Needles in Our Technology Haystacks: Defining Efficacy Is Easy, Characterizing Complications Is the Challenge

HHS Public Access

Author manuscript

Circ Cardiovasc Interv. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Circ Cardiovasc Interv. 2017 November ; 10(11): . doi:10.1161/CIRCINTERVENTIONS.117.006059.

THE NEEDLE IN OUR TECHNOLOGY HAYSTACK: DEFINING EFFICACY IS EASY, CHARACTERIZING COMPLICATIONS IS THE CHALLENGE

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In this issue of *Circulation: Cardiovascular Interventions*, Tae-Min and colleagues address an interesting aspect of technology development – the delineation of device complications in an era of accelerating innovation. They specifically sought to validate longitudinal stent deformation (LSD) as a design-dependent complication, pooling data from several studies using precise definitions and longer periods of evaluation to overcome what they cite as "shortcomings" of prior studies[1].

This challenge of identifying failure modes is a modern feature of the ancient domain of innovation. From the beginning of time nature, need, and innovation have been coupled. Indeed, the idea that "Art imitates Nature, and Necessity is the Mother of Invention." is ascribed variably to Plato in the 4th century BCE and Richard Franck in the 17th century CE *Art* here adheres to its original definition, the harnessing of human creativity and the expression of innovation to provide new things to improve the human condition – *technology*. This dictum, irrespective of who elaborated it first, remains the governing principle of therapeutics – iterative and innovative imitation of nature to develop ever new means of treating disease. The flip side of this argument that is less well appreciated is that the complications that limit technology are the *sine qua non* for innovation. Without complications there is no drive for creative solutions. The question that confronts us now more than ever is how to detect complications in the march of increasingly sophisticated innovation.

The story is well tread. Bypass grafting to reperfuse ischemic myocardium was embraced wholeheartedly until it became evident that only those with the most significant disease benefited and with a significant price. Balloon angioplasty allowed for immediate and minimally invasive intervention and, though originally intended to save time for the most ill to make it to the surgical theater, was soon viewed as an acceptable end onto itself until it became evident that 40% of patients required further intervention in a year. As elastic recoil was deemed culprit, the stent was born. Stents lead to restenosis from intimal hyperplasia, and thus drug eluting stents were created to address smooth muscle cell proliferation and on and on.

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DISCLOSURES

None.

The question that arises then is not whether complications will arise, they always do, but how to identify them. If complications cannot be identified, continued innovation is stilled and the chain of iterative development is broken. Intriguingly, the tables have now turned. Where we used to be concerned about defining efficacy knowing that we could always characterize safety, we are increasingly concerned by challenges in identifying complications. This is now the dilemma in technology development, and innovation is making the ability to evaluate technology even more acute. As technology advances and increases in complexity, complications become harder to find and even harder to explain. Half of all patients with stent thrombosis will die, but less than 1% of all stents clot over years[2]. What then can be done to identify and design out rare but immensely significant flaws? Software developers release beta version product to have users to identify and prioritize flaws, and even create solutions to flaws. This cannot be done in medicine. The day may come when we rely on patients and physicians to decide if they are willing to use a medical product with definitive risk that can outweigh benefit in certain patients, but it is not today. Devices are not chemotherapeutic agents and are held to regulatory standard that may exceed the idea of *relative* safety. The fact that we cannot introduce products with known complications into the clinical space leaves us either pretending that we have finally created a perfect product or trying to identify complications, i.e. find the proverbial *needle in the haystack*.

Pretending that a product is perfect is delusional. The bioresorbable scaffold recently pulled from the market failed because hope and the best of intentions transcended basic materials science. One cannot make a material degrade rapidly without a cellular reaction, nee inflammation, and one cannot recapitulate the strength of a device made from a material inherently many orders weaker than the standard without increasing thickness. Thickness breeds flow disruption and together with inflammation produce cellular infiltration that sets off the very cascade of effects the devices are intended to countermand. But at the same time waiting for a product to declare itself is similarly flawed, especially when the complication we seek to emerge is infrequent. Perhaps for this reason it took so very long to validate suspicions regarding bioresorbable platforms. Thus, in evaluating emerging stent technologies we find ourselves then not only looking for a needle but not knowing whether it resides in the coating, dimensions, or drug haystack.

Needle searching is impossible as the parable tells. The standard device trials have hundreds not tens of thousands of patients per arm and are not designed to detect events that occur in a fraction of a percentage of population. Pooling data has merits but technology changes rapidly; it becomes challenging to find and then meld homogenous data sets of patients who receive the same device under the same conditions. Science offers the hope of added discrimination. The right haystacks can be identified and perhaps subdivided if specific hypotheses are generated. Fundamental biology, engineering, and science can point to potential problem areas and allow directed scrutiny of patient subsets, specific devices, or failure modes.

Tae-Min et al.[1] tried a hybrid approach to identifying complication and defining its cause. They focused on LSD, the shortening or distortion of a stent in the longitudinal axis following stent deployment[3]. Their fundamental premise was that design dictates

performance. Indeed, this is another of the basic issues in device development. There has raged for as long as there have been devices the question as to whether *device design* or *device use* dominates performance. Usually the first to introduce a concept or product tries to tip the scales in indicting *use* well above *design*. They seek to deflect failure from device to user, to dominate intellectual property for a single overwhelming idea, control market shares by noting identity of all like designs, establish legacy through claims of effect over the longest time and greatest numbers, and attribute complications as class effects. Those who invent iteratively on existing inventions tread their own fine line - they need to simultaneously create distance from predicate devices and claim regulatory equivalency to them. In their world view, complications are the limits of predicate technology that are specifically eliminated by new designs and not indicative of inherent limitations of a whole class of device.

Determining if stent deformation is device-dependent is worthy as designs have evolved greatly and compression remains incompletely understood. Strut dimensions, designs, and materials have all been evolved from the original stainless steel corrugated ring stents but the balance has yet to be fully realized in reducing recoil, maximizing lumen area, minimizing micro-flow disruptions, and increasing flexibility without sacrificing radial strength and durability[4–6]. In particular, as the recent stents are far smaller, radial and longitudinal malapposition have emerged as a major complication. LSD has been reported in ~0.2%[7] of all interventions and can lead to stent thrombosis, emergent coronary artery bypass grafting (CABG), and even death[8]. Tae-Min began with the premise that the Promus Element Platinum-Chromium stent strut dimensions and configuration placed the device at risk of deformation, and then compared incidence of deformation to two different Cobalt-Chromium designs. They appropriately noted that previous studies indicting specific designs were anecdotal, did not rely on a specific standard definition of deformation, and did not look at long term effects. To address these “shortcomings”, they pooled data from two nationwide multicenter studies, one randomized trial and one registry, covering a total of 9,299 lesions in 6,811 patients. They found an incidence rate of LSD of 1.12%, almost six times higher than reported by others, but no correlation with design. Instead, in these pooled studies LSD was driven most by use of secondary devices and ancillary interventions surrounding stenting.

So did they find the complication needle in the right haystack? Perhaps yes, perhaps no.

The use of two different metals and two different designs could have detected a difference if all other factors were held equal. They were not and maybe then this explains why, despite a high incidence of LSD, design was not an independent risk factor. LSD is multifactorial and while some studies indict the Promus Element platform because of its lower longitudinal strength, reduced number of connectors and offset peak-to-peak design[7, 9–13], procedure-related factors such as passage or withdrawal secondary devices through previously deployed stents, and lesion factors such as highly calcified lesions and ostial disease also dominate[7–9, 14].

The idea that others had not looked at LSD consistently enough, long enough, or rigorously enough is probably proved valid and indeed with a larger mass of observations and more

consistent definitions they present an incidence of deformation far higher than expected. But the inability to prove that design determines LSD does not mean that LSD is not device-dependent. Proof that device design matters is in this day and age becoming more and more difficult to appreciate. Optimization of stent design involves the balance of ease of insertion, strength, visibility, and durability as well as interaction with a range of independent and interdependent biologic processes. Enhancing any single attribute may adversely affect others and what is optimum for one person, one lesion, one artery, one disease state may not be for another. Given the multiplicity of parameters at play, providing a pre-hoc power analysis to define if effects could be extracted becomes extremely difficult.

Tae-Min and colleagues should be congratulated on advancing the field. They confirmed that there is no such thing as a perfect device and showed us specifically that LSD is more of an issue that we might be willing to admit. Moreover, their study highlights that we need to define new means of correlating clinical effect with clinical observation, i.e. unexpected complication with undesirable performance. They force us though to confront the question as to how best identify complication of innovation and to consider whether we should innovate in this regard as well. Continued advancements in material science, benchtop testing apparatus, and computational modeling techniques coupled with continuous improvements in clinical study design and implementation, will present newer devices for consideration and perhaps also newer methods for identification of problem areas. If we do not change and innovate in seeking failure modes, we will continue to be restricted to simply looking for needles in haystacks.

Acknowledgments

SOURCES OF FUNDING

The authors are supported in part by a grant from the National Institutes of Health (GM R01 49039).

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