The Cypher stent: no longer efficacious at three months in the porcine model?

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See article by Carter et al. [2] (pages 617–624) in this issue.

Drug-eluting stents have represented one of the most exciting, innovative technologies, and the 0% restenosis rate has led to overwhelming enthusiasm in the medical world, even if a careful examination of the results did not show any effect on the occurrence of death and acute myocardial infarction [1]. The study of Carter et al. [2] in this issue of Cardiovascular Research brings a key message that tempers our enthusiasm, since they surprisingly discovered that, in the pig model, the Cypher stent failed to reduce restenosis at 3 and 6 months. Moreover, although the drug is still present, there is more smooth muscle cell proliferation and inflammation with the Cypher stent than with the bare stent. Since the study was conducted by Robert Falotico, the “father” of the Cypher stent [3], there is no doubt regarding the validity of these data. This initiates a huge controversy: now the question is, how is this possible? The primary suspect is the anti-restenosis strategy, i.e., inhibition of smooth muscle cell proliferation via the cell cycle [4]. Impairing the healing may not automatically mean that the reaction to the injury process is definitely abolished but only that it is delayed, as learned from extensive evaluation of intracoronary brachytherapy [5,6]. Other mechanisms may be overstimulated in reaction to the drug inhibition, and the question is whether these mechanisms have been underestimated. The second, but not the least important, concern is the polymer coating. The presence of giant cells illustrates a possible foreign body reaction that is consistent with the time course, i.e., 3–6 months, reflecting a process more related to the incompatibility of this new compound and the body than the injury process itself; this feature has been recently described by Virmani et al. [7] in humans.

It is interesting to note that the Cypher stent has never been compared in animals or humans with the coated stent without rapamycin but always with a bare stent carrying no coating. A third group of animals with the coated stent without rapamycin is missing that would have given us the answer with regards to proliferation, inflammation, and the presence of giant cells, as recommended by a consensus group [8]. Unfortunately, this point has been treated too briefly in the discussion [2]. Eventually, the endothelium that regenerates may still present with dysfunction, which has never been studied with drug-eluting stents. This dysfunction may represent a failure to protect the artery wall from inflammatory cells and processes, leading to smooth muscle cell proliferation. The authors can be congratulated for presenting informative, although negative, data, and the Journal should be commended as well for publishing them, since this happens too infrequently. However, I do not share the authors’ analysis of the failure when they conclude that the model itself may be inappropriate and that human data are in contradiction with animal data. The Cypher stent, as well as all other stents or medical devices or new strategies, would have theoretically never been allowed to be used in humans if it had failed to show a consistent efficacy in animal models. Animal models have their limits, and the way to avoid extrapolations is to carefully design models for appropriate goals [9]. In this case, the pig model is a well-accepted model that has been widely used and validated by the FDA in the past 20 years to evaluate restenosis after coronary stenting [8–10]. In the
recent past, animal models have proven to be useful in understanding unexpected adverse events.

The problem of the choice of the time course is a critical issue that we may need to further examine, especially when using strategies targeting the healing process via the cell cycle: when late stenosis occurred after brachytherapy in humans, this event was unexpected when one considers the results obtained with the animal models [11]. Indeed, the follow-up in animal models did not extend further than 1 month. It is instructive to note that brachytherapy, i.e., a similar target strategy, induced late restenosis in the pig model as long as the follow-up extended for more than 3 months [6]. The problem in this study is not so much to question the model retrospectively but rather to elucidate what is the time relationship between 3 and 6 months in the pig model and in humans. According to Fischell and Virmani [10], human coronary arteries may react three to six times longer than porcine arteries. Indeed, the authors of the present study [2] agree somewhat with this interpretation since they mentioned in their conclusions that the studies in humans should be pursued for 3–5 years.

The third question that one can logically address when such results are published is what message the company wants to deliver. Certainly, this is to the credit of the scientific group to divulge negative data even if they can overshadow the popularity of the device. However, these data have arrived very late and should have been produced before the use in humans, since two new compounds were added, i.e., the drug and the coating.

The first, clear, take-home message is that more vigilance should be used in a longer follow-up in a real-world population [12]. The second message is that one should not think that this concerns only the Cypher stent. Rather, the knowledge of the other experimental studies with active coated stents with 1-month follow-up is no longer satisfactory, and 3–6 months or even a 1-year follow-up should be provided. The last message is that these ambitious devices are complex and potentially fragile: from one simple compound (i.e., 316 L steel), we end up with the association of two other compounds whose biocompatibility and toxicity may present potential questions in the long-term follow-up. Why a polymer coating?—because of the drug. Why a drug?—because of the permanent metal. This opens the door to the concept of bioresorbable stents, as long as they are “friendly” and leave the artery free of a foreign body. The good news is that most companies are actively involved in developing a bioresorbable stent program.

References


