequency events such as death. Prior meta-analyses have focused on either IVUS or OCT separately compared with angiography or have included observational studies with their attendant limitations when comparing therapeutic strategies[1,11–15] or not included the most recently published RCTs in their analyses.[16–18] There have been additional recent RCT data, with the publication of 1 large new trial and additional follow-up from previously published trials.[2,4,5] We therefore sought to perform an updated systematic review and study-level meta-analysis to incorporate the totality of randomized clinical trials, with a focus on complex lesion subsets.

METHODS

The authors declare that all data used for the analyses included in this study are available within the article and the supplemental files. Any additional data not presented in this manuscript is available from the corresponding author upon reasonable request. The analysis was registered with the international prospective register of systematic reviews (PROSPERO) (CRD42023409668) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance.[19] Institutional review board approval and informed patient consent for study participation were not required, as this study is a systematic review and meta-analysis of previously published publicly available data in indexed databases.

Search Strategy

We performed a systematic search of the MEDLINE, Embase, and Cochrane databases from inception through March 2023 for RCTs assessing outcomes after IVUS or OCT-guided PCI compared with angiography-guided PCI. We also manually searched the bibliographies of previous meta-analyses, reviews, and selected studies to identify additional eligible trials, and reviewed conference abstracts from Transcatheter Cardiovascular Therapeutics, EuroPCR, American College of Cardiology, European Society of Cardiology, and American Heart Association meetings. The searches were performed by 2 independent investigators (J.S. and A.M.). Further full-text review was conducted by 3 independent investigators (J.S., A.M., and Y.J.) for the final assessment and inclusion of the studies that satisfy the inclusion and exclusion criteria. Any disputes or concerns were resolved by consensus and discussion with the senior author (Y.A.). Our search strings and the detailed search strategy with commands are provided in Table S1.

Inclusion Criteria, Data Extraction, and Risk-of-Bias Assessment

We included only RCTs comparing intravascular imaging–guided PCI versus angiography-guided PCI for this meta-analysis. We included trials that compared IVUS-guided or OCT-guided PCI separately or in combination, with angiography alone as the reference standard, and reported at least 1 of the main outcomes as detailed below. We did not exclude any trials on the basis of sample size or duration of follow-up. We excluded trials involving implantation of bioresorbable stents or bare metal stents. Observational studies were also not included in the present analysis. We did not include studies comparing only IVUS-guided PCI with OCT-guided PCI.

Two investigators (J.S. and A.M.) independently extracted the clinical outcomes data and resolved any conflicts in consultation with a third independent investigator (Y.A.). The data on baseline characteristics of study participants; study characteristics; and study outcomes, including crude estimates, risk estimates, sample size, and follow-up were extracted directly from the published articles, supplemental files, and subsequent publications, including post hoc analyses, patient-level meta-analyses, and subgroup analyses. The end points at the maximum available follow-up period were extracted, adhering to the intention-to-treat principle if available for all included trials. The principal investigators of each trial were contacted to provide additional relevant data not reported in the publications.

Risk of bias was evaluated by 2 independent investigators (J.S. and A.M.) using the Cochrane Risk of Bias Tool for the following domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective outcome reporting; and (7) other bias. The potential source of bias in each domain was judged high or low on the basis of the study characteristics as outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[20] Certainty of evidence was assessed

with the Grading of Recommendations, Assessment, Development, and Evaluations system.[21]

Outcomes

The prespecified main outcomes of interest were MACEs, cardiac death, and all-cause death. Most of the included trials defined MACE as a composite of cardiac death, myocardial infarction (MI), and repeat revascularization. Other clinical outcomes of interest were MI, target-vessel revascularization (TVR), TLR, target-vessel MI, periprocedural MI, stent thrombosis, and target-vessel failure. The outcomes were defined as per the individual study definitions of each outcome and are summarized in Table S2. Composite outcomes were assessed only if reported by the individual trials (ie, composite rates were not obtained by summing of individual components).

Statistical Analysis

Outcomes were assessed on an intention-to-treat basis. Random-effects meta-analyses were performed using the restricted maximum likelihood estimator. Outcomes were assessed as relative risks (RRs) and absolute risk reductions at the last follow-up available for each constituent trial. The number needed to treat to prevent 1 event was calculated for each outcome as the reciprocal of the absolute risk reductions.[22] The I^2 statistic was used to assess heterogeneity.[22] However, as the I^2 statistic measures the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error, it may be considered to be an indirect measure of heterogeneity.[23] To directly quantify the presence of interstudy heterogeneity, we also performed Cochrane's Q test, and provide Q statistics calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies. Sensitivity analyses were performed with a fixed-effect model, and a jackknife sensitivity analysis was also performed excluding each trial in turn for the main outcomes. We also performed sensitivity analyses using the Fisher exact test for all main outcomes. Publication bias was assessed with funnel plots.

We performed prespecified subgroup analyses of patients undergoing PCI of a complex lesion. The complex lesion subgroup was defined as any of the following: (1) unprotected left main PCI; (2) bifurcation PCI; (3) chronic total occlusion PCI; (4) PCI involving long lesions (>28 mm); (4) multivessel PCI involving at least 2 major epicardial coronary arteries being treated at the same time; (5) PCI involving the use of multiple stents (≥3); (6) PCI of in-stent restenosis; or (7) PCI of a severely calcified stenosis or ostial stenosis of a major epicardial coronary artery. This definition was primarily based on that used in the RENOVATE-COMPLEX-PCI (Randomized Controlled Trial of Intravascular Imaging Guided Versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention) trial except for stent length, as most other trials defined a long stenosis as >28 mm in length.[4] An additional, stricter definition complex PCI was also used as a sensitivity analysis including left main lesions, chronic total occlusions, and the complex PCI subgroup from the ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions) trial (multivessel disease, bifurcation with 2 stents implanted, moderate or greater calcification, chronic total occlusion, >3 stents implanted, and total stent length >90 mm).

We also performed subgroup analyses based on the type of imaging modality used (IVUS or OCT), type of clinical presentation (acute coronary syndrome versus stable coronary artery disease) and follow-up duration of RCTs (short-term follow-up, <1 year; intermediate follow-up, at least 1 year but <3 years; long-term follow-up, at least 3 years). Interactions between subgroups were assessed with meta-regression using a mixed-effects model,[24] with the subgroup characteristic as a moderator and the individual trial as a random effect.[25] Mean values are expressed as mean±SD unless otherwise stated. Significance testing was performed at the 2-tailed 5% significance level. The statistical programming environment R with the *metafor* package was used for all statistical analyses (R Foundation for Statistical Computing, Vienna, Austria).[24,26]

RESULTS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram depicts the process of study selection (Figure S1). A total of 16 RCTs (7814 participants [imaging group, 4307; angiography group, 3507]; mean age, 64.3±2.4 years; men, 73.7±2.6%) were included.[2,4,5,27–39] The weighted mean follow-up duration was 28.8 months (range, 6 months to 5 years). Among the study population, 6026 participants underwent PCI of complex lesion subsets. Among the included trials, 9 trials exclusively used IVUS, 4 trials exclusively used OCT, and 3 trials used both IVUS and OCT for imaging-guided PCI compared with angiography-alone–guided PCI. The baseline characteristics of the study population of individual studies are summarized in Table 1. The procedural characteristics of each trial are reported separately in Table S3. The study inclusion and exclusion criteria are listed in Table S4. The risk-of-bias assessment is summarized in Table S5. All included RCTs had a low risk of bias, and hence, the overall body of evidence was judged to have a low risk of bias. Direct assessment

Table 1. Baseline Characteristics of Included Trials

Trial	Year	Design	Region	Recruitment period	Follow-up	Arms	N	Age, y	Male	Hypertension	Dyslipidemia, n (%)	Diabetes, n (%)	Current smoker, n (%)	CHF	LVEF, %	Prior MI, n (%)	Prior PCI, n (%)	Prior CABG, n (%)	Stable angina, n (%)	UA	STEMI/ Acute MI, n (%)	UA/ NSTEMI, n (%)
HOME DES IVUS[31]	2009	Prospective, single-center RCT	Czech Republic	Jan 2004–Dec 2005	18 mo	Angiography	105	60.2±11	75 (71)	75 (71)	69 (66)	47 (45)	37 (35)			34 (32)	15 (14)	11 (10)	42 (40)		22 (21)	41 (39)
						IVUS	105	59.4±13	77 (73)	70 (67)	66 (63)	44 (42)	42 (40)			39 (37)	18 (17)	15 (14)	40 (38)		31 (29)	45 (43)
AVIO[30]	2012	Multicenter, open-label, investigator-driven RCT	International	May 2008–Jul 2011	2 y	Angiography	142	63.6±11.0	109 (77)	95 (66.9)	109 (76.8)	38 (26.8)	44 (31.0)		55.9±8.6					37 (26.1)		
						IVUS	142	63.9±10.1	117 (82)	100 (70.4)	100 (70.4)	34 (23.9)	49 (34.5)		55.3±8.5					42 (29.6)		
RESET substudy[34]	2013	Prospective, open-label, multicenter RCT	South Korea	Apr 2009–Dec 2010	1 y	Angiography	269	64.5±8.6	130 (52.8)	156 (63.4)	144 (58.5)	77 (31.3)	38 (15.4)		53.9±25.1	8 (2.9)			133 (54.1)	92 (37.4)	21 (8.5)	
						IVUS	274	62.8±9.2	197 (66.3)	187 (63.0)	190 (64.0)	90 (30.3)	67 (22.6)		55.2±23.9	3 (1.1)			151 (50.8)	116 (39.1)	30 (10.1)	
OCTACS[28]	2014	Prospective, single-center RCT	Denmark	Aug 2011–May 2013	6 mo	Angiography	45	62.6±11.0	34 (68.0)	28 (56.0)		5 (10.0)	18 (36.0)			0 (0.0)	2 (4.0)	0 (0.0)				
						OCT	40	61.8±9.4	36 (72.0)	28 (56.0)		8 (16.0)	23 (46.0)			2 (4.0)	3 (6.0)	0 (0.0)				
Kim et al[35]	2015	Prospective, single-center, open-label RCT	South Korea	Dec 2011–VDec 2012	1 y	Angiography	59	61.6 (9.7)	37 (72.5)	25 (49.0)	37 (72.5)	16 (31.4)	15 (29.4)		63.6 (8.6)	8 (2.0)			31 (60.8)		20 (39.2)	
						OCT	58	58.8 (10.8)	39 (78.0)	27 (54.0)	33 (66.0)	16 (32.0)	16 (32.0)		64.2 (7.4)	3 (6.0)			31 (62.0)		19 (38.0)	
CTO-IVUS[33]	2015	Prospective, multicenter RCT	South Korea	Mar 2012–VAug 2013	1 y	Angiography	201	61.4±10.1	162 (80.6)	128 (63.7)		68 (33.8)	69 (34.3)	10 (5.0)	56.7±11.4	16 (8.0)	32 (15.9)	5 (2.5)				
						IVUS	201	61.0±11.1	162 (80.6)	126 (62.7)		70 (34.8)	71 (35.3)	12 (6.0)	56.9±13.1	16 (8.0)	31 (15.4)	3 (1.5)				
Tan et al[37]	2015	Single-center, open-label RCT	China	Oct 2009–Sep 2012	2 y	Angiography	62	75.85±3.49	43 (70)	29 (46.8)		18 (29.5)	29 (46.8)		53.33±7.14	13 (21.0)			21 (34)	41 (66)		
						IVUS	61	76.54±4.95	38 (62)	25 (41.0)		21 (34.4)	27 (44.3)		55.32±5.02	10 (16.4)			18 (30)	43 (71)		
AIR-CTO[38]	2015	Multicenter RCT	China	Oct 2010–Nov 2011	2 y	Angiography	115	66±11	92 (80.0)	81 (70.4)	32 (27.8)	31 (27.0)	45 (39.1)			35 (30.4)	24 (20.9)	5 (4.3)	87 (75.7)	11 (9.6)	17 (14.8)	
						IVUS	115	67±10	102 (88.7)	86 (74.8)	25 (21.9)	34 (29.6)	45 (39.1)			24 (20.9)	23 (20.0)	3 (2.6)	82 (71.3)	10 (8.7)	23 (20.0)	
DOCTORS[36]	2016	Prospective, multicenter RCT	France	Sep 2013–Dec 2015	6 mo	Angiography	120	60.2±11.3	91 (75.8)	50 (41.7)	56 (46.7)	19 (15.8)	51 (42.5)							9 (7.5)		
						OCT	120	60.8±11.5	95 (79.2)	67 (55.8)	59 (49.2)	26 (21.7)	47 (39.2)							10 (8.3)		
ROBUST substudy[32]	2017	Multicenter, open-label RCT	Czech Republic	Feb 2011–Oct 2012	9 mo	Angiography	96	59 (47–72)	84 (87)	50 (52)		25 (26)	57 (59)			6 (6)	3 (4)	0				
						OCT	105	57 (46–70)	87 (83)	53 (50)		18 (17)	67 (64)			1 (1)	4 (4)	0				
Liu et al[39]	2019	Open-label, single-blind RCT	China	Dec 2010–Dec 2015	1 y	Angiography	169	64.9±11.2	108 (63.9)	122 (72.2)	64 (37.9)	52 (30.8)	60 (35.5)	33 (19.2)	58.4±10.5	24 (14.2)	28 (16.6)	2 (1.2)	18 (10.7)	126 (74.6)	21 (12.4)	
						IVUS	167	65.3±10.6	106 (63.5)	116 (69.5)	63 (37.7)	56 (33.5)	62 (37.1)	31 (18.6)	55.6±11.7	29 (17.4)	33 (19.8)	2 (1.2)	20 (12.0)	127 (76.0)	17 (10.2)	

(*Continues*)

Table 1. Continued

Trial	Year	Design	Region	Recruitment period	Follow-up	Arms	N	Age, y	Male	Hypertension	Dyslipidemia, n (%)	Diabetes, n (%)	Current smoker, n (%)	CHF	LVEF, %	Prior MI, n (%)	Prior PCI, n (%)	Prior CABG, n (%)	Stable angina, n (%)	UA	STEMI/ Acute MI, n (%)	UA/ NSTEMI, n (%)
IVUS-XPL[5]	2020	Investigator-initiated, multicenter RCT	South Korea	Oct 2010–Jul 2014	5 y	Angiography	700	63±9	409 (69)	373 (63)	458 (65)	223 (38)	134 (23)		62.3±10.2	27 (5)	60 (10)	16 (3)	307 (52)	189 (32)	98 (17)	
						IVUS	700	63±9	408 (69)	382 (65)	471 (67)	189 (32)	155 (22)		62.8±9.8	30 (5)	66 (11)	16 (3)	291 (49)	211 (36)	87 (15)	
ULTIMATE[2]	2021	Prospective, multicenter, investigator-initiated RCT	China	Aug 2014–Oct 2020	3 y	Angiography	709	65.9±9.8	530 (73.2)	521 (72.0)	400 (55.2)	226 (31.2)									567 (78.3)	
						IVUS	714	65.2±10.9	535 (73.9)	512 (70.7)	389 (53.7)	217 (30.0)									569 (78.6)	
ILUMIEN III: OPTIMIZE PCI[27]	2021	Prospective, 3-arm, single-blind, multicenter RCT	29 International centers	May 2015–VApr 2016	1 y	Angiography	142	67 (56–75)	104 (73)	107 (75)	109 (77)	40 (28)	33 (23)			32 (22)	15 (10)	8 (5)	50 (35)		51 (36)	
						IVUS	136	66 (61–73)	101 (74)	106 (78)	102 (75)	49 (36)	18 (13)			29 (20)	8 (5)	11 (8)	48 (35)		49 (36)	
						OCT	153	66 (59–72)	106 (69)	119 (78)	112 (73)	50 (33)	26 (17)			35 (22)	11 (7)	3 (2)	52 (34)		50 (33)	
iSIGHT[29]	2021	Prospective, single-center, active-controlled, noninferiority RCT	Brazil	Jan 2015–Dec 2016	1 y	Angiography	49	58.59±10.2	38 (77.5)	39 (79.6)	28 (57.2)	22 (44.9)	14 (28.6)			17 (34.7)	14 (28.6)		21 (42.9)	16 (32.6)	12 (24.5)	
						IVUS	50	59.32±10.37	36 (72.0)	42 (84)	30 (60)	20 (40)	14 (28)			17 (34.0)	13 (26.0)		18 (36)	22 (44)	10 (20.0)	
						OCT	51	59.92±8.92	31 (60.8)	46 (90.2)	36 (70.6)	17 (33.3)	17 (33.3)			15 (29.4)	12 (23.5)		22 (43.1)	20 (39.2)	9 (17.7)	
RENOVATE-COMPLEX-PCI[4]	2023	Prospective, multicenter, investigator-initiated, open-label, RCT	South Korea	2020–2021	2.1 y	Angiography	547	66.0±10.0	431 (78.8)	323 (59.0)	280 (51.2)	246 (45)	95 (17.4)		59.3±11.0	42 (7.7)	127 (23.2)		275 (50.3)	173 (31.6)	111 (20)	87 (15.9)
						IVUS/OCTI	1092	65.3±10.3	869 (79.6)	682 (62.5)	560 (51.3)	422 (39)	212 (19.4)		58.4±11.9	75 (6.9)	268 (24.5)		532 (48.7)	361 (33.1)	227 (21)	171 (15.7)

Data are presented as mean ± SD and proportions as (%). AIR-CTO indicates angiographic and clinical comparisons of intravascular ultrasound- versus angiography-guided drug-eluting stent implantation for patients with chronic total occlusion lesions; AVIO, Angiography Vs. Intravascular Ultrasound Optimization trial; CABG, coronary artery bypass graft; CHF, congestive heart failure; CTO-IVUS, Impact of Intravascular Ultrasound-Guided Chronic Total Occlusion Intervention With Drug-eluting Stents; DOCTORS, Optical Coherence Tomography to Optimize Results of Percutaneous Coronary Intervention in Patients with Non-ST-Elevation Acute Coronary Syndrome; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents with or without the Intravascular Ultrasound Guidance trial; ILUMIEN III, OPTIMIZE PCI, Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation; iSIGHT, Optical Coherence Tomography Versus Intravascular Ultrasound and Angiography to Guide Percutaneous Coronary Interventions; IVUS, intravascular ultrasound; IVUS-XPL, Effect of Intravascular Ultrasound–Guided vs Angiography-Guided Everolimus-Eluting Stent Implantation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; OCT, optical coherence tomography; OCTACS, Optical Coherence Tomography Guided Percutaneous Coronary Intervention With Nobori Stent Implantation in Patients With Non-ST-Segment-Elevation Myocardial Infarction trial; PCI, percutaneous coronary intervention; RCT, randomized controlled trial STEMI; RENOVATE-COMPLEX-PCI, Randomized Controlled Trial of Intravascular Imaging Guidance versus Angiography-Guidance on Clinical Outcomes after Complex Percutaneous Coronary Intervention; RESET, Real Safety and Efficacy of a 3-Month Dual Antiplatelet Therapy Following Zotarolimus-Eluting Stents Implantation) trial; ROBUST, OCT guidance during stent implantation in primary PCI trial; ST-segment, elevation myocardial infarction; UA, unstable angina; and ULTIMATE, Intravascular Ultrasound Guided Drug-Eluting Stents Implantation in "All-Comers" Coronary Lesions.

of heterogeneity across the primary analyses with Cochrane's *Q* test did not reveal any significant heterogeneity, providing evidence to support the assumption that the true treatment effect of intravascular imaging in PCI is similar across trials and observed variations are likely due to chance. There was no evidence of publication bias (Figure S2). Previously unpublished additional data regarding all-cause death obtained directly from principal investigators are summarized in Table S6. The study definitions for optimal intravascular imaging–guided stent implantation and the percentage success rate of achieving optimal stent implantation in each included trial are summarized in Table S7. The findings with assessment of certainty of evidence for each outcome are summarized in Table 2.

Major Adverse Cardiac Events

Across all patients, intravascular imaging–guided PCI conferred a lower risk of MACEs as compared with angiography-guided PCI (RR, 0.67 [95% CI, 0.55–0.82]; P<0.001; Figure 1). Heterogeneity was I^2=7.7%. In patients who underwent complex PCI, intravascular imaging–guided PCI conferred a lower risk of MACEs as compared with angiography-guided PCI (RR, 0.61 [95% CI, 0.49–0.74]; P<0.001; Figure S3). There was no important heterogeneity (I^2=0.0%), with no differences in patients undergoing noncomplex PCI (Figure S3). Meta-regression identified a significant association between complex PCI and MACEs ($P_{interaction}$=0.03; Tables S8 and S9).

Cardiac Death

Across all patients, intravascular imaging–guided PCI conferred a lower risk of cardiac death compared with angiography-guided PCI (RR, 0.49 [95% CI, 0.34–0.71]; P<0.001; Figure 2). There was no important heterogeneity (I^2=0.0%). In patients who underwent complex PCI, intravascular imaging–guided PCI conferred a lower risk of cardiac death compared with angiography-guided PCI (RR, 0.44 [95% CI, 0.28–0.68]; P<0.001; Figure S4). There was no important heterogeneity (I^2=0.0%), with no significant differences among patients who underwent noncomplex PCI (Figure S4). Meta-regression did not identify a significant association between complex PCI and cardiac death ($P_{interaction}$=0.97; Tables S8 and S9).

All-Cause Death

Across all patients, the point estimate for all-cause death with intravascular imaging–guided PCI compared with angiography-guided PCI was a RR of 0.81 (95% CI, 0.61–1.07; P=0.14; Figure 3). There was no important heterogeneity (I^2=0.0%). In patients who underwent complex PCI, the point estimate for all-cause death with intravascular imaging–guided PCI compared with angiography-guided PCI was a RR of 0.75 (95% CI, 0.55–1.02; P=0.07; Figure S5). There was no important heterogeneity (I^2=0.0%). Meta-regression did not identify a significant association between complex PCI and all-cause death ($P_{interaction}$=0.32; Tables S8 and S9).

Myocardial Infarction

Across all patients, the point estimate for MI with intravascular imaging–guided PCI compared with angiography-guided PCI was a RR of 0.82 (95% CI, 0.62–1.07; P=0.14; Figure 4). There was no important heterogeneity (I^2=0.6%). In addition, the point estimate for spontaneous MI was a RR of 0.52 (95% CI, 0.27–1.03; P=0.06) and for periprocedural MI was a RR of 0.91 (95% CI, 0.55–1.53; P=0.73) when intravascular

Table 2. Summary of Findings With Quality of Evidence

Outcomes	Relative effect, RR (95% CI)	Absolute effect, per 1000 patients			ARR, % (95% CI)	NNT (95% CI)	Certainty of evidence* (GRADE)
		IVI-guided PCI	Angiography-guided PCI	Difference			
MACEs	0.67 (0.55 to 0.82)	74	113	39	3.93 (2.27 to 5.59)	26 (18 to 45)	High
Cardiac death	0.49, (0.34 to 0.71)	11	24	13	1.28 (0.65 to 1.91)	79 (53 to 155)	High
All-cause death	0.81 (0.61 to 1.07)	24	29	5	0.50 (–0.26 to 1.25)	202 (80 to 382)	Low due to imprecision
Myocardial infarction	0.82 (0.62 to 1.07)	38	49	11	1.15 (–0.05 to 2.35)	87 (43 to 1887)	Low due to imprecision
TLR	0.67 (0.49 to 0.91)	32	54	22	2.20 (0.86 to 3.55)	46 (29 to 117)	High
TVR	0.60, (0.45 to 0.80)	38	68	30	3.02 (1.53 to 4.52)	34 (23 to 66)	High
Stent thrombosis	0.63 (0.40 to 0.99)	10	15	5	0.53 (0.003 to 1.05)	190 (96 to 34 199)	Moderate due to imprecision

ARR indicates absolute risk reduction; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; IVI, intravascular imaging; MACEs, major adverse cardiac events; NNT, number needed to treat; PCI, percutaneous coronary intervention; RR, relative risk; TLR, target-lesion revascularization; and TVR, target-vessel revascularization.

*All the estimates are based on direct comparison of absolute event rates from randomized controlled trials with low overall risk of bias. The provided estimates had no important heterogeneity.

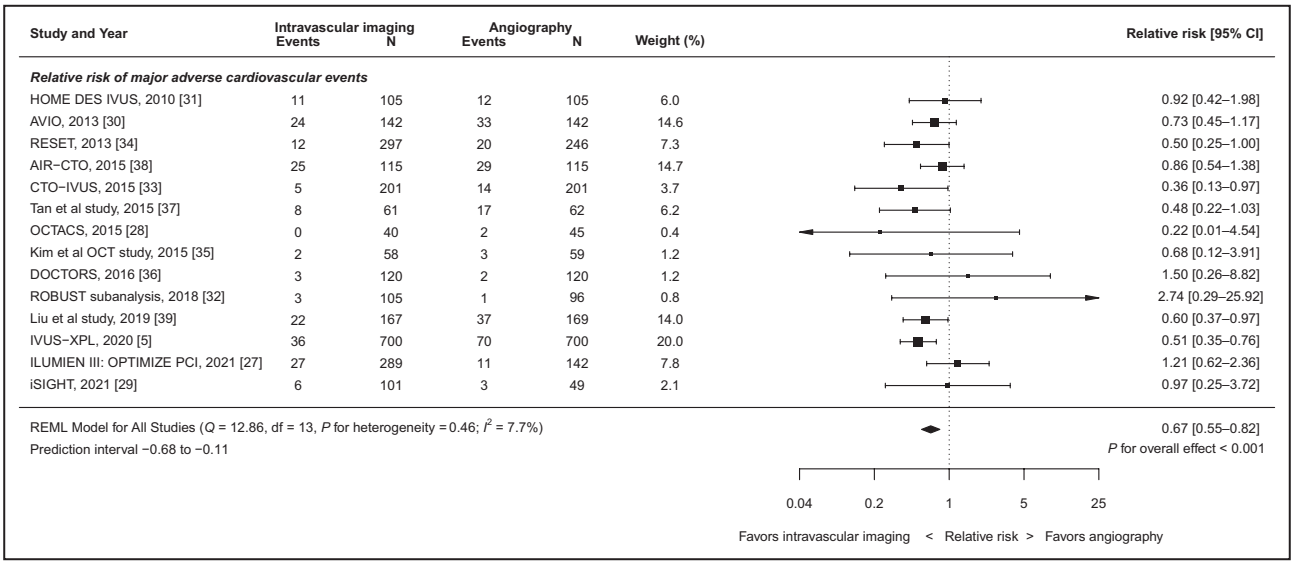

Figure 1. Outcomes for MACEs following intravascular imaging-guided PCI and angiography-guided PCI among all included patients.

AIR-CTO indicates angiographic and clinical comparisons of intravascular ultrasound- versus angiography-guided drug-eluting stent implantation for patients with chronic total occlusion lesions; AVIO, angiography vs intravascular ultrasound optimization trial; CTO-IVUS, impact of intravascular ultrasound-guided chronic total occlusion intervention with drug-eluting stents; DOCTORS, optical coherence tomography to optimize results of percutaneous coronary intervention in patients with non-ST-elevation acute coronary syndrome; HOME DES IVUS, long-term health outcome and mortality evaluation after invasive coronary treatment using drug eluting stents with or without the intravascular ultrasound guidance trial; ILUMIEN III, OPTIMIZE PCI, optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation; iSIGHT, optical coherence tomography versus intravascular ultrasound and angiography to guide percutaneous coronary interventions; IVUS-XPL, effect of intravascular ultrasound–guided vs angiography-guided everolimus-eluting stent implantation; MACEs indicates major adverse cardiac events; OCTACS, optical coherence tomography guided percutaneous coronary intervention with nobori stent implantation in patients with non-ST-segment-elevation myocardial infarction trial; PCI, percutaneous coronary intervention; RENOVATE-COMPLEX-PCI, randomized controlled trial of intravascular imaging guidance versus angiography-guidance on clinical outcomes after complex percutaneous coronary intervention; RESET, real safety and efficacy of a 3-month dual antiplatelet therapy following zotarolimus-eluting stents implantation) trial; ROBUST, OCT guidance during stent implantation in primary PCI trial; and ULTIMATE, intravascular ultrasound guided drug-eluting stents implantation in "all-comers" coronary lesions.

imaging–guided PCI was compared with angiography-guided PCI. There was no important heterogeneity for spontaneous MI (I^2=0.0%), however, for periprocedural MI (I^2=40.9%; Table S10). There were no differences in MI among patients who underwent complex PCI or noncomplex PCI (Figure S6). Meta-regression did not identify a significant association between complex PCI and MI ($P_{interaction}$=0.63; Tables S8 and S9).

Target-Lesion Revascularization

Across all patients, intravascular imaging–guided PCI conferred a lower risk of TLR compared with angiography-guided PCI (RR, 0.67 [95% CI, 0.49–0.91]; *P*=0.01; Figure 5). There was no important heterogeneity (I^2=0.0%). In patients who underwent complex PCI, intravascular imaging–guided PCI conferred a lower risk of TLR compared with angiography-guided PCI (RR, 0.61 [95% CI, 0.44–0.86]; *P*=0.005; Figure S7). There was no important heterogeneity (I^2=0.0%). There were no significant differences in TLR in patients who underwent noncomplex PCI (Figure S7). Meta-regression did not identify a significant association between complex PCI and TLR ($P_{interaction}$=0.35; Tables S8 and S9).

Target-Vessel Revascularization

Across all patients, intravascular imaging–guided PCI conferred a lower risk of TVR compared with angiography-guided PCI (RR, 0.60 [95% CI, 0.45–0.80]; *P*<0.001; Figure 5). There was no important heterogeneity (I^2=0.0%). In patients who underwent complex PCI, intravascular imaging–guided PCI conferred a lower risk of TVR compared with angiography-guided PCI (RR, 0.59 [95% CI, 0.45–0.79]; *P*<0.001; Figure S8). There was no important heterogeneity (I^2=0.0%).

Stent Thrombosis

Among all patients, intravascular imaging–guided PCI conferred a lower risk of stent thrombosis (RR, 0.63 [95% CI, 0.40–0.99]; *P*=0.046) compared with angiography-guided PCI. There was no important heterogeneity (I^2=2.6%; Figure 6).

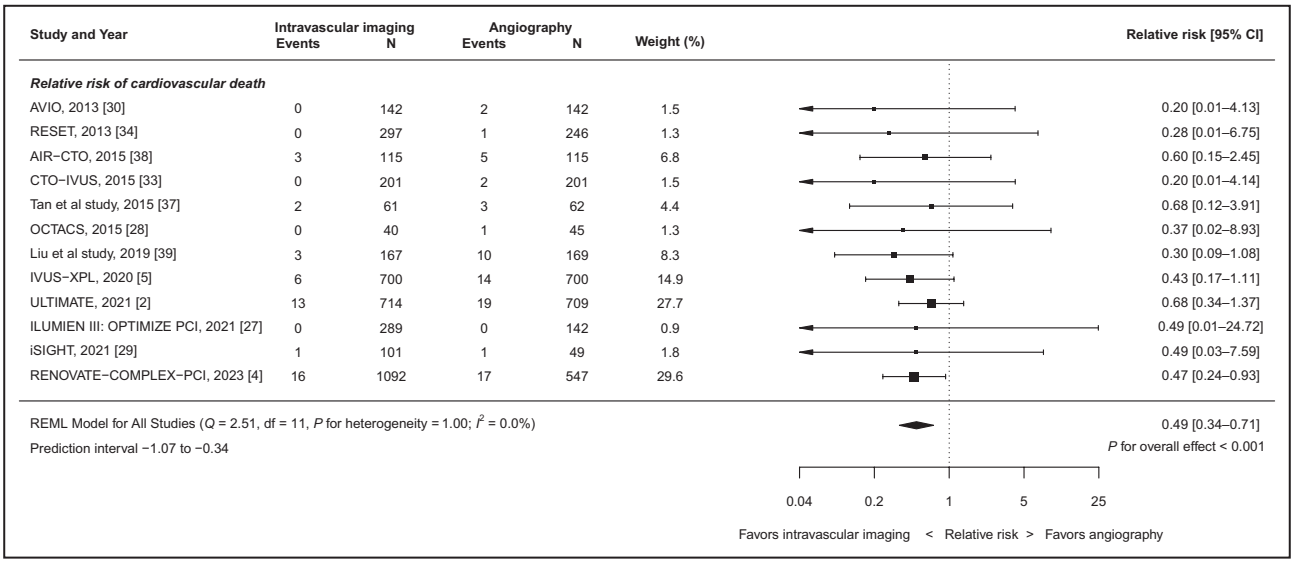

Figure 2. Outcomes for cardiac death following intravascular imaging–guided PCI and angiography-guided PCI among all included patients.
PCI indicates percutaneous coronary intervention.

Other Secondary Outcomes

Among all patients, intravascular imaging–guided PCI conferred a lower risk of target-vessel failure (RR, 0.62 [95% CI, 0.49–0.79]; $P<0.001$; $I^2=0.0\%$), target vessel MI (RR, 0.61 [95% CI, 0.42–0.89]; $P=0.01$; $I^2=0.0\%$), and clinical TLR (RR, 0.60 [95% CI, 0.44–0.82]; $P=0.001$; $I^2=0.0\%$) compared with angiography-guided PCI (Figure 4; Figure S9). There was no important heterogeneity for all these outcomes. The results for other secondary outcomes are provided in Table S10.

Subgroup Analyses

The forest plots for the meta-analyses of trials of IVUS and OCT considered separately are shown in Figures S10 through S17. The subgroup analysis with interaction testing based on the type of clinical presentation and follow-up duration of RCTs are summarized in Tables S11 and S12. There was no significant interaction between type of presentation (acute coronary syndrome versus stable coronary artery disease) or follow-up duration for any of the assessed outcomes.

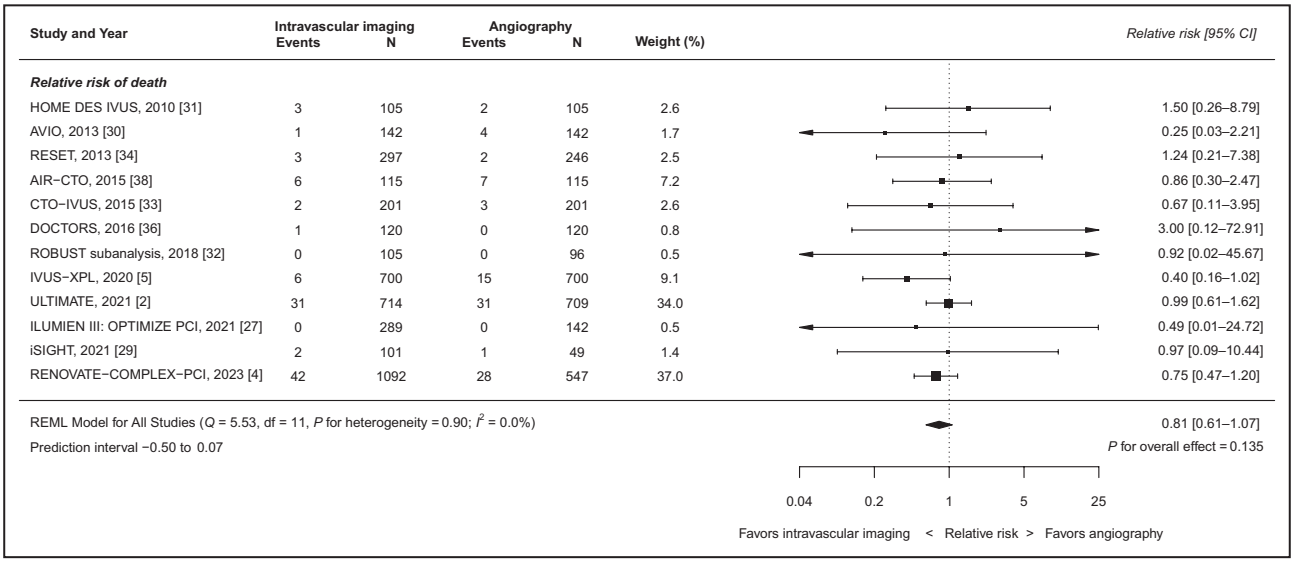

Figure 3. Outcomes for all-cause death following intravascular imaging–guided PCI and angiography-guided PCI among all included patients.
PCI indicates percutaneous coronary intervention.

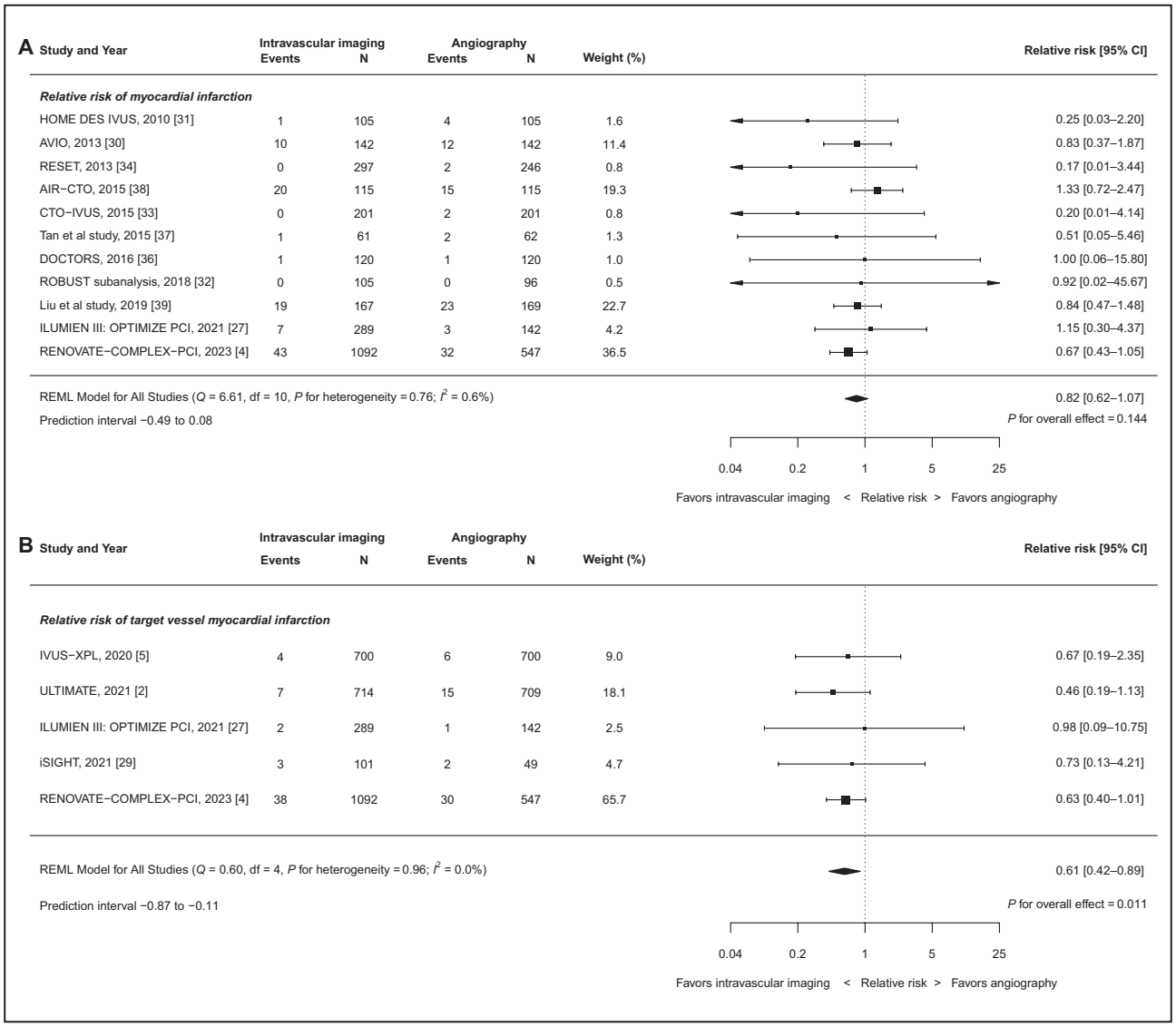

Figure 4. Outcomes for MI (A) and target-vessel MI (B) following intravascular imaging–guided PCI and angiography-guided PCI among all included patients.
MI indicates myocardial infarction; and PCI, percutaneous coronary intervention.

Sensitivity Analysis

A jackknife sensitivity analysis excluding each trial in turn for all primary end points revealed broadly consistent results, as shown in Tables S13 through S18. Additional sensitivity analysis was performed using fixed effects for each of the main primary outcomes with consistent results similar to the primary analysis, as shown in Tables S19 through S23. The sensitivity analyses using the Fisher exact test yielded concordant results for all outcomes (Tables S19 through S23). The additional analyses using the stricter definition of complex PCI (chronic total occlusions, left main PCI, and the complex PCI subgroup of ULTIMATE) demonstrated results consistent with the main complex PCI subgroup analysis (Figures S18 through S24).

DISCUSSION

The present study represents the most contemporary systematic review and meta-analysis of intravascular imaging–guided PCI and incorporates the totality of the randomized data available with 16 included trials and 7814 patients. The principal findings of this study (summarized in Figure 7) are that an intravascular imaging–guided approach, as compared with using angiography alone, improves clinical outcomes, with a 33% reduction in MACEs, 51% reduction in cardiac death, 37% reduction in stent thrombosis, 33% reduction in TLR, 40% reduction in TVR, and 39% reduction in target-vessel MI. The magnitude of these benefits is large, and statistical heterogeneity was absent or low for all analyses, indicating a consistency of effect

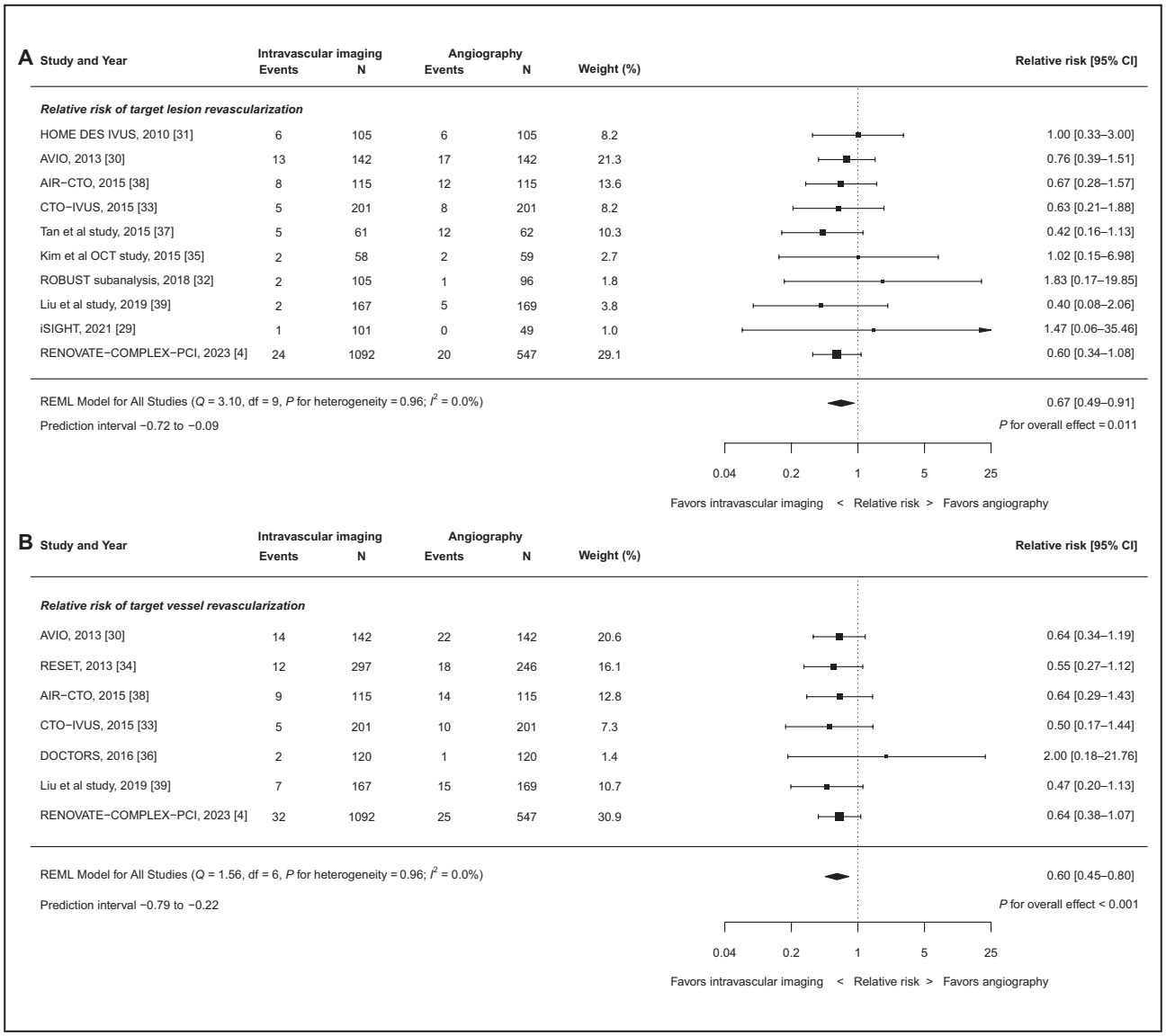

Figure 5. Outcomes for target lesion revascularization (A) and target-vessel revascularization (B) following intravascular imaging–guided PCI and angiography-guided PCI among all included patients.
PCI indicates percutaneous coronary intervention.

across studies. Meta-regression analysis did suggest a significant interaction between complex PCI and MACEs, indicating that complexity of PCI moderates the observed relationship between intravascular imaging and MACEs and further reinforcing the increased clinical benefit of intravascular imaging in the most complex patients. We believe these findings are sufficient to lead to changes in guideline recommendations with class I recommendations for an intravascular imaging–guided approach for PCI, especially for complex lesion subsets.

Our analysis differs from prior published meta-analytic work in several ways.[10,11–15,17,40] First, it includes newly available trial data with the publication of 1 new large trial and longer-term follow-up from 2 other trials. Second, we were able to obtain additional previously unpublished data from the principal investigators of some trials for certain outcomes and subgroups, ensuring that this study is the most exhaustive and complete representation of the existing trial data in the field (Table S6). Third, we excluded observational studies, which are susceptible to bias in the form of both measured and unmeasured confounders. Fourth, we considered all trials of intravascular imaging together irrespective of the imaging modality, as we believe it is the use of an image-guided approach that will improve outcomes rather than the use of one imaging modality above another. Fifth, we specifically examined the most complex lesion subsets, for which it has been assumed the benefit of intravascular imaging is greatest.

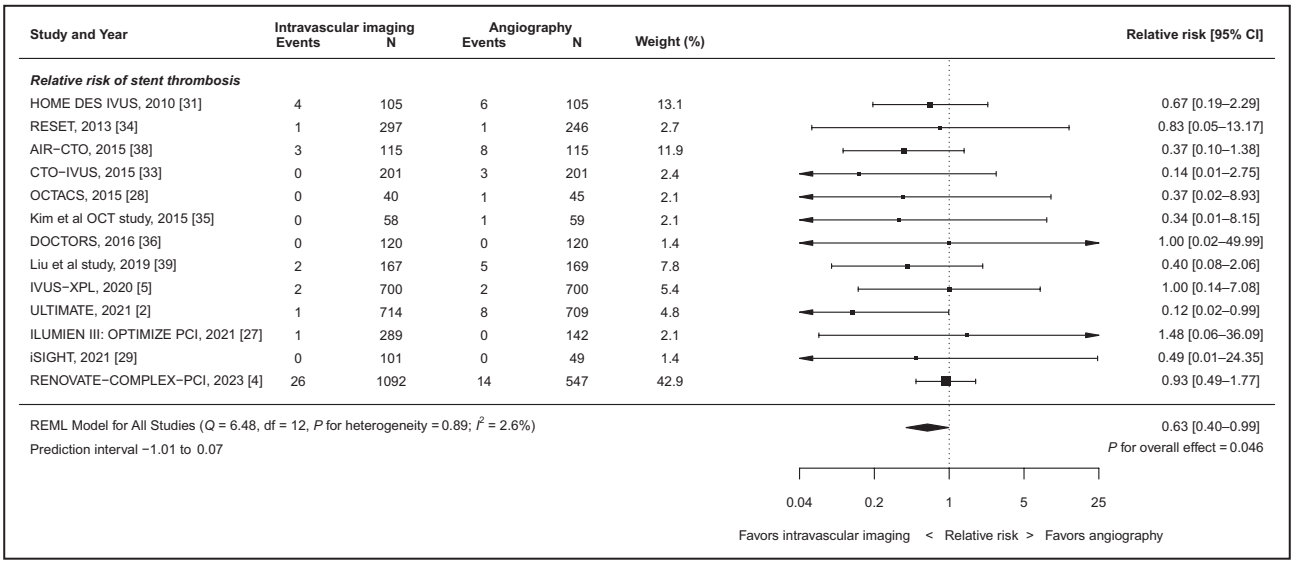

Figure 6. Outcomes for stent thrombosis following intravascular imaging–guided PCI and angiography-guided PCI among all included patients.
PCI indicates percutaneous coronary intervention.

Improved clinical outcomes with an intravascular imaging–guided approach are likely a result of implantation of larger stents with greater final minimal stent areas achieved, as well as avoiding significant plaque burden at the edges of stents and untreated edge dissections. Clinical outcomes with an intravascular imaging–guided approach may be further improved with establishing criteria for an optimal stent result such as that used in the ULTIMATE trial, in which the clinical benefit was determined by achieving optimal stent expansion, defined as minimal stent area >90% distal reference luminal area or an overall minimal stent

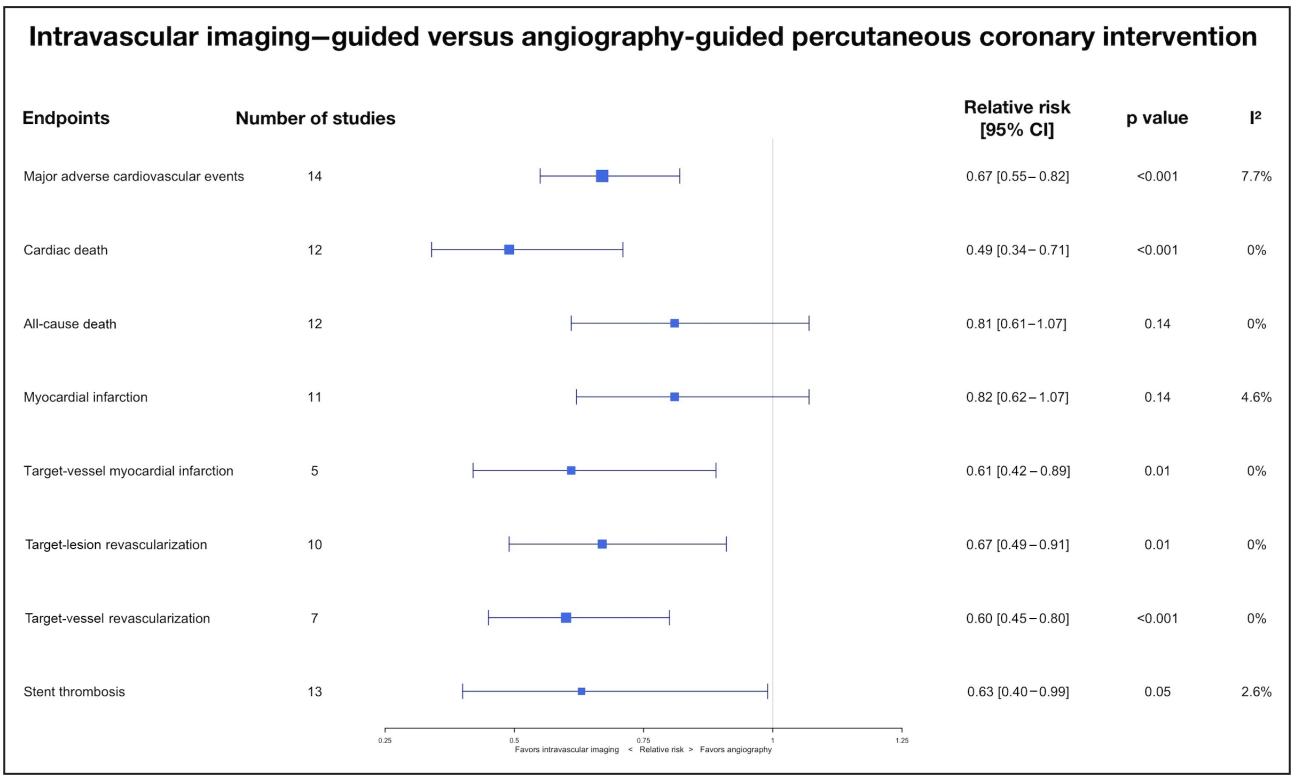

Figure 7. Summary of clinical outcomes for intravascular imaging–guided PCI versus angiography-guided PCI.
PCI indicates percutaneous coronary intervention.

area ≥5 mm^2.[2] Conversely, these clinical benefits were obviated if these criteria were not achieved. Further improvements in clinical outcomes with an imaging-guided approach could be achieved by establishment of key benchmarks for an optimal stent result by imaging criteria.

The magnitude of benefit of an intravascular imaging–guided approach is large, with a one-third reduction in MACEs, one-third reduction in TLR, 40% reduction in stent thrombosis and TVR, and, most strikingly, a 50% reduction in cardiac death. By way of comparison, drug-eluting stents as compared with bare-metal stents were associated with a possible slight (but statistically nonsignificant) 11% reduction in cardiac death as compared with bare-metal stents in an individual patient meta-analysis of 20 RCTs.[41] Drug-eluting stent use, as compared with bare-metal stents, is associated with 37% reductions in stent thrombosis and 45% reductions in TVR, which are findings similar to those observed with imaging-guided PCI as compared with angiography-guided PCI. Drug-eluting stent use receives class I recommendations from guidelines. The clinical benefits of imaging guidance come with no downside or trade-off, aside from the cost of the imaging catheter and a small, insignificant increase in procedural time. Our analysis suggests that the benefit of intravascular imaging is greatest in complex lesion subsets, and in terms of economic implications and resource use, an initial focus on complex lesions might be most appropriate.

Our analysis suggests a potential benefit in terms of all-cause death, although this result was not statistically significant. Across all patients, the point estimate for all-cause death for intravascular imaging as compared with angiography was a RR of 0.81 (95% CI, 0.61–1.07; *P*=0.14), and for complex lesion subsets, the point estimate was a RR of 0.75 (95% CI, 0.55–1.02; *P*=0.07). We believe that a therapy that significantly reduces MACEs, cardiac death, stent thrombosis, TLR, TVR, and target-vessel MI to the extent that intravascular imaging does is very likely to lead to reductions in all-cause death, but our present analysis is underpowered to demonstrate a statistically significant benefit. With the addition of new trials with increased patients and events, it is likely that the precision around the point estimates will increase and the reduction in death will become statistically significant. These new trials are forthcoming, including ILUMIEN IV (Optical Coherence Tomography [OCT] Guided Coronary Stent Implantation Compared to Angiography: A Multicenter Randomized Trial in PCI; NCT03507777), OCTOBER (European Trial on Optical Coherence Tomography Optimized Bifurcation Event Reduction; NCT03171311), IMPROVE (Impact on Revascularization Outcomes of Intravascular Ultrasound-Guided Treatment of Complex Lesions and Economic Impact Trial; NCT04221815), and OPTIMAL (Optimization of Left Main PCI With Intravascular Ultrasound Trial; NCT04111770).[42–49]

Limitations

This is a study-level meta-analysis, and individual patient data were not available to us. This prevents us from performing more granular subgroup analyses or assessing temporality of events with Kaplan–Meier plots and landmark analyses. Many trials did not report hazard ratios, which are the most appropriate method for analyzing survival data and account for varying follow-up durations. To help overcome this, we also performed analyses at varying time early intervals. Definitions of clinical outcomes and subgroups are never entirely consistent across included trials, which is a problem common to all meta-analyses. This problem will only be overcome when trialists commit to standardizing end point definitions and subgroups across all trials to facilitate better synthesis of pooled data. However, statistical heterogeneity was absent or low for the majority of our meta-analyses. Follow-up duration of most trials was relatively short, limiting our ability to study the longer-term impact of intravascular imaging when compared with angiography. We would expect longer-term follow-up to lead to accrual of events with subsequent increasing of precision and narrowing of CIs, but this cannot be studied from the available data. Randomization is the only way to avoid bias from measured and unmeasured confounders when assessing an effect of therapy, and we therefore limited our analysis to randomized trials, which necessarily exclude all patients who do not meet their narrow eligibility criteria and can limit generalizability. The larger RCTs in this analysis are primarily based on study populations from countries like China or South Korea, where adoption of intravascular imaging is higher, and familiarity with image interpretation to guide intervention is likely to be present.[2,4,5] This may somewhat limit generalizability of their results to other regions where adoption is lower. Our definition of complex PCI was based in large part on the recent RENOVATE-COMPLEX-PCI trial, but led to the majority of lesions in this study being classified as complex, which may not be representative of clinical practice in most settings. We also used an additional, stricter definition of complex PCI to include left main lesions, chronic total occlusions, and the complex PCI cohort from ULTIMATE, which demonstrated consistent results.

CONCLUSIONS

In patients undergoing PCI, intravascular imaging is associated with a significant reduction in MACE, cardiac death, stent thrombosis, TLR, and TVR. The magnitude of benefit is large and consistent across all included

studies. There may also be benefits in all-cause death, particularly in complex lesion subsets. These results support the use of intravascular imaging as the standard of care for all patients undergoing PCI, providing a compelling argument for upgraded guideline recommendations that reflect the totality of contemporary randomized evidence.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S23
Figures S1–S24

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