Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials

CRD summary
This review assessed the effect of drug-eluting stents on the development of late thrombosis. The authors concluded that drug-eluting stents appear to increase the risk for late thrombosis, although the incidence of very late stent thrombosis (after more than 1 year) is low. A lack of reported methodology and study quality limit the interpretation of these results.

Authors' objectives
To determine the effect of drug-eluting stents (DES) on the development of late thrombosis.

Searching
MEDLINE, and the Cochrane CENTRAL Register were searched from 2000 to 2005 for publications in the English language; the search terms were reported. Relevant journals and recently presented data from cardiology conferences were checked, and experts in the field were contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared paclitaxel stents or sirolimus stents with bare metal stents (BMS) were eligible for inclusion. Concurrent treatment with dual antiplatelet therapy (aspirin with clopidogrel or ticlopidine) was also required. Studies that used cilostazol instead of thienopyridine were excluded. Studies that used a nonpolymeric stent platform or experimental antiproliferative agents were excluded, as were studies that directly compared paclitaxel stents with sirolimus stents. Most of the sirolimus trials required dual antiplatelet therapy between 2 and 3 months with duration of clinical follow-up ranging from 8 to 48 months. Dual antiplatelet therapy lasted 6 months in all of the paclitaxel trials, with clinical follow-up ranging from 9 to 24 months.

Participants included in the review
The authors did not specify any inclusion criteria relating to the participants.

Outcomes assessed in the review
The primary outcome was angiographic stent thrombosis, defined as a filling defect in proximity to a previously placed stent on repeat coronary angiogram. Thrombotic events were classified as late if they occurred more than 30 days after percutaneous coronary intervention (PCI); late events were further classified as more than 30 days, more than 6 months, and more than 1 year.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed the quality of the primary studies.

Data extraction
Three reviewers independently extracted data for each thrombosis on type of stent used and the number of days after revascularisation that the event occurred. The risk of thrombosis was calculated for each study (number of thrombotic events during clinical follow-up divided by the number of individuals at risk for thrombosis). Risk ratios (RRs) for stent thrombosis were calculated.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis; summary estimates were calculated as RRs along with 95% confidence intervals (CIs).

How were differences between studies investigated?
It is unclear whether statistical heterogeneity was assessed.

Results of the review
Fourteen RCTS (n=6,675) were included in the review: 9 sirolimus trials and 5 paclitaxel trials.

The incidence of late thrombosis more than 30 days after PCI was 5.0 events per 1,000 DES patients compared with 2.8 events per 1,000 BMS patients (RR 1.56, 95% CI: 0.77, 3.16). The incidence of thrombosis based on type of stent (sirolimus or paclitaxel) did not significantly change this result.

The incidence of late thrombosis more than 6 months after PCI was 4.4 events per 1,000 DES patients compared with 0.6 events per 1,000 BMS patients (RR 3.67, 95% CI: 1.30, 10.38). The incidence of late thrombosis was 3.5 events per 1,000 DES patients and 1.4 events per 1,000 BMS patients (RR 1.99, 95% CI: 0.50, 7.91) in the sirolimus trials, and 5.1 events per 1,000 DES patients with no events in BMS patients (RR 7.07, 95% CI: 1.28, 39.09) in the paclitaxel trials.

The incidence of very late thrombosis (more than 1 year after PCI) was 5.0 events per 1,000 DES patients, compared with no events in BMS patients (RR 5.02, 95% CI: 1.29, 19.52). In the sirolimus trials, the incidence of very late thrombosis was 3.6 events per 1,000 drug DES patients with no events in BMS patients (RR 3.99, 95% CI: 0.45, 35.62). In the paclitaxel trials, the incidence of very late thrombosis was 5.9 events per 1,000 DES patients with no events in BMS patients (RR 5.72, 95% CI: 1.08, 32.45).

Results for overall risk of thrombosis and risk of early thrombosis were also reported.

Authors’ conclusions
DES appear to increase the risk for late thrombosis, although the incidence of very late stent thrombosis (after more than 1 year) is low. Although a greater risk was seen with paclitaxel stents, it is possible that sirolimus stents may similarly increase the risk of late thrombosis in comparison with BMS.

CRD commentary
The research question was supported by clear inclusion criteria. Several sources were used to find relevant papers, although the search strategy was restricted by language and might have resulted in publication bias. The authors did not indicate whether procedures to minimise review bias or error were undertaken in the study selection process, nor did they indicate whether the quality of the primary studies was assessed; this reduces the ability to fully interpret the results obtained. The analysis appears appropriate, although it is unclear whether heterogeneity was assessed. In view of these considerations, these results should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors suggested that there may not be a safe period for DES after which clopidogrel can safely be stopped. They stated that patients with DES may need to remain on dual antiplatelet therapy longer than the current Food and Drug Administration labelling of 6 months for sirolimus and 3 months for paclitaxel.

Research: The authors stated that the optimal duration of antiplatelet therapy for DES is unknown.

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