EuroIntervention

Why we should never return to bare metal stents?

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Even though the long-term innocuousness of drug-eluting stents has been the subject of much controversy over the past two years, I am convinced that we will never return to bare metal stents.

The wave of panic that swept over the scientific community has resulted in the stabilisation and even a slight decrease of DES penetration in Europe, and a substantial decrease in the US where DES were very widely used. The steep increase in DES use has continued to follow its upward trend in Asia.

This controversy has had two very positive effects in that it has resulted in the uniformitisation of cardiac event definitions, especially with respect to stent thrombosis, and that genuine meta-analyses, including case per case analyses, have been undertaken independently from the industry. These analyses show that currently available DES decrease the event rate and reduce considerably the number of re-interventions. DES are not associated with higher mortality or myocardial infarction rate, even though a moderate increase in late stent thrombosis has definitely been observed after DES implantation because of slower endothelialisation requiring prolonged anti-platelet treatment.

Have the culprits been identified?

First and foremost, the operator itself. The results of early DES studies led to the rather naïve belief that mere placement of a stent in a patient's coronary artery was sufficient to ensure complete cure of the disease. Unfortunately, this is not the case.

Stents tend to generate more thrombosis when they are inadequately implanted or under-deployed in complex lesions.

Secondly, patient-related factors, such as diabetes and renal insufficiency, may induce stent thrombosis. Instances of resistance to aspirin or clopidogrel have been recently observed by means of in vivo analysis of platelet function.

The type of lesions treated may also account for the occurrence of stent thrombosis. Implantation of several overlapping stents in tortuous, calcified or bifurcated lesions constitutes a strong predictor of stent thrombosis.

Thanks to the numerous studies conducted over the past few years, the interventional cardiologists are well aware of the limitations of their specialty and have learned not to outstretch them so that their patients may not lose the benefits of bypass surgery.

The Syntax score which measures the complexity of coronary lesions is a perfect illustration of the above.

As far as the stent itself is concerned, two of its components may bear the responsibility of stent thrombosis

1) The polymer used for stents currently available in the market (Taxus and Cypher) is not resorbable and is suspected of generating hypersensitivity reactions.
2) Though very efficient, the anti-proliferative drugs (paclitaxel and sirolimus) delay the endothelialisation process or may even suppress it.

Can we solve these problems?

Yes we can, by complying with technical requirements ensuring optimal implantation of the stent. These include a wider use of endo-coronary ultrasound guidance, high-pressure deployment and selection of appropriate stent size.

In a number of centres, the efficacy of aspirin and clopidogrel is routinely tested, especially in high-risk patients. As outlined earlier, the physicians have learned to accept their limitations and identify lesions not amenable to stenting.

What else can be done?

The technical recommendations mentioned above should be widely applied and stent technology should be enhanced. Several stents with biodegradable polymer are becoming available and are being investigated in clinical studies. Let us hope that they will lead to real advances.

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With respect to the anti-healing effect of drugs, drug combinations of potentially improved efficacy are currently being tested. A stent covered in antibodies has recently been developed. This device captures pro-endothelial cells, thus accelerating the healing process (a few hours) of the lesion treated. We may reasonably expect that anti-proliferative combinations of smooth muscle cells and pro-healing agents will help solve this issue.

Antiplatelet treatment must be adjusted since it has been demonstrated that certain patients do not respond to the aspirin or clopidogrel dosage prescribed. The phenomenon of dual resistance is very dangerous indeed for the patient. We know now that one third of diabetic patients are not protected by the doses of aspirin or clopidogrel prescribed and that an increase in the dosage should be considered after thorough testing.

Progress in interventional cardiology has never followed a linear pattern; it has been achieved by a succession of major leaps forward. Bare metal stents reduced the restenosis rate and, above all, increased the safety of PCI compared to balloon angioplasty. It is irrefutable that DES represent a major enhancement. Though they have engendered the problem of late thrombosis, I have absolutely no doubt that this issue will be solved quickly. If we put PCI in perspective over the past 25 years since it was invented by A. Gruentzig, we observe that the quality of care provided to coronary patients has never been as optimal as it is today thanks to DES. Indeed, in many industrialised countries, coronary artery disease is no longer the first cause of mortality. This may certainly be explained by the efficiency of preventive measures and medical treatment but also by the progress achieved in the field of interventional cardiology. Would we go back to horse-drawn carts as a reaction to the occurrence of a high-speed train accident? Of course we would not, because minor drawbacks should never overshadow the magnitude of major advances.

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Balloon coronary angioplasty was a highly unpredictable procedure but relatively successful. Intracoronary bare metal stents (BMS) made the technique much safer and immediately robust but created the almost untreatable condition of diffuse in-stent restenosis (ISR). Complex treatments including intracoronary brachytherapy were invented to treat diffuse ISR, a condition which interventional cardiologists had created. Drug eluting stents (DES) have not only helped in dramatically reducing ISR and target vessel revascularisation (TVR) but has also led to any ISR being "focal" in nature and more easily treated. Various data in 2006 raised the issue as to whether this angiographic benefit was offset by increased stent thrombosis and resultant clinical events including MI and death[1,2]. Subsequent registry and patient-level randomised trial data has demonstrated that the major (60-70%) reduction in the symptom driven TVR (which in itself results in MI and death) counteracts the small negative effect of late stent thrombosis[3,4]. In the United Kingdom we have recently experienced a cost effective analysis of DES vs. BMS carried out by the National Institute for Clinical Excellence (NICE). The initial draft guidance suggested DES were not cost effective and there was the very real prospect of this technology being withdrawn from the UK[5]. Safety issues, interestingly, did not play a part in this draft guidance. It was assumed by NICE that UK interventionalists would default from DES to BMS thereby saving the National Health Service money in the delivery of revascularisation. The resulting discussions and arguments certainly focused the mind of the interventional cardiology community in the UK. The British Cardiovascular Intervention Society (BCIS) argued that the randomised literature (ARTS 1) favoured CABG over BMS in multivessel disease and that interventionalists would default to CABG rather than BMS[6]. We argued that this would result in >10,000 patients having to be referred for surgery which would not be necessary if we had access to DES. This would have hugely increasing the waiting times for revascularisation in the UK (which are currently virtually zero) and would cost the NHS 60 million pounds. Of course we all await the first presentation of the SYNTAX trial with great anticipation[7]. NICE continue to debate the cost effectiveness of DES but the latest version of the guidance suggest we will continue to have access to this technology. I believe the debate has moved on. Safety issues are no longer a concern with DES (over and above BMS), with multiple registries suggesting a mortality benefit for DES over BMS. The debate is not about DES versus BMS but is now about DES versus CABG. Interventional cardiologists have possibly pushed the clinical use of DES beyond that which is appropriate from the published literature, for the moment. The challenge for our community is not to argue for or against DES vs BMS but to re-establish the trust of our general cardiology and surgical colleagues and to ensure the best method of revascularisation for an individual patient is made within the setting of an multidisciplinary team including non interventionalists and cardiac surgeons.

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Why we should never return to DES? ...
Or why we should never return to the ice age...
In general, we stay with something new when we like it, either for personal reasons or for more profound reasons - 'evidence-based' - demonstrating superiority and benefit of a new technique compared to the established approach. Nowadays, the daily clinical practice of drug-eluting stents (DES) utilisation sometimes appears to be influenced by personal preferences and opinions affected by disastrous events picked and reported, or bad cohorts without considering the global evidence available today. This is certainly the wrong way to answer the question mentioned above. So let us stick to the data. Just last week I did a re-angio of one of the first patients receiving the prototype of drug-eluting stents in 1999, the Quanam QP-2 eluting coronary stent. It was a kind of clumsy device with a drug load which exceeded x-fold the dosage identified today to be really needed for neointimal suppression. However, it was the first proof-of-concept which eventually led to the developments of the past nine years, namely the introduction of one of the most powerful and successful devices in interventional cardiology. There is no other device used in the field of interventional cardiology which is so intensely and excessively evaluated in both preclinical and clinical studies as drug eluting stents. Shortly after their introduction in the clinical field, we were certainly overwhelmed by their efficacy to reduce the need for recurrent interventions given the power of local neointimal suppression. Restenosis was believed to be cured. We then rapidly learned that drug eluting stents can restenose... but they are certainly less likely to do so as compared to conventional stents. And there is broad evidence today, supported by all pivotal studies, registries and meta-analysis, that this reduction in restenosis is evident in all major clinical lesion subsets, particularly the ones that hold a high risk for restenotic events such as diabetics. So there is no question that DES are more efficacious than conventional bare metal stents, at least with regard to effects measurable by angiographic documentation (restenosis) or at the level of vascular histomorphology (neointimal suppression). There is a long and old discussion whether these effects translate into clinical differences which is right now not fully established in some lesion types. But this is probably in the majority of subsets related to the study power, meaning the volume of enrolled subjects. One needs certainly large studies to find significant differences if the difference is small, but one will find it. So with regard to efficacy, DES are superior to bare-metal stents (BMS) and therefore preferable. Efficacy is certainly only one of two parameters to establish superiority. A new efficacious device will never replace the old gold-standard if the safety profile is not comparable. We have heard and learned a lot in the past nine years about DES safety, late restenosis, stent thrombosis, mortality differences etc. Fact is that DES and BMS do not differ in the hard clinical endpoints mortality and myocardial infarcts as demonstrated by the latest world-wide meta-analyses of more than 21 randomised clinical trials with about 9,000 patients as well as registries with more than 161,000 patients reported by Gregg Stone and co-workers. In contrast, DES appear to provide an overall benefit with regard to these safety endpoints. There might be a slightly higher risk for late stent thrombosis but this is not a special event only seen with DES.

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BMS cause late stent thrombosis, too; not as much as DES but they do. Anyway, this slightly higher thrombosis risk on the DES site is counterbalanced by the risk of death and MI related to restenosis which is more pronounced with BMS. It is therefore only fair to conclude that there is no relevant safety issue related to DES in comparison to BMS in the overall analysis.

So, which technique would you prefer given two equally safe techniques but one being more efficacious?

BMS will continue to be useful, but DES should be and will be the gold-standard strategy. The first generation DES have certainly some flaws, so had the first generation BMS, the Palmaz-Schatz stent. However the product development process continues and will further continue, which eventually will bring us smart DES which precisely address vascular pathologies by bio-molecular modulations with anti-inflammatory, antiproliferative, immunomodulating or prohealing agents. Beside primary prevention this is certainly the modern and future way to attack coronary artery stenosis. Longer-term data are certainly needed and further research is mandatory. But this will be done. Nine years after Quanam, my patient is doing fine, with a superb angiographic long-term outcome without late restenosis or other late adverse events.

And that is the reason why we should never return to BMS.

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The availability of drug-eluting stents (DES) has almost eliminated or significantly reduced restenosis compared to bare metal stents (BMS). The recently published results of ARTS II have shown a very low incidence of myocardial infarction and death at one year follow-up, and a low incidence for repeat revascularisation.[1] Recently, the three years results became available giving the same message.[2] Even if repeat revascularisation would not be eliminated and remain higher compared to the rate achieved following CABG, most cardiologists and patients would accept that slightly higher need for a second percutaneous procedure (PCI) in order to avoid CABG. It is important to reach this goal without any increase in the risk of death or myocardial infarction.

The above statements summarise the mission of DES: make complex coronary interventions more predictable in order to become the most important way to revascularise our patients with ischaemic heart disease.

The issue is not DES vs. BMS but DES vs. CABG.

The recently published study by the group of S. J. Park is a very nice attempt to highlight this concept.[3] In a very important group of patients with significant stenosis of the left main trunk, the utilisation of DES was not associated with a higher rate of myocardial infarction and/or death and carried a slightly higher risk of reintervention compared to CABG.

Hopefully we will soon have similar data later this year following the presentation of the results of the SYNTAX study.[4]

Our goal is to demonstrate that DES implantation can be safely and effectively utilised in patients with triple vessel disease and/or left main trunk stenosis rather than CABG. The major endpoints we need to focused on should be death, myocardial infarction, quality of life, the possibility to return to work and total costs. In this last respect, we cannot forget that CABG carries additional costs related to rehabilitation and prolonged time out of work or even early retirement. The costs ascribed to DES are "a moving variable" and it is very conceivable to assume that an expansion of the market, more patients eligible for treatment and more devices available for sale, will bring the prices to a significantly lower level.

The problem of stent thrombosis should be taken into account only if it leads to a higher myocardial infarction or death rate. Of course, this statement does not signify we should disregard and leave a blank space in our follow-up events the occurrence of stent thrombosis. As a matter of fact a careful containment of this complication may even lead to a significant reduction of death and myocardial infarction compared to CABG. The problem could then become: lower death and myocardial infarction with a slight higher need for re-interventions.

How do we proceed?

1. Avoid panic and inappropriate reactions: even with all the mistakes we are making now, such as the absence of a uniform "state-of-the-art" stent implantation technique and no monitoring of antiplatelet responsiveness, the rates of myocardial infarction following DES implantation are lower compared to the ones following BMS implantation in comparable lesions[5];
2. Become more alert that implanting longer stents in more complex patients demands greater attention to achieve an optimal result. This consideration may also be true for more simple lesions in light of the fact that DES delay endothelisation and therefore may be intrinsically more thrombogenic;
3. Understand that clopidogrel responsiveness may vary from patient to patient and dose adjustments may become necessary.

Let us not stray from the target of making coronary revascularisation less risky, simpler and more predictable for all our patients.

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