TRYTON MEDICAL: GOING AGAINST THE FLOW IN BIFURCATED STENTS

Many device companies, large and small, have tried unsuccessfully to come up with a stent to treat bifurcated lesions, primarily by focusing on the main vessel. Tryton is taking a different approach: using a bare-metal device designed to treat the side branch. The company believes this contrarian strategy pairs perfectly with current drug-eluting stents, making them an ideal acquisition target for a large CV company.

- Bifurcation disease remains one of the largest unmet clinical needs in interventional cardiology, affecting roughly 20% of patients who undergo PCI and comprising a $1.3 billion worldwide market.
- Most of the companies trying to develop a dedicated stent for this market are focusing on treating the main vessel, leaving the side branch either untreated or treated with less than ideal outcomes that may require additional PCI or CABG surgery.
- Tryton Medical is taking a different approach by focusing on the side branch with a stent that can be paired with any other traditional stent in the main vessel.
- The company believes this approach will make it an attractive acquisition candidate for a large cardiology company looking to differentiate its drug-eluting stent business.

BY STEPHEN LEVIN

Most device innovations are incremental improvements on the status quo that don't significantly change a physician's technique or how a particular procedure is performed. Even major product advances like drug-eluting stents often do not require physicians to substantially alter the way they treat a disease or condition, utilizing basically the same techniques they have traditionally used.

But where incremental improvements in current techniques aren't able to successfully address unmet clinical needs, device innovation often moves to the next level: product solutions that change the way physicians approach and treat a particular clinical problem. Introducing a device that changes physician practice patterns, however, carries increased risk. Getting physicians to adopt a product that requires a new technique or procedure often poses significant clinical and marketing challenges for a start-up that not only has to make the clinical case, but also drive adoption. That risk, however, also presents a potentially significant market opportunity, a powerful incentive for entrepreneurs and investors to try to break new ground. That was the path that Durham, NC-based **Tryton Medical Inc.** chose to pursue in developing a stent to treat bifurcated coronary disease.

There has been no shortage of attempts by device companies, big and small, to address the problem of bifurcation disease—atherosclerosis at a location in the coronary vasculature where a smaller artery branches off of a main vessel—by developing a stent dedicated to treating lesions at those locations. Those efforts have all failed, largely because they have primarily focused on treating the main vessel, resulting in a variety of awkward, unwieldy products and techniques not well suited to the unique anatomy of bifurcations. These devices have yielded unsatisfactory clinical results, most notably high restenosis rates that often require follow-up treatment, either PCI or in the case of left main disease (a frequent site of bifurcated lesions), CABG surgery.

Tryton founder and chief medical officer Aaron V. Kaplan, MD, himself an interventional cardiologist, recognized that traditional tubular-shaped stents are designed to work best in straight or gently curved vessels, not in the sharply-angled arteries that comprise bifurcations. Indeed, until recently, all traditional stent clinical trials excluded bifurcations. The tortuous anatomy often forces interventionalists to make a difficult choice: either stent the main vessel and ignore the side branch in the hope that the disease there does not hamper flow (an approach known as provisional stenting) or attempt to place stents in both the main and side branches, forcing these devices into an anatomy for which they were not designed.

But give the failures of others, Kaplan chose to go a different route. His idea: since the market already has a number of drug-eluting stents (DES) that are well-suited

to treating the main vessel, what really is needed is a device designed specifically to treat the side branch that could be paired with any standard workhorse DES in the main vessel. The result: the *Tryton Side Branch Stent System*.

One important difference in this approach, however, is that it calls for interventionalists to change the way they currently approach bifurcations. Instead of ignoring the side branch and treating only the main vessel, the Tryton device actually requires the physician to treat the side branch first and then address the main vessel. In Kaplan's view, "Currently there is no easy and reliable way to stent complex bifurcation lesions, so interventionalists have reverted to angioplasty." In his view, "When a dedicated system is available that allows for definitive stenting while preserving the operator's main branch stent choice, interventionalists will adopt it, just as they have adopted stents suited for other lesion categories."

The company's contrarian approach is manifest in another decision Kaplan made: to develop a bare-metal side-branch stent at a time when the whole industry seemed to move toward drug-eluting stents—a move that, in hindsight, looks smart, given the concerns about late stent thrombosis raised a couple of years ago. Tryton's contrarian stance has enabled it to differentiate itself from the host of other companies working on bifurcated stents, making it the only company with a balloon-expandable side-branch device. Now, with its technology earning praise in an early roll-out in Europe, it's up to Tryton's new CEO, former Guidant executive, J. Greg Davis, to prove that that contrarian approach will quickly become mainstream thinking about bifurcated lesions.

FINDING A VC PARTNER

Tryton Medical is not Aaron Kaplan's first device start-up. He has long balanced the demands of an active interventional cardiology practice—first at **Stanford University Medical Center** and the VA Hospital, and now at **Dartmouth-Hitchcock Medical Center**—with a longstanding entrepreneurial interest. Kaplan was the founder of LocalMed, an early intravascular drug delivery start-up created in 1992, and he also played a key role in the launch of Perclose, a pioneering femoral artery closure device company. (Both companies were acquired by **Abbott Laboratories Inc.**; LocalMed primarily for the IP in 1998 and Perclose a year later for $680 million in a deal that marked the launch of Abbott's vascular device business.)

Kaplan also spent some time as an entrepreneur-in-residence at venture capital firm Three Arch Partners. He credits this stint with providing him an understanding of both the entrepreneur's and the investor's side of the start-up world, to go along with his clinical perspective. In his time at **Stanford University** and at Three Arch, Kaplan worked closely with many of the pioneering physician entrepreneurs active in the San Francisco area, including John Simpson, PhD, MD, and Thomas Fogarty, MD, who he acknowledges were among his early mentors.

In 2002, Kaplan moved back east (he's a native New Yorker) to accept a position at Dartmouth. "Dartmouth's been a very good place for me because not only is it a superb clinical base, but they've allowed me to have a 50% clinical appointment, which gives me the freedom to pursue my medical device entrepreneurial activity working closely with the Tuck School [Dartmouth's business school] and the Dartmouth Institute, which is very active on health care regulatory and policy issues," he explains.

Much like his relationship with Three Arch, Kaplan was able to develop close ties with an East Coast venture firm, Boston-based Spray Venture Partners. Tom Fogarty introduced Kaplan to Dan Cole, a device partner at Spray, who formerly managed the *Fogarty* line of catheters for **Edwards Lifesciences Corp.** and later went on to head SciMed Life Systems and **Boston Scientific Corp.**'s vascular business following its acquisition of SciMed.

Kaplan describes his relationship with Dan Cole and Spray as being much like an incubator, where he could test out potential new technology ideas and combine his clinical/entrepreneurial expertise with Cole's corporate/venture experience. "I never shopped things around to various VCs because we were able to work collaboratively," he says, adding, "I remember many meetings in which Dan reminded me that just because I was an interventional cardiologist didn't mean I could automatically turn an idea into a successful company, and he was right." Indeed, Kaplan credits Cole as a co-founder of Tryton, someone who continues to play an important role in the company's development.

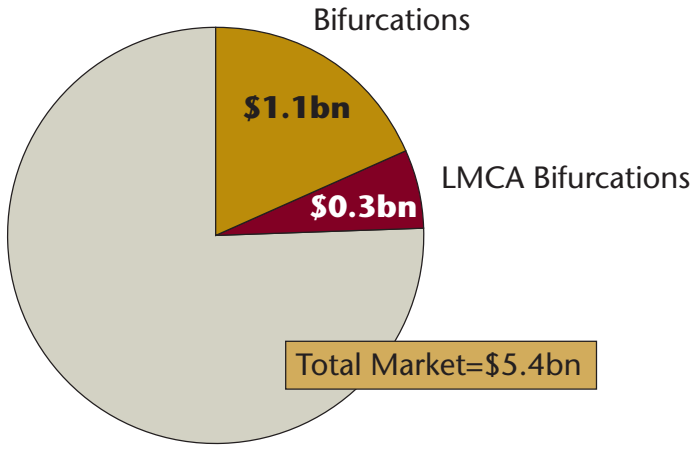
After looking at several possible new product ideas, the pair quickly decided on the bifurcation project, and Tryton was formed in 2003. "We both knew stenting very well and understood that bifurcations remained one of the biggest unsolved problems in coronary disease, one that was not being properly treated by existing stent technology," Cole explains.

BIG MARKET, PAST FAILURES

Bifurcations constitute one of the few remaining interventional cardiology market opportunities that legitimately exceeds the $1 billion threshold that VCs so eagerly seek for their start-up investments. Indeed, combined with the estimated $300 million opportunity for left main angioplasty with stenting, the potential global bifurcation stent market is around $1.4 billion. (*See Exhibit 1.*)

Exhibit 1

2010 Estimated Global Stent Revenues



LMCA = Left Main Coronary Artery

SOURCE: Tryton Medical

Cardiologists generally estimate that 20% of all PCI patients and two thirds of those with left main coronary disease present with bifurcated lesions, totaling around 500,000 cases annually worldwide.

Aaron Kaplan's idea for the Tryton stent came from his own practice and from watching his colleagues employ the provisional stenting approach that most interventionalists currently use to treat bifurcations, producing less than stellar results. In Kaplan's view, the practice of provisional stenting has evolved because of a lack of a proper device to treat the side branch.

"There is always a risk of placement issues because while we believe our eyes and hands are excellent, we might be just one part of a millimeter off, which will create a gap that can produce restenosis."
— Pieter Stella, MD, PhD

Provisional stenting involves first stenting the main branch of the bifurcated vessel, and then making a decision about whether to treat the side branch, which generally depends on whether there is sufficient blood flow through the main vessel alone. If it is necessary to treat the side branch, interventionalists must employ two traditional stents—one in the main vessel and another in the side branch—which generally produces poorer results (including higher restenosis rates). As a result, most interventionalists simply treat the main vessel and ignore the side branch.

Michael S. Norell, MD, an interventionalist at the Heart and Lung Centre in Wolverhampton, UK, who has treated many bifurcation patients (including 29 using the Tryton device and who has no affiliation with the company), estimates that in around one-third of all bifurcation PCIs, once the main branch stent is deployed, interventionalists then determine that they also need to treat the side branch. "The question is whether the side branch is big enough to matter, which generally means vessels 2.5mm or larger that supply blood to a relatively large territory," Norell explains. But treating the main vessel first presents a challenge because often the interventionalist has "jailed the side branch" by having the main vessel stent block the side branch opening. By its very nature, provisional stenting is what Norell calls a "bail-out strategy." To then stent the side branch requires using a second guidewire and stent that must be forced through the main branch stent by bending or deforming its struts in order to gain access to the side branch. The procedure then generally requires the use of two balloons that are inflated after both stents are placed in what is called a kissing procedure to restore the proper shape and expansion of the two stents.

A large variety of techniques with awkward-sounding names like crush, reverse crush, and culotte have been developed to treat bifurcated disease with current stents. Indeed, the European Bifurcation Club, a group of interventionalists who meet annually to focus on this area, developed a classification system called MADS (an acronym for main, across, distal, and side) that identifies more than 20 different approaches to treating bifurcated lesions. All of these approaches are more complex and take longer than traditional PCI. Perhaps the biggest challenge is properly positioning the main branch stent over the side branch opening, which requires rotating the stent to orient it properly. Pieter Stella, MD, PhD, of the **University Medical Centre** in Utrecht, the Netherlands, who has studied bifurcations, observes, "There is always a risk of placement issues because while we believe our eyes and hands are excellent, we might be just one part of a millimeter off, which will create a gap that can produce restenosis." These current approaches also involve risks such as crossing guidewires (since multiple wires are often required) and creating what Kaplan calls the "Brillo pad effect" of having multiple stents with deformed struts creating three layers of metal at the site of the bifurcation.

The results of these current approaches in terms of patient outcomes are higher rates of complications and restenosis, which not only can require additional PCI but, particularly in the case of left main disease, can involve CABG surgery. Michael Norell summarizes the current approaches this way: "Using traditional stents to treat bifurcations is messy and lacks the necessary degree of finesse and customization because you're trying to rebuild a complex geometrical anatomy using two cylindrical structures. When you think about what you're trying to achieve in a bifurcation lesion using stents that were designed for cylindrical vessels, it's not surprising that you tie yourself in knots." This led Kaplan to decide to develop a dedicated bifurcation device that could produce better results. "The various types of crush techniques made sense, but they had real problems primarily because they needed a specific side-branch stent, which didn't exist, so I saw an opportunity there for a better approach," he says.

Aware of the inadequacies of current approaches, numerous companies have tried to develop dedicated bifurcation stents to improve the process, generally without success. (To date, all of the experience with bifurcation stents has been in Europe because none of these devices are available in the US.) Boston Scientific and **Abbott Vascular Devices**, a division of Abbott Laboratories, are both currently in the process of re-evaluating their bifurcation programs, according to industry executives. Boston Scientific's *Petal* stent, which came from its acquisition of Advanced Stent Technologies, has reportedly run into tracking problems, and Abbott's *Pathfinder* stent (formerly the Guidant *Frontier* device) has been redesigned as a DES but has also produced disappointing results. **Medtronic Inc.** has 55 patients enrolled in its BRANCH BMS trial, which uses a Y-shaped bare-metal stent.

In addition to the large companies, there are a number of start-ups also working on bifurcated stents. **Cappella Inc.** is developing a self-expanding side branch stent. (*See "Cappella Inc.,"* START-UP, *February 2006.*) **Stentys SAS** also has developed a self-expanding stent, but the company has recently shifted its focus from bifurcations to the AMI market. (*See "Stentys' Shifting Focus: Moving Beyond Bifurcations, Stenting for AMI,"* IN VIVO, *December 2009.*) Other companies in this space include Invatec (which is in the process of being acquired by Medtronic), **Minvasys**, **TriReme Medical Inc.**, and **Devax Inc.**, which is developing a drug-eluting stent and, after running into regulatory issues, has received approval of its IDE application. (*See "Invatec: Translating Global Success in Vascular Devices to the US Market,"* IN VIVO, *October 2009; "Minvasys: Tailoring the Stent to Fit the Lesion in Bifurcations,"* IN VIVO, *March*

2008; and "Bifurcation Stenting: The Next Generation," START-UP, *December 2006*.)

NO ROTATION NECESSARY

Aaron Kaplan and Dan Cole were well aware of the competitive landscape when they were evaluating the viability of the Tryton project. "At that particular time, every other bifurcated stent employed a main branch access approach, and these are, by definition, problematic," Cole explains, because it requires rotating the stent to precisely align the hole in the main branch stent with the side branch opening, a difficult process that, when not positioned properly can increase the risk of restenosis.

To address that positioning challenge, Kaplan came up with the idea of devising a device designed to fit the side branch that would be implanted first, thus ensuring proper placement in the smaller vessel and eliminating the access issue associated with placing the main vessel stent first. Then any traditional stent could be used with the Tryton device to treat the main vessel. Kaplan also was looking to develop a device that most interventionalists could implant using the same techniques they employ everyday in the cath lab—notwithstanding the contrarian approach of treating the side branch first—one that would not require a significant learning curve or increase procedure times, and one that produces outcomes that are closer in quality to those of non-bifurcated lesions. And finally, the device had to deliver coverage and radial strength to the artery independent of the angle of the bifurcation because many of the previous devices were limited by the angle of the side branch and, as Kaplan notes, "Interventionalists are not accustomed to measuring angles in order to determine whether to use a device." The result was a stent that, according to Pieter Stella, requires virtually no learning curve and, unlike any of the two-stent approaches, is easy to implant.

In Kaplan's view, "The fundamental problem of other bifurcation technologies was that they required rotational orientation in order to be properly positioned over the side-branch opening," which is difficult and time-consuming for interventionalists. He was, therefore, intent on coming up with a device that obviated the need for that precise positioning. The stent that Tryton developed is a standard cobalt chromium, slotted tube device, but unlike most other stents, this one has three different regions: the distal section that fits into the side branch is a standard design; the mid-section is what the company calls a transition zone that has three panels that can accommodate any anatomy and is built for coverage of the vessel and hoop strength; and the proximal third of the stent that joins those three panels in what Tryton calls a wedding band design that resides in the main vessel and enables the device to be mounted on a standard delivery system. (*See Exhibit 2*.)

The middle and proximal sections are the unique design aspects of Tryton's stent. In addition to the standard distal and proximal markers on the stent, this device also includes two markers that identify the transition zone, with the proximal marker placed in the main vessel and the other one in the side branch, thereby eliminating the need for the kind of rotational orientation to properly position the stent that made working with many of the other bifurcation devices so challenging for clinicians. Further adding to the ease of use of this device, Kaplan explains, is that it can be delivered over a single wire, eliminating the need for two guidewires that other approaches require.

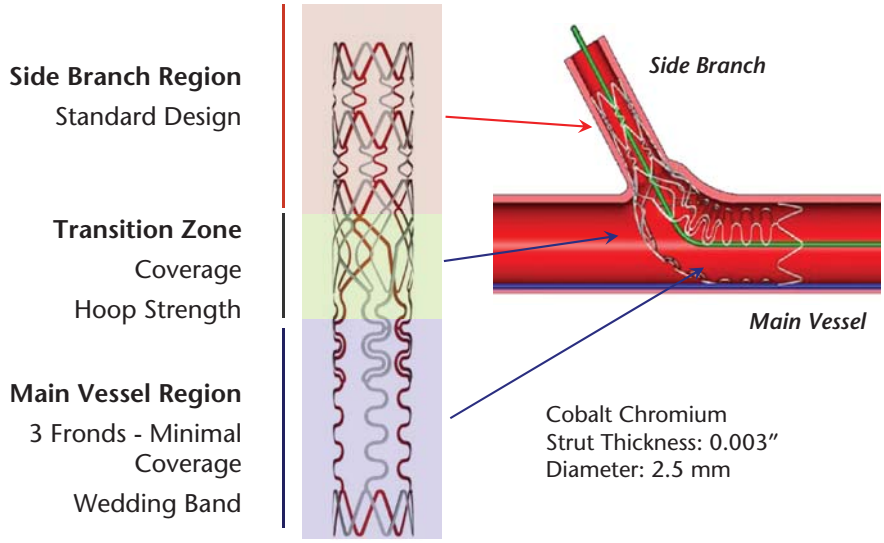
In addition to the design of its device, the other big product development question for Tryton was whether to make its stent drug-eluting. Tryton's device was being developed at the time when clinician enthusiasm for DES was at its peak, with US adoption rates pushing 90%. Indeed, Aaron Kaplan acknowledges that, initially, Tryton's plans called for the device to be drug-coated. But because of the increased cost and complexity involved in developing a DES, along with the longer regulatory path such a product would require, the company decided to go with a bare-metal stent instead, which would be used as part of a hybrid treatment strategy, paired with a DES in the main vessel. This decision proved prescient in light of subsequent events.

Not long after that decision was made, the industry was rocked by the concerns over the increased late-stent thrombosis (LST) risk from DES that emerged in August of 2006 based on data from a Swedish registry. The immediate result was broad concern among interventionalists about the use of drug-eluting stents and adoption declined precipitously, both in the US and Europe, while the use of bare-metal stents in certain patients gained renewed interest. Subsequent data called into question the validity of that initial Swedish LST analysis and DES adoption has since increased, albeit more quickly in the US than in Europe. But even now, US adoption rates remain in the low 70% range, whereas in Europe they are below 50%.

For Tryton, this sea change in DES usage was an unanticipated benefit, validating its

Exhibit 2

Tryton's Side Branch Stent System



SOURCE: Tryton Medical

hybrid strategy. The company demonstrated the clinical benefits of that approach in its 30-patient, first-in-man study, which was conducted in 2007 at three sites in Europe, headed by three thought leaders: Eberhard Grube, MD, in Siegburg, Germany, Patrick Serruys, MD, PhD, in Rotterdam, the Netherlands, and Marie-Claude Morice, MD, in Massey, France. According to Kaplan, the trial produced "DES-like late loss results in both branches, while also validating that the device was easy to use." In the side branch, which is at higher risk for increased restenosis, the late loss was 0.17 mm, which is very close to what was reported for **Johnson & Johnson**'s *Cypher* DES in the main vessel. Also, the nine-month follow-up showed a low target lesion revascularization rate of 3% and no side-branch failures. Although the LST concerns and this initial clinical data made this approach more palatable to interventionalists worried about excessive use of DES, the company still needed to demonstrate that this approach produced superior clinical results in a larger patient population. Armed with CE mark approval, Tryton's next challenge was to do that through a controlled roll-out of its stent in Europe, but doing so meant expanding the company's capabilities.

"We wanted to be very quiet and measured, and make sure we really knew that we had a solution for the problem that we had identified before bringing on a senior guy like Greg Davis and building out more infrastructure."

—Aaron Kaplan, MD, Tryton Medical

A VIRTUAL BEGINNING

For the first several years, Tryton really operated as a virtual company and kept a low profile. Kaplan and H. Richard Davis (a catheter engineer, who is now the company's chief technology officer) went through numerous iterations of the device until they established proof-of-principle. "We went through close to 30 designs before we got to where we are now, which is a very rapid iterative process," Kaplan recalls. "The good thing about that process is that we can develop next-generation designs very quickly."

Kaplan says that Tryton's goal "was to run silent, run deep early on to really make sure we had something." This strategy came from his venture experience on Sand Hill Road, where he too often saw a start-up "get an idea, raise a $3 million Series A, and spend a lot of money unnecessarily" before they knew they had something that worked, "instead of having a product before you raise that venture money."

In Kaplan's view, part of the problem with the traditional device start-up model is that it burns early cash unnecessarily by hiring employees and creating infrastructure at a point where the product is not yet established and those people are not really contributing to the company's growth. "We wanted to be very quiet and measured, and make sure we really knew that we had a solution for the problem that we had identified before bringing on a senior guy like Greg Davis and building out more infrastructure," he explains.

And indeed, Tryton placed a premium on capital efficiency in its early days. The company raised a total of $2.9 million from Spray in its Series A and B rounds, and used that funding to establish its IP, conduct preclinical research to ensure the device worked effectively, and lock in a prototype that received CE mark approval. And all of this was accomplished with Kaplan working part-time out of Hanover, NH, and Richard Davis working full-time based in Florida as the only employees, using outside consultants as necessary. "For a company to obtain CE mark approval on a product with only two employees and $2.9 million is quite remarkable," Greg Davis points out.

The combination of Kaplan's start-up experience and Spray's history of backing these initial bare-bones projects made this kind of launch possible. For Spray, starting with this type of virtual company is not that unusual. Dan Cole estimates that approximately one-third of the venture firm's investments "are essentially company formation kinds of deals that we start ourselves much like Tryton, with varying degrees of virtualness, if you will, although Tryton was one of the most capital efficient device projects I'm familiar with." The other two-thirds of Spray's deals are more classic early-stage syndications with other venture firms, in which an entrepreneur has brought in a deal where some founder or friends and family money has already been provided as seed funding.

Cole points out that Kaplan's previous start-up experience and general understanding of the venture process has been very valuable and aided in Tryton's ability to operate on a shoestring budget. "Aaron is unusual for an entrepreneur in that he was already pretty high up on the learning curve in terms of understanding the facts of life in the entrepreneurial, venture, and start-up communities, which has made it much easier to get things done," he says.

However, Cole points out that launching this type of virtual start-up also has its drawbacks, the biggest being that the lack of resources can slow the pace at which the company can grow. "Tryton was quite fortunate to get as far as it did, in terms of doing our first-in-man trial and reaching proof-of-concept, on such a small amount of money, because as a virtual company, you do pay a penalty in terms of development speed, and we also paid that penalty," he admits. "If Tryton had staffed up earlier with a bigger team, the company would probably have grown a good bit faster, although it would have been less capital efficient." Aaron Kaplan agrees, noting, "While this strategy has probably taken us a bit longer than if we'd raised more money early on, by maintaining our capital efficiency, we are now in a very strong position."

By early 2008, having established proof-of-principle and armed with a working prototype, Tryton was ready to staff up and move on to build the capabilities the company needed to begin developing the clinical data and infrastructure necessary to commercialize its device. The first step was to raise additional money and Tryton's $14 million Series C financing in March 2008 was the company's first true syndicated venture round. In addition to Spray, the other investors in that round were PTV Sciences and RiverVest Venture Partners. This financing occurred before the economic downturn, and according to Dan Cole, "Frankly, it wasn't too difficult because early in the process we started talking to the two firms that ultimately invested and they both knew the space very well and saw our vision immediately, knew what we were trying to do and agreed with our approach."

The next step was to begin building the company's management team and infrastructure, which led to the hiring of Greg Davis as Tryton's president and CEO. Davis has more than 20 years of experience in the device industry, most of that spent with Guidant, including running that company's Japanese operations. As Tryton has continued to grow, however, it still retains somewhat of a virtual feel, with only 11 full-time employees who are at diverse locations (along with 10 other contract employees). The company's headquarters are in Durham, NC, because that is Greg Davis' home, but only half of its employees are based there. Kaplan remains in Hanover, Richard Davis in Florida, Doug Ferguson, the clinical and regulatory VP is in Boston, and Olivier Delporte, the European VP of sales and marketing, is based in Brussels, managing the company's initial product launch.

SELLING IN EUROPE FIRST

Device companies'—particularly start-ups'—attitudes toward initially commercializing their products in Europe have undergone a 180-degree shift over the past few years. A decade ago such an approach was a popular means of generating early revenue. But that popularity quickly faded as companies found out how expensive and complex a European launch could be, especially given the different regulatory and reimbursement environments in each country, and many companies pulled back from this approach. More recently, however, companies have found that targeted European roll-outs in specific countries with favorable clinical and regulatory climates can actually help both generate revenue and produce clinical data that can be used to support an FDA submission for US commercialization. Companies such as CoreValve in percutaneous heart valves, Ablation Frontiers in atrial fibrillation, and St. Francis Medical in orthopedics (all of which, coincidentally, are now part of Medtronic) are examples of start-ups that successfully employed targeted European product launches that helped boost sales and garner clinical data, while also serving to validate the safety and efficacy of their respective products, and undoubtedly boosting their value in the eyes of prospective acquirers.

Tryton is adopting just such a targeted rollout strategy in Europe, where the company's product appears to be well received, with over 700 implants to date. As noted, bifurcation stents of all types have been used to date almost exclusively in Europe, so clinicians there are experienced with a variety of products. At this past October's European Bifurcation Club meeting in Berlin, 122 physicians and industry representatives (two thirds from Europe) from 31 countries were polled on their preference among eight different bifurcation devices and Tryton was the clear winner with 66% indicating they would use the Tryton stent to treat their bifurcation cases. The next closest competitor was Minvasys with 55%.

One of the main concerns that US start-ups have about launching in Europe goes to the reimbursement constraints that certain countries there impose, such as Germany. Historically, for example, that has been a significant part of the problem in gaining adoption of drug-eluting stents (along with a generally more conservative physician population). Tryton doesn't see pricing as a problem in most European countries.

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Greg Davis makes clear that, although the Tryton device is a bare-metal stent, "We are not adopting bare-metal stent prices. We are going after a premium that is going to be much closer to DES pricing and we believe we can do that because this is a highly differentiated product that satisfies a large, unmet medical need."

For Tryton, pricing its device at a premium, however, can be a double-edged sword. While this strategy can help the company keep the value of its technology high pending US commercial approval, it also runs the risk of limiting adoption, particularly in the cost-constrained environments of Europe. Pieter Stella, one of Tryton's strongest clinical supporters, notes, "I may be able to use this device in between 50% and 75% of my bifurcation patients, but pricing will make a significant difference in how often I use it. If it is priced closer to a bare-metal stent, I can use it much more often than if it costs as much as a drug-eluting stent."

Davis also notes that Tryton's sales strategy is to focus on gaining deep penetration into a few, select hospitals. "We'd rather sell to some high-volume accounts—those that we can get to use Tryton for 10% to 15% of all their PCIs—than sell only a few stents to whomever will buy them," he explains. "We can drive sales for a long time selling to everybody, but it is the re-use that is the important thing in establishing the value of the device." One of the main drivers behind this deep penetration strategy is that it presents a scalable approach that company executives believe will increase interest among prospective large-company acquirers.

Tryton first launched its stent in Italy, which because of a more favorable reimbursement climate has become a recent European favorite of device companies after years of having a reputation as a country to be avoided because of an impenetrable bureaucracy and poor payment policies. Tryton is working through an established distributor and is getting DES pricing with high repeat usage.

From the outset, Tryton has recognized that the best way to build the case for its device and to get physicians to change the way they treat bifurcations is by assembling a compelling body of clinical data demonstrating the benefits for patients, particularly given the inadequate results delivered by current products. In addition to its European FIM trial, the company is compiling the eTryton European multi-center registry tracking patients with the device.

In the US, the company started its discussions with the FDA very early concerning an IDE and believes the trial design is nearing approval. Tryton hopes to begin enrolling its US pivotal trial later this year, which the company estimates will take nearly one year to enroll. A major advantage of Tryton's decision to go with a bare-metal, rather than drug-eluting, device is that the cost, complexity, and length of the regulatory pathway is significantly less. "From an investor's perspective, it would have been capitally prohibitive to do a US drug-eluting stent

pivotal trial," says Dan Cole. According to Greg Davis, the US pivotal trial will be a randomized controlled study at centers across North America and Europe, comparing Tryton's device and an approved DES against a DES with balloon angioplasty in the side branch. The principal investigator will be Martin B. Leon, MD, of **Columbia University**'s **New York-Presbyterian Hospital/Columbia University**. The company is hoping for PMA approval in 2013.

Tryton is planning additional studies, including one focusing on IVUS analysis and another so-called real-world study that encompasses a wide variety of patients. In addition, the next major clinical area that the company is planning to focus on is left-main disease, which as noted, comprises a high percentage of bifurcated lesions. The level of interest in Tryton's stent has been evidenced by the initiation in Europe of investigator-sponsored studies. Most recently, Pieter Stella, who has done more than 20 cases with the Tryton device (and has no affiliation with the company), has initiated a feasibility study using the Tryton device with Abbott's *Xience Prime* DES in patients with bifurcated lesions involving the left main coronary artery.

Left main blockages are difficult to treat because of their hard to access location. Stella points out that, as a result, many patients are either left unstented or undergo CABG surgery. "Because of the anatomical challenges, stenting the left main is a technically difficult procedure, and with the current stents, you have to essentially change the anatomy, which often produces more restenosis," he explains. "The advantage of having a device designed for bifurcations is that it enables the physician to do less mechanical work in the bifurcation, which should potentially decrease the restenosis rate." Another problem with the left main artery is that it is one of the larger side branches in diameter, although it can be short in length, so properly sizing a stent there can be a challenge, even for the Tryton stent. "One of my suggestions to the company has been to develop a larger stent specifically for the left main," he says. Michael Norell, who has treated three left main patients with the Tryton device, echoes that concern, noting, "Future iterations of the device to address left main disease may not only need to be bigger in diameter, but also shorter in length." Despite that shortcoming, he notes that, both for the left main and other bifurcations, "If I'm going to treat a side branch with a two-stent strategy, I now only use the Tryton device and won't use any of the approaches we were previously using."

BUILT TO SELL

Tryton has sufficient funding to finance its continued operations through the end of this year, with the focus on the continued European rollout and the initiation of the US clinical trial. To complete that trial and support ongoing investigator-initiated trials, the company has just begun work on raising a Series D financing round that they expect will close by the middle of this year. The round is being supported by inside investors, but Tryton also hopes to bring in new funding sources.

As expected, Tryton is also in contact with all of the major strategic cardiovascular companies that, as noted, have not been able to successfully develop a dedicated bifurcated stent, either on their own or through acquisitions. Greg Davis says Tryton is not for sale yet—for one thing, the company still needs to accumulate additional clinical data demonstrating the safety and efficacy of its device—but Tryton executives recognize that the company's business model may make it particularly attractive to one of the large cardiovascular device companies, not just because the product works, but because it fits well strategically within a larger company that already has a DES product. "We could essentially be a plug-and-play to any one of the big companies' stent programs," Dan Cole says.

The prospect of a future acquisition by a large company has ramifications for Tryton's current fund-raising efforts. There is an advantage for Tryton to remain agnostic when it comes to the major DES companies to demonstrate that its device can work effectively with all workhorse stents, both DES and BMS. There is also an advantage for a large company to affiliate in some way with Tryton sooner rather than later as the company starts its US trial because, should the Tryton trial be successful with that company's drug-eluting stent, that relationship could result in its DES functionally being approved, along with the Tryton device, for the indication of bifurcations. As such, Tryton could provide an advantage in differentiating one existing DES from the others.

"We're in a great position," Greg Davis contends, "because we are fine going one of two ways: we're prepared to go it ourselves for a while with our existing and new investors, or we could collaborate with one of the strategics and go with their stent, along with significant development financing." Davis also suggests that Tryton can provide a pull-through advantage for a large company, by effectively expanding the market and displacing Tryton's biggest current competitor, which is provisional stenting. "As drug-eluting stent market growth slows," he argues, "DES product differentiation becomes more difficult and the market dynamics are heading in a direction more common to commodity products than innovative, physician-choice devices. Tryton provides a clear opportunity to sell other products—stents, balloons, and guidewires—to this same physician customer and provide meaningful growth in an increasingly competitive market."

While it may have taken the company longer than expected to develop its technology, Aaron Kaplan believes Tryton's timing is right, both clinically and competitively. "The doctor in me knows that today when I leave the cath lab after doing a bifurcation case, I'm not delivering state-of-the-art therapy to my patients and often don't get a great result; and the business guy in me sees that, with four DES on the market in the US, the differences between them are getting smaller, and those companies need a way to differentiate themselves in a meaningful way. I think Tryton fills important needs in both areas, and we think those companies recognize this as an important part of their story going forward."

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