CORONARY ANGIOGRAPHY, INTRAVASCULAR ULTRASOUND, AND OPTICAL COHERENCE TOMOGRAPHY

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Circulation

ORIGINAL RESEARCH ARTICLE

Coronary Angiography, Intravascular Ultrasound, and Optical Coherence Tomography for Guiding of Percutaneous Coronary Intervention: A Systematic Review and Network Meta-Analysis

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Intro

- Invasive coronary angiography (ICA) is the ordinary guidance for percutaneous coronary intervention (PCI).
- Nevertheless, ICA provides only a global, 2-dimensional view of coronary artery structures that comes with inherent limitations to comprehensively assess atherosclerotic burden, discern plaque characteristics, define the vessel diameter, ensure optimal stent expansion, and identify acute complications including stent edge dissections, stent mal-apposition, tissue protrusion, and endoluminal thrombosis.
- Against this background, intravascular imaging (IVI) techniques such as intravascular ultrasound(IVUS) and optical coherence tomography (OCT) have emerged as complementary diagnostic tools to overcome ICA shortcomings by serial cross-sectional images of the arteries.

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WHAT IS THE Q/ METHODS?

- Results from multiple randomized clinical trials comparing outcomes after intravascular ultrasound (IVUS)– and optical coherence tomography (OCT)–guided percutaneous coronary intervention (PCI) with invasive coronary angiography (ICA)–guided PCI as well as a pivotal trial comparing the 2 intravascular imaging (IVI) techniques have provided mixed results.
- Considering the uncertainty surrounding the role of IVUS and OCT compared with ICA for guiding PCI and the substantial amount of additional evidence from recent randomized trials, it was decided to conduct a comprehensive and updated network meta-analysis comparing ICA-, IVUS-, and OCT-guided PCI.

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NETWORK META-ANALYSIS(NMA)

- Network meta-analysis is a technique for comparing multiple treatments simultaneously in a single analysis by combining direct and indirect evidence within a network of randomized controlled trials.
- Network meta-analysis may assist in assessing the comparative effectiveness of different treatments regularly used in clinical practice, and therefore has become attractive among clinicians.
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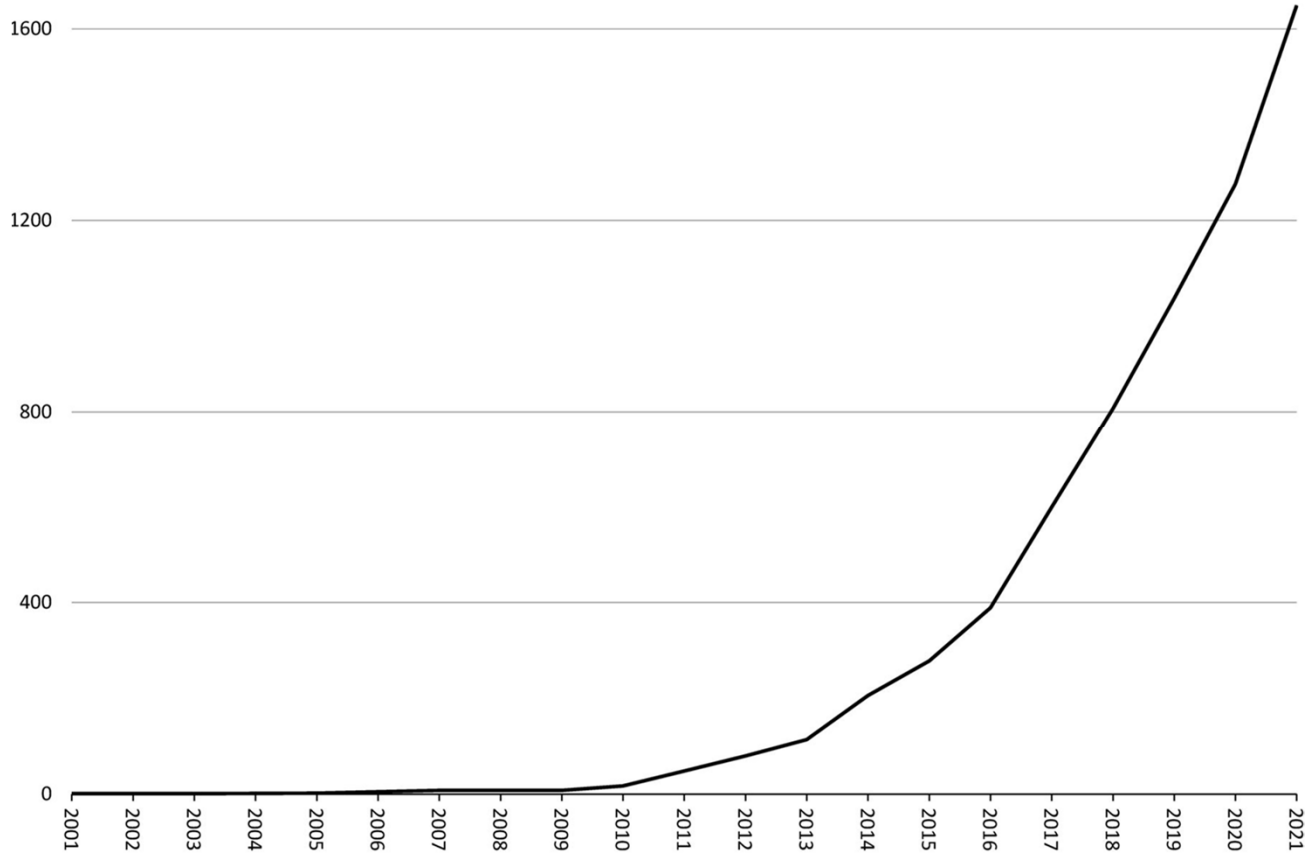
Number of PubMed indexed network meta-analysis publications.



Behnam Sadeghirad et al. BMJ EBM 2023;28:204-209

BMJ Evidence-Based Medicine

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PAIRWISE, BAYESIAN AND FREQUENTIST FRAMEWORKS FOR NETWORK META-ANALYSIS

- Conventional pairwise meta-analysis compares two treatments at a time and relies only on direct evidence (i.e., direct comparison of the two treatments).

- The frequentist method:

operates by assessing the probability of significance and a 95% confidence interval (CI) leading to the acceptance or rejection of a research hypothesis.

In contrast

- Bayesian method:

computes the posterior probability of a research hypothesis by integrating the information inherent in the data with the prior probability derived from previously known information.

In Bayesian analyses, summary estimates are reported along with 95% credible intervals (CrIs). However, the CrI presents a different definition and meaning compared with CI since it is the range containing a particular percentage (i.e., usually 95%) of the posterior probable values

NMA offers the ability to simultaneously estimate the relative benefits and harms of multiple interventions or diagnostic tests, thus better supporting complex decision-making processes. In network meta-analyses, treatment estimates result from the combination of the direct evidence deriving from the head-to-head comparison (i.e., direct connection in the network) with the indirect evidence deriving from the network

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BAYESIAN, Frequentist AND pairwise

- By combining direct evidence with indirect evidence, NMA improves the precision of relative effect estimates.
- Further, its results can guide rating treatment options and reduce the uncertainty of parameters for cost-effectiveness models.
- The past few years have seen important advances in statistical methods, software development, and methodologies to facilitate interpretation and decision-making. But…

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FUNDAMENTALS OF STATISTICAL MODELS FOR NMA

In frequentist statistics, the parameters that represent the characteristics of the population are fixed, but an unknown constant can be inferred using the likelihood of the observed data. In other words, the probability that the research hypothesis is true within the observed data is specified; thus, the frequentist framework can only help decide whether to accept or reject a hypothesis based on the statistical significance level—based on estimation. The results from an analysis using the frequentist approach are given as a point estimate (eg, OR, relative risk, or mean difference) with a 95% CI.

⑩ Bayesian statistics have a different perspective on uncertainty that mostly involves conditional probability—the probability of an event A, given event B. Unlike the frequentist approach which only uses the likelihood from the observed data, the Bayesian framework relies on the probability distribution of the model parameters given the observed data and the prior beliefs from external information about the values of the parameters. Combining these two using Markov Chain Monte Carlo (MCMC) simulations, which intends to reproduce the model many times until it stabilizes and converges, generates a posterior probability. The results of the Bayesian framework are presented as a point estimate with a 95% credible interval (CrI), which is interpreted as the interval in which there is a 95% probability that the values of the point estimate will lie. For ratio measures (eg, OR, relative risk, or HR), medians are used as a point estimate, whereas either the mean or median can be reported for the pooled mean difference or standardized mean difference.

BUT

❿ Despite the appealing advantages, NMA presents challenges:

The two key assumptions of NMA:

1-Transitivity that there are no systematic differences between the available comparisons other than the treatments being compared . *Transitivity* ensures that indirect evidence (obtained from different sets of trials sharing one or more common comparators) validly describes the treatment effect of the corresponding unobserved treatment comparison.

2- Consistency signifies agreement between direct and indirect evidence, ensuring a valid mixed (NMA) treatment effect. Consistency is the statistical manifestation of transitivity to the data.

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- The approaches for checking inconsistency can be classified in two categories: the global approaches and the local approaches.
- *For the global approaches, inconsistency is evaluated in the entire network by modifying the NMA model to account for potential inconsistency, whereas the local approaches detect potential "hot spots" of inconsistency in the network, such as by examining individual loops of evidence separately. It is generally recommended to use both types of methods for inconsistency. Inconsistency can be checked using routines in either Stata or R or WinBUGS codes*

- Coherence, relies on the agreement of different sources of evidence (direct and indirect evidence for the same treatment comparison and their similarity), which may be challenging to justify in practice.
- Despite all the advancements that have made it easier to produce NMAs, many published NMAs are of poor quality.

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STATISTICAL ANALYSES

❿METHODS

❿This study follows the recommendations of Preferred Reporting for Network (PRISMA-NMA) and pairwise meta-analyses (PRISMA) of randomized clinical trials and Cochrane Collaboration.

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ELIGIBILITY CRITERIA

- Trials could be included in the network meta-analyses when the following criteria were satisfied:
- (1) patients from any clinical setting and with any coronary artery disease pattern undergoing PCI
- (2) implantation of drug-eluting stents
- (3) random allocation to at least 2 PCI guidance strategies among ICA, IVUS, and OCT
- (4) clinical follow-up >6 months.
- Trials comparing IVI- (OCT and IVUS) versus ICA-guided PCI that met all the other inclusion criteria were included in the secondary pairwise meta-analyses.

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OUTCOMES

- The prespecified primary outcome:
  target lesion revascularization
- Coprimary outcomes :
  myocardial infarction
- Secondary outcomes:
- ischemia-driven target lesion revascularization
- target vessel myocardial infarction
- all-cause death
- cardiac death
- stent thrombosis
- major adverse cardiac events.
- The preferential follow-up time was 24 months

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RESULTS

- A total of 24 randomized trials
- 15 489 patients:
- IVUS versus ICA,46.4%, 7189 patients
- OCT versus ICA, 32.1%, 4976 patients
- OCT versus IVUS, 21.4%, 3324 patients
- No trial including ICA guidance systematically used quantitative coronary angiography and stent enhancement techniques for PCI optimization.
- The design of trials was predominantly 2-arm
- (except for the ILUMIEN III and Isight trials, which were 3-arm (ie, ICA versus IVUS versus OCT).

RESULTS

- The individual sample size ranged from 80 to 2487 patients
- 17 trials were multicenter
- 16 trials were conducted exclusively in East Asia
- 16 trials intended to primarily assess mid- to long-term clinical outcomes.
- Median F/U: 6 to 30 months
- Mean age 64.4 years
- female sex 25.9%
- Diabetes 33.5%
- target lesions per patient were not >1.6
- Bifurcation disease was an exclusion criterion in some trials and a mandatory inclusion criterion in the OCTOBER trial
- Similarly, left main disease was an exclusion criterion in some trials and a mandatory inclusion criterion in the trial by Liu et al
- Two trials comparing IVUS versus ICA focused only on chronic total occlusion

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RESULTS

- IVUS was associated with reduced target lesion revascularization compared with ICA (odds ratio [OR], 0.69 [95% CI, 0.54–0.87]), whereas no significant differences were observed between OCT and ICA (OR, 0.83 [95% CI, 0.63–1.09]) and OCT and IVUS (OR, 1.21 [95% CI, 0.88–1.66]).
- Myocardial infarction did not significantly differ between guidance strategies (IVUS versus ICA: OR, 0.91 [95% CI, 0.70–1.19]; OCT versus ICA: OR, 0.87 [95% CI, 0.68–1.11]; OCT versus IVUS: OR, 0.96 [95% CI, 0.69–1.33]).
- OCT was associated with a significant reduction of stent thrombosis compared with ICA (OR, 0.49 [95% CI, 0.26–0.92]) but only in the frequentist analysis.
- Similarly, the results in terms of survival between IVUS or OCT and ICA were uncertain across analyses.
- A total of 25 randomized trials (17 128 patients) were included in the pairwise meta-analyses IVI versus ICA where IVI guidance was associated with reduced target lesion revascularization, cardiac death, and stent thrombosis.

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DISCUSSION

- The analysis of available evidence from randomized trials indicates that IVUS-guided PCI was associated with reduced any-type and ischemia-driven target lesion revascularization as well as target vessel revascularization
- Compared with ICA-guided PCI, whereas no significant differences were observed between OCT guided and ICA-guided PCIs for the same outcomes.
- However, neither IVUS- nor OCT-guided PCI was associated with reduced myocardial infarction and target vessel myocardial infarction compared with ICA-guided PCI.
- Although some analyses indicated that IVUS- and OCT-guided PCI were associated with lower mortality and stent thrombosis compared with ICA-guided PCI, these results were significantly influenced by individual trials and the statistical methodology used.
- When pooling trials comparing IVI- versus ICA-guided PCI, the use of IVI was associated with significant reductions in target lesion revascularization, cardiac death, target vessel myocardial infarction, ischemia-driven target lesion revascularization, target vessel revascularization, and stent thrombosis in the frequentist analyses; the effects in terms of target vessel myocardial infarction and ischemia-driven revascularization were mitigated in the Bayesian analyses.

- The results of the RENOVATE-COMPLEX-PCI trial, including 1639 patients randomly assigned to IVI- (IVUS or OCT at the physician's discretion) or ICA-guided PCI, showed that IVI-guided PCI was associated with decreased target vessel failure because of a significantly lower incidence of cardiac death and numerical reductions in target vessel myocardial infarction and target vessel revascularization. These findings were considered as a prelude to the upcoming conclusive results of the large-scale, long-awaited ILUMIEN IV and OCTOBER trials, and secondarily as a background for the confirmatory evidence from the OCTIVUS and GUIDE-DES trials.
- However, these trials yielded controversial results.
- The ILUMIEN IV trial, including a total of 2487 patients with clinical and angiographic high-risk criteria randomly assigned to OCT- or ICA-guided PCI, showed no significant difference in 2-year target lesion failure between guidance strategies.
- In contrast, the OCTOBER trial including 1201 patients with bifurcation disease randomly assigned to OCT- versus ICA-guided PCI showed a significant reduction in major adverse cardiac events at 2 years associated with OCT guidance.
- The OCTIVUS trial, including 2008 patients randomly assigned to OCT or IVUS-guided PCI, showed the noninferiority of OCT guidance in terms of 1-year target vessel failure.
- Finally, the GUIDE-DES trial (Quantitative Coronary Angiography Versus Intravascular Ultrasound Guidance for Drug- Eluting Stent Implantation) added further uncertainty by showing no significant differences between IVUS- and ICA-guided PCI for all the outcomes

⑩ To the best of our knowledge, there is currently no comprehensive and up-to-date network meta-analysis available on this topic. Previous meta-analyses predated the reporting of numerous large-scale trials, focused upon a single IVI modality trial using outdated devices, and used simpler meta-analysis methodology, relying generally only on frequentist statistics, pairwise comparisons, and a very limited number of sensitivity analyses. The present study intends to critically analyze the available evidence on ICA, IVUS-guided PCI, and OCT-guided PCI beyond subjective considerations. In a network meta-analysis, indirect comparisons of treatment effects are built on the assumption that studies making different comparisons are similar and exchangeable (ie, transitivity). Consistency or coherence, in this context, refers to the statistical measure of transitivity.

In this NMA, significant inconsistency was detected in the present network meta-analyses in terms of target lesion revascularization, ischemia-driven target lesion revascularization, and major adverse cardiac events.

In these conditions, direct evidence holds greater reliability than network evidence (ie, the combination of direct and indirect evidence) for these outcomes, and sensitivity analyses showed that the conflict between direct and indirect evidence primarily stems from the ILUMIEN IV trial. In the comparison OCT versus ICA, the potential advantage of OCT over ICA as promoted by the OCTOBER trial was attenuated by the substantial influence of the ILUMIEN IV trial in terms of relative weight and effect heterogeneity. Consequently, the comparison OCT versus ICA yielded neutral and inconsistent results when set against the comparisons OCT versus IVUS and IVUS versus ICA.

- Specifically, the comparison OCT versus IVUS did not show significant differences, with a mild numerical advantage toward OCT driven by the OCTIVUS trial, whereas the comparison IVUS versus ICA portrayed a distinctly favorable effect of IVUS across various analytic approaches.
- The transitivity assumption is violated because if IVUS and OCT are deemed comparable (OCT versus IVUS comparison) and IVUS is superior to ICA (IVUS versus ICA comparison), it follows that OCT should also be superior to ICA. Yet, as detailed above, this effect was not observed because of the ILUMIEN IV trial, which is the largest trial on the topic.
- GUIDE-DES was the other trial providing results on target lesion and vessel revascularization that were not in line with the IVUS-XPL and ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in “All-Comers” Coronary Lesions) trials.
- Nevertheless, although GUIDE-DES was the largest and most recent trial comparing IVUS- versus ICA-guided PCI, its impact in the meta-analyses was generally negligible because of very low event rates.

- Interpreting accumulated evidence is challenging, especially when the granularity of information is variable and individual patient data are not available.
- The observed differences in the direction and magnitude of effects among available trials demonstrate some heterogeneous patterns across outcomes, frequently complicating the construction of clear explanations.
- Nevertheless, it is plausible that variations among individual trial outcomes are, to some extent, influenced by diverse clinical conditions and coronary artery disease patterns.
- In general, the prevalence of diabetes and acute coronary syndrome was heterogeneous across trials.
- Although diabetes is a major ischemic risk factor and is frequently associated with worse outcomes after revascularization, this condition per se is not synonymous with complex coronary artery disease. In the ILUMIEN IV trial, the inclusion of diabetes among the key inclusion criteria may have produced a study population that was dissimilar to that of other trials.
- Similarly, some trials did not include particularly long lesions, and high-risk patterns such as left main disease and chronic total occlusions were generally more represented in IVUS-based trials.

- Of note, although in general the average number of target lesions across available trials was limited, in ILUMIEN IV, patients had predominantly single-target lesion coronary artery disease.
- The OCTOBER trial exclusively included patients with bifurcation disease who in 64.1% of cases required a 2-stent strategy. In contrast, in the ILUMIEN IV trial, only 3.3% of patients underwent a 2-stent strategy for the treatment of bifurcation disease. Although this substantial difference may partially explain the different conclusions of the 2 trials, it is worth also noting that in the OCTOBER trial, an explorative subgroup analysis revealed that the main effect was numerically driven by patients who underwent 1-stent strategy PCI.
- Against this background, it should also be acknowledged that the recent trials showed lower-than-expected incidences of the primary outcome (ILUMIEN IV control: 8.2% observed versus 12.0% expected; OCTIVUS control: 3.1% observed versus 8.0% expected; GUIDE-DES control: 3.8% observed versus 8.0% expected; OCTOBERcontrol: 14.1% instead of 16.0%).

- The uncertain findings raise questions about whether the results of certain trials were affected by the inclusion of noncomplex lesions or, conversely, were influenced by the selection of a specific pattern of coronary artery disease that significantly benefited from IVUS or OCT guidance.
- Nevertheless, differences between exclusively East Asian and primarily non-East Asian trials may provide additional explanations.
- Indeed, beyond the possible advantages of IVI in treating smaller mean reference vessel diameters in East Asian patients compared with those who are non–East Asian, East Asian operators traditionally have larger experience with IVUS and OCT, and this condition has been linked to improved outcomes

- In summary, the present study highlights that IVI guidance for PCI improves clinical outcomes, primarily target lesion revascularization, cardiac death, and stent thrombosis. These results are driven by the trials using IVUS.
- However, accrued evidence is still insufficient, especially for the crucial outcomes of target vessel myocardial infarction and stent thrombosis, and more analysis is warranted to elucidate the reasons for the inconsistent spectrum of outcome improvements between trials favoring IVUS or OCT compared with ICA and understand whether the prognostic advantages of IVI are linked to specific patterns of coronary artery disease.
- In addition, although OCT provides more valuable and informative images compared with IVUS, there remains uncertainty about whether these advantages translate into improved outcomes after OCT-based stent optimization and acute assessment of PCI results.
- In comparison with IVUS, the technical advantages of OCT may be more valuable for assessing the pattern of coronary artery disease and less relevant for improving the results of PCI.

LIMITATIONS

- First, the absence of access to individual patient data hindered the capability to discern the factors contributing to dissimilar conclusions across trials.
- Nevertheless, multiple sensitivity analyses were conducted to identify the clinical settings and coronary artery disease patterns that would gain more benefits from IVI guidance during PCI.
- Second, there was inconsistency in outcomes definition and reporting across trials.
- Moreover, the present study intentionally avoided focusing on major adverse events because of the extreme, unmanageable heterogeneity across trials.
- Finally, follow-up length differed across trials. However, in the primary analyses, almost all trials exhibited a median follow-up ranging from 12 to 24 months, and final follow-up data from the ULTIMATE (ie, 3 years) and IVUS-XPL (ie, 5 years) trials were deliberately not used to reduce heterogeneity in follow-up length. It is important to note that the sensitivity analysis accounting for differences in follow-up length by incidence rate ratios computed from approximated incident rate patient-years of follow-up between groups did not reveal overall significant inconsistency.

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CONCLUSIONS

- IVI-guided PCI was associated with a reduction in ischemia-driven target lesion revascularization compared with ICA-guided PCI, with the difference most evident for IVUS. In contrast, no significant differences in myocardial infarction were observed between guidance strategies.

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