

ART: BUCKING THE TREND IN BIOABSORBABLE STENTS

- Though research on bioabsorbable stents predates the development of drug-eluting stents, the dramatic success of drug-eluting stents during the middle years of this decade pushed development efforts on bioabsorbable stents to the back burner.
- Advocates of bioabsorbable stents argue that the new stents have one major advantage over current stents, both bare metal and drug-eluting. They obviate the need for a permanent implant when only a temporary scaffolding effect is needed.
- More recently, the safety concerns surrounding drug-eluting stents and their link to late-stent thrombosis have knocked the drug-eluting stent market back, and even though many researchers now question that link, more and more interventionalists are arguing against aggressive adoption of drug-eluting stents.
- Many stent companies are hedging their bets, working on stents that incorporate both drug elution and bioabsorbability—but not Paris-based ART, which is arguing that natural healing, not drug therapy, is the best approach to therapeutically active stents.
- Bioabsorbable stents arouse great enthusiasm among both interventionalists and industry executives, though some say that we're years away from knowing whether a viable stent is even possible.

Many industry executives believe bioabsorbable devices may be the next big thing in coronary stents after drug-eluting stents. Most bioabsorbable stent companies are hedging their bets, combining drug elution with stents that disappear. Not ART, who's betting that natural healing beats drug therapy.

BY DAVID CASSAK

For years, the development of bioabsorbable coronary stents (BAS) lived in the shadow of drug-eluting stents—this despite the fact that early BAS research actually predates and served as a precursor to the initial work on drug-eluting stents (DES). Some cardiovascular researchers claim that the first work on bioabsorbable stents goes back 20 years, before the first bare-metal stents hit the market and around the same time that the large cardiovascular players first began to conceive of putting a therapeutic agent on a stent. (Technically, there are important differences between materials that are biodegradable and bioabsorbable; for the purposes of this article, the term “bioabsorbable” will be used somewhat generically to describe stents that go away some period of time after implant.)

In fact, many of the companies developing DES saw from the early days a natural connection between BAS and DES. Bioabsorbable devices would, in time, become the way to deliver therapeutic agents, and for most bioabsorbable stent companies, a drug-eluting version of their device has long represented a logical and inevitable development of their technology.

But the early and dramatic success of drug-eluting stents soon obscured what

many believed to be the natural evolution of stents toward bioabsorbable devices. Rather than encouraging the development of new and alternative stent concepts, the rapid uptake of DES—and the attendant clinical and commercial development efforts this required—served only to dampen enthusiasm for anything that wasn't a DES and didn't have a short development time line.

Indeed, so compelling was the early clinical success of DES that clinicians and company executives asked themselves, What could possibly ever improve on a drug-eluting stent? Not that there hasn't always been a handful of companies quietly pursuing bioabsorbable stents. But given that BAS themselves pose development challenges every bit as significant as DES, interest in bioabsorbable stents didn't so much disappear as get pushed to the back-burner. Bioabsorbability is a great idea, everyone said, but it's going to be hard to do, if it's even possible. The consensus view became: we'll get around to it someday—just not today given the success of DES.

But that unbridled enthusiasm for DES itself seems a thing of the past. Safety concerns about the risk of late stent thrombosis, though now less urgent than they were two

years ago, combined with a shrinking delta in the restenosis rates of bare metal and drug-eluting stents, have caused something of a rethinking of DES usage by some interventionalists and their institutions. As a result, the companies that have been steadily working on bioabsorbable stents may now find that their window is opening.

Some DES companies believe that the best next-generation iteration of their device may lie in adapting drug elution to bioabsorbable stents, arguing that the combination of bioabsorbability and drug elution creates the optimum stent. Paris-based **Arterial Remodeling Technologies (ART)** is one of the next-generation BAS companies and comes at bioabsorbability with a twist on the historic DES/BAS relationship. ART isn't betting that drug elution necessarily makes a better bioabsorbable stent, but actually the opposite: that bioabsorbable stents alone, supported by the natural healing of the body, might just create the optimal therapeutic effect all by themselves.

WORKING WITH POLYMERS

Antoine Lafont was a young French interventional cardiologist doing an internship at The Cleveland Clinic in the early 1990s, on leave from Inserm, the Institut National de la Santé et de la Recherche Médicale, when the idea of a bioabsorbable stent first occurred to him. Lafont was experimenting with drugs to treat restenosis and, more specifically, the hyperplasia that at the time was believed to cause restenosis. In time, however, Lafont's research found no real correlation between hyperplasia and restenosis; instead, he says, he began to explore the relationship between restenosis and arterial remodeling. "What we began to realize was that the arteries were not behaving like rigid tubes, and we were able to remodel both positively and negatively," says Lafont.

Lafont notes that the realization that vessel wall remodeling was behind restenosis led him to understand the need for something like a stent—"This was just when we first began to hear about the *Palmaz-Schatz* and *Wiktor* stents," he says—but Lafont believed from the very beginning that putting a metal stent into the arteries is a mistake. "I thought, Why not apply the concept behind a bioabsorbable suture to a stent?" he says.

A discussion with a biomaterials scientist at Cleveland Clinic named Fred Cornhill led

to an introduction to another biomaterials scientist in Cleveland, James Anderson of Case Western Reserve University. Knowing that Lafont would soon be returning to France, it was Anderson who suggested Lafont contact Michel Vert, a research scientist at the National Center for Scientific Research (CNRS), based at Montpellier University, and an expert on polymer chemistry with 45 years in the field, and who would eventually join Lafont in founding ART. (Because CNRS is a public institution and Vert therefore a public employee, by French law he officially served ART as a consultant until last year, when he retired from CNRS.)

One of only a handful of scientists working on optically active polymers, Vert first began exploring medical applications for polymers over 30 years ago. Vert soon realized that optically active polymers, a form of plastic, had little future generally speaking as a source of plastic goods—they're too expensive—but could have promising applications in medical devices "because you could adapt the properties of the polymer through the chiral structure of the polymers," he explains.

Vert's first efforts, well before ART, revolved around developing a polymer-based bone cement used in orthopedics; the polymers could be made porous and thus function well as a cement. At the time, bioabsorbable sutures, manufactured by companies such as Davis & Geck, then a division of American Cyanamid, now part of **Covidien Ltd.**, and **Ethicon Inc.**, a **Johnson & Johnson** operating company, had demonstrated the potential of bioabsorbable materials used inside the human body. "We really didn't want to develop another suture," says Vert. "That was already done. But we were very interested in orthopedics, trying to replace bone fixation devices," such as the screw and plates used in trauma repair and joint replacement.

A STENT, BUT FIRST A PHD THESIS

By 1981, Vert was part of a team at CNRS that had tested polymers made of polylactic acid in humans; by 1982, he had been contacted by a major French orthopedics company about developing bioabsorbable devices to be used in orthopedics. Eventually a company was launched based on the R&D done by CNRS, but it took almost ten years to bring to market the first bioabsorbable screw, used in ACL repair.

Vert notes that the first work on bioabsorbable stents had actually begun nearly a decade earlier, in development efforts done by folks like Richard Stack of **Synecor LLC**, and others. (*For Synecor's work in bioabsorbable stents, see "Synecor's Golden Touch," IN VIVO, June 2006.*) When Lafont approached Vert, following the recommendation of Jim Anderson, who had been following Vert's work on bone fixation devices, Vert suggested he and Lafont meet in Paris where Lafont could explain his ideas about a bioabsorbable stent. "By the end of the conversation, I was convinced that the [bioabsorbable] stent had promise," Vert recalls. But neither Lafont nor Vert thought much about starting a company or producing, commercially, bioabsorbable stents; rather, Lafont decided to pursue his interest in the new stents as part of the PhD thesis he would need to become a professor of medicine in France, with Vert and the enormous research facilities of CNRS behind him.

In fact, Vert took Lafont in as a PhD student and between 1992 and 1996. The two experimented with a variety of different polymers to create their bioabsorbable stent. Using a co-polymer the two developed, Lafont and Vert were, within a couple of years, able to prove the feasibility of bioabsorbable stents, and Lafont earned his PhD.

By 1997, however, Lafont had decided that he wanted to explore the idea of bringing a bioabsorbable stent to market—though not necessarily by launching his own company. In fact, Lafont approached a number of large companies working in interventional cardiology with a business plan and had a deal with the USCI division of [CR Bard Inc.] all but struck, when it fell apart because Bard's interventional business was acquired by then-AVE, Arterial Vascular Engineering. "We had been talking to them for two years and had had meetings and more meetings and more meetings, and then just when we were going to sign the deal, Bard [i.e., USCI] was bought by AVE," recalls Lafont.

Discussions might have continued with AVE, though it wasn't clear that AVE officials were as interested in ART's technology as USCI had been. It doesn't really matter—shortly after the USCI deal, in 1998, AVE itself was acquired by Medtronic, and this time the acquiring company had no interest in the bioabsorbable project. "Suddenly we were back at

the beginning,” says Michel Vert, who was advising Lafont at the time. “We lost five years looking for a partner.”

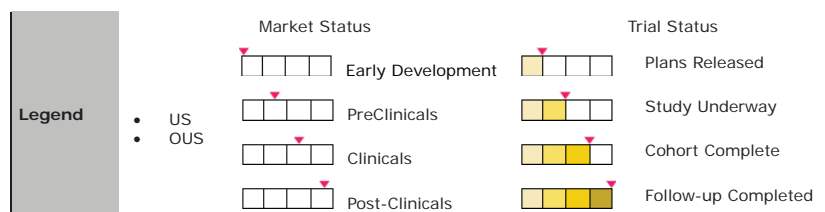
Vert and Lafont concede that they were unnerved a bit by the back-to-back sales of USCI and AVE. “It was a very good lesson for us,” says Lafont. As noted, Lafont

never intended to launch a company—he just wanted to get his bioabsorbable stent into clinical practice. But as efforts to license the technology went nowhere, he

WANTED: CEO

Exhibit 1

Bioabsorbable Stents in Development



Company	Device	Target Market	Market Status (US/OUS)	Trial Name	Trial Status
Abbott	BVS (Fully bioabsorbable balloon-expandable DES based on poly-lactic acid that elutes everolimus...)	De novo lesion Single vessel lesion		ABSORB	
				ABSORB Imaging Substudy	
				ABSORB IVUS Substudy	
				ABSORB OCT Substudy	
Amaranth	Layered Biodegradable Stents (Stent made from biodegrading and drug-eluting polymer materials; it features a simple helical layered design; the technology permits use of multiple or single polymers, multiple drugs, and/or a range of drug release kinetics...)	De novo lesion Single vessel lesion		NA	NA
ART	ART Bioresorbable Stent (Hemocompatible, biocompatible bioresorbable stent that minimizes thrombus and inflammation, while degrading over time to promote natural tissue remodeling...)	De novo lesion Single vessel lesion Vulnerable plaque		ART FIM CE Mark	
Bioring	Bioring Biodegradable Stent (Biodegradable stent designed as alternative to metallic- or ion-coated stents...)	De novo lesion Single vessel lesion Vulnerable plaque		NA	NA
Biosensors	Resorbable DES (Next-generation DES featuring Biolimus A9 and a fully resorbable stent design...)	De novo lesion Single vessel lesion Vulnerable plaque		NA	NA
BIOTRONIK	DREAMS (Program combining Biotronik's magnesium bioresorbable stent with Conor's drug delivery reservoir technology; features a bioresorbable matrix as the drug carrier; the drug is pimecrolimus...)	De novo lesion Single vessel lesion Vulnerable plaque Complex lesions		PROGRESS AMS	
Boston Scientific	BSC Bioabsorbable DES (Boston Scientific said during a May 4, 2006 presentation that it is working on a bioabsorbable DES...)	De novo lesion Single vessel lesion Vulnerable plaque Complex lesions		NA	NA

had little choice but to create a company to commercialize his stent. Lafont concedes that, particularly after the USCI experience, he was cautious about what he could and should say to potential investors about

his technology—more so because he was also unsure of the company’s IP position at the time. “We lost a year trying to find a venture capital firm,” says Lafont about his early fund-raising efforts. “We were like two

blind guys knocking on doors in a friend’s apartment, trying to find the bathroom. You try to do it very discreetly because you don’t want to wake everyone up.”

But just as importantly, Lafont and

Company	Device	Target Market	Market Status (US/OUS)	Trial Name	Trial Status
BTI	IDEAL (Fully biodegradable stent; polymer is comprised of salicylic acid and the coating layer uses sirolimus; stent is biodegraded by 6 months...)	De novo lesion Single vessel lesion Vulnerable plaque Complex lesions		WHISPER	
Cordis	BDES (Balloon-expandable bioabsorbable DES; polymer material comes from the family of polyester; company says the product will have a higher drug load and a slower elution than CYPHER, and that the stent will be absorbed by appx. 18 months...)	De novo lesion Single vessel lesion Vulnerable plaque Complex lesions		NA	NA
Kyoto Medical	IGAKI-TAMAI (Bioabsorbable stent formed from poly-L-lactic acid (PLLA); dissolves into water and carbon dioxide and absorbed into vessel tissue within a “few years” after implantation...)	De novo lesion Single vessel lesion Vulnerable plaque Complex lesions		IGAKI-TAMAI Coronary	
mNEMOSCIENCE	BIO-SMP Stent (Biodegradable stent with shape memory properties...)	De novo lesion Single vessel lesion Vulnerable plaque Complex lesions		NA	NA
REVA	REVA DES (Fully resorbable, paclitaxel-eluting DES featuring an ultra-thin stent with a “slide and lock” feature...)	De novo lesion Single vessel lesion Vulnerable plaque Complex lesions		RESORB Paclitaxel	
				RESORB Bare	
Sahajanand	Sahajanand Bioabsorbable (Balloon expandable bioabsorbable stent with PLLA and heparinized PLLA...)	De novo lesion Single vessel lesion Vulnerable plaque Complex lesions		NA	NA
TheraCardia	TheraCardia bioabsorbable stent (A bioabsorbable stent based on a biopolymer...)	De novo lesion Single vessel lesion Vulnerable plaque Complex lesions		NA	NA
TissueGen	Absorbable DES (Fully resorbable polymeric DES technology; base polymer is polylactic acid; company is initially focused on the peripheral market...)	De novo lesion Single vessel lesion Vulnerable plaque Complex lesions		NA	NA

Source: MarketMonitors Inc.

Vert soon realized that having a promising technology wasn't enough. To build a company around his BAS design, ART would need an experienced manager, and for that he turned to Patrick Sabaria, who had helped J&J launch the *Palmaz-Schatz* stent in Europe and would eventually join ART as CEO.

A biologist by training, Patrick Sabaria spent much of his career in the device industry with Johnson & Johnson in Europe, working first in the intraocular lens business and then, in the early 1990s, joining the

company's cardiovascular business, Johnson & Johnson Interventional Systems, as it was then known. In the days before it acquired **Cordis Corp.** to beef up and fill out its interventional cardiology product line, JJS was largely, if not exclusively, a cardiovascular stent business, responsible for bringing the first successful bare-metal stent, the *Palmaz-Schatz*, to market.

Sabaria saw firsthand the dramatic success of the *Palmaz-Schatz* stent: with a near-monopoly on the market, J&J grew its stent business to nearly \$1 billion a year and 90% market share before an onslaught of competitors, including Boston Scientific, Guidant Corp., and AVE, emerged in the late 1990s. Still, Sabaria notes, from his perch now running a company developing a bioabsorbable stent, we shouldn't forget what stents, in the early days, were designed to do. "Of course, we were trying to make balloon angioplasty better," he says—and J&J's early **BENESTENT** clinical trials demonstrated that stents did improve care, reducing the rate of restenosis from around 50% in angioplasty without stenting to something closer to 20-30% with stents, leading to significantly lower re-intervention rates.

By the mid 1990s, four years after it had launched the first stent and before it had even acquired Cordis, J&J was selling more than €250 million in stents annually in Europe. Sabaria, who headed J&J's European cardiovascular business at the time, notes that adoption of stents came earlier and faster in Europe than the US—Sabaria points out that the first coronary stent implant was done in Toulouse, France.

Indeed, J&J's biggest challenge at the time, he says, lay in predicting stent demand and making sure that J&J's stent production could keep up. Once an initial reluctance or skepticism on the part of European interventionalists was overcome, he says, "it was like a domino effect. Our biggest issue was

trying to assess the needs of the marketplace—figuring how far we could go and what production was going to be next month."

In fact, Sabaria goes on, as leading interventionalists began to tout the value of coronary stents,

adoption rates soared. Today, around 75% of all angioplasty cases in Europe end in the implantation of a stent; in the US, the rates are even higher. (That's for all stents, bare-metal as well as drug-eluting; DES penetration rates are lower, particularly given the safety scare of the past couple of years, and similarly track slightly higher in the US than in Europe.) "Interventionalists are, of course, very eager to use the latest innovation," he points out—but, he says, not necessarily always for the better. Indeed, drug-eluting stents, with the attendant safety issues, "demonstrate the negative side of the positive [adoption rates]," Sabaria argues, as cardiovascular device companies have just now begun to come to terms with the implications of putting cytotoxic agents on their stents.

FROM CARBON-COATED TO BIOABSORBABLE STENTS

By the mid 1990s, with stent sales soaring, J&J saw an opportunity to become a powerhouse in cardiovascular devices and announced its hostile takeover move for Cordis. "At the time we were a single-product company, only selling stents, but J&J decided they wanted to build a major cardiovascular business, which for them meant a billion-dollar business and the easiest way to do that was to buy another company," says Sabaria. With the Cordis acquisition complete, Sabaria himself found that he'd be reporting to Cordis' senior European executive and decided to leave the company in 1997. (Sabaria was also undergoing treatment for cancer at the time and was reluctant to relocate.)

Soon after Sabaria had started StentTech, Lafont came calling again, this time sharing his idea for a bioabsorbable stent.

Sabaria also worried about the challenges and distractions of merging the JJS and Cordis organizations, particularly in Europe—suddenly, he reasoned, his job would go from trying to drive revenues to working through the personal and cultural issues of the integration. And he could foresee that the stent business was in for a change. By 1997, major competition loomed on the horizon, and J&J's edge as the only company selling coronary stents would soon disappear. In its place would come price competition, margin pressure, and, perhaps even a bit of a backlash against J&J from doctors and hospital administrators who felt that J&J had used its near-monopoly to drive prices high. Moreover, with the advent of new stent companies, J&J's market position had nowhere to go but down—indeed, when Sabaria left J&J, the company had a market share of 75% in Europe; within two years, its share was in the single digits, having been bypassed by Boston Scientific and Guidant.

Sabaria decided against joining one of the other cardiovascular giants in Europe, as some of his JJS colleagues would eventually do—several went to Boston Scientific, who eagerly awaited the fallout from the JJS/Cordis integration. Having completed his cancer treatments, Sabaria began to toy with some ideas he had about how to create a superior coronary stent and formed a company, StentTech, to develop the first carbon-coated stent. "The idea was that the problem with metal stents was that it was the ions in the stainless steel that were a cause of [in-stent] restenosis," he notes, a growing problem as stent use caught on.

Sabaria worked on that project until 2002 when he was approached by Antoine Lafont. Sabaria had first met Lafont years earlier when Lafont, then a student, approached him at a cardiology conference and told him that he didn't think the *Palmaz-Schatz* stent was a good stent. Sabaria's reply at the time isn't printable—after all, the JJS booth at the congress had been filled with interventional thought leaders, all of whom thought metal coronary stents the best thing since sliced bread and were lining up to use it in their practices. But Lafont's reason why the *Palmaz-Schatz* stent wasn't a good one intrigued Sabaria, and he invited Lafont to keep in touch. "He said, 'I don't believe stents should be permanent,'" Sabaria recalls. "I asked him how he thought he could make a better stent and told him to tell me more when he had developed his ideas further."

Soon after Sabaria had started StentTech, Lafont came calling again, this time sharing his idea for a bioabsorbable stent. Lafont wanted StentTech to develop the stent, but Sabaria was leery—he thought the project would be too expensive and take too long. But he did volunteer to help Antoine set up his own company, which would become ART, and even offered to help him write the business plan, more as a friend or mentor than anything else. Within a couple of years, Sabaria had shuttered StentTech and had joined Lafont and Michel Vert as one of three co-founders of ART, and the company's CEO.

RAISING THE FIRST MONEY

Launched in 2001, ART's early years weren't easy. Raising venture capital for device companies in Europe is never easy, but raising money for a bioabsorbable stent was, during the early 2000s, particularly challenging because of the dramatic success of drug-eluting stents at the time. Moreover, none of ART's three founders had had much experience raising money, certainly neither Lafont, the interventionalist, nor Vert, the polymer scientist; even Sabaria, for all his experience at J&J, had never launched a venture-backed company before—he had funded StentTech out of his own pocket.

"We went to so many different investors and we got a different answer each time," Sabaria recalls. "Some told us we were too early-stage, some that the technology was too complex, some that DES were the ultimate answer to restenosis and here to stay since nothing could do better; in fact, we got all of the answers you can imagine." Raising money for stent companies has never been easy; modular stent company Xtent Inc. is one of the few stent success stories that relied on venture funding early on; more typical is Conor Medsystems, which went deep into its development before it was able to raise what might be called conventional venture funding. (See "Xtent and the Next DES Boom," IN VIVO, February 2008.)

With a kind of perverse circular logic, ART's bioabsorbable stent technology struggled to find an early backer: many of the companies who were reluctant to fund the high risk and uncertainty of drug-eluting stents now used the success of DES and the similar risk profile of bioabsorbable stents to say no to ART. But with Sabaria now on board, ART could address at least one of the concerns of potential investors:

the lack of a committed CEO. Just over a year after Sabaria joined ART full-time in late 2001, ART got its first venture financing, a €4 million round from two Paris-based venture firms, Matignon Technologies and Société Générale Asset Management. (The company also had some early angel investors, including Sabaria, who put the money he was going to invest in StentTech into ART.) A Series B round led by Matignon last summer raised an additional €6 million.

(As would be expected given the backgrounds of both Lafont and Michel Vert, ultimately the intellectual property underlying Lafont's bioabsorbable stent is owned not by ART but by The Cleveland Clinic, the Centre National pour la Recherche Scientifique (CNRS) at the University of Montpellier in France, and Inserm. But ART has licensed exclusive rights to the technology, and all three institutions are also equity investors in ART.)

A SAFETY DEBATE?

If the early—and striking—success of DES caused problems for ART in its initial fund-raising efforts, it is the more recent struggles of DES—most notably the safety concerns surrounding the relationship of DES and late stent thrombosis (LST)—that, say ART executives, offer bioabsorbable stents a new and compelling opportunity.

There's still some debate about precisely what causes the higher risk of LST with DES or whether there is, in fact, any higher risk at all. The same Swedish SCAAR registry that first caused the DES safety debate to explode in 2006 reported in 2007 that follow-on data not only showed that DES pose no higher risk of LST, but may in fact, actually be safer than bare-metal stents.

Still, the DES safety debate began, or perhaps accelerated, a rethinking of the clinical value and cost/benefit of DES. Almost immediately after the 2006 data was reported at the European Society of Cardiologists meeting in Barcelona, DES adoption began a precipitous decline. In Sweden itself, DES use fell by more than 50%, from 80% penetration to around 30%; in the US, DES penetration fell from a peak of over 90% three years ago to around 60% today, while European penetration dropped to less than 50% of PCI cases. And while the fall in DES use seems to have leveled off—in fact, DES use in the US has been rising steadily, if slowly, over the past several months and now stands around 67%—few expect DES use to return to pre-2006 levels.

More importantly, anecdotally, there are reports that some institutions are beginning to significantly rethink the appropriateness of DES use for clinical, safety, and cost reasons. At institutions such as Montefiore Medical Center in New York and Washington Medical Center in Washington, DC, DES use is down to around 50% of PCI cases, as interventionalists come to the conclusion that while DES efficacy has been demonstrated in some patient populations, it hasn't been proven in all. Even if the DES/LST link has been largely called into question, some interventionalists take the approach, "Why run any risk at all?"—especially as improvements in bare-metal stent technology has diminished the difference in restenosis rates between DES and bare-metal stents.

Indeed, in 2001-2002, when early clinical trials such as *Cypher's* RAVEL and FIM trials showed 0% restenosis rates for DES compared to rates of around 20% for bare-metal stents, the arguments for DES use seemed compelling. More recently, DES restenosis rates have scored in the low single digits—early claims that the zero-percent restenosis rates wouldn't be sustainable have proven true—while bare-metal stent restenosis rates have fallen to the low teens.

THE ULTIMATE DELIVERY PLATFORM

Suddenly the difference in restenosis prevention doesn't seem so great, causing any safety concerns to seem that much greater. Bioabsorbable stents sit somewhere outside the safety debate—no one is, after all, claiming that the safety risk comes from the implanting of the metal stent, since the DES risk is compared to bare-metal stents themselves. But the larger concerns about DES and the diminished sense of the infallibility of the drug-coated versions have opened the door to broader questions about appropriate DES use.

Indeed, at virtually every leading interventional clinical meeting, discussions of DES lead invariably to discussions about bioabsorbable stents, and vice versa. That's true, in part, because like DES, BAS have always seemed like an evolution beyond bare-metal stents. But it's also true because a lot of companies playing in DES believe that eventually all DES will use some kind of bioabsorbable platform.

At a session on bioabsorbable stents at this year's EuroPCR meeting in Barcelona, one prominent interventionalist framed

the question about BAS precisely in terms of DES use. “Why would I use a drug-eluting stent in 90% of my cases when I know that only 20% of my patients really need them?” he asked. It’s not a huge intellectual leap to go from questioning the unquestioned use of DES to asking other questions, most notably in the case of bioabsorbable stents, whether we should be putting a permanent metal scaffolding in the body when a temporary scaffolding effect is all that is really needed.

ART is, of course, only one of a handful of companies betting on bioabsorbable stents. Japanese stent company **Igaki Medical Planning Co. Ltd.** was an early player (with the Igaki-Tamai stent), though most industry executives believe it is **Abbott Vascular**, a division of **Abbott Laboratories Inc.**—which inherited its program from Guidant) and its joint venture with Synecor’s **Bioabsorbable Vascular Solutions**—that is the industry leader. (See “From Guidant to Abbott: An Interview with John Capek,” IN VIVO, May 2008.) In addition, there are a half a dozen other players, including **Reva Medical Inc.**, which has an alliance with **Boston Scientific Corp.**, and **Biotronik GMBH & Co.**, a leading European cardiovascular device company that has done extensive work in bioabsorbable stent use in the peripherals. (See “Biotronik’s Disappearing Act,” IN VIVO, October 2004.)

Indeed, if the great debate in DES development today rests on the overriding importance of stent delivery systems and stent platforms—precisely the bet that most DES start-ups, including Xtent and CardioMind Inc., for two, are making—bioabsorbable stents may be the ultimate delivery system or platform play.

ART officials leave open whether they will eventually incorporate a drug on their polymer-based stent. But for now, they don’t think it’s necessary. “We believe there’s no reason to transform a stent, which can treat a problem that’s pretty treatable on its own, into a drug-delivery system loaded with a powerful, aggressive anti-proliferative drug,” says Patrick Sabaria.

Rather, says Sabaria, “our position is that anything that goes against the natural healing process of the human body is not the right solution.” What ART’s BAS does, he argues, is to “help the artery remodel, and then vanish when it’s not needed anymore. We believe that putting a drug on a stent to treat a problem

that’s pretty easily treated isn’t good for anyone, patients, doctors, industry, except those companies that make anti-proliferative drugs.”

THE GRAVY TRAIN STOPS

Indeed, Michel Vert, who has spent much of his career looking at drug delivery as well as polymers, says he really doesn’t believe stents can be an effective vehicle for drug delivery. “From a chemical and physical perspective, it’s very hard to see how they can work, using such a low dose of drug released so rapidly into the blood stream,” he says. “I have a hard time matching what I know about drug delivery with what I hear about how drug-eluting stents work.”

Still, where once the success of DES was a thorn in the side of bioabsorbable stent companies, what Sabaria calls “the disarray that took place in September 2006” has become “a pleasant surprise.” No longer “the gravy trains” they once appeared to be for large cardiovascular companies, he goes on, “DES use is debated in most major congresses and are now subject to questions,” perhaps most pointedly that of the long-term potential of the market. (From a peak of \$6 billion a couple of years ago, most analysts today place the market potential of DES at around \$4 billion—nothing to sneeze at, but still a one-third reduction in the overall market.)

In Europe particularly, the impact on the DES market of the safety debate has been substantial. Until about 2005, unit sales of all coronary stents in Europe were rising 7%, while bare-metal stent units were falling 24% annually. More to the point, measured by sales dollars, while stent sales were up 19% over that period, bare-metal stent sales had fallen 28%, suggesting that the only real growth in the market lay in the higher-priced DES, with their then-clinically compelling profile.

But today, with the DES safety concerns and lower adoption rates have come intense competition and price erosion and a softening of the DES market, as drug-eluting stent prices have dropped by half in some markets. Patrick Sabaria points to recent studies in Europe that suggest that for all but a small, select group of patient populations—those with small-vessel disease, for example, or diabetic patients—the cost-effectiveness of bare-metal stents now matches that of DES. “I don’t know how you can make a case to use a drug-eluting

stent in most patients,” he says, concluding that, “A lot of companies that were once banking on the revenue from drug-eluting stents can’t count on that anymore.”

Instead, Sabaria goes on, “investors as well as cardiologists are asking, what other options do I now have, what are the alternatives to drug-eluting stents?” All of which is an interesting change of climate for ART. VCs who once wouldn’t return ART’s telephone calls now phone to ask whether they can participate in the company’s next round of financing. Of course, bioabsorbable stents themselves raise similar if not exactly the same safety and efficacy issues that DES development does. Sabaria says that what ART is trying to do is “to bring a temporary solution to a temporary problem.” But every bioabsorbable stent has to answer some critical questions, including how long the stent must remain in place to achieve a sustainable remodeling effect, as well as what happens to the stent materials when they begin to degrade.

Sabaria himself notes that based on his early experience in coronary stents, he worried that as bioabsorbable stents began to degrade, bits of the stent would “end up in the artery and cause trouble.” Histology studies done by ART, he says, have allayed those concerns—“you can pretty clearly see that the polymer is trapped in the tissue and degrades after a time,” he says—but it took some time to demonstrate the safety in animal studies.

Efficacy—even if you can prove that the stent leaves nothing behind when it degrades, does it last long enough to create a scaffolding effect and is that effect permanent?—represents the other major technical challenge for BAS companies. Some early clinical trials, including those of Biotronik’s below-the-knee application, not only failed to show that the stent was better than balloon angioplasty alone, but reported that some patients’ condition deteriorated after the stents’ disappearance.

Sabaria calls Biotronik “very courageous” for publishing the results of its clinical trials—not that it had much choice—but argues that ART isn’t likely to face similar problems because its stent is made from polymers, not a metal like Biotronik’s magnesium stent. ART’s stent material is what Michel Vert calls “an artificial biopolymer” made of polylactic acid (PLA), which is derived from materials that

“are normally found in our body. So when they degrade, they go back to where they came from.” (ART is also developing the manufacturing capability to produce its own PLA polymers.)

Many of the questions ART’s competitors have had to answer about durability and efficacy are questions ART will have to answer, though ART executives say they are now doing the appropriate studies. Antoine Lafont acknowledges that there are important material differences between metal and polymer and that means there are design challenges to ensure adequate scaffolding and radial force in bioabsorbable stents. “Bioabsorbable materials don’t have the same properties as metallic materials, so making a stent with a bioabsorbable compound the same way you would using metal is a big mistake,” he says.

As for some of the critical performance characteristics of the bioabsorbable stent—perhaps the most important of which is durability or time to degradation—much uncertainty remains. Patrick Sabaria notes that ART is targeting a 12-18 month degradation cycle, but whether that’s the right time isn’t clear yet. “Exactly how long a stent should remain in place is a very good question and needs to be answered by the experts, namely the clinicians,” he says. “Today, as we develop a new generation of stents, no one knows whether a stent should remain in place six weeks or six months or six years.” (The good news about polymers, say ART officials, is that you can adjust time to degradation, using, says Antoine Lafont, “the body’s own properties to make a better stent.”)

ART officials believe they’ve addressed the questions about the radial force of their stents and about stent recoil, and early studies suggest ART’s stent has demonstrated a “controlled to positive recoil,” depending on the PLA L/D ratio used. (Some clinicians worry that recoil is a greater issue with BAS than with metal-based permanent stents because of the fact that they disappear over time.) Still, there are unanswered questions about BAS technology in general, and the early experiences of some BAS companies have only underscored those questions. Indeed, Biotronik’s failed clinical trial wasn’t necessarily good news for other bioabsorbable stent companies—the specific and immediate impact on Biotronik arguably pales in comparison with the impact on the whole technology, as the trial raised questions

beyond simply Biotronik’s BAS, but also about the efficacy of bioabsorbable stents as a whole. Here, too, ART officials believe the company’s adoption of a PLA polymer for its stent gives them a clear edge and they are clearly frustrated at critics who don’t make a distinction between a metal like magnesium, which until Biotronik employed it for a BAS, was largely untested, and PLA, which has a long history in biomedical use. “It’s not even possible to express how safe and efficacious and innocuous PLA is,” says Michel Vert.

While ART’s combination of traditional 6-French balloon angioplasty and a proprietary PLA synthesis is innovative, say company officials, neither angioplasty nor PLA are themselves at all new technologies. Vert insists that critics who charge that PLA, because of its acid base, is harmful to or not accepted by cells “are absolutely wrong. They just don’t understand the material. We can prove conclusively that our stents are endothelialized.” Moreover, recalling the orthopedic products he helped develop years ago, Vert notes “there are more than 100,000 devices that have been sold for use in bone surgery and to my knowledge there hasn’t been a problem with them.”

Antoine Lafont argues that one of the mistakes Biotronik made was in its selection of target vessels to treat. “Starting with below-the-knee applications was a mistake because below-the-knee is the worst scenario for any angioplasty case,” he says. (ART is itself exploring peripheral applications, notes Lafont.) More recently, the first positive results on a bioabsorbable clinical trial, Abbott’s ABSORB trial, were released this spring and showed a 3% MACE rate with no signs of stent thrombosis, adding to the perception that Abbott is the leader in this field, paving the way for smaller companies like ART while at the same time creating something of a challenge when commercialization comes, should Abbott hold its early lead.

A MOVING TARGET

The good thing about polymers, says Michel Vert, is that they can be designed for different degradation times. “What you want to have is a stent whose degradation matches the remodeling stages of the cell machinery,” he notes. Still, even ART officials

concede that the question of how long a stent should remain before it degrades is only one of two critical questions for ART. The other is whether the company will eventually have to incorporate a drug onto its stent to be commercially viable.

Antoine Lafont argues that the appeal of ART’s technology is three-fold. First, early studies have

shown a controlled recoil; second, ART officials are confident they’ve found the right balance between mechanical strength and degradation times; finally, he says, “we don’t use cytotoxic drugs.”

Still, ART officials aren’t opposed to using a drug down the road, though in their second-generation devices, not in their first-generation. Moreover, they say, if they do, they’d prefer to use “a pro-healing agent,” rather than “an aggressive drug,” such as a cytotoxic agent. Says Patrick Sabaria, “We won’t incorporate an aggressive anti-proliferative drug, but we may add pro-healing factors in the future as an added feature.”

On some level, ART officials believe a stent without an anti-proliferative drug offers the best therapeutic effect. But they’d also like to avoid the added complexity and uncertainty that incorporating a drug would inevitably bring to their bioabsorbable stent—why add a further complication to an already complex technology? “A lot of the companies that have run into problems have done so because of the drug,” says Sabaria. “That’s exactly what we don’t want to do, because it makes the product more difficult to develop, produce, and even register. We believe we have an advantage because of the simplicity of our device and the lack of any side effects.”

Indeed, the success of—and even the controversy over—DES is likely to affect bioabsorbable stent delivery in one other

As for some of the critical performance characteristics of the bioabsorbable stent—perhaps the most important of which is durability or time to degradation—much uncertainty remains.

way: ratcheting up the clinical and regulatory hurdles that the new stents will face in proving both safety and efficacy. And drug-eluting bioabsorbable stents may represent a clinical and regulatory challenge that is of even greater complexity.

As it nears the start of its own clinical trials, ART officials have had numerous discussions with French regulatory officials about the studies necessary to ensure their stent's approval, and Sabaria insists that planning for a clinical trials process in an era of safety concerns over DES has become like "trying to hit a moving target."

ART officials say they understand why regulators would see the leap from bare-metal stents to drug-eluting stents as a major evolution; they argue, however, that the leap from bare-metal stents that don't degrade to polymer-based stents that do isn't as great an evolution and that bioabsorbable stents should face no greater regulatory hurdle than conventional metal stents. Still, they say, they understand why regulators are treading lightly. Sabaria sees BAS as the third major cardiovascular innovation in the past two decades—the first two being brachytherapy and DES—and, he notes, "the third generation technology is going to have to pay for the problems [regulators] encountered with the first two."

Indeed, says Sabaria, "if you look at the circus that we've seen in interventional cardiology, beginning with lasers, which were supposed to solve every problem, and then going on to brachytherapy and drug-eluting stents," it's no wonder regulators have grown cautious in their approval process and are demanding more and more data. And the recent DES safety concerns, as noted, have only underscored the dual-edge impact of DES on bioabsorbable companies. "As things get worse with DES," Sabaria goes on, "the barriers to entry have become even higher, not just for ART, but for all companies. Right now, we don't know if the regulatory bodies will ask us for nine-month follow-up or two year follow-up. We just don't know."

A EUROPEAN LAUNCH?

To date, ART has been pretty efficient in developing its stent. The company has raised a total of €10 million and will enter human clinical trials in 2009. Chris Douat, a principal at Matignon, believes that ART has the funding it needs to get to its first-in-man studies. "We've pretty much financed the first clinical trials," he says. "Once we com-

plete them, we should start hitting some pretty significant valuation points." At that point, ART could raise another private round or, perhaps, even do an IPO. "We think there's going to be a lot of value created for investors," says Douat. (In part, ART's capital efficiency was made possible because much of the basic and materials research was done at one of the three institutions, Cleveland Clinic, CNRS, and Inserm, which own the patents.)

Getting the technology just right is, of course, the major challenge for any bioabsorbable stent company. But it's not the only challenge. The fact that the presumptive leader in bioabsorbable stents is Abbott Vascular and that the company, as Guidant, began working on this more than a decade ago, is likely to be an issue for a small company like ART. That alone may make Europe a more realistic market than the US in which to launch its device.

Taking DES as an analog, Europe has proven to be a much more receptive market for small DES companies—there are currently more than 20 firms with CE-marked DES sold in Europe. The US is, by contrast, a much more concentrated market: with a five-year gap between the FDA approvals of *Cypher* and *Taxus* and those of the next generation DES, *Xience* and *Endeavor*, few US executives believe that there will be anything like 20 DES companies in the US market in the near- to mid-term—indeed, whether there will be many more than four remains something of a question. (ART officials believe they could have CE mark sometime in 2009.)

COLD FUSION

There are also likely to be adoption issues, notwithstanding the compelling argument for a stent that goes away once it's no longer needed. BAS enthusiasts predict that bioabsorbable stents could replace conventional stents, both bare-metal and drug-eluting, in 80% of the cases within five years of commercial launch. But even ART officials are cautious. Antoine Lafont points to what he calls "cultural" issues that come with the adoption of any new technology, as well as the uncertainties of a device's evolution. Here, too, DES provide a cautionary tale. Lafont notes that in 2000, as ART was preparing to launch, "no one really thought that drug-eluting stents would be as successful as they became." Two years later, he goes on, many people were predicting 100% penetration, only now to have those same people telling

everyone to be cautious. "That's why even in America, drug-eluting stents have fallen from 90% to 65%," says Lafont.

Moreover, the fate of bioabsorbable stents will also be influenced by the first products to make it to market. If the first-generation stents wind up disappointing in clinical use, they could muddy the water for those that follow. Perhaps that's why Patrick Sabaria says that it will take two to five years just to get a handle on the kind of penetration bioabsorbable stents will achieve.

Perhaps the most accurate reading of bioabsorbable stents is one that shares in equal measure much optimism and much skepticism, a combination of intrigue, enthusiasm, and reserve. Says one prominent interventionalist, "I've never seen a concept that everyone loves so much. All of the big companies are enthralled with the idea [of bioabsorbable stents]. The problem is, I still haven't seen one that works."

Indeed, while some supporters argue that bioabsorbable stents will achieve an 80% penetration rapidly, others put the chance that bioabsorbable stents will prove successful at only about 50%. Perhaps the one thing that everyone agrees on: the *potential* of bioabsorbable stents is enormous, but it's still early in the game. Thus, one senior executive at a cardiovascular giant calls BAS "the cold fusion" of interventional cardiology. "It's great if we can do it, but it's going to be difficult," he says. "Still we remain interested in the field and continue to investigate it."

For ART officials, who've now been at it for almost 20 years, timing is everything. Seven years ago, as the heady success of DES was transforming cardiovascular medicine and the cardiovascular device industry, almost no one wanted to talk about bioabsorbable stents. Today, as DES face a fresh set of challenges, interest in BAS has clearly picked up. Says Antoine Lafont, "Two years ago, the time wasn't right. Today, when you talk about bioabsorbable stents, everyone is eager to listen."

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