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EDITOR'S PAGE

Devices, Biology, Imaging, and the Regulatory Processes. . .

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With the explosive growth in percutaneous interventions and their relative success, an increasingly large number of patients are carrying intravascular devices. Moreover, successful intervention, coupled with other advances in therapy, has lengthened the useful in-vivo "life time" of such devices. Thus, patients are being exposed to complicated device–drug combination platforms (DDCPs) for increasingly longer periods of time. At the same time, these devices are getting more complicated; drug–platform–device combinations often introduce previously unanticipated or uncharacterized clinical and pathological phenomena beyond what a drug or device can cause by itself. This is especially true when the drug has a different purpose (e.g., reduce injury, repair induced restenosis) than the device alone (cause vascular injury). In addition, the bridge between the two (polymer or other platforms) can induce its own set of problems such as inflammation and nonphysiololgical local concentrations or release kinetics of the drug. All of these factors are starting to reveal a new natural/unnatural history in patients with coronary artery disease (1); some changes are quite different from what was known until now and indeed, some of that was not anticipated from or revealed in extensive preclinical animal studies—the current de facto cornerstone of a drug's regulatory journey. Therefore, it stands to reason that this changing natural history should also radically change our approach towards anticipating, predicting, detecting, and interdicting the new clinical complications that are unfolding. One could make a case for an increasing role for powerful imaging modalities in this scenario.

All of the regulatory agencies require rigorous pre-clinical animal studies under good laboratory practice conditions. Multiple time points up to 6 months are needed under U.S. and European regulations (2). The choice of an animal model is left to investigators but this is not always a simple and straightforward decision. Pigs, dogs, and, to a lesser extent, primates are the most often studied models for evaluating coronary stents. Each of these models has significant limitations, but the pig is thought to be the model most close to human stent pathophysiology. Unfortunately, while accepted as a best consensus model (3), evaluating a stent in a normal porcine artery is completely different from the biology of a stent in an atherosclerotic human coronary artery. Rigorous comparative studies between stent behavior in pigs and humans are lacking but some disadvantages are quite obvious. The time course of healing is quite different between pigs and humans (4). The influence of irregular plaque geometry on in vivo strut anatomy (and thus the repair response) is not clear from animal studies (5). The impact of clinical scenarios like compliance with antiplatelet therapy, risk factor profile, and cytokinemia/peri-surgical stress cannot be evaluated easily in animal studies; such phenomenon have important clinical correlates and inflammation has been shown to increase tissue factor levels and possibly can augment thrombogenecity of drug-eluting stents (DES) (6). Finally, there is a trend among toxicologists to utilize increasingly smaller numbers of animals for research (7), and this might reduce the

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power of detecting crucial evidence in animals with complex device–drug implants.

Not surprisingly, questions have been raised whether animal data can predict natural history in humans (8) and there is some data with DES that short to intermediate results in pigs might not be concordant with results in humans at similar time points (8). Healing occurs more rapidly in healthy porcine arteries compared with diseased human lesions. Thus, a negative result in pigs (more tissue proliferation) at 6 months might not necessarily mean there is no benefit in humans in a comparative time frame. Conversely, adequate healing in the short to intermediate time frame in animal models does not necessarily mean similar efficacy in human models at comparable time points; indeed, the DES experience in humans illustrates some of this discordance. As pointed out in the consensus document (3), true efficacy and safety can only be proven in man. With all of these uncertainties, it is quite surprising that additional tools to refine in vivo risk and risk prediction, have not received greater attention.

At the other end, possibly offering greater certainty, is a process involving long-term post-marketing clinical follow-up. This strategy has been used with some success with drugs and now, following unexpected and costly debacles, is being considered for devices (9). This model, while reassuring, has tremendous costs; since events have to happen for them to be detected, it entails a significant cost in terms of human misery. In addition, it also remains open ended—we do not know if and/or when events will occur in the natural history of the device. This strategy is likely to be inefficient; events, while of high impact, are likely to be rare, and thus a large number need to be followed to detect these few events. This entails economic and opportunity costs to society and a "product uncertainty" cost to the industry.

Imaging is a powerful medium and its reach is rapidly and progressively extending into understanding structure and function at an organ, tissue, cell, and molecular level. While the biology of DDCPs is complex, most of its adverse phenomenon described so far are rather expected or could be anticipated. End points, like vessel structure, degree of proliferative repair, tissue composition (lipid deposition, neointima or thrombus formation, smooth muscle cell/fibrous tissue proliferation) and flow limitation, can be seen to varying degrees using commonly available instrumentation and expertise. End organ effects, like microvascular flow, distal embolization, and infarction, can be seen and quantitated. Some more invasive techniques are now showing active biology of tissue–stent interactions; one such study in this issue of *iJACC*, by Higo et al (10), provides an interesting insight into the biology of DES–tissue interaction. Using angioscopy at 2 time points 10 months apart following coronary stenting, they found that DES-induced neointima is associated with lipid-laden regions of new atheroma (unrelated to the original atheromatous lesion) in some regions in proximity to the stent. Other regions, with the usual white neointima, did not show excess of lipid accumulation. Interestingly, regions with lipid-laden neointima were significantly more thrombogenic than areas with white neointima. Bare-metal stents were not associated with such changes. This suggests that absence of a healthy endothelial barrier can allow lipid transudation and can mediate accelerated atheroma under a DES. It is obvious that such invasive methods cannot be routinely applied to clinical surveillance; nevertheless, it highlights the possibility of what imaging can do. With better imaging technology, one can envisage noninvasive surveillance to identify patients who do not develop an adequate endothelial barrier over a stent or those that are in the process of developing a thrombus before a clinical event happens or those who are developing accelerated atheroma with a high lipid content (and therefore, portend an adverse clinical outcome).

Of course, while conceptually appealing, such enthusiasm about imaging needs to be tempered with the reality of what is available today. None of the currently effective imaging technologies is sufficiently noninvasive for routine use in monitoring device–drug–tissue interactions. Those that are available are not yet fully developed and the incremental value of their application needs to be defined. Neverthe-
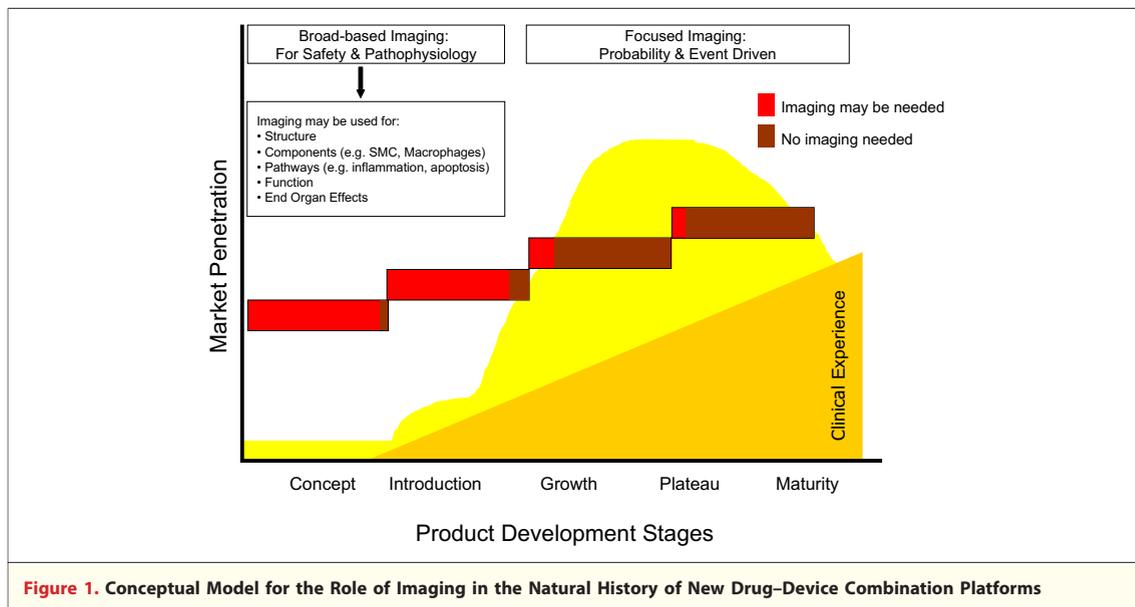
Figure 1. Conceptual Model for the Role of Imaging in the Natural History of New Drug–Device Combination Platforms

less, imaging is improving and it is just a matter of time before we will be using it for defining risk and refining success of device–drug combination platforms. Initial acceptance is unlikely due to regulatory pressure. Voluntary adoption of novel imaging protocols will be based on the attractiveness of having a window into the future events, ability to offer mechanistic explanation of phenomenon, and the possibility that it might improve device technology. The greatest amount of adoption will only occur if imaging can produce viable surrogate end points that shorten the costly and often fragile product development cycle for devices, especially those hitched to "biologics"—a notorious regulatory minefield.

How would robust imaging technologies best be utilized in the future? We envisage the following model. Market theory suggests that a device is likely to follow a journey of 5 stages (Fig. 1). We anticipate a similar model for ongoing investigation to anticipate and predict adverse outcomes with device–drug implants. The proof of concept stage will still depend on pre-clinical animal studies as currently done. However, rather than using fixed time points for a "sacrifice and look" strategy, there will be a need to use imaging to obtain a more "dynamic view" of changing vascular biology. This will also help define subsets of characteristics that identify and predict animals with a subop-

timal outcome. Pre-approval clinical studies (phase 2 and possibly substudies of phase 3 trials for supporting a new device) would incorporate imaging parameters to identify natural and unnatural changes to in vivo device-induced biology in humans. The idea here is that identifying concerning changes in the biology of device–drug–tissue interaction early on might help predict adverse clinical outcomes down the road. If these studies consistently identify high-risk predictors with any certain device, some form of noninvasive monitoring might be needed post-introduction (akin to post-market surveillance). The growth, plateau, and mature stages of the devices' journey can be limited to surveillance for clinical end points (based on probability) should the previous investigation reveal no concerning findings. Some companies might continue to invest in sophisticated imaging in a small subset of patients, in an effort to eke out some competitive edge for their DDCP, in the face of multiple other new entrants challenging their mature technology.

Of course, these investigatory protocols need to be carefully thought out, not be smothering in their burden, and not delay introduction/percolation of life altering DDCPs. Economics will undoubtedly play a role but will eventually be worked out. Given the magnitude of clinical utilization, unexpected clinical events are likely to have a larger economic impact than some upfront regulatory costs.

Imaging is partnering *intervention* in the clinical arena and it is but a matter of time that it will start to partner in the pre-clinical product development arena as well. While clinician-investigators are likely to be ready to enthusiastically adopt such value-added technology, it is less likely that the regulatory apparatus will be so accepting. It is time to start thinking about the changing role of imaging and imaging-related surrogate end points in the regulatory framework. As imaging technology continues to mature, we hope our readers, the device industry, and possibly experts at regulatory agencies vigorously join us in thoroughly airing out this debate. We foresee that sophisticated imaging will be the best alternative to an ex vivo examination.

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