Preventing Restenosis with Stent Drug Coatings

Uncertainties with Drug-Eluting Stents

Percutaneous coronary revascularization is a worldwide accepted technique as part of the treatment of coronary artery disease. Despite the use of stents, restenosis continues to be the major limitation of this modality, that ranges from 30–50%, depending on the patients and lesion characteristics. Recently, drug-eluting stents appeared in the field as one of the most promising tools in order to decrease and perhaps abolish the restenosis process. The recently reported results of the RAVEL trial show an astonishing 0% restenosis rate in the drug-eluting stent group. Even though the results are very impressive, new technologies have to be taken with some precautions before they are used abroad. During this brief summary, I would like to point out some uncertainties and concerns with the use of drug-eluting stents, which will be most likely answered over the time with the results of the ongoing trials.

The first issue that has to be addressed is the choice of the right agent or right drug. On this issue, it is important to understand the mechanism of action of the agent to be used. The intensive research on the field of vascular injury carried out in the last decade provides a significant background for the understanding of the mechanism of restenosis. Several questions could be raised regarding the right agent, but it appears that agents inhibiting the proliferation of the smooth muscle cell will be a good candidate. Once the agent is chosen, the doses of the drug to be used is also an important point. It is well known from animal work that lower doses may not be effective, whereas high doses may be deleterious with an increase of complications such as acute or subacute occlusions. Another important item regarding the drug selected is the timing in which this drug will be given. Based on experimental work, it seems that the drugs should be present and effective for at least 2–3 weeks from the moment of angioplasty. Toxicity is always an issue regarding the drug, not only based on the doses, but also on the mechanism of action. This is an important item, because toxic effect on the vessel wall can cause significant problems. The last point regarding the agent is the process of avoiding the reendothelization. Endothelial regrowth is highly considerable, as it decreases the proliferation process as well as diminishes the likelihood of thrombosis. It is important to take into consideration which agent to select at the time to choose the right drug, since many of the agents that will inhibit proliferation of the smooth muscle cell will also inhibit proliferation of endothelial cells.

The second issue to be taken into account is the necessity of a drug carrier. The need for a long period of treatment over several days requires a system that will allow the drug to be released at certain doses and over certain time. Several systems have been developed generally using different types of polymers that will incorporate the agent and will allow it to be released over time. It is considerable to point out that the biocompatibility of the polymer is important, since several polymers or their degradation products might produce injury to the vessel wall favoring the development of different types of complications. In addition, the polymeric material has to be stable to the different processes an angioplasty has, such as sterilization, stability over time, persistence on the stent after its manipulation and deployment, and compatibility with the drug chosen.

The stent design is another issue to be considered. It is important to mention that after the stent is deployed, an uneven opening of the strut will produce a significant difference in the concentration of the drug in contact with the vessel wall. Besides, when more than 1 stent is needed, the overlapping regions may produce different concentrations of the agent as well, which may have implications in the results. The stent should also maintain many of the properties of the regular stent, like scaffolding, visibility, and strength to be clinically indicated.

Finally, patients’ characteristics have to be included in this game, since the initial studies only comprise very selective types of patients, and the use of these new devices as a probe has to be tested. For instance, patients with diabetes, patients with restenotic lesions, lesions in small vessels, long lesions, diffuse disease, chronic total occlusions, saphenous vein graft lesions, and their use in the setting of acute coronary lesions are all questions that need to be answered before the very exciting results of the initial evaluation of the drug-eluting stents could be applied to a large population of patients.

Jorge Belardi, MD

Moderator: Kirk Garratt
Panel Members: Tim Fischell; Chris Cates; Philip Walker; Roberto Falotico

Chris Cates: I guess I will act as devil’s advocate here. Obviously, there have been few technologies that truly have the potential to profoundly change the way we practice medicine, particularly in interventional cardiology. This technology has the potential to do that, but I would qualify it by saying that in biology, I don’t think there is anything that is a true zero. I am rather skeptical, therefore, of the initial hype over the RAVEL data — I wonder if we will see some developments later on that change things. In addition, I am not sure that all potentially toxic drugs are the same or that all methods of adherence to the stent are the same. Therefore, I think there may be confusion once some of these products come on the market. Perhaps the good products will be affected by the bad ones; maybe we won’t be smart enough to discern the differences between them and will lump the good and the bad together. Certainly, with zero as the initial par, there is only one way to go.

My real concern is what this will do to the business of medicine. In fact, the American College of Cardiology feels that this is such an important issue that they plan to cover the topic at one of the upcoming meetings. Rick Kuntz will put together some
economic modeling on exactly what the impact this type of technology will have on the practice of medicine, including tertiary care referrals. In the hands of the physicians who perform 20 angioplasties a year, many patients with a stent who show zero restenosis, zero late loss, and thus zero impact, in terms of risk, will suddenly be referred to centers that do more procedures. In addition, we have discussed this extensively with the managed care people who are very concerned about this technology and its financial impact. As you pointed out, if we are slamming 3,000 stents in like they’re water, there will be a significant financial impact. There is a lot more to this issue than just the science; I think we need to “stay tuned.”

Tim Fischell: Chris has raised a number of good points. Drug-eluting stents are still new and we need to see a lot more data on them. It is fair to say that zeros probably don’t exist in medicine, partly because the operators are not perfect. Thus, there will be dissections, injury zones outside the stent (i.e., geographic miss), and so forth. Unless the operators are very careful, I suspect that we will see some restenosis outside the stent margins, where there is balloon injury but little or no drug. We have followed up on approximately 21 drug-eluting stent patients at our hospital for the past 8 months, and there is virtually no trace of neointima in the stents at 9-month follow-up. There is essentially no edge restenosis either. Having worked with radioactive stents and knowing there is substantial trauma at the edges of stents, the observation of no-edge restenosis with drug-eluting stents was a surprise for me. It must mean that these drugs are eluting, at least a short distance, into the tissue surrounding the end struts and inhibiting neointima and negative remodeling just outside the stents. I also believe that it will be very important to see the late follow-ups. Six months, or even eight to nine months may not be an adequate follow-up time frame for these stents, particularly those with drugs that are perhaps more cytotoxic and act more like radiation. In these cases, it will be crucial to see the results of 9-, 12-, and 24-month follow-ups to determine if there is further late-loss. In the clinical trials, the angiographic follow-up studies are quite revealing. Although the trials are "blinded," it is usually pretty evident regarding whether the patient received a bare or drug-eluting stent. The follow-ups are striking. The drug-eluting stents are going to allow us to do a lot of things that we have been shying away from out of fear of restenosis. Furthermore, I predict that drug-eluting stents will reduce bypass surgery rates by about 30–35% in the first year or two. As the devices improve, we may actually be able to reduce bypass rates even further with chronic total occlusion treatments, etc. I think drug-eluting stents have the potential to profoundly alter the practice of interventional cardiology.

Robert Falotico: I do think mechanism of action is important. You want a drug that will be safe for the vessel wall since the concentration of drug that is actually in contact with the tissue around the stent is quite high when it elutes from the stent. Drugs that have safer mechanisms will ultimately have better long-term effects. Safety is paramount, of course, because restenosis is not a life-threatening process. A drug delivery matrix that provides control of the release of drug release is important, as is the ability for the operator to deliver the stent to the site without the drug dissolving or flaking off from the stent. Thrombo-resistance of the coating is a feature that is not highlighted often enough. Some polymer coatings offer a degree of thrombo-resistance in their own right, which partly contributes to the low SAT rates that we observe. Nevertheless, the medical community needs to see the long-term data which are currently being compiled. We are all committed to providing long-term data on drug-eluting stents, but for now, we have 2-year data from our PILOT trial, which we hope to present at the next ACC meeting. Also, one-year data are now available from the RAVEL trial and the > 90% event-free survival reported at 7 months continues to hold up. In the U.S., we are collecting 8-month angiographic follow-up data from the patients in the SIRIUS trial. Thus, there is solid commitment to provide randomized trial data that should thoroughly evaluate the effectiveness of drug-eluting stents. I do believe that these stents will transform patient care in the coming years.

Philip Walker: As a peripheral vascular surgeon, it is fascinating to watch this coming down the pike, particularly when you think back to Andreas Gruntzig when he began work on the femoro-popliteal segment. Yet all these years later, we are still trying to find a device that will work for the long-term. I believe these options in therapy also have the potential to change the management of peripheral vascular disease significantly. Rather than treating claudicants conservatively with exercise programs or wasting our time with stents in the SFA, we would be far more comfortable intervening on them. Balloon angioplasty has been performed in cases of short lesions. The data coming from the coronaries are fascinating. From the peripheral vascular surgeon’s point of view, we have come to understand that every vessel in the body is somewhat different, and although much of the work presented here involves the coronaries, we know that the aorta behaves differently than the common iliac, the external iliac, and the femoro-popliteal segment. With the amount of movement those particular peripheral vessels undergo, stent deflation and fatigue of the stents over time become quite important. Although we may have the agent, there are still some concerns — certainly in the periphery — about stent design and durability. Perhaps we need biodegradable stents that won’t be subject to those external deflation forces. I would be interested to hear what other panel members have to say about these issues.

Chris Cates: I agree that this technology in the periphery, particularly in the SFA, will have a major impact on treatment. I hope the material will be put on self-expanding nitinol stents, a development which I suspect is already in the pipeline. Obviously, there will be a need for different dosing, based on your point about differences between vessels — renal being different from SFAs which are different from the iliacs — both in tissue burden, propensity to restenosis and problems of wall necrosis if the drug is highly toxic in a very thin wall.

Philip Walker: I am not sure that nitinol will necessarily be the answer. Actually, John Anderson, who is here today, has a lot of experience in the periphery. He has some excellent data showing the changes in position in the deformation in those arteries. Perhaps he can comment on nitinol stents in that regard. Certainly, stents alone — any type of stent really — have been a failure in the SFA thus far.
John Anderson: Since you’ve put me on the spot, I will comment on this issue! You are all probably aware that a trial is currently underway in the periphery to evaluate the role of drug-eluting stents in the femoral artery. The drug is rapamycin and the carrier is the SMART® Stent (Cordis Corporation). As Philip has alluded to, the femoral artery does not behave like other arteries. In a simplistic sense, you can divide the artery into 3 regions: the adductor canal, the adductor hiatus and the popliteal. In terms of dynamic movement, each such segment behaves quite from each of the other regions. Also, you must also factor in the presence of the 2 joints that are associated with this vessel; the hip and knee joints. Flexion of those joints can cause significant and radical changes to vessel anatomy that may lead to a high rate of stent strut fracture and deformation. Some, but not all stent fractures are associated with adverse clinical events. More commonly, you may observe in-stent stenosis or occlusion associated with fracture; uncommonly, you may see more serious events such as false aneurysm or arterial rupture. Drug-eluting stents do not show a higher rate of strut fracture or adverse events when compared with non-drug-coated stents. There does not appear to be an effect where this drug actually delays healing to a degree that it may increase the incidence of strut fracture and associated adverse outcome. I have been looking at this problem for several years and have observed that in many cases that nitinol may not be the perfect material for the femoral artery. In fact, nitinol has the highest rate of strut fracture of all the materials used in the femoral artery.

Chris Cates: Do you think that has more to do with the design of the nitinol stent? Tom Fogarty is working on a new torsion design specifically for the SFA. I wonder if that type of nitinol stent would be a better one, in your opinion, than just the mesh stent presently in use.

John Anderson: Stent design does make a significant difference. There are stents that use spiral configurations, some of which are covered with PTFE, such as the S-Fire® stent; at this point, it is unclear that such a design may make a difference. To take the point a little further, companies such as Bard and Cordis have taken the same identical tube stock subject it to different heat treatments and differences in design to produce their respective stents. If you put these stents in a test rig whose purpose is to test durability in relation to moderate elongation and flexion — bear in mind that the basic stent material starts off identical in both cases — by the time that 300,000 cycles have been completed, every Memotherm® stent is fractured. In the same rig, the SMART® testing was stopped at 1,000,000 cycles without evidence of strut fracture. Since both stents start from the same base stock, this would indicate that both stent design and materials treatment make significant differences. Fracture results from stress and strain applied to the nitinol, such forces resulting from the dynamic anatomy of the femoral popliteal arteries during joint flexion and extension.

Jim Zidar: Do you think the fracture makes any difference?

John Anderson: Some fractures do make a difference and some do not. There are incidents where stents fracturing within 6 months have lead to false aneurysm formation. The exact incidence of fracture in the past has been difficult to determine because we did not specifically look for this problem. Following treatment we have tended to follow-up patients with duplex ultrasound, which does not show stent structural integrity. In those patients with recurrent lesions and symptoms, the repeat intervention was most frequently the time when the fracture was noted. Since that time, plain radiographs have been used to assess stent integrity. All I can say is that some fractures are associated with restenosis — presumably an intimal injury — and some are not. Thus, fracture is not necessarily associated with an adverse event, but I can’t tell you that if a stent fractures, there will be no adverse event. In fact, in some cases, there are significant adverse events.

Tim Fischell: I have a question for Gary Roubin regarding carotid stenting. In our small series, we have observed a couple of instances of restenosis. Of course, restenosis in the carotid is really not a pleasant occurrence. Do you think drug-eluting stents, presumably on a self-expanding platform, will become the standard treatment for carotid disease? Is there a need for drug-eluting stents in the carotid artery, given the relatively low rate of restenosis? Will drug-eluting stents, along with distal protection devices, become the standard of care in treating carotid artery disease?

Gary Roubin: That’s a very interesting question. In fact, restenosis in the carotid bifurcation is an even more benign event than in the coronary arteries. If you think about the pathophysiology of carotid disease, it’s the embolic and plaque rupture issues we are concerned about. As with endarterectomy, restenosis is usually benign. Even if we see significant intimal hyperplasia within the stents on angiography or duplex studies, we are usually able to reassure the patients that it is not of concern. On the other hand, it would be ideal to restudy the patients who demonstrate very low intimal hyperplasia results at a later time. The late outcomes — eight-year data now — have been incredibly good, with the Wallstent initially and with the shorter nitinol stents later. John has seen at least ten fractures in nitinol carotid stents. Since the late outcome data have been so encouraging, I would hate to replace what seems to be a good device with something that perhaps does not have sufficient endothelial growth and leaves the patient open to platelet aggregation and thrombotic events, which could be much more devastating. In the long-term, I think there will be carotid stents coated with drugs to limit intimal hyperplasia and drugs to limit thromboembolic events as well.

Chris Cates: It would not be good to have toxic stuff going to the brain, killing off furo-neurons. We would create a sort of iatrogenic Alzheimer’s.

Gary Roubin: Well, in fact, it’s the embolic debris we all get a little of every day of our lives that is the most toxic. (laughter)

John Anderson: I would like to elaborate on that point. The highest incidence of stent fracture in the femoral artery is seen with multiple stents, so the longer the segment stented — which will be
the attraction with drugs such as rapamycin — the greater the likelihood of fracture. If you place three stents in the proximal superficial femoral artery, which is a common site of disease, it is the middle stent which fractures — not the top or bottom stent. Nearly all the observed fractures occur in the middle stent. Thus, in the carotid arteries, since we use very short stents, we are unlikely to see fractures.

Jorge Belardi: We have done a lot of work with Quanam trials, so our input would be very interesting.

Luis de la Fuente: We started working with the Quanam Drug Delivery stent in 1995 in animal studies. Dr. Belardi outlined a number of problems regarding the different stents, and the type and the toxicity of the drugs.

At the beginning, we used a stent in animals with a polymer for drug delivery; we tested approximately 40 different drugs. We ended up using paclitaxel and later a chemically modified version of it, the 7-Hexanoyltaxol. Paclitaxel is a microtubule inhibitor that inhibits arterial smooth muscle cell proliferation and migration. The drug that is incorporated into the polymer sleeve is 7-Hexanoyltaxol (referred to as QP2) which is highly lipophilic, insoluble in water, and antimitotic, tubulin disassembly inhibitor. The metabolism action and toxicity are similar to paclitaxel, and its esterification at the C-7 position with caproic acid slows the drug release from the polymer, but does not alter its biological activity. In vivo studies with QP2 failed to detect any drug systematically when it was administered locally from the stent in animals, even when loaded with 4,000 ug. Although QP2 is in the polymer sleeves alone, its detection longitudinally between the sleeves and up to 10 mm beyond proximal and distal metal stent margins has been established in the porcine model. The results were excellent in pigs and rabbits, in a project that spanned several years. We observed in animals that 7-Hexanoyltaxol can last up to 6 months when delivered in the appropriate amount. While 7-Hexanoyltaxol concentration decreases in the stent, it increases in the tissue. We also thought there was a need for a polymer sleeve that would not cover the total length of the stent in order to avoid endothelial problems later on. I think it is very important, not only the drug, but how you deliver the drug and for how long, in order to avoid restenosis.

In November 1998, in Buenos Aires, we implanted the Quanam bare metal stent in 4 patients; we proved that the stent had a good radial force and behaved like any other good stent in the market. In the first week of February 1999, we began our trial in humans in Buenos Aires with the Quanam Drug Delivery stent. The trial, comprised of 38 patients with 40 DDS-QP2, and lasted over 2 years and was stopped in May 2001. Our trial was a registry because we did not want to be included in the future randomized study; we told Quanam that in order for this stent to be useful, it had to be implanted in all types of pathologies, like those seen daily in the cath lab. Quanam told us that we might want to destroy the project, but we said that the FDA in Argentina approved the registry for the real world, except for left main trunk and major sidebranches. However, it is very important to predilate the lesion before the DDS-QP2 implant to avoid the polymer damage. The stent should not be undersized; we recommend the use of high-pressure deployment 14-16 Bar to avoid malposition of the stent with the subsequent subacute or late thrombosis. We have not had either subacute or acute thrombosis.

Jim Zidar: Raoul, before you show that — and before we get off the topic — I want to ask the panel about the potency of these drugs and the potential for stent malapposition over time. There has been a lot of discussion about the RAVEL data and whether the distal end of the stent is malpositioned — not truly fully deployed at the time because it was not IVUS-guided — or whether it is truly a positive remodeling, as the drug elutes off the stent over time. Will this be a problem with paclitaxel? Is it rapamycin? Does it have to do with improperly deployed stents? There hasn’t been any discussion about that yet. Before we move on to restenosis, I would like to discuss the opposite side of the spectrum where the drug may be so potent that remodeling occurs.

Robert Falotico: We placed Sirolimus stents in approximately 18 patients at our institution and have nearly completed the 8-month angiographic and IVUS follow-ups. We participated in the IVUS sub-study, so almost all of our stents were IVUS-guided. I have a couple of slides summarizing this incomplete apposition issue that has received considerable attention. I want to show a couple of the IVUS images. We have now followed up on 21 of these stents and have not seen one strut incompletely apposed, nor have we seen any aneurysms or expansion. All of the stents look similar to the LAD case we performed: the post-procedure, the 8 and 18-month follow-up and the IVUS image. The entire stent looked like that: the struts are clearly touching. When you IVUS-guide the stent going in, you don’t have struts that are not touching coming out. All of the incomplete apposition cases were due to stent undersizing in Europe, and I have some data to support that opinion. Regarding the IVUS image, I don’t know if this stent is drug-coated, but it so quickly "unblinds" itself that we are 99% convinced these “B” stents were the drug-coated ones. We don’t know for certain if “A” is the drug-coated stent or if “B” is, but I can tell you that after following up on a number of these, it is very obvious which is which. This is another 8 1/2-month follow-up in 36 mm worth of stent in the SIRIUS trial. Regarding the IVUS image, the struts are all touching the wall. Absolutely no signs of remodeling or black holes are observed. We did not see anything on the distal end of the stent or on the edges. In fact, the edges are the only place where we see the slightest sliver of tissue — and only occasionally. This incomplete apposition is due to undersized stent implants in Europe where they used 12 mm mean pressure for the Bx velocities, 5.5 thousandths wall thickness stents — a very strong stent. You need at least 15-18 atm to deploy these stents. How do I know they were undersized? The mean diameter stenosis after implant was 13%. Jim, you know as well as anyone that in the US trial, even without IVUS guidance, we had a 1.8% stenosis in the VENUS trial in most of the cases using the...
This indicates that they were not placing these stents very well in Europe. It probably led to a couple of struts not exactly touching the wall in a couple of the cases. Incomplete apposition, in Patrick Serruy’s definition, included any case with even one strut anywhere in the stent that was not touching the wall — this even included cases where there was a strut over a septal perforator. This is an incredibly liberal definition. It is probably fair to say that the control group and the Sirolimus group in RAVEL were both undersized — but at 6 months, the control group had neointima, and it filled in the gaps. In the Sirolimus group, there was virtually no neointima; the gap that was there when the stent was placed was still there at 6 months. That is why you see it more at 6 months; there was no IVUS guidance. Patients received only 2 months of Plavix in the RAVEL cases. Stent thrombosis was zero, which is very different than a brachytherapy model. If you think this is like brachytherapy and these stents are pulling away, the wall is pulling away, and the struts aren’t endothelialized, then at between 2 and 6 months with no Plavix, you would expect to see about 15 stent thromboses. However, we did not see any, so it is not like brachytherapy at all. This means that just like in the porcine model, where the endothelial cell regrowth with Sirolimus was identical to a bare stent, there must be endothelial cells on the struts, even if they are not touching the wall in 1 or 2 places. Otherwise, we would have seen stent thromboses. This incomplete apposition is not a factor. We are seeing no incomplete apposition when the stents are IVUS-guided and appropriately sized. The RAVEL data, in the control group and in the Sirolimus group, showed there was no difference in EEL measurements. There was absolutely no sign of positive remodeling in RAVEL; so what is the problem? Peter Fitzgerald has reviewed all the IVUS images and believes that the hype about incomplete apposition is unfounded.

Jim Zidar: Will the sites that don’t perform IVUS be able to show these results? How many sites performed IVUS in the SIRIUS trial?

Robert Falotico: How many of the 1,100 patients?

Tim Fischell: I don’t know, Robert. There is a sizable IVUS sub-study, but I don’t have the exact number.

Jim Zidar: Tim, do you think it will be acceptable to go to 15–16 atm without using IVUS, or will there be a mandate to use IVUS for correct sizing?

Tim Fischell: This stent is so strong that you want to get very close to a 0% angiographic visual estimate, like in the US VENUS study. If there is a 15–16% residual stenosis, then you have undersized it. That type of result with a bare stent should be post-dilated. However, despite what appears to be a modest undersizing of the stents in the RAVEL trial, resulting in a few struts that were not opposed at the time of stent implantation, there were actually no clinical events related to this “incomplete apposition”. So, if there is no restenosis or stent thrombosis with one-hundred and twenty 2.4 mm diameter stents at one year in the RAVEL study, then what is all the hype about?

Gary Roubin: Have there been any late deaths in RAVEL patients?

Robert Falotico: There have been no deaths. The event rate at 1 year in the drug-treated group remains, I believe, at 94% event-free survival. The 1-year data look excellent.

Jeff Werner: Is there any reason to believe that Sirolimus or any of the other drugs are cell-specific? I want to know what happens with brachytherapy, for example, if that thrombosis begins later on because they weren’t endothelializing, which Tim just alluded to. Is there any reason to think that Sirolimus, or other drugs, specifically attack these muscle cells, but not endothelial cells, such that you can expect endothelialization without intense proliferation? Also, is that an important mechanism by which we might not expect late subacute thrombosis?

Robert Falotico: I believe that Sirolimus is cell-specific. There may be other drugs that have this property, but we are seeing a very unusual phenomenon in vivo in which endothelialization is taking place during the elution phase of the drug. This is clear in all of the animal studies; in humans, it translates into no subacute or chronic SATs. There does seem to be some specificity and we are continuing to explore why that is the case. There will be, I believe, a common thread to the drugs that work in treating this problem. Companies are embarking on programs that look at migration, inflammation, and thrombosis. I believe that you have to target smooth muscle cells. I think that is why radiation works and why, in part, Sirolimus works.