



Clinical Outcomes Following Hemodynamic Parameter or Intravascular Imaging-Guided Percutaneous Coronary Intervention in the Era of Drug-Eluting Stents: An Updated Systematic Review and Bayesian Network Meta-Analysis of 28 Randomized Trials and 11,860 Patients

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Background: Coronary angiography (CAG) is the standard imaging modality for guiding percutaneous coronary interventions (PCI). Intracoronary imaging techniques such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), and hemodynamic parameter like fractional flow reserve (FFR) can overcome some limitations of CAG.

Objective: We sought to explore the clinical outcomes of different PCI guidance modalities in the era of drug-eluting stent (DES).

Methods: A network meta-analysis of 28 randomized trials and 11,860 patients undergoing different modalities-guided PCI in the era of DES was performed. Odds ratio (OR) with 95% credible interval (CrI) were calculated.

Results: In comparison with CAG, IVUS was associated with a significant reduction in major adverse cardiovascular events (MACE, OR: 0.60; 95% CrI: 0.46–0.79), cardiovascular death (OR: 0.46; 95% CrI: 0.20–0.94), target vessel/lesion revascularization (TVR/TLR, OR: 0.55; 95% CrI: 0.41–0.74), and a trend toward decreased risk of stent thrombosis (OR: 0.44; 95% CrI: 0.17 to 1.00). FFR/quantitative flow ratio (QFR) could significantly reduce stroke compared with CAG, IVUS, and OCT/optical frequency domain imaging (OFDI). However, myocardial infarction (MI), all-cause death, stent thrombosis, and any revascularization presented similar risks for different PCI guidance modalities.

Conclusion: In the era of DES, IVUS led to lower risks of MACE than CAG, which was mainly due to lower risks of cardiovascular death and TVR/TLR. A trend toward decreased risk of stent thrombosis was also observed with IVUS. Hemodynamic parameter (FFR/QFR)-guided PCI could significantly reduce the stroke risk compared with CAG, IVUS, and OCT/OFDI.

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Keywords: percutaneous coronary interventions (MeSH: D062645), drug-eluting stent (DES), coronary angiography, intravascular ultrasound (IVUS), optical coherence tomography (OCT), fractional flow reserve (FFR)

INTRODUCTION

Coronary angiography (CAG) is the traditional and most widely used invasive imaging modality for guiding percutaneous coronary intervention (PCI). However, the two-dimensional projection of CAG cannot depict the structure of complex 3-dimensional arterial vessel wall, and thus evaluate the vessel dimensions and plaque characteristics, nor directly assess the result of stent implantation. Instead, intracoronary imaging through intravascular ultrasound (IVUS) and optical coherence tomography (OCT) can provide valuable incremental information that can be used clinically to optimize the stent implantation and minimize the stent-related problems (1–3). Fractional flow reserve (FFR) is a lesion-specific physiological index to evaluate the functional significance of coronary stenosis, and its benefit in guiding PCI has been proven by many clinical studies (4–6).

Although numerous meta-analyses and randomized trials have been published to compare the clinical outcomes between CAG and IVUS (1, 7, 8), CAG and OCT (9, 10), CAG and FFR (11, 12), yet just a few network meta-analyses are designed to compare the effects of all available modalities [CAG, IVUS, OCT/optical frequency domain imaging (OFDI), and FFR] for the guidance of PCI within a single analytical framework (13, 14). Moreover, randomized trials performed in the era of bare-metal stents (BMS) were also included in the aforementioned network meta-analyses, which may not be applicable to current clinical practice where drug-eluting stents (DES) have been widely used (15, 16). Pharmacological therapeutics have undergone great changes from BMS to DES era, especially the development of proprotein convertase subtilisin-kexin type 9 (PCSK-9) inhibitors, which can reduce levels of low-density lipoprotein cholesterol (LDL-C) by 50–70% when added to statins (17). Additionally, the previous network meta-analysis may be influenced by including observational studies. As more randomized trials and modalities have become available on PCI guidance, an updated comprehensive network meta-analysis of randomized trials is needed to evaluate the clinical outcomes associated with hemodynamic parameter (FFR or FFR related) or intravascular imaging (IVUS, OCT, or OFDI related)-guided PCI compared with CAG-guided PCI in the era of DES.

METHODS

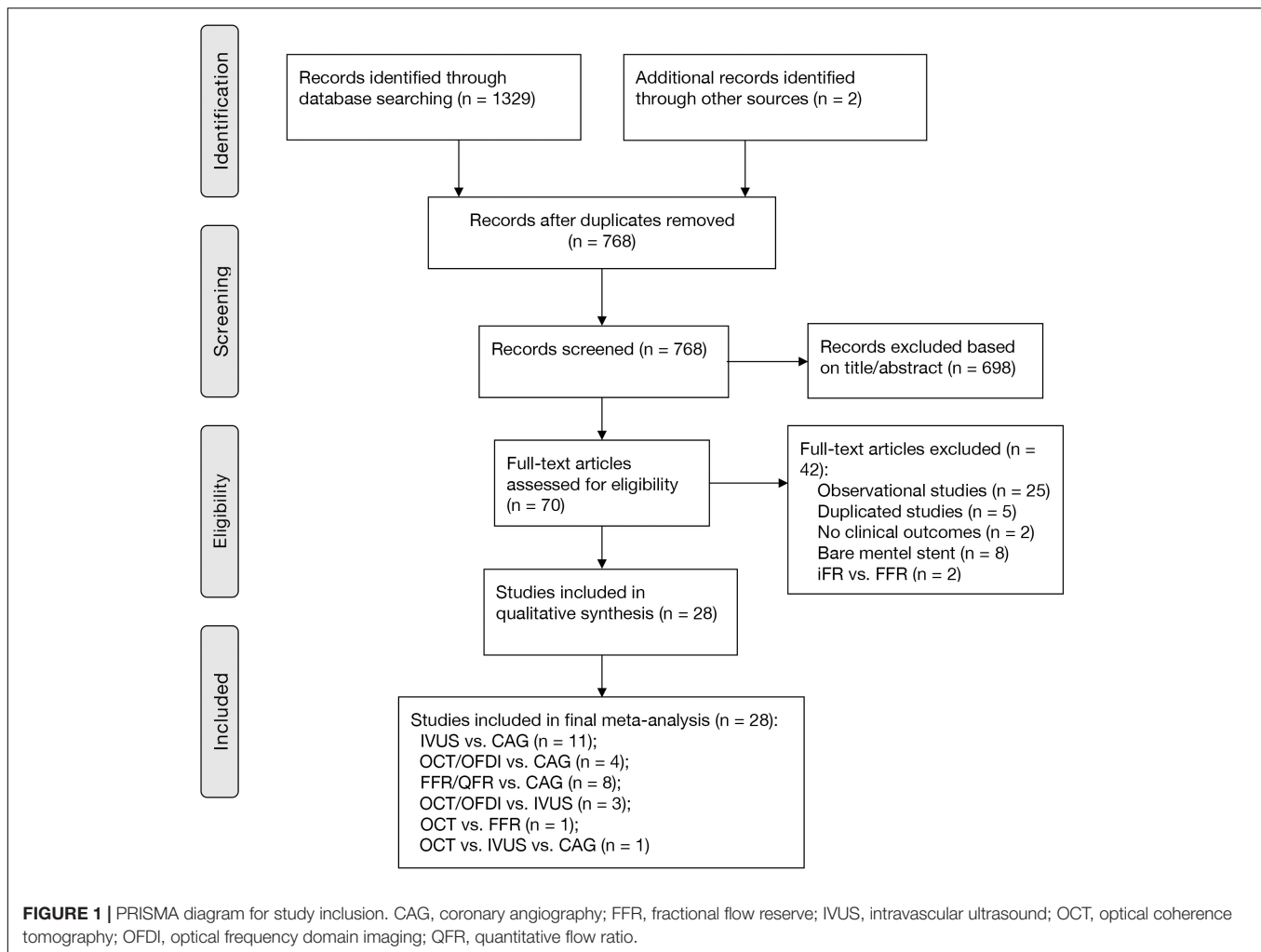
This network meta-analysis was conducted according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) network meta-analysis extension statement (18). The summary data were obtained from the published randomized trials with approval from the respective institutional review committees. Therefore, no further sanction was required for our network meta-analysis. This meta-analysis has been registered at the PROSPERO international prospective register of systematic reviews (CRD42021291442).

SEARCH STRATEGY

We conducted a systematic search of the literature on October 12, 2021. The databases included Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and Web of Science. We also searched TCTMD, ClinicalTrials.gov, and major congress proceedings to identify potential studies. The medical subject headings or keywords included the following: coronary angiography, CAG; intravascular ultrasound, IVUS; optical coherence tomography, OCT; optical frequency domain imaging, OFDI; fractional flow reserve, FFR; instantaneous wave-free ratio, iFR; quantitative flow ratio, QFR; percutaneous coronary intervention, PCI; randomized controlled trial, RCT. The research syntax has been provided in **Supplementary Table 1**. Moreover, relevant randomized trials from reference lists of identified systematic reviews, meta-analyses, and relevant reviews were additionally hand searched to supplement the search of the electronic databases.

SELECTION CRITERIA AND DATA EXTRACTION

We included all randomized trials that compared any combination of the four category modalities: hemodynamic parameter-guided PCI [FFR, instantaneous wave-free ratio (iFR), quantitative flow ratio (QFR)], IVUS-guided PCI, OCT/OFDI-guided PCI, and CAG-guided PCI with DES implantation. Randomized trials without reporting our interested clinical



outcomes were excluded. When multiple publications from the same randomized trial existed, we included the publication with the longest follow-up duration. The selection and data extraction processes were carried out in duplicate by two independent reviewers (HU MJ and GAO XJ), and any disagreement was resolved by consensus with a third-party reviewer (YANG JG).

QUALITY ASSESSMENT OF RISK OF BIAS

The risk of bias for all included studies was assessed using the Cochrane risk of bias assessment tool (19). Publication bias was investigated with comparison adjusted funnel plots.

OUTCOMES

Our primary outcomes were major adverse cardiovascular events (MACE), cardiovascular death, myocardial infarction (MI), and target vessel/lesion revascularization (TVR/TLR) as reported by the trial authors. Secondary outcomes included all-cause

death, stroke, stent thrombosis, and any revascularization. The definition of clinical outcomes was prescribed according to each randomized trial and can be found in **Supplementary Table 2**.

STATISTICAL ANALYSIS

The Bayesian network meta-analysis was performed with a random effects model. Outcomes were reported as odds ratio (OR) with 95% credible interval (CrI) for all outcomes of interest. Four Markov chains were run simultaneously with 100,000 simulated draws after a burn-in of 10,000 iterations. We evaluated consistency with a node-splitting technique that compared the direct and indirect estimates for each comparison. The surface under the cumulative ranking curve (SUCRA) metric was used to compare the hierarchy of clinical outcomes of different PCI guidance modalities. SUCRA values vary between 0 and 100%, the higher the value, the higher the likelihood that a modality is in the top rank or highly effective (20). All analyses were conducted using R software (version 3.4.3) equipped with the “gemtc” package.

TABLE 1 | Baseline characteristics of included randomized trials.

Study/References	Location	Number of patients	Multicenter center	Primary endpoint	Mortality reported	Maximum follow-up	Lost to follow-up (%)
IVUS versus CAG							
Jakabcin et al. (21)	Czech Republic	105/105	NO	MACE	YES	1.5 years	NA
AVIO, (22)	International	142/142	YES	post-procedure in lesion minimal lumen diameter	NO	2 years	3.2
RESET, (23)	Korea	269/274	YES	MACE	YES	1 year	0
MOZART, (24)	Brazil and Spain	41/42	NA	total volume contrast agent used	YES	4 months	0
IVUS-XPL, (25)	Korea	700/700	YES	MACE	NO	1 year	5.0
CTO-IVUS, (8)	Korea	201/201	YES	cardiac death	YES	1 year	0.2
Tan et al. (26)	China	61/62	NO	MACE	NO	2 years	NA
AIR-CTO, (1)	China	115/115	YES	in-stent late lumen loss	YES	2 years	1.7
Wang et al. (27)	China	38/42	NO	MACE	NO	1 year	0
ULTIMATE, (2)	China	724/724	YES	target-vessel failure	YES	1 year	0.3
SURF, (28)	Australia	688/700	NO	Major bleeding and MACE	YES	30 days	3.4
OCT/OFDI versus CAG							
DOCTORS, (10)	France	120/120	YES	FFR at the end of the procedure	YES	6 months	0.4
ROBUST, (29)	Czech Republic	105/96	YES	MACE	YES	9 months	11.4
OPTICO BVS, (30)	Europe	19/19	YES	in-scaffold minimal lumen area	YES	6 months	0
OPTIMUM, (3)	Japan	56/54	YES	percentage of malapposed struts	YES	1 year	4.5
FFR/QFR versus CAG							
FAME, (31)	International	509/496	YES	MACE	YES	5 years	13.9
DKCRUSH-VI, (12)	China	160/160	YES	MACE	YES	1 year	0
FAMOUS-NSTEMI, (4)	United Kingdom	176/174	YES	medical management	YES	1 year	0
DEFER-DES, (5)	Korea	114/115	YES	MACE	NO	5 years	3.5
Zhang et al. (32)	China	110/110	NO	MACE	YES	1 year	NA
Quintella et al. (6)	Brazil	34/35	NO	MACE	YES	<12 months	1.4
FLOWER-MI, (33)	France	586/577	YES	MACE	YES	1 year	0.4
FAVOR III China, (34)	China	1913/1912	YES	MACE	YES	1 year	0.5
OCT/OFDI versus IVUS							
Habara et al. (35)	Japan	35/35	NO	stent expansion	YES	in-hospital	0
OPINION, (36)	Japan	412/405	YES	target vessel failure	NO	1 year	1.2
MISTIC-1, (37)	Japan	54/55	YES	in-segment minimum lumen area	YES	3 years	0.9
OCT versus FFR							
FORZA, (38)	Italy	174/176	NO	MACE	YES	13 months	NA
OCT versus IVUS versus CAG							
ILUMIEN III, (39)	International	158/146/146	YES	minimal stent area	YES	1 year	4.2

ACS, acute coronary syndrome; CAG, coronary angiography; FFR, fractional flow reserve; IVUS, intravascular ultrasound; MACE, major adverse cardiac events; OCT, optical coherence tomography; OFDI, optical frequency domain imaging; QFR, quantitative flow ratio.

RESULTS

Characteristics of Included Studies and Bias Assessment

Figure 1 shows that a total of 1,329 citations met the search criteria, and the full text of 70 potentially eligible articles was scrutinized, resulting in including 28 randomized trials from 2010 to 2021 and 11,860 participants. Overall, eleven studies were comparisons between IVUS and CAG (1, 2, 8, 21–28), four studies were comparisons between OCT/OFDI and CAG (3, 10, 29, 30), eight studies were comparisons between FFR/QFR and

CAG (4–6, 12, 31–34), three studies were comparisons between OCT/OFDI and IVUS (35–37), one study was comparison between OCT and FFR (38), one study was comparison among OCT, IVUS, and CAG (39). A total of 3,645 participants were randomly assigned to CAG, 3,396 to IVUS, 1,041 to OCT/OFDI, 3,778 to FFR/QFR (Table 1). The definition of clinical outcomes for each randomized trial can be found in Supplementary Table 1. The network evidence plots for all outcomes of interest are shown in Supplementary Figure 1. The risk of bias assessment was performed for each randomized trial and summarized in Supplementary Figure 2. Most of the studies were in the lowest categories for risk of bias: random sequence

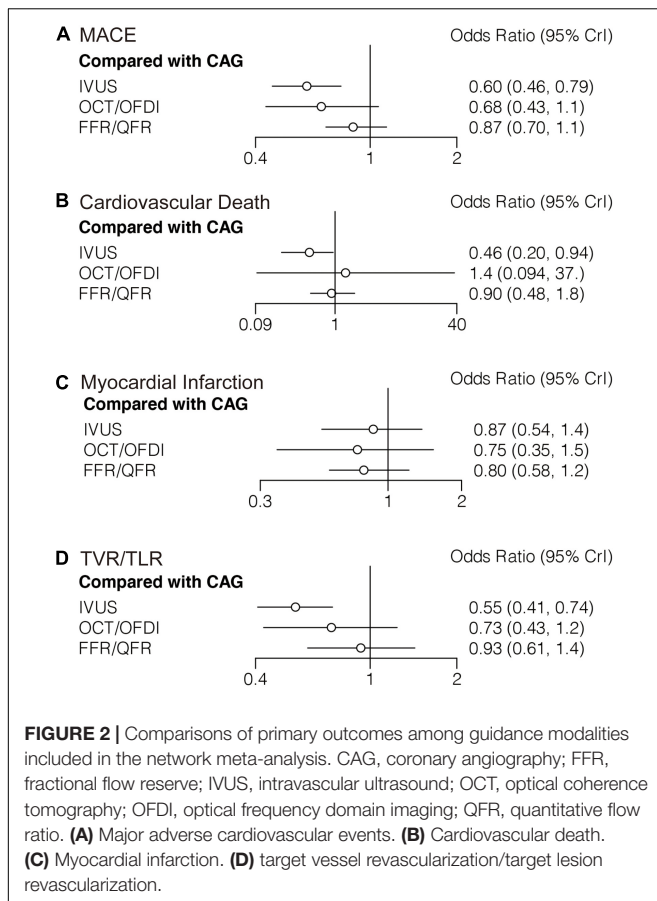


FIGURE 2 | Comparisons of primary outcomes among guidance modalities included in the network meta-analysis. CAG, coronary angiography; FFR, fractional flow reserve; IVUS, intravascular ultrasound; OCT, optical coherence tomography; OFDI, optical frequency domain imaging; QFR, quantitative flow ratio. **(A)** Major adverse cardiovascular events. **(B)** Cardiovascular death. **(C)** Myocardial infarction. **(D)** target vessel revascularization/target lesion revascularization.

generation (25/28), allocation concealment (26/28), blinding of outcome assessment (20/28), incomplete outcome data (28/28), selective reporting (28/28), and other bias (terminated early, 25/28). However, blinding of participants and personnel (9/28) was in the highest category for risk of bias. The funnel plots of publication bias are shown in **Supplementary Figure 3**. Visual analysis of funnel plots demonstrated no evidence of publication bias.

Primary Outcomes

Major Adverse Cardiovascular Events

Twenty-two randomized trials (14,876 patients) reported 1,199 (8.06%) MACE events as classified by individual trial definitions. In comparison with CAG, IVUS was associated with a significant reduction in MACE (*OR*: 0.60; 95% *CrI*: 0.46–0.79), whereas MACE was not significantly reduced with OCT/OFDI or FFR/QFR (**Figure 2A**). There were no significant differences observed in the left guidance modality comparisons (**Table 2**). **Figure 3A** demonstrated that IVUS had high rankings (low likelihoods) for causing MACE.

Cardiovascular Death

Sixteen trials (10,985 patients) reported 123 (1.12%) cardiovascular death events. In comparison with CAG, IVUS could significantly reduce cardiovascular death (*OR*: 0.46; 95% *CrI*: 0.20–0.94), whereas OCT/OFDI or FFR/QFR showed no

TABLE 2 | Comparisons of primary outcomes among guidance modalities included in the network meta-analysis.

	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)
MACE			
CAG	0.60 (0.46, 0.79)	0.68 (0.43, 1.10)	0.87 (0.70, 1.10)
IVUS		1.11 (0.72, 1.73)	1.44 (1.03, 2.08)
		OCT/OFDI	1.30 (0.82, 2.07)
		FFR/QFR	
Cardiovascular death			
CAG	0.46 (0.20, 0.94)	1.40 (0.09, 37.00)	0.90 (0.48, 1.80)
IVUS		2.96 (0.20, 77.72)	1.96 (0.73, 5.96)
		OCT/OFDI	0.66 (0.02, 11.01)
		FFR/QFR	
Myocardial infarction			
CAG	0.87 (0.54, 1.40)	0.75 (0.35, 1.50)	0.80 (0.58, 1.20)
IVUS		0.86 (0.41, 1.79)	0.92 (0.54, 1.76)
		OCT/OFDI	1.07 (0.52, 2.38)
		FFR/QFR	
TVR/TLR			
CAG	0.55 (0.41, 0.74)	0.73 (0.43, 1.20)	0.93 (0.61, 1.40)
IVUS		1.33 (0.79, 2.22)	1.68 (1.02, 2.83)
		OCT/OFDI	1.26 (0.68, 2.44)
		FFR/QFR	

significant difference (**Figure 2B**). There were also no significant differences among the left guidance modality comparisons (**Table 2**). Similarly, IVUS had high rankings (low likelihoods) for causing cardiovascular death (**Figure 3B**).

Myocardial Infarction

Twenty-six randomized trials (15,643 patients) reported 527 (3.37%) MI events. In comparison with CAG, there were no significant differences with IVUS, OCT/OFDI, or FFR/QFR (**Figure 2C**). In addition, no significant differences among the left guidance modality comparisons were observed (**Table 2**). However, OCT/OFDI had high rankings (low likelihoods) for causing MI, whereas CAG had low rankings (high likelihoods) for causing MI (**Figure 3C**).

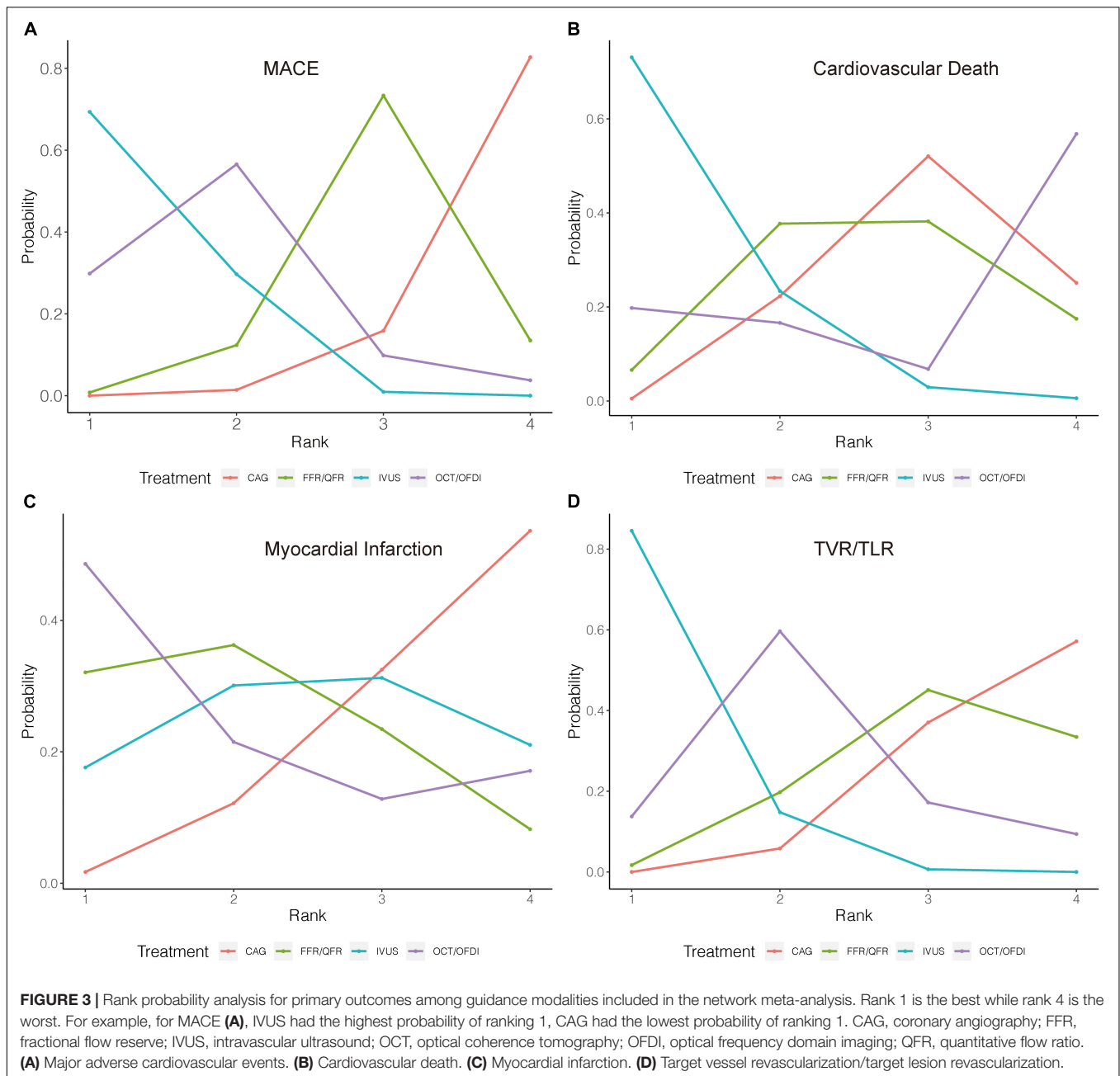
Target Vessel/Lesion Revascularization

Twenty-two trials (12,810 patients) reported 379 (2.96%) TVR/TLR events. In comparison with CAG, IVUS was associated with a significant reduction of TVR/TLR (*OR*: 0.55; 95% *CrI*: 0.41–0.74), whereas OCT/OFDI or FFR/QFR were not (**Figure 2D**). There were also no significant differences among the left guidance modality comparisons (**Table 2**). IVUS had high rankings (low likelihoods) for causing TVR/TLR (**Figure 3D**).

Secondary Outcomes

All-Cause Death

Twenty-two randomized trials (12,768 patients) reported 246 (1.93%) cases of all-cause death. In comparison with CAG, there were no significant differences with IVUS, OCT/OFDI, or FFR/QFR in terms of all-cause death (**Figure 4A**). Similarly, no significant differences were observed among the left guidance modality comparisons (**Table 3**). However, IVUS



had high rankings (low likelihoods) for causing all-cause death (Figure 5A).

Stroke

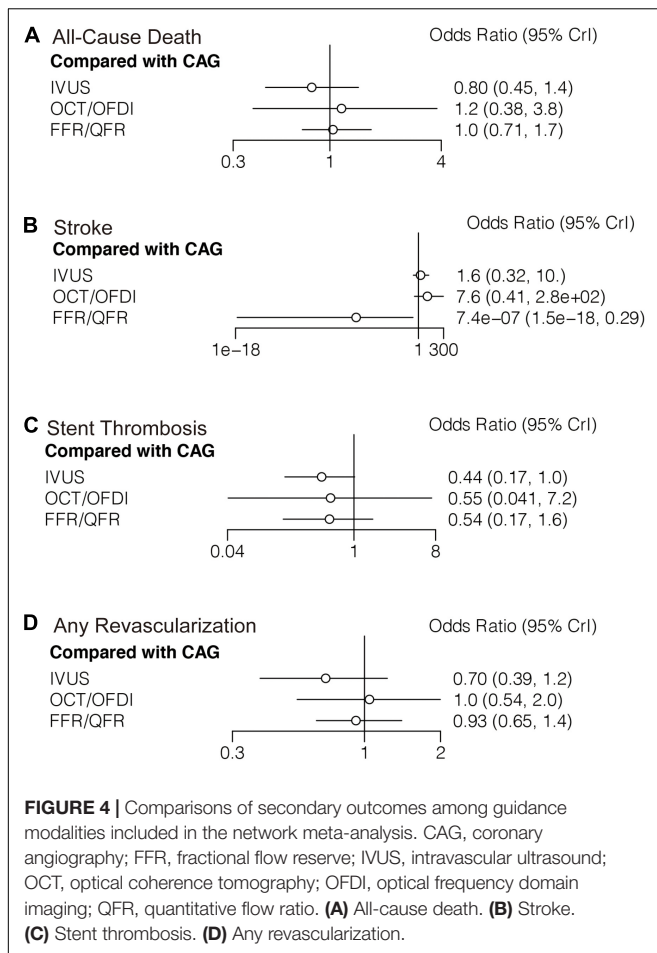
Six trials (4,214 patients) in total reported 17 (0.40%) stroke events. In comparison with CAG, FFR/QFR could significantly reduce stroke events ($OR: 7.4e-07$; 95% $CrI: 1.5e-18-0.29$), whereas IVUS or OCT/OFDI were not (Figure 4B). Moreover, FFR could significantly reduce stroke compared with both IVUS ($OR: 0$; 95% $CrI: 0-0.21$) and OCT/OFDI ($OR: 0$; 95% $CrI: 0-0.06$) (Table 3). Figure 5B revealed that FFR had high rankings (low likelihoods) for causing stroke.

Stent Thrombosis

Fifteen randomized trials (11,269 patients) reported 62 (0.55%) stent thrombosis. In comparison with CAG, IVUS had a trend to decrease stent thrombosis ($OR: 0.44$; 95% $CrI: 0.17-1.00$), while OCT/OFDI or FFR/QFR were not (Figure 4C). In addition, no significant differences were observed among the left guidance modality comparisons (Table 3). CAG had low rankings (high likelihoods) for causing stent thrombosis (Figure 5C).

Any Revascularization

Fifteen randomized trials (9,683 patients) reported 510 (5.27%) any revascularization events. In comparison with CAG, there were no significant differences with IVUS, OCT/OFDI, or



FFR/QFR in terms of any revascularization (Figure 4D). There were also no statistically significant differences in any revascularization risk among the left guidance modality comparisons (Table 3). However, IVUS had high rankings (low likelihoods) for causing any revascularization (Figure 5D).

Figure 6 illustrates the risk of cardiovascular death versus TVR/TLR of different PCI guidance modalities compared with CAG. Overall, the results favored IVUS-guided PCI for fewer cardiovascular death and TVR/TLR compared with CAG.

Network Coherence

The network node-split outcomes for MACE (Supplementary Figure 4A), cardiovascular death (Supplementary Figure 4B), MI (Supplementary Figure 4C), TVR/TLR (Supplementary Figure 4D), all-cause death (Supplementary Figure 4E), stroke (Supplementary Figure 4F), stent thrombosis (Supplementary Figure 4G), and any revascularization (Supplementary Figure 4H) revealed that there were no noticeable differences between direct and indirect estimates in closed loops that allowed the assessment of network coherence.

Sensitivity Analysis

As a sensitivity analysis, results based on fixed effect model were also calculated and similar results were observed (Supplementary Figure 5).

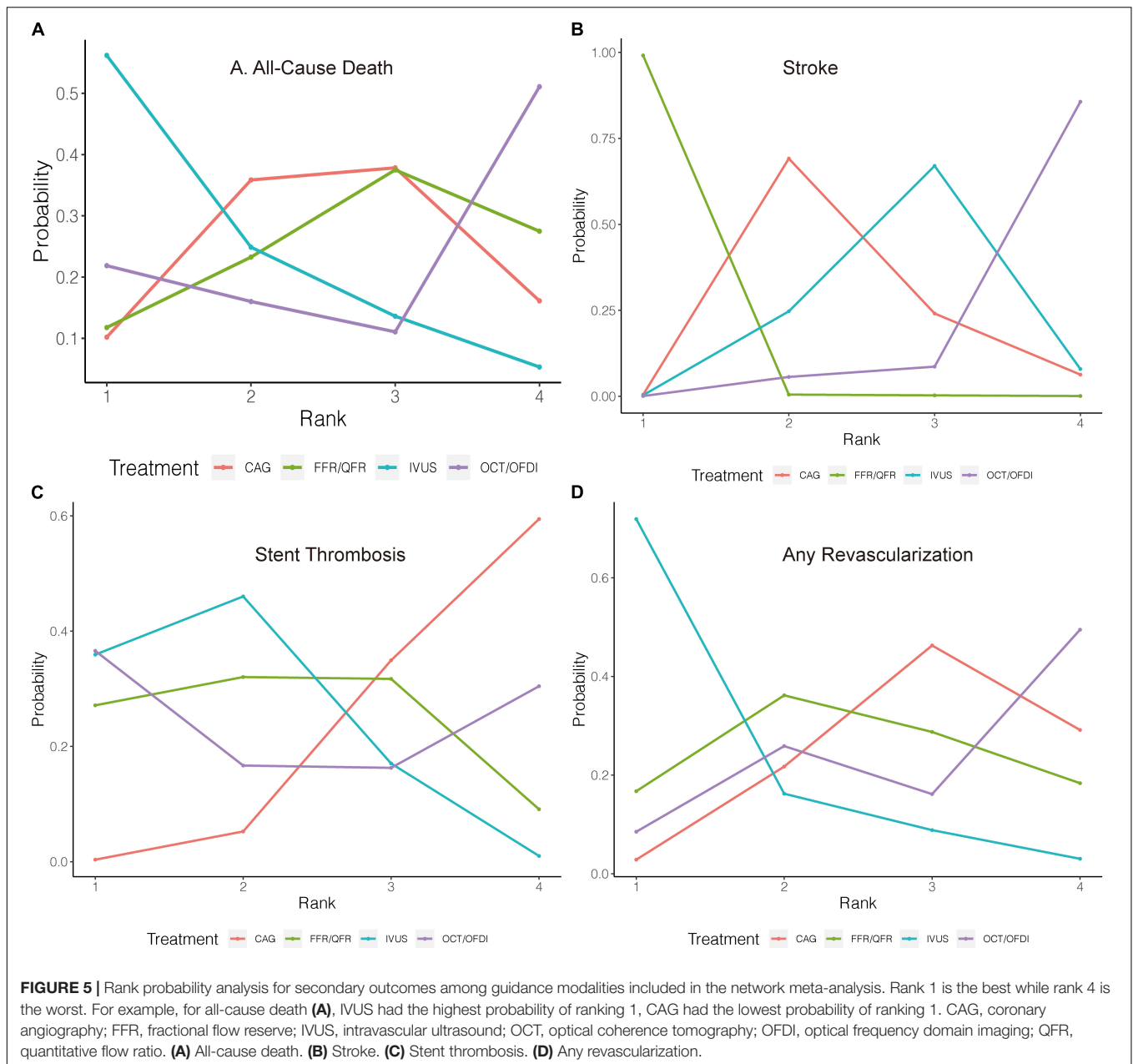
TABLE 3 | Comparisons of secondary outcomes among guidance modalities included in the network meta-analysis.

	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)
All-Cause death			
CAG	0.80 (0.45, 1.40)	1.20 (0.38, 3.80)	1.00 (0.71, 1.70)
IVUS		1.45 (0.48, 4.86)	1.32 (0.67, 2.66)
		OCT/OFDI	0.91 (0.28, 2.85)
		FFR/QFR	
Stroke			
CAG	1.60 (0.32, 10.00)	7.60 (0.41, 280.93)	0 (0, 0.29)
IVUS		4.53 (0.40, 110.00)	0 (0, 0.21)
		OCT/OFDI	0 (0, 0.06)
		FFR/QFR	
Stent thrombosis			
CAG	0.44 (0.17, 1.00)	0.55 (0.04, 7.20)	0.54 (0.17, 1.60)
IVUS		1.27 (0.10, 15.29)	1.23 (0.29, 5.24)
		OCT/OFDI	0.97 (0.05, 16.70)
		FFR/QFR	
Any revascularization			
CAG	0.70 (0.39, 1.20)	1.00 (0.54, 2.00)	0.93 (0.65, 1.40)
IVUS		1.48 (0.77, 2.96)	1.32 (0.68, 2.75)
		OCT/OFDI	0.89 (0.42, 1.91)
		FFR/QFR	

DISCUSSION

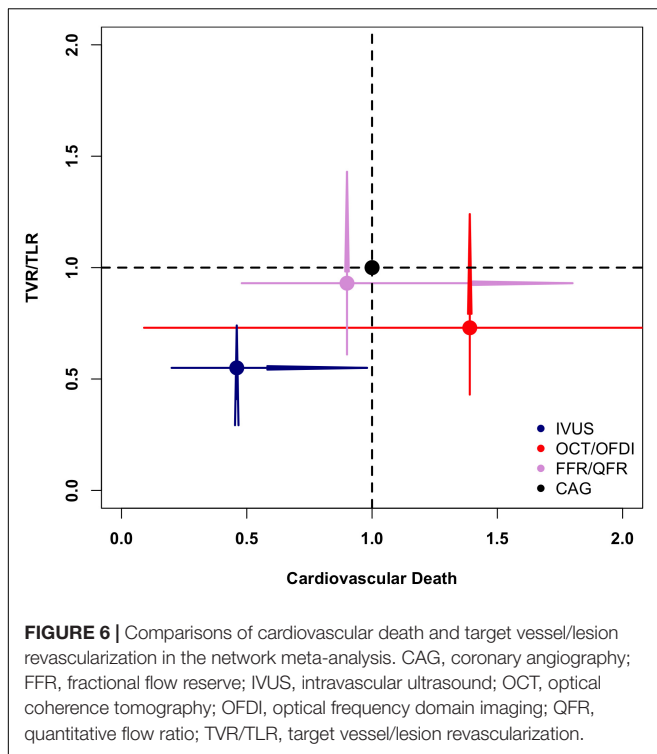
In our network meta-analysis, which included 28 randomized trials and 11,860 patients, we analyzed the clinical outcomes of four category PCI guidance modalities (CAG, IVUS, OCT/OFDI, and FFR/QFR) in the era of DES, and the findings can be summarized as follows. Firstly, IVUS led to lower risks of MACE than CAG, which was mainly due to lower risks of cardiovascular death and TVR/TLR. A trend toward decreased risk of stent thrombosis was also observed with IVUS. Secondly, hemodynamic parameter (FFR/QFR)-guided PCI could significantly reduce stroke compared with CAG, IVUS, and OCT/OFDI. Thirdly, MI, all-cause death, stent thrombosis, and any revascularization presented similar risks for the four category PCI guidance modalities.

Similar with our findings, a meta-analysis including seven trials with 3192 patients in the era of DES also revealed that IVUS-guided PCI was associated with a reduction in the risk of MACE (6.5 versus 10.3%; OR: 0.60; 95% CI: 0.46–0.77), which was mainly because of reduction in the risk of TLR (4.1 versus 6.6%; OR: 0.60; 95% CI: 0.43–0.84). The risk of stent thrombosis (0.6 versus 1.3%; OR: 0.49; 95% CI: 0.24–0.99) also appeared to be lower in the IVUS-guided group, and there was a trend toward lower risk of cardiovascular mortality (0.5 versus 1.2%; OR: 0.46; 95% CI: 0.21–1.00). After all, IVUS allows for easier visualization of the entire vessel structure, particularly when extensive circumferential calcification or attenuated plaques are not encountered (14). Moreover, in the Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study which enrolled an all-comers population, IVUS-guided PCI was also associated with



lower rates of stent thrombosis, MI, and TVR/TLR compared with CAG-guided PCI. Compared with CAG-guided PCI, a larger stent or balloon and/or higher inflation pressures (that would minimize under-expansion) were used in approximately 60% of IVUS-guided procedures, and additional stents (that would mitigate inflow/out-flow issues) were used in about 20% of patients. These strategies are most likely responsible for the lower rates of stent thrombosis and TVR/TLR observed in the IVUS-guided cohort in the present study (40). The aforementioned studies also confirmed that IVUS-guided PCI was superior to CAG-guided PCI not only in selected patients from randomized trials but also in all-comers from real-world scenarios.

An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions claimed that IVUS and OCT are equivalent (and superior to CAG) in guiding and optimizing most PCI procedures (41). In our meta-analysis, it is indeed that no significant differences were observed between IVUS and OCT/OFDI. However, IVUS could decrease the risks of MACE, cardiovascular death, and TVR/TLR compared with CAG, where OCT/OFDI could not. Due to lower tissue penetration, especially in lipid-rich tissue, OCT is limited in assessing plaque burden and detecting vessel size in the presence of diffuse disease, whereas IVUS is an approach used to guide stenting sizing. Moreover, OCT is frequently unable to visualize the ostium as proper blood clearance



is probably a challenge. Also, blood clearance needed for image acquisition in OCT increases the radio-contrast burden, which is particularly detrimental in patients with renal disease, whereas IVUS can minimize the use of iodine contrast in PCI procedure (24, 42). All of the aforementioned characteristics may contribute to the positive prognosis associated with IVUS and negative prognosis associated with OCT/OFDI. Meanwhile, it is noteworthy that compared with IVUS with numerous randomized trials comparing IVUS-guided versus CAG-guided PCI, there is limited research evidence on OCT-guided versus CAG-guided PCI with respect to clinical outcomes and no RCT is powered for clinical outcomes. Therefore, the lack of significant difference between OCT-guided versus CAG-guided PCI may be a result of limited number of patients and underpowered for the outcomes of interest. In addition, IVUS has been used clinically for almost three decades and extensive clinical experience has been gained, which may translate into positive prognosis.

In our meta-analysis, decreased risk of stroke associated with hemodynamic parameter (FFR/QFR)-guided PCI was also observed. As revealed in the British Heart Foundation FAMOUS-NSTEMI randomized trial, the proportion of patients treated initially by medical therapy was higher in the FFR-guided group than in the CAG-guided group [40 (22.7%) versus 23 (13.2%), difference 95% CI: 1.4–17.7%, $p = 0.022$], whereas the aggressive coronary revascularization was higher in the CAG-guided PCI (86.8 versus 77.3%). In a propensity score matching study including a total of 1,299 patients with left ventricular ejection fraction $\leq 50\%$ (433 FFR-guided PCI, 866 CAG-guided PCI), FFR-guided PCI was associated with a lower risk of stroke compared with CAG-guided PCI (0 versus 2%; HR :

0.84; 95% CI: 0.62–0.96) during 1-year follow-up, whereas the differences disappeared after 5-years follow-up (3 versus 3%; HR : 0.68; 95% CI: 0.37– 1.65) (43). Therefore, it seems that CAG-associated stroke was mainly confined during peri-procedural and short-term follow-up, possibly due to more aggressive treatments in the CAG-guided group. However, we have to admit the fact that in our meta-analysis, just six trials (4,214 patients) in total reported 17 (0.40%) stroke events, which was too small in scale and maybe the reason for wide CrI . Considering the limited number of randomized trials focusing on the issue of stroke, further randomized trials are warranted to validate the rationality of different modalities in guiding PCI in the era of DES. The currently enrolling ILUMIEN III trial (NCT03507777) will randomize between 2,490 and 3,656 patients with high-risk clinical characteristics (diabetes) and/or complex angiographic lesions to compare the clinical outcomes between OCT-guided versus CAG-guided PCI. The principal results are expected to be published in 2022, which will provide significant evidence on the role of OCT in the guidance of PCI (44).

Despite the better prognosis associated with IVUS, yet CAG is still the mostly used modality in clinical practice. Moreover, the drawbacks associated with DES should be acknowledged. For example, although the healing response was similar and neoatherosclerosis was low in patients receiving durable- or biodegradable-polymer (45), histopathology, and intravascular imaging have detected neoatherosclerosis earlier and more frequently with DES compared with BMS (45). However, with the advancement in medical management (46) and techniques (47), it is promising that the prognosis associated with cardiovascular disease will improve greatly.

LIMITATIONS

The present study should be interpreted with caution in light of some limitations. First, this is a study-level meta-analysis providing average treatment effects. The absence of patient-level data prevents us from assessing the effect of baseline clinical characteristics in PCI guidance modalities which might affect clinical outcomes. Second, subgroup analysis based on stable or acute coronary symptom is impossible because both stable and acute coronary symptom patients were included in the same trial. However, the ADAPT-DES study revealed that IVUS-guided PCI was superior to CAG-guided PCI in both stable and acute coronary symptom patients (40). Third, just six trials (4,214 patients) in total reported 17 (0.40%) stroke events, which was too small in scale and maybe the reason for wide CrI . Therefore, more randomized trials are warranted to validate the rationality of different modalities in guiding PCI in the era of DES. Fourth, IVUS has been used clinically for almost three decades and extensive clinical experience has been gained. However, the same scenario was not obtained for other PCI guidance modalities (OCT, OFDI, FFR, and QFR). Considering the fact that a long learning curve is required to commend a new PCI guidance modality, therefore, unfamiliar with the newly developed PCI guidance modality may negatively affect prognosis.

CONCLUSION

Our comprehensive network meta-analysis provides evidence that IVUS-guided PCI resulted in less MACE, cardiovascular death, and TVR/TLR. FFR/QFR-guided PCI resulted in decreased risk of stroke in the DES era. Further studies are still required to validate the rationality of different modalities in guiding PCI in the era of DES.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

M-JH: conceptualization, investigation, methodology, resources, validation, visualization, writing – original draft, and writing – review and editing. J-ST: methodology, resources, validation, visualization, and writing – original draft. LY, Y-YZ, J-GY, and X-JG: data curation, formal analysis, methodology, software, and writing – original draft. Y-JY: formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing – review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2022.860189/full#supplementary-material>

Supplementary Figure 1 | Network evidence plot for major adverse cardiovascular events (A), Cardiovascular death (B), Myocardial infarction (C), Target vessel/lesion revascularization (D), All-cause death (E), Stroke (F), Stent thrombosis (G), and Any revascularization (H). CAG, coronary angiography; FFR, fractional flow reserve; IVUS, intravascular ultrasound; OCT, optical coherence tomography; OFDI, optical frequency domain imaging; QFR, quantitative flow ratio.

Supplementary Figure 2 | Methodological quality assessment for each included randomized trial. +, low risk of bias; -, high risk of bias; ?, unclear risk of bias.

Supplementary Figure 3 | Funnel plot of publication bias for major adverse cardiovascular events (A), Cardiovascular death (B), Myocardial infarction (C), Target vessel/lesion revascularization (D), All-cause death (E), Stroke (F), Stent thrombosis (G), and Any revascularization (H). CAG, coronary angiography; FFR, fractional flow reserve; IVUS, intravascular ultrasound; OCT, optical coherence tomography; OFDI, optical frequency domain imaging; QFR, quantitative flow ratio.

Supplementary Figure 4 | Network node-split for major adverse cardiovascular events (A), Cardiovascular death (B), Myocardial infarction (C), Target vessel/lesion revascularization (D), All-cause death (E), Stroke (F), Stent thrombosis (G), and Any revascularization (H). CAG, coronary angiography; FFR, fractional flow reserve; IVUS, intravascular ultrasound; OCT, optical coherence tomography; OFDI, optical frequency domain imaging; QFR, quantitative flow ratio.

Supplementary Figure 5 | Forest plot for major adverse cardiovascular events (A), Cardiovascular death (B), Myocardial infarction (C), Target vessel/lesion revascularization (D), All-cause death (E), Stroke (F), Stent thrombosis (G), and Any revascularization (H) with a fixed effects mode. CAG, coronary angiography; FFR, fractional flow reserve; IVUS, intravascular ultrasound; OCT, optical coherence tomography; OFDI, optical frequency domain imaging; QFR, quantitative flow ratio.

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