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### Permalink

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### Journal

European Heart Journal, 42(27)

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### Publication Date




2021-07-15

### DOI

10.1093/eurheartj/ehab280

Peer reviewed

# Long-term follow-up after ultrathin vs. conventional 2nd-generation drug-eluting stents: a systematic review and meta-analysis of randomized controlled trials

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Received 11 March 2021; revised 30 March 2021; editorial decision 21 April 2021; accepted 12 May 2021; online publish-ahead-of-print 18 May 2021

See page 2655 for the editorial comment on this article (doi:10.1093/eurheartj/ehab359)

## Aims

Contemporary 2nd-generation thin-strut drug-eluting stents (DES) are considered standard of care for revascularization of patients undergoing percutaneous coronary intervention. A previous meta-analysis of 10 randomized controlled trials (RCTs) with 11 658 patients demonstrated a 16% reduction in the 1-year risk of target lesion failure (TLF) with ultrathin-strut DES compared with conventional 2nd-generation thin-strut DES. Whether this benefit is sustained longer term is not known, and newer trial data may inform these relative outcomes. We therefore sought to perform an updated systematic review and meta-analysis of RCTs comparing clinical outcomes with ultrathin-strut DES ( $\leq 70 \mu\text{m}$  strut thickness) with conventional 2nd-generation thin-strut DES.

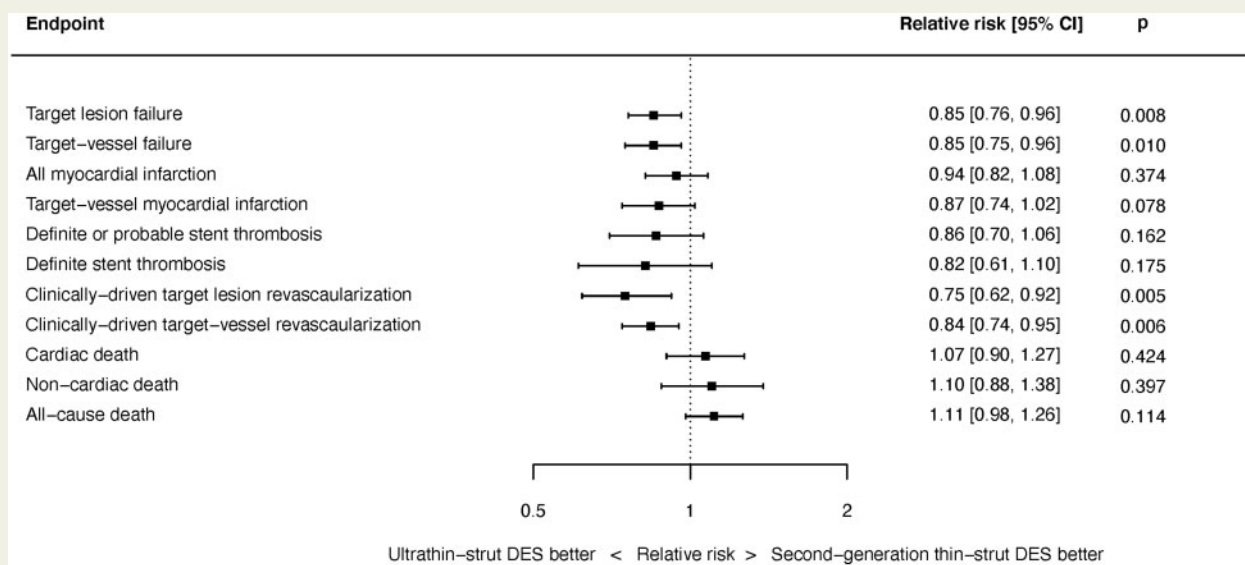
## Methods and results

We performed a random-effects meta-analysis of all RCTs comparing ultrathin-strut DES to conventional 2nd-generation thin-strut DES. The pre-specified primary endpoint was long-term TLF, a composite of cardiac death, myocardial infarction (MI), or clinically driven target lesion revascularization (CD-TLR). Secondary endpoints included the components of TLF, stent thrombosis (ST), and all-cause death. There were 16 eligible trials in which 20 701 patients were randomized. The weighted mean follow-up duration was 2.5 years. Ultrathin-strut DES were associated with a 15% reduction in long-term TLF compared with conventional 2nd-generation thin-strut DES [relative risk (RR) 0.85, 95% confidence interval (CI) 0.76–0.96,  $P=0.008$ ] driven by a 25% reduction in CD-TLR (RR 0.75, 95% CI 0.62–0.92,  $P=0.005$ ). There were no significant differences between stent types in the risks of MI, ST, cardiac death, or all-cause mortality.

## Conclusions

At a mean follow-up of 2.5 years, ultrathin-strut DES reduced the risk of TLF, driven by less CD-TLR compared with conventional 2nd-generation thin-strut DES, with similar risks of MI, ST, cardiac death, and all-cause mortality.

## Graphical Abstract



Summary of pooled estimates for key clinical endpoints at latest follow-up. Results from a random-effects meta-analysis of 16 trials in which 20 701 patients were randomized to ultrathin-strut drug-eluting stents ( $\leq 70 \mu\text{m}$  strut thickness) compared with conventional 2nd-generation thin-strut drug-eluting stents. The weighted mean follow-up duration was 2.5 years.

### Keywords

Coronary artery disease • Drug-eluting stents • Meta-analysis • Percutaneous coronary intervention • Ultrathin-strut

## Introduction

Contemporary 2nd-generation drug-eluting stents (DES) are considered standard of care for revascularization of patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) and have improved safety and effectiveness compared with 1st-generation DES platforms.<sup>1,2</sup> These clinical advances have arisen from optimization of anti-proliferative agents,<sup>3</sup> the use of more biocompatible polymers,<sup>4</sup> and a reduction in stent strut thickness with use of more malleable metal alloys.<sup>5</sup> Despite these improvements, conventional 2nd-generation thin-strut DES are not event-free and remain associated with an ongoing risk of adverse clinical events beyond the 1st year of implantation.<sup>6</sup>

Ultrathin-strut DES ( $\leq 70 \mu\text{m}$ ) with biodegradable polymers were developed to further improve outcomes after PCI by reducing vessel injury and late polymer-induced inflammation and promoting more rapid endothelialization. A previous meta-analysis demonstrated that ultrathin-strut DES were associated with a significant reduction in the 1-year risk of target lesion failure (TLF) compared with conventional 2nd-generation thin-strut DES.<sup>7</sup> However, since this report, longer-term follow-up of prior studies has been reported and additional relevant trials have been completed. We therefore performed an updated systematic review and meta-analysis of randomized controlled trials (RCTs) comparing clinical outcomes between ultrathin-strut and conventional 2nd-generation thin-strut DES.

## Methods

This analysis was prospectively registered at the PROSPERO international prospective register of systematic reviews (CRD42020220738) and was conducted in accordance with published guidance.<sup>8</sup>

### Search strategy

We performed a systematic search of the MEDLINE, Cochrane Central Register of Controlled Trials, and Embase databases from December 2010 through March 2021 for all RCTs comparing ultrathin-strut DES to conventional 2nd-generation thin-strut DES for the treatment of CAD. Our search strings are shown in the [Supplementary material online, Appendix Table S1](#). We manually searched the bibliographies of selected studies and meta-analyses to identify further eligible studies. Abstracts were reviewed for suitability, and articles were accordingly retrieved. Conference abstracts were also searched for relevant studies. Two independent authors performed the search and literature screening (Y.A. and A.N.), with disputes resolved by consensus following discussion with a 3rd author (M.V.M.).

### Inclusion criteria

Only RCTs were included. Trials were eligible if they reported clinical outcome data following randomization to ultrathin-strut DES vs. conventional 2nd-generation thin-strut DES with all forms of CAD. Ultrathin-strut stents were defined as those with strut thickness  $\leq 70 \mu\text{m}$ . Conventional 2nd-generation thin-strut DES were defined as all DES with strut thickness  $> 70 \mu\text{m}$ , excluding 1st-generation Cypher and Taxus DES.

## Endpoints

The pre-specified primary endpoint was TLF, defined as a composite of cardiac death, target-vessel myocardial infarction (TV-MI) or clinically driven target lesion revascularization (CD-TLR), at the latest follow-up reported. The TLF composite was only assessed if it was reported; i.e. if the composite TLF rate was not provided in a study, summing of its individual components to provide a value for TLF was not performed. Secondary pre-specified endpoints included target vessel failure [TVF; the composite of cardiac death, TV-MI or clinically driven target vessel revascularization (CD-TVR)], the individual components of TLF and TVF, as well as all myocardial infarction (MI), definite/probable and definite stent thrombosis (ST) by Academic Research Consortium criteria,<sup>9</sup> any revascularization, all-cause mortality, and non-cardiac death. If not specifically reported, non-cardiac death was calculated as the difference between all-cause mortality and cardiac death. The pre-specified definitions of TLF and TVF used in each trial are summarized in [Supplementary material online, Appendix Table S2](#). In some cases, there were slight deviations from the standard TLF and TVF definitions, in which case the trial-specific definition was used.

## Data extraction and analysis

Two authors (Y.A. and A.N.) independently abstracted the data from included trials in duplicate, verified by a 3rd author (M.V.M.). Included studies were assessed using the Cochrane Risk of Bias tool.<sup>10</sup> Publication bias was assessed using a funnel plot.

All outcomes were assessed by intention-to-treat. Random-effects meta-analyses were performed using the restricted maximum likelihood estimator. All outcomes were assessed as relative risks (RRs) at the time of latest follow-up available for each trial. Additional analyses were performed to assess early events ( $\leq 1$  year) and late events ( $> 1$  year) whenever such data were available. We used the  $I^2$  statistic to assess heterogeneity.<sup>11</sup> Sensitivity analyses were performed with a fixed-effect model, using hazard ratios (HRs) as the outcome measure when reported. We performed additional sensitivity analyses using incidence rate ratios (IRRs) as the outcome measure, and a further sensitivity analysis looking only at trials included in the prior 2018 meta-analysis. We also performed a Jackknife sensitivity analysis excluding each trial in turn for the primary endpoint. We performed sensitivity analyses looking at the types of ultrathin-strut and control stents. Pre-specified subgroup analyses for the primary endpoint were performed according to age, sex, diabetes, chronic kidney disease, presentation with acute coronary syndromes or ST-elevation MI, small vessels, long lesions, in-stent restenosis lesions, and multivessel disease. Interactions between subgroups were assessed with meta-regression using a mixed-effects model, with the subgroup characteristic as a moderator and the individual trial as a random effect. A moderating effect of the length of follow-up was assessed using a mixed-effects meta-analytical model with a random effect for each individual study, as well as tests for interaction between results at 1 year and beyond 1 year. We also performed regression tests for the type of stent used in both the ultrathin DES and control DES arms, the anti-proliferative drug used in the control DES arm, and the delta strut thickness between the two arms.

Mean values are expressed as mean  $\pm$  SD unless otherwise stated. Statistical significance was set at  $P < 0.05$ .  $P$ -values are two-tailed and were not adjusted for multiplicity. The statistical programming environment R<sup>12</sup> with the metaphor package<sup>13</sup> was used for all statistical analyses.

## Results

Sixteen trials<sup>14–41</sup> randomizing 20 701 patients were eligible for inclusion in this meta-analysis ([Supplementary material online, Appendix Figure S1](#)); 10 884 patients were randomized to ultrathin-strut DES and 9817 to conventional 2nd-generation thin-strut DES. The weighted mean follow-up duration across all trials was 31.0 months. The longest follow-up duration was 5 years in three trials, 3 years in six trials, 2 years in three trials, 1 year in three trials, and 9 months in one trial. The ultrathin stents studied included Orsiro (12 trials), MiStent (2 trials), BioMime (1 trial), and Supraflex (1 trial). Control stents in these trials were Xience (10 trials), Resolute (3 trials), Nobori (1 trial), BioFreedom (1 trial), and Endeavor (1 trial). The characteristics of each of these stents are listed in [Supplementary material online, Appendix Table S3](#).

The characteristics of the included trials are summarized in [Supplementary material online, Appendix Table S4](#) and the risk of bias is shown in the [Supplementary material online, Appendix Table S5](#). There was no evidence of publication bias ([Supplementary material online, Appendix Figures S2–S6](#)).

### Target lesion failure

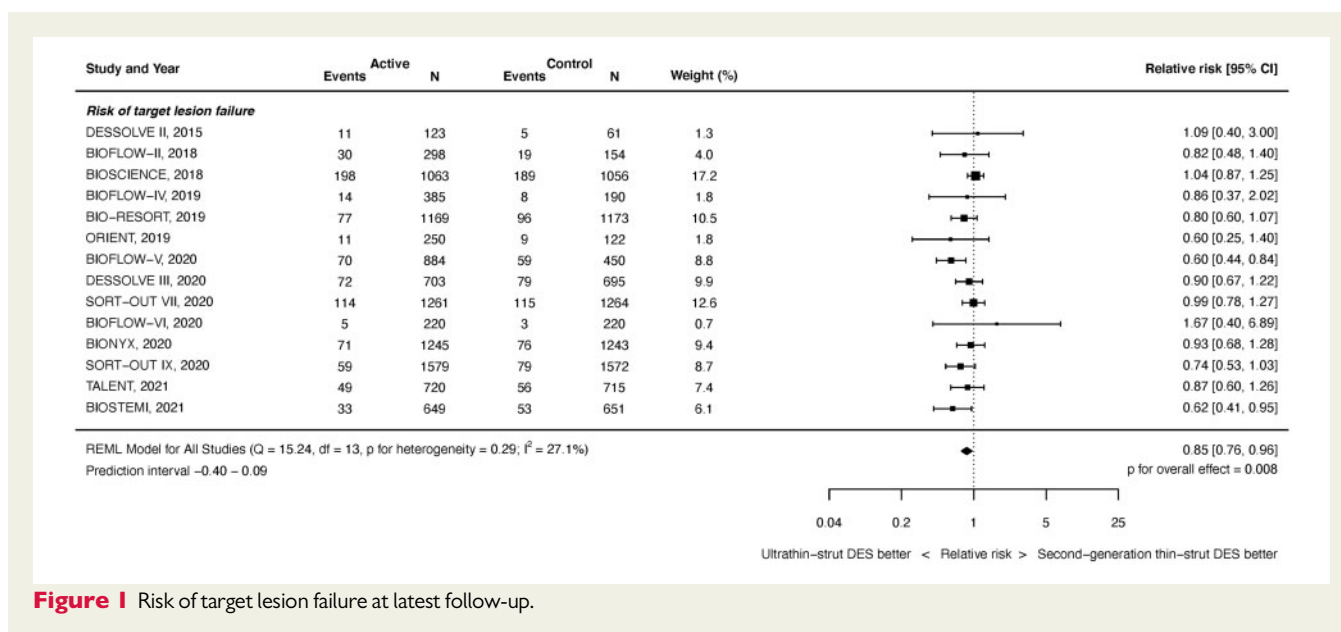
Target lesion failure outcomes were available from 14 studies with 20 115 randomized patients. As shown in [Figure 1](#), at latest follow-up ultrathin-strut DES reduced the risk of TLF compared with conventional 2nd-generation thin-strut DES [RR 0.85, 95% confidence interval (CI) 0.76–0.96,  $P = 0.008$ ]. There was mild heterogeneity present between studies ( $I^2 = 27.1\%$ ). Reduced risks of early ( $\leq 1$  year) events (RR 0.84, 95% CI 0.74–0.95,  $P = 0.005$ ,  $I^2 = 0.0\%$ ) as well as late ( $> 1$  year) events (RR 0.86, 95% CI 0.76–0.98,  $P = 0.019$ ,  $I^2 = 32.9\%$ ) with ultrathin-strut DES compared with conventional 2nd-generation thin-strut DES were present ([Supplementary material online, Appendix Figures S7 and S8](#)). The RRs between the stent types for TLF were consistent before and after 1 year ( $P_{\text{interaction}} = 0.501$ ).

### Target vessel failure

Target vessel failure outcomes were available from 13 studies with 14 695 randomized patients. As shown in [Figure 2](#), at latest follow-up ultrathin-strut DES were associated with a reduced risk of TVF compared with conventional 2nd-generation thin-strut DES (RR 0.85, 95% CI 0.75–0.96,  $P = 0.010$ ). There was moderate heterogeneity ( $I^2 = 29.3\%$ ). There was a reduced risk of early events (RR 0.88, 95% CI 0.77–1.00,  $P = 0.045$ ,  $I^2 = 0.0\%$ ) and later events (RR 0.85, 95% CI 0.75–0.97,  $P = 0.017$ ,  $I^2 = 36.1\%$ ) ([Supplementary material online, Appendix Figures S9 and S10](#)). The RRs between the stent types for TVF were consistent before and after 1 year ( $P_{\text{interaction}} = 0.893$ ).

### Myocardial infarction

All MI outcomes were available from 15 studies with 19 367 randomized patients. As shown in [Figure 3](#) top, at latest follow-up, there was no significant difference between ultrathin-strut DES and conventional thin-strut DES for the risk of any MI (RR 0.94, 95% CI 0.82–1.08,  $P = 0.374$ ). There was no heterogeneity present ( $I^2 = 0.0\%$ ). Similarly, there were no significant differences in the risk of early or later MI events noted between groups ([Supplementary material online,](#)



**Figure 1** Risk of target lesion failure at latest follow-up.

Appendix Figures S11 and S12). The RRs between the stent types for all MI were consistent before and after 1 year ( $P_{\text{interaction}} = 0.732$ ).

Target-vessel MI outcomes were available from 14 studies with 19 999 randomized patients. As shown in Figure 3 bottom, there was no significant difference between stent types for the risk of TV-MI at time of latest follow-up (RR 0.87, 95% CI 0.74–1.02,  $P = 0.078$ ). There was mild heterogeneity ( $I^2 = 2.4\%$ ). Similarly, there were no significant differences in the risks of early or later TV-MI noted between groups (Supplementary material online, Appendix Figures S13 and S14). The RRs between the stent types for TV-MI were consistent before and after 1 year ( $P_{\text{interaction}} = 0.933$ ).

## Stent thrombosis

Definite or probable ST outcomes were available from 15 studies with 20 371 randomized patients. As shown in Figure 4, at latest follow-up, there was no significant difference between ultrathin-strut DES and conventional 2nd-generation thin-strut DES for the risk of definite or probable ST (RR 0.86, 95% CI 0.70–1.06,  $P = 0.162$ ). There was no heterogeneity ( $I^2 = 0.0\%$ ). Similarly, there were no significant differences in the risk of early or later ST events between stent types (Supplementary material online, Appendix Figures S15 and S16). The RRs between the stent types for definite or probable ST were consistent before and after 1 year ( $P_{\text{interaction}} = 0.795$ ). Nor were there significant differences between stent types in the risk of definite ST at any time period (Supplementary material online, Appendix Figures S17 and S19).

## Repeat revascularization

Clinically driven TLR outcomes were available from 15 studies with 20 371 randomized patients. As shown in Figure 5 top panel, at latest follow-up, ultrathin-strut DES were associated with a reduced risk of CD-TLR compared with conventional 2nd-generation thin-strut DES (RR 0.75, 95% CI 0.62–0.92,  $P = 0.005$ ). There was moderate heterogeneity ( $I^2 = 43.6\%$ ). The reduction in early events did not reach

statistical significance (RR 0.78, 95% CI 0.61–1.02,  $P = 0.068$ ,  $I^2 = 41.4\%$ ) whereas the reduction in later events did (RR 0.82, 95% CI 0.70–0.96,  $P = 0.013$ ,  $I^2 = 20.8\%$ ) (Supplementary material online, Appendix Figures S20 and S21). However, the RRs between the stent types for CD-TLR were consistent before and after 1 year ( $P_{\text{interaction}} = 0.660$ ).

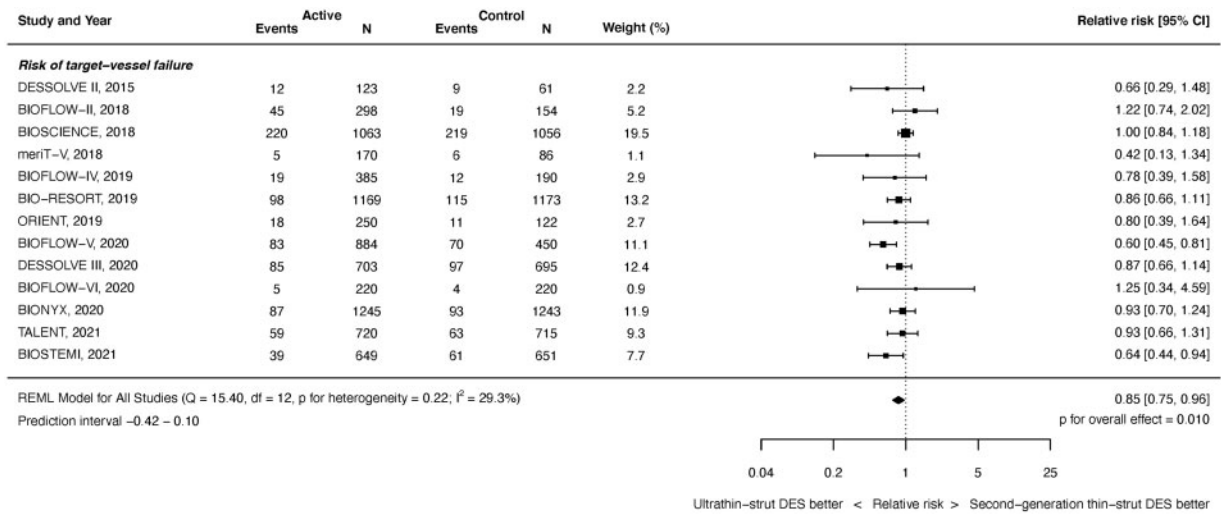
Clinically driven target vessel revascularization outcomes were available from 15 studies with 20 371 randomized patients. As shown in Figure 5 bottom, at latest follow-up, ultrathin-strut DES were associated with a reduced risk of CD-TVR compared with conventional 2nd-generation thin-strut DES (RR 0.84, 95% CI 0.74–0.95,  $P = 0.006$ ). There was mild heterogeneity ( $I^2 = 18.6\%$ ). A reduced risk of early events (RR 0.84, 95% CI 0.71–0.99,  $P = 0.040$ ,  $I^2 = 15.0\%$ ) and later events (RR 0.85, 95% CI 0.74–0.97,  $P = 0.019$ ,  $I^2 = 26.3\%$ ) were present (Supplementary material online, Appendix Figures S22 and S23). The RRs between stent types for CD-TVR were consistent before and after 1 year ( $P_{\text{interaction}} = 0.891$ ).

There were no significant differences between stent types for all TLR, all TVR, and all repeat revascularization at any timepoint (Supplementary material online, Appendix Figures S24–S32).

## Mortality

All-cause death outcomes were available from 16 studies with 20 701 randomized patients. As shown in Figure 6 top panel, there was no significant difference between ultrathin-strut DES and conventional 2nd-generation thin-strut DES for the risk of death (RR 1.11, 95% CI 0.98–1.26,  $P = 0.114$ ). There was minimal heterogeneity noted ( $I^2 = 4.4\%$ ). The difference in deaths between the devices was statistically significant in the early ( $\leq 1$  year) period (RR 1.25, 95% CI 1.04–1.51,  $P = 0.020$ ,  $I^2 = 0.0\%$ ), but not in the later ( $> 1$  year) period (RR 1.08, 95% CI 0.94–1.24,  $P = 0.300$ ,  $I^2 = 12.1\%$ ) (Supplementary material online, Appendix Figures S33 and S34). However, the RRs between stent types for all-cause death were not significantly different before and after 1 year ( $P_{\text{interaction}} = 0.309$ ).





**Figure 2** Risk of target vessel failure at latest follow-up.

Cardiac death outcomes were available from 16 studies with 20 701 patients. As shown in *Figure 6* middle, at latest follow-up, there was no significant difference between ultrathin-strut DES and conventional thin-strut DES for the risk of cardiac death (RR 1.07, 95% CI 0.90–1.27,  $P=0.424$ ). There was no heterogeneity ( $I^2 = 0.0\%$ ). Similarly, there were no differences between groups for the risks of early or later cardiac death (*Supplementary material online, Appendix Figures S35* and *S36*). The RRs between stent types for cardiac death were consistent before and after 1 year ( $P_{\text{interaction}} = 0.599$ ).

Non-cardiac death outcomes were available from 16 studies with 20 701 patients. As shown in *Figure 6* bottom, at latest follow-up, there was no significant difference between ultrathin-strut DES and conventional thin-strut DES for the risk of non-cardiac death (RR 1.10, 95% CI 0.88–1.38,  $P=0.397$ ). There was mild heterogeneity ( $I^2 = 23.7\%$ ). The difference in non-cardiac deaths between the devices was statistically significant in the early ( $\leq 1$  year) period (RR 1.39, 95% CI 1.03–1.88,  $P=0.029$ ,  $I^2 = 0.0\%$ ), but not in the later ( $>1$  year) period (RR 1.10, 95% CI 0.86–1.42,  $P=0.441$ ,  $I^2 = 33.5\%$ ) (*Supplementary material online, Appendix Figures S37* and *S38*). However, the RRs between stent types for all-cause death were not significantly different before and after 1 year ( $P_{\text{interaction}} = 0.195$ ).

### Subgroup and stent-type analyses

There were no significant interactions between stent type and any of the subgroups tested on the risk of TLF at latest follow-up (*Supplementary material online, Appendix Table S6*). Similarly, there was no evidence that the type of ultrathin-strut DES or 2nd-generation thin-strut DES had a moderating effect on the risk of any of the clinical outcome measures (*Supplementary material online, Appendix Table S7*). There was no evidence that the delta strut thickness between the arms or the anti-proliferative drug-type on the stents had a moderating effect on the risk of any of the clinical outcomes (*Supplementary material online, Tables S8* and *S9*). There was also no

evidence of a moderating effect of follow-up duration on any clinical outcomes (*Supplementary material online, Table S10*).

### Sensitivity analyses

The results of the random-effects meta-analyses were consistent when assessed by fixed effect (*Supplementary material online, Appendix Figures S39–S49*). Fewer trials reported outcomes as HRs; the results are shown in *Supplementary material online, Appendix Figures S50–S56*. Results were consistent when assessed by IRRs (*Supplementary material online, Appendix Figures S57–S66*), although the reduction in TV-MI reached statistical significance (IRR 0.83, 95% CI 0.69–0.99,  $P=0.043$ ,  $I^2 = 18.1\%$ , *Supplementary material online, Figure S60*). The primary outcome of TLF at latest follow-up remained significantly lower with ultrathin-strut DES compared with conventional 2nd-generation thin-strut DES after removing each individual trial one-by-one, except after removing BIOFLOW V (RR 0.92, 95% CI 0.83–1.01,  $P=0.08$ ) (*Supplementary material online, Appendix Table S11*). Sensitivity analyses of only trials in the prior Bangalore meta-analysis<sup>7</sup> are shown in *Supplementary material online, Appendix Figures S67–S75*.

### Discussion

The present systematic review and meta-analysis of 16 trials enrolling 20 701 patients is to our knowledge, the largest study to date examining outcomes after PCI with ultrathin-strut DES compared with conventional 2nd-generation thin-strut DES (which still represent the most widely used stents in the USA). The principal findings of this study (as summarized in the *Graphical abstract*) are (i) at a mean follow-up of 2.5 years, ultrathin-strut DES were associated with reduced risks of TLF and TVF compared with conventional 2nd-generation thin-strut DES; and (ii) there were no significant differences in the rates of cardiac death, MI, or ST between stent types, although

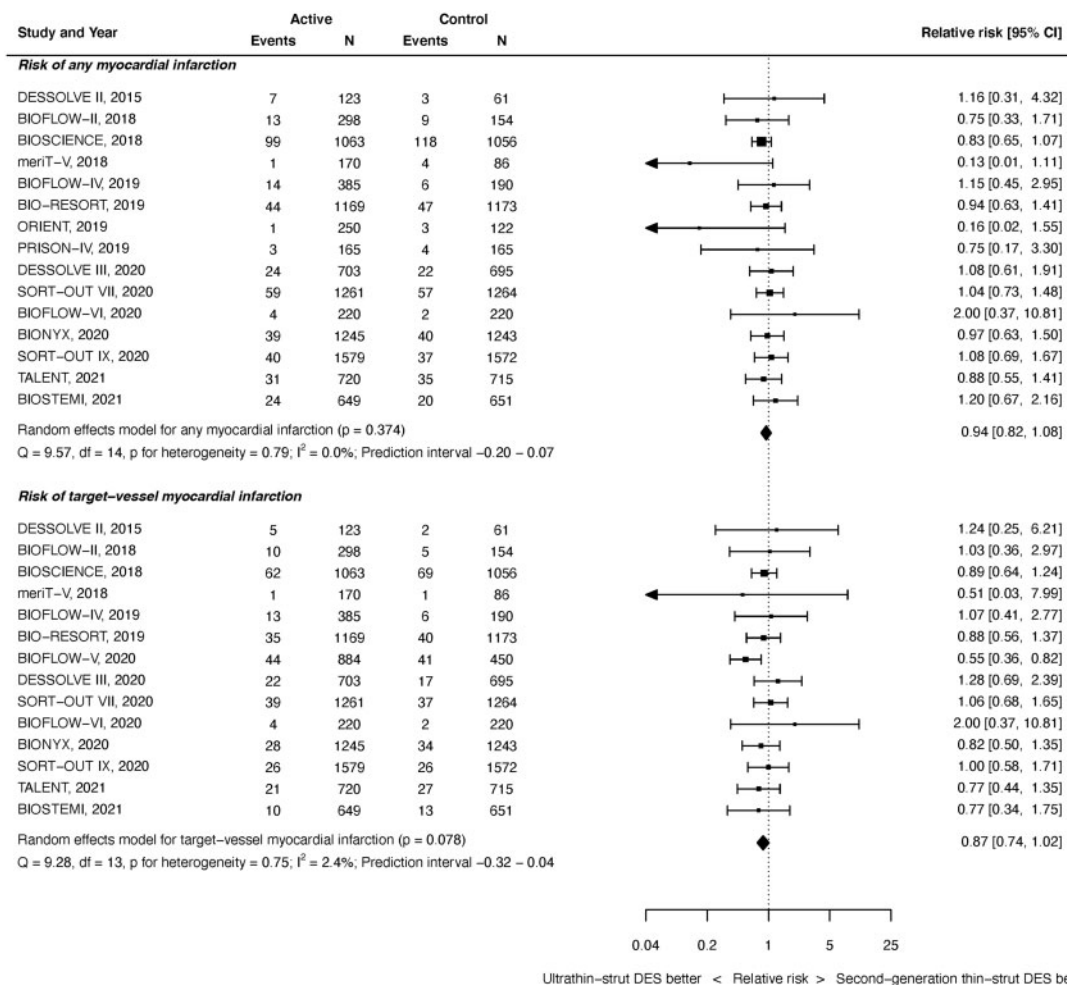


Figure 3 Risk of myocardial infarction at latest follow-up.

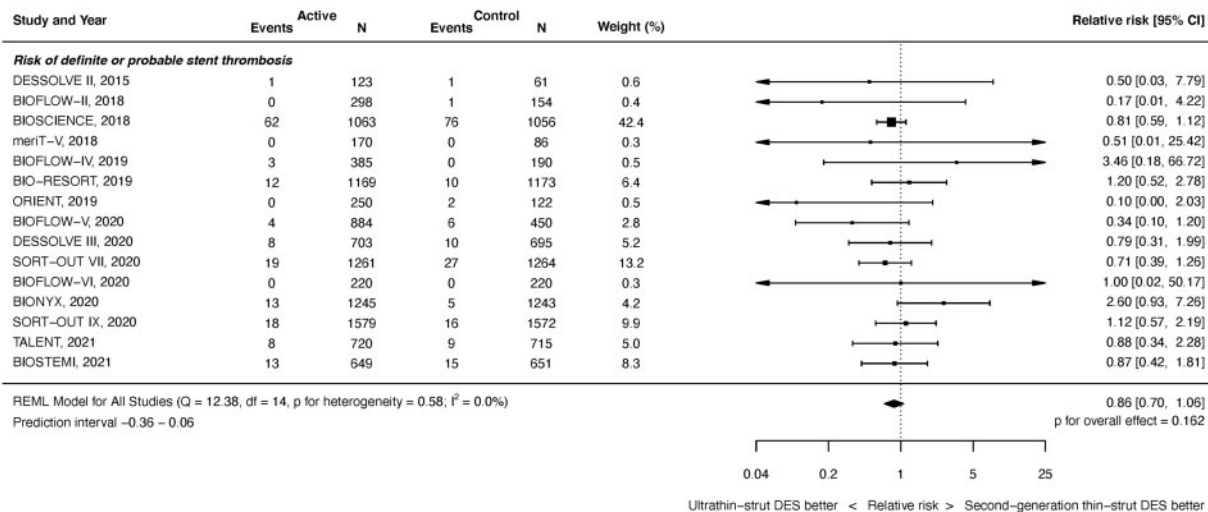
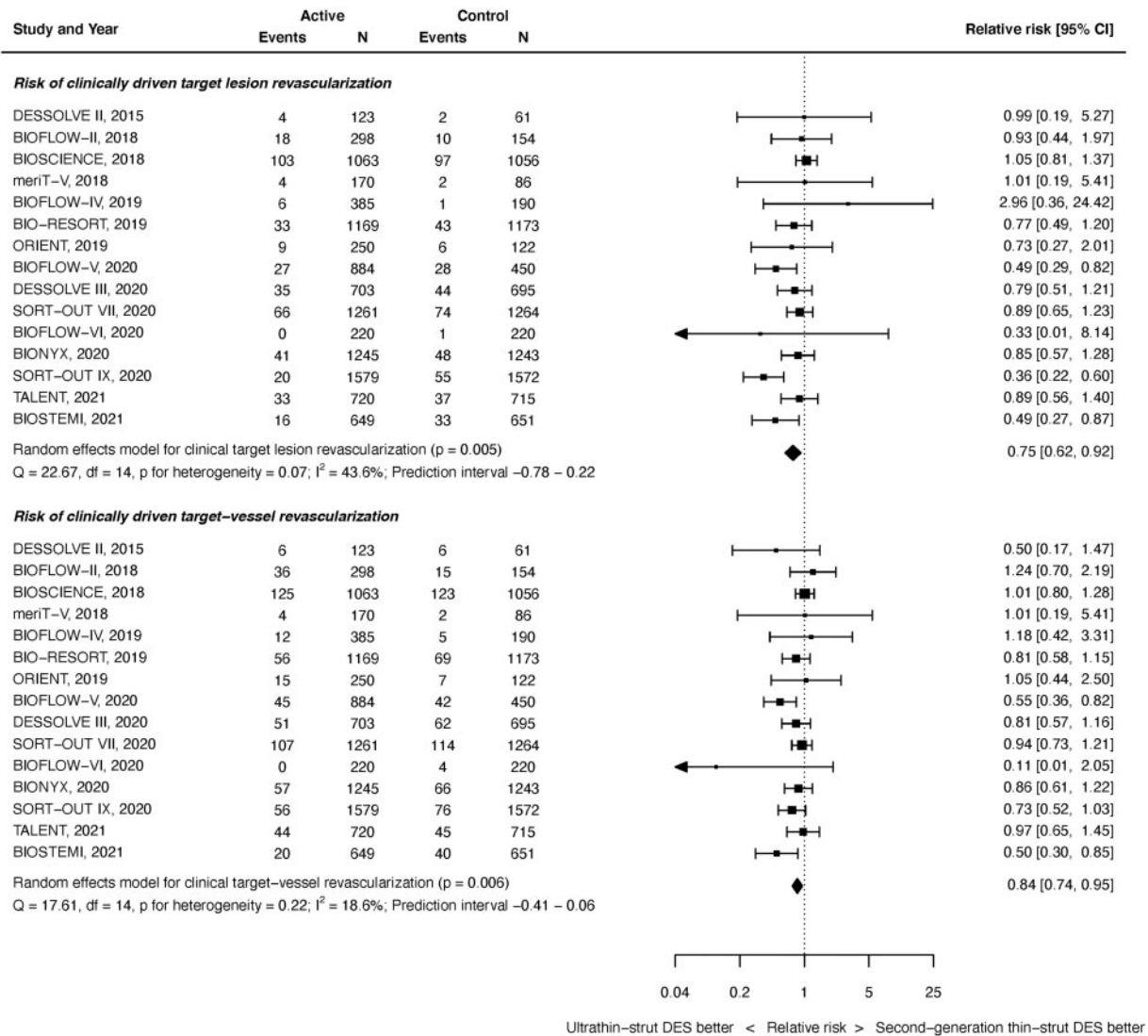


Figure 4 Risk of definite or probable stent thrombosis at latest follow-up.



**Figure 5** Risk of clinically driven revascularization at latest follow-up.

CD-TLR and CD-TVR occurred less frequently with ultrathin-strut DES.

Outcomes with contemporary 2nd-generation thin-strut DES (most of which have strut thicknesses between 80 and 100 μm) are excellent and have not been improved upon by various iterative designs including bioresorbable polymer-based DES,<sup>42</sup> polymer-free DES,<sup>43</sup> or bioresorbable scaffolds.<sup>44</sup> In contrast, ultrathin-strut stents (strut thickness ≤70 μm) have potential advantages in terms of deliverability, are less likely to disturb flow in side-branches, and may promote more rapid endothelialization. Bangalore and colleagues<sup>7</sup> previously reported a meta-analysis of ultrathin-strut DES vs. conventional 2nd-generation thin-strut DES in 10 trials with 11 658 randomized patients, reporting lower 1-year rates of TLF and MI. However, the benefits were modest (e.g. 16% reduction in TLF) and of borderline statistical significance.

The present study is distinct from the Bangalore meta-analysis in several ways. Nearly twice as many patients were included in the present study (with six additional trials included) and with mean follow-up duration of 2.5 years rather than 1 year, affording a substantially greater number of events for more study power. Furthermore, to examine the time-relatedness between stent types, outcomes were categorized as occurring before or after the 1st year from stent implantation. We also performed detailed analyses by subgroup and stent type and have included other detailed sensitivity analyses that had not been performed previously.

The present study has confirmed a modest 15% long-term RR reduction of TLF with ultrathin-strut DES compared with conventional 2nd-generation thin-strut DES, with consistent reductions in risk before and after 1 year following stent implantation. Although the strength of evidence for the reduction in long-term TLF with



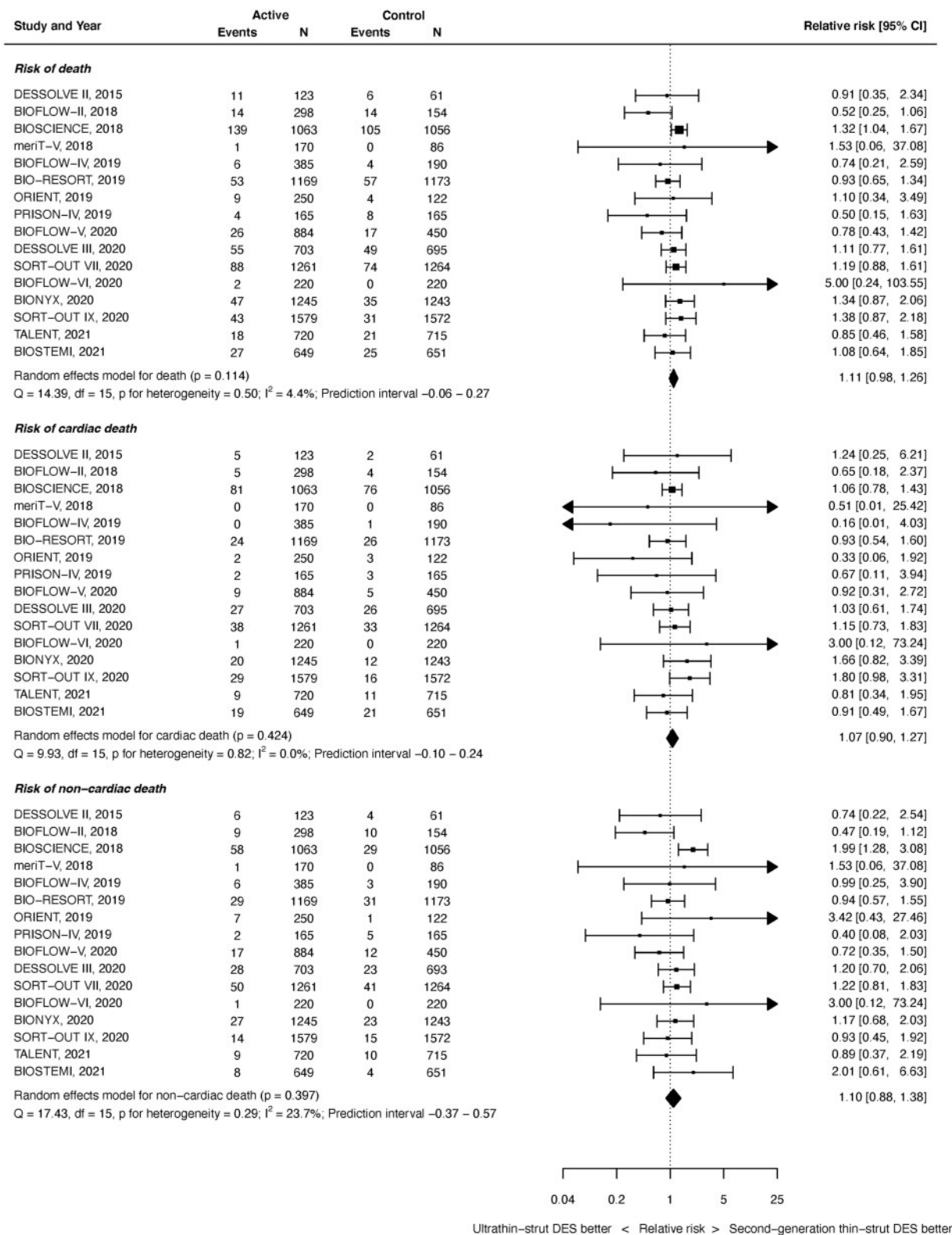


Figure 6 Risk of death at latest follow-up.

ultrathin-strut DES ( $P=0.008$ ) is improved compared with the Bangalore report,<sup>7</sup> the 95% CI was still wide, consistent with a reduction in TLF ranging from 4% to 24%. The composite endpoint of TVF at latest follow-up was also reduced by 15% with ultrathin-strut DES, with similar magnitude of risk reductions before and after 1 year.

The reductions in TLF and TVF with ultrathin-strut DES were driven by relative 25% and 16% reductions in CD-TLR and CD-TVR, respectively, favouring ultrathin-strut DES both before and after 1 year. In contrast, there were no significant differences between stent types in the risk of MI. These findings vary from those from the prior meta-analysis by Bangalore and colleagues<sup>7</sup> in which the reduction in TLF between stent types was driven by a lower risk of MI with no difference in repeat revascularization. Mechanistically, thicker strut dimensions increase vascular injury, flow separation, and stagnation, thereby modulating thrombogenicity and neointimal hyperplasia.<sup>45</sup> Increasing strut thickness is also associated with delayed or impaired endothelialization (in part related to these flow disturbances<sup>45</sup>), which may also promote increased neointimal formation.<sup>46</sup> The independent impact of strut thickness on angiographic neointimal hyperplasia and clinical restenosis after bare-metal stents was previously demonstrated in the ISAR-STEREO trials.<sup>5,47</sup> Despite the smaller amount of neointimal hyperplasia and lower CD-TLR rates after 2nd-generation thin-strut DES compared with 1st-generation DES or bare-metal stents, the present report confirms that further reducing strut thickness to  $<70\mu\text{m}$  has a favourable effect on freedom from repeat revascularization. As the present outcomes were consistent across subgroups, the absolute benefit of ultrathin-strut DES would be expected to be greatest in patients (e.g. diabetics) and lesions (e.g. small vessels, diffuse disease) at high risk for restenosis.

In the present study, there was no significant difference in the risk of MI between stent types, either at latest follow-up or before or after 1 year. This was true for TV-MI as well as any MI. However, the point estimates favoured ultrathin-strut DES, and a small difference in MI between stent types cannot be excluded. Similarly, the difference in ST between stent types did not reach statistical significance, although given the point estimate again favouring ultrathin-strut DES (RR 0.87), a small reduction in ST might have emerged had more events accrued.

Thus, ultrathin-strut DES were associated with early and late reductions in CD-TLR with numerically fewer MI and ST events. Nonetheless, ultrathin-strut DES were associated with a non-significant 11% increase in the risk of all-cause mortality compared with conventional 2nd-generation thin-strut DES, with minimal heterogeneity between trials. Given the numerically lower rates of ST, TV-MI, any MI, and CD-TLR with ultrathin-strut DES (all of which have been associated with reductions in subsequent mortality after stent implantation),<sup>48-52</sup> the mechanism(s) underlying a plausible increase in all-cause death is uncertain, especially as the difference was driven by greater non-cardiac mortality occurring within 1 year after implantation. Considering individual trials, all-cause death was significantly increased with the ultrathin-strut Orsiro stent in the BIOSCIENCE trial at 5-year follow-up<sup>18</sup> and with the ultrathin-strut Supraflex stent in the TALENT trial at 1-year follow-up,<sup>28</sup> but not at 2-year follow-up.<sup>40</sup> In the BIOSCIENCE trial, the excess in all-cause mortality was driven by greater non-cardiac deaths, specifically with more patients dying from cancer in the Orsiro arm. The 1-year

mortality difference observed in the TALENT trial was believed to be a chance finding related to a lower-than-expected all-cause death rate in the control (Xience) stent arm (0.6%), a hypothesis that appears to be confirmed with the 2-year results. Nevertheless, the present analysis demonstrates numerically greater all-cause mortality with ultrathin-strut DES with directional associations of increased cardiac and non-cardiac mortality. The upper limit of the 95% CI for all-cause mortality was 0.98, and the number of events required to shift the  $P$ -value to beyond the threshold for statistical significance is estimated to possibly only be 4 (although this number itself should be interpreted with caution as not all trials included had 1:1 randomization between arms, which is a prerequisite for the calculation of the fragility index, or reverse fragility index). Longer-term follow-up from the present trials, and ideally additional randomized studies, are necessary to clarify this uncertainty.

Twelve of the 16 trials included in our analysis used the  $60\mu\text{m}$  cobalt-chromium bioabsorbable-polymer-based sirolimus-eluting Orsiro stent as the ultrathin-strut DES, and 10 of the trials used the  $81\mu\text{m}$  cobalt-chromium durable polymer-based everolimus-eluting Xience stent as the thin-strut DES control. Interaction tests for both the ultrathin and the control stent type were negative for all outcomes, suggesting that the strut thickness rather than specific stent type drove the observed differences in outcomes. Nor were significant interactions for the primary outcome of TLF demonstrated between the stent type and any of the subgroups tested. However, these analyses should be interpreted with caution as not all trials provided detailed subgroup data, introducing selection bias and increasing the likelihood of type II error.

## Limitations

This was a study-level meta-analysis, and as such is limited by the scope and shortcomings of each individual trial. Inter-study variability in the definitions of MI, TLF, and TVF were present in a few of the trials, which may have added some imprecision to our results, although statistical heterogeneity was generally low for most analyses. A pooled individual patient data analysis of these studies would prove useful in enabling more granular subgroup analyses, multivariable analysis to reduce variability from observed differences, and affording a structure to examine the temporal relationships in outcomes with greater accuracy. Second, HRs are often considered the most appropriate method for analysing time-to-event data, but most trials did not report their outcomes using this metric. The secondary analyses using this methodology, while included for completeness, are thus of limited utility. Instead, we assessed the primary outcome using RRs from individual event counts provided by the trials. Such effect sizes may be influenced by the follow-up time points. To address this (and recognizing the typical differential in risk after stent implantation beyond 1 year), we provided analyses for early ( $\leq 1$  year) and later ( $>1$  year) events when reported, for which the  $P$ -values for interaction were non-significant. However, we were not able to landmark events at 1 year to specifically evaluate outcomes in the late period. To further address variable follow-up duration, we assessed the impact of follow-up duration on clinical outcomes as a regression analysis, with no evidence of a significant moderating effect on any clinical outcomes. We also performed additional sensitivity analysis including IRRs, which were consistent with our primary analyses.

A variety of stent types were used in both the ultrathin group and the control group, although the most common ultrathin-strut stent was Orsiro and the most common control stent was Xience. We tested for an effect of stent type within both the ultrathin-strut group and the control group, and the statistical tests for interaction were non-significant in both groups. The Orsiro stent has thicker struts for larger stent diameters ( $\geq 3.5$  mm). However, the median reference vessel diameters or maximum implanted stent diameters did not exceed 3.5 mm in any of the included trials, and in the majority, the mean reference vessel diameters were below 3.0 mm with standard deviations of 0.4–0.5 mm. We therefore believe that the use of 3.5 mm Orsiro stents would have been in a small minority of patients, likely under 10% of the total included patients. Individual patient data could help to clarify this further.

Finally, to avoid bias from measured and unmeasured confounders, our study was limited to randomized trials, which by their nature included a selected cohort of patients, introducing concerns of generalizability. However, several of the individual studies were of an ‘all-comers’ design,<sup>18,19,28,30,33,34,38</sup> and collectively, the 16 trials recruited a broad cross-section of patients including those with acute coronary syndrome and complex CAD.

## Conclusions

In the present meta-analysis of 16 trials randomizing 20 701 patients and with a mean follow-up of 2.5 years, ultrathin-strut DES were associated with a modestly reduced long-term risk of TLF and TVF compared with conventional 2nd-generation thin-strut DES, the differences driven by lower rates of CD-TLR and CD-TVR. There were no significant differences in the risks of MI, ST, cardiac death, or all-cause mortality.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

## Data availability

The data underlying this article are available in the article and in its online supplementary material.

## Funding

M.V.M. was supported by a grant from the National Institutes of Health/National Heart, Lung, and Blood Institute to Columbia University Irving Medical Center (T32 HL007854). This research was funded in whole, or in part, by the Wellcome Trust [grant 212183/Z/18/Z awarded to J.P.H.]. For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

**Conflict of interest:** Dr. Madhavan was supported by a grant from the National Institutes of Health/National Heart, Lung, and Blood Institute to Columbia University Irving Medical Center (T32 HL007854). Dr. Stone has received speaker honoraria from Cook and Terumo; has served as a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, and Matrizyme; and owns equity/options in Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, the

Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, the MedFocus family of funds, and Valfix. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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