Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

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Although the safety profiles of coronary stents eluting sirolimus or paclitaxel do not seem to differ from those of bare metal stents in the short-to-medium term, concern has arisen about the potential for late stent thromboses related to delayed endothelialisation of the stent struts. We report four cases of angiographically-confirmed stent thrombosis that occurred late after elective implantation of polymer-based paxlitaxel-eluting (343 and 442 days) or sirolimus-eluting (335 and 375 days) stents, and resulted in myocardial infarction. All cases arose soon after antiplatelet therapy was interrupted. If confirmed in systematic long-term follow-up studies, our findings have potentially serious clinical implications.

Metallic coronary stents are implanted in more than 1·5 million patients per year. Polymer-based coronary stents eluting sirolimus or paclitaxel substantially reduce the need for repeat percutaneous intervention compared with bare-metal stents, and drug-eluting stents are rapidly replacing bare-metal stents. A meta-analysis[1] of 11 randomised trials (5013 patients) showed no evidence that the short-to-medium-term safety profiles of sirolimus-eluting or paclitaxel-eluting stents differed from those of bare-metal stents. However, these trials were not powered to detect or exclude an effect of drug-eluting stents on rare events such as stent thrombosis.

Stent thrombosis usually results in ST-segment elevation myocardial infarction or death. Angiographically documented late (>6 months) stent thrombosis is extremely rare with bare-metal stents except after intracoronary irradiation, which delays vascular healing. There is concern that drug-eluting stents might also be susceptible to late thrombosis related to delayed endothelialisation of the stent struts.[2] We report four cases of late stent thrombosis when antiplatelet therapy was interrupted after elective implantation of drug-eluting stents.

In March, 2003, a 63-year-old man presented with unstable angina and angiographically significant lesions (>50% diameter stenosis) in the left anterior descending artery and a non-dominant right coronary artery. He underwent percutaneous intervention of the left anterior descending artery in June, 2003, with one paclitaxel-eluting stent (3 mm diameter, 16 mm long; Taxus Express 2, Boston Scientific, Natick, MA, USA) and had no further angina. Aspirin was stopped in May, 2004, before elective resection of bladder polyps. 5 days later, 343 days after stenting, the patient presented with an anterior myocardial infarction. Angiography showed stent occlusion. Percutaneous intervention restored vessel patency; peak concentration of creatine kinase was 6500 IU/L.

A 73-year-old man sustained an aborted out-of-hospital cardiac arrest with documented ventricular fibrillation. In the preceding weeks, he had atypical chest pain. The admission electrocardiogram was normal. Coronary angiography showed an isolated proximal lesion of the left anterior descending artery (figure 1A). Electrophysiological investigations were negative. The patient underwent percutaneous intervention with one paclitaxel-eluting stent (3·5 mm diameter, 16 mm long; Taxus Express 2), in April, 2003 (figure 1B and 1C) and was subsequently asymptomatic. In June, 2004, aspirin was discontinued before resection of a newly diagnosed colon carcinoma. 1 week later, on the evening of surgery, 442 days after stenting, the patient developed anterior myocardial infarction. Angiography showed stent occlusion (figure 1D) and extensive thrombus after guidewire passage (figure 1E). Percutaneous intervention restored vessel patency; peak concentration of creatine kinase was 3500 IU/L.

A 42-year-old man admitted to hospital with chest pain in May, 2003, developed ventricular fibrillation. After successful cardioversion, angiography showed significant lesions in the left anterior descending artery (the culprit lesion) and left circumflex artery. Two bare-metal stents (3·0 mm diameter, 18 mm long; Vision, Guidant Santa Clara, CA, USA) were placed in the left anterior descending artery. 2 days later, the patient underwent elective stenting of the left circumflex artery with one sirolimus-eluting stent (3 mm diameter, 33 mm long; Cordis, Miami Lakes, FL, USA) in a second obtuse marginal branch, and was subsequently asymptomatic. In November, 2003, after negative nuclear stress testing, clopidogrel was discontinued. In May, 2004, the patient stopped taking aspirin. 2 weeks later, 375 days after stenting, he presented with chest pain. Angiography showed patent bare-metal stents (figure 2A) but the sirolimus-eluting stent was occluded (not shown). Intravascular ultrasonography after thrombectomy ruled out both malapposition (figure 2B) and edge restenosis. Percutaneous intervention was successful.

A 62-year-old man with stable angina and two-vessel coronary disease underwent successful percutaneous intervention with one sirolimus-eluting stent (3 mm diameter, 18 mm long; Cordis) in the left anterior descending artery, and one bare-metal stent (3 mm diameter, 18 mm long; Vision) in an obtuse marginal

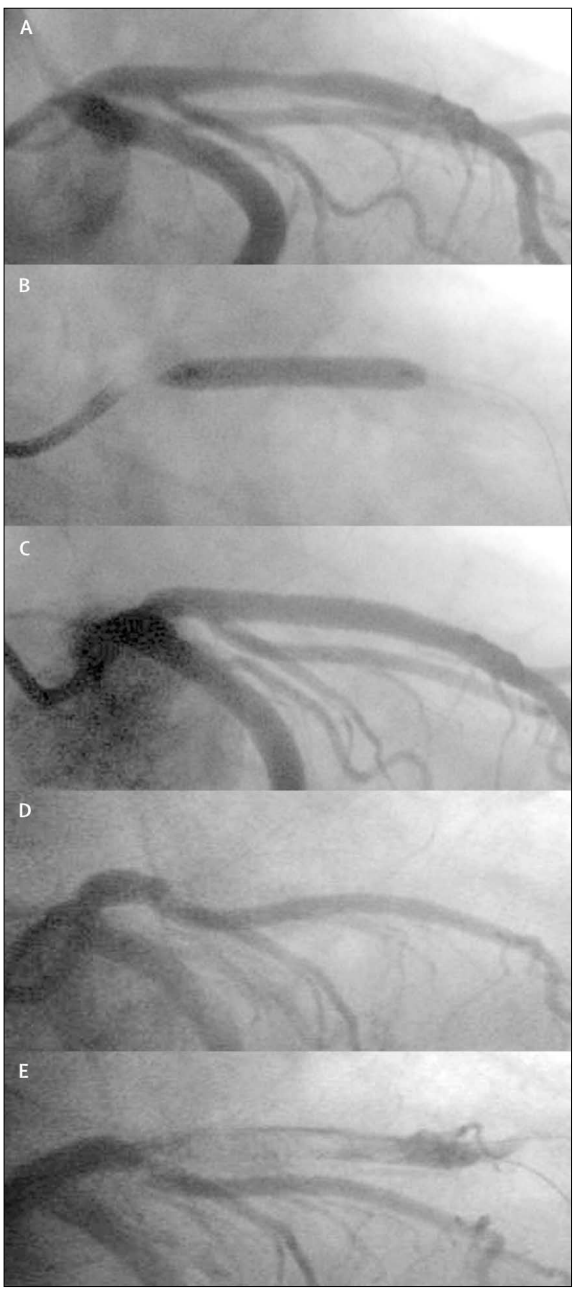

Figure 1: **Coronary angiography showing implantation of a paclitaxel-eluting stent and subsequent thrombosis**
Concentric lesion in the mid left anterior descending artery at baseline (A), during (B) and after (C) implantation of a paclitaxel-eluting stent. (D) Occlusion at the proximal margin of the stent. (E) Angiogram after passage of guidewire showing large thrombus in the stent.

branch in July, 2003. In June, 2004, the patient stopped clopidogrel and aspirin before colonoscopy and polypectomy. 4 days later, 335 days after stenting, he presented with an anterior myocardial infarction. Angiography showed occlusion of the sirolimus-eluting stent, whereas the bare-metal stent was patent. Percutaneous intervention was successful.

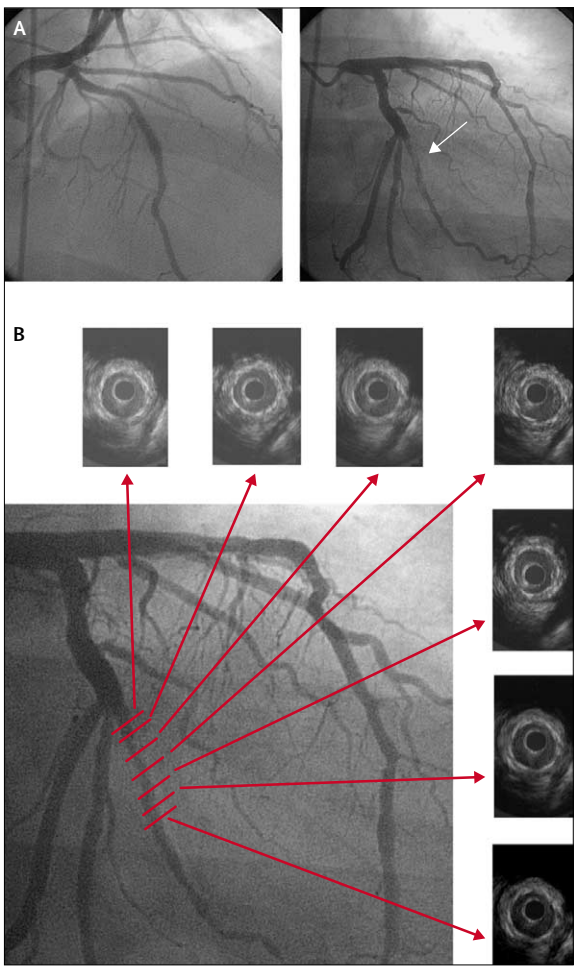

Figure 2: **Angiographic and intravascular ultrasound images on presentation with stent thrombosis in a patient previously treated with sirolimus-eluting and bare-metal stents**
(A) Left coronary angiogram, after mechanical thrombectomy, showing the widely patent bare-metal stent in the left anterior descending coronary artery (left) with residual thrombotic material (white arrow) in the sirolimus-eluting stent (right). There was no "edge" restenosis. (B) Intravascular ultrasound images within the stent (white lines), after mechanical thrombectomy, showing optimal stent apposition.

Late thrombosis after bare-metal stenting is a well documented, albeit rare, complication when intracoronary irradiation is used as an adjunct to stent placement to reduce restenosis after percutaneous intervention. This problem has been attributed to delayed vascular healing that renders the surface of the stent prothrombotic, and, in the presence of an appropriate physiological stimulus, can result in thrombotic occlusion.

Studies in animals have generated concern that drug-eluting stents could also be prone to late stent thrombosis, although extrapolation of such findings to human beings might be unreliable.[2] Evidence from animal models suggests that the Cypher sirolimus-eluting stent does not impede endothelialisation.[3] By contrast, animal studies with paclitaxel-eluting stents

clearly show delayed re-endothelialisation.[4] However, these studies were done with stents in which the polymer coating, design, and drug-release kinetics differed substantially from those of the Taxus paclitaxel-eluting stents; to our knowledge, no reports have been published about the effects of Taxus stents on re-endothelialisation. There are also differences between the drug-release kinetics of Cypher and Taxus stents. With the Taxus stent, about 10% of the paclitaxel is released by 10 days; the rest remains in the polymer indefinitely. With the Cypher stent, almost all the sirolimus has eluted by 6 weeks, leaving a polymer-coated bare-metal stent. It is unclear whether this difference is of any clinical importance, in terms of the potential for long-term adverse events.

Based on the design of the pivotal clinical trials that led to approval of such stents, dual antiplatelet therapy is prescribed on an empirical basis, for 2–3 months after implantation of sirolimus-eluting stents, and for 6 months after implantation of paclitaxel-eluting stents, with life-long aspirin. Our report shows that thrombosis can arise very late after uncomplicated placement of a single drug-eluting stent, in a large vessel, when antiplatelet therapy is discontinued. In two of four patients, a bare-metal stent implanted in a different vessel, at or around the same time, remained patent when the drug-eluting stent occluded.

Three of these late occlusions happened when antiplatelet therapy was discontinued for non-cardiac surgery. In the bare-metal stent era, an initial report showed that non-cardiac surgery more than 2 weeks after stent placement was associated with a prohibitive rate of adverse events (32% mortality).[5] Findings from a subsequent larger series suggested that discontinuation of antiplatelet therapy, later than 6 weeks after placement of a bare-metal stent, for non-cardiac surgery was relatively safe.[6] The time window of the occlusions we encountered far exceeds that reported for bare-metal stents.

Our report has limitations. Intravascular ultrasound definitively excluded restenosis as a contributing factor to late thrombosis in only one patient. The others were haemodynamically unstable, precluding intravascular ultrasound. However the absence of symptoms after stenting, coupled with the acute presentation and the angiographic findings, suggest that the mechanism was purely thrombotic. Second, we only report angiographically-confirmed cases; highly suspect presumed cases have been reported; thus, the true rate might be higher.[7]

We report these cases to draw attention to a problem, with serious clinical implications, that might be under-reported. We suggest that the potential risk of stent occlusion should be considered when discontinuation of antiplatelet therapy is contemplated in patients with drug-eluting stents. Finally, as the use of drug-eluting stents becomes widespread, careful long-term follow-up of patients with such stents is needed to assess the true rate of late thrombosis.

Contributors

E P McFadden and E Stabile wrote and revised the report; both authors contributed equally. The other authors reviewed the report. For the authors in Europe: E P McFadden did initial procedures for two patients and follow-up procedure for one patient; E Regar did the other follow-up procedure; A T L Ong collected data; P W Serruys, as head of the department, was also responsible for patient care. For the authors in the USA: E Stabile was involved in data collection and patient care; E Cheneau and T Kinnaird helped in adjudicating the events and drafting the manuscript; W O Suddath participated in patient care; N J Weissman assessed the intravascular ultrasound; R Torguson was the research coordinator and helped in data collection; K M Kent, A D Pichard, and L F Satler participated in care of patients; R Waksman helped in drafting the letter and participated in patient care.

Conflict of interest statement

E P McFadden has received travel grants and/or speaker's fees from Boston Scientific, Cordis, Centocor (a Johnson and Johnson company), Guidant, Medtronic, and Sorin Biomedica, and has no other conflicts of interest. The authors declare that they have no conflict of interest.

References

1 Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet* 2004; **364:** 583–91.

2 Schwartz RS, Chronos NA, Virmani R. Preclinical restenosis models and drug-eluting stents: still important, still much to learn. *J Am Coll Cardiol* 2004; **44:** 1373–85.

3 Carter AJ, Aggarwal M, Kopia GA, et al. Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model. *Cardiovasc Res* 2004; **63:** 617–24.

4 Farb A, Heller PF, Shroff S, et al. Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. *Circulation* 2001; **104:** 473–79.

5 Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol* 2000; **35:** 1288–94.

6 Wilson SH, Fasseas P, Orford JL, et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *J Am Coll Cardiol* 2003; **42:** 234–40.

7 Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003; **108:** 788–94.