Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis


CRD summary
The authors concluded that cobalt-chromium everolimus-eluting stents significantly reduced rates of stent thrombosis at one year compared with other drug-eluting stents and up to two years compared with bare-metal stents. The authors' conclusion reflected the evidence but review reporting issues and uncertainties associated with network analysis suggest caution is warranted when interpreting the findings.

Authors' objectives
To compare the risk of stent thrombosis between first and second generation drug-eluting stents, or between drug-eluting and bare-metal stents.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched for relevant trials without date or language restrictions. Search terms were reported. TCTMD, ClinicalTrials.gov, ClinicalTrialResults.org, Cardioource and abstracts/presentations from major cardiovascular meetings (not specified) were searched.

Study selection
Randomised controlled trials (RCTs) that compared the risk of definite and definite or probable stent thrombosis between two or three drug-eluting stents approved by the US Food and Drug Administration (FDA) and between drug-eluting and bare-metal stents were eligible for inclusion. Eligible drug-eluting stents included sirolimus, paclitaxel, cobalt-chromium everolimus, platinum-chromium everolimus, phosphorylcholine-based zotarolimus and resolute zotarolimus.

The primary outcome was one-year rate of definite stent thrombosis according to Academic Research Consortium (ARC) criteria. Secondary outcomes were one-year rates of ARC definite or probable stent thrombosis, early (≤30 days), late (31 days to one year), very late (one to two years) and two year definite and definite or probable stent thrombosis. RCTs that reported stent thrombosis but not according to ARC criteria were abstracted but not included in the meta-analysis. Patients who experienced multiple episodes of stent thrombosis were recorded, but each patient was only counted once in the cumulative analysis at one and two years.

Most trials were multi-centre non-inferiority or superiority designs. The mean age of patients, where reported, ranged from 59 to 69.3 years. Some trials were restricted to patients with diabetes, saphenous vein graft, ST-segment elevation myocardial infarction, restenosis or unprotected left main coronary artery disease. Where reported, between 11% and 100% had diabetes, between 24.4% and 82.6% had hypertension and between 22.7% and 86.7% had hyperlipidaemia. Where reported, between 1.5% and 59% had prior myocardial infarction and between 9.3% and 63.5% had acute coronary syndrome. Most trials excluded patients with high risk or complex lesions. In most trials patients received dual antiplatelet therapy for six or 12 months.

Two reviewers independently screened studies for inclusion. Discrepancies were resolved through consensus.

Assessment of study quality
Trial quality was assessed with criteria for allocation concealment, blinding of outcome data and intention-to-treat analysis.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Dichotomous outcome data were extracted to calculate odds ratios (ORs) and 95% credible intervals (CrI).
The authors did not state how many reviewers extracted the data.

**Methods of synthesis**

A Bayesian network analysis was conducted with a random-effects model to combine odds ratios and 95% credible intervals for direct and indirect comparisons. Each analysis was based on non-informative prior distributions. Sensitivity analyses (fixed-effect model) assessed the impact of patients without ST-segment elevation myocardial infarction and patients without diabetes. Trials from Asia were excluded. Statistical heterogeneity and inconsistency between direct and indirect comparisons was assessed using $I^2$.

Publication bias was assessed through visual inspection of funnel plots.

**Results of the review**

Forty-nine RCTs (number of patients reported as 50,844; calculated as 51,144) were included in the review. Forty-eight RCTs reported allocation concealment, 48 reported intention-to-treat analysis and 47 reported blinding to outcome assessment. The maximum length of follow-up ranged from seven months to two years.

**One-year definite stent thrombosis (46 RCTs):** Definite stent thrombosis was statistically significantly reduced with cobalt-chromium everolimus-eluting stents compared to bare-metal stents (OR 0.23, 95% CrI 0.13 to 0.41), paclitaxel-eluting stents (OR 0.28, 95% CrI 0.16 to 0.48), sirolimus-eluting stents (OR 0.41, 95% CrI 0.24 to 0.70), phosphorylcholine-based zotarolimus-eluting stents (OR 0.21, 95% CrI 0.10 to 0.44) and resolute zotarolimus-eluting stents (OR 0.14, 95% CrI 0.03 to 0.47). Statistically significant reductions in definite stent thrombosis were reported with sirolimus-eluting stents compared to bare-metal stents (OR 0.57, 95% CrI 0.36 to 0.88) and when phosphorylcholine-based zotarolimus-eluting stents were compared to sirolimus-eluting stents (OR 1.92, 95% CrI 1.07 to 3.90). No other comparisons showed statistically significant differences.

**One-year definite or probable stent thrombosis (44 RCTs):** When the definition was broadened to probable stent thrombosis, the comparisons between cobalt-chromium everolimus-eluting stents versus sirolimus-eluting stents and cobalt-chromium everolimus-eluting stents versus resolute zotarolimus-eluting stents were no longer statistically different. The difference between sirolimus-eluting stents versus paclitaxel-eluting stents became statistically significant in favour of sirolimus-eluting stents (OR 0.60, 95% CrI 0.41 to 0.87). There was evidence of significant statistical heterogeneity for the comparison cobalt-chromium everolimus-eluting stents versus resolute zotarolimus-eluting stents ($I^2=66\%$).

**Two-year definite stent thrombosis (24 RCTs):** Statistically significant reductions were reported for cobalt-chromium everolimus-eluting stents compared with bare-metal stents (OR 0.35, 95% CrI 0.17 to 0.69) and paclitaxel-eluting stents (OR 0.34, 95% CrI 0.19 to 0.62). No other comparisons were significantly different.

**Two-year definite or probable stent thrombosis (23 RCTs):** When the definition was broadened to probable stent thrombosis, the results for comparisons between cobalt-chromium everolimus-eluting stents versus bare-metal stents and cobalt-chromium everolimus-eluting stents versus paclitaxel-eluting stents remained significant. Cobalt-chromium everolimus-eluting stents was also associated with a statistically significant reduction compared to phosphorylcholine-based zotarolimus-eluting stents (OR 0.40, 95% CrI 0.17 to 0.89).

Statistically significant reductions with cobalt-chromium everolimus-eluting stents compared with bare-metal stents were also apparent for early and late definite and definite or probable stent thrombosis. Sensitivity analyses did not significantly alter the results. Other findings were reported in the review.

Direct and indirect effect estimates for cobalt-chromium everolimus-eluting stents versus bare-metal stents were highly consistent for both one-year definite and one-year definite or probable stent thrombosis ($I^2=0\%$ for both analyses). Visual inspection of funnel plots showed no evidence of publication bias.

**Authors’ conclusions**

Cobalt-chromium everolimus-eluting stents significantly reduced rates of definite stent thrombosis compared with other first and second generation drug-eluting stents and significantly reduced rates up to two years compared with bare-metal stents.
CRD commentary
The review question and supporting inclusion criteria were clearly defined. The literature search was comprehensive and included attempts to reduce language and publication biases. Formal assessment showed no evidence of publication bias. Study screening was performed in duplicate, but it was unclear whether the same procedure was carried out for quality assessment and data extraction so reviewer error and bias could not be ruled out. Quality assessment methods were limited; the criteria assessed indicated that the RCTs were generally acceptable.

A comprehensive network analysis was performed; the limitations inherent with this type of analysis and the indirect nature of some comparisons should be considered when interpreting the findings. Statistical heterogeneity was observed in one comparison. There appeared to be variability in patients and trials, with too few details to assess whether there was evidence of methodological heterogeneity. The authors acknowledged some of the limitations of the review, including the potential for some analyses to be underpowered and the restricted number of trials that reported outcomes at two years. This review involved a comprehensive network analysis on a large set of data.

Although the authors' conclusions reflect the available evidence on US FDA approved stents, review reporting issues suggest caution is warranted when interpreting the conclusions.

Implications of the review for practice and research
Practice: The authors stated that thrombosis was only one outcome associated with drug-eluting stents. Other safety and efficacy outcomes should be considered in individual patients when making stent selection decisions.

Research: The authors stated that further large RCTs were needed to verify the findings for everolimus-eluting stents versus bare-metal stents and versus other contemporary drug-eluting stents.

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