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A pre-eminent interventional cardiologist shares his experience as PI of seminal clinical trials, thoughts on late thrombosis, and what TCT 2007 has in store.

As principal investigator of the TAXUS pivotal trial, you saw firsthand the benefit that drug-eluting stents (DESs) can offer patients with coronary artery disease. Have the recent developments regarding late thrombosis changed your feelings at all about DESs?

I think it is important to differentiate what we have learned about on-label use of DESs from off-label use of DESs. The results of any clinical trial are meant to examine specifically safety and efficacy issues in the types of patients enrolled in that study. In the prospective, double-blind TAXUS trials, specifically TAXUS II, IV, V, and VI—I was privileged to be the principal investigator of TAXUS IV and V—we examined patients predominately with stable angina pectoris with simple to only moderately complex single *de novo* coronary lesions in native vessels. Strict entry criteria limited the lesions studied in vessels with reference diameter ranging from 2.25 mm up to 4 mm and lesion length up to 46 mm.

In these types of patients and lesions, we demonstrated that Taxus stents were overall safe and effective. Specifically, we found that there was no overall difference in the rates of death or myocardial infarction (MI) between Taxus and bare-metal stents out to a total of 4 years of clinical follow-up, although we did note a slight increase in late stent thrombosis after 1 year. Therefore, between 1 and 4 years of treatment, there was approximately one additional stent thrombosis per every 500 patients per year. However, this did not translate into any demonstrable difference in death or MI.

We believe this discordance may be explained by the fact that Taxus stents are so effective compared to bare-metal stents in reducing both angiographic and clinical restenosis, with fewer episodes of recurrent angina and less recurrent ischemia requiring repeat angioplasty procedures and coronary artery bypass graft surgeries during follow-up. This is important because restenosis is not always a benign entity and, in a small but finite proportion of patients, can present as either death or MI, and the procedures that are required to treat symptomatic restenosis can result in death or MI. As such, there are counterbalancing effects of a slight increased risk of stent thrombosis with Taxus (with a high rate of death or MI) offset by a marked reduction in clinical restenosis, resulting in net overall similar rates of death and MI. Thus, after 4 years of follow-up, we are left with a safe therapy that markedly reduces target lesion and target vessel revascularization, which improves quality of life for patients compared to the previous reference standard.

Those results hold for on-label use—that is, the types of patients and lesions for which DESs have been approved for marketing by the FDA on the basis of the results of those pivotal trials (specifically for Taxus lesions up to 28 mm in length in native coronary arteries with 2.5 to 3.75 mm reference vessel diameter). It now remains to be shown that those results can be extended to more complex and/or high-risk patients and lesions, such as those with bifurcation lesions, multivessel disease, acute MI, saphenous vein grafts, etc.

Currently, there are fewer data that have been generated from high-quality studies to examine in these patients, and no large-scale randomized trials to date (although small- to moderate-sized studies have been completed with DESs in chronic total occlusions, saphenous vein grafts, and acute MI). First, such patients are more complex and/or high risk; therefore, their outcomes with any sort of treatment tend to be less favorable than those that were studied in the pivotal TAXUS trials. We would expect, for example, that medical therapy or treatment with bare-metal stents or bypass surgery would result in higher rates of death and/or MI in patients with complex multivessel disease, diabetes, and reduced left ventricular ejection fraction. We would expect higher stent thrombosis rates with many types of therapies in patients with acute MI and in thrombotic lesions.

Whether the safety and efficacy profile of the Taxus stents compared to bare-metal stents is the same in such off-label use compared to on-label use needs to be proven. That is the question that has been raised by several of the recent studies, with concerns being fostered by a

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lack of data. Most of the studies to date reporting the results of DESs for such off-label use consist of registry studies without a concurrent control group, often with inadequate monitoring and follow-up. These studies, which are confounded by selection bias and other limitations, have raised concerns about DESs, but without randomization to appropriate controls, we have no way of knowing if DESs are doing similar, better, or worse than other reference therapies.

There are three ongoing large-scale, prospective, randomized trials examining the outcomes of patients with multivessel disease, left main disease, diabetics, and acute MI, with DESs compared to other approaches, either with bare-metal stents or coronary artery bypass graft surgery. Over the next 2 years, we will have the results from two of these studies, which will provide much-needed insight and, hopefully, reassurance that DESs are as safe and as effective in those off-label conditions as in the on-label use.

The lay press also picked up on the story of late thrombosis. Do you think this has had any impact on the desire of patients to have a DES placed?

The extraordinary media coverage of the late DES thrombosis issue has certainly led to a great deal of concern among patients. Not a day goes by that a patient doesn't ask questions about whether he or she should receive a drug-eluting or bare-metal stent. It used to be that patients insisted that we place a DES, even if it was off-label and even if we did not necessarily think it was in the patient's best interest. Now, the pendulum has swung the other direction—some patients are insisting that we only place bare-metal stents, even if the data strongly suggest that outcomes for that patient would be improved with a DES.

To explain many of the nuances of the offsetting potential risks and benefits of DESs compared to bare-metal stents requires a significant amount of time and commitment on the part of the physician. What is being lost in this debate is the fact that stent thrombosis is only one of the many potential adverse effects of revascularization procedures. The overall results of DES placement, very importantly, must be put into context and perspective with the alternatives. How do patients with coronary artery disease who receive DESs fare overall? How is their quality of life? What is their longevity and overall freedom from MI? How do these outcomes compare to the alternative therapies—bare-metal stents, balloon angioplasty, medical therapy, and bypass graft surgery? I believe that in most cases, when one critically considers the alternatives, DESs still emerge as a remarkably effective therapy that has improved the quality of life for most patients with coronary artery disease who can undergo percutaneous revascularization, without significantly producing harm.

What did you learn from being the principal investigator of a major internationally recognized trial with respect to trial design and coordinating all of the various elements that go into the planning and conduct, and ultimately collection, of the results in such trials?

I have been the principal investigator of more than 20 trials. With each study, the honor of being allowed to sit in that role is that it allows one to glean incredible insights into trial design and regulatory requirements, trial performance, nuances of power analysis, statistical design, statistical analysis and interpretation, and publication—basically every aspect of the clinical trial process. Through the 2 decades that I have been functioning in this role, with each study that I have been involved, my level of sophistication and knowledge as a clinical trialist has advanced, which has permitted me to help design and monitor the performance of optimal clinical investigations that, at study end, have a high likelihood to reveal reality, which to prove beyond any doubt would require randomization of an infinite number of patients, which is of course not possible. Therefore, we choose a finite, logistically manageable number of patients, but hopefully design the trial with adequate rigor, sufficient quality control measures, and a large enough sample size (based on predefined power analysis) such that a high likelihood of the trial reflecting the truth is present.

Which areas in coronary artery disease need the most attention from physicians and industry in the next several years?

There are several areas that require further investigation. Coronary artery disease can be categorized as symptomatic or asymptomatic disease. Symptomatic disease can then be subdivided into stable coronary artery disease and acute coronary syndromes. Acute coronary syndromes—acute MI and unstable angina—still represent a high-risk group of patients with high rates of death and MI. With regard to acute MI, we are running the ongoing HORIZONS pivotal trial, which is actively investigating the optimal pharmacologic and stent-based therapy (DES vs bare-metal stents) in 3,600 patients undergoing primary angioplasty to improve the acute and late outcomes of these patients. This trial will determine whether the direct thrombin inhibitor bivalirudin and DESs are safe and effective in this patient population. There are other challenges in acute MI patients, however, in terms of achieving rapid and effective reperfusion, while at the same time salvaging as much myocardium as possible. Unfortunately,

the duration from symptom onset to hospital arrival and, at times, to reperfusion therapy is often prolonged to the extent that we do not salvage as much myocardium as desirable. Novel approaches toward salvaging more myocardium, prolonging the effect of time to reperfusion, and improving the rapidity of reperfusion are required, as well as post-MI therapies such as cell therapy or genetic approaches to improve the prognosis in patients who sustain large infarcts.

For patients with stable coronary artery disease, we clearly need safer and more effective DESs. We need stents that altogether eliminate thrombosis at all time periods, let alone late stent thrombosis. In my estimation, any stent thrombosis is unacceptable. We also need stents that have truly inert polymers or no polymers, that do not fracture, and that do not result in late acquired malapposition. There are still multiple ways, some subtle and some not so subtle, that these devices can be improved. Restenosis still occurs with DESs, and I believe that we can have more effective and safer bioactive devices by using combinations of drugs, improved polymers, biodegradable polymers, and potentially completely bioabsorbable stents.

Asymptomatic as well as symptomatic patients are likely to have so-called vulnerable plaques—that is, a type of underlying atherosclerosis in a setting of systemic inflammation in which plaques may rupture and lead to coronary syndromes, acute MI, and/or sudden death. The goal of prophylactically identifying patients with vulnerable plaques (vulnerable patients), and then applying either local or regional invasive cardiac interventions, or systemic therapies to stabilize vulnerable plaque, is truly the holy grail if long-term survival free from infarction and heart failure is to be achieved. By treating ruptured plaques, whether in patients with acute MI or unstable angina, angioplasty has been shown to improve survival compared to alternative therapies. But for stable coronary artery disease, we are primarily treating symptoms and improving quality of life. To improve longevity further and reduce the future risk of MI and plaque rupture, we need to be able to identify and stabilize the vulnerable plaque.

Can you tell us about your practice and what you have established at Columbia University?

We are very fortunate to be at Columbia University Medical Center, which is one of the largest and most sophisticated medical institutions in the country, if not the world. We have established at Columbia New York-Presbyterian Hospital the Center for Interventional Vascular Therapy that is aligned with the Cardiovascular Research Foundation, which is a public charity in New York City. We have more than 20 physicians in the Center for Interventional Vascular Therapy, in which we are able to comprehensively manage essentially all complex and high-risk areas of interventional cardiology and endovascular intervention.

Our goal has been to try to recruit the leaders in the field for each specific subspecialty of interventional cardiology and endovascular intervention. For example, we were able to recruit William Gray, MD, from Seattle, who is responsible for carotid stent approval in the US, as the Director of Endovascular Intervention. Robert Sommer, MD, is one of the leading practitioners treating adults with congenital heart disease. Within the Center for Interventional Vascular Therapy, led by Jeffrey Moses, MD, one of the pre-eminent interventional cardiologists and technical operators in the world, Martin Leon, MD, who is the founder of the Cardiovascular Research Foundation and has been involved in almost every seminal new device introduced in interventional cardiology since the balloon, along with many other physicians, including Roxana Mehran, MD, George Dangas, MD, Gary Mintz, MD, and Alexander Lansky, MD, we have been able to put together an all-star cast to allow us to thoroughly engage the myriad challenges that arise in patients with coronary, endovascular, and structural cardiac disorders.

What is the main difference between how coronary artery disease is treated now versus when you entered medicine, and what changes will be observed by fellows entering the field today versus the same time frame in the future?

When I entered medicine, the era of balloon angioplasty had just recently begun. Most patients with coronary artery disease were treated medically; most patients with severe disease (eg, left main or triple vessel disease) were treated surgically. During the last 20 years, explosive advances in technology and technique, and advances in adjunct pharmacology have markedly improved the prognosis for patients with stable and unstable coronary artery disease, treated medically with interventional cardiovascular procedures or with surgery. Surgical techniques and surgical outcomes have improved for coronary and valvular disease, as well as for thoracic and abdominal aortic disease.

Interventional cardiology has gone through several transforming revolutions, first with the introduction of balloon angioplasty in the late '70s, then the coronary stent, and now finally the DES. Medical therapies also have markedly improved. First of all, standard medical therapies for any patients with atherosclerosis, not only the recognition of the importance of aspirin but also statins, ACE inhibitors, angiotensin receptor blockers, beta blockers, and the enhanced role of drugs, such as spirono-

lactone, have improved. Defibrillators and resynchronization pacing have improved the quality of life and survival for patients with heart failure and left ventricular dysfunction. Equally important has been recognition of the significance of adjunct pharmacology in patients undergoing percutaneous coronary interventions.

The interventional cardiologist now essentially has to be a hematologist to be able to understand the complexities of antiplatelet and antithrombin agents and the nuances of their use in order to provide the best possible care to patients; first with aspirin, then thienopyridines, glycoprotein IIb/IIIa inhibitors, direct thrombin inhibitors, and multiple types of heparins, both unfractionated and low-molecular-weight heparin, and factor X inhibitors. The list goes on, and new classes of drugs are being introduced every few years.

Outcomes continue to improve. We have now entered an era of biomolecular medicine that is markedly affecting how we deliver patient care, from which there is no return. DESs represent the perfect combination of the discoveries realized from molecular cardiology and biotechnology interfacing with simple interventional cardiology. The companies that manufacture DESs are becoming biotech companies, and in some respects they are becoming pharma companies with extensive expertise, for example, in polymer chemistry. They have all hired numerous polymer specialists to understand drug release control mechanisms for DESs to be able to effectively tailor drug dose when added to DESs and delivered site-specifically in the coronary tree. This trend will only grow, and the sophistication will continue to increase.

We will also be entering an era of personalized medicine. I believe that during the next 10 years, our ability to prognosticate patient risk on the basis of their underlying genome or RNA expression will be markedly enhanced. As a result, instead of being frightened by genetic testing, most patients will elect to undergo genetic screening, and patients will be treated differentially based on their underlying genetic risk profile. It is a very exciting time to be practicing medicine and research in our specialty. The vision of bench-to-bedside translational medicine is being realized at a breakthrough pace. Innovative concepts, the emergence of new devices, and the integration of scientists previously isolated in different fields is leading to more complex and sophisticated implantable devices and will transform the delivery of medical care as we know it today.

What can we expect from TCT 2007?

TCT 2007 will build on the success of past years and attempt to present the state of the art in coronary and endovascular intervention, as well as structural heart disease diagnosis and therapies, as it is practiced today, and how it will be practiced tomorrow. We expect to have the largest attendance in our history, with the most broad-based faculty, impactful late-breaking trials, an unparalleled depth of peer-reviewed abstract presentations with original clinical science presented at the meeting for the first time in the world, and more than 30 live case sites with over 100 live cases presented. There will be new seminars, new ways of approaching patients, and new learning vehicles introduced, all emphasizing an evidence-based medicine approach to patient care decisions. I invite you to attend TCT in October 2007 for what we expect to be a memorable experience that will immediately lead to improved outcomes for your patients. ■