Delayed neointimal healing after drug-eluting stent implantation: seeing is believing

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This editorial refers to 'Angioscopic differences in neointimal coverage and in persistence of thrombus between sirolimus-eluting stents and bare metal stents after a 6-month implantation' by Takano et al., on page 2189

Ever since its introduction in 1977, the long-term benefit of percutaneous coronary intervention has been limited by the phenomenon of restenosis, i.e. recurrence of significant stenosis at the site of intervention. Whereas, after plain balloon angioplasty, restenosis is for roughly two-thirds due to negative vessel wall remodelling, the late lumen loss after stent implantation is virtually exclusively caused by neointimal hyperplasia, a proliferation of smooth muscle cells with deposition of abundant extracellular matrix. Over the last years, a multitude of anti-proliferative drugs have been tested, several of which have been found effective in inhibiting this neointimal hyperplasia when locally delivered from a polymer-encapsulated stent. The two compounds with the largest clinical experience are paclitaxel and sirolimus, a cytostatic macrocyclic lactone with both anti-inflammatory and anti-proliferative properties.

Although the efficacy of these drug-eluting stents (DES) in preventing restenosis has been well established over the last years, recently, concerns have been raised about a possibly increased incidence of late stent thrombosis (more than 6 months after stent implantation) when compared with the very low incidence of late stent thrombosis after implantation of bare metal coronary stents (BMS). At the annual congress of the American College of Cardiology in March 2006, Matthias E. Pfisterer presented a new analysis of the Basel Stent Cost Effectiveness Trial (BASKET), a randomized study that compared BMS and DES. This new analysis, known as Late Clinical Events Related to Late Stent Thrombosis After Stopping Clopidogrel (BASKET-LATE), was performed to determine the risk of late stent thrombosis after discontinuation of clopidogrel and focused on 746 patients from the BASKET study who experienced no cardiac complications within the first 6 months of stent implantation and were advised to discontinue clopidogrel at that time. The investigators continued to follow-up with these patients for another 12 months, in order to determine the comparative rates of late stent thrombosis in patients treated with BMS and DES stents and the clinical consequences of this complication, including cardiac death, myocardial infarction (MI), and the need for a procedure to re-establish blood flow through the stented artery. An average of 1.9 stents were used per patient. Principal findings showed that in the year following clopidogrel discontinuation, the primary composite endpoint of cardiac death or MI occurred significantly more frequently in the DES group (4.9 vs. 1.3%). Non-fatal MI was also higher in the DES group (4.1 vs. 1.3%) and cardiac death trended higher (1.2 vs. 0%). There was no difference in restenosis-driven target vessel revascularization (4.5 vs. 6.7%). Late stent thrombosis (combination of angiographically documented stent thrombosis and thrombotic clinical events) occurred in 2.6% of the DES group and 1.3% of the BMS group. The median time of the late thrombotic event was 116 days after clopidogrel discontinuation, but events occurred throughout the 1-year follow-up. Many trials have demonstrated a reduction in target lesion revascularization with DES compared with BMS in recent years, but none has ever demonstrated an effect on the hard endpoints of death or MI. This adds to the concerns created by BASKET-LATE, showing a more than three-fold increase in death or MI with DES in the year after clopidogrel discontinuation.

It must be acknowledged, however, that these figures are the highest reported to date. Ong et al. reported the angiographic incidence of late stent thrombosis in an unselected population of 2006 patients who had received a DES. In this population, the rate of early stent thrombosis had earlier been reported to be at 1%. More than 30 days after DES implantation, during a follow-up of at least 1 year (mean 1.5 years), eight cases of late stent thrombosis were angiographically documented in seven patients, three of 1017 with sirolimus-eluting stents (SES), and five of 989 with paclitaxel-eluting stents, yielding an incidence
of angiographically proven late stent thrombosis of at least 0.35%. Three cases were related to complete cessation of antiplatelet therapy, two cases occurred while patients were on aspirin therapy within 1 month of cessation of clopidogrel, and three cases occurred at a time when patients were apparently clinically stable on aspirin monotherapy. Two deaths occurred directly as a result of the late stent thrombosis. Obviously, the main limitation of this report is that it is confined to patients who presented with acute symptoms and angiographically proven late stent thrombosis, thus precluding an accurate assessment of the overall rate of late stent thrombosis.

In a recent report on the 1-year follow-up of the e-Cypher Registry, in which data were collected on 15157 patients who underwent implantation of at least one SES at 279 medical centres from 41 countries, rates of acute, subacute, and late stent thrombosis of 0.13, 0.56, and 0.19% of patients, respectively, were reported, representing a 12-month actuarial incidence of 0.87%. Cumulative rates of major adverse cardiovascular events were 1.36% at 30 days, 3.38% at 6 months, and 5.80% at 1 year. Although this analysis suggests a higher degree of safety of SES, it should be interpreted with some caution because of the potential under-reporting of adverse events in large multicenter registries, despite the audit process in this registry. Furthermore, stent thrombosis was considered likely when the patient had a target vessel-related MI or died of a coronary event possibly caused by stent thrombosis, but only within 30 days of the index procedure. One should also take notice that at 1 year after the index procedure, 43% of patients were still on dual antiplatelet therapy. And finally, this report underscores that stent thrombosis is not a benign condition: among the 126 patients with adjudicated stent thrombosis, 53 died (42.1%), 55 suffered an MI (43.7%), and 63 underwent a TLR (50%). The interventional team at The Washington Hospital recently published their incidence of stent thrombosis after implantation of SES and paclitaxel-eluting stents: from a total cohort of 2974 consecutive patients treated with DES since April 2003, they identified 38 patients who presented with angiographic evidence of stent thrombosis (1.27%). The stent thrombosis occurred acutely in five patients, subacutely (<30 days) in 25 patients, and late (>30 days) in eight patients. Multivariate analysis detected cessation of clopidogrel therapy, renal failure, bifurcation lesions, and in-stent restenosis as significant correlates of stent thrombosis. The authors acknowledge, however, that they did not include in the analysis seven patients with Q-wave MI and 23 patients who died. It is therefore possible that the 38 thromboses within the time period specified is an underestimate.

In contrast, the longer term follow-up of randomized clinical trials with presently available DES is rather reassuring. In a meta-analysis on eight trials in 3817 patients with coronary artery disease who were randomized to paclitaxel-eluting or BMS, Bavry et al. found no increased hazard for thrombosis up to 12 months [risk ratio = 1.06 (95%CI 0.55–2.04, P = 0.86)].

In another meta-analysis pooling 10 randomized studies comparing DES and BMS, comprising 5030 patients, Moreno et al. found a similar incidence of stent thrombosis for DES (0.58%) and BMS (0.54%) [OR 1.05 (95%CI 0.51–2.15; P = 1.000)].

All these data leave the clinician with a puzzled mind: what is now the exact incidence of late stent thrombosis? Is late stent thrombosis after DES implantation a real problem or only a perceived problem? It is indeed difficult and even impossible to derive the true incidence of late stent thrombosis from the published data. For sure, when only angiographically confirmed stent thrombosis is taken into account, the incidence of late stent thrombosis is underestimated: some patients who experience a late stent thrombosis at home supposedly die suddenly and never make it to the hospital. In contrast, it is clear that not all MIs and sudden deaths after DES implantation can be attributed to stent thrombosis. In addition, the comparison with the rates of stent thrombosis after BMS is not entirely valid, because BMS patients are usually treated with a thienopyridine for 1 month or a few months at the most, whereas patients after DES implantation remain on treatment with clopidogrel for at least 3–6 months, or even years.

And if late stent thrombosis after DES implantation is a real issue, the next logical question is how long this increased risk persists. Indeed, if the delayed endothelial healing, thought to play an important role in the pathophysiology of stent thrombosis after DES implantation, would pertain to the presence of a non-erodable polymer (as present on the commercially available DES most used to date), it is not absolutely excluded that the increased risk of stent thrombosis persists for a much longer period of time than the follow-up periods available at present for larger patient groups after DES implantation. Practically speaking, while we may accept a slight excess risk of late stent thrombosis during e.g. 1 year in exchange for a major reduction in the incidence of restenosis, this might not be the case if this slight excess risk would actually be an annual risk during several years.

In this context of uncertainty, it is interesting to read the paper by Takano et al., on the angioscopic differences in neointimal coverage and in thrombus disappearance between SES and BMS 6 months after implantation.

In short, they studied 46 patients, of whom 36 had stable angina and 10 presented with an acute coronary syndrome, treated with 33 SES and 33 BMS immediately and 6 months after stent implantation using coronary angioscopy. This technique was developed in the early 1980s in order to obtain direct visual imaging of the interior of coronary arteries. The equipment used basically consists of a catheter containing optical fibres of which some are used for illumination and the vast majority for imaging. At its distal tip, this catheter has an occlusion balloon that is made of a very compliant material. After inflation of this balloon, a crystalloid solution is flushed distally to clear the field of view for the angioscope, thus allowing direct visualization of the coronary vessel wall. The information provided by directly looking at the coronary vessel wall in this manner has in general yielded limited clinically useful information at the expense of a somewhat increased risk because of the more invasive nature of this procedure when compared with angiography and higher cost. As a consequence, coronary angioscopy, nowadays, is rarely if ever used outside Japan. Nevertheless, this technique allowed the authors of the present article to obtain information that is almost impossible to obtain by other means and is in a way seminal. They graded the degree of neointimal coverage
of the stent struts (0, absent neointima; 1, visible struts through thin neointima; 2, invisible struts) and evaluated the presence of thrombi. Their main finding was that the neointimal coverage 6 months after implantation of SES was significantly lower than after BMS implantation (edge: 1.4 ± 0.7 vs. 1.9 ± 0.2; body: 1.0 ± 0.5 vs. 1.8 ± 0.5; overlapping segment: 0.6 ± 0.7 vs. 1.8 ± 0.5; \( P < 0.0001, P < 0.0001, P = 0.0069 \), respectively). In fact, 27 of the 153 segments (18%) of the SES were judged to have a complete absence of neointimal coverage, with exposure of the struts on angioscopy.

In addition, they found a marked difference in the presence of thrombus: at baseline, thrombus was observed in seven lesions of seven SES patients and in seven lesions of seven BMS patients. In the SES group, six of seven thrombi found at baseline remained present at the 6-month follow-up, and one thrombus was newly recognized at follow-up. In the BMS-group, only two of seven thrombi found at baseline remained at 6-month follow-up, and there was no new thrombus formation during this time period. These findings result in an incidence of persistence of thrombus of 86% in the SES group when compared with 29% in the BMS group (\( P = 0.031 \)). Hence, this study suggests a delayed neointimal stent coverage and slower thrombus disappearance in SES as compared with BMS.

There is no discussion that this study has some major limitations: the number of patients studied was relatively small, because of the non-randomized nature of the study the reference vessel diameters were different in the two stent groups (although there is no available prior knowledge supporting any influence of this variable on the findings reported), and angioscopy has limitations in confirming the existence of very thin neointima.

Nonetheless, this study provides clear evidence that one of the best currently available DES has a clear shortcoming regarding re-endothelialization and thrombus protection when compared with BMS. It also calls into question the optimal duration of dual antiplatelet therapy, especially when overlapping stents are implanted. Many interventionists have, be it more or less intuitively, adopted the habit of prescribing clopidogrel for a more extended period after implantation of overlapping DES, and that approach seems to be supported by the present study.

If however, the recommended duration of therapy with clopidogrel would be extended as time goes by—as has been the case after brachytherapy—this would not only markedly increase the total costs of DES implantation, but also put the patients at an increased risk for bleeding, or for very late stent thrombosis if clopidogrel needs to be stopped for whatever reason, e.g. non-cardiac surgery. It seems unimaginable that the path of DES will be deserted. Therefore, we will need novel stent/polymer designs with erodable polymers or polymers that do not cause inflammation nor hypersensitivity, or no polymers whatsoever, with continued research for the optimal drug to be delivered, at an optimal dose and with optimized elution profiles. In the mean time, a targeted use of DES seems warranted: in a non-diabetic patient with a discrete lesion in a large vessel, only a very small absolute clinical benefit of using a DES can be expected. For the time being, let us reserve the currently available DES for the patients for whom the greatest benefit can be expected: diabetics, and those with longer lesions in smaller vessels, and patients who are stented in sites where a restenosis would bring along an especially high risk, such as the unprotected left main stem.

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**References**