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

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Background—Intravascular ultrasound (IVUS) guidance during percutaneous coronary intervention (PCI) offers tomographic images of the coronary vessels, allowing optimization of stent implantation at the time of PCI. However, the long-term beneficial effect of IVUS over PCI guided by coronary angiography (CA) alone remains under question. We sought to investigate the outcomes of IVUS-guided compared with CA-guided PCI.

Methods and Results—We performed a comprehensive search of PubMed, Medline, and Cochrane Central Register, looking for randomized controlled trials and observational studies that compared PCI outcomes of IVUS with CA. Data were aggregated for the primary outcome measure using the random-effects model as pooled risk ratio (RR). The primary outcomes were the rate of cardiovascular death, need for target lesion revascularization, occurrence of myocardial infarction, and rate of stent thrombosis. A total of 19 studies met the inclusion criteria, comprising 27 610 patients divided into IVUS (n=11 513) and CA (n=16 097). Compared with standard CA-guided PCI, we found that the risks of cardiovascular death (RR, 0.63; 95% CI, 0.54–0.73), myocardial infarction (RR, 0.71; 95% CI, 0.58–0.86), target lesion revascularization (RR, 0.81; 95% CI, 0.70–0.94), and stent thrombosis (RR, 0.57; 95% CI, 0.41–0.79) were all significantly lower using IVUS guidance.

Conclusions—Compared with standard CA-guided PCI, the use of IVUS imaging guidance to optimize stent implantation is associated with a reduced risk of cardiovascular death and major adverse events, such as myocardial infarction, target lesion revascularization, and stent thrombosis. **(*J Am Heart Assoc*. 2020;9:e013678. DOI: 10.1161/JAHA.119.013678.)**

Key Words: coronary imaging • coronary intervention • intravascular ultrasound • optical coherence tomography

Percutaneous coronary intervention (PCI) is a mainstay for the treatment of coronary artery disease, a major cause of morbidity and mortality worldwide.[1] Although coronary angiography (CA) is the standard imaging modality used for coronary stent implantation, it is limited to 2-dimensional projections of coronary anatomical characteristics. This limitation can be overcome using high-resolution intracoronary imaging modalities, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), that offer detailed 3-dimensional tomographic views of coronary plaque, blood vessel, and stent morphological characteristics, thus enabling greater information to guide optimal stent implantation.[2–5]

Several randomized controlled trials (RCTs) and observational studies examining intracoronary imaging during and after stent implantation have demonstrated that IVUS-guided stent implantation was associated with the reduction of major adverse cardiac events and target vessel revascularization in patients with complex coronary lesions, including long lesions, severe calcification, bifurcations, chronic total occlusions, and unprotected left main disease.[3–7] However, despite accumulating data supporting the use of IVUS to optimize PCI, the adoption of intracoronary imaging to guide stent implantation in real-world interventional clinical practice remains low, in part because of a perceived lack of supporting clinical evidence.[8] Therefore, we sought to

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Accompanying Figures S1 through S7 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013678

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Clinical Perspective

What Is New?

- This study demonstrated that use of intravascular ultrasound imaging–guided percutaneous coronary intervention was associated with lower cardiovascular death, myocardial infarction, target lesion revascularization, and stent thrombosis, compared with coronary angiography alone.
- Our study encourages the routine use of intracoronary imaging to optimize coronary stent implantation.

What Are the Clinical Implications?

- Intracoronary imaging is an innovative technology presented to overcome the limitations of standard routine angiography.
- This technique offers more details about the coronary atherosclerotic plaque, vessel wall, and facilitated stent delivery, which subsequently improve the outcomes of percutaneous coronary interventions.
- The routine use of intracoronary imaging to optimize coronary stent implantation is encouraged.

synthesize all available data by conducting a comprehensive meta-analysis exploring the clinical outcomes of PCI guided by angiography with adjunctive IVUS imaging compared with angiography alone.

Methods

Inclusion Criteria

We searched Medline, EMBASE, and Cochrane library for RCTs or observational studies that compared IVUS with CA outcomes as invasive imaging modalities for guiding PCI with stent implantation. Studies using both bare metal stents and drug-eluting stents (DESs) were eligible. In an attempt to decrease the risk of bias inherent with including observational studies, only nonrandomized studies that used matching algorithms were included. We also excluded all the studies that used intravascular imaging for stent implantation in the presence of flow-limiting dissections or residual stenosis after plain balloon angioplasty. The analysis was restricted only to studies in which at least 100 patients were enrolled in each treatment arm. The data that support the findings of this study are available from the corresponding author upon reasonable request.

The combinations of medical terms "percutaneous coronary intervention,"" intravascular ultrasound," "intravascular imaging," "IVUS," and/or "coronary angiography" were used to conduct a comprehensive search in the above-mentioned databases. All searches were restricted to studies conducted in human subjects published from the date of the databases' inception through April 2019. 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for network meta-analyses[9] (Figure 1).

End Point Outcomes

The primary outcome of this meta-analysis was cardiovascular mortality. Secondary end points were myocardial infarction (MI), target lesion revascularization (TLR), and stent thrombosis (ST).

Data Extraction and Statistical Analysis

After careful title checking and reviewing full texts of all the studies, 2 investigators (E.O. and M.A.) independently verified the inclusion criteria and abstracted the data from all the articles that met the inclusion criteria. Disagreements were resolved by consensus. All extracted data from the included studies were collected into a spreadsheet and verified by a third author (Y.A.). Summarized and weighted means and rates from each individual trial or observation study for baseline characteristics were reported. Data were pooled for the primary and secondary outcomes using summary risk ratios (RRs) and 95% CIs using random effects models, while taking into account the within and between study variance. Two-sided P values were calculated, with $P<0.05$ considered significant for all tests. Heterogeneity was assessed by means of the I^2 statistic (with an I^2 value >50% being considered the result of severe heterogeneity).

Sensitivity analysis was performed for different study design and baseline characteristics to evaluate for the consistency of the main results across all studies that were included in the analysis. Sensitivity analysis and meta-regression were used to explore the treatment effect and elucidate the relationship between confounding factors and IVUS guidance. We used a linear regression (Littenberg and Moses linear model) approach.[10] Random-effects model was selected because of the difference in the designs of the studies included in this meta-analysis (observation versus RCTs). A 2-tailed $P<0.05$ was considered statistically significant. All data and supporting materials have been provided with the published article, and all supporting data are available within the article.

The methodological quality of observational studies was assessed by the Newcastle-Ottawa scale, which consists of 3

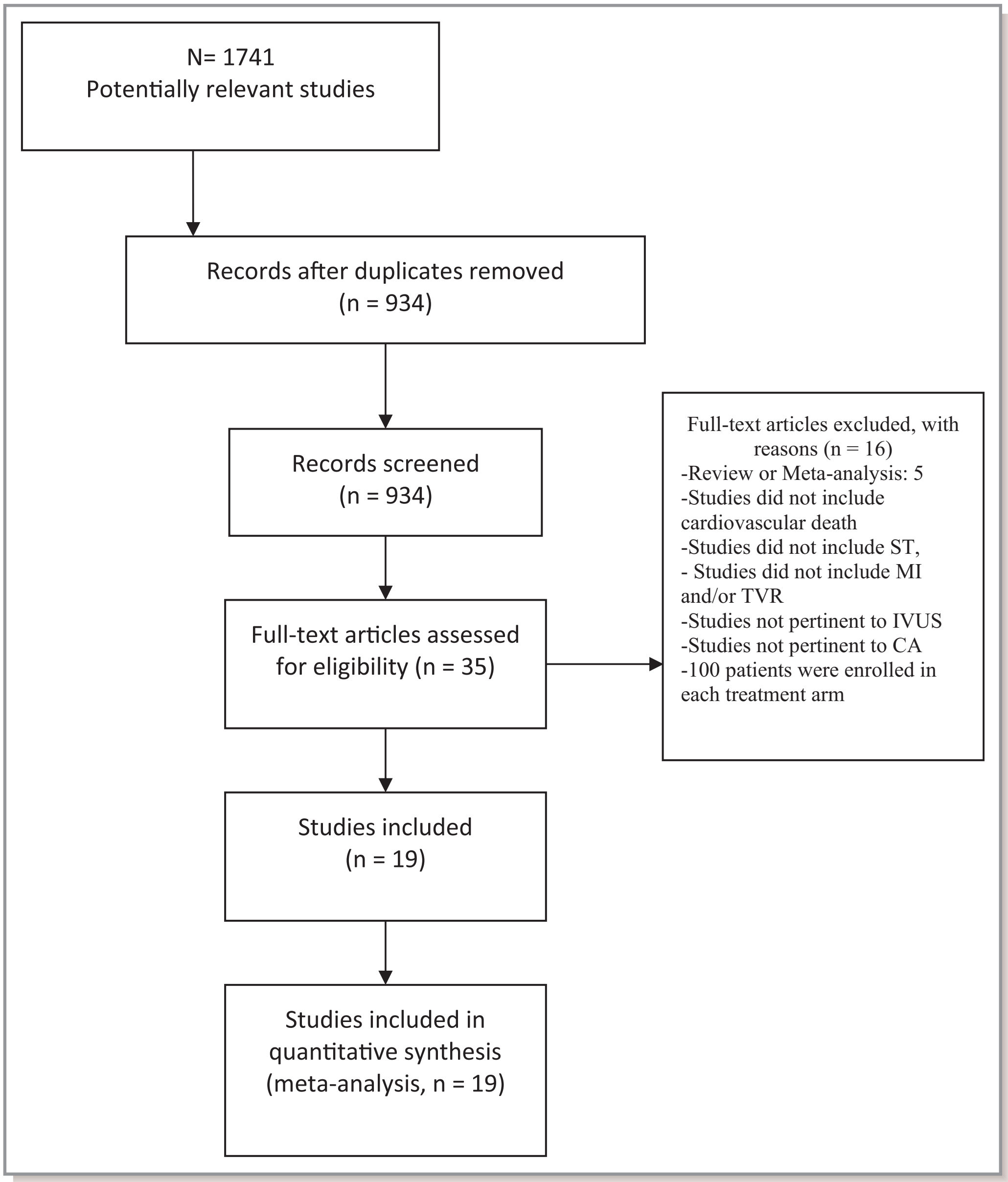

Figure 1. Flow diagram of the literature search. CA indicates coronary angiography; IVUS, intravascular ultrasound; MI, myocardial infarction; ST, stent thrombosis; TVR, target vessel revascularization.

factors: patient selection, comparability of the study groups, and assessment of outcomes. A score of 0 was considered as an exclusion criterion from a statistical standpoint, and we selected a score cutoff of 0.7 and 1 for observational studies and RCTs, respectively, to ensure the consistency of our meta-analysis results.[11,12]

Results

Nineteen eligible studies, including a total of 27 637 patients, were identified in the current meta-analysis, with 11 540 patients in the IVUS guidance group and 16 097 patients in the CA guidance group. The detailed study design included in this meta-analysis is summarized in Table 1.[13–31] Patient characteristics are summarized in Table 2.[29–47] Briefly, 16 of 19 studies (84.2%) used DESs as the primary stent type (1 study used a combination of both bare metal stents and DESs). A total of 10 studies were adjusted observational studies with propensity score matching, and 9 studies were RCTs. The follow-up period ranged from 6 months to a maximum of 64 months. Left main lesions constituted 26.7% of the treated vessels in the CA group and 15.4% of the treated vessels in the IVUS group. A total of 71.6% of the CA-guided PCI group had a

Table 1. Study Design of the Included Studies

Study	Year	No. of Patients (CA/IVUS)	Design	Stent Type	Follow-Up, mo
AIR-CTO[13]	2015	115/115	RCT	DES	12
AVID[14]	2009	406/394	RCT	BMS	12
Chen et al[15]	2012	123/123	Observational, PSM	DES	12
Choi et al[16]	2019	4331/1674	Observational	DES	64
CTO-IVUS[17]	2015	201/201	RCT	DES	12
de la Torre Hernandez[18]	2014	505/505	Observational, PSM	DES	36
DIPOL[19]	2007	80/83	RCT	BMS	6
EXELLENT[20]	2013	463/463	Observational, PSM	DES	12
Gao et al[21]	2014	291/291	Observational, PSM	DES	12
HOME DES IVUS[22]	2010	105/105	RCT	DES	18
Hong et al[23]	2014	201/201	Observational, PSM	DES	24
IVUS-XPL[24]	2015	700/700	RCT	DES	12
Kim et al (RESET)[25]	2013	274/269	RCT	DES	12
MATRIX[26]	2011	548/548	Observational, PSM	DES	24
OPTICUS[27]	2001	275/273	RCT	BMS	12
Roy et al[28]	2008	884/884	Observational, PSM	DES	12
ULTIMATE[29]	2018	724/724	RCT	DES	12
Wakabayashi et al[30]	2012	637/637	Observational, PSM	BMS/DES	12
Witzenbichler et al[31]	2014	5234/3349	Observational	DES	12

AIR-CTO indicates Angiographic and Clinical Comparisons of Intravascular Ultrasound-Versus Angiography-Guided Drug-Eluting Stent Implantation for Patients With Chronic Total Occlusion Lesions; AVID, Angiography Versus Intravascular Ultrasound-Directed Stent Placement; BMS, bare metal stent; CA, coronary angiography; CTO-IVUS, Intravascular Ultrasound-Guided Chronic Total Occlusion Intervention; DES, drug-eluting stent; DIPOL, Direct Stenting vs Optimal Angioplasty Trial; EXCELLENT, Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS, intravascular ultrasound; IVUS-XPL, Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; REST, Real Safety and Efficacy of a 3-Month Dual Antiplatelet Therapy Following Zotarolimus-Eluting Stents Implantation; MATRIX, Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions; OPTICUS, Optimization With ICUS to Reduce Stent Restenosis; PSM, propensity score matching; RCT, randomized controlled trial; ULTIMATE, Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "AllComers" Coronary Lesions trial.

diagnosis of diabetes mellitus, compared with 70.9% in the IVUS-guided group. Finally, 43.3% and 34.4% of the IVUS and CA groups, respectively, underwent PCI for acute coronary syndromes.

From the 11 540 patients included in the IVUS group and 16 097 patients included in the CA group, IVUS-guided PCI reduced the risk of cardiovascular death compared with CA alone (216 [1.9%] versus 627 [3.9%]; RR, 0.63; 95% CI, 0.54–0.73; heterogeneity χ^2=15.65; I^2=0%; P<0.001). IVUS-guided PCI also reduced postprocedural MI (314 [2.7%] versus 645 [4.0%]; RR, 0.71; 95% CI, 0.58–0.86), TLR (514 [4.5%] versus 841 [5.2%]; RR, 0.81; 95% CI, 0.70–0.94), and ST (160 [1.4%] versus 360 [2.2%]; RR, 0.57; 95% CI, 0.41–0.79). Statistical heterogeneity for MI was I^2=32% (P=0.09); and for TLR, I^2=36% (P=0.06). Higher heterogeneity was observed with ST (I^2=40%; P=0.04). The primary and secondary outcomes are presented in Figures 2 through 5. Furthermore, meta-regression analysis revealed that the beneficial effect of IVUS when compared with angiography-guided PCI remained significant regardless of diabetes mellitus, hypertension, sex, acute coronary syndrome, or left main lesion (Figures S1 through S7).

Discussion

The principal findings from this study are as follows: meta-analysis of 19 studies showed that, compared with CA alone, IVUS-guided PCI (1) decreased the risk of cardiovascular death, with a relative risk reduction of 33%; (2) lowered MI risk, with a number needed to treat of 91 to prevent 1 MI; (3) decreased the need for TLR; and (4) was associated with less ST.

Since the inception of PCI decades ago, x-ray CA has been the standard imaging platform used to guide coronary intervention procedures. However, a major drawback of CA is that it relies on 2-dimensional projections to define the structure of complex 3-dimensional coronary artery lumens. In the modern era, through the use of IVUS and OCT,

Table 2. Baseline Clinical Characteristics of the Included Studies

Study	Age, y	DM, %	ACS, %	Hypertension, %	Men, %	LVEF, %	LM, %	LAD, %	LCx, %	RCA, %
AIR-CTO[13]	66/67	27/30	24/29	70/75	80/89	56/55	3/0	36/44	15/21	46/35
AVID[14]	63/62	17/15	NA	45/46	68/73	55/53	1/1	37/40	18/15	32/35
Chen et al[15]	64/63	18/19	11/15	61/67	74/81	60/61	27/42	61/40	9/14	3/4
Choi et al[16]	62/59	25/22	8/9	47/43	68/72	57/58	2/8	50/59	21/12	34/25
CTO-IVUS[17]	61/61	34/35	37/28	64/63	81/81	57/57	0/0	47/42	16/14	37/44
de la Torre Hernandez[18]	67/66	35/36	61/59	64/68	79/80	55/55	100/100	NA	NA	NA
DIPOL[19]	54/56	10/13	39/38	58/61	73/71	48/52	0/0	46/41	24/26	30/32
EXELLENT[20]	63/63	38/37	52/51	74/73	63/66	NA	0/0	23/54	23/20	27/27
Gao et al[21]	67/66	34/32	10/9	72/72	77/81	57/58	100/100	13/10	8/6	10/7
HOME DES IVUS[22]	60/59	45/42	60/72	71/67	71/73	NA	4/3	54/56	15/11	24/29
Hong et al[23]	62/62	31/30	42/39	60/58	77/77	NA	1/1	34/44	25/16	NA
IVUS-XPL[24]	64/64	37/36	49/49	63/65	69/69	62/63	0/0	60/65	15/14	15/14
Kim et al (RESET)[25]	64/62	31/30	47/49	66/61	55/66	54/55	54/55	57/50	18/21	24/29
MATRIX[26]	64/64	31/32	36/33	81/81	74/74	NA	3/3	51/51	38/38	28/28
OPTICUS[27]	62/60	17/17	32/36	52/48	78/77	58/56	0/0	50/51	14/18	35/30
Roy et al[28]	66/66	34/36	61/62	82/82	70/69	48/47	2.3/2	33/3	23/25	34/34
ULTIMATE[29]	65/66	30/31	67/64	71/72	74/73	61/60	10/9	47/47	17/17	25/28
Wakabayashi et al[30]	67/67	40/42	56/58	90/91	69/68	NA	4/4	25/26	23/23	32/32
Witzenbichler et al[31]	63/64	31/33	43/43	78/81	73/75	60/53	3/4	NA	NA	NA

Data are presented as intravascular ultrasound guidance/coronary angiography guidance. ACS indicates acute coronary syndrome; AIR-CTO, Angiographic and Clinical Comparisons of Intravascular Ultrasound-Versus Angiography-Guided Drug-Eluting Stent Implantation for Patients With Chronic Total Occlusion Lesions; AVID, Angiography Versus Intravascular Ultrasound-Directed Stent Placement; CTO-IVUS, Intravascular Ultrasound-Guided Chronic Total Occlusion Intervention; DIPOL, Direct Stenting vs Optimal Angioplasty Trial; DM, diabetes mellitus; EXCELLENT, Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS-XPL, Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main coronary artery; LVEF, left ventricular ejection fraction; MATRIX, Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions; OPTICUS, Optimization With ICUS to Reduce Stent Restenosis; RCA, right coronary artery; ULTIMATE, Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "AllComers" Coronary Lesions trial.

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Random, 95% CI
AIR-CTO 2015	3	115	4	115	1.1%	0.75 [0.17, 3.28]
AVID 2009	12	395	7	406	2.9%	1.76 [0.70, 4.43]
CHEN et al 2012	0	123	4	123	0.3%	0.11 [0.01, 2.04]
Choi et al	98	1647	416	4331	53.6%	0.62 [0.50, 0.77]
CTO-IVUS 2015	0	201	2	201	0.3%	0.20 [0.01, 4.14]
De la Torre Hernandez 2014	17	505	30	505	7.2%	0.57 [0.32, 1.01]
DIPOL 2007	1	83	1	80	0.3%	0.96 [0.06, 15.15]
EXELLENT 2013	2	463	2	463	0.6%	1.00 [0.14, 7.07]
Gao et al 2014	5	291	15	291	2.4%	0.33 [0.12, 0.91]
HOME DES IVUS 2010	3	105	2	105	0.8%	1.50 [0.26, 8.79]
Hong et al 2014	2	201	5	201	0.9%	0.40 [0.08, 2.04]
IVUS-XPL 2015	3	700	5	700	1.2%	0.60 [0.14, 2.50]
Kim et al 2013	0	269	1	274	0.2%	0.34 [0.01, 8.30]
MATRIX 2011	5	548	10	548	2.1%	0.50 [0.17, 1.45]
OPTICUS 2001	5	273	1	275	0.5%	5.04 [0.59, 42.83]
Roy et al 2008	16	884	24	884	6.2%	0.67 [0.36, 1.25]
Ultimate 2018	5	724	10	724	2.1%	0.50 [0.17, 1.46]
Wakabayashi et al 2012	12	637	28	637	5.4%	0.43 [0.22, 0.84]
Witzenbichler et al 2014	27	3349	60	5234	11.9%	0.70 [0.45, 1.11]
Total (95% CI)		**11513**		**16097**	**100.0%**	**0.63 [0.54, 0.73]**
Total events	216		627			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 15.65$, df = 18 (P = 0.62); $I^2 = 0\%$
Test for overall effect: Z = 5.91 (P < 0.00001)

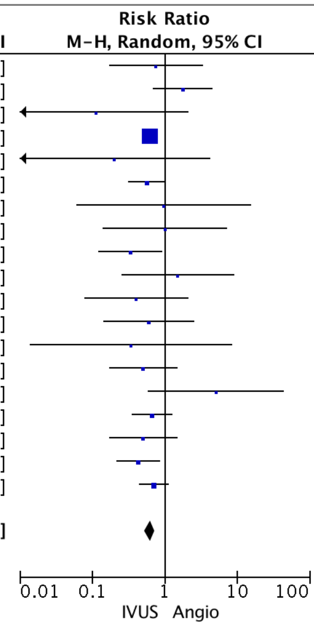

Figure 2. Forest plots for major adverse cardiovascular events. Risk ratio of cardiovascular death associated with intravascular ultrasound (IVUS)–guided compared with angiography (Angio)–guided percutaneous coronary intervention. AIR-CTO indicates Angiographic and Clinical Comparisons of Intravascular Ultrasound-Versus Angiography-Guided Drug-Eluting Stent Implantation for Patients With Chronic Total Occlusion Lesions; AVID, Angiography Versus Intravascular Ultrasound-Directed Stent Placement; CTO-IVUS, Intravascular Ultrasound–Guided Chronic Total Occlusion Intervention; DIPOL, Direct Stenting vs Optimal Angioplasty Trial; EXCELLENT, Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS-XPL, Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; MATRIX, Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions; OPTICUS, Optimization With ICUS to Reduce Stent Restenosis; ULTIMATE, Intravascular Ultrasound Guided Drug Eluting Stents Implantation in “AllComers” Coronary Lesions trial; M-H: Mantel–Haenszel.

intracoronary imaging can overcome the inherent limitations of CA by providing high-resolution axial cross-sectional images with detailed tomographic structural information on lesion and vessel characteristics. Thus, intracoronary imaging promotes an enhanced understanding of coronary anatomical characteristics at the time of PCI, facilitating protocols to optimize coronary stent sizing, avoid stent malapposition and underexpansion, and identify unrecognized complications, such as edge dissection. Overall, by precisely guiding stent implantation at the index procedure, intracoronary imaging aims to improve short- and long-term cardiovascular PCI outcomes.

In the bare metal stent era, a meta-analysis of 7 randomized trials showed a neutral effect on mortality and MI over a follow-up period of 6 months to 2.5 years; however, IVUS use was associated with a reduction in both angiographic restenosis at 6 months and the rate of subsequent revascularization.[32] These early encouraging results coupled with the introduction of DESs paved the way for IVUS-guided DESs as an attractive strategy to further improve PCI outcomes. Indeed, the evidence base supporting the theoretical benefits of an IVUS-guided DES implantation approach has been increasing over the past several years, with several meta-analyses and randomized studies showing a decrease in major adverse cardiac events,[33–40] particularly in complex lesions and high-risk patients.

The recently completed all-comers ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in “AllComers” Coronary Lesions) trial, enrolling 1148 patients in the largest randomized IVUS-guided PCI trial to date, demonstrated that the routine use of IVUS during DES implantation reduced cardiovascular death and ST when compared with CA alone. These findings are reinforced by the current study, the largest IVUS-guided PCI meta-analysis performed pooling 19 observational studies and RCTs with a total of 29 637 patients with complex and noncomplex coronary lesions and long-term follow-up between 6 and 64 months. Although the variation in the included studies created low to moderate outcome heterogeneity, the overall I^2 remained <50%. To investigate the sources of moderated heterogeneity in our

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Random, 95% CI
AIR-CTO 2015	18	115	15	115	6.7%	1.20 [0.64, 2.26]
AVID 2009	25	395	19	406	7.5%	1.35 [0.76, 2.42]
CHEN et al 2012	4	123	12	123	2.8%	0.33 [0.11, 1.01]
Choi et al	56	1674	213	4331	14.7%	0.68 [0.51, 0.91]
CTO-IVUS 2015	0	201	2	201	0.4%	0.20 [0.01, 4.14]
De la Torre Hernandez 2014	23	505	33	505	8.7%	0.70 [0.42, 1.17]
DIPOL 2007	1	83	4	80	0.8%	0.24 [0.03, 2.11]
EXELLENT 2013	10	463	2	463	1.6%	5.00 [1.10, 22.69]
Gao et al 2014	36	291	44	291	11.2%	0.82 [0.54, 1.23]
HOME DES IVUS 2010	1	105	4	105	0.8%	0.25 [0.03, 2.20]
Hong et al 2014	2	201	8	201	1.5%	0.25 [0.05, 1.16]
IVUS-XPL 2015	0	700	1	700	0.4%	0.33 [0.01, 8.17]
Kim et al 2013	0	269	2	274	0.4%	0.20 [0.01, 4.22]
MATRIX 2011	10	548	31	548	5.8%	0.32 [0.16, 0.65]
OPTICUS 2001	6	273	10	275	3.3%	0.60 [0.22, 1.64]
Roy et al 2008	18	884	26	884	7.3%	0.69 [0.38, 1.25]
Ultimate 2018	10	724	13	724	4.6%	0.77 [0.34, 1.74]
Wakabayashi et al 2012	13	637	18	637	5.8%	0.72 [0.36, 1.46]
Witzenbichler et al 2014	81	3349	188	5234	15.7%	0.67 [0.52, 0.87]
Total (95% CI)		**11540**		**16097**	**100.0%**	**0.71 [0.58, 0.86]**
Total events	314		645			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 26.44$, df = 18 (P = 0.09); $I^2 = 32\%$
Test for overall effect: Z = 3.40 (P = 0.0007)

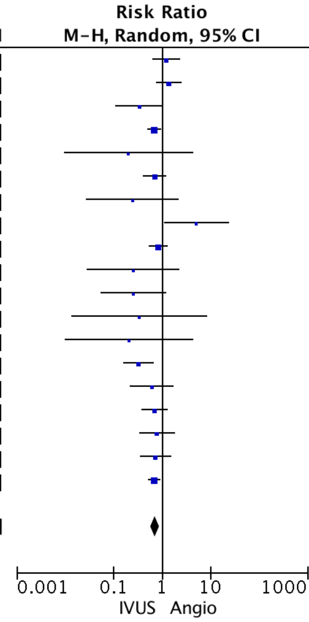

Figure 3. Forest plots for major adverse cardiovascular events. Risk ratio of myocardial infarction associated with intravascular ultrasound (IVUS)–guided compared with angiography (Angio)–guided percutaneous coronary intervention. AIR-CTO indicates Angiographic and Clinical Comparisons of Intravascular Ultrasound-Versus Angiography-Guided Drug-Eluting Stent Implantation for Patients With Chronic Total Occlusion Lesions; AVID, Angiography Versus Intravascular Ultrasound-Directed Stent Placement; CTO-IVUS, Intravascular Ultrasound–Guided Chronic Total Occlusion Intervention; DIPOL, Direct Stenting vs Optimal Angioplasty Trial; EXCELLENT, Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS-XPL, Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; MATRIX, Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions; OPTICUS, Optimization With ICUS to Reduce Stent Restenosis; ULTIMATE, Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "AllComers" Coronary Lesions trial; AIR-CTO indicates, Angiographic and Clinical Comparisons of Intravascular Ultrasound- Versus Angiography-Guided Drug-Eluting Stent Implantation for Patients With Chronic Total Occlusion Lesions; AVID, Angiography Versus Intravascular Ultrasound-Directed Stent Placement; CTO-IVUS, Intravascular Ultrasound–Guided Chronic Total Occlusion Intervention; DIPOL, Direct Stenting vs Optimal Angioplasty Trial; EXCELLENT, Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS-XPL, Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; MATRIX, Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions; OPTICUS, Optimization With ICUS to Reduce Stent Restenosis; ULTIMATE, Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "AllComers" Coronary Lesions trial; M-H, Mantel–Haenszel.

study, additional meta-regression analyses were performed to evaluate the relationship between study characteristics and IVUS use, revealing that IVUS guidance continued to demonstrate benefit over CA-guided PCI, irrespective of the presence of diabetes mellitus, acute coronary syndrome, hypertension, sex, or left main lesion location.

Overall, accumulating clinical studies support the use of intracoronary imaging to improve outcomes after stent implantation. However, despite increasingly compelling data, the use of intracoronary imaging guidance during PCI procedures continues to be significantly underused in the United States. A recent report showed that intracoronary imaging (IVUS and/or OCT) in the United States increased from 2.1% in 2004 to 6.6% in 2014, heavily weighted toward IVUS (94.3% IVUS versus 6.6% OCT).[41] The infrequent use of intracoronary imaging by many operators may be explained by perceived time or cost constraints or a belief that visual assessment of coronary anatomical characteristics with x-ray angiography is sufficient.[42,43] However, multiple studies have demonstrated that angiographic lesion assessment alone is severely limited, especially in complex lesions,[44] and that intracoronary imaging is cost-effective by preventing the need for repeated procedures.[45] Although the data supporting the benefit of intracoronary imaging-guided PCI on cardiovascular outcomes are limited to IVUS to date, a recent trial comparing IVUS with a protocolized OCT stent implan tation algorithm demonstrated similar short-term procedural

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Random, 95% CI
AIR-CTO 2015	5	115	9	115	1.8%	0.56 [0.19, 1.61]
AVID 2009	39	395	45	406	7.6%	0.89 [0.59, 1.34]
CHEN et al 2012	11	123	13	123	3.2%	0.85 [0.39, 1.81]
Choi et al	86	1674	275	4331	12.0%	0.81 [0.64, 1.02]
CTO-IVUS 2015	5	201	10	201	1.8%	0.50 [0.17, 1.44]
De la Torre Hernandez 2014	39	505	32	505	6.7%	1.22 [0.78, 1.91]
DIPOL 2007	3	83	6	80	1.2%	0.48 [0.12, 1.86]
EXELLENT 2013	9	463	8	463	2.2%	1.13 [0.44, 2.89]
Gao et al 2014	8	291	24	291	3.0%	0.33 [0.15, 0.73]
HOME DES IVUS 2010	6	105	6	105	1.7%	1.00 [0.33, 3.00]
Hong et al 2014	17	201	17	201	4.2%	1.00 [0.53, 1.90]
IVUS-XPL 2015	17	700	33	700	4.9%	0.52 [0.29, 0.92]
Kim et al 2013	12	269	18	274	3.6%	0.68 [0.33, 1.38]
MATRIX 2011	60	548	66	548	9.4%	0.91 [0.65, 1.26]
OPTICUS 2001	31	273	30	275	6.4%	1.04 [0.65, 1.67]
Roy et al 2008	61	884	43	884	8.2%	1.42 [0.97, 2.07]
Ultimate 2018	20	724	37	724	5.4%	0.54 [0.32, 0.92]
Wakabayashi et al 2012	34	637	45	637	7.1%	0.76 [0.49, 1.16]
Witzenbichler et al 2014	51	3349	124	5234	9.6%	0.64 [0.47, 0.89]
Total (95% CI)		**11540**		**16097**	**100.0%**	**0.81 [0.70, 0.94]**
Total events	514		841			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 27.95$, df = 18 (P = 0.06); $I^2 = 36\%$
Test for overall effect: Z = 2.71 (P = 0.007)

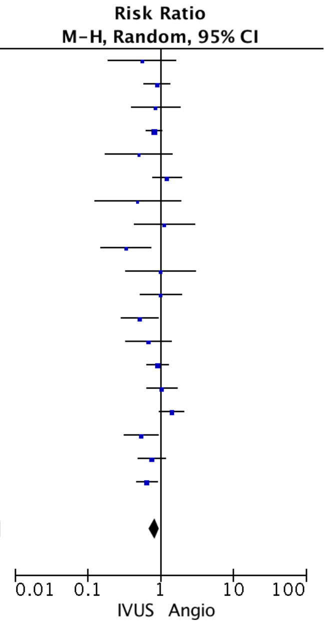

Figure 4. Forest plots for major adverse cardiovascular events. Risk ratio of target lesion revascularization associated with intravascular ultrasound (IVUS)–guided compared with angiography (Angio)–guided percutaneous coronary intervention. AIR-CTO indicates Angiographic and Clinical Comparisons of Intravascular Ultrasound-Versus Angiography-Guided Drug-Eluting Stent Implantation for Patients With Chronic Total Occlusion Lesions; AVID, Angiography Versus Intravascular Ultrasound-Directed Stent Placement; CTO-IVUS, Intravascular Ultrasound–Guided Chronic Total Occlusion Intervention; DIPOL, Direct Stenting vs Optimal Angioplasty Trial; EXCELLENT, Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS-XPL, Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; MATRIX, Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions; OPTICUS, Optimization With ICUS to Reduce Stent Restenosis; ULTIMATE, Intravascular Ultrasound Guided Drug Eluting Stents Implantation in “AllComers” Coronary Lesions trial; M-H, Mantel–Haenszel.

results,[46] implying that OCT may offer similar long-term benefits to IVUS. The ongoing ILUMIEN IV (Optical Coherence Tomography [OCT] — Guided Coronary Stent Implantation Compared to Angiography) trial, which will enroll up to 3650 patients, focusing on high-risk, complex disease at 125 international centers, comparing outcomes after coronary stent implantation using OCT with routine CA will provide further important insight into the generalizability of an intracoronary imaging–guided PCI approach.[47]

This study has several limitations. First, as specific IVUS criteria for optimal stent implantation were not precisely described or consistent among studies, preintervention imaging assessment and stent postdilation were often at the discretion of the operator, likely leading to variability in the final stent result. Second, studies included in the current analysis used both first- and second-generation DESs as well as bare metal stents, which could affect the outcome. Third, our analysis included a mixture of lesion locations and multivessel disease interventions. Fourth, the definition of cardiovascular death and ST (probable versus definite) varied substantially among included studies and played a role in creating heterogeneity. To mitigate this influence, we avoided unadjusted cohorts and down weighted/excluded 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.

Conclusions

IVUS imaging–guided PCI was associated with lower cardiovascular death, MI, TLR, and ST, compared with CA alone. These results encourage the routine use of intracoronary imaging to optimize coronary stent implantation.

Disclosures

None.

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Random, 95% CI
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DIPOL 2007	0	83	0	80		Not estimable
EXELLENT 2013	1	463	1	463	1.3%	1.00 [0.06, 15.94]
Gao et al 2014	1	291	7	291	2.2%	0.14 [0.02, 1.15]
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Witzenbichler et al 2014	18	3349	53	5234	13.3%	0.53 [0.31, 0.90]
Total (95% CI)		**11540**		**16097**	**100.0%**	**0.57 [0.41, 0.79]**
Total events	160		360			

Heterogeneity: Tau² = 0.13; Chi² = 28.18, df = 17 (P = 0.04); I² = 40%

Test for overall effect: Z = 3.41 (P = 0.0006)

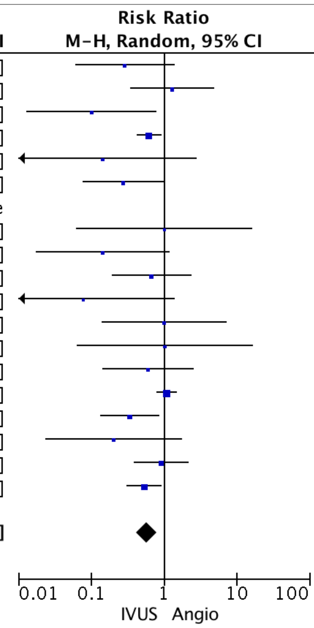

Figure 5. Forest plots for major adverse cardiovascular events. Risk ratio of stent thrombosis with intravascular ultrasound (IVUS)–guided compared with angiography (Angio)–guided percutaneous coronary intervention. AIR-CTO indicates Angiographic and Clinical Comparisons of Intravascular Ultrasound- Versus Angiography-Guided Drug-Eluting Stent Implantation for Patients With Chronic Total Occlusion Lesions; AVID, Angiography Versus Intravascular Ultrasound-Directed Stent Placement; CTO-IVUS, Intravascular Ultrasound–Guided Chronic Total Occlusion Intervention; DIPOL, Direct Stenting vs Optimal Angioplasty Trial; EXCELLENT, Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS-XPL, Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; MATRIX, Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions; OPTICUS, Optimization With ICUS to Reduce Stent Restenosis; ULTIMATE, Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "AllComers" Coronary Lesions trial; M-H, Mantel–Haenszel.

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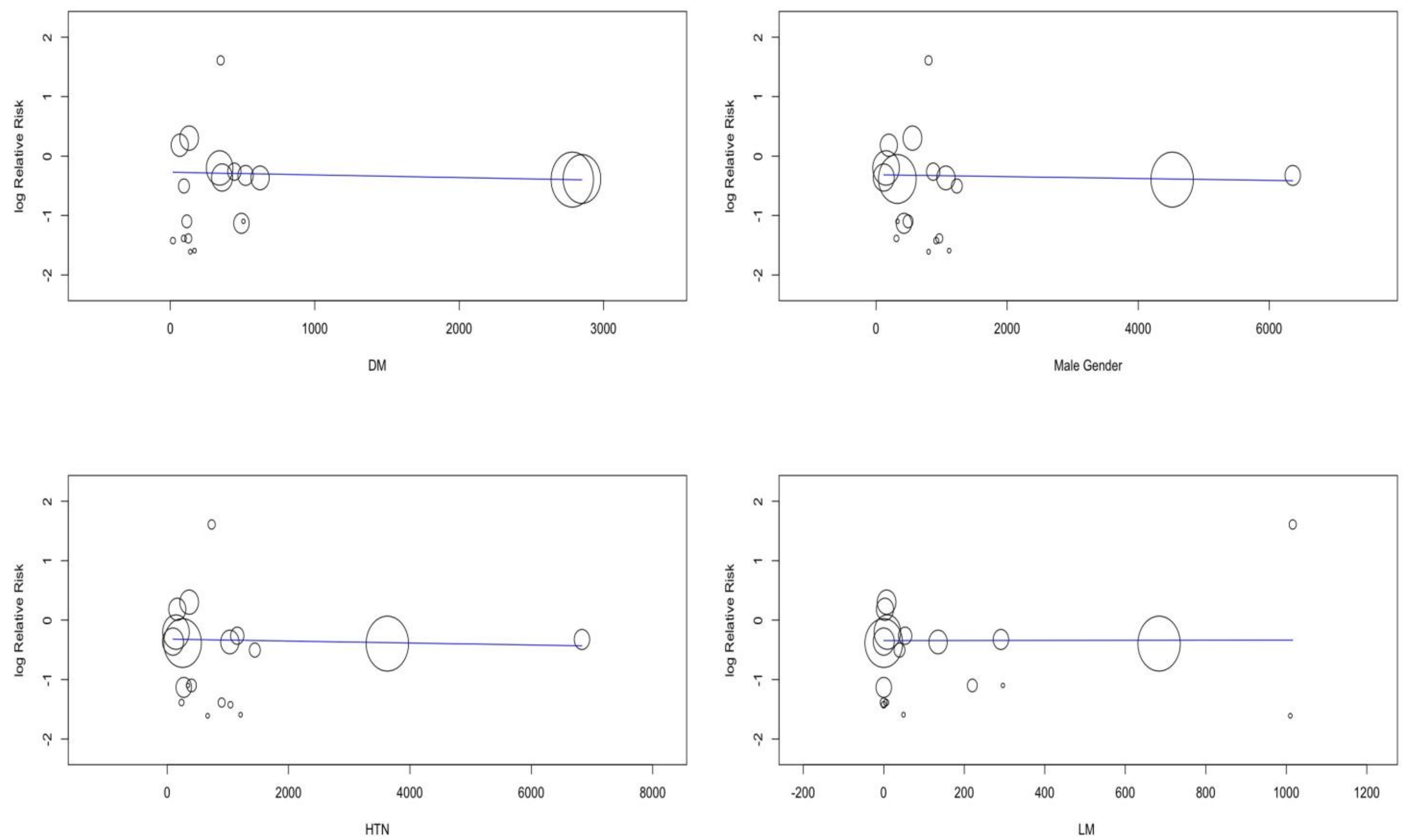
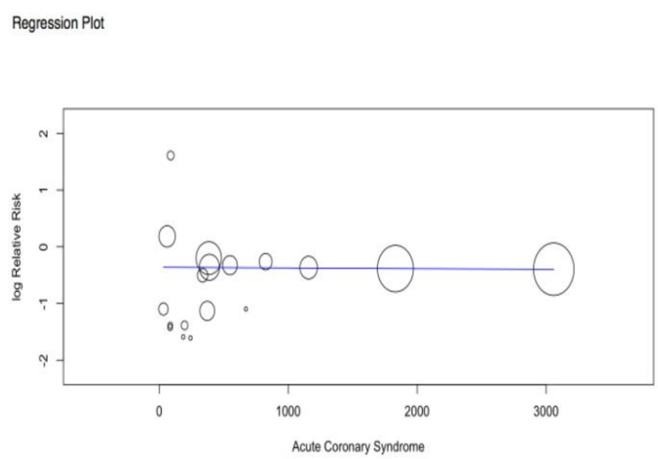
Supplemental Material

Figure S1. Meta-regression of risk for diabetes, hypertension, acute coronary syndrome, sex and left main lesion by MI in study population.





Meta-Regression

Metric: Relative Risk

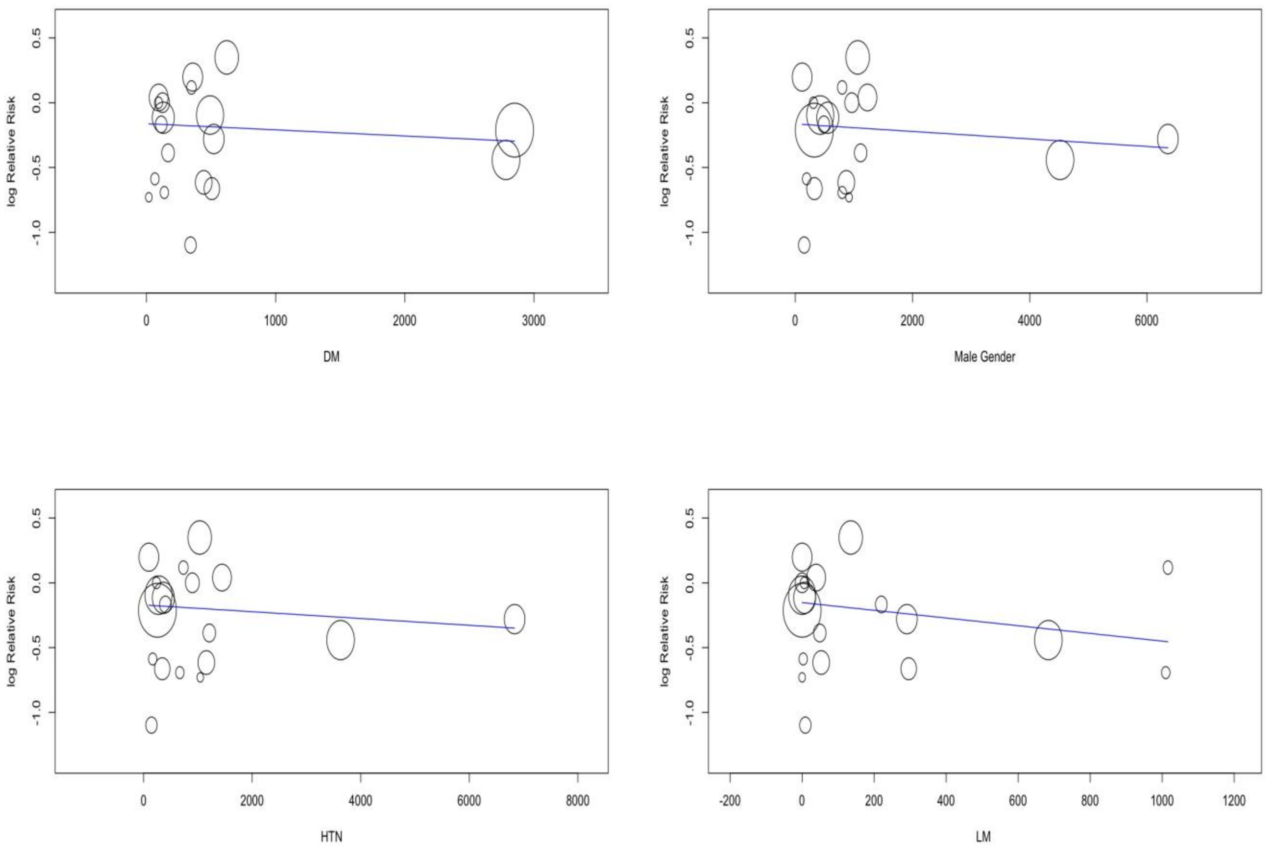
Model Results

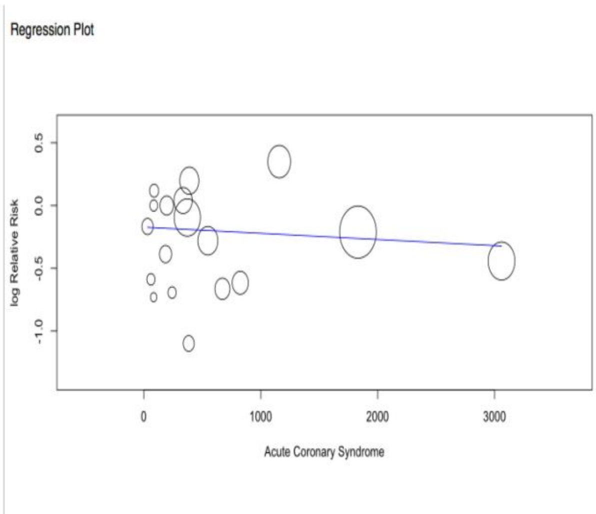
Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	-0.435	-0.727	-0.143	0.149	0.003
DM	-0.000	-0.000	0.000	< 0.001	0.926
HTN	0.001	-0.000	0.002	< 0.001	0.143
Male Gender	-0.001	-0.002	0.000	< 0.001	0.122
LM	0.001	0.000	0.003	< 0.001	0.042
Acute Coronary Syndrome	0.000	-0.001	0.001	< 0.001	0.764

Omnibus p-Value

0.503

Figure S2. Meta-regression of risk for diabetes, hypertension, acute coronary syndrome, sex and left main lesion by target lesion revascularization in study population.





Summary

Meta-Regression

Metric: Relative Risk

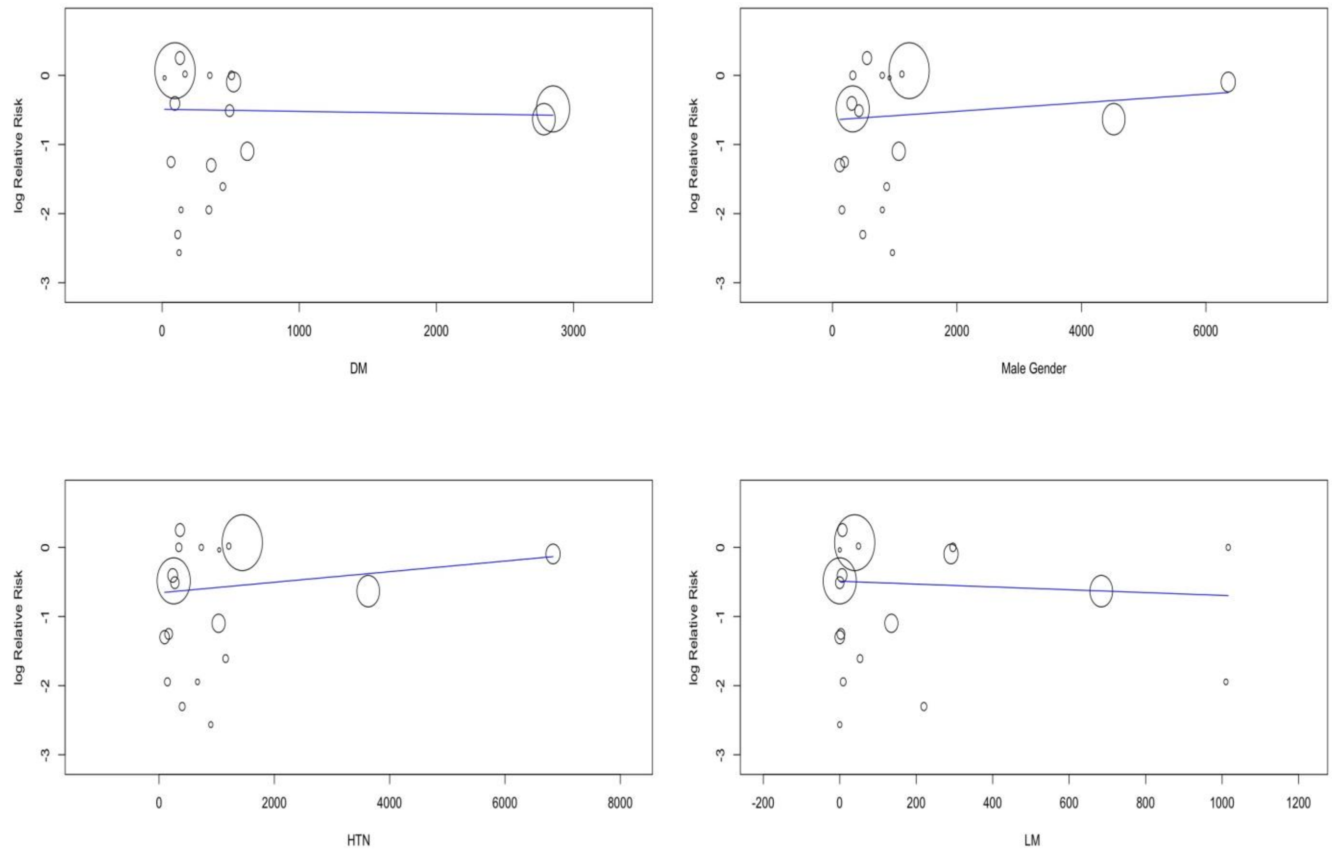
Model Results

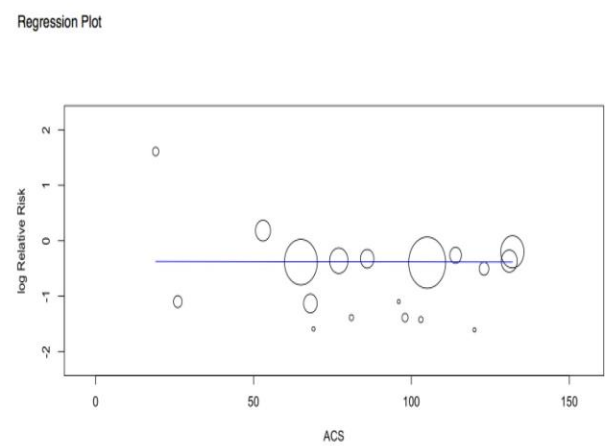
Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	-0.119	-0.370	0.131	0.128	0.351
DM	-0.000	-0.000	0.000	< 0.001	0.622
HTN	-0.000	-0.001	0.001	< 0.001	0.854
Male Gender	0.000	-0.001	0.001	< 0.001	0.881
LM	-0.000	-0.001	0.000	< 0.001	0.410
Acute Coronary Syndrome	0.000	-0.000	0.001	< 0.001	0.803

Omnibus p-Value

0.894

Figure S3. Meta-regression of risk for diabetes, hypertension, acute coronary syndrome, sex and left main lesion by stent thrombosis in study population.





Meta-Regression

Metric: Relative Risk

Model Results

Covariate	Coefficients	Lower bound	Upper bound	Std. error	p-Value
Intercept	-0.793	-1.398	-0.189	0.308	0.010
DM	-0.000	-0.001	0.001	< 0.001	0.967
HTN	0.001	-0.001	0.003	< 0.001	0.348
Male Gender	-0.001	-0.003	0.001	0.001	0.428
LM	-0.000	-0.002	0.002	0.001	0.925
Acute coronary syndrome	0.000	-0.001	0.002	< 0.001	0.754

Omnibus p-Value

0.659

Figure S4. Fixed effect, risk ratio of cardiovascular death associated with intravascular ultrasound (IVUS)-guided compared with angiography-guided PCI.

	IVUS		Angio			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
AIR-CTO 2015	3	115	4	115	0.9%	0.75 [0.17, 3.28]	
AVID 2009	12	395	7	406	1.6%	1.76 [0.70, 4.43]	
CHEN et al 2012	0	123	4	123	1.1%	0.11 [0.01, 2.04]	
Choi et al	98	1647	416	4331	53.5%	0.62 [0.50, 0.77]	
CTO-IVUS 2015	0	201	2	201	0.6%	0.20 [0.01, 4.14]	
De la Torre Hernandez 2014	17	505	30	505	7.0%	0.57 [0.32, 1.01]	
DIPOL 2007	1	83	1	80	0.2%	0.96 [0.06, 15.15]	
EXELLENT 2013	2	463	2	463	0.5%	1.00 [0.14, 7.07]	
Gao et al 2014	5	291	15	291	3.5%	0.33 [0.12, 0.91]	
HOME DES IVUS 2010	3	105	2	105	0.5%	1.50 [0.26, 8.79]	
Hong et al 2014	2	201	5	201	1.2%	0.40 [0.08, 2.04]	
IVUS-XPL 2015	3	700	5	700	1.2%	0.60 [0.14, 2.50]	
Kim et al 2013	0	269	1	274	0.3%	0.34 [0.01, 8.30]	
MATRIX 2011	5	548	10	548	2.3%	0.50 [0.17, 1.45]	
OPTICUS 2001	5	273	1	275	0.2%	5.04 [0.59, 42.83]	
Roy et al 2008	16	884	24	884	5.6%	0.67 [0.36, 1.25]	
Ultimate 2018	5	724	10	724	2.3%	0.50 [0.17, 1.46]	
Wakabayashi et al 2012	12	637	28	637	6.5%	0.43 [0.22, 0.84]	
Witzenbichler et al 2014	27	3349	60	5234	10.9%	0.70 [0.45, 1.11]	
Total (95% CI)		**11513**		**16097**	**100.0%**	**0.62 [0.54, 0.73]**	
Total events	216		627				

Heterogeneity: $Chi^2 = 15.65$, df = 18 (P = 0.62); $I^2 = 0\%$

Test for overall effect: Z = 6.01 (P < 0.00001)

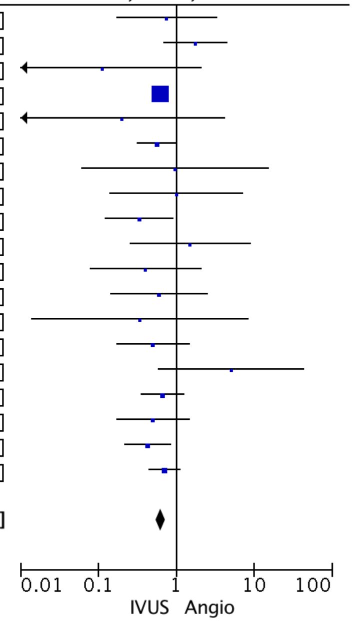


Figure S5. Fixed effect, risk ratio of myocardial infarction associated with intravascular ultrasound (IVUS)-guided compared with angiography-guided PCI.

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AIR-CTO 2015	18	115	15	115	2.9%	1.20 [0.64, 2.26]
AVID 2009	25	395	19	406	3.7%	1.35 [0.76, 2.42]
CHEN et al 2012	4	123	12	123	2.3%	0.33 [0.11, 1.01]
Choi et al	56	1674	213	4331	23.3%	0.68 [0.51, 0.91]
CTO-IVUS 2015	0	201	2	201	0.5%	0.20 [0.01, 4.14]
De la Torre Hernandez 2014	23	505	33	505	6.5%	0.70 [0.42, 1.17]
DIPOL 2007	1	83	4	80	0.8%	0.24 [0.03, 2.11]
EXELLENT 2013	10	463	2	463	0.4%	5.00 [1.10, 22.69]
Gao et al 2014	36	291	44	291	8.6%	0.82 [0.54, 1.23]
HOME DES IVUS 2010	1	105	4	105	0.8%	0.25 [0.03, 2.20]
Hong et al 2014	2	201	8	201	1.6%	0.25 [0.05, 1.16]
IVUS-XPL 2015	0	700	1	700	0.3%	0.33 [0.01, 8.17]
Kim et al 2013	0	269	2	274	0.5%	0.20 [0.01, 4.22]
MATRIX 2011	10	548	31	548	6.1%	0.32 [0.16, 0.65]
OPTICUS 2001	6	273	10	275	2.0%	0.60 [0.22, 1.64]
Roy et al 2008	18	884	26	884	5.1%	0.69 [0.38, 1.25]
Ultimate 2018	10	724	13	724	2.5%	0.77 [0.34, 1.74]
Wakabayashi et al 2012	13	637	18	637	3.5%	0.72 [0.36, 1.46]
Witzenbichler et al 2014	81	3349	188	5234	28.7%	0.67 [0.52, 0.87]
Total (95% CI)		**11540**		**16097**	**100.0%**	**0.70 [0.61, 0.80]**
Total events	314		645			

Heterogeneity: $Chi^2 = 26.44$, df = 18 (P = 0.09); $I^2 = 32\%$
Test for overall effect: Z = 5.18 (P < 0.00001)

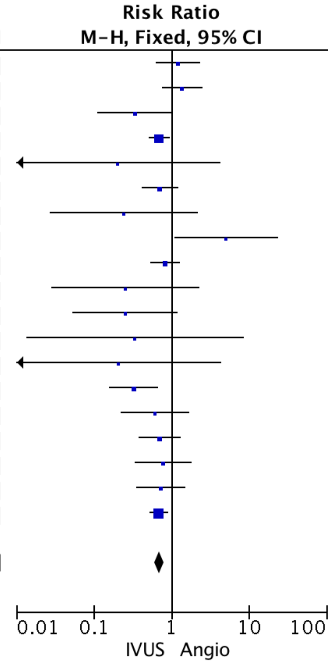


Figure S6. Fixed effect, risk ratio of target lesion revascularization associated with intravascular ultrasound (IVUS)-guided compared with angiography-guided PCI.

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AIR-CTO 2015	5	115	9	115	1.3%	0.56 [0.19, 1.61]
AVID 2009	39	395	45	406	6.4%	0.89 [0.59, 1.34]
CHEN et al 2012	11	123	13	123	1.9%	0.85 [0.39, 1.81]
Choi et al	86	1674	275	4331	22.2%	0.81 [0.64, 1.02]
CTO-IVUS 2015	5	201	10	201	1.4%	0.50 [0.17, 1.44]
De la Torre Hernandez 2014	39	505	32	505	4.6%	1.22 [0.78, 1.91]
DIPOL 2007	3	83	6	80	0.9%	0.48 [0.12, 1.86]
EXELLENT 2013	9	463	8	463	1.2%	1.13 [0.44, 2.89]
Gao et al 2014	8	291	24	291	3.5%	0.33 [0.15, 0.73]
HOME DES IVUS 2010	6	105	6	105	0.9%	1.00 [0.33, 3.00]
Hong et al 2014	17	201	17	201	2.5%	1.00 [0.53, 1.90]
IVUS-XPL 2015	17	700	33	700	4.8%	0.52 [0.29, 0.92]
Kim et al 2013	12	269	18	274	2.6%	0.68 [0.33, 1.38]
MATRIX 2011	60	548	66	548	9.5%	0.91 [0.65, 1.26]
OPTICUS 2001	31	273	30	275	4.3%	1.04 [0.65, 1.67]
Roy et al 2008	61	884	43	884	6.2%	1.42 [0.97, 2.07]
Ultimate 2018	20	724	37	724	5.4%	0.54 [0.32, 0.92]
Wakabayashi et al 2012	34	637	45	637	6.5%	0.76 [0.49, 1.16]
Witzenbichler et al 2014	51	3349	124	5234	14.0%	0.64 [0.47, 0.89]
Total (95% CI)		**11540**		**16097**	**100.0%**	**0.82 [0.73, 0.91]**
Total events	514		841			

Heterogeneity: $Chi^2 = 27.95$, df = 18 (P = 0.06); $I^2 = 36\%$

Test for overall effect: Z = 3.67 (P = 0.0002)

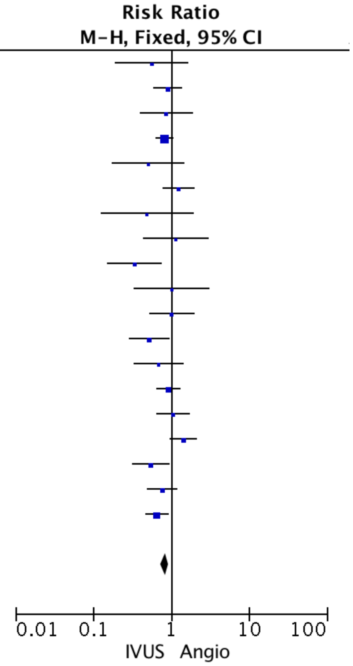


Figure S7. Fixed effect, risk ratio of stent thrombosis associated with intravascular ultrasound (IVUS)-guided compared with angiography-guided PCI.

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AIR-CTO 2015	2	115	7	115	2.5%	0.29 [0.06, 1.35]
AVID 2009	5	395	4	406	1.4%	1.28 [0.35, 4.75]
CHEN et al 2012	1	123	10	123	3.5%	0.10 [0.01, 0.77]
Choi et al	35	1674	147	4331	28.9%	0.62 [0.43, 0.89]
CTO-IVUS 2015	0	201	3	201	1.2%	0.14 [0.01, 2.75]
De la Torre Hernandez 2014	3	505	11	505	3.9%	0.27 [0.08, 0.97]
DIPOL 2007	0	83	0	80		Not estimable
EXELLENT 2013	1	463	1	463	0.4%	1.00 [0.06, 15.94]
Gao et al 2014	1	291	7	291	2.5%	0.14 [0.02, 1.15]
HOME DES IVUS 2010	4	105	6	105	2.1%	0.67 [0.19, 2.29]
Hong et al 2014	0	201	6	201	2.3%	0.08 [0.00, 1.36]
IVUS-XPL 2015	2	700	2	700	0.7%	1.00 [0.14, 7.08]
Kim et al 2013	1	269	1	274	0.3%	1.02 [0.06, 16.20]
MATRIX 2011	3	548	5	548	1.8%	0.60 [0.14, 2.50]
OPTICUS 2001	67	273	63	275	22.1%	1.07 [0.79, 1.45]
Roy et al 2008	6	884	18	884	6.3%	0.33 [0.13, 0.84]
Ultimate 2018	1	724	5	724	1.8%	0.20 [0.02, 1.71]
Wakabayashi et al 2012	10	637	11	637	3.9%	0.91 [0.39, 2.13]
Witzenbichler et al 2014	18	3349	53	5234	14.6%	0.53 [0.31, 0.90]
Total (95% CI)		**11540**		**16097**	**100.0%**	**0.64 [0.53, 0.76]**
Total events	160		360			

Heterogeneity: $Chi^2 = 28.18$, $df = 17$ ($P = 0.04$); $I^2 = 40\%$

Test for overall effect: $Z = 4.85$ ($P < 0.00001$)