COMMENTARY

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First-Generation Drug-Eluting Stents … and Beyond

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This issue of *Drug Safety* includes an authoritative and detailed review of the efficacy and safety performance of first-generation drug-eluting stents, summarized in a carefully prepared review by Byrne and colleagues.[1] Few groups in the world can claim a track record comparable to the one achieved by this group of investigators, with respect to the evaluation of drug-eluting stents. Indeed, the group from the Deutsches Herzzentrum in Munich, under the leadership of Professor Schömig, has contributed countless manuscripts on this topic, the majority of which are published in the most prestigious journals. The extensive series of ISAR (Intracoronary Stenting and Angiographic Restenosis) trials has now come to represent a highly regarded collection of timely, perfectly designed, randomized investigations, each addressing the exact question one would like to see answered at the moment an answer was needed. Also noteworthy is the fact that all these investigator-driven studies are performed in a single centre, and completed quickly from conception to publication. Chapeau bas!

1. First-Generation Drug-Eluting Stents are Great …

Considering all the available evidence and summarizing all the accumulated data, the authors have come to the conclusion that first-generation drug-eluting stents have a favourable safety profile, are efficacious and are potentially cost-effective for some indications, at least in westernized healthcare systems. The authors also support the contention that sirolimus-eluting stents perform slightly better than paclitaxel-eluting stents. They recognize a very small increase in the risk of (very) late stent thrombosis, when compared with bare-metal devices. However, the deaths and myocardial infarctions associated with this rare adverse effect are 'compensated' for in two ways: first, polymer-covered metallic stents are slightly less thrombogenic during the first few weeks after implantation than their naked, metallic counterparts; and second, peri-procedural adverse effects that used to occur at the time of repeat treatment for in-bare-metal stent restenosis have decreased in proportion to the 50–75% relative risk reduction in restenosis that is portended by initial treatment with drug-eluting stents. Because the net balance between efficacy and safety is neutral with respect to death and infarction rates, and very significantly in favour of drug-eluting stents with respect to restenosis and re-intervention rates, drug-eluting stents are recommended by Byrne et al.[1] as a default therapy in many, if not all, cases.

2. First-Generation Drug-Eluting Stents are Great … but They are not Perfect

Although the authors acknowledge that permanent implantation of first-generation drug-eluting stents is associated with a small increased risk for (very) late stent thrombosis, it may be of interest to qualify the impact of these events on late outcome with some detail.

Even though there is no definite proof that extending the duration of dual antiplatelet therapy beyond 12 months (some would even argue

beyond 6 months) is desirable in all cases, many patients are currently prescribed thienopyridines for longer periods of time, hoping that this precautionary approach might prevent some late thrombosis events. Whether this good intention does translate into improved outcomes is currently being investigated in large prospective trials. What we know for sure is that no such therapy is given to patients receiving bare-metal stents. To which extent this asymmetry in pharmacotherapy might affect differential outcome during the long term follow-up of patients randomized to either device is unknown. The majority of death and myocardial infarction events that occur beyond 1 year after stenting are unrelated to the initial target. It is possible, but unproven, that the perceived obligatory long-term need for dual antiplatelet therapy after drug-eluting stent implantation confers additional protection against disease progression, again compensating for the very few unwanted late stent thromboses, shown to occur at the yearly rate of 0.6% definite cases in real life.[2]

A second issue that is often underestimated pertains to the impact of 'per protocol' or systematic repeat angiography 6–9 months after the initial implant. The authors recognize that this leads to some degree of overestimation of the efficacy metrics. This is because mild, or even severe, in-stent restenoses, but not causing angina, will be recognized as a failure of the bare-metal stent and treated. Prejudice against the angiographic appearance after bare-metal stent implantation can be influenced by the unblinded study design. Indeed, in subsets of patients with clinical follow-up only, bare-metal restenosis rates, hence repeat revascularization rates, are consistently lower than when repeat angiography is mandated, even between predefined subgroups within the same randomized trial population. Surprisingly enough, how this might impact on the evaluation of safety has not been investigated. In patients initially randomized to bare-metal stenting, in-stent restenosis is usually treated by implantation of a drug-eluting stent, i.e. by crossing over to the better therapy from the efficacy perspective. From a safety perspective, these patients are now exposed to an additional risk of (very) late stent thrombosis, one that is specific for first-generation drug-eluting stents. Depending on the crossover rates and the duration of follow-up, outcome in the bare-metal group will thus be contaminated by a number of unwanted events that are caused by the device under scrutiny, but attributed to the bare-metal stent therapy that was assigned to the patient by the initial randomization. This effect also will be amplified by systematic repeat angiography.

Both of the above-described effects are likely to influence the differential outcome of randomization groups that are analysed according to the initial intention to treat, particularly when extending the follow-up to 4–5 years. This level of detailed analysis is required to fully understand the impact of rare adverse effects on the longer term outcome of patients included in these unblinded, relatively small sized, device-oriented trials.

3. First-Generation Drug-Eluting Stents are Great … but They are not Perfect and … Next Generation's Drug-Eluting Stents will (have to) be Even Better

Until recently, the cause and mechanisms of (very) late stent thrombosis after implantation of first-generation drug-eluting stents were poorly understood. Not surprisingly, uncertainties and controversies were many. Cook et al.[3] have now identified the strong and unique association between late drug-eluting stent thrombosis, necrotizing vasculitis around stent struts and incomplete strut apposition against the vessel wall. Local inflammatory infiltration with eosinophils or macrophages is consistent with delayed hypersensitivity reaction of type IVb or IVc, respectively. Any component of the drug-polymer-device iteration can possibly cause delayed hypersensitivity reactions. However, the most likely suspects are the less than optimally biocompatible polymers that are used to control drug delivery. Much effort goes into designing the next generation drug-eluting stents that should retain the strong anti-restenosis properties of the earlier devices but be devoid of the unwanted late adverse effect. A number of options using either durable or

Table I. New drug-eluting stents (DES) with potentially improved (polymer) biocompatibility

Drug	Polymer	Proprietary stent name
First-generation DES		
Sirolimus	PBMA (poly[butyl methacrylate])	Cypher®
Paclitaxel	SIBS (styrene-isobutylene-styrene triblock)	Taxus®
New DES with durable polymers		
Everolimus	PVDF-HFP fluoropolymer	Xience-V™ and Promus™
Zotarolimus	Phosphorylcholine™	Endeavor®
	Blend[a]	Endeavor Resolute®
New DES with bioerodable polymers		
Sirolimus	PLGA (poly [*D,L* lactide-co-glycolide])	Nevo™
Biolimus A9®	PLA (polylactic acid)	Nobori™ BioMatrix™ Axxess™ Custom NX™

a C19 + C10 (butylmethacrylate) + polyvinylpyrrolidone.

bioerodable polymers are already available in Europe for trial investigation or clinical testing, some of which are listed in table I. Many of these newer devices have shown promising preclinical data and some outstanding short- and mid-term results in clinical practice. However, long-term results from large trials and registries are still awaited before improved safety can be claimed. If indeed the late hypersensitivity reaction can be avoided, long-term dual antiplatelet therapy will no longer be required. From a clinical perspective, it will be very useful to learn about the length of the 'vulnerable period', i.e. the minimum duration of obligatory dual antiplatelet therapy that is required for each device, until vessel healing is completed. Given the permanent nature of this vascular implant, exquisite attention is required at each step of the process; indeed, recent history has shown that even the smallest detail matters. The adoption of a new stent depends on many factors, including its deliverability, in addition to its propensity for restenosis. Rather than blindly buying into the latest device iteration, patients and physicians should consider the well known and thoroughly documented performance of first-generation drug-eluting stents. At the same time, raising unrealistic hurdles in front of newer generation devices may paradoxically delay the adoption of better, more biocompatible solutions. Thus the following proposition comes into mind: only the 'perfect' shall deserve to replace the 'great'.

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References

1. Byrne RA, Sarafoff N, Kastrati A, et al. Drug-eluting stents in percutaneous coronary interventions: a benefit-risk assessment. Drug Saf 2009; 32 (9):749-70
2. Wenaweser P, Daemen J, Zwahlen M, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice: 4-year results from a large 2-institutional cohort study. J Am Coll Cardiol 2008; 52: 1134-40
3. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathologic analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation. Epub 2009 Jul 20

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