ROUNDTABLE DISCUSSION

Surveying the Landscape: SFA Drug Delivery Trial Designs and Data

Experts discuss key elements of SFA trials, whether a global algorithmic approach to treating SFA disease is possible, and the limitations of cross-trial platform comparisons.

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PANEL: GARY M. ANSEL, MD; KOEN DELOOSE, MD; MICHAEL R. JAFF, DO; AND PETER A. SCHNEIDER, MD

Dr. Gray: What are the key elements of a superficial femoral artery (SFA) study, including design, inclusion criteria, and endpoints? Are any specific to drug delivery?

Dr. Jaff: The key elements include primary/secondary endpoints (safety and efficacy), study design, patient population, adverse events, and duration of the primary endpoint.

Dr. Ansel: The key elements for SFA trials have certainly changed over time. We are ahead of where we were a few years ago, with a lot of technology and very little rigorous data. The key elements of SFA trials may also differ between investigational device exemption (IDE) device approval trials and real-world trials or registries. When evaluating a new technology, such as the drug-based technologies, there are many variables to assess beyond safety from amputation and efficacy, such as binary restenosis or clinical revascularization. We need to understand as much as we can about the technology and its effect on quantitative minimal luminal diameter, downstream effects, and clinical drug levels. The IDE trials almost have to be undertaken in a very selective population that is not necessarily representative of the general population, so that you can control enough variables to allow reasonable scrutiny of outcomes. In a perfect world, data after IDE approval would look at much more heterogeneous populations. In the future, we would like to see more comparison data with randomization between technologies, as well as more clinically based revascularization and adverse outcomes. Larger data sets are needed in the general population to help guide physicians regarding application of the technologies in the most optimal and cost-effective populations. These variables may then include subintimal treatment, various levels of calcification, smaller vessel diameters, and the effect of various methods of application of the technology with various types of vessel preparation. More specific to drug-based technology may be the pattern of restenosis, which could help us evaluate any type of heterogeneous response to the drug. We could also evaluate drug effects in different patient subsets with comorbidity variables such as renal failure and critical limb ischemia (CLI).

Dr. Schneider: The key elements we have used in the past will likely continue to be used. We may see more rigor around defining clinically driven target lesion revascularization (TLR) and how much investigator blinding there should be with regard to clinical and duplex results in deciding whether to perform TLR. We might also include additional information about the volumetric aspects of recurrent stenosis rather than focus on the location of the worst narrowing. With drug delivery, it is possible that the binary concept of restenosis versus no restenosis will become less important because drug delivery may offer the possibility of less volume of restenosis when it occurs.

We should also acknowledge that there are some key challenges to drug delivery studies going forward. Is it ethical to compare plain old balloon angioplasty with various drug delivery devices, especially in patients with long, complex, or highly calcified lesions or in-stent restenosis? Another key element of drug delivery trials going forward will be the manner in which vessel preparation is performed. How should dissection be managed after drug-coated balloon (DCB) use? My bias is that focal dissection repair should be practiced in this setting. How restenosis is judged in general might also be challenged in the drug delivery era. For example, is a moderate (50%) restenosis important if it is stable and not associated with symptoms?

Dr. Deloose: In my opinion, every step of the SFA study is key! Everything depends on what you want to prove, on the ultimate goal of the trial. Health care providers, insurance companies, and governments are most interested in health/economic benefits. Patients want to hear the freedom from TLR and safety outcomes, and physicians are also interested in a scientific background and outcomes such as late lumen loss and primary patency. An efficient combination of these endpoints is the ultimate way to success. Nowadays, more trials are set up based on government reimbursement criteria than on pure scientific analytical criteria. To address the drug delivery question, other than the efficacy endpoint, I assume the safety endpoints remain crucial. Also, a very precise protocol-based definition of the procedural steps (eg, vessel prep, prolonged inflations, bailout stent criteria) is essential.

Dr. Gray: Do you evaluate each platform's ability to deliver its therapeutic agent or just its efficacy in reducing restenosis?

Dr. Schneider: We don't have any good way in vivo to monitor drug delivery. This is unfortunate, but there is no shortcut at this point. We don't have a surrogate endpoint. The closest we have is late lumen loss, which is indirect and necessitates arteriography. It is possible that some type of noninvasive imaging will become detailed enough to be used to calculate late lumen loss. Could antiproliferative drugs be labeled with nanosensors?

Dr. Jaff: The ability to deliver the therapeutic agent is based on bench and animal testing. In human clinical trials, it is about efficacy and freedom from adverse events.

Dr. Deloose: I believe both are important and that the ability to deliver the agent and reducing restenosis are directly correlated. From a scientific perspective, it is beneficial to know each platform's ability and timing to deliver more or less drug or if the therapeutic agent is short or longer acting, but I'm sure my patients (and health care providers) are most interested in its ability to reduce restenosis.

Dr. Ansel: A drug delivery platform's ability to deliver its therapeutic agent is currently an animal lab exercise. Although a surrogate, it only provides some insight because we don't have a good atherosclerotic animal model. This certainly provides the ability to evaluate for the agent alone or with its excipient in uniformity of application, which has been somewhat lacking to date. In the DCB world, and to some extent the drug-eluting stent world, we are applying heterogeneous material in a very heterogeneous environment with calcium, plaque, and thrombus. So, we certainly hope that future generations of drug-based therapy improve upon the uniformity of drug application as well as provide the safest delivery vehicle possible. We hope that these improvements will lead to decreased restenosis, but more importantly, a decreased need for repeat intervention. We also need to expand the evaluation from claudicants, in whom most of the devices have been tested, to CLI patients who may not tolerate distal debris as well.

Dr. Gray: With the combination of vessel prep and drug delivery gaining popularity, but with data somewhat scarce, how do we separate the results of one platform from the other?

Dr. Jaff: Honestly, the only way we are going to answer this question is to compare a DCB with vessel prep to DCB alone. If the combination is superior, DCB would need to be combined with one type of vessel prep and compared to a DCB with a different vessel prep technology.

Dr. Ansel: Trying to compare data sets with vessel prep is problematic. Unless the devices are randomized for comparison, I find it hard to separate the results.

Dr. Deloose: This is a perfect example why cross-trial platform comparisons are dangerous. In some trials, vessel prep is mandatory, whereas in others, nothing is mentioned or it is at each physician's discretion. Also, there is no clear and unequivocal definition of "vessel prep." Vessel prep methods vary and can include angioplasty, prolonged angioplasty (30 seconds or 3 minutes), scoring or sculpting, and/or debulking. In some trials of specific devices, you need to create an almost perfect result before the study device can be implanted. In others, a device can be used directly without any preparation. It seems impossible to compare such different approaches.

Dr. Schneider: The biggest challenge is how to preapprove two treatment modes simultaneously. These two modes consist of the drug we want to deliver as definitive therapy and the method of vessel prep. There is a proposed synergy that makes practical sense, but it is not proven. If drug delivery in the noncoronary arteries is in its adolescence, then vessel prep is in its infancy. Vessel preparation in my opinion is a combination of factors, including lumen gain, plaque modification, leaving a smooth and noninjured flow surface behind, and improved vessel compliance (this is more theoretical).

One interesting idea, at least as it pertains to DCBs, is whether we need specific structural portals of entry into the vessel wall for medication to be delivered. We want to minimize dissection of the vessel wall, but do we need some type of intrusion into the vessel wall, such as dissection, to deliver the medication more efficiently?

Dr. Gray: With all of the various platforms being evaluated, can you envision a trial/data set that could successfully unify the global algorithmic approach to treating SFA disease?

Dr. Ansel: As the VIVA Physicians group has done in the past, we hope to obtain raw data sets from the various trials in an effort to compare the different platforms with more rigid definitions. A large trial with several industry sponsors would be problematic and would probably be outdated before it was even completed due to the rapid nature of technologic advancement. We should try to utilize the large real-world data sets that have undergone core lab adjudication to help tease this out. Even then, specific patient and lesion combinations will allow for more generalizations than a cook book.

Dr. Jaff: Absolutely, but it is hard to imagine that commercial manufacturers would sponsor such a trial, and it would need to be a head-to-head trial.

Dr. Deloose: There are two difficulties with this idea. First, the ultimate global algorithmic approach to SFA disease is not yet defined. This algorithm is mainly money-driven and influenced by reimbursement issues throughout the world. The use, overuse, and nonuse of debulking atherectomy devices in different countries is a perfect example. Second, creating the ultimate prospective, multicenter, randomized (multiarm) trial with the highest rigor and extensive blinding to remove any kind of bias seems to be an unaffordable, extremely complex, highly time-consuming exercise and thus, "mission impossible."

Dr. Schneider: No, I can't imagine a definitive trial, and I do not think it will happen. This is not because it's not possible, but rather because the technology is changing too quickly. The definitive trial may actually set us back if innovation took a wait-and-see approach while the trial was underway. If you did a head-to-head trial with all approved DCBs, there will be two or three more on the market by the time it is finished. I believe it is too soon for anything definitive. We may have a different drug that emerges to be better than paclitaxel or one excipient may prove to be better than the others. We are developing vessel preparation and it may get so good that the relative differences of some of the DCBs are narrowed. Focal dissection repair is also in development. Therefore, I believe that we don't yet have the right method for DCB trials in CLI patients.

Dr. Gray: If cost were not an issue, how would such a trial be designed?

Dr. Deloose: As previously mentioned, even without the cost issue, the ultimate, globalizing, all-inclusive, extremely rigorous SFA algorithm trial design remains a mission impossible until we have more clarification in the subcategories of devices and technologies. New technologies are always running in front of enrolling and analyzing trials. I imagine it would take years to set up this dream trial, and meanwhile, more drug-eluting technologies, other drugs, and new vessel prep technologies will become available.

Dr. Schneider: We should focus on the following aspects that I believe are the natural next steps in the advancement of this field: optimal DCB technique and vessel prep, research and development of the next generation of devices, and prove the safety of devices in CLI.

Dr. Jaff: It would need to be a prospective, multicenter, randomized, open-label trial.

Dr. Ansel: Testing approved products is very problematic, because physicians will already have a bias toward what they think works in particular patient subsets. Even if cost were not an issue, I don't ever see something like this occurring. The best we can do is to try to drive consensus from physicians based on given parameters of outcome, timeline, and cost. However, the only way to do it is to have clinical event committees (CECs) and core lab–controlled data and allow physicians to use whatever they want for particular patients and then record the specifics for those patients utilizing specific definitions. A small percentage of the data sets would then be audited to ensure the data are relatively accurate. The costs of the particular techniques would need to be evaluated as well. The most likely time frame would be 2-year patency and clinical revascularization, major amputation, and cost. The patient population would include Rutherford classes 2 through 5.

Dr. Gray: With cost and enrollment as key barriers in making such a trial a reality, what design might actually be feasible?

Dr. Schneider: What would be doable right now is a head-to-head comparison of the market-leading DCBs that are currently available. As previously mentioned, although possible to do, I'm not sure how much this would solve our current challenges.

Dr. Jaff: A trial evaluating a DCB plus vessel prep compared to a DCB without vessel prep would be feasible.

Dr. Ansel: The most difficult part is the amount of work the investigators would need to do. Trials would need to include several thousands of patients. As previously described, letting physicians do what they do best and then look at the outcomes may be reasonable, noting the inherent selection bias.

Dr. Deloose: Right now, we can define some categories of SFA treatment: modern-generation bare-metal stents, DCBs, drug-eluting stents, covered stents, debulking strategies, bypass surgery, and different combinations of these categories. I like the ongoing trend of head-to-head comparisons in the different domains, mainly based on similar protocols (IMPERIAL trial, COMPARE-1 trial). I miss this in other categories such as bare-metal stents and debulking strategies. Once we have clear data within these categories, we can start comparing technologies; we have some early examples (Real PTX study, ZILVERPASS study), but we need more, ideally with three or four comparison arms. Overall, we need uniform endpoint definitions, more objective scaling of calcium, and quantitative grading of flow-limiting dissections.

Dr. Gray: What are the potential benefits and shortcomings of prospective real-world data collection?

Dr. Ansel: The benefit is that we would get some comparative data both clinically and financially. A shortcoming would be the number of patients needed, given the large number of devices for vessel preparation. In addition, by the time patients are enrolled, the data may be out of date because of improvements in technology and technique.

Dr. Jaff: The benefits include actual patients who present the greatest challenges to physicians without restrictions. Currently, these patients are routinely excluded from clinical trials. One shortcoming would be the difficulty in comparing patients in real-world cohorts, as they are so different both clinically and anatomically.

Dr. Schneider: Prospective real-world data give us signals of potential success and failure, although these are rarely, if ever, definitive. This tells us what the majority of patients will experience given that the majority of patients are not going to qualify for a trial. To do an excellent real-world study, it would have to be adjudicated better than most real-world studies have been in the past. It would be really beneficial to include a duplex-derived patency endpoint in these types of studies.

Dr. Deloose: As we all know, pivotal trials are a bit artificial because they are based on ideal circumstances, the best operators, and a less diseased population. Adding real-world data collection offers answers on existing questions from the pivotal trials, provides an extension of already approved indications (longer lesions, in-stent restenosis, more calcified lesions), and allows a better understanding of risks and benefits in real-world clinical practice. Limitations include problems with underlying data relevance, quality, reliability, and biases. If the parties responsible for these trials create similar follow-up, endpoint definitions, and event adjudication as those of the pivotal trials, high-quality data can be ensured, even though the patients represent a more real-world population.

Dr. Gray: What are the limitations and pitfalls of cross-trial platform comparisons?

Dr. Ansel: Cross-trial platform comparisons are fraught with problems. We may use the data from various trials for very general comparisons, but the marketing of one trial's results versus another's is often directly misleading to physicians and patients, and this practice, although common, should be frowned upon. Trying to compare technologies across trials is very problematic. Even when inclusion and exclusion criteria are similar, the trials may not be comparable. For example, when we find out the results of the first trial, we may learn which patients or lesions respond more optimally from that treatment or we might learn that a different vessel preparation method may be best. So, early data sets may improve results of later trials. With DCBs, we had to learn that certain dissections are acceptable.

Even the area of the world in which a trial is based may affect results. Some countries may try harder not to use certain treatments, such as bailout stents, or the patient population may be more stoic and not report recurrent symptoms as readily, which may affect reintervention rates. Another variable to consider is trial design. Trials that utilize CECs and core lab controls often have much different results than those that do not. Without CECs and core labs, site-reported data can be very suspect, unreliable, and have inherent sponsor bias. Data from randomized trials are also often different than registry data, although each has its role. In fact, the types of patients who agree to participate in a randomized trial may be different than those who participate in a registry. Thus, comparisons can again be problematic. Even comparing core lab–controlled data versus CEC-controlled data can be problematic because the definitions and techniques for measurements may vary. What one study defines as severe calcium may be categorized as mild or moderate in another trial. Duplex ratios are also sometimes different, which can certainly affect results. Finally, the time frames for the results can vary and significantly impact the results.

Dr. Deloose: Post hoc comparisons must be evaluated with extreme caution and healthy skepticism. Differences in trial constructions with different parameters, endpoint definitions, rigor, and blinding techniques already create huge pitfalls. Various patient cohorts, operators (each with their own individual expertise), treatment protocols, and time frames add even more limitations on possible comparisons. Postprocedural follow-up and collection and analysis of data also have an important influence on final outcomes of trials and might confound comparison.

Dr. Jaff: If two device platforms are not studied head to head, there is no way to avoid the introduction of bias into study interpretation, as the patient populations, device selection protocol, and operator techniques are not identical.

Dr. Schneider: I agree with these points; they are all quite valid. Over the long term, it must be viewed as a developmental process. We are definitely into the long term now because we are 10+ years into drug delivery in the peripheral arteries. This is how our field makes progress; we learn from one trial how to plan the next. We learn from one technique or device how to develop the next. None of the trials were conducted in a vacuum. We have to look at them in context. But, at the same time, we have to deal with the practicalities of life, the complexity of these patients, the cost, and the significant pressures on research trials from every direction, which makes our full wish list impossible. We have to compare some aspects of these trials, but we have to do it with a lot of caveats and nuance, and we definitely have to get into the details of each trial to see where they are comparable and where they are not. The best we can get out of comparing different trials is to understand directionality, and we usually do not get a definitive answer as to whether one device is better than the other.

Dr. Gray: Under which circumstances can data from separate trials be compared? Which elements are comparable, and what are the characteristics of trials that produce cross-compatibility?

Dr. Schneider: The characteristics of cross-compatibility for comparison of trials include the patient populations, endpoints, and methods of adjudication. If these are not the same or at least close to the same between trials, then there is no cross-compatibility. Full disclosure of this information in the published manuscript is extremely helpful.

Dr. Jaff: If the primary endpoint is an imaging endpoint, with identical definitions and independent of adjudication of the endpoint, that is a comparable endpoint.

Dr. Deloose: First, one must assess the trial construction and its rigor. Having the same algorithm, identical primary (and secondary) endpoint definitions, independent core lab–based analysis, independent Data and Safety Monitoring Board and CEC control, and the same level of blinding are steps in a good direction. If clinical and angiographic inclusion and exclusion criteria are defined on the same basis, the potential for comparison

increases because patient and lesion demographics likely won't differ too much. If selected sites have the same level of expertise and are used to enroll in clinical trials, procedural characteristics will end up in the same area. Finally, a similar method of data collection and statistical analysis can add an extra tool to compare. These are good steps, but as previously mentioned, always approach comparisons with caution and skepticism.

Dr. Ansel: Under the guidance of our Director of Research, Dr. Krishna Rocha-Singh, we at VIVA have tried to help in this process. Bringing together the raw data from randomized data sets can help with technology comparisons. At a minimum, it is necessary to have CEC and core lab adjudication as the cornerstone, with consistent definitions of variables and time frames. However, site-reported data, which are economically attractive, are not substantiated enough to use for comparison, and in my view, should simply be recognized as potentially fraught with bias and under- or overreporting. Short of this, it is very difficult to compare trial data, as previously stated. ■

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