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Bioresorbable stents: the next horizon after drug eluting stents?

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Drug eluting stents have been designed in order to tackle the problem of in-stent restenosis encountered with bare metal stents deployed in coronary arteries. The concept was to implement the bare metal stent with a drug delivered from a coating placed on the metal surface in order to inhibit neointimal hyperplasia. The drugs used for this purpose have been targeted against smooth muscle cell proliferation. After a first year follow-up, the goal has been clearly obtained, reducing target vessel revascularisation close to 10% with the three major products (Sirius, Taxus 2, Endeavor 2[1,2,3]). Unfortunately, the error was to consider that the time period for events was within one year. Since the follow-up has now reached three years, two major issues have been increasingly reported, mainly from registries, showing the real world population. The first one, the most tragic, although uncommon, is in-stent thrombosis, mainly due to interruption of the antiplatelet therapy due to the fact that the indications given by companies for simple lesions was limited at up to three to six months, whereas the use of drug eluting stents goes beyond simple lesion anatomy and the patient risk profile on the basis of their success on restenosis[4]. Interruption has been also occurring because of the need for surgery, dental care, or cost of the antiplatelet therapy[4,5]. Other risk factors have been detected, including diabetes, number of stents, stent length, renal failure, low ejection fraction, and bifurcation lesion[5]. The most worrisome is that stent thrombosis is resulting in more than 40% of deaths or acute myocardial infarction[5,7]. It has been pointed out that the terms of MACE (i.e., major cardiac adverse events) itself is mixing hard (i.e., death and acute myocardial infarction) with soft endpoints (i.e., need for revascularisation), although they do not carry the same prognostic value[4]. The explanation of this complication, predicted by Virmani et al since 2004, is likely due to the toxicity of the drugs on the endothelial cells, and/or the non-endothelialised coating[7,8]. This is supported by human angioscopic and autopsy studies showing lack of re-endothelialisation with drug eluting stents as compared with bare metal stents beyond 40 months[8,9]. The scientific sessions of the American College of Cardiology and more recently the European Society of Cardiology have confirmed this phenomenon[10-12]. Is the price to pay for the inhibition of restenosis worthy of such a complication? Although there is a debate on the overstatement of the most recent analysis, this seriously questions the justification of the 100% association of the use of drugs with stents: indeed, "soft" drugs (i.e., not interfering with the cell cycle) have failed to demonstrate their efficacy to inhibit in-stent restenosis. The second adverse event is the occurrence of late restenosis, as seen in the increasing rate of target revascularisation in the randomised trials. This had been predicted in 2004 for the Cypher stent in an experimental study showing that the benefit of in-stent restenosis reduction obtained at one month was no longer present at 3 and 6 months[13]. Moreover, this was associated with an increased smooth muscle cell proliferation around the struts of the Cypher stent as compared with the bare metal stent. There are no data published with the two other drug eluting stents showing a sustained effect beyond one month in animals. The reasons for a rebound may be multiple: rebound after disappearance of the drug while the metallic foreign body is still present, and poor biocompatibility of the coating[14]. What do these two complications teach us? We use drug eluting stents to inhibit restenosis, and we pay the high price of ending up with delayed restenosis and thrombosis. The most striking point is that we use a lifetime support (i.e., metal) to tackle a transient phenomenon, the healing process. However, the healing process is mandatory to insure both haemocompatibility and histocompatibility.

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Rather than persisting to render transiently biocompatible the metal by imposing on the artery a more complex and hazardous device made of metal, coating and drug, the concept of a transient (i.e., bioresorbable) stent appears appealing; it avoids the need of a cell-cycle toxic drug, a non biocompatible coating necessary for the drug storage and elution, because the support time-life is appropriately adapted to the healing, without loosing the necessary mechanical properties during this period. Thus the justification of a bioresorbable stent is led by the initial scaffolding of the artery wall during the healing process, and the ability of the artery to undergo positive remodelling without the mechanical constraint, and the absence of a long term foreign body which is responsible of iatrogenic side effects, i.e., in-stent thrombosis and restenosis[15,16]. Without any permanent anti-remodelling device, the bioresorbable stents should afford a world free of in-stent restenosis, which might be an invaluable improvement. Their indications go beyond the coronary arteries, with peripheral and paediatric applications. Last, their use is in accordance with all non invasive as well as invasive imaging technologies. The problems encountered with bioresorbable stents have been mainly due to poor compatibility of the substance used[17]. Although this remains a key issue, the results from the stent of Igaki Tamai, and more recently the BVS stent, exhibited a satisfactory biocompatibility[18]. However, the concept of bioresorption is not new since we have been routinely using bioresorbable sutures for more than 50 years. The compatibility of the substance is not only related to its chemical formula, but also to the quality of its synthesis. For example, polylactic acids, which are known for their theoretical biocompatibility since they degrade into water and carbon dioxide, can in fact wrongly degrade into lactic acid oligomer cristals which are highly proinflammatory[19]. Therefore, although there is a need for better expertise in the choice and the manipulation of bioresorbable platforms, the complications encountered with drug eluting stents drive us towards a new revolution, i.e., not only abandoning biostable coatings but also biostable platforms for bioresorbable platforms, which greatly simplifies the final product without need for coating and drugs. The initial pioneering work of Igaki and Tamai has shown that polylactic acid polymer stents are safe and efficient although the timing of degradation is too long[18]. Other studies have demonstrated faster degradation and the question is the appropriate lifetime required to ensure scaffolding during healing. The original approach of the magnesium stent (Biotronik) opens other horizons although recoil is too important[20]. The ABSORB trial evaluating a polylactic acid stent eluting everolimus recently showed a 0.44±0.35 mm late loss at six month follow-up. Eventually, the present teaches us to simplify the device, without the need for cytotoxic drugs plus non biocompatible coating since the platform is conceived to disappear, thus not requesting supplementary hazardous and complex technology.

Whether the bioresorbable stents will challenge the drug eluting stents in the field of efficacy is a long term issue that includes a better approach of the healing, a safer long term follow-up, and in particular, a superiority in lack of requiring long term drugs, both systemic (anti-aggregants) and by local delivery, thus restoring a native artery free of any potential late side effect.

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