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MARKET TRACK

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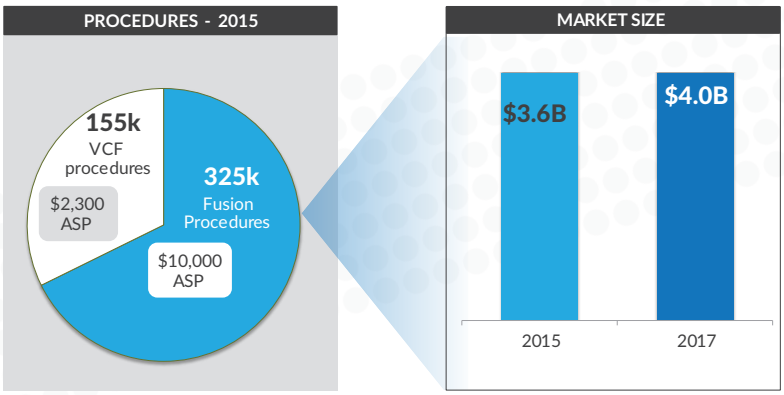
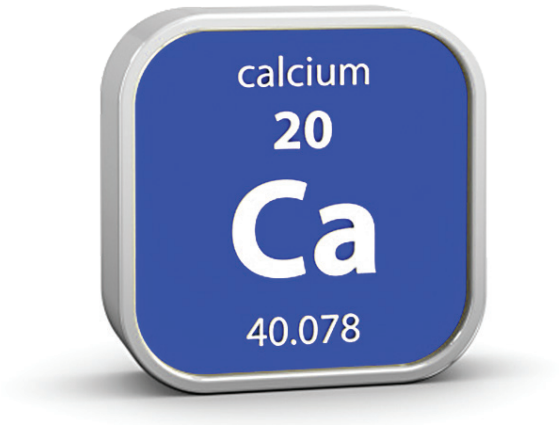
US Spinal Fracture and Fusion Markets



Shockwave Medical:

Cracking the Calcium Code in Cardiology



The good news: patients with vascular disease are living longer. The bad news: more of them are developing calcified lesions for which interventionalists lack a truly safe and effective therapy. Shockwave Medical believes it has the answer, transforming a 30-year-old technique into a new procedure with the goal of creating an important new vascular player in the process.

by
STEPHEN LEVIN

Innovation in medtech takes a variety of forms. There is the *de novo* discovery of a new method or tool for performing a procedure or treating a disease. There is also the advance of figuring out new applications for an existing technology to treat new patient populations. For Fremont, CA-based **Shockwave Medical Inc.**, the "Ah, ha" moment fell into the latter category with the discovery of how to use lithotripsy (a 30-year-old therapy for kidney stones) to treat one of the most vexing challenges in vascular disease: calcified lesions.

Always difficult to treat, calcified lesions have become more prevalent as interventional cardiology evolved over the nearly 40 years since its inception. To a certain extent, the specialty has become a victim of its own success, causing some to question whether there remains room for significant innovation. (*See "The Future of Cardiovascular Innovation: An Insiders' View,"* The MedTech Strategist, *March 30, 2015, and "Innovation in Cardiology: The Glass Remains Half Full – An Interview with William Wijns,"* The MedTech Strategist, *April 27, 2015.*) The efficacy of drugs like statins and other medical therapy, along with lifestyle changes like increased exercise, are changing the types of patients and cases coming into the cath lab. Patients are living longer, and, because of the natural biology of vascular disease, that added longevity means their diseased vessels are increasingly calcified.

While innovations like drug-eluting stents have dramatically improved treatment options and quality of life for many patients—for example, interventionalists now are seeing fewer re-do patients—devices have not evolved sufficiently to keep pace in order to provide optimal treatment for patients with calcified lesions. Most apparent in the peripheral vasculature, where its prevalence is highest, calcium-based stenosis is also not uncommon in coronary vessels and heart valves, with estimates of calcification occurring in nearly one-third of all patients with vascular disease.

Shockwave's apparent breakthrough, which the company calls *Lithoplasty*, could literally crack open the challenge of treating calcified lesions. Shockwave is starting with peripheral vascular disease because that is where current devices, most notably traditional angioplasty balloons and stents (both bare metal and drug-eluting), have been least effective, but *Lithoplasty* also looks promising for coronary artery disease and heart valve applications. This creates the opportunity for a true platform technology that can be used in three major clinical markets, which would be one of the most significant recent innovations in cardiovascular technology.

Technology Almost Lost

The underlying technology for *Lithoplasty* nearly never saw the light of day. The early work on the project was done at

Aspen Medtech, a defunct Seattle-based medtech incubator formed by venture funds Three Arch Partners and Prospect Venture Partners, by a pair of entrepreneurs-in-residence (EIRs), Daniel Hawkins and John Adams. The two had met when Hawkins was an EIR at Three Arch, and they went on to launch, with Clif Alferness, Seattle Medical, which became Calibra Medical. Calibra developed a body-worn bolus insulin delivery system for type 2 diabetes and was acquired by **Johnson & Johnson** in 2012 (*see "Simple Infusers: Unlocking the Potential of Insulin in Type 2 Diabetes," this issue*).

Hawkins and Adams are both prolific inventors, although they came to medtech with different backgrounds and along different routes. Adams, an electrical engineer based in Seattle, has more than 35 years of industry experience with both large and small companies, including **Medtronic PLC**. In addition to Calibra, Adams was a founder of **EndoGastric Solutions Inc.** (endoluminal treatment for GERD) and InControl (atrial arrhythmia therapy), which was acquired by Guidant in 1998 for $135 million. Hawkins was hit with the medtech bug while in business school at Stanford and traveled a diverse path, starting at angioplasty pioneer ACS (Advanced Cardiovascular Systems, which eventually became Guidant and is now part of **Abbott Vascular**), and including stints at Omnicell (automated pharmacy dispensing systems) and **Intuitive Surgical Inc.** (surgical robotics), with the latter stop perhaps most important for introducing him to Fred Moll, MD, a leading medtech entrepreneur and investor, and founder of Intuitive and **Hansen Medical Inc.** (intravascular robotics). Hawkins is also an inveterate inventor and spent a couple of years with the intellectual property venture firm Intellectual Ventures. He has 150+ patents and applications to his credit, including around 15 of Shockwave's 55 IP filings.

As an EIR for Three Arch looking for new medtech opportunities, Hawkins studied existing core technologies, looking to see if they could be used differently. One of the areas he focused on was lithotripsy, which, as noted, has traditionally been employed almost exclusively to break up kidney stones using high-energy, mechanical shock waves. Hawkins would also regularly review the weekly filings with the US Patent and Trademark Office (PTO) that included any of a list of key words he had created. While looking at the range of angioplasty filings, he recalled his time at ACS where they discussed internally the fact that if there were a way to change the compliance of a vessel prior to dilation, then lower pressures could be used and likely would spare vascular injury, including dissections, a significant risk for standard angioplasty balloons and other technologies. That's when the light bulb went on: why not use lithotripsy to break up that calcium?

A couple of months earlier, Adams told Hawkins about a time early in his career when he had seen an electrophysiologist accidentally hold two pacing leads too close together, causing them to arc and start a fire. Adams went back to the lab to figure out why that happened and learned the principles underlying electrohydraulic lithotripsy (EHL). EHL involves creating an electric high-voltage spark between two isolated electrodes located at the tip of a wire. The sparks are delivered in short pulses that immediately cause the surrounding liquid to expand and collapse in a few micro-seconds, producing a spherical shock wave. Through its oscillation, that shock wave generates sufficient pressure to fragment a bile duct or pancreatic stone, which is how EHL is sometimes used.

Hawkins' idea was to see if the wires necessary for EHL could be made small enough to fit into an angioplasty balloon. He immediately emailed this notion to John Adams, who got right back to him saying, "That actually could work." The two of them set to work in Bellevue, WA, developing a prototype that they eventually demonstrated in a memorable video captured on Hawkins' cell phone, showing the *Lithoplasty* pulse waves traveling through an egg, cracking the external shell device, while leaving the internal membrane intact. That demonstration shows how the physics of *Lithoplasty* make it inherently tissue-selective—it will crack hard objects while leaving soft tissue undisturbed.

Around this same time, Prospect's Scott Wolf introduced Hawkins and Adams to one of the firm's advisors, Todd Brinton, MD, an interventional cardiologist at Stanford and an entrepreneur closely involved with the Stanford Biodesign program. Coincidentally, Brinton was in the process of designing a study he hoped to have funded by **Boston Scientific Corp.** to look at using a cutting balloon to dilate calcified lesions to determine if better vessel preparation would produce better stent deployment. Brinton recalls being frustrated by not being able to consistently get the cutting balloon and stent to cross the calcified lesion. He notes, "I remember telling Daniel that what we need are two things: a tool that is very flexible and deliverable that any operator can use, and that upon delivery, the device can treat the lesion, and he said, 'I've got it.'"

Their timing, however, was less than propitious. All of this was taking place in late 2008 and early 2009, following the economic collapse and the exit of venture investors from medtech. Three Arch and Prospect initially supported the idea but could not attract any other VCs. Brinton remembers the co-founders going up and down Sand Hill Road in Palo Alto, as well as reaching out to other VCs for nearly a year without success. According to Brinton, there were two main reasons that investors gave for turning the deal down: "No one recognized calcified lesions as being a big enough clinical problem," and there were already two VCs involved at such an early stage. At that point, Three Arch and Prospect decided they could no longer support Aspen Medtech so they shut down the incubator. But Hawkins, Adams, and Brinton were committed to the lithotripsy idea, so they created an IP holding company, DJT LLC (which stood for

Daniel, John and Todd), and negotiated a buyout of the intellectual property (which surrounds the notion of lithotripsy inside of an inflatable, flexible membrane).

Shockwave was founded in 2009 with Hawkins as CEO, Adams as chief technology officer, and Brinton serving as a consultant to the company. DJT then granted the start-up an exclusive license to the IP for all cardiovascular applications.

Angels to the Rescue

The difficult financing climate made it hard for Shockwave to raise early money from venture investors, so the company turned to friends and family to raise around $300,000 in seed money. Brinton says he was frustrated with the fundraising, but encouraged by what he was seeing with the early bench research to the point where, after explaining the project to his family, Brinton's parents wrote a check to the company for $50,000, which represented the first outside investment in Shockwave.

Initially, Hawkins and Adams remained in Seattle, while the company hired an engineer and rented a 900 square foot space in Sunnyvale, CA. The engineer worked during the day and Brinton came in at night, after spending his days in the cath labs at Stanford and the VA Hospital, to work on cadaveric tissue samples using an old intravascular ultrasound (IVUS) machine that the company bought for $400 on eBay. None of the principals were paid and Brinton would frequently commute up to Seattle to report on the progress of the early research until these experiments demonstrated feasibility, at which point Hawkins moved the company down to Fremont.

Shockwave's seed money carried the company through 2011, providing a foundation for preclinical research supporting the potential viability of *Lithoplasty*. At that point, the company graduated to what Hawkins calls "super angel investors" in doing its Series A round of funding, which raised $4 million in 2012, all from individuals. This round was led by Fred Moll, who became chairman of Shockwave and brought in many of these investors, several of whom had also invested in Mako Surgical (orthopedic robotics), where Moll was a board member and which was acquired by **Stryker Corp.** in 2013 for $1.65 billion.

A Contrarian Strategy

In addition to demonstrating *Lithoplasty*'s viability, Shockwave's early preclinical research also helped re-focus the company to make peripheral arterial disease (PAD) the first leg of the three potential clinical applications for this technology. Todd Brinton explains that initially the plan was to focus first on coronary artery disease. However, during the fundraising process, when most VCs and many officials of large cardiology companies minimized the need for *Lithoplasty*, Shockwave executives switched gears, adopting a contrarian perspective, convinced that PAD represented a more compelling clinical need and a less competitive commercial opportunity than the coronaries, largely because peripheral angioplasty balloons and stents have proven much less effective than their coronary counterparts.

"We had frank discussions with many industry executives when we were trying to raise money and the consensus was that stents have solved a lot of the problems in coronaries, and peripherals were a cemetery of dead technology. One guy said, 'The worst decision you could make is to try peripherals,'" Brinton recalls. "They basically told us we were foolish to pursue this at all but wished us luck."

The more critical investors and industry executives were of the peripheral opportunity, the more Shockwave's founders realized that was exactly the reason to pursue that market first. "Those discussions made us recognize that the value proposition is higher and we can learn about the technology faster in PAD because we potentially could do something that traditional balloons and stents can't since interventionalists don't want to put in peripheral stents because they don't work," Brinton explains. Despite the advice to the contrary, in his view, the ultimate decision to focus first on PAD was based on "believing what we saw on the bench and in the animal data, not listening to what outsiders had to say." Hawkins adds that the lower risk profile and less complex regulatory pathway for peripherals also made it an attractive first opportunity. And, he notes, "We also got a little lucky there because we didn't really know how prophetic the choice of peripherals was going to be."

Among investors, Fred Moll went through a similar thought process that ultimately led him to invest in Shockwave. Moll's company, Hansen Medical, was experiencing clinical difficulties in using its early generation *Magellan* robotic system on PAD patients with calcified lesions in Europe. That experience made Moll realize that *Lithoplasty* would address an important unmet need, and it set in motion the process by which he helped lead Shockwave's Series A round in the face of the overwhelming doubts of the investment community and industry.

According to Shockwave executives, while investors and large strategics generally minimized the need for *Lithoplasty*, categorizing the opportunity as only a niche market, clinicians immediately understood that this technology would be a valuable addition to an interventionalist's armamentarium. Todd Brinton points out that early investor due diligence relied much more heavily on feedback from corporates than from clinicians, a perspective that, in this case, worked to Shockwave's disadvantage. "The process was very corporate-based," he says. "They brought in some clinicians, but most of the clinicians they brought in worked for corporates." Brinton suggests that a better way to analyze potential product opportunities would be to follow a principle of the Stanford Biodesign program, which is, "Just because you don't have a solution doesn't mean there isn't a problem. Go look for the problem because that's where the open markets for growth can be found." And ultimately, that is the strategy Shockwave

executives adopted, despite what they were hearing from many in the industry.

Calcium: Hard Problem to Crack

Shockwave's decision to rely on the judgment of clinicians, rather than industry officials, raises the question of why interventionalists see calcified lesions as clinical challenges. As noted earlier, the nature of coronary disease has changed since 1977 when Andreas Gruentzig performed the first angioplasty procedure. Successful therapies, both device and drug, combined with lifestyle changes, mean clinicians are now seeing more older patients with calcified lesions that are becoming increasingly mineralized over time due to the nature of vascular disease, making them harder to treat. And the etiology of PAD is linked even more closely with calcified lesions due to their greater prevalence in leg vessels versus coronaries. For all the medtech innovations that have occurred in cardiology, technology has not kept pace to provide optimal therapy as vascular disease evolves.

"In order to treat these lesions, interventionalists have to push their existing tools to their limits, and this is revealing many shortcomings," Daniel Hawkins explains. These include ineffective dilation with balloons and excessive injury from angioplasty or cutting/scoring balloons or atherectomy, leading to worse patient outcomes.

Typically, the most common device used to treat peripheral lesions or pre-treat (prior to stenting) coronary lesions is a balloon. To be able to overcome the resistance of the calcium in a vessel, the balloon pressure needs to be quite high because, for these patients, parts of the vessel are essentially solid calcium or, at a minimum, very fibro-calcific, making them quite rigid. The physics of static pressure means that force follows the path of least resistance, so when a balloon is inflated to a high pressure but is unable to crack the calcified lesion, the balloon is going to force the pressure along the path of least resistance and overdilate the non-calcified portion of the vessel wall. Unable to sustain that increased level of stress, the result is vascular injury, often a dissection or a tearing of a flap in the vessel wall that must be repaired because it can block blood flow. In PAD, flow-limiting dissections occur in about 40% of cases, on average, which means that about 40% of patients require peripheral stents to treat these procedure-caused dissections. As a point of reference, during angioplasty, interventionalists try to match the balloon size with the healthy vessel size, a one-to-one ratio, and then they inflate the balloon to push back the lesion, typically to a pressure of around 8-12 atmospheres (ATM), and as high as 18-20 ATM in highly calcified lesions. *Lithoplasty* is performed at a balloon pressure of anywhere from 4-7 ATM, and in the DISRUPT PAD 1 CE mark trial of 35 patients, Shockwave had no flow limiting dissections, and stent-like results without the need for stents.

Also, because *Lithoplasty* waves are tissue-selective, as noted, these pulse waves, traveling faster than the speed of sound, will pass through anything soft, such as the wall of a balloon. If the pulse wave is powerful enough when it hits something hard, it will break it, but if it doesn't hit anything hard, the wave simply dissipates without damaging anything in the area, such as surrounding tissue. As Hawkins puts it, "It's inherently hard on the hard tissue and soft on the soft tissue."

Another issue with calcified lesions is elastic recoil, an element of blood flow dynamics in which a vessel in its natural state returns to its normal lumen size. In calcified lesions, clinicians can't crack the calcium with a balloon. As a result, the balloon over-stretches the vessel's soft tissue, which wants to return to its normal size, but is prevented from doing so by the stent that is often implanted. Stents often lack the radial strength to resist the hoop stress or pressure from the vessel. The result can be a smaller than optimal lumen because the stent has been essentially squeezed down to less than the full size of the vessel, which restricts blood flow.

Further compounding the problem with calcific lesions is that there are two kinds of calcium: superficial and deep, both of which can be treated safely and effectively with *Lithoplasty*. The deep calcium is what really limits vessel expansion and that is found closest to the adventitia, which is closest to the vessel wall. According to Hawkins, "Atherectomy is not really used to treat deep calcium because it takes away tissue, and the closer you get to the outer wall of the vessel, the more you increase the risk of perforation and aneurysms."

New Device, Old Procedure

Lithoplasty employs balloons with lithotripsy emitters inside, which are essentially tiny electrodes. When the emitters are triggered, they create cracks or fault lines that penetrate completely through the calcified plaque. But because the plaque is embedded in the vessel wall, surrounded by tissue, the plaque remains in place; it doesn't break up and become emboli in the bloodstream. Hawkins compares the final result to expansion joints in a sidewalk or safety glass in a car's windshield after it is cracked, employing the principles of fracture mechanics. "Creating a crack provides space so that when the interventionalist then expands the balloon and dilates, there is room to move the plaque, and gently and evenly open the vessel," he explains.

For clinicians, the *Lithoplasty* procedure is the same as angioplasty with or without stenting. (While indications are that *Lithoplasty* can be very successful as a stand-alone therapy in peripheral vessels, Hawkins says it's too soon to determine whether it has that potential in coronary lesions. "That will be determined by the data," he says, leaving open the question as to whether this technology will potentially disrupt the coronary stent market.) The *Lithoplasty* system consists of a generator, connector, cable, and *Lithoplasty* balloon catheter. The learning curve for physicians is minimal, Hawkins says, since the system automatically determines the duration and strength of the pressure waves. "The device prepares, wires,

delivers, and has a compliance chart like a standard balloon," he adds. The clinician just connects the device, listens for the beep, and presses a button to trigger the *Lithoplasty*; there are no dials or settings as the system calibrates automatically. The pressure waves travel through the balloon wall at a rate faster than the speed of sound, providing a wave-speed pressure of 70 ATM for one to two microseconds, disrupting calcium in the lesion. "Since the balloon has a burst pressure of ten, the speed of the waves means they are going through the balloon wall like it's not even there, which is the same way it treats soft tissue," he notes.

There are multiple emitters positioned along the length of a *Lithoplasty* balloon to ensure complete coverage. *Lithoplasty* waves are emitted in a spherical shape, creating a ball-shaped pressure wave at each position along the balloon, which has proximal and distal markers just like standard balloons, so it can be accurately placed in the lesion. During *Lithoplasty*, the waves are delivered at a non-dilating pressure, the balloon is inflated to the healthy vessel diameter, and then withdrawn, completing the procedure. Shockwave is developing a range of balloon lengths and diameters all with multiple emitters to treat a variety of sized lesions and vessels.

The company did its first peripheral patient in 2012 with Andrew Holden, MD, in Auckland, NZ. At present, Shockwave is only treating PAD above and through the knee in the superficial femoral/popliteal artery, where calcified lesions are found in about half of all patients. Later this year, the company expects to begin treating below-the-knee (BTK) patients with PAD in their tibial vessels, where the calcification rates average around 70%. Hawkins points out that there are not many effective treatment options for BTK patients, noting that a couple of BTK drug-eluting balloon trials have already failed and the vessels are too small to dilate well enough for stents. Shockwave has already developed coronary *Lithoplasty* balloons, which are small enough to also be used below the knee, with 2.5 mm balloons in use and 2.0 mm balloons under development.

Moving Into the Clinic

Shockwave's first clinical trial, DISRUPT PAD 1, provided the data the company used to get CE mark approval in December 2014. The study enrolled 35 patients at three centers, two in Austria and one in New Zealand. All of the patients were pre-screened with CT, MR, or X-ray to ensure they had significantly calcified lesions, and then were angiographically re-confirmed for moderate or severe calcification. The core lab adjudicated the severity as one-third moderate and two-thirds severe. (Shockwave used two core labs to confirm the study's results to avoid suggestions that the outcomes were operator-dependent.) The patients enrolled had an average pre-treatment stenosis rate of 76%, and 23% of the patients had chronic total occlusions (CTOs), which Hawkins says is consistent with other peripheral studies.

The primary endpoint was to achieve less than or equal to 50% residual restenosis. Shockwave also had an exploratory endpoint of 30% restenosis, which is a stent-like result, in order to determine whether they could achieve outcomes similar to stents using only a balloon. In fact, *Lithoplasty* achieved better results than stenting, with a 23% average residual stenosis rate. In addition, by cracking the calcium, which prevented the normal pulsatile function in vessels, Shockwave also demonstrated that *Lithoplasty* restored that important physiologic function, which Hawkins points out could be particularly helpful in decreasing angina in coronary patients. At six months, patency, as determined by Duplex ultrasound, was 83% and no patients had returned for retreatment. With traditional angioplasty, that number would more typically exceed 40%.

Hawkins acknowledges that it is too soon to determine whether calcified lesions will re-emerge once a calcification load is present in a vessel, since *Lithoplasty* does not remove the calcium; there is some thought that there may be a higher predisposition for continued calcium build-up in those locations. However, once fractured, the calcium is flexible and is likely to remain flexible for years, he suggests, given the time it takes for a calcified lesion to form. And if a flow-limiting lesion does re-appear, *Lithoplasty* can be performed again to re-fracture the calcification.

The *Lithoplasty* principles that Shockwave is applying in its first clinical application, PAD, will be the same for coronaries and heart valves. "We don't have to redesign the fundamentals of *Lithoplasty* to pursue a new indication; in the coronaries as well as in our early valve work, we are using essentially the same emitters and the same 'no dials' system," Hawkins explains. "In the coronaries, it's going to be exactly the same as a traditional coronary balloon, except that you connect the device and press a button, just like for *Lithoplasty* PAD cases."

Valves will require a slightly different technique because the anatomy differs from the vasculature. The calcium is cracked using a custom balloon, which makes the valve leaflets more flexible, thereby returning function.

Another initial difference between using *Lithoplasty* to treat valves versus treating PAD and coronary vessels is that the first-in-man valve procedure will take place in a surgical, not an interventional, setting. Hawkins explains that in order to determine the safety and efficacy of *Lithoplasty* in valves, the initial patients will be those already scheduled to receive a surgical valve replacement. Before the patient is put on heart-lung bypass, a pressure gradient monitor will assess the valve's functionality, *Lithoplasty* will be administered, and the monitor will be re-inserted to determine if the gradient had changed. "If we reduce the pressure gradient, then we know the therapy has had a significant impact," he notes. Shockwave eventually plans for valvular *Lithoplasty* to be a transfemoral interventional procedure, but demonstrating its initial viability surgically enables the company to confirm that this approach is efficacious before

having to finalize the valve model of the catheter system.

Shockwave plans to launch its peripheral *Lithoplasty* balloon dilatation catheter system first, but even though that device is already CE mark approved, the company is holding off on commercializing it in order to focus on other clinical studies for both the coronary and valve devices, leading to the need to raise additional financing. In 2013, Shockwave raised its first institutional money from Paris-based Sofinnova Partners in a $10 million round that also included existing investors, which helped the company complete the CE mark study, but the additional clinical trials required putting a syndicate together.

Second Time's the Charm

Having demonstrated the success of *Lithoplasty* for PAD in the first DISRUPT trial, Shockwave found fundraising to be much easier the second time around. Company executives started the process in December 2014 and found even the large strategics that were dismissive of the technology and the opportunity just a few years earlier were much more interested this time. While some of the increased investor interest can be attributed to a somewhat improved overall medtech funding climate, Hawkins attributes the greater attention primarily to Shockwave's positive clinical data, combined with the ensuing years of frustration that companies and clinicians have encountered with other device therapies for PAD.

Shockwave set out to raise $20 million in this most recent round, but quickly adjusted that goal when it found investor interest was high. "The market told us they would prefer the company have some fuller milestones," Hawkins explains, "so we increased our total to $30 million and pushed the milestones."

In less than six months, Shockwave closed the round, which was significantly over-subscribed, at $40 million. "We reached the point where we were comfortable with the valuation and we didn't feel we could make good use of more money in the near term, so that's where we stopped," Hawkins notes.

Hawkins had a specific trilateral strategy in mind for creatively building this syndicate in order to keep open several future financing options. The result was an unusually diverse investor group. The round was led by Sofinnova Partners, and also included other traditional venture capital funds, Ally Bridge Group, based in Hong Kong, and Venrock. The syndicate also included several crossover investors (funds that invest primarily in public companies and when they invest in private companies, it is with an eye toward positioning themselves as insiders for a potential public offering).

Crossover investors were much more interested in medtech during the growth years of the mid-2000s, largely abandoning the sector when the economy tanked. The emerging device IPO market appears to be triggering renewed interest by crossovers in the sector. For Shockwave, these investors included Deerfield Management, RA Capital, Sectoral Asset Management (based in Montreal), and the recently-created Venrock Healthcare Capital Partners, a crossover arm of Venrock separate from the firm's traditional VC group.

In addition, the syndicate includes two unnamed strategics. Hawkins pointed out that neither of the large companies have any additional rights; both are simply observers.

> ***Lithoplasty achieved better results than stenting, with a 23% average residual stenosis rate. In addition, by cracking the calcium, which prevented the normal pulsatile function in vessels, Shockwave also demonstrated that Lithoplasty restored that important physiologic function.***

By organizing the syndicate along these tripartite lines, Shockwave was looking to protect all of its future options. "It's like the points on a triangle," Hawkins explains. "I protected the stay-private option by including traditional VCs. Having two large companies helps protect the strategic-acquisition option, and with the crossovers, we're offering the optionality of going public."

The relative ease with which Shockwave raised its most recent funding round, especially when compared with the company's previous financing, reflects a dramatic change in investors' attitudes towards the *Lithoplasty* opportunity across all investor categories. For while the current medtech investment climate has improved somewhat over 2012, device CEOs still report that early-stage fundraising remains challenging, particularly among traditional VCs, many of whom have abandoned medtech for biotech, mobile health, and other sectors. Indeed, the creative make-up of Shockwave's most recent syndicate, while having a strategic component as outlined above, also implicitly speaks to how medtech investing is evolving. The problem isn't that there aren't investors interested in medical device opportunities, it's just that management needs to look at what used to be called non-traditional funding sources to find them. One need look no further than the fact that Shockwave's investors are based in France, China, and Canada to see how this environment is changing.

For Shockwave, another big change from 2012 was the newfound investor interest in what funders had previously dismissed as either not being a significant clinical problem or only representing a small niche market. For lead investor Antoine Papiernik

of Sofinnova, what ultimately swayed him was the data from the DISRUPT PAD 1 trial, which helped eliminate the clinical risk.

Papiernik recalls first meeting with Todd Brinton at the 2012 Bohemian Medical Device CEO Summit in Istanbul (founded by Sofinnova, PricewaterhouseCoopers, Wilson Sonsini Goodrich & Rosati, and *The MedTech Strategist*), where the two were introduced by long-time medtech executive and investor, Jay Watkins (formerly of Guidant and De Novo Ventures). Papiernik was looking for a peripheral play and Brinton showed him Shockwave's first-in-man data from four patients, based on a device prototype that did not yet include the final version of the electrode design. "My original bias was, 'Is this a big enough opportunity for us?'" Papiernik admits, since Sofinnova is known for looking at large opportunities, most notably CoreValve, which helped pioneer transcatheter aortic valve devices and was acquired in 2009 by Medtronic for $700 million.

Coincidentally, one of Sofinnova's venture partners, Gerard Hascoet is one of the early patent holders on lithotripsy technology, and he was able to help validate Shockwave's technology and the clinical opportunities it presented. Papiernik realized that if *Lithoplasty* could dilate calcified lesions without the dissection and other risks of current technologies, "then you'd have something that was paradigm-shifting on the peripheral side alone, and if you could do the same in both coronaries and heart valves, this could be something special."

When Papiernik also realized that, going back to 2012, there was not overwhelming VC interest in Shockwave, he saw this as an opportunity for Sofinnova to become the lead investor, which led to the firm's initial investment. Papiernik then helped build the syndicate, bringing in Venrock (which invested with Sofinnova in **RefleXion Medical**, a start-up developing biologically guided radiotherapy), Deerfield, RA Capital, and Sectoral, the latter two having previously done biotech deals with Sofinnova. As a result of Shockwave's and Sofinnova's efforts, the company got eight term sheets from venture investors (including Sofinnova), unusually high for a medtech deal, and as Hawkins likes to remind Papiernik, "You didn't have the best term sheet [another's valuation was higher], but you are by far the best partner."

Papiernik's timing was fortuitous because the DISRUPT PAD 1 data triggered increased interest in the company. "When they started presenting this positive clinical data, that led to interest from the clinicians, which led to interest from corporates and VCs," Papiernik recalls. "There was a buzz about Shockwave potentially being a stent killer in the peripherals." Indeed, he notes that two corporate investors expressed interest in funding the entire next round, but the company declined, knowing there would be strings attached that would restrict Shockwave's future options.

Building a True Platform

For Shockwave's other major venture investor, Venrock, represented by Colin Cahill, who is also a board member, the company met a number of the firm's investment criteria, but perhaps none was more important than the ability to create that which is often promised but rarely delivered in medtech: a true platform technology. In Cahill's view, "The hope with Shockwave is that the company can apply this core technology, expertise, and IP across multiple applications to provide the basis for a novel cardiovascular device platform that can support a stand-alone company."

Cahill, who describes Venrock's medical device investment strategy as "opportunistic and agnostic in terms of deal stage," explains that the company had laid the foundation, largely through its clinical work, to make a compelling investment case. Among the key factors for Venrock was Shockwave's management team, but as Cahill notes, "Sometimes you see a great medtech team, but that alone isn't enough to invest. That wasn't the case with Shockwave."

According to Cahill, what really stood out to Venrock about the company was the opportunity to address a large, unmet clinical need in a variety of applications. "Shockwave has a chance to help change the way calcified lesions are treated in the periphery, coronary vessels, and valves, and that is a compelling story," he says.

Cahill was also attracted by the fact that *Lithoplasty* was different from many of the other vascular technology advances; it wasn't another stent. "It's different enough that you don't have to spend six months trying to figure out exactly how to differentiate it from everything else," he notes.

And while the technology is quite different from other interventional innovations, Cahill points out another important attribute: *Lithoplasty* is "compatible with clinicians' existing workflow." He goes on, "When you look at a new technology that doesn't require a doctor to learn completely new techniques, that is compelling. It allows us to see how, if this works clinically—and there is a lot yet to be proven—lots of doctors can learn this technique quickly and adopt it. It's not going to be for just the top one percent."

Todd Brinton points out that the ability to have this device be used by as many interventionalists as possible was a critical factor in designing the *Lithoplasty* system. "I'm a believer that you don't design for the best that there is; you design for the doctors that want to do it every day, so you enable clinicians to do what they want to do," he says. Current tools like atherectomy carry risks, and Brinton says those risks discourage many physicians who don't do a lot of calcified cases from adopting those techniques. In addition, current tools require substantial preparation in the cath lab and as a result, he says, the staff also dislikes these procedures. "You're left with a tool

that physicians rarely use, which means they don't like it, the staff doesn't like it, and, as a result, you don't want it as a patient," he adds. "By coming up with a balloon-based device that used the same technique the doctor employs every day in the cath lab, we addressed those issues."

For Shockwave, the next set of challenges are more of the same. Despite being armed with CE mark approval, the company is not looking to rush into commercialization. Rather, Shockwave is very aware of the positive impact the data from its first clinical trial has had on clinicians, investors, and strategics. As a result, Daniel Hawkins says the company will be spending much of this year and early next continuing to build the clinical foundation for *Lithoplasty* in each of its three respective applications. This includes a follow-up 60-patient DISRUPT PAD 2 trial; completion of a coronary study, known as DISRUPT CAD 1, with the hope of gaining CE mark approval of the coronary device in 2016; and first-in-man work on the heart valve system. Commercialization is likely to begin sometime next year in Europe with the peripheral device, followed by the coronary system. Also in the works is a separate trial that will focus on BTK patients and will require a smaller, longer, and narrower balloon.

Can Shockwave Stand Alone?

While much work still remains for Shockwave in order to establish the viability of *Lithoplasty*, the company's success to date certainly presents some exciting opportunities for its future growth, both clinically and as a company, that could distinguish it from most other medtech start-ups. And it has the opportunity to do so in a field largely devoid of competition. (One other company, **Sanuwave**, is exploring applications of similar technology in other clinical areas, specifically orthopedics and wound closure.)

Shockwave's initial opportunity to treat PAD has the potential to address a clinical area where other devices have struggled. Moreover, with the increased attention being paid to cost throughout the healthcare system, to be able to treat calcified peripheral lesions without a stent could prove to be an advantageous value proposition. *Lithoplasty* also has the potential to double the size of the drug-coated balloon (DCB) market by enabling effective use of DCB devices in calcified lesions, a market where they have not shown much benefit to date. (S*ee "Drug-Coated Balloons: Will They Transform PAD Treatment?"* The MedTech Strategist, *December 18, 2014.*)

Using *Lithoplasty* to treat coronary disease could be a much larger market than peripherals. In this area, too, Shockwave's timing may be good. As interventionalists move from second generation coronary devices—permanent drug-eluting stents—to third generation bioresorbable drug-eluting scaffolds, vessel preparation becomes much more meaningful, and *Lithoplasty* could have an important impact there. (*See "Elixir Medical's Contrarian Play in Cardiology: Go Bioresorbable or Go Home,"* The MedTech Strategist, *June 30, 2015.*)

But the real game-changer for the company could be heart valves. While this remains the earliest of all of Shockwave's technologies, using *Lithoplasty* to treat calcified valves could be disruptive to that market on two fronts. First, it has the potential to help the patients who are not currently candidates for either surgical or transcatheter valve therapy (TAVI), which would have no impact on either of those markets; those patients' only current option is medical therapy. The second area, however, could be quite disruptive to current TAVI therapy by returning valve functionality without using an implant. Either of those valve advances alone would represent a significant medical advance and a large commercial opportunity; together they could propel Shockwave to major-player status in the structural heart market.

Along with positioning Shockwave as a potential clinical leader, the value of *Lithoplasty* also opens a number of future doors for the company as it continues to grow and, as noted, Daniel Hawkins outlined how he and the board structured its most recent financing to maximize those future opportunities. The renewed interest of multiple strategics makes the traditional device M&A route one logical exit. So, too, is a possible public offering with the medtech IPO window remaining open, but who knows for how long? (*See "Medtech IPO Market Stays Open: Dampens M&A,"* The MedTech Strategist, *April 27, 2015*.)

Most intriguing, however, is the possibility that Shockwave will become that rarity of rarities—the start-up that becomes a stand-alone independent mid-cap company. With a technology that addresses unmet needs in three large, important markets, Shockwave has the potential to become much more than an acquisition target. In doing so, the company can help fill a significant void in the device industry, where megamergers are swallowing up companies much more quickly than they can be built.

Antoine Papiernik experienced a similar situation with his investment in TAVI pioneer, CoreValve, which was ultimately acquired by Medtronic. He acknowledges Shockwave's unique standing among medtech start-ups. In his view, "In medtech, conventional wisdom is that start-ups need to have one product to avoid diluting their focus, unlike biotechs that can have product lines. Shockwave is different. We think this company should not be built to buy, as they say, but is something that you can build a business around that would actually be quite large and self-sustaining."

Shockwave's potential, both clinically and commercially, was perhaps best captured when Daniel Hawkins described *Lithoplasty* to noted medtech inventor/entrepreneur, David Auth, who invented rotational atherectomy (*Rotoblator*) and invested personally in Shockwave. Auth's response: "I'm really happy you were not around when I was building Heart Technologies [creator of the Rotoblator] to treat calcified lesions because you would have screwed the whole thing up."