Scientific with the *Filterwire EX* developed by **Embolic Protection Inc.** (EPI); Cordis/J&J with the *Angioguard XP* from **AngioGuard Inc.**; **Abbott Laboratories Inc.** with **Mednova Ltd.**'s *Neuro-Shield*; and Guidant's *Accunet.* In addition, a smaller company, **Microvena Corp.**, with its *Trap* device, has also attracted interest.

Filters have some advantages over balloons: they preserve brain perfusion during the procedure and allow the physician to perform an angiogram during the procedure if necessary. There's also the intuitive appeal to physicians of maintaining blood flow to the brain. Despite the differences in approach between the PercuSurge device and the filter systems, they share what is seen by some as the biggest potential drawback to both—the fact that, since these devices are deployed distal to the occlusion, the physician has to cross the lesion in order to properly position the protection device, which risks exactly the kind of injury these devices are designed to protect against—dislodging emboli that will trigger a stroke. Filters also, depending on the size of the pore openings, permit small particles to pass through to the brain during the procedure and may also leave debris behind during retrieval—there is currently a lively debate and much research ongoing to determine the particle size, individually and cumulatively, that puts the brain at risk. Andrea Venturelli argues that the debate over particle size misses the point. "The question of what size debris is acceptable is the wrong question," he claims. "The important question is, 'Debris or no debris?' And if you talk to physicians, most will agree that the real goal is no debris."

The risk triggered by having to cross the lesion significantly distinguishes two protection devices from the rest of the group. Invatec's *Mo.Ma* device and the *Parodi Anti-Emboli System* (*PAES*) from **ArteriA Medical Science Inc.**, despite their different approaches, are the only two protection devices currently available that can be deployed without crossing the lesion. Those two systems and the PercuSurge device are also able to remove all debris, unlike the filters. The *PAES* employs the concept of flow reversal that is achieved by occluding both the common and external carotid arteries by means of two different devices, and then setting a shunt between the carotid artery and the femoral vein. This reverses blood flow through the internal carotid, carrying all debris backwards through the *PAES*, where emboli are filtered and flow out through the femoral vein.

Invatec's system occludes blood flow in both the common and external carotid arteries by means of a single device placed at the point of the carotid bifurcation, and removes debris by aspirating the blood through temporary retrograde flow through one of the three lumens within the catheter, effective flushing out all debris no matter the size. And while the *Mo.Ma* device is deployed, the system monitors the patient's back pressure, which is the blood pressure at the carotid bifurcation to assure that the brain's collateral vessels, through a section of the vasculature called the Circle of Willis, are providing sufficient perfusion to avoid ischemia while the carotids are occluded. This back pressure provides the physician with a sufficient period of time, depending on how the patient tolerates the occlusion, to perform the carotid angioplasty. "This is a standard type of procedure that every interventional cardiologist is capable of performing," says Bob Reeders, who estimates that 85-90% of patients are able to tolerate the use of the *Mo.Ma* system.

The idea for the *Mo.Ma* device came to Invatec in the same way as the rest of the company's products—from a physician, in this case Italian vascular surgeon, Gioacchino Coppi, MD, of St. Agostino Hospital in Modena. Coppi approached Andrea Venturelli with the idea of developing a protection device that could be put in place without running the risk of triggering a shower of emboli by crossing the lesion. In proposing this approach, Coppi drew on the principle surgeons use in performing CEAs—flow blockage. But whereas the vascular surgeon blocks blood flow through direct clamping of the internal carotid artery, distal to the lesion, Coppi's idea was to develop a system that the interventionalists could use to percutaneously block flow in the common and external carotids using balloons, which is the basis for the *Mo.Ma* device. In spite of the differences between the PercuSurge device and *Mo.Ma*, Invatec executives acknowledge that PercuSurge paved the way for Invatec's approach by being the first to establish that a protection device could safely occlude blood flow in the carotids. "It would have been a totally different story had filters been approved first because, rightly or wrongly, physicians probably would have assumed that they needed to maintain constant blood flow in order to perform carotid angioplasty, and would have been reluctant to then try a device that would block flow," says Andrea Venturelli. To date, in Invatec's clinical trials in Germany and Italy, directed by Professor Biamino, no patients have suffered strokes following carotid angioplasty using *Mo.Ma*.

A Big Niche With Big Competition

For Invatec, the cerebral protection market represents one of those niche markets that Stefan Widensohler described with one major difference—this is an area large device companies have not overlooked. All of the big players are actively involved in both coronary and cerebral protection, most through acquisitions of technology developed by start-up companies. Invatec is one of the few small companies going it alone. Adding to the challenge: in cerebral protection, device companies are looking to dramatically change physician practice patterns by convincing doctors that using these products will enable them to convert treatment for carotid artery disease from what is currently a traumatic but highly successful open surgery into a safe and efficacious interventional procedure.

The presence of large device companies in this market does not mean that cerebral protection is at all a mature product area. Technology continues to evolve, and it is not at all clear that the ultimate solution has yet been developed. In this way, the cerebral protection market closely resembles the abdominal aortic aneurysm (AAA) product area, where large companies, rather than waiting until

winners and losers were determined before entering the market, chose to pair up early with start-ups through acquisitions, hoping to stake out early dominant positions in what they knew would be a good-sized opportunity.

And while carotid artery disease is not as large a market as coronary, the consensus is that physicians will use a cerebral protection device in most interventional carotid procedures, while that is not likely to be the case, at least immediately, for coronary interventions. From a sales and marketing perspective, "Selling this concept to physicians is not a hard sell," explains Stefan Widensohler, "because physicians are very, very careful about working in the carotids, and once they understand how protection devices work, they agree nearly all carotid cases should use them—nobody disputes that. Carotids are the classic protection market."

Estimates of the potential size of the cerebral protection market are extrapolated from the number of CEAs currently performed. CEA is the most commonly performed major vascular operation in the US, where 150,000 cases are performed annually, with twice that many performed worldwide. As many as two million Americans are estimated to have carotid artery disease and fit the inclusion criteria for carotid angioplasty but are not currently treated. In Europe, where numerous cerebral protection devices are already on the market, Bob Reeders estimates 9,000 carotid angioplasties are performed annually, 80% of which utilize a cerebral protection device. He predicts a 15-20% growth rate in the European market with high profit margins, selling to a broad customer base that includes interventional cardiologists, interventional radiologists, vascular surgeons, and neuroradiologists.

Reeders acknowledges that training physicians to use the *Mo.Ma* device will be critical to the product's adoption since it involves a different approach than the other protection devices on the market. "We have a 'Train the Trainer' program in which we certify each site once we teach the physicians and nurses how to use the system," he says. While this is a labor intensive approach, Reeders believes it is essential for the long-term success of *Mo.Ma* because it ensures that the best trained physicians will be the ones spreading the word to their peers about the device. "Not every cardiologist today performs carotid stenting," he explains. "but now that they can use protection devices, more and more physicians will start doing the procedure and we want to use a controlled roll-out to make sure everything's done right."

From Head to Foot

While cerebral protection represents an exciting market opportunity for Invatec, the company is unlike all of the other small embolic protection companies for which this is their only product area. In addition to pushing out the *Mo.Ma* system, Andrea Venturelli intends to continue developing Invatec's interventional vascular business, on both a branded and an OEM basis. The next

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major vascular market for the company is the peripheral area, particularly below the knee.

As physicians gain a greater understanding of vascular disease, they are coming to recognize that, while a patient may come in initially with a coronary problem, it is not uncommon for the same factors that resulted in that coronary artery disease to produce problems in the carotid, renal or peripheral vasculature. In the peripheral arteries, the disease etiology is the same as with other forms of vascular disease; the big difference is in the small size of the vessels, particularly below the ankle. This creates unique challenges particularly in terms of catheter size. Andrea Venturelli believes that's why peripherals are such a natural fit for Invatec, a company built around its specialty catheter expertise.

Invatec already is active in the peripheral market through its OEM business, where it supplies catheters manufactured by Fogazzi to **Spectranetics Corp.** for peripheral laser ablation. Fogazzi currently is Spectranetics' exclusive non-US catheter source, and the two companies are negotiating an agreement aimed at expanding that to cover the US market as well.

"For a long time, we had a large part of our business in OEM products," he says, and while that is declining as Invatec develops its own branded products, OEM continues to play an important role in the company's development and not simply as a revenue source. Venturelli points to the *RX* stent delivery systems Invatec provides for Biocompatibles' *BiodivYsio* stents, which are distributed in the US by Abbott. "If we build the stent delivery systems for Biocompatibles, we have to deliver a more than perfect product because otherwise Biocompatibles wouldn't think twice about doing it themselves or getting another supplier," Venturelli explains. "But Biocompatibles wants us to continue because they must like our work. And that is important to Invatec because these days, you can't build a $100-200 million company on your own; you need strategic alliances," he says. "We need Krauth in Germany, we need Getz in Japan, we need Biocompatibles worldwide—all of those factors together, on top of our company's unique qualities, will enable Invatec to grow," he goes on.

In terms of growth, the one gaping hole in Invatec's global sales and marketing strategy is the fact that the company has yet to enter either the North or South American markets and, in particular, the US. Andrea Venturelli plans on bringing Invatec into the US market but wants to be sure the timing is right. "I've never brought a product to the US, and I believe you only get one shot at the US market," he explains. "If you try to put a product on the market in the US and you fail because you didn't do everything right, you don't get a second chance. So we want to understand all aspects of the market, like regulatory and distribution, and go in slowly; we're not in a hurry." Venturelli also believes that as Invatec develops OEM alliances with companies like Biocompatibles and Spectranetics through which the Italian company's designs are successfully adopted in the US, that will ease the way for Invatec to come in with its branded products.

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The Next Big Leap

For a small company, one might assume Invatec has all it can handle among its various interventional vascular businesses, coronary, peripheral and protection products, both OEM and branded. Yet Andrea Venturelli already has a project in the works that will take the company out of its traditional comfort zone—the vasculature—and into a new area, radio frequency (RF) ablation of tumors. Venturelli explains that this is really not as big a leap as it may seem since this project centers around Invatec's traditional catheter-building expertise.

In the same way that Fogazzi currently manufactures OEM catheters for Spectranetics to use to transmit laser energy to the peripheral vasculature, the *Miras* RF ablation device uses specialty catheters to deliver energy to treat tumors currently either inaccessible or hard to reach using current treatment methods. Invatec's first targets will be tumors in the liver, gall bladder, pancreas, and prostate.

Bob Reeders dismisses the notion that RF ablation takes Invatec far afield of its core competency. "We are catheter builders, and when we looked at RF ablation, physicians told us that the main reason the technology has not been embraced worldwide is the difficulty in effectively delivering energy directly to the tumor," he explains.

One of the reasons that RF ablation seems like a big leap for Invatec is that the market is accustomed to thinking about RF ablation being performed using a needle, not a catheter. "We're the first ones to have cooled, flexible catheters that can run on a wire and be placed directly on tumors that previously were impossible to reach," Reeders claims.

This third leg of Invatec's business, along with its interventional cardiology and peripheral vascular (including cerebral protection) businesses, demonstrates another way in which Invatec utilizes its in-house plastics and metals expertise, as well as its ongoing relationship with Fogazzi, which continues to function as the company's R&D unit, headed by Luigi Venturelli. Invatec is able to manufacture both the plastic catheter and the metal electrode without going to an outside vendor.

Bob Reeders also points out that the RF ablation business will give Invatec something else to sell without having to radically alter its distribution patterns. "We're

already seeing many of these physician customers for our other products," he says. "We're already talking to the radiologist but now we have a broader portfolio with an RF ablation device." Invatec has signed an exclusive distribution agreement with Aloka for the European distribution of the *Miras* product line.

Preserving the Dreaming House

As Invatec expands its product offerings, the company is positioning itself to transition from a specialty and OEM supplier to a more broad-based product provider looking to establish its branded products in the marketplace. The challenge: preserving the principles on which the company has been established, such as being quick to respond in translating physician ideas into new products, while driving growth. Andrea Venturelli believes that the company's in-house expertise in both plastics and metals can provide Invatec with a competitive advantage that it can use to build a technology platform applicable to a wide range of future products, depending on what clinical problems physicians present for the company to solve.

Venturelli's vision is to retain what he calls the "dreaming house" part of the company, akin to what Fogazzi does in providing the R&D function, to provide device solutions to physicians' inquiries, and then build the rest of the company to address mainstream corporate functions such as regulatory, sales, and marketing. And once a product is developed and commercialized, "then we go back to dreaming," he says, in order to come up with the next device.

Now that Venturelli has made the commitment to grow Invatec beyond its OEM roots, the question is how large? "We're going to be a $100 million company soon; that's no secret," he says, "But we don't want to be another behemoth." Indeed, though the company will likely find itself competing with much larger cardiovascular suppliers, it will do so, say Invatec officials, with a self-consciously different approach. "The unique nature of Invatec and its products comes from its vendor independence, its responsiveness to physicians, its ability to fill underserved product niches, and to develop devices internally, rather than through acquisitions," argues Stefan Widensohler. "That represents a different strategy than what other larger device companies employ."

The challenge for Invatec to sustain its initial momentum as the company grows is made more difficult because the current landscape in both Europe and the US has grown less hospitable to small device companies that hope to grow into large, independent companies. One of the few to successfully make that transition has been Jomed. Yet even Tor Peters, Jomed's president and CEO, admits that growing a European vascular device company was easier in the mid-1990s than it is now, in large part because of the current price constrained environment and the increasingly rigorous regulatory requirements.

The interventional vascular business has historically been one in which the best technology ultimately wins, no matter the size of the company. Cordis, despite its size and resources, went from dominating the coronary stent market to becoming a marginal player, leapfrogged by other companies with superior, next-generation technology. However, as product markets such as interventional cardiology mature, the technology improvements in existing products become more incremental—it's harder to come up with a blockbuster new PTCA catheter, for example. In fact, the threat of bundling cardiac cath lab products, while yet to happen, becomes increasingly likely as the new technology curve for these products plateaus and competition begins to occur more on price. For a company like Invatec, this trend makes competing against large device companies even more difficult. Some industry executives believe embolic protection devices may soon fall victim to the same phenomenon, with every large cardiovascular company having a protection device that it makes part of a larger bundle of interventional vascular products.

Invatec enthusiastically subscribes to the "better technology wins" theory for that is what the company prides itself on. Has the company been successful in raising its profile to the point where major device companies have begun to take notice? Stefan Widensohler says, "They know Invatec is here and that's even before the big push in peripherals, which is where the company may hurt these big companies most." Jomed's Tor Peters, on the other hand, doesn't really see Invatec on his company's competitive radar screen yet, noting, "We still see them as an OEM supplier."

As an OEM supplier, the Venturellis' fortunes were tied directly to the success of companies often much larger than theirs. Now as Invatec seeks to establish its own branded identity, the company will more directly challenge those larger companies. If Invatec is successful, it will be because it has mastered the art of fighting its battles on multiple fronts, both geographical and technological.

By their own admission, Invatec officials aren't likely to directly challenge the larger cardiovascular players any time soon. Indeed, the company's success has been built on strategies and philosophies—most notably a quick and sensitive responsiveness to the needs of individual physicians—that only small companies can pull off. But as it grows, such small-company strategies may no longer suffice. Rather, aided by strong distribution partners such as Krauth and Getz, and with products designed in collaboration with some of the leading interventional cardiologists in Europe, Invatec hopes to build sustainable businesses in selected niches, such as embolic protection and peripheral vascular disease, using a strategy that finds a middle ground between the singular focus of device start-ups and the broad leveraging of cardiovascular's giants.

Comments? Send an e-mail message to the author at slevin@windhover.com