John Fritz Angle, MD

Dr. Angle discusses his predictions for future developments in interventional radiology and the device approval process.

What is the latest on the OSPREY trial, which is evaluating the Misago self-expanding stent system (Terumo Interventional Systems, Somerset, NJ)?

Terumo entered the peripheral occlusive disease market through the launch of its nitinol self-expanding stent that has recently gone through clinical trial here in the United States. The 1-year follow-up data should be completed in the next few months. The Misago stent has a rapid exchange (monorail) configuration, which is helpful for up-and-over superficial femoral artery (SFA) applications and tortuous anatomy because of the flexibility of its delivery system. The stent appears to maintain a good luminal diameter within a lesion due to its wall apposition and radial force features. We're looking forward to seeing the long-term patency results.

The OSPREY trial is part of the Harmonization by Doing (HBD) program, a partnership between the US Food and Drug Administration (FDA) and Japan's Pharmaceutical and Medical Device Agency (PMDA), which is intended to streamline product approvals in both health care markets. How do you think the HBD program will affect the future of bringing devices to market?

I think the OSPREY application to the FDA and Japan's PMDA using the HBD program was very advantageous because there is a huge need for approved SFA stents in Japan.

The rapid accumulation of patient data provides Terumo the possible opportunity to introduce their first peripheral product sooner, both in the United States and Japan. There are a lot of devices that have gone through a lengthy sequential process to achieve approval in the United States, Japan, and other countries. I think this HBD process may be the wave of the future for a lot of different products. The rising cost of health care is not sustainable, and developing new technology is very expensive, especially if the process has to be repeated in different countries for the same product. Therefore, it makes a lot of sense to pursue this concept of cost-sharing and rapid patient enrollment to allow more efficient evaluation of devices in different countries at the same time.

Do you think there are any drawbacks to the HBD system?

Terumo has certainly been a trailblazer in this process. When we started the OSPREY trial, we were concerned about the slightly different patient populations, and whether the outcomes data would be comparable. We were asking ourselves, "Would the results be similar enough in the two countries that the data would be applicable for a combined submission in both countries?" The answer to that question was a bit of an unknown, but I think we will find that, due to our study design, it will not be a major concern for this trial. Hopefully in designing future device trials, we can take advantage of larger study populations or more rapid patient enrollment by including patients accrued in Japan and/or other countries.

The other concern we had with this trial was the slight differences in patient care standards between the two countries. It was fascinating to think about the things we take for granted in this country. For example, we'll put all the patients on clopidogrel after an SFA stent. Well, that's not done in Japan. Is that wrong? No, but it is different, so we had to think about how to design a single study protocol that would be compatible with the standards of practice in two different countries. It took more forethought and time to design a study protocol that would be acceptable to investigators and regulators in both countries, but I think this trial will reveal that our attention to detail will result in "harmonized" and very applicable results for both countries. The time involved on the front end should not be a barrier to doing future HBD studies, because the initial investment saved a lot of time and money on the back end.

What are some of the most important developments in the understanding of neointimal hyperplasia over the last 5 to 10 years? What strategies do you think are most promising to reduce intimal hyperplasia?

One thing I have learned the hard way over the years is that the SFA can't take a lot of trauma. The basic treatment principles still apply—treat as short a segment as you can, keep it simple, and don't stent a longer segment than you need to get a good result. Sometimes, our efforts to make a good cosmetic result may not be

what is best in the long run. Although there is level 1 evidence that stenting is superior to PTA for longer lesions, I think most operators would agree that there are subsets of SFA lesions that do very well with PTA alone and do not necessarily need a stent. We are rediscovering that careful balloon sizing and prolonged inflations make a difference in the SFA. I think part of the reason we are seeing a resurgence in PTA is because of the added benefits associated with the use of drug-eluting balloon (DEB) technology. Drug-eluting stents (DES) are also going to be an important tool in our armamentarium. Having an FDA-approved DES for the SFA and getting real-world feedback is going to be interesting to watch.

Ultimately, using DEBs in combination with stents or atherectomy devices is what excites me the most. If there is a focal, eccentric, and calcified SFA lesion, atherectomy can debulk the lesion, and then the DEB can be used to optimize the luminal diameter while depositing an agent that minimizes the effect of intimal hyperplasia without leaving any hardware behind. I'm placing my bet over the next few years on this combination of atherectomy and DEB angioplasty as an important new therapy. Of course, bare-metal stents plus DEBs will need to be compared to the promising results with DES. This is definitely an exciting time for the treatment of SFA disease.

At VIVA 2012, you presented on when and how to intervene for submassive pulmonary embolism (PE). What are the barriers to this being widely practiced?

There is still a lot of investigative work to be done with catheter-directed therapy (CDT) in patients with acute submassive PE. We do not know if CDT for patients with submassive acute PE really improves patient survival or prevents late complications or disability as compared to anticoagulation alone. What we do know from large registries and cases series is that patients with acute massive PE with refractory hypoxemia or who are hemodyamically unstable have better outcomes with CDT. It also appears that patients with acute submassive PE that have moderate to severe right ventricular dysfunction on echocardiography and/or elevated troponin or brain natiuretic peptide levels are more likely to become hemodynamically unstable. However, we do not know if we intervene earlier on these patients if their out-

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comes are better. Catheter-directed thrombolysis for acute PE also appears less likely to cause a bleeding complication as compared to systemic thrombolysis.

Therefore, acute submassive PE is an area where a lot of new technologies like the ClearWay balloon (Atrium Medical Corporation, Hudson, NH), the Ekos catheter (Ekos Corporation, Bothell, WA), or the wide variety of mechanical thrombectomy devices provide us investigative opportunities. Maybe it's time to design a study where we evaluate the efficacy of some of these newer technologies, especially in the subset of patients with signs of right ventricular dysfunction by echocardiography, mild persistent hypoxemia, or elevated biomarkers, but who are hemodynamically stable. For this patient population, it appears that the technical and hemodynamic success rates with CDT are high, and the major complications rate is low.

How do you foresee the field of interventional radiology changing and adapting in the coming years as specialties' procedures continue to overlap more?

Interventional radiologists are elevating their level of service, providing more complete and longitudinal patient care, while becoming more expert in the specialized care they are providing. The recent approval of the dual primary certificate of training in diagnostic radiology and interventional radiology, thanks to the efforts of folks like John Kaufman, Gary Becker, and James Borgstede, is also an exciting development for the specialty. Creating this new interventional radiology training pathway will provide the extra clinical training that traditional radiology training lacks. I am particularly hopeful that trainees in this new pathway will have the time and perspective to make significant contributions to the care of vascular patients and to endovascular therapies.

What are your thoughts on the state of evidence-based endovascular therapies, and how will that affect referral patterns?

I've been doing percutaneous endovascular interventions for 20 years now. Over that time period, it's been wonderful to see that, as many endovascular procedures become more commonplace, we're collecting more and more outcomes data and evidence that help us better define the indications, contraindications, and appropriateness for the endovascular procedures we perform. Everyone involved in this field is very keen to generate new information that will drive quality initiatives toward directing health care dollars to favorable treatment algorithms and away from less effective therapy.

Everyone is tiptoeing around these issues at this time while trying to figure out where we're going to be in 5 or 10 years. The answer is, in my mind, that we all need to become engaged in doing clinical research to prove the comparative effectiveness of our endovascular procedures. We need to get beyond just looking at 6-month patencies and evaluate whether we are improving patient survival and quality-of-life outcomes in a cost–efficient manner.

Interventional radiologists, like vascular surgeons, interventional cardiologists, and other specialists that practice endovascular therapy, should be energized by the pipeline of new devices and techniques coming from many different directions. Physicians coming together at multispecialty meetings like VIVA and ISET is an important thing for patients now and in the future; it's a great time to be in a great field. At the same time, we can't turn a blind eye to the fact that a lot of what we do is very expensive and high-tech therapy, some of it without the appropriate evidence base. Without the evidence, ultimately, we're not going to move the field forward.

What are the large quality initiatives in a peripheral vascular lab these days?

Hospital administrators and practicing endovascular specialists need to be engaged in finding methods to track the important quality measures, prevent medication and wrong site errors, shorten lapses in treatment, improve longitudinal follow-up, provide better access to supervised exercise programs, optimize medical therapy, and develop cost-effective treatment plans. We're seeing more literature about the importance of doing a preprocedure timeout, site marking, and using checklists to make sure that all the details of a procedure are assessed to make sure a patient's outcome is as good as possible. Because a lot of our treatment decisions are made in real time, we tend to lose sight of how much of what we do still needs to be protocolled and standardized—the timing of antibiotic prophylaxis, venous thromboembolism prevention, etc.

I understand that some physicians find it a bit frustrating to spend time on a mundane checklist, but there is evidence that these lists make a difference in patient outcomes. The future is going to be all about outcomes, comparative effectiveness, and utilization management. Practices with the most rock-solid protocols will likely be the most successful. Functioning like a cockpit, where the pilot and copilot are routinely going through checklists together, is a frontier in which the endovascular specialists need to take a lead. ■

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