New endovascular stent designs are displacing tried-and-true devices for use in an ever-broader array of lesions. Yet disagreement remains as to which device is most advantageous and whether design determines outcome. Preclinical research says that this should be the case, but clinical trials have failed to validate design dependence. Is this yet another demonstration of the dichotomy between preclinical and clinical experience, or can divergent data be reconciled?

**Bench-Top Data**

More than 50 different stent configurations are available, with 12 having received regulatory approval in the United States and a larger number in Europe. The very processes of industrial development and federal regulatory evaluation support the importance of design. Stents are made from a spectrum of materials with a range of manufacturing techniques, providing variable surfaces, dimensions, surface coverage, and strut configurations. Classifications have been proposed, but the number of parameters involved may doom the number of subsets to approach the number of designs. Moreover, each device seems to have a unique optimal mode of placement. It is not surprising, then, that differences have been reported in flexibility, tracking ability, expansion, radiovisability, side-branch access, and resistance to compression and recoil for different devices. Regulatory approval includes safety standards for toxicity, biocompatibility, structural and material analysis, and fatigue testing, and it has been suggested that hoop strength, surface cracking, uniformity of expansion, and other features become standardized as well.

The evolution of stent design, which has produced increasingly safer and easier-to-use devices, indicates that there is not a single safety threshold but rather a continuous spectrum of performance. Every device that has been introduced into the clinic has undergone revision. In every case, designs that met regulatory guidelines were changed to make devices better. Whether diseased human arteries are subject to the same deep stent-induced injury as animals is debatable. However, the impact of design may extend far beyond the induction of injury. Variable tissue growth along stent length can be accounted for by variation in lumenal geometry imposed by repeating stent subunits. Vessel-device-hemodynamic interactions produce variable neointima, perhaps in an attempt to restore laminar flow even in the absence of deep injury.

Animal Experiments

The central element of stent-vessel biology is the degree to which each strut incises the vessel wall with expansion. Deeper penetration generates greater late tissue growth. Correlation between injury and response is retained across species from rabbits, pigs, and dogs to nonhuman primates and is so sensitive that differences in injury for adjacent struts can explain differences in overlying intima. Stents designed to produce lesser injury produce correspondingly less tissue growth. We compared 2 prototype stents differing only in geometry and found one superior for every parameter evaluated, including injury score, thrombosis, endothelial denudation, inflammation, and intimal thickening. When 3 commercial stents were evaluated in an experimental model, they also exhibited variable effects on injury and repair.

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The question then is whether the compelling rationale and extensive data from preclinical studies indicating design-dependent responses can be confirmed or refuted in the clinical arena.

**Stent-Versus-Stent Trials**

Four different direct comparisons of first-generation Palmaz-Schatz slotted-tube stents and second-generation stents have been made. In 3,11,13-15 there were no significant differences in restenosis at follow-up, including minimal luminal diameter (MLD), percent diameter stenosis, late loss, or binary restenosis rate. In the fourth study,12 restenosis was far greater for the Gianturco-Roubin II (GR-II) stent (Cook) than the Palmaz-Schatz stent (Cordis-Johnson & Johnson). Interestingly, the data for all stents bunch across trials; with the exception of the GR-II stent, variability between the test stent groups was no greater than the variability between the Palmaz-Schatz stent groups in the different trials.

Three distinct possibilities exist to explain the absence of clinical evidence that different designs behave differently: (1) no differences in clinical outcomes exist between devices; (2) differences exist but are so slight as to be clinically meaningless; and (3) differences exist that may be clinically meaningful, but trials performed to date were not designed to detect them.
Changes in Stent Design Make No Difference

With the exception of GR-II data, trials performed to date comparing stents do not demonstrate a statistical difference between designs. One might reason that “a stent is a stent,” shoring up diseased or dissected arteries; how it does so is immaterial and irrelevant, only that it does so is important. Why might this be the case? Either preclinical data are mechanistically different from and not predictive of human vascular diseases, or engineering differences between stents are not sufficient to make a clinical difference. As in the decades-old discussion surrounding attempts to harness restenosis, it is difficult if not impossible to extrapolate directly from animal data to human responsiveness. Animal models provide mechanistic insight. The notion that controlled vascular injury in a laboratory animal can resemble human disease may be appealing but is simplistic. It is not possible in an animal either to reproduce the multifactorial processes that enable complex human lesions to evolve over decades or to mimic precisely the acute, high-intensity injuries of vascular interventions.

Differences in Stents Are Slight and Without Clinical Significance

Another interpretation is that engineering differences between stents have the potential to elicit different biological effects in humans, but these differences are too small to be detected in clinical trials. Subtle changes in stent configuration might make a device more flexible and less injurious but insignificantly so relative to the full extent of the injury imparted during vessel dilation and stent implantation. In this argument, design is not dismissed as an important feature of a stent but becomes moot within the greater context of the overall procedural vascular injury. Effects of vascular anatomy, lesion morphology and location, deployment strategy, and patient comorbidity may dwarf any impact of stent design.

Clinical Trials Have Not Been Designed to Illustrate the Biological Difference Between Stents

Equivalency Trials

Stent-versus-stent trials are equivalency trials, designed to show that a test device performs “as well as” a standard, currently acceptable device. This is a valid regulatory threshold but not the means to evaluate the full potential of a device. Equivalency trials must by definition commence with a patient population for whom the standard device is safe. Trials with currently approved devices as the standard equivalency must commence with a patient population for whom the standard device is safe. Trials with currently approved devices as the standard necessity that patient entry and lesion selection be determined by limitations of the standard, not the test, device. As depicted in the Figure, the only way to observe a difference in such a trial is when the test device performs worse than the standard. For the test device to perform better, both the test and the standard must be challenged. This was not the case for the trials in which the average reference vessel size was 3.0±0.05 mm and American College of Cardiology type B2 and C lesions accounted for only ~65% of lesions. These lesions are those for which the Palmaz-Schatz stent is approved and technically suited, but they represent only a minority of those lesions now receiving stents. Whether similar results would be obtained with broadened indications is impossible to know, because the standard stent could not be used.

Furthermore, the conception that none of the trials showed a difference is incorrect. As used in the study, the GR-II stent did not perform as well as the Palmaz-Schatz stent. MLD at follow-up was higher, and the percent stenosis and late loss were lower for the Palmaz-Schatz stent. Much has been said to explain this difference, including issues of predilation, stent sizing, and length, but the data unequivocally show that one stent design provoked a different biological response from the other. The most telling parameter was the late loss index. In virtually all trials for interventional devices to date, this value has been ~0.5. In the GR-II stent trial, this value was 0.76 for the GR-II stent, 33% greater than that observed with the Palmaz-Schatz stent. Stent design made a difference, and these data set the stage for other stents to demonstrate a difference, better or worse than the standard.

Although the GR-II data alone should be convincing enough, the other stent-comparison trials should not be dismissed out of hand. The magnitude of differences between different stents was equivalent to the magnitude of difference between angioplasty and stenting in BENESTENT (BELgian NEtherlands STENT Study) and STRESS (STent REStenosis Study). Binary restenosis rates, for example, in ASCENT (ACS multi-link Stent Clinical Equivalence in de Novo lesions Trial) and NIRVANA (medinol NIR primo stent Vascular Advanced North America trial) were lower for the test stents than for the standard stents (16.5% versus 20.8% and 15.7% versus 25.4%, respectively). In addition, mortality at 1 and 6 months was design dependent: in the ASCENT trial, 1.2% of patients died within 1 month and 3.1% within 6 months of Palmaz-Schatz standard stent placement, whereas
patients receiving the Multi-Link (Guidant) test stent had mortality rates of 0% and 1.5%, respectively. Similarly, subacute thrombosis was undetected in the group receiving NIR (Medinol) test stents compared with a 1.2% thrombosis rate for Palmaz-Schatz standard devices. There may be a significant difference between the thrombotic potential of 2 stents, but because one can do no better than “no thrombosis,” this difference is invisible. It is only when the thrombotic potential becomes a significant problem based on lesion selection that one might see a difference between 2 devices (Figure).

Complexity, Equivalence, and Better

In truth, it may be most appropriate to think about parameters of device success and safety as a continuum, describing a correlation between events such as thrombosis or restenosis and a continuous measure of indication, vessel dimension, or lesion complexity (Figure). A given device may be represented by a characteristic response over a range of indications. When there is a lateral offset to the curves, differences in potential performance are anticipated. Curves might even cross, rather than run parallel, indicating that devices might be matched to lesions and indications. Open trials would consider the entire range of the curves; equivalency trials are limited to a small region of the curve.

Conclusions

The first-generation stents were a major innovation in interventional cardiology, and their place in medical history and biotechnology is unassailable. Demonstration that new stents are better than old will require that evaluations be performed in lesions for which current devices have marginal or limited application. Complex or acutely unstable lesions, small arteries, and diseased bypass grafts are the next great challenges of interventional cardiology. Perhaps in these settings, future stent trials will provide firm evidence that the manner in which blood vessels are manipulated dictates biological sequelae. Proof that stent design can alter clinical outcomes may then unleash the potential to change the way in which we consider design, approval, and use of new devices.

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References


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