Coronary stent restenosis and occlusion: messages from the dead for the living

Constantin von zur Muhlen1, Philipp Kahlert2, and Christoph Bode1*

1Heart Center Freiburg University, Department of Cardiology and Angiology I, Freiburg, Germany; and 2West-German Heart Center, Essen University Hospital, Department of Cardiology, Essen, Germany

Online publish-ahead-of-print 2 October 2013

This editorial refers to ‘Human autopsy study of drug-eluting stents restenosis: histomorphological predictors and neointimal characteristics†, by M. Nakano et al., on page 3304

The advent of drug-eluting stents (DES) has revolutionized percutaneous coronary interventions (PCIs) by combining the properties of radial vessel support with the possibility of local drug delivery. While in-stent restenosis had previously been a major problem, occurring in 20–40% of patients with early-generation bare metal stents (BMS),1,2 it has been impressively reduced by the concept of DES. Studies have not only proven a reduction of target vessel revascularization by the use of DES, but have also demonstrated their safety and efficacy beyond prevention of restenosis. Therefore, DES implantation has been further transferred into high-risk populations and yielded promising results in diabetic patients, in-stent restenosis, and multivessel disease. Yet, the concept of DES was questioned by data presented during the annual congress of the European Society of Cardiology in Barcelona 2006 suggesting increased rates of stent thrombosis after DES implantation, also known as the ‘Barcelona fire storm’.3–5 However, more recent data during the last 5 years have proven the safety of DES and dispelled irrational fears.6,7 Subsequent generations of DES with improved properties of the platform have been developed, e.g., smaller strut thickness, optimized deliverability, as well as improved drug delivery, resulting in improved safety.8–11 Nevertheless, even DES implantation entails the less frequent, but clinically important problems of restenosis and chronic occlusion, which interventional cardiologists are still facing in their current daily routine. These two events are often connected with certain patient characteristics and lesion types (Figure 1), but there is still uncertainty about their exact mechanisms or predictors. Is it the type of drug the metallic stent is eluting? Is it the property of the target lesion, and, consequently, what lesion properties should alert the interventionalist? And how can we transfer our current knowledge into stent design and interventional strategies?

The study presented by Masataka et al. sheds some light into the present darkness.12 The authors present a plethora of histopathological data, which highlight interesting aspects with clinical ramifications. Fortunately, restenosis and late occlusion are still rather rare events in DES compared with BMS. However, the increasing numbers of PCIs performed with DES cause a considerable absolute number of subjects to be affected by these adverse outcomes. Coronary autopsies obtained from patients with DES implants were categorized into four groups, according to the maximum cross-sectional luminal narrowing: patent (<50%), intermediate (50–74%), restenotic (>75% with residual lumen), and total occlusion (organized thrombus within stent). Both restenosis and occlusion were significantly associated with total stent length, as compared with patent DES. Also, restenosis and occlusion were more frequently found in the distal regions of coronary vessels, which exhibited more pronounced vessel injury or uneven strut distribution, suggesting a local drug gradient. Whereas maximum inter-strut distance was associated with DES restenosis, medial tear length was a predictor of DES occlusion. Interestingly, no difference between different drug coatings could be found (sirolimus, paclitaxel, and everolimus). As shown by histological examination of the autopsy specimens, neointimal areas of restenotic DES lesions demonstrated greater proteoglycan depositions and fewer smooth muscle cells when compared with duration-matched restenotic BMS lesions, which demonstrated higher cell densities and collagen deposition.

What is the message from these data for the interventional cardiologists? First of all, to express the situation emphatically, DES work, and it is not only stented length that seems to matter. Longer lesions requiring longer stents tend to end up in restenosis or occlusion more often. However, this might also be due to complex lesions requiring longer stent coverage, or to patient co-morbidities.13 This notion is supported by the finding that restenotic and occluded stents have been observed to be located mainly in the mid and distal regions of coronary vessels, in parallel showing more pronounced vessel injury and uneven strut distribution. Such uneven
strut distribution, potentially leading to an unbalanced local drug delivery and, thus, pronounced intimal thickening, was observed especially in the presence of severe calcification, causing greater separation of the stent struts. In their histological findings, Masataka et al. nicely demonstrate an association between neointimal thickening and inter-strut distance in an example of a stented lesion with segmentally localized calcification and, hence, uneven stent strut expansion.

What about the differentiation and mechanisms of restenosis and occlusion, as suggested in this study? The authors demonstrate certain morphological differences between these two entities. Total occlusions showed a low smooth muscle cellularity with microcapillaries and a higher degree of inflammation, while a proteoglycan–collagen matrix was predominant in patent, intermediate, and restenotic DES. Moreover, medial disruption, more frequently seen after treatment of eccentric plaques, appears to play a central role in occlusion. Cross-sectional histology of a total occlusion in a paclitaxel-eluting stent implanted for 9 months convincingly showed media disruption and co-localized inflammatory cells as well as microvessels adjacent to the stent struts. With this observation, the authors transfer the concept of medial tears and occlusion, which has already been described in 1986 in the context of percutaneous transluminal coronary angioplasty (PTCA), into the era of DES implantation.\(^1\) The length of the medial tear was larger in the occluded group (2.5 ± 1.2 vs. 1.2 ± 0.4 in the intermediate and restenosis group) and therefore should have an important impact on clinical outcome.

As the authors correctly point out, there are a number of inherent limitations to this well-executed study. First, it is an autopsy study, but this is one approach to study factors that affect in-stent restenosis reliably and specifically. Interestingly, ‘only’ a total of 65 patients with 82 DES lesions could be studied, in spite of the generally large number of DES implanted today, specifically during the last decade, and in spite of the large database for which the expert authors are widely known.\(^1\) Therefore, the autopsy data presented here can only be seen as hypothesis-generating. This is especially important for the interesting data on occlusion based on only 10 samples, showing the drawback to defining predictors of total occlusion categorically also in terms of dependence on the type of DES used. However, interventionalists have encountered similar problems in clinical studies.\(^1\) Furthermore, we might also miss important plaque characteristics since sections were obtained from areas of the most severe stenosis or the middle of the occlusion. Significant plaque pathology and vulnerability can often be found not only at the area of maximal lumen obstruction, but also need assessment in remote or non-culprit regions, where significant inflammatory processes can often be found. Moreover, the coronary artery specimens used in this study have been obtained during 2005 and 2011 and, consequently, involve only even earlier implantation dates and therefore older generations of DES. Whether we can fully transfer these data to newer generations of DES, with smaller strut thickness and better deliverability, therefore remains speculative.

What are the clinical ramifications of the data presented? First of all, we feel convinced that it has been confirmed that DES is the gold standard for treating coronary stenosis today, irrespective of whether lesions are located in proximal, mid, or distal segments. Also in the setting of calcified lesions, the best choice is to implant a DES. However, we can learn from these data that we should pay more attention to potential confounders, specifically inter-strut distance with potential problems in local drug delivery and injury of the vessel media, possibly resulting in occlusion. More routine use of invasive intracoronary imaging technologies might help us to assess these issues more carefully in order to recognize and ultimately prevent such problems, e.g. by intravascular ultrasound imaging

---

**Figure 1** Stent implantation resulting in arterial injury has different procedural confounders. As suggested in the autopsy study of Masataka et al.,\(^1\) different factors influence development of coronary restenosis or occlusion. DES, drug-eluting stent.
Conflict of interest: C.B. has received grants from Merck, and personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, and Sanofi-Aventis, during the conduct of the study; and personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, and Sanofi-Aventis, and grants from GlaxoSmithKline, outside the submitted work. The other authors have no conflicts to declare.

References


