# Intravascular imaging-guided coronary drug-eluting stent implantation: an updated network meta-analysis

*Gregg W Stone, Evald H Christiansen, Ziad A Ali, Lene N Andreasen, Akiko Maehara, Yousif Ahmad, Ulf Landmesser, Niels R Holm*

## Summary

**Background** Previous meta-analyses have shown reduced risks of composite adverse events with intravascular imaging-guided percutaneous coronary intervention (PCI) compared with angiography guidance alone. However, these studies have been insufficiently powered to show whether all-cause death or all myocardial infarction are reduced with intravascular imaging guidance, and most previous intravascular imaging studies were done with intravascular ultrasound rather than optical coherence tomography (OCT), a newer imaging modality. We aimed to assess the comparative performance of intravascular imaging-guided PCI and angiography-guided PCI with drug-eluting stents.

**Methods** For this systematic review and updated meta-analysis, we searched the MEDLINE, Embase, and Cochrane databases from inception to Aug 30, 2023, for studies that randomly assigned patients undergoing PCI with drug-eluting stents either to intravascular ultrasound or OCT, or both, or to angiography alone to guide the intervention. The searches were done and study-level data were extracted independently by two investigators. The primary endpoint was target lesion failure, defined as the composite of cardiac death, target vessel-myocardial infarction (TV-MI), or target lesion revascularisation, assessed in patients randomly assigned to intravascular imaging guidance (intravascular ultrasound or OCT) versus angiography guidance. We did a standard frequentist meta-analysis to generate direct data, and a network meta-analysis to generate indirect data and overall treatment effects. Outcomes were expressed as relative risks (RRs) with 95% CIs at the longest reported follow-up duration. This study was registered with the international prospective register of systematic reviews (PROSPERO, number CRD42023455662).

**Findings** 22 trials were identified in which 15 964 patients were randomised and followed for a weighted mean duration of 24·7 months (longest duration of follow-up in each study ranging from 6 to 60 months). Compared with angiography-guided PCI, intravascular imaging-guided PCI resulted in a decreased risk of target lesion failure (RR 0·71 [95% CI 0·63–0·80]; p<0·0001), driven by reductions in the risks of cardiac death (RR 0·55 [95% CI 0·41–0·75]; p=0·0001), TV-MI (RR 0·82 [95% CI 0·68–0·98]; p=0·030), and target lesion revascularisation (RR 0·72 [95% CI 0·60–0·86]; p=0·0002). Intravascular imaging guidance also reduced the risks of stent thrombosis (RR 0·52 [95% CI 0·34–0·81]; p=0·0036), all myocardial infarction (RR 0·83 [95% CI 0·71–0·99]; p=0·033), and all-cause death (RR 0·75 [95% CI 0·60–0·93]; p=0·0091). Outcomes were similar for OCT-guided and intravascular ultrasound-guided PCI.

**Interpretation** Compared with angiography guidance, intravascular imaging guidance of coronary stent implantation with OCT or intravascular ultrasound enhances both the safety and effectiveness of PCI, reducing the risks of death, myocardial infarction, repeat revascularisation, and stent thrombosis.

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## Introduction

Societal guidelines provide a recommendation (class IIa and level of evidence B) for the use of intravascular imaging with either intravascular ultrasound or optical coherence tomography (OCT) to guide implantation of coronary drug-eluting stents, on the basis of randomised trials showing superior outcomes with this technique compared with angiography guidance alone.[1,2] Although previous meta-analyses of these studies have shown reduced rates of composite adverse cardiac events and repeat revascularisation with intravascular imaging guidance,[3–7] no previous meta-analysis limited to randomised trials has shown a reduction in all-cause death or all myocardial infarction with intravascular imaging guidance of percutaneous coronary intervention (PCI). In addition, few randomised trials have examined the outcomes of PCI with OCT guidance, which provides superior resolution and tissue characterisation compared with intravascular ultrasound but has reduced depth penetration in lipid-rich lesions.

At the scientific sessions of the European Society of Cardiology on Aug 25–29, 2023, four new major randomised trials of intravascular imaging guidance were presented, of which one compared intravascular ultrasound-guided PCI with angiography-guided PCI (with quantitative measurements),[8] two compared OCT-guided PCI with angiography-guided PCI,[9,10] and one compared OCT-guided PCI with intravascular

## Research in context

### Evidence before this study

Before this investigation, there had been numerous meta-analyses of intravascular imaging-guided percutaneous coronary intervention (PCI) versus angiography-guided PCI. However, the methodology of these meta-analyses varied in terms of the numbers of studies included; whether they examined outcomes with bare metal stents or drug-eluting stents; whether data from non-randomised studies were included with data from randomised trials; and whether studies using intravascular imaging for lesion selection were mixed with those using intravascular imaging for stent optimisation. The best and most recent of these meta-analyses showed reductions in composite events with intravascular imaging guidance after drug-eluting stents ranging from 20% to 45% but were underpowered to establish whether intravascular imaging guidance resulted in reduced rates of all-cause death and all myocardial infarction. In addition, few previous trials had assessed intravascular imaging guidance with optical coherence tomography (OCT), a newer imaging modality that, compared with intravascular ultrasound, has notable advantages but some limitations.

### Added value of this study

The present study has incorporated data from numerous randomised trials that had not previously been considered in any meta-analysis, including four large-scale trials presented and published in August, 2023, three of which evaluated OCT-guided PCI. In addition, the present meta-analysis overcomes many of the limitations from previous studies by restricting the analysis to randomised trials of drug-eluting stents; considering outcomes at the longest follow-up duration reported; using network methodology to consider indirect as well as direct comparison data; assessing all intravascular imaging (intravascular ultrasound or OCT) versus angiography guidance as well as all pairwise comparisons of intravascular ultrasound guidance, OCT guidance, and angiography guidance; and verifying the outcomes of the frequentist analysis with a Bayesian assessment. The present report, based on data from 15 964 randomised patients from 22 trials done between March 1, 2010 and Aug 30, 2023, with a weighted mean follow-up duration of 24·7 months, shows that intravascular imaging guidance of coronary drug-eluting stent implantation reduces target lesion failure by 29%, driven by a 45% reduction in cardiac death, an 18% reduction in target vessel-myocardial infarction, and a 28% reduction target lesion revascularisation. In addition, stent thrombosis is reduced by 48% with intravascular imaging guidance, and the present study has shown, for the first time, significant reductions in all-cause death (by 25%) and all myocardial infarction (by 17%) with intravascular imaging guidance. All outcomes were similar following OCT-guided and intravascular ultrasound-guided PCI.

### Implications of all the available evidence

The present updated network meta-analysis, based on a systematic review and synthesis of all available randomised trial data, shows that intravascular imaging guidance with either OCT or intravascular ultrasound of coronary drug-eluting stent implantation improves survival and reduces major adverse events compared with angiography guidance, enhancing both the long-term safety and effectiveness of PCI in patients with coronary artery disease. Attention should now shift to overcoming obstacles to the routine use of intravascular imaging, including improving reimbursement and optimising clinician training. Future studies are warranted to identify which patient and lesion types benefit most from intravascular imaging guidance; to establish whether there are subtle differences in outcomes between OCT and intravascular ultrasound guidance (and if so, for which lesions); and to establish the optimal techniques and procedural objectives for intravascular imaging-guided drug-eluting stent implantation.

ultrasound-guided PCI.[11] These four trials, in which 7224 patients were randomised, have greatly expanded the evidence base for intravascular imaging-guided PCI, and in particular OCT-guided PCI. Therefore, we did an updated systematic review and network meta-analysis of all randomised trials of intravascular imaging-guided PCI with drug-eluting stents to assess the comparative performance of intravascular ultrasound-guided PCI and OCT-guided PCI with angiography-guided PCI.

## Methods

### Search strategy and selection criteria

For this systematic review and network meta-analysis, we assessed the comparative outcomes of PCI guided by intravascular imaging (either intravascular ultrasound or OCT) or by angiography alone. Studies were eligible for inclusion if they randomly assigned patients undergoing PCI with drug-eluting stents either to intravascular ultrasound or OCT, or both, or to angiography alone to guide the intervention. Alternatively, studies were eligible if they randomly assigned participants either to intravascular ultrasound or to OCT to guide the intervention. Only data from randomised trials that reported clinical outcomes were included in the present analysis. We did not exclude any trial on the basis of sample size or duration of follow-up. The data obtained for this analysis were study-level summary estimates.

We did a systematic search of the MEDLINE, Embase, and Cochrane databases from inception to Aug 30, 2023, for randomised trials that fulfilled the eligibility criteria. There were no language restrictions. A representative search string is provided in the appendix (p 8). We manually searched the bibliographies of previous meta-analyses, reviews, and selected studies to identify additional

See Online for appendix

eligible trials, and reviewed conference abstracts from the scientific sessions of the European Society of Cardiology, the American College of Cardiology, the American Heart Association, Transcatheter Cardiovascular Therapeutics, and EuroPCR. The searches were done by two independent investigators (YA and Yasser Jamil [Yale University, New Haven, CT, USA]). Any disputes or concerns were resolved by consensus between the two investigators.

### Data analysis

Data were extracted independently and in duplicate and entered into a case report form. The sources of these data were the primary and secondary publication manuscripts and, for one recent study,[8] a conference presentation. We extracted baseline characteristics of study patients, trial characteristics, and follow-up duration (appendix pp 9–14). The longest available follow-up duration was used for each trial. We also extracted data for clinical outcomes, including numbers of patients in each group and the numbers of patients with a clinical event.

We extracted data for the following clinical outcomes: all-cause death and cardiac (or cardiovascular) death; target vessel-myocardial infarction (TV-MI) or target lesion-myocardial infarction (TL-MI) and all myocardial infarction; ischaemia-driven or clinically driven target lesion revascularisation and target vessel revascularisation; and stent thrombosis (definite or probable). We also extracted data for composite cardiovascular events as reported from each study.

The primary outcome for the present analysis was target lesion failure, defined as the composite of the composite of cardiac (or cardiovascular) death, TV-MI (or TL-MI), and ischaemia-driven or clinically driven target lesion revascularisation, measured at the latest follow-up duration reported. Target lesion failure was chosen for the primary study endpoint as it is the most specific composite outcome referable to events arising from the PCI site. Composite outcomes were assessed only if reported by or otherwise available from the sponsors of the individual trials (ie, we did not obtain composite rates by the summing of individual components). Secondary outcomes included cardiac and all-cause death; TV-MI and all myocardial infarction (including procedural and non-procedural myocardial infarction events); ischaemia-driven or clinically driven target lesion revascularisation and target vessel revascularisation; and stent thrombosis (definite or probable). In two studies, cardiovascular death was reported rather than cardiac death.[12,13] In two studies, TL-MI was reported rather than TV-MI.[10,14] In three studies,[15–17] only definite stent thrombosis was reported. The following rules were applied: if cardiac or cardiovascular death were not available from any individual study, all-cause death was substituted; if TV-MI or TL-MI were not available from any individual study, all myocardial infarction was substituted; and if target lesion revascularisation was not available from any individual study, target vessel revascularisation was substituted. As a post-hoc analysis, we also assessed the outcomes of definite stent thrombosis for the direct comparison of intravascular imaging guidance versus angiography guidance. The component outcomes were defined as per the individual definitions from each study.

Risk of bias was evaluated at the study level using the Cochrane Risk of Bias Tool for the following domains: (1) random sequence generation; (2) allocation concealment; (3) masking of participants and personnel; (4) masking of outcome assessment; (5) incomplete outcome data; (6) selective outcome reporting; and (7) other biases. The potential source of bias in each domain was judged high or low on the basis of study characteristics, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[18]

As the largest dataset with the greatest number of trials, patients, and events, the primary analysis was the comparison of PCI guided by any intravascular imaging (either intravascular ultrasound or OCT) versus PCI guided by angiography alone. Secondary analyses were done on smaller datasets for the comparisons of intravascular ultrasound versus angiography guidance; OCT versus angiography guidance; and OCT versus intravascular ultrasound guidance. One trial[16] randomly assigned patients undergoing PCI either to intravascular ultrasound or OCT (with the specific modality chosen per operator discretion) or to angiography alone. As this randomisation was not stratified, these data are included in the analysis of PCI guided by any intravascular imaging versus angiography alone, but not in any of the other grouped pairwise comparisons.

For each analysis, we did (1) a standard frequentist meta-analysis using restricted maximum likelihood estimators to generate direct data and (2) a network meta-analysis to generate indirect data and overall treatment effects, the latter of which was specified as the primary outcome from this study. A direct, two-stage meta-analysis was done with studies in which the outcomes from the two randomised groups were directly compared and from which summary data were available. A continuity correction of 0·5 was used for data in studies in which one group had zero events.[19] Studies with no events in the two groups were excluded from the relevant analyses. Both random-effects outcomes, using the method of DerSimonian and Laird,[20] and fixed-effects outcomes are reported, with the random-effects result prioritised. Outcomes were assessed as relative risks (RRs) with 95% CIs at the longest reported follow-up from each constituent trial. The $I^2$ statistic was used to assess heterogeneity.[21] No heterogeneity was defined as 0%; low heterogeneity was defined as 1–25%; moderate heterogeneity was defined as >25–50%; and significant heterogeneity was defined as >50%. The Cochran Q test, with corresponding p values for heterogeneity, was also reported. Publication bias was assessed using comparison-adjusted funnel plots and Egger's tests.[22]

For the second analysis, the back-calculation method[23] was used to report and compare the direct and indirect treatment effects using network meta-analyses within a frequentist framework for the same comparisons and outcomes. The back-calculation method uses the three direct estimated treatment effects: (intravascular ultrasound *vs* angiography)$^{direct}$; (OCT *vs* angiography)$^{direct}$; and (intravascular ultrasound *vs* OCT)$^{direct}$; and variances, to derive the indirect estimate. The indirect estimate (ie, OCT *vs* angiography$^{indirect}$) was calculated as the direct effect of intravascular ultrasound *vs* angiography minus the direct effect of intravascular ultrasound *vs* OCT (ie, [intravascular ultrasound *vs* angiography]$^{direct}$ – [intravascular ultrasound *vs* OCT]$^{direct}$) and was then compared with the direct evidence to form a measure of the discrepancy between the two (ie, [OCT *vs* angiography]$^{direct}$ – [OCT *vs* angiography]$^{indirect}$), where a Z test of the difference indicates evidence for inconsistency. The proportion of direct evidence that contributed to the summary network estimate was calculated as: (SE of the network)²/(SE from the direct comparisons)². To evaluate the validity of the network, net heat plots were inspected visually to identify hotspots of inconsistency in the network.[24]

As a sensitivity analysis, the network outcomes for the primary composite outcome were also analysed under a Bayesian random-effects framework.[25] Markov-chain Monte Carlo simulations were used to estimate the posterior distributions. Four chains, 50 000 adaptations, and 500 000 iterations were used for the final Bayesian hierarchical models. The convergence of the models was confirmed by visualising trace plot and density plots. The back-calculation method was also used to determine the direct and indirect treatment effects for the outcomes.

All outcomes were assessed on an intention-to-treat basis. Significance testing was performed at the two-tailed 5% significance level. The statistical programming environment R, with the meta,[26] netmeta,[27] and gemtc[28] packages, was used for all statistical analyses. This analysis was done and reported in accordance with the preferred reporting items for systematic reviews and network meta-analyses (PRISMA) guidance (appendix pp 4–7),[29] and has been registered with the international prospective register of systematic reviews (PROSPERO, number CRD42023455662; submission on Aug 18, 2023, and final registration on Aug 29, 2023). Institutional review board approval and informed patient consent were not required because this study is a systematic review and meta-analysis of previously published, publicly available data.

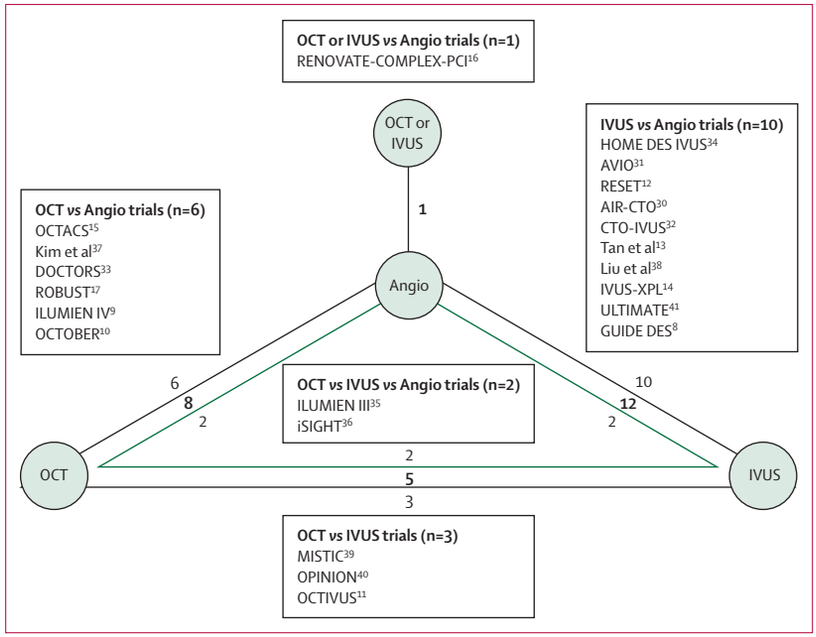



***Figure 1:*** **Nodal map describing the direct randomised comparisons within the network**
The bold numbers denote the number of trials for each randomised comparison, which are derived from the total number of trials where two or three of the guidance modalities were studied (non-bold numbers). Angio=angiography. IVUS=intravascular ultrasound. OCT=optical coherence tomography.

### Role of the funding source
The present study was initiated and sponsored by the investigators and was done without funding other than for the statistical support provided by Abbott (Santa Clara, CA, USA) under the supervision of the investigators. Abbott otherwise had no input into the study design or data interpretation and did not participate in the preparation or review of the manuscript before its submission.

## Results
The systematic search identified 22 randomised trials of intravascular imaging-guided PCI with drug-eluting stents published between March 1, 2010, and Oct 19, 2023.[8–17,30–41] The data available from each study, the timing of imaging, optimisation criteria, the components used for the primary composite outcome in the present analysis, the longest follow-up duration, and the risk of bias from each trial are summarised in the appendix (pp 9–16). In total, 15 964 patients were randomised (ranging from 85 to 2487 patients per trial); 4888 patients from 15 trials were randomly allocated to intravascular ultrasound-guided PCI, 3831 patients from 11 trials were randomly allocated to OCT-guided PCI, 1092 patients from one trial were randomly allocated to intravascular ultrasound-guided or OCT-guided PCI (per operator discretion), and 6153 patients from 19 trials were randomly allocated to angiography-guided PCI. The longest follow-up duration reported from each trial ranged from 6 to 60 months (weighted mean follow-up duration of 24·7 months; median 21 months [IQR 12–24]).

Intravascular imaging-guided PCI versus angiography-guided PCI was compared in 13 030 patients from 19 trials, including intravascular ultrasound-guided PCI versus angiography-guided PCI in 6856 patients from 12 trials, OCT-guided PCI versus angiography-guided PCI in 4726 patients from eight trials, and intravascular ultrasound-guided or OCT-guided PCI (at operator discretion) versus angiography-guided PCI in

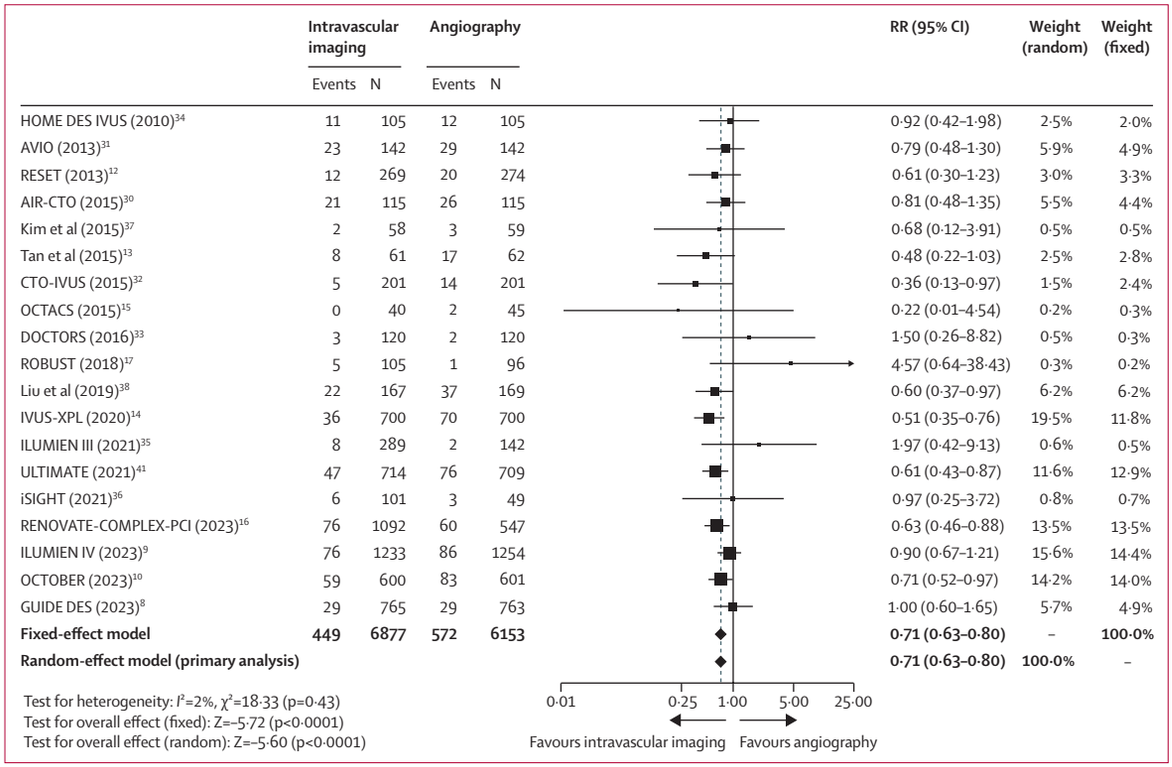



***Figure 2:*** **Study-level meta-analysis of the direct randomised comparisons of intravascular imaging-guided PCI *vs* angiography-guided PCI for target lesion failure**

RR=relative risk. PCI=percutaneous coronary intervention.

1639 patients from one trial (figure 1). OCT-guided PCI was directly compared with intravascular ultrasound-guided PCI in 3324 patients from five trials. Of note, 20 of the 22 trials compared two guidance strategies, whereas two trials[39,40] randomly assigned patients (1:1:1) to intravascular ultrasound guidance versus OCT guidance versus angiography guidance and contributed data to multiple pairwise comparisons.

For the direct randomised comparisons of intravascular imaging-guided PCI versus angiography-guided PCI for the primary composite outcome (figure 2), data were contributed from 13 030 patients randomised in 19 trials, among whom 1021 events occurred during follow-up. Compared with angiography guidance, intravascular imaging guidance resulted in a 29% reduction in the risk of target lesion failure (RR 0·71 [95% CI 0·63–0·80]; p<0·0001). There was minimal heterogeneity between trials ($I^2$=2%). No studies contributed indirect data for this analysis, and thus the network treatment effect estimate (the primary outcome of the present analysis) was identical (RR 0·71 [95% CI 0·63–0·80]; figure 3A).

For the other direct pairwise comparisons for the primary composite outcome, data were contributed from 6856 patients randomised in 12 trials (556 events) of intravascular ultrasound versus angiography guidance; from 4726 patients randomised in eight trials (334 events) of OCT versus angiography guidance; and from 3324 patients randomised in five trials (154 events) of OCT versus intravascular ultrasound guidance (appendix pp 18–20; figure 3B). The network treatment effect estimates showed reductions in target lesion failure with intravascular ultrasound guidance (RR 0·70 [95% CI 0·60–0·81]) and OCT guidance (RR 0·76 [95% CI 0·63–0·91]) compared with angiography guidance. The network treatment effect estimate for target lesion failure was similar with OCT and intravascular ultrasound guidance (RR 1·08 [95% CI 0·89–1·33]).

The treatment effect estimates for target lesion failure analysed in a Bayesian framework were concordant with these frequentist treatment effects (appendix p 17).

For the randomised comparison of intravascular imaging-guided PCI versus angiography-guided PCI for cardiac death (figure 4A; appendix p 21), direct data were contributed from 12 913 patients randomised in 18 trials, among whom 178 events occurred during follow-up. Compared with angiography guidance, intravascular imaging guidance resulted in a 45% reduction in the risk of cardiac death (RR 0·55 [95% CI 0·41–0·75]; p=0·0001). There was no heterogeneity between trials ($I^2$=0%).

The network treatment effect estimate for cardiac death was similar with OCT guidance and intravascular ultrasound guidance (RR 1·08 [95% CI 0·64–1·80]; figure 4C; appendix pp 22–24).

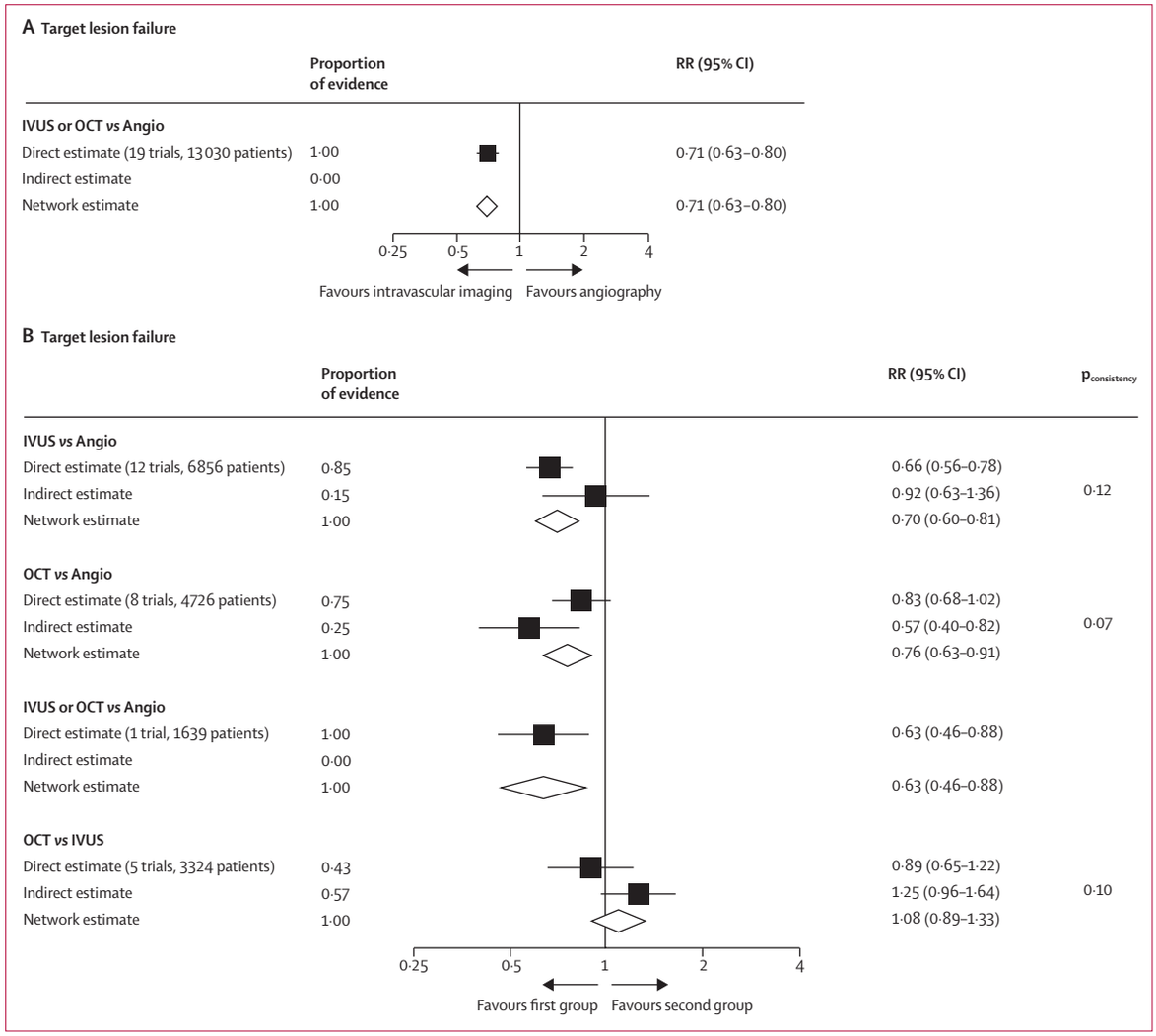


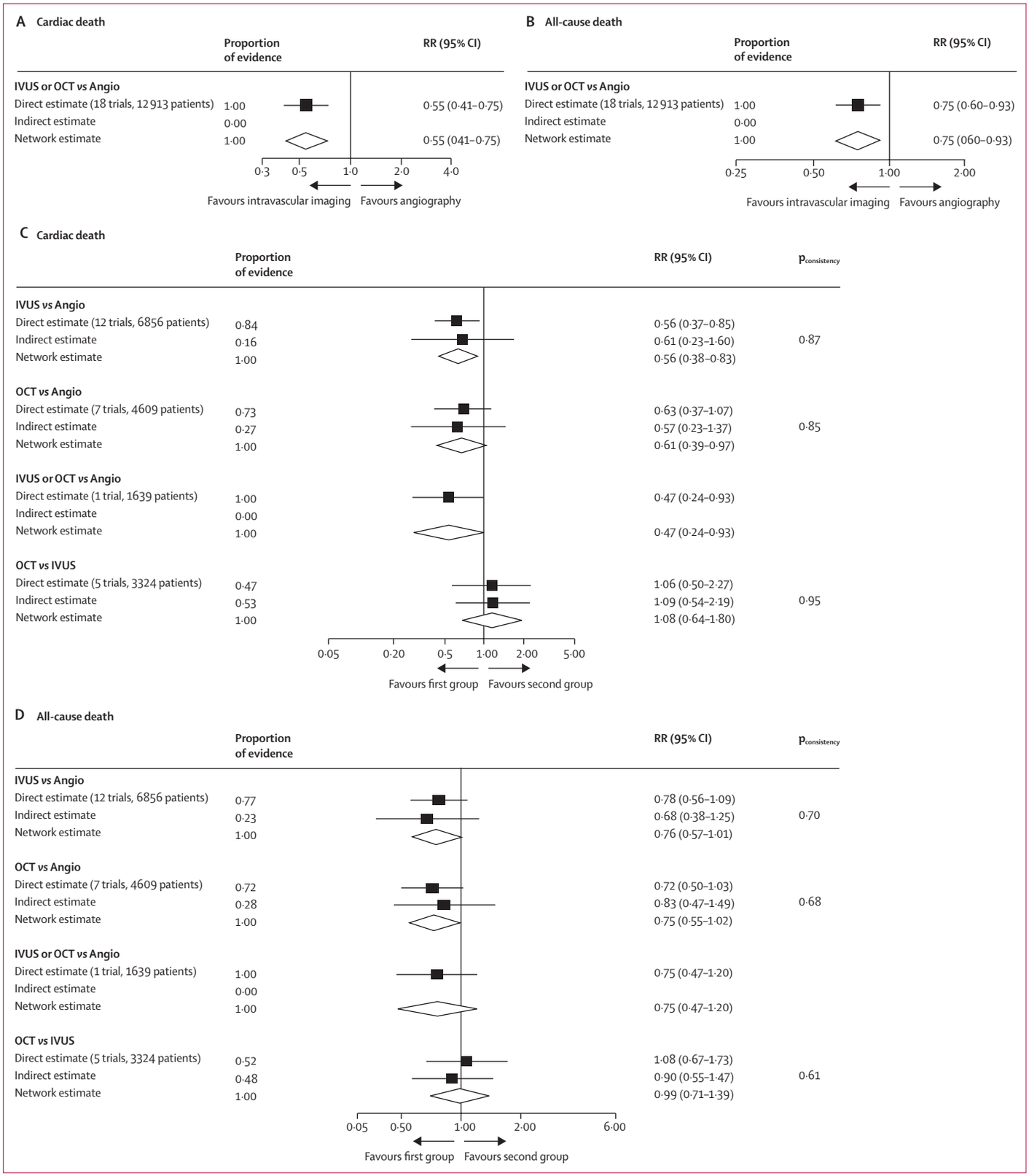

***Figure 3:*** **Direct, indirect, and network treatment effect estimates for target lesion failure**
(A) Intravascular imaging (OCT or intravascular ultrasound)-guided PCI versus angiography-guided PCI. (B) Intravascular ultrasound-guided PCI versus angiography-guided PCI, OCT-guided PCI versus angiography-guided PCI, OCT or intravascular ultrasound (at operator discretion)-guided PCI versus angiography-guided PCI (from the RENOVATE-COMPLEX-PCI trial),[16] and OCT-guided PCI versus intravascular ultrasound-guided PCI. $P_{consistency}$ refers to the consistency of the RR (95% CI) between the direct and indirect data. Angio=angiography. IVUS=intravascular ultrasound. OCT=optical coherence tomography. PCI=percutaneous coronary intervention. RR=relative risk.

For the randomised comparison of intravascular imaging-guided PCI versus angiography-guided PCI for all-cause death (figure 4B; appendix p 25), direct data were contributed from 12 913 patients randomised in 18 trials, among whom 331 events occurred during follow-up. Compared with angiography guidance, intravascular imaging guidance resulted in a 25% reduction in the risk of all-cause death (RR 0·75 [95% CI 0·60–0·93]; p=0·0091).

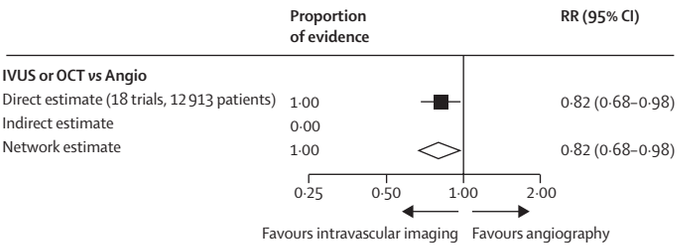
The network treatment effect estimate for all-cause death was similar with OCT guidance and intravascular ultrasound guidance (RR 0·99 [95% CI 0·71–1·39]; figure 4D; appendix pp 26–28).

For the randomised comparison of intravascular imaging-guided PCI versus angiography-guided PCI for

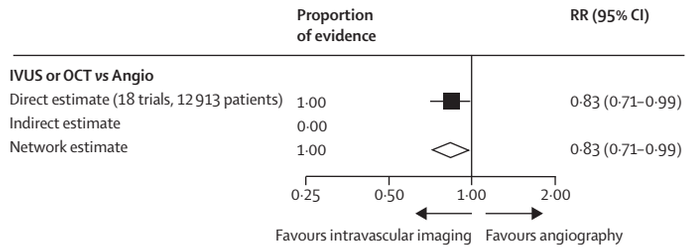
***Figure 4:*** **Direct, indirect, and network treatment effect estimates for fatal events**
Intravascular imaging (OCT or intravascular ultrasound)-guided PCI versus angiography-guided PCI for cardiac death (A) and all-cause death (B). Intravascular ultrasound-guided PCI versus angiography-guided PCI, OCT-guided PCI versus angiography-guided PCI, OCT or intravascular ultrasound (at operator discretion)-guided PCI versus angiography-guided PCI (from the RENOVATE-COMPLEX-PCI trial),[16] and OCT-guided PCI versus intravascular ultrasound-guided PCI for cardiac death (C) and all-cause death (D). $P_{consistency}$ refers to the consistency of the RR (95% CI) between the direct and indirect data. Angio=angiography guidance for PCI. IVUS=intravascular ultrasound guidance for PCI. OCT=optical coherence tomography guidance for PCI. PCI=percutaneous coronary intervention. RR=relative risk.


A Cardiac death
Proportion of evidence
RR (95% CI)
IVUS or OCT vs Angio
Direct estimate (18 trials, 12 913 patients) 1·00 0·55 (0·41–0·75)
Indirect estimate 0·00
Network estimate 1·00 0·55 (041–0·75)
0·3 0·5 1·0 2·0 4·0
Favours intravascular imaging Favours angiography
B All-cause death
Proportion of evidence
RR (95% CI)
IVUS or OCT vs Angio
Direct estimate (18 trials, 12 913 patients) 1·00 0·75 (0·60–0·93)
Indirect estimate 0·00
Network estimate 1·00 0·75 (060–0·93)
0·25 0·50 1·00 2·00
Favours intravascular imaging Favours angiography
C Cardiac death
Proportion of evidence
RR (95% CI)
pconsistency
IVUS vs Angio
Direct estimate (12 trials, 6856 patients) 0·84 0·56 (0·37–0·85)
Indirect estimate 0·16 0·61 (0·23–1·60) 0·87
Network estimate 1·00 0·56 (0·38–0·83)
OCT vs Angio
Direct estimate (7 trials, 4609 patients) 0·73 0·63 (0·37–1·07)
Indirect estimate 0·27 0·57 (0·23–1·37) 0·85
Network estimate 1·00 0·61 (0·39–0·97)
IVUS or OCT vs Angio
Direct estimate (1 trial, 1639 patients) 1·00 0·47 (0·24–0·93)
Indirect estimate 0·00
Network estimate 1·00 0·47 (0·24–0·93)
OCT vs IVUS
Direct estimate (5 trials, 3324 patients) 0·47 1·06 (0·50–2·27)
Indirect estimate 0·53 1·09 (0·54–2·19) 0·95
Network estimate 1·00 1·08 (0·64–1·80)
0·05 0·20 0·5 1·00 2·00 5·00
Favours first group Favours second group
D All-cause death
Proportion of evidence
RR (95% CI)
pconsistency
IVUS vs Angio
Direct estimate (12 trials, 6856 patients) 0·77 0·78 (0·56–1·09)
Indirect estimate 0·23 0·68 (0·38–1·25) 0·70
Network estimate 1·00 0·76 (0·57–1·01)
OCT vs Angio
Direct estimate (7 trials, 4609 patients) 0·72 0·72 (0·50–1·03)
Indirect estimate 0·28 0·83 (0·47–1·49) 0·68
Network estimate 1·00 0·75 (0·55–1·02)
IVUS or OCT vs Angio
Direct estimate (1 trial, 1639 patients) 1·00 0·75 (0·47–1·20)
Indirect estimate 0·00
Network estimate 1·00 0·75 (0·47–1·20)
OCT vs IVUS
Direct estimate (5 trials, 3324 patients) 0·52 1·08 (0·67–1·73)
Indirect estimate 0·48 0·90 (0·55–1·47) 0·61
Network estimate 1·00 0·99 (0·71–1·39)
0·05 0·50 1·00 2·00 6·00
Favours first group Favours second group

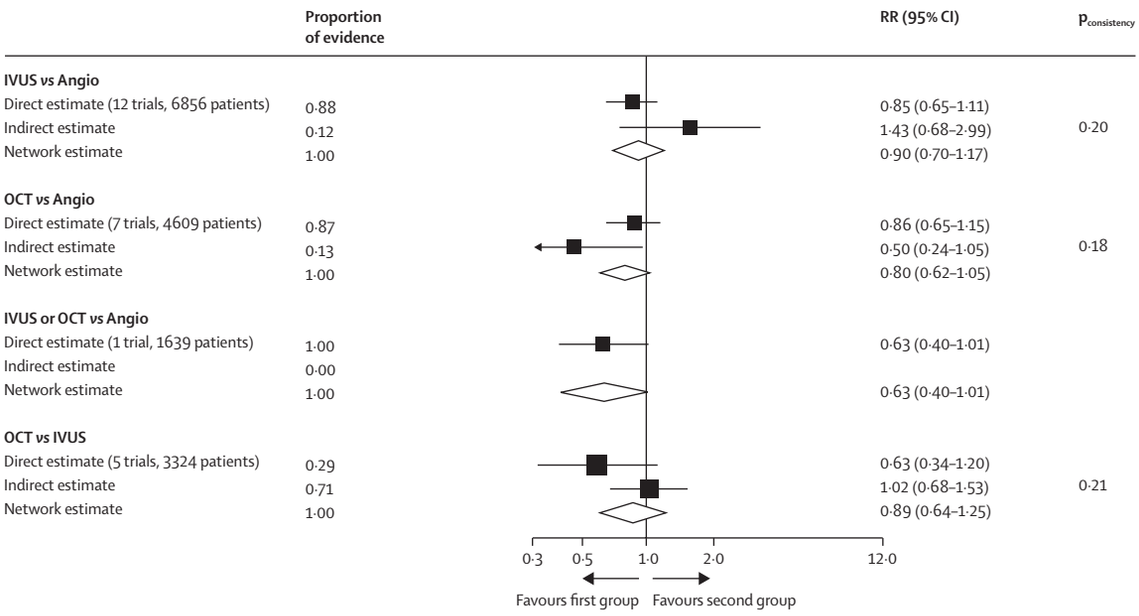
**A** Target vessel-myocardial infarction



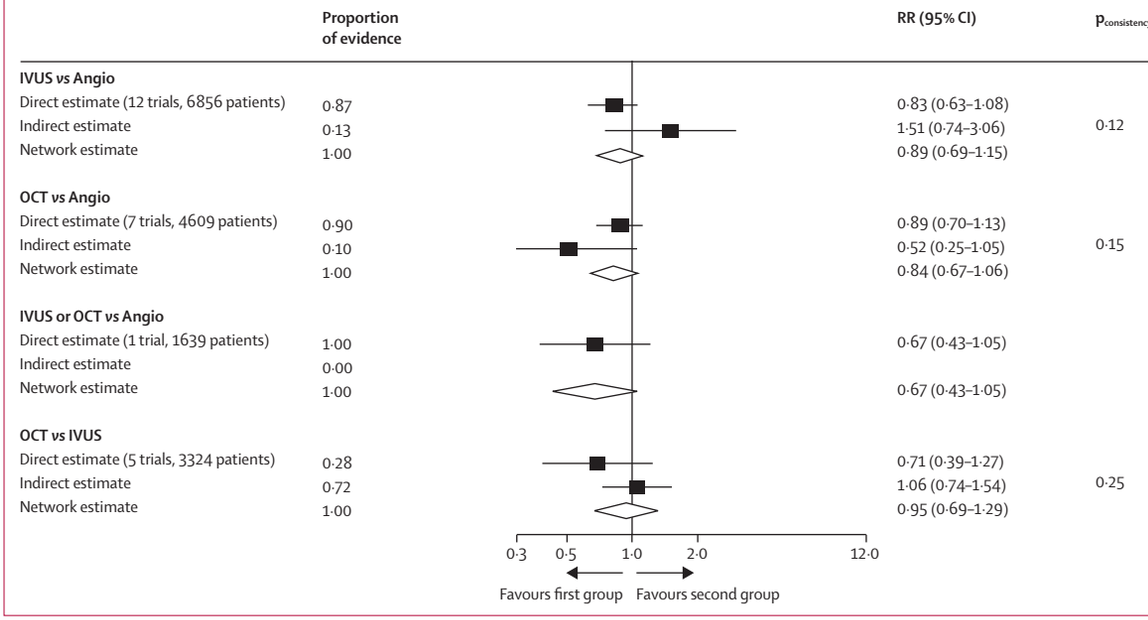

**B** All myocardial infarction




**C** Target vessel-myocardial infarction




**D** All-cause death



TV-MI (figure 5A; appendix p 29), direct data were contributed from 12 913 patients randomised in 18 trials, among whom 442 events occurred during follow-up. Compared with angiography guidance, intravascular imaging guidance resulted in an 18% reduction in the risk of TV-MI (RR 0·82 [95% CI 0·68–0·98]; p=0·030). The results were similar when only the nine trials in which TV-MI was reported were included (appendix p 30). There was no heterogeneity between trials in either analysis ($I^2$=0%).

The network treatment effect estimate for TV-MI was similar with OCT guidance and intravascular ultrasound guidance (RR 0·89 [95% CI 0·64–1·25]; figure 5C; appendix pp 31–33).

For the randomised comparison of intravascular imaging-guided PCI versus angiography-guided PCI for all myocardial infarction (figure 5B; appendix p 34), direct data were contributed from 12 913 patients randomised in 18 trials, among whom 531 events occurred during follow-up. Compared with angiography guidance, intravascular imaging guidance resulted in a 17% reduction in the risk of all myocardial infarction (RR 0·83 [95% CI 0·71–0·99]; p=0·033). There was no heterogeneity between trials ($I^2$=0%).

The network treatment effect estimate for all myocardial infarction was similar with OCT guidance and intravascular ultrasound guidance (RR 0·95 [95% CI 0·69–1·29]; figure 5D; appendix pp 35–37).

For the randomised comparison of intravascular imaging-guided PCI versus angiography-guided PCI for target lesion revascularisation (figure 6A; appendix p 38), direct data were contributed from 12 945 patients randomised in 18 trials, among whom 507 events occurred during follow-up. Compared with angiography guidance, intravascular imaging guidance resulted in a 28% reduction in the risk of target lesion revascularisation (RR 0·72 [95% CI 0·60–0·86]; p=0·0002). There was no heterogeneity between trials ($I^2$=0%).

The network treatment effect estimate for target lesion revascularisation was similar with OCT guidance and intravascular ultrasound guidance (RR 1·14 [95% CI 0·87–1·50]; figure 6C; appendix pp 39–41).

***Figure 5:*** **Direct, indirect, and network treatment effect estimates for myocardial infarction events**

Intravascular imaging (OCT or intravascular ultrasound)-guided PCI versus angiography-guided PCI for TV-MI (A) and all myocardial infarction (B). Intravascular ultrasound-guided PCI versus angiography-guided PCI, OCT-guided PCI versus angiography-guided PCI, OCT or intravascular ultrasound (at operator discretion)-guided PCI versus angiography-guided PCI (from the RENOVATE-COMPLEX-PCI trial),[16] and OCT-guided PCI versus intravascular ultrasound-guided PCI for TV-MI (C) and all myocardial infarction (D). $P_{consistency}$ refers to the consistency of the RR (95% CI) between the direct and indirect data. Angio=angiography guidance for PCI. IVUS=intravascular ultrasound guidance for PCI. OCT=optical coherence tomography guidance for PCI. PCI=percutaneous coronary intervention. RR=relative risk. TV-MI=target vessel-myocardial infarction.

The target vessel revascularisation treatment effect estimates were similar to those for target lesion revascularisation for all comparisons (figure 6B, D; appendix pp 42–45).

For the randomised comparison of intravascular imaging-guided PCI versus angiography-guided PCI for definite or probable stent thrombosis (figure 7A; appendix p 46), direct data were contributed from 13 030 patients randomised in 19 trials, among whom 98 events occurred during follow-up. Compared with angiography guidance, intravascular imaging guidance resulted in a 48% reduction in the risk of definite or probable stent thrombosis (RR 0·52 [95% CI 0·34–0·81]; p=0·0036). Intravascular imaging guidance resulted in a 61% reduction in the risk of definite stent thrombosis (data from 13 studies; RR 0·39 [95% CI 0·21–0·74]; p=0·0037; appendix p 47). There was no heterogeneity between trials in either of these analyses ($I^2$=0%).

The network treatment effect estimate for definite or probable stent thrombosis was similar with OCT guidance and intravascular ultrasound guidance (RR 0·75 [95% CI 0·43–1·69]; figure 7B; appendix pp 48–50).

There were no hotspots of inconsistency within the network for any of the primary or secondary endpoints (appendix pp 51–58), and publication bias was not detected (appendix p 59).

## Discussion

The present network meta-analysis summarises data from 15 964 patients who were randomly assigned to intravascular ultrasound guidance, OCT guidance, or angiography guidance for implantation of coronary drug-eluting stents in 22 trials and followed for a weighted mean duration of 24·7 months. In comparison with previous meta-analyses,[3–7] the addition of new data from 7224 randomised patients recently reported from four major trials[8–11] has markedly expanded this evidence base. The principal findings from the present report are: (1) the risk of target lesion failure (the primary outcome measure of the study) was reduced by 29% with intravascular imaging-guided PCI with OCT or intravascular ultrasound compared with angiography-guided PCI, driven by 45% reductions in cardiac death, 18% reductions in TV-MI, and 28% reductions in target lesion revascularisation with intravascular imaging guidance; (2) the risk of definite or probable stent thrombosis was reduced with intravascular imaging guidance by 48% compared with angiography guidance, and definite stent thrombosis was reduced by 61% with intravascular imaging guidance; (3) the risk of all-cause death was reduced with intravascular imaging guidance by 25% and the risk of all myocardial infarction was reduced with intravascular imaging guidance by 17%, compared with angiography guidance; and (4) all outcomes were similar with OCT-guided PCI and intravascular ultrasound-guided PCI.

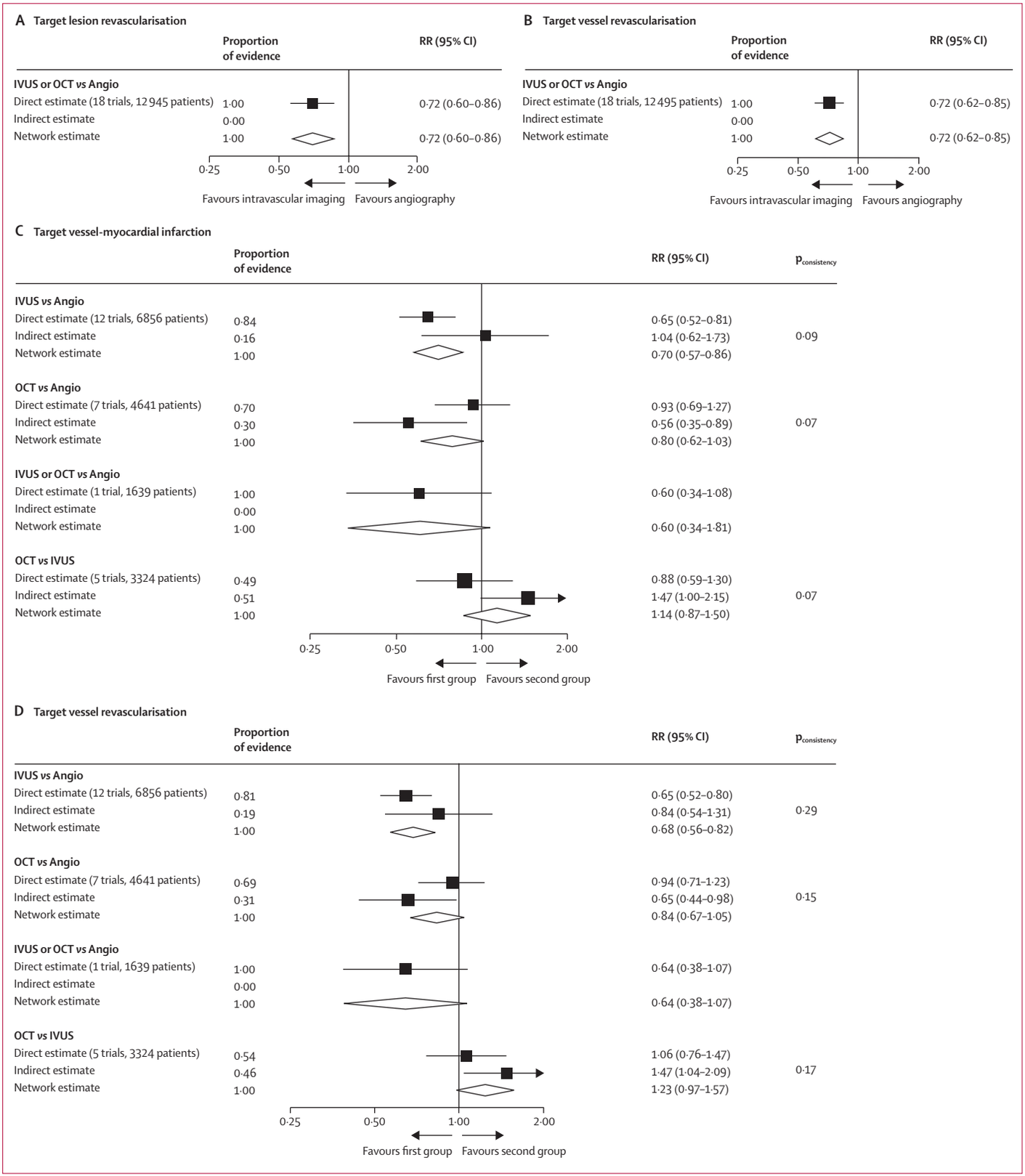

A Target lesion revascularisation
Proportion of evidence
RR (95% CI)
IVUS or OCT vs Angio
Direct estimate (18 trials, 12 945 patients) 1·00 0·72 (0·60–0·86)
Indirect estimate 0·00
Network estimate 1·00 0·72 (0·60–0·86)
0·25 0·50 1·00 2·00
Favours intravascular imaging Favours angiography
B Target vessel revascularisation
Proportion of evidence
RR (95% CI)
IVUS or OCT vs Angio
Direct estimate (18 trials, 12 495 patients) 1·00 0·72 (0·62–0·85)
Indirect estimate 0·00
Network estimate 1·00 0·72 (0·62–0·85)
0·25 0·50 1·00 2·00
Favours intravascular imaging Favours angiography
C Target vessel-myocardial infarction
Proportion of evidence
RR (95% CI)
pconsistency
IVUS vs Angio
Direct estimate (12 trials, 6856 patients) 0·84 0·65 (0·52–0·81)
Indirect estimate 0·16 1·04 (0·62–1·73) 0·09
Network estimate 1·00 0·70 (0·57–0·86)
OCT vs Angio
Direct estimate (7 trials, 4641 patients) 0·70 0·93 (0·69–1·27)
Indirect estimate 0·30 0·56 (0·35–0·89) 0·07
Network estimate 1·00 0·80 (0·62–1·03)
IVUS or OCT vs Angio
Direct estimate (1 trial, 1639 patients) 1·00 0·60 (0·34–1·08)
Indirect estimate 0·00
Network estimate 1·00 0·60 (0·34–1·81)
OCT vs IVUS
Direct estimate (5 trials, 3324 patients) 0·49 0·88 (0·59–1·30)
Indirect estimate 0·51 1·47 (1·00–2·15) 0·07
Network estimate 1·00 1·14 (0·87–1·50)
0·25 0·50 1·00 2·00
Favours first group Favours second group
D Target vessel revascularisation
Proportion of evidence
RR (95% CI)
pconsistency
IVUS vs Angio
Direct estimate (12 trials, 6856 patients) 0·81 0·65 (0·52–0·80)
Indirect estimate 0·19 0·84 (0·54–1·31) 0·29
Network estimate 1·00 0·68 (0·56–0·82)
OCT vs Angio
Direct estimate (7 trials, 4641 patients) 0·69 0·94 (0·71–1·23)
Indirect estimate 0·31 0·65 (0·44–0·98) 0·15
Network estimate 1·00 0·84 (0·67–1·05)
IVUS or OCT vs Angio
Direct estimate (1 trial, 1639 patients) 1·00 0·64 (0·38–1·07)
Indirect estimate 0·00
Network estimate 1·00 0·64 (0·38–1·07)
OCT vs IVUS
Direct estimate (5 trials, 3324 patients) 0·54 1·06 (0·76–1·47)
Indirect estimate 0·46 1·47 (1·04–2·09) 0·17
Network estimate 1·00 1·23 (0·97–1·57)
0·25 0·50 1·00 2·00
Favours first group Favours second group

***Figure 6:*** **Direct, indirect, and network treatment effect estimates for repeat revascularization events**
Intravascular imaging (OCT or intravascular ultrasound)-guided PCI versus angiography-guided PCI for TLR (A) and TVR (B). Intravascular ultrasound-guided PCI versus angiography-guided PCI, OCT-guided PCI versus angiography-guided PCI, OCT or intravascular ultrasound (at operator discretion)-guided PCI versus angiography-guided PCI (from the RENOVATE-COMPLEX-PCI trial),[16] and OCT-guided PCI versus intravascular ultrasound-guided PCI for TLR (C) and TVR (D). $P_{consistency}$ refers to the consistency of the RR (95% CI) between the direct and indirect data. Angio=angiography guidance for PCI. IVUS=intravascular ultrasound guidance for PCI. OCT=optical coherence tomography guidance for PCI. PCI=percutaneous coronary intervention. RR=relative risk. TLR=target lesion revascularisation. TVR=target vessel revascularisation.

Drug-eluting stents have undergone iterative enhancements in design that have steadily improved patient outcomes. The incorporation of thin malleable metallic struts, biocompatible non-reactive polymers, and non-toxic sirolimus analogues have resulted in a current generation of devices that might not be much improved with further incremental technological advancements.[42] Nonetheless, peri-procedural complications and late adverse events after coronary stent implantation occur at unacceptable rates in high-risk patients and after treatment of complex lesions.[43,44] In contrast to the plateau in clinical outcomes that has been reached with drug-eluting stent technology, event-free survival might still be substantially improved by implanting drug-eluting stents with intravascular imaging guidance. In this regard, the present report confirms the results of previous meta-analyses[3–7] that showed that composite clinical outcomes (whether target lesion failure, target vessel failure, or major adverse cardiac events) after drug-eluting stent implantation are reduced with intravascular imaging guidance compared with angiography guidance alone. However, the present report meaningfully extends these results by having sufficient power to show for the first-time that intravascular

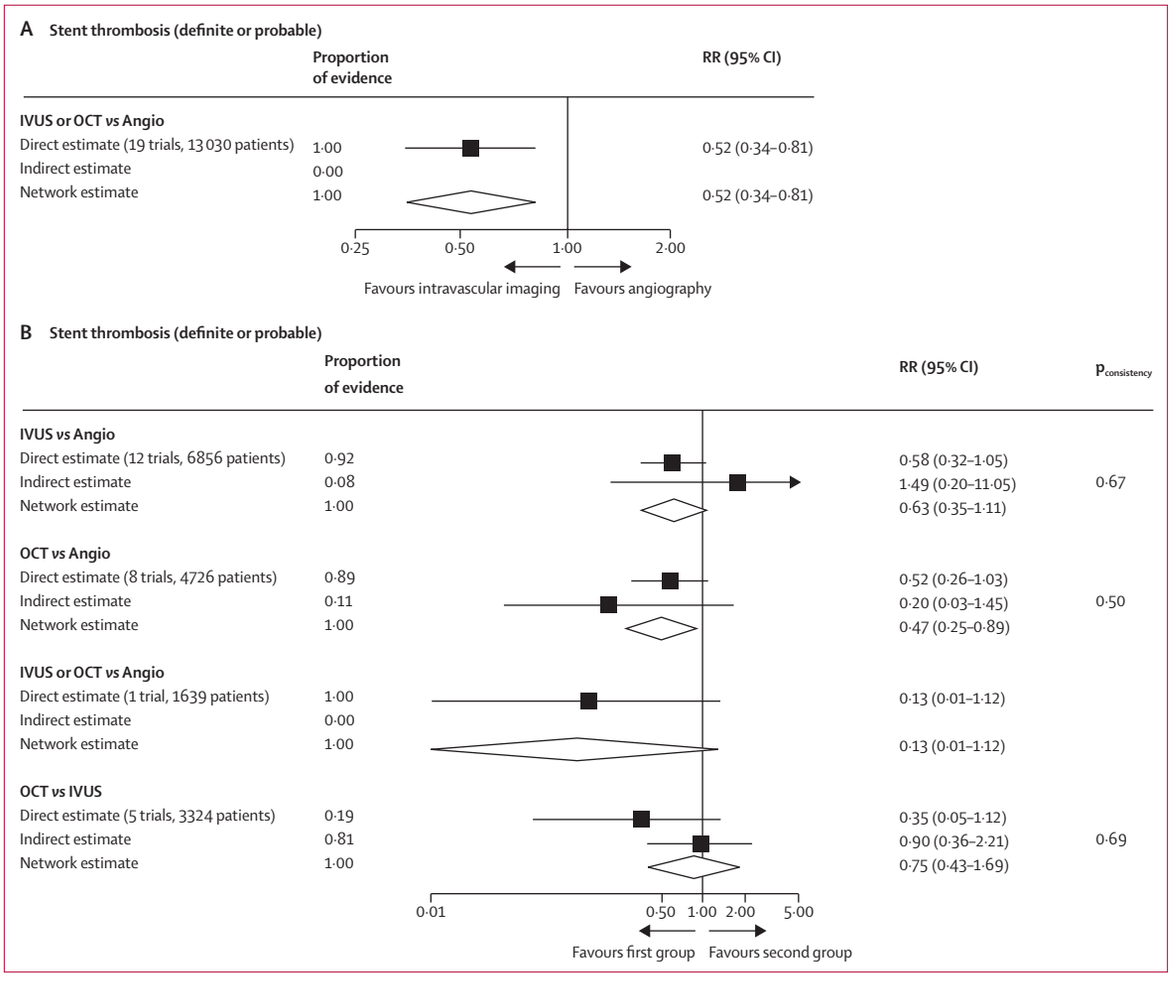



***Figure 7:*** **Direct, indirect, and network treatment effect estimates for definite or probable stent thrombosis**
(A) Intravascular imaging (OCT or intravascular ultrasound)-guided PCI versus angiography-guided PCI. (B) Intravascular ultrasound-guided PCI versus angiography-guided PCI, OCT-guided PCI versus angiography-guided PCI, OCT or intravascular ultrasound (at operator discretion)-guided PCI versus angiography-guided PCI (from the RENOVATE-COMPLEX-PCI trial),[16] and OCT-guided PCI versus intravascular ultrasound-guided PCI. $P_{consistency}$ refers to the consistency of the RR (95% CI) between the direct and indirect data. Angio=angiography guidance for PCI. IVUS=intravascular ultrasound guidance for PCI. OCT=optical coherence tomography guidance for PCI. PCI=percutaneous coronary intervention. RR=relative risk.

imaging-guidance significantly reduces all-cause mortality (by 25%, driven by a 45% reduction in cardiac mortality) and all myocardial infarction (by 17%, driven by an 18% reduction in TV-MI). Underlying the safety benefits of intravascular imaging guidance is the reduction by 48% in the risk of definite or probable stent thrombosis (driven by a 61% reduction in definite stent thrombosis), the most devastating complication of drug-eluting stent use that results in myocardial infarction in as many as 80% of patients and death in as many as 45% of patients.[45,46] Beyond these safety benefits, intravascular imaging guidance also reduced the risks of target lesion revascularisation and target vessel revascularisation after drug-eluting stent implantation by 28% compared with angiography guidance alone, thus representing the rare adjunct that is able to enhance both the safety and effectiveness of PCI. To place these results in perspective, drug-eluting stents do not reduce death, myocardial infarction, or stent thrombosis compared with bare metal stents,[47] yet are recommended with class I evidence in societal guidelines for their reduction in repeat revascularisation alone.[1,2] The principal mechanisms underlying the beneficial effects of intravascular imaging guidance have been established to be the greater minimal stent area and freedom from major edge dissections and untreated focal reference segment disease achieved, compared with angiography guidance alone.[48,49]

Compared with intravascular ultrasound, OCT is a newer imaging modality that is characterised by superior resolution and greater accuracy in plaque characterisation and dimensional measurements but requires contrast for blood clearance and has less depth penetration in lipid-rich lesions. These attributes and limitations might provide offsetting advantages and disadvantages in guiding stent procedures. The present network meta-analysis includes data from five trials in which 3324 patients were directly randomised to OCT versus intravascular ultrasound guidance and further incorporated indirect treatment estimates derived from trials in which intravascular ultrasound and OCT were separately randomised to angiography guidance. Similar rates of target lesion failure and safety and effectiveness outcomes were observed with OCT and intravascular ultrasound guidance in both direct comparisons and in the network. Of note, the treatment estimates from the head-to-head intravascular ultrasound versus OCT analyses are more compelling than side-by-side examination of the treatment effects of intravascular ultrasound guidance versus angiography guidance, and OCT guidance versus angiography guidance, given differences in studies, patients, operators, and endpoint definitions between these datasets. However, the studies in which angiography guidance was a connecting link did contribute substantial indirect data to the network comparisons of OCT guidance versus intravascular ultrasound guidance. These indirect treatment effects were consistent with those from the direct randomised comparisons, providing further reassurance that there are no major differences in outcomes between OCT and intravascular ultrasound guidance.

The evidence network is very robust for the comparison of intravascular imaging guidance versus angiography guidance, especially for the composite target lesion failure endpoint, for which outcome estimates were derived from more than 1000 events. With the addition of the four major recent studies,[8–11] the breadth of the network for the first time provided adequate power to show significant reductions in all-cause death and all myocardial infarction with intravascular imaging guidance, despite attenuation from non-cardiac deaths and non-TV-MIs, the occurrence of which are not affected by intravascular imaging stent guidance. Even for stent thrombosis, a relatively uncommon event, the RR and 95% CI for its risk reduction was sufficiently precise (RR 0·52 [95% CI 0·34–0·81]) to provide compelling evidence of a meaningful benefit with intravascular imaging guidance. Between-study heterogeneity was minimal or absent for all endpoints examined in each pairwise comparison, publication bias was not detected, no areas of inconsistency were noted within the network, and the direct and indirect data were consistent for each comparison within the network. Analysis with Bayesian and frequentist methods also provided similar treatment effect estimates.

Nonetheless, the present report shares the same limitations of all meta-analyses that aggregate study-level data: the component trials might vary in study design, patient characteristics, enrolment geography, operators, techniques, data collection, definitions and adjudication, and follow-up duration. Without access to individual patient data from most of these trials, we were unable to explore the temporal effects of intravascular imaging guidance on outcomes or identify clinical subgroups or anatomic lesion subtypes that might particularly benefit (although the included studies enrolled patients and lesions across the spectrum of coronary artery disease). Nor could we identify the optimal imaging criteria that should be strived for to optimise clinical outcomes. In addition, patients in the individual studies were enrolled from varying countries and health-care systems around the world, raising questions about generalisability. However, the minimal or absent heterogeneity between studies ($I^2$≤2%) for all the endpoints examined for each comparison group suggests that the results are likely to be applicable to most patient and lesion subtypes and operators. For the pairwise comparisons of intravascular ultrasound guidance versus angiography guidance and OCT guidance versus angiography guidance, the numbers of events might have been insufficient to detect differences in some outcomes. About half of the data network for the comparison of OCT versus intravascular ultrasound guidance consisted of indirect evidence. Although the direct and indirect estimates of the treatment effects were not statistically different for all outcomes, additional head-

to-head trials are required to determine whether there are subtle differences in outcomes between OCT and intravascular ultrasound guidance (and if so, for which lesions). Finally, the present study was not designed to determine the mechanisms through which intravascular imaging guidance of drug-eluting stent implantation might reduce cardiovascular and all-cause death. However, intravascular imaging was strongly associated with reduced rates of myocardial infarction and stent thrombosis, which might directly cause death, as well as with fewer repeat revascularisation procedures, the need for which has also been associated with mortality.[50] Furthermore, sudden cardiac deaths are often triggered by myocardial infarction or stent thrombosis events after 30 days, which, without autopsy data, are not adjudicated as such in clinical trials. The present study was also not designed to assess complications directly attributable to the use of intravascular imaging catheters or the specific interventions that arise from their use (eg, stent post-dilatation or treatment of dissections or malapposition), although in the largest single randomised trial to date, total angiographic complications were lower after drug-eluting stents implanted with OCT guidance than with angiography guidance.[9]

The present network meta-analysis shows that the routine use of OCT or intravascular ultrasound to guide PCI procedures improves survival and freedom from major adverse events, enhancing both the long-term safety and effectiveness of coronary artery intervention. These data warrant efforts to overcome remaining impediments to the routine use of intravascular imaging, including training and reimbursement issues. Additional investigation is required to determine which patient and lesion types benefit most from intravascular imaging guidance and to establish the optimal techniques and procedural objectives for OCT-guided and intravascular ultrasound-guided stent implantation.

#### Contributors

All authors designed the parameters of the study. GWS and YA accessed and verified the data. GWS supervised the statistical analysis and prepared the first draft of the manuscript. All authors critically reviewed and revised the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

GWS has received speaker honoraria from Medtronic, Pulnovo, Infraredx, Abiomed, Amgen, and Boehringer Ingelheim; has served as a consultant to Abbott, Daiichi Sankyo, Ablative Solutions, CorFlow, Apollo Therapeutics, Cardiomech, Gore, Robocath, Miracor, Vectorious, Abiomed, Valfix, TherOx, HeartFlow, Neovasc, Ancora, Elucid Bio, Occlutech, Impulse Dynamics, Adona Medical, Millennia Biopharma, Oxitope, Cardiac Success, and HighLife; and has equity or options from Ancora, Cagent, Applied Therapeutics, the Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter. GWS's employer, Mount Sinai Hospital, receives research grants from Abbott, Abiomed, Bioventrix, Cardiovascular Systems, Phillips, Biosense-Webster, Shockwave, Vascular Dynamics, Pulnovo, and V-wave. EHC has received speaker honoraria from Abbott and receives research grants from Abbott, Asahi Intecc, Biosensors, Biotronik, Boston Scientific, OrbusNeich, and Philips. ZAA reports institutional grant support from Abbott, Abiomed, Acist Medical, Boston Scientific, Cardiovascular Systems, Medtronic, the National Institute of Health, Opsens Medical, Philips, and Teleflex; consulting fees from AstraZeneca, Philips, and Shockwave; and equity in Elucid, Spectrawave, Shockwave, and VitalConnect. AM has received speaker honoraria from Nipro and is a consultant for Boston Scientific. YA is a consultant for Cardiovascular Systems and Shockwave, and serves on the Medical Advisory Board of Boston Scientific. UL has received speaker or advisory honoraria from Abbott, Boston Scientific, Amgen, Bayer, NovoNordisc, Pfizer, and Sanofi. NRH has received institutional research grants from Abbott, Biosensors, Boston Scientific, Medis Medical Imaging, and Reva Medical, and speaker fees from Abbott, Cardirad, and Terumo. LNA declares no competing interests.

#### Data sharing

Data collected for this study will not be made publicly available. However, we will consider proposals for collaboration with other investigators who wish to perform additional analyses from the study database. Any such requests should be emailed to Gregg W Stone at gregg.stone@mountsinai.org.

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