The incidence of stent thrombosis following drug-eluting stent (DES) implantation has been reported to range between 0.5-5%. 1-3 Although most reported cases have been documented within the first 30 days,3-5 DES thrombosis may occur up to 4 years following implantation.3 We have previously reported a case of sirolimus-eluting stent (SES) thrombosis as late as 17 months after SES implantation.6 We now present a case of very late stent thrombosis, 51 months after SES implantation and 15 months after clopidogrel discontinuation. This case underlines the possible need for long-term antiplatelet medication in patients receiving sirolimus-eluting stents.

Case presentation

A 43-year-old man, a smoker with arterial hypertension, was referred for coronary angiography following an episode of unstable angina with evidence of ischaemia in the anterior left ventricular wall. Coronary angiography revealed subtotal occlusion in the mid left anterior descending (LAD) coronary artery, with late peripheral filling (Figure 1, left panel). The patient was preloaded with 300 mg of clopidogrel per os and primary stenting of the LAD lesion was undertaken with implantation of a Cypher (Cordis Corp., Johnson & Johnson, Warren, New Jersey) stent (3.0 × 13 mm at 14 atm) and an excellent angiographic result (Figure 1, right panel). A subsequent intravascular ultrasound assessment confirmed adequate stent expansion, and fractional flow reserve (FFR) evaluation verified the absence of any haemodynamically significant residual stenosis (FFR value of 0.94) along the stent. The procedure was uneventful and the patient was put on aspirin 100 mg and clopidogrel 75 mg per os daily. He remained asymptomatic and discontinued his clopidogrel 3 years after the procedure, continuing only on aspirin, statin and beta blockade. Fifteen months later he developed an anteroseptal myocardial infarction. Coronary angiography revealed stent thrombosis and total LAD occlusion (Figure 2). Platelet count and aggregation studies as well as coagulation profile were unremarkable. He was treated with a repeat procedure and three months later he remains asymptomatic. He has been advised to continue on aspirin and clopidogrel indefinitely.

Discussion

Although the majority of the current trials consistently show that DES are associated with a better clinical outcome when com-
pared with bare metal stents, stent thrombosis is nevertheless still considered one of the major limitations of DES. The need for long-term dual antiplatelet treatment has been widely recognized, but the exact duration has not yet been clearly determined. The potential role of aspirin or clopidogrel resistance may also be of importance in this respect, while the potential use of new antiplatelet agents such as prasugrel is under investigation.

To the best of our knowledge, this the first report of an SES thrombosis more than four years following stent implantation and 15 months after discontinuation.

Figure 1. A: Baseline coronary angiography in right anterior oblique (30° 15°) cranial view showing significant lesion subtotal occlusion of the left anterior descending (LAD) artery (black arrow) and delayed filling at the periphery (white arrow). B: Post-procedure coronary angiography in postero-anterior (15°) cranial view after direct stenting in the mid segment of LAD. There is no residual stenosis (black arrow) and TIMI 3 flow has been restored in the distal vessel.

Figure 2. Coronary angiography in right anterior oblique (30° 15°, A) and left anterior oblique (40° 20°, B) cranial views 51 months after the procedure, showing total occlusion at the proximal edge of the proximal Cypher stent implanted in the mid segment of the left anterior descending artery (black arrow).
of clopidogrel therapy. It should be noted that the particular patient did not have other clinical and angiographic risk factors that predispose to stent thrombosis. There have been early concerns about delayed healing and polymer-related hypersensitivity reactions, with consequent risks of delayed thrombosis following DES implantation.\(^{10,11}\) Sirolimus and paclitaxel effectively reduce restenosis by inhibiting neointimal hyperplasia, but they also delay the healing process far beyond the 3 to 6-month period usually required with bare metal stents.\(^{13}\) Impaired intimal healing is a recognised cause of late stent thrombosis in humans.\(^{12}\) Furthermore, polymer coatings used in currently commercially available drug-eluting stents as reservoirs of medications may result in marked intimal inflammation.\(^{11}\) Pathology studies have provided evidence of hypersensitivity vasculitis within the stented arterial segment after SES implantation, with polymer fragments surrounded by giant cells and eosinophils.\(^{10}\)

It has recently been shown that even a small (<1%) incremental risk of thrombosis in DES might be sufficient to outweigh the benefit of restenosis prevention and favour BMS use for the overall PCI population.\(^{13}\) The threshold excess risk of very late DES thrombosis compared with BMS, above which BMS would be the preferred strategy, was 0.14%/year (over 4 years of follow-up). A small absolute increase in DES thrombosis compared with BMS after 1 year (>0.14%/year) would result in BMS being the preferred strategy for the overall PCI population.\(^{12}\) Although the actual risk of late DES thrombosis is still being debated,\(^{14,15}\) it is certainly not negligible. A recent FDA Circulatory Devices panel has estimated the annual thrombotic risk at between 1-5%.\(^1\) Thus, every effort should be made to diminish such a risk. Farb et al\(^{12}\) have argued in favour of prolonged anti-platelet medication when treating high-risk lesions, even with conventional stents. Our case report further supports this recommendation.

In conclusion, our case report presents evidence of very late stent thrombosis with the use of SES and argues in favour of prolonged antiplatelet medication in this setting, at least until data from randomised trials address this important issue.

References