

Bifurcation Stenting: The Next Generation

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Summary: The proper course of action for treating lesions at bifurcations remains controversial. In the face of numerous small studies with conflicting results and in the absence of large-scale studies investigating whether—or how—to stent the side branch of a bifurcation, cardiologists are searching for solutions. It's all very confusing, but one thing is becoming increasingly clear. Drug-eluting stents, which work so well in straight segments of vessels, aren't working in bifurcated vessels because bifurcations are distinct segments of anatomy, with particular shapes and unique flow characteristics. Start-ups have picked up on the fact that there is a \$1 billion interventional cardiology market just waiting to be served with the right technology, and almost a dozen young companies have crowded into the field.

Further Analysis:	Title	Magazine	Issue	Article ID
	At TCT, DES Use and Safety Concerns: Irrational Exuberance or Irrational Anxiety?	<i>IN VIVO</i>	Nov. 2006	<u>2006800200</u>
	Stents Branch Out and Return to Their Start-Up Roots	<i>IN VIVO</i>	Dec. 2002	<u>2002800270</u>

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Bifurcation Stenting: The Next Generation

The cardiology community clamors for tools to treat its most difficult patients—the 20% of stent patients that have lesions in bifurcations. Now that it's clear that today's drug-eluting stents won't be the panacea, young companies are innovating to fill the gap.

By Mary Stuart

In interventional cardiology, it's almost axiomatic that as new technology begins to successfully address one problem, it creates a new one. Not so long ago, it seemed that drug-eluting stents (DES), in preventing the restenosis caused by bare-metal stents, would be able to solve most of the major problems in coronary artery disease. That major market opportunity—\$5.4 billion in 2006, based on the devices of just two manufacturers, **Johnson & Johnson** and **Boston Scientific Corp.**—has been occupying much of the attention of the big cardiology companies, and it will continue to do so, as the clinical community and the competitive landscape shift from a focus on efficacy to safety. Recently, the issue of late stent thrombosis—thrombosis that occurs more than 12 months after stent implantation, has been dominating much of the talk about drug-eluting stents.

The potential for late stent thrombosis in DES patients was identified several years ago, but a growing number of trials and registries based on four years of experience are starting to reveal that drug-eluting stents are associated with a statistically significant increase in mortality, casting a cloud of caution over the field.

Although the reported rates of sub-acute and late thrombosis are low—less than half a percent, according to various studies, that level of risk was enough to cause the Circulatory Systems Devices Advisory Panel of the FDA to convene in early December for a drug-eluting stent safety hearing. After two days of presentations, the panel cautioned against the off-label use of DES, which it viewed as presenting a greater risk of stent thrombosis, myocardial infarction, and death.

The panel identified at least two specific cases in which off-label DES use seemed especially likely to increase the risk of stent thrombosis: stents in arterial bifurcations and situations requiring overlapping stents. The panel's conclusion served as just one more reminder that existing drug-eluting stents won't serve all patients. It's a reminder that won't go unnoticed by a group of start-ups developing stents that can be used on a large population that continues to frustrate interventional cardiologists: people with lesions occurring at coronary bifurcations.

Bifurcation lesions, that is, stenosis that occurs in the coronary vasculature at the point where a parent vessel meets a side branch that is more than 2 millimeters in diameter, are quite common; they're present in some 20% of patients undergoing percutaneous coronary interventions, for a total of 540,000 bifurcation coronary lesions treated each year. These cases have interventional cardiologists pulling their hair out. Stenting branching anatomy is complicated and time-consuming, and outcomes have been poor in terms of procedure failure rates, thrombosis, and restenosis rates as high as 40 to 60% for bare-metal stents according to various studies, and 23 to 26% for drug-eluting stents. (*See Exhibit 1.*)

Exhibit 1

Bifurcation Stenting Restenosis Rates

PUBLICATION	TECHNIQUE/STENT	RESTENOSISRATE
Lefèvre et al, J Am Coll Cardiol 2005;46:592-598	<i>Frontier</i> (Guidant) no drug elution	44.8%
Tannabe et al, Am J Cardiol 2004;91:115-118	Two <i>Cypher</i> (J&J Cordis), various techniques	22.7%
Colombo et al, Circulation 2004;109:1244-1249	1 vs. 2 <i>Cypher</i> , T-stenting	25.7%

SOURCE: Stentys SAS

The proper course of action for treating lesions at bifurcations remains controversial. For several years now, the problem has been often discussed at the major cardiology meetings—TCT, EuroPCR, and the American College of Cardiology—and it has been the focus of at least one new meeting. The European Bifurcation Meeting is becoming an annual event, and its minutes reside at www.bifurc.net, an online community known as the European Bifurcation Club.

Field Remains Controversial

In the face of numerous small studies with conflicting results and in the absence of large-scale studies investigating whether—or how—to stent the side branch of a bifurcation, cardiologists are searching for solutions. Some are stenting the main vessel with a standard bare-metal or drug-eluting stent, and simply dilating the side branch with a balloon. They're scaffolding the various angles between the main vessel and the side branch with combinations of two stents, the stent for the side branch pushed through a hole in the main vessel stent, and positioned or crushed against the other stent in the form of a T, V, or Y. Clinicians are debating the benefits of using one stent versus two; of stenting the side branch first, or not at all; of using dedicated stents with pre-formed shapes that address both sides of the bifurcation; or provisional strategies that stent the main vessel first and leave open the option of adding a side branch stent. The goal of all of these attempts is to strike a balance between not undertreating and not overtreating patients because implanted devices—drug-eluting or not—all bear some risk of undesirable consequences. (See *Exhibit 2*).

Exhibit 2

Techniques of Stent Deployment in Bifurcation Lesions

TREATMENT OPTION	PROCEDURE
Type A	
Includes classic "T" stenting beginning with side branch stenting, modified "T" stenting, and "Crush" technique	Placement of a stent at the side branch ostium followed by placement of another stent in the main branch covering the ostium of the side branch.
Type B	
Includes classic "T" stenting beginning with main branch stenting, and Provisional "T" stenting	Stenting of the main branch followed by stenting of the side branch at the ostium level through the struts of the main branch stent.
Type C	
Includes "Culotte" or "trousers", and "Skirt" technique.	Implantation of a first stent from the proximal to the distal segment of the main branch, jailing the side branch ostium. A second stent is then placed from the proximal main branch towards the side branch while jailing the ostium of the distal main branch. This results in a double layer of stents in the proximal part of the main branch.
Type D	
Includes "Touching stents" completed or not as Y technique, "Trouser legs and seat" technique, a classic "touching stents" technique completed proximally by a "skirt" technique; and "Kissing stents" technique	Placing two stents at the level of the ostia, followed by implantation of another stent in the proximal segment if necessary. Also known as the "Y" technique.

SOURCE: Thierry Lefèvre, Yves Louvard, Marie-Claude Morice, Institut Cardiovasculaire Paris Sud, Massy, France, "Percutaneous coronary intervention for bifurcation coronary disease," *Heart* 2004; 90:713-722

The clinical community is also engaged in an effort to try to understand bifurcation lesions, and various researchers have established systems to classify them, by the distribution of plaque—its presence in one or both branches, or its location as proximal or distal to the ostium (the opening between the two vessels); according to the degree of narrowing of the lumens of vessels; and by the angle of the bifurcation (less than 70%, greater than 70%), in an attempt to sort out treatment options and patient variations.

It's all very confusing, but one thing is becoming increasingly clear. The standard stenting techniques that work so well in straight segments of vessels aren't working in bifurcated vessels because bifurcations are distinct segments of anatomy, with particular shapes and unique flow characteristics. The physiology of bifurcations isn't well understood, so in developing for a large unmet clinical need, several companies are undertaking their own research to elucidate the functioning of these forks in the arterial road, in which flow disturbances lead to atheroma and perhaps also restenosis.

Flow patterns in bifurcations are influenced by wall curvature, and the main vessel and side branch are in an interdependent relationship with one another. When the main vessel remodels in response to plaque, the dynamics change in the side branch and vice versa, which is partly why this isn't as straightforward an application as stenting a straight vessel.

It seems that lack of success in the field is due to the failure of early devices to adequately scaffold the unique shape of the bifurcation, and to preserve the proper flow characteristics of the bifurcation. They've fallen short in other areas as well; many solutions have been difficult to deliver, requiring two guidewires and complex maneuvers to position them accurately at the opening of the side branch. Many of these solutions require compressing large amounts of metal into vessels, and the damage that occurs in the process of trying to align them may also encourage restenosis.

The large cardiology companies in the field have thus been at a disadvantage. They've focused primarily on developing drug-eluting stents for straight vessels, and then applying those stents to bifurcations. But smaller companies that early on recognized the importance of designing for the unique characteristics of bifurcations have a head start in this market.

Advanced Stent Technologies was founded in 1997 to develop the *Petal* stent, a device with a pre-wired side branch port that could be aligned and opened up to provide support at the ostium. The company was in clinical trials in 2004 when Boston Scientific acquired it for \$120 million. [W#200410277] (Boston Scientific has since made design changes to the device, and it recently estimated it would require \$125-\$150 million to complete the development of the *Petal* bifurcation device; it also has estimated, in a recent financial filing, that the device would be commercially available on a worldwide basis by 2010 in a drug-eluting configuration.)

Of the first-generation of new stent companies targeting coronary bifurcations, **Devax Inc.** is the furthest along with its *AXXESS* biolimus-eluting stent, a self-expanding nitinol stent with a conical shape designed for the bifurcation. (See, "*Stents Branch Out and Return to Their Start-Up Roots*," *IN VIVO*, December 2002). [A#2002800270] Devax was the first new company to publish clinical outcomes, the results of its *AXXESS* Plus study, in which it experienced restenosis rates of only 7.9%, and it is now conducting a trial called *DIVERGE*, a 600-patient study at 40 centers in the US, Europe, Australia, and New Zealand in support of its US PMA application. *DIVERGE* is the largest single study of bifurcation lesions conducted to date. The company is on track to commercialize its device in the second half of next year.

These two pioneers have drawn attention to the fact that there is a \$1 billion interventional cardiology market waiting to be served with the right technology, and in recent years, several new companies have crowded into the space: **Minvasys**, **Invatec SRL**, **OrbusNeich**, **Trireme Medical Inc.**, **Tryton Medical Inc.**, **Cappella Inc.**, **Y-Med Inc.**, and the newest, **Stentys SAS**. (See *Exhibit 3*.)

Exhibit 3

Selected Bifurcation Stent Companies

COMPANY (LOCATION)	APPROACH/INVESTORS
Cappella (Auburndale, MA)	<i>Sideguard</i> trumpet shaped self expanding stent can be delivered into the side vessel using same balloon technique that physicians use for stainless steel. /PolyTechnos Venture Partners, ACT Venture Capital, Individual investors.
Devax Inc. (Irvine, CA)	<i>AXXESS</i> biolimus-eluting stent is a conical self-expanding nitinol stent that conforms to the bifurcation anatomy and provides full access to both branches for additional interventional procedures. In clinical trials, will be first drug-eluting bifurcation stent on the market./InterWest Partners, US Venture Partners, Bio-Star Private Equity, International Biomedicine Holdings, Rock Creek Partners, Medfocus Fund.
Invatec (Roncadelle, Italy)	<i>Twin-Rail</i> is premounted on double balloons in its proximal position and only on the main vessel balloon in its distal portion. Proper opening of the stent cell facing the side branch is achieved by the side branch balloon, avoiding jailing. Also <i>Avion Bifurcation RX2</i> , bifurcation balloon catheter has pushable hypotube which splits distally into two shafts/balloons.
Minvasys (Gennevilliers, France)	<i>Nile</i> platform is single-operator device in which two independent catheters delivering a single stent that conforms to the bifurcation anatomy, are held together. More than 400 patients have been treated to date.
OrbusNeich (Wanchai, Hong Kong)	<i>SUPRA</i> involves one dedicated stent in the main branch—the <i>R Stent</i> , and balloon dilatation, but no stent, in the side branch. The R stent has a modular structure with the center zone consisting of a continuous dual helix lattice. This configuration provides omni-directional flexibility and extremely high radial strength. The cells in this region can be expanded to up to 4.5 mm in diameter to enable side branch access for bifurcation stenting.
Stentys (Paris, France)	Self-expanding nitinol stent is deployed in the main vessel. Balloon catheter disconnects mesh at appropriate side branch position, and stent fully expands to cover conical bifurcation anatomy. First product will be drug-eluting stent. In GLP animal studies. /Sofinnova, Individual Investors.
Tirreme Medical (Pleasanton, CA)	Betting on provisional stenting with <i>TMI Ariste</i> stent, main branch stent is small and flexible, and has elements that protrude into the side branch and cover the ostium. The side vessel may or may not be stented at the physician's option. First-in-Man studies are ongoing in Europe./Individual investors, Yellowstone Capital.
Tryton Medical (Newton, MA)	<i>Side-Branch Stent</i> is balloon-expandable system that tracks over a single wire and can be used in conjunction with any existing standard coronary stent for the main vessel. Has completed more than 20 clinical cases./Spray Venture Partners.
Y-MED Inc. (San Diego, CA)	<i>sideKick</i> is a lower profile, 6F guide compatible stent delivery system that integrates a rapid exchange steerable guidewire with a fixed-wire platform. Designed to preserve side branch access during bifurcation stenting. First-In-Man study is ongoing at three centers, including the Heart Center in Siegburg, led by Eberhard Grube.

SOURCE: Windhover's Strategic Intelligence Database

The approaches of the new companies basically fall into four categories: pre-formed stents with side ports (Tirreme Medical, Invatec); Y shapes (OrbusNeich); conical stents for the geometry of the ostium (Devax, Minvasys, Stentys); stents designed specifically for treating the side branch first (Cappella, Tryton); and delivery systems (Y-Med Inc.)

Many of these companies are founded by interventional cardiologists to apply what the industry has learned about bifurcation stenting so far: that the delivery technology needs to be simpler and faster, it needs to preserve the physician's option to use either one or two stents during the procedure, and it needs to be adapted to fit the unique anatomy of a bifurcation like a glove. In particular, the founders of Stentys, who were behind first-generation company Devax, insist on this last point.

Not Totally Tubular (Anatomically correct Stents)

On the Web site for the aforementioned bifurcation society, Marie–Claude Morice, MD, an eminent cardiologist at the Institut Cardiovasculaire Paris Sud, says, "The **coronary arteries** are like tree trunks in that their sole purpose is to produce branches: it would, therefore, be preposterous to treat a trunk without taking into account its branches." Jacques Séguin, MD, PhD, founder of Devax, and now of second–generation bifurcation company Stentys, would definitely agree. His experience as a heart surgeon led him to believe that a bifurcation is not just a main vessel with a less important side branch jutting out; the bifurcation is an integrated system that exists to optimally carry flow. "The vasculature progressively branches as it goes down to enhance vascularization of the body," he says. A bifurcation has a particular shape, and it is not, unlike straight segments of vessels, cylindrical. "The main vessel progressively enlarges itself in diameter and then gives rise to two vessels in a V shape. The T shape does not exist," he says. "That is an invention of the cardiologists. It is not a tube out of which another tube comes out."

Bearing that in mind, Séguin says, rather than creating a tube that has a hole in it, or in which a hole can be created to access the side branch, as other new stent developers have done, for Devax he created a self–expanding stent in a truncated cone shape to be placed immediately before the point where the branches arise, in the part of the main vessel that progressively expands. The shape of that company's device has probably been responsible for low restenosis rates of less than 8% in clinical trials.

Now, 12 years after the founding of Devax, Séguin hopes to apply what the clinical community has learned to new company Stentys. Although the Devax technology is getting great results, he says, it is fairly difficult to place because it needs to be precisely nested within the bifurcation. Placing it too high or too low at the site of the side branch makes it less effective, Séguin explains. Striving for the efficacy of the Devax stent, but improving on deliverability was Séguin's goal in starting Stentys. CEO Gonzague Issenmann, (who was formerly with the Cordis Corp. stent division of J&J) says, "Our intent is to offer a procedure that is as simple as a workhorse stent in any cath lab in the world."

Stentys is developing a self–expanding nitinol stent made of Z–shaped mesh linked by small connections. The connections can be separated *in situ* with a balloon to allow the proximal part to expand. The Stentys stent is implanted in the main vessel with an approximate positioning. The cardiologist chooses the optimal location for the side–branch opening by inserting a balloon through the stent mesh, and the balloon inflation disconnects the mesh to create the opening to the side branch. "The opening that we can create through the struts can happen anywhere. This is why we have placement tolerance," Issenmann says. "We think we have the best of both worlds. We have the simplicity of a standard stent in terms of delivery and placement, and we also have the potential efficacy—still to be demonstrated—of a Devax stent because of our self–expanding properties and adapting to the conical anatomy of the bifurcation."

Unlike many companies in the field that are validating mechanical concepts in bare–metal stents first, Stentys plans, in its first product iteration, to offer a drug–eluting bifurcation stent. In this day of drug–eluting stents, it doesn't make sense not to, Séguin believes. As the newest company, Stentys lags others in development, but Séguin believes Stentys will catapult ahead as the first second–generation bifurcation company offering a DES. Issenmann notes that if competitors with bare–metal stents get good results, Stentys will probably claim that drug elution will yield results that are even better, but they'll still have to prove it, and that will take time. Furthermore, says Issenmann, large companies only want to acquire small companies that, at the very least, have eliminated product development risk, and ideally that have sales, so it makes sense to get to market with a drug–eluting stent as soon as possible.

Stentys doesn't want to disclose the details of its drug–elution platform yet, but Séguin says it has chosen a polymer and a drug that are both widely accepted and which don't present any regulatory issues.

The company has finalized and frozen its design and is completing GLP animal trials. "It was an achievement to develop a frangible stent that 'splits' when you want it to and not when you don't," Séguin says. The company expects first-in-man studies to begin in the middle of next year.

Stentys, like many of the new companies, sees future markets in stenting other bifurcations in the body, in particular, bifurcations in the left main coronary artery, a stenting application that cardiologists avoid today. The left main separates the circumflex artery and the LAD (left anterior descending) artery, which supply blood to a large portion of the myocardium. Blockages here can quickly lead to fatal infarctions. Having a good bifurcated stent for the left main could grow the overall market by 5 to 8%, Issenmann believes.

Issenmann says the Stentys device does possess the qualities of an ideal bifurcation stent. "You need to have good scaffolding of the entire area, to support the ostium. You need a good opening to the side branch, and you need good release of drug in vessels. Gaps in all of these areas are the cause of most of the restenosis right now. We have tried to address these issues from a technical standpoint, and we hope this will translate into good clinical results," he says.

Funding for Stentys has come from individual investors and venture firm Sofinnova Partners.

Strictly for the Side Branch

At cardiology meetings today, clinicians are asking if it's better to use one stent or two in bifurcations. Small studies that have been done to date aren't likely to provide the definitive answer to the question because they're based on stent technologies designed for straight arterial segments. Aaron Kaplan, MD, an interventional cardiologist at the Dartmouth-Hitchcock Medical Center, and a device entrepreneur who co-founded LocalMed, the innovator of a technology to deliver drug to the arterial wall during angioplasty procedures, and Perclose (now merged into Abbott Laboratories), developer of an arteriotomy closure device, believes that what's needed is a stent specifically designed for the side branch of a bifurcation.

Chief technology office Richard Davis, who was formerly at interventional cardiology company Orbus Medical (now OrbusNeich), believes that provisional stenting—the practice of stenting the main vessel first, and only then opting, or not, to treat the side branch by one method or another—is "like sticking a square peg into a round hole." He says, "Clinicians are using straight stents designed for straight vessels in Y-shaped anatomy with disease. After stenting the straight section, if the physician sees no flow in the side branch of the Y, he or she addresses it with another balloon or a straight stent. This compromises the flow in the main vessel and in the side branch, and everyone is settling for sub-optimal results."

Because of the outstanding success of DES at reducing intimal hyperplasia and restenosis in lesions in straight vessels, it was a normal progression to use them in bifurcation lesions. But there is a mechanical mismatch, Davis says, between straight stents and Y-shaped lesions, and DES haven't improved outcomes here.

"Two years ago, when I started running Tryton, we looked at the landscape. Physicians were screaming for a new solution because they were treating patients with provisional stenting. They placed the straight stent in, looked at the vessel by angiography, and if everything looked fine, they sent patients home. A few months later a patient would present with chest pain because the side branch had shut down."

Kaplan decided to do something different—to create a stent to scaffold the side branch first. He developed the *Tryton Side-Branch Stent*, a low-profile device with an outer diameter of approximately one millimeter that can be deployed with a balloon over a guidewire in a familiar procedure. The *Side-Branch Stent* has three zones—a side-branch zone (that treats disease in the side branch), a transition zone (that should be positioned at the side-branch origin), and a main vessel zone, the latter having three fronds designed to grab onto the main vessel stent.

After the Tryton stent is deployed, the guidewire initially placed in the side-branch is repositioned into the main vessel and any standard workhorse stent can then be deployed. "We treat the side branch first and then our stent couples with the main vessel stent. It has fingers that extend from the stent and grab onto the main vessel stent to create a Y shape," says Davis.

Davis admits that Tryton's approach goes against the conventional wisdom of first stenting the main vessel to maintain flow, but he says Tryton's approach actually matches the way physicians work around the heart. "As you enter the heart, you typically treat the most distal disease, where you require smaller devices, and you work your way back. You require larger devices when you come back proximally. If you treated the larger vessels first, you would be required to pass through those extra stents as you worked your way down the vasculature, and that results in a lot of friction. That's where the idea for the Tryton stent came about. We came up with a stent to treat the side branch definitively, and it doesn't inhibit anything else the physician wants to do."

Davis emphasizes that his company's device fulfills the ease-of-use requirements in other ways as well. "Other devices require millimeter and submillimeter precision to place them correctly," he says, but Tryton, "has a four-millimeter landing zone where you have a bit more room to maneuver. "A credit card is approximately 1 mm in thickness. Most devices require that type of precision for optimal placement. The Tryton device, with its 4-mm transition zone, allows the user to obtain the expected results within a much larger tolerance," he says.

Tryton is in clinical trials at three international cardiology centers, with a prestigious group of investigators that includes Eberhard Grube, MD, of the Heart Center in Siegburg, Germany; Patrick Serruys, MD of the Thoraxcenter, Erasmus, in Rotterdam, the Netherlands; and Marie-Claude Morice, MD of the Institut Cardiovasculaire Paris Sud in Massy, France. Investigators have implanted the *Side-Branch* stent in more than 20 patients with 100% procedural success, Davis claims. It's still early; the company has yet to achieve six-month follow-up.

Tryton has been solely funded by Spray Venture Partners. Davis doesn't want to disclose the amount, but he says, "We have sufficient funds to go forward. Spray has been a great venture partner, and money is not an issue."

Keeping Options Open

In keeping with a strategy similar to Tryton's, Cappella Inc., founded by Antonio Colombo, MD, director of the Cardiac Cath Lab at the EMO Centro Cuore Columbus SRL in Milan, Italy, is developing a stent dedicated to the side branch. The company was founded in 2004 with venture funding from PolyTechnos Venture Partners, ACT Venture Capital, and individual investors, including its founders and affiliates. CEO Guy Neev relates that during a live case at a clinical meeting in early 2004, Dr. Colombo was trying to navigate tortuous anatomy with a very high profile dedicated bifurcation stent. He couldn't get through the lesion with the stent, and had to send the patient for more invasive surgery. As with other things in life, timing is everything. A physician sitting in the audience proposed to the frustrated presenter the idea of looking at bifurcations in a composite manner with a tailored solution for the side branch. That's how Dr. Colombo came to found Cappella.

As members of the second-generation in bifurcation stenting, Cappella's founders have learned that clinicians prefer to leave the main vessel open to their stent of choice. One of the problems with earlier dedicated bifurcation stents was that they forced interventionalists to use a different main vessel stent than they normally would, explains Neev. "We also learned that simplicity, deliverability, and ease of use are critical to the success of bifurcation procedures. These procedures consume significant amounts of time and expose interventionalists and patients to radiation. That's why we have been focusing on developing a platform that would simplify the procedure and yet provide the desired wall apposition and scaffolding along the

bifurcation." In its first two human cases done by Eberhard Grube recently, procedure times were incredibly short, implantation was very smooth, and final angiographic and wall apposition results were excellent, according to Neev. "Clinicians have stepped back from the two–stent approach recently because of the safety issues related to the integration of two stents" [culottes techniques, T–stenting, crush technique, and simultaneous ‘kissing’], says Neev. "We have been developing a technology that would enable continuous coverage but would not integrate a stent within another stent. This is the most logical compromise between the partial provisional stenting approach and the aggressive two–stent approach," he believes.

Cappella’s management also learned that wall apposition is critical. Says Neev, "On IVUS (intravascular ultrasound) it is often observed that there is malapposition of the stents in the ostial area and separation between the stent struts and the vessel wall. That’s because the shape of the ostium is not cylindrical. The side vessel often tapers from the ostium borderline into the side branch vessel." Neev says that Cappella accordingly designed a self–expanding trumpet–shaped nitinol stent that echoes the natural anatomy of the ostium, rather than reforming it. "By doing that, we ensure excellent wall apposition in this unique anatomy," he says. One of his company’s great innovations, believes Neev, is that "We have developed a smart balloon sheath delivery system for self–expanding stents, which enables clinicians to use the same balloon deployment mechanisms that they use today for stainless steel stents."

The implantation procedure begins with the wiring of both vessels. The *Sideguard* delivery system is advanced over the side branch wire, and by inflating a balloon, it opens a sheath that releases the self–expanding device. The balloon is deflated, the whole delivery system is removed, and the wire is taken out of the side branch. In the next stage, any main vessel stent is advanced over the main vessel wire, and the procedure ends with kissing balloon inflation. The *Sideguard* stent is placed at the ostium of the side vessel, the main vessel stent is deployed in the main vessel, and there is a gentle contact between the two.

Neev expects Cappella to complete enrollment for its clinical trial in February or March 2007, and to be able to present a first report at EuroPCR next year. Its first product iteration will be a bare–metal stent. Meanwhile, the company is in development with a drug–eluting stent that focuses on the issue of late stent thrombosis.

Definitively Provisional

At a breakfast meeting at this year’s TCT conference, cardiologist Martin Leon, MD, chairman and founder of the Cardiovascular Research Foundation, polled the 400 cardiologists in attendance. Almost unanimously, the group voted that provisional stenting—attacking the main artery first—was the best approach to bifurcation stenting. Eitan Konstantino, PhD, the founder of Trireme Medical, a founder and former president of AngioScore, chief technical officer of ByPass, and the former CEO of Advanced Stent Technologies, says that Trireme is focused on developing the second– and third–generation products for provisional stenting.

In the years since the sale of Advanced Stent Technologies, Konstantino says he worked with a team of engineers in California and Israel, most notably from the **Technion Israel Institute of Technology**, and with a high volume interventional cardiologist, on a "wish list" for the ideal solution to bifurcation stenting. The multinational engineering team created some sophisticated mathematical models to allow a breakthrough in stent design, according to Konstantino. The team created a new stent design, and Konstantino took it to some private investors and physicians with whom he’d previously worked. These individuals, along with Yellowstone Capital, ended up providing A and B rounds of financing for the company. Trireme, named after a Greek warship designed to be the fastest of the fleet, is moving rapidly; just founded in 2005, it’s already advanced its *Ariste* stent into clinical trials.

Trireme’s *Ariste Side Branch Adaptive Stent* is a main vessel stent that can open into a side branch and protect it, Konstantino says, and everything is delivered in a package that is smaller than the marketed *Cypher* stent. "The device is very low profile and flexible, and its deliverability is very good. Our goal is not just to solve the problem but to also simplify the procedure. We are after better anatomic compliance, smaller profile, and

most importantly, ease of use so that every cardiologist can tackle bifurcations and not just experts."

The concept is to stent the main vessel first with the *Ariste*, and the physician can use any stent he or she chooses for the side branch before or after deploying the *Ariste* stent—the Tryton or Cappella stents, or even regular stents. Or, the clinician may use the *Ariste* without side branch stenting. "We have elements that protrude approximately 2 mm into the side branch veering into the ostium. Research demonstrates that a large amount of side branch restenosis occurs in the ostium," Konstantino says.

Trireme will address three market opportunities, Konstantino says. First, bifurcations, then left main bifurcations, and finally, a market that Konstantino believes is unique to its device: applications requiring overlapping stents. He says there's a problem with using long and overlapping main vessel stents, and indeed the recent FDA Circulatory Systems Devices Advisory Panel singled out that niche as problematic. "When using long and overlapping main vessel stents, you might occlude branches that are not diseased and you might occlude branches that are not involved in the lesion. In some large DES studies, long-term results, restenosis, and MACE are compromised relative to shorter stents. Our third market opportunity is a main vessel stent deployed in one shot without any need to treat the side branch, but which will at the same time provide support and not occlude incidental side branches," says Konstantino.

Trireme is conducting its first-in-man studies, beginning with a bare-metal stent. "DES does have to be part of our portfolio, and we are working on this aspect extensively, but in our opinion we need to go through a cycle and continue to refine our product to the point where we can prove beyond any doubt that our product and approach are superior to anything that is out there," says Konstantino. Speed is important, but he says his experience at AST taught him an important lesson: "The best product wins, and the patients will benefit."

"One needs to invest substantial amounts of resources and thought at the very early stages of a product, at the conceptual stage," he says. "Many critical parameters are set in the beginning. I'm hoping that with our vast experience in the field, with the really superb cardiologists and business advisors intimately involved in the company, that time will show *Ariste* to be the best product."

Classic Device Innovation Model

The new companies in bifurcation stenting seem to be operating under the classic model of device innovation, where small companies innovate and develop devices far enough along to remove technological and market risks, at which point large companies buy them. This model still holds true in stent markets—witness Johnson & Johnson's recent \$1.26 billion acquisition of **Conor Medsystems Inc.**, which has a novel stent with a controlled-release drug delivery platform.[W#200610199] Bifurcation stent companies will probably enjoy similar prospects for exits (despite the outlying early acquisition of AST by Boston Scientific, which may have been premature, given that Boston has to spend so heavily to redesign the acquired device). That being the case, there is a long way to go.

The field remains controversial, and second-generation bifurcation stent companies are only just entering clinical trials. When devices finally demonstrate efficacy in clinical trials, only then will the clinical community have some answers to the mysteries of bifurcation lesions. And—if we've learned anything from the experiences of Johnson & Johnson and Boston Scientific with their own drug-eluting stents—revolutionary products that are sometimes hailed as "The Answer" may actually only be the preamble to an entirely new set of questions.