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Ardian: Succeeding Where Drugs Fail--Treating Hypertension in the Cath Lab

By **Stephen Levin**, *In Vivo* 11/01/2009

Feature Articles | Word Count: 6159 | Art # 2009800207

EXECUTIVE SUMMARY

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ARTICLE

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By **Stephen Levin**

- Ardian has developed the first catheter-based device for the interventional treatment of hypertension, a condition normally treated with drugs, not devices.
- Since hypertension is an underlying mechanism for other serious chronic conditions, including heart failure, kidney disease and diabetes, the company is hopeful that this device-based therapy may be effective in treating those diseases as well.
- Pioneering a new therapy to treat chronic disease states requires expensive and complex clinical trials that place a major burden on a start-up company.
- The promise of Ardian's technology has made the company one of the recent device financing success stories despite the economic climate, attracting blue-chip venture and strategic investors.

Large market opportunities have always been high on the checklists of investors, both venture and strategic, in evaluating prospective investments in device start-up companies. And with the constraints of the current financing climate, big market opportunities become an even more important criterion for emerging companies in order to satisfy investors' reduced appetites for risk.

There is often a disparity, however, between a start-up's assessment of a particular market's size and a venture capitalist's view of the same market. As one VC

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remarked, "Judging by the business plans we receive, I never knew there were so many billion-dollar markets in medical devices."

Whatever questions remain to be answered regarding the viability of Palo Alto, CA-based **Ardian Inc.**'s pioneering catheter-based renal denervation technology for lowering blood pressure, there can be no doubt that, if successful, the company's device will satisfy that major-market requirement, possibly several times over. Ardian is initially aiming at using this technology to treat drug-resistant hypertension patients, and if successful, extending that application more broadly to other hypertensives. Because of both demographics and lifestyle factors, hypertension is truly reaching pandemic proportions, both in the US and worldwide, and uncontrolled hypertension comprises a significant and growing portion of that patient population.

Ardian is clear that its initial focus is on treating patients with high blood pressure who are refractory to medical therapy, and company officials are reluctant to discuss other possible applications for their technology at this early stage. But it cannot be ignored that hypertension is a root cause of many other conditions that may also be well-served by Ardian's technology. Indeed, in addition to the hypertension market, Ardian executives acknowledge that in the future physicians may be able to use the company's *Symlicity* system to treat both heart and kidney failure, since the same physiological mechanism underlies each of those conditions—major markets both.

In addition to looking to serve large markets, Ardian's device may also achieve another highly valued, but over-hyped and difficult to define criterion by being a truly disruptive technology. The conditions that Ardian is looking to address are all currently treated either exclusively or most often by drug, rather than device therapy. Converting any significant portion of patients in those markets from first-line drug to device therapy would constitute a significant change in treatment patterns, a rarely realized clinical goal for device companies that would likely qualify as disruptive by most standards.

There is no doubt that the challenges for Ardian are as large as the opportunities. It is the only company that has a catheter-based device to lower hypertension, and is one of only two companies with devices approved for treating hypertension; **CVRx Inc.**, whose *Rheos* device is surgically implanted, is the other. (See "CVRx: Can Devices Succeed Where Drugs Fail for High Blood Pressure?," IN VIVO, September 2007 [2007800140].) Both companies' devices have CE mark approval and are investigational in the US.

Pioneering a new technology in an area that requires a dramatic shift in physician practice patterns from drugs to devices is heavy lifting for a start-up. That is why Ardian is looking to walk before it runs, and is focusing not on the broad hypertension market, but rather on those patients who are refractory to medical therapy, figuring that these are the patients for whom physicians will be most interested in adopting new therapies. But this strategy represents a shift from Ardian's original target for this technology when it was acquired by The Foundry

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incubator, which was heart failure. So far, the company's revised strategy appears to be succeeding both clinically—having recently reported positive safety and efficacy data—and with investors: witness the large Series C round the company raised this past spring, during the depths of the current economic downturn.

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Born Outside an Incubator

Ardian was the eighth company launched out of The Foundry, but the idea for the technology came from outside the incubator. Howard Levin, MD, a cardiologist, and Mark Gelfand, an electrical engineer, who have worked together to launch a number of cardiology device start-ups, including **CHF Solutions Inc.** and **Cardiac Concepts Inc.**, came up with the idea of developing a device to treat heart failure through renal denervation (severing the kidney's nerves).

The idea itself wasn't a new one. Previous research had documented that denervating the kidney could have a positive effect on heart failure and hypertension. Indeed, in the early 20th century, surgeons employed a traumatic surgery, sometimes called sympathectomy or splanchnicectomy, to treat severe hypertension. In fact, it was the discovery of research papers dating back to the early 1930s discussing this procedure that ultimately convinced The Foundry to take on this project.

Levin and Gelfand had conducted some preclinical research that used urine output as a proxy to measure renal denervation. Based on that research, they were able to demonstrate the apparent physiological benefit of this procedure in terms of increasing fluid output, thereby reducing the fluid overload cascade of heart failure.

In early 2003, Levin and Gelfand contacted Advanced Technology Ventures (ATV) about raising money to start a company around this idea. ATV wasn't ready to fund the project solely on the basis of the preclinical research that had been done to date, but thought the idea had potential, and Steve Shapiro of ATV suggested that Levin and Gelfand contact The Foundry to see if the incubator would take on the project. For a venture firm like ATV, having The Foundry take on a project serves two purposes: first, it validates a clinical concept, and, second, it provides additional developmental resources to more quickly move the project along.

Hanson Gifford, president and CEO of The Foundry, admits that he had significant questions about the concept when approached by the two inventors, largely because of certain limitations of the preclinical research that made it hard to determine the actual benefit of the procedure. Also, Levin's and Gelfand's initial idea was to use either a permanent drug infusion pump or an implantable neurostimulator to block the renal nerves. Neither of those seemed like attractive clinical options to The Foundry, which was initially looking at this project as a heart failure therapy. "We were aware that there was a growing interest in neuromodulation and neurostimulation for a variety of clinical applications, but while we were intrigued by that, we also saw a lot of uncertainty and risk there,"

Gifford notes.

The flip side of the risk was the novelty of Levin's and Gelfand's approach. The incubator had been looking around for new ideas to treat heart failure for a while, but most of those it had seen were less invasive variations on the idea of devices that limited or restricted the heart's ability to enlarge. "But because we had significant questions about whether this approach would work, we were quite skeptical and really struggled with whether or not to take this project on," Gifford recalls.

What ultimately convinced The Foundry to move ahead with this project was the discovery by Mark Deem, The Foundry's chief technical officer and one of its first employees, of the 1950s research by Reginald H. Smithwick, MD, and others documenting the success that these crude, traumatic denervation surgical procedures had on improving heart failure and hypertension in chronic patient populations, albeit at the cost of significant risks and side effects. Deem explains that initially the incubator didn't fully understand the role of the renal nerves in regulating blood pressure. Indeed, hypertension was seen as a potential secondary clinical application of this technology, with heart failure as the primary goal.

In the course of mulling the idea over for several months, Deem recalls meeting with a nephrologist at the **Stanford University Medical Center**, who explained more about the role of the renal nerves and the renin-angiotensin-aldosterone system, while also remarking that this sounded a lot like an old surgical procedure that had been abandoned 50 or so years ago. That caused Deem to head to the bowels of the Stanford medical library, where he turned up old research papers, including Smithwick's 1953 *JAMA* article presenting the results of 1,266 cases of the surgical denervation procedure (splanchnicectomy) to treat hypertension. "These papers included radiographic evidence of hearts that had remodeled after this surgery, while also showing significant blood pressure declines," Deem says.

These surgeries were not the precise procedures we are used to today; instead of specifically targeting the renal nerves, these surgeries attempted to interrupt the sympathetic nervous system's activity to the lower half of the body by targeting the spine, often causing significant complications. One of the most serious risks was orthostatic hypotension, which meant that when patients stood up quickly, they would often faint. With the advent of diuretics and other drugs to treat hypertension, these surgeries became obsolete, largely because of these risks and complications.

Despite the inherent problems with those early surgical procedures, Mark Deem says they served a valuable purpose as part of The Foundry's diligence process on Levin's and Gelfand's project: that early research demonstrated that the underlying physiological concept of using renal denervation to treat heart failure and lower blood pressure was viable. "The fact that we found several publications from different reputable centers across the US and from overseas documenting a large number of cases showed us that this was not a case of one outlier physician

treating a few patients," Deem explains. "That helped validate the idea for us."

Another important factor in The Foundry's decision to take on this project was Deem's and Gifford's repeated consultations with Gerald F. DiBona, MD, a nephrologist at the **University of Iowa College of Medicine**, and an expert on renal nerves. Deem recalls, "Gerry DiBona advised us that, based on his 40 years of research, it is impossible to maintain a hypertensive state in the absence of renal nerve activity. That was so compelling a confirmation of what we are trying to do that we put it in our funding presentations."

Shifting from Heart Failure to Hypertension

So encouraged were Foundry officials that, in October 2003, they acquired the IP for the renal denervation project from Levin and Gelfand, and started work on what became Foundry company number eight. Gifford, Deem, and entrepreneur-in-residence Denise Zarins comprised the initial Foundry team working on the project. The project officially became Ardian in January 2005, with the name derived from the acronym for renal denervation (RDN).

Zarins had joined The Foundry after having worked with two device start-ups based on technology developed by noted physician-entrepreneur Thomas Fogarty, MD: AAA stent graft company AneuRx (which was acquired by **Medtronic Inc.**), and Bacchus Vascular, which developed a device to treat peripheral deep vein thrombosis (and was acquired earlier this year by **Covidien Ltd.**). [199610077] [200910131] Zarins also worked with Foundry co-founder (and Ardian board member) Allan Will at AneuRx, where he was president and CEO.

In developing its initial strategy for this project, the Foundry team realized that being the first renal denervation device would bring with it a heavy clinical and regulatory burden. Their search criteria for a full-time CEO placed a premium on someone with background in those areas, rather than candidates with previous experience running a start-up or those with more of an operations background. The incubator also has been successful with several of its other companies in grooming talented executives into first-time CEO roles. The choice for the position, Andrew Cleeland, fit that mold, and he became Ardian's CEO in January 2006.

Cleeland started his 21-year medical device career by working for Australia's equivalent of the FDA, the Australian Therapeutic Goods Administration. He then went on to work for Telectronics, the Australian pacemaker/defibrillator company, before it was eventually acquired by **St. Jude Medical Inc.** [199610220] Cleeland then worked for **Baxter Healthcare Inc.** and spent the last seven years prior to joining Ardian with **Radiant Medical Inc.**, a developer of endovascular temperature management products.

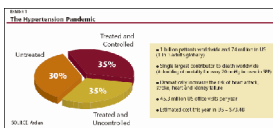
When Cleeland joined Ardian, the company was still focusing on treating heart failure. However, Ardian's management team realized early on the difficulties inherent in conducting heart failure clinical trials, particularly in defining the patient population and determining reliable hard end points for these studies that would meet regulatory approval.

By contrast, changes in hypertension could be measured by clear, easily defined parameters that are well understood and accepted by clinicians and regulatory bodies. Indeed, Hanson Gifford recalls a heart failure cardiologist remarking at a recent clinical meeting that the FDA really only recognizes two strong clinical surrogates as trial end points: blood pressure and cholesterol levels.

The result: by mid-2006, Ardian had shifted its primary focus from heart failure to hypertension. "This provided us with a clearer, more well-defined clinical trial pathway. We also recognized that, with a solid clinical foundation in hypertension, it would be easier to investigate heart failure and other indications later," Cleeland explains.

Hypertension also, of course, offers a huge and growing potential market, with significant unmet clinical needs. The demographics of an aging population, coupled with lifestyle factors like obesity, and an improved understanding of this condition have resulted in hypertension truly reaching pandemic proportions worldwide. One in three adults, both in the US and globally, have high blood pressure, based on the currently accepted standard of 120mmHg/80mmHg. That amounts to one billion people worldwide and 74 million people in the US (one in three adults globally), with 30% of Americans with high blood pressure going untreated.

Of the remaining 70% that are receiving treatment, only half have their hypertension under control. The other half remain uncontrolled, largely because they are refractory to medical therapy (so-called drug-resistant hypertension [DRH]), which usually consists of a combination of several types of drugs including ACE inhibitors, angiotensin receptor-, calcium channel- and beta-blockers, and diuretics.. In addition, for the remainder of these patients, their hypertension remains uncontrolled because there is significant non-compliance with medical regimens, either because of the number of pills a patient is taking or the side effects they produce (most commonly a loss of energy or sense of fatigue) or both. (See Exhibit 1.)



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There are two types of hypertension: essential and secondary. Secondary hypertension results from some other disease state and comprises only a small group—10-15%—of the total hypertensive population. The remaining 85-90% have essential hypertension, for which the precise etiology remains unknown. It is generally agreed that the causes of hypertension are multi-factorial, with a significant factor being the chronic hyper-activation of the sympathetic nervous system (SNS), especially the renal sympathetic nerves. That also happens to be a common characteristic of heart failure and kidney disease.

Traffic along the renal sympathetic nerves is bidirectional. Signals coming in to the

kidney travel along what are called efferent pathways and influence renal blood flow, trigger fluid retention, and activate the renin-angiotensin-aldosterone system cascade. Renin is a precursor to the production of angiotensin II, which is a potent vasoconstrictor, while aldosterone regulates how the kidneys process and retain sodium. All of these mechanisms serve to increase blood pressure.

Signals coming out of the kidney travel along what are referred to as afferent nerve pathways integrated within the central nervous system, and lead to increased systemic sympathetic nerve activation. Chronic over-activation can result in vascular and myocardial hypertrophy and insulin resistance, causing heart failure and kidney disease. Ardian's *Symplicity* system is designed to ablate the renal nerves, hence the term renal denervation, in order to disrupt this chronic activation process.

Last Minute Design Change Does the Trick

While the original technology that The Foundry licensed from Levin and Gelfand employed an implantable device, Hanson Gifford notes that the incubator's goal was always to develop a percutaneous approach. This plays to one of The Foundry's strengths, which is its vast experience in developing catheter-based devices for a variety of clinical applications.

One of the most significant technology development challenges turned out to be the choice of the proper energy source to ablate the renal nerves. The *Symplicity* system employs a radio frequency generator, but Gifford acknowledges that the Foundry team tried just about every possible energy source before deciding on RF. Indeed, the first-generation device was almost introduced powered by a different energy source that did not function as well as the current system. Gifford credits Denise Zarins with both convincing the team to hold off on releasing the product until they resolved the problems with the energy source and coming up with the solution that led to the current RF system.

The anatomy of the renal nerves presents both a challenge and an opportunity because the nerve fibers form a hard-to-reach, lattice-like network in the adventitia (outer layer) of the renal artery wall. Ardian addresses this by employing multiple treatments delivered circumferentially from within the blood vessel to disable the surrounding nerves. "We did a number of studies trying to understand how the renal nerves are distributed throughout the artery and found that because they were so small and embedded several millimeters within the artery wall, we were better off designing a series of ablation treatments during the course of a procedure to ensure we achieved full coverage," Zarins explains. The biggest potential risk of such an approach is that ablating tissue frequently produces a bad healing response that could produce stenosis, which could result in blockages within the vessel.

Denise Zarins points out that, with certain previous RF ablation procedures, this risk often became reality. As a result, among certain physicians, there is a concern about using RF ablation in a blood vessel. "Certain doctors recall that stenosis was associated with pulmonary vein ablation, for example, so in approaching those

physicians, we have to make sure they understand how our approach is very different from what was offered previously," she says.

According to Gifford, the company's initial choice for an energy source produced an intermittent response that posed a risk of injuring the vessel wall. Zarins and her team developed an alternative approach that she says delivers energy in such a way as to avoid that risk. Ardian actually delayed the pending final design of the first-generation device and ended up replacing the energy source with Zarins' RF design, which currently powers the *Symlicity* system.

Just as with any catheter procedure, there is a risk of operator error that could result in perforation or dissection. However, one anatomical benefit of ablating around the renal arteries is there is little risk of damaging collateral organs as is the case with ablation around the heart or other vital organs. That is because the renal arteries are surrounded by fatty tissue, which serves to protect adjacent organs. Zarins also points out that people can function perfectly well following renal denervation, as has been demonstrated in kidney transplant patients and others with various types of kidney disease.

The procedure using the *Symlicity* system is performed in a cardiac cath lab using standard interventional equipment and techniques, and can be done generally in around 40 minutes—about the time of a typical angioplasty with stenting. Under fluoroscopy, the catheter-based device, which has a one millimeter-sized electrode at the tip, is inserted into the femoral artery through an off-the-shelf 8 French guiding catheter—Cleeland says a 6 French version is in early clinical study—and threaded to the renal artery. Once the catheter reaches the desired location, the physician triggers the device to deliver a controlled, low-power burst of RF energy for two minutes. The device lets the physician know when it is placed against the vessel wall and, using pre-set algorithms, automatically determines how much energy can be safely delivered. Cleeland says the current protocol is to deliver four such treatments equally spaced around the circumference of the artery in order to cover the entire vessel wall, penetrating to ablate the renal nerves. The procedure is then repeated on the other kidney.

The procedure does require the use of an analgesic; otherwise, patients would feel some discomfort during the actual ablation. However, Cleeland says morphine or other mild pain medications generally suffice, and patients do not need to undergo general anesthesia nor is there need for an attending anesthesiologist.

How Much Lower is Enough?

But Ardian needs to do more than just prove its device's safety—it must demonstrate efficacy, which also entails breaking new ground. Among the big questions the company needs to answer are: by how much can it reduce a patient's blood pressure and how long will that improvement last? As the first percutaneous renal denervation procedure, this is uncharted territory.

Physicians agree that there is a doubling of cardiovascular mortality for every 20mmHg increase in systolic blood pressure (the top number in a blood pressure

reading). In addition, according to the American Heart Association, a 5mmHg reduction in systolic pressure results in a 14% decrease in stroke, a 9% decrease in heart disease, and a 7% decrease in overall mortality.

Cleeland points out that blood pressure medications are deemed effective if they reduce systolic pressure by at least 10mmHg, so that is one metric Ardian is using to assess the success of its procedure. "We are saying that if we don't see greater than a ten millimeter drop in patients, we are counting them as non-responders," he says. According to Cleeland, in its clinical experience to date, the company is seeing a positive response rate among patients of close to 90%. And in terms of duration, Ardian has reported sustained effectiveness out to at least 12 months, and the company hopes to be able to demonstrate that the process is effective for a lifetime following a single treatment.

Ardian recently completed its initial 12-month clinical safety trial, SYMPLICITY I, at 12 sites in the US, Australia, and Europe. The company enrolled approximately 100 patients, focusing on the drug-resistant hypertension population. Thus, the inclusion criteria for the trial require patients to have a systolic blood pressure of greater than 160 despite being on at least three anti-hypertensive medications. The trial excludes people with known secondary causes of hypertension and diabetics.

Henry Krum, MD, the study's co-principal investigator from The Alfred Hospital in Melbourne, Australia, presented some initial data from the trial at this year's TCT conference in San Francisco. The data covered the first 45 patients treated with the device, and there were no significant complications, leading Krum to conclude that the procedure is simple to perform and safe.

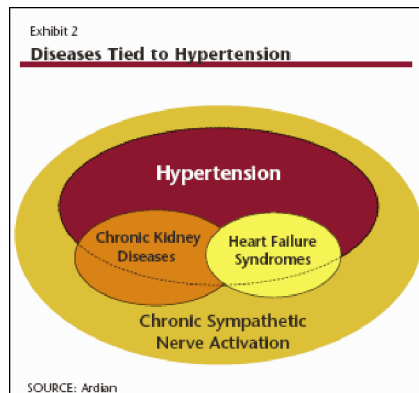
In terms of effectiveness, in the 34 patients with 12-month follow-up data, Krum reported average reductions of 27mmHg in systolic and 13mmHg in diastolic blood pressure. In addition, despite having an average baseline systolic blood pressure of 177mmHg, 44% of those patients now have what is considered to be controlled blood pressure (≤140mmHg). In addition, there has been no evidence of any decline in renal function resulting from renal denervation. In fact, Krum noted that the data suggests renal function is actually being preserved following the procedure, which could be evidence of a reno-protective effect, although he noted that this finding was not statistically significant. He concluded that this initial trial showed "significant and sustained reductions in blood pressure" in drug-resistant hypertension patients.

Ardian is proceeding with its next study, SYMPLICITY HTN-2, a randomized clinical trial of 110 patients at 30 sites in Europe and Australia using the same inclusion/exclusion criteria as the safety study. Cleeland expects the data from this trial to be presented sometime around the middle of 2010. The company decided to run this large-scale randomized trial in Europe and Australia before doing a major US study so that they will be prepared for any issues that may arise and avoid problems with its PMA trial. "We've seen so many companies run their first large randomized trial in the US, only to run into issues that ultimately delay their US approval and product launch, and we wanted to avoid that," Cleeland says.

"Our strategy is to use this first randomized study to provide solid safety and efficacy data, to better understand the study design, and also to use it as a dry run for the US PMA trial."

Beyond Hypertension

While Ardian is understandably reluctant to address possible future clinical applications for its renal denervation technology before the *Symplivity* system is approved in the US for its first target market, drug-resistant hypertension, the common underlying physiologic mechanisms between hypertension and heart failure, kidney disease, and other chronic conditions cannot be ignored. (See *Exhibit 2*.) Indeed, though it is using a different approach to treating hypertension, CVRx has documented cases where there is regression of left ventricle hypertrophy in heart failure patients whose hypertension has decreased. Physicians generally agree that this kind of ventricular remodeling can help reverse heart failure and is a result of reducing the level of central sympathetic nervous system response. Although hesitant to discuss potential heart failure applications for Ardian's technology in great detail, Andrew Cleeland agrees that *Symplivity* is likely to produce a similar response since it has the same effect as CVRx's *Rheos* device on hypertension because it also reduces SNS activity.



Ardian's strategy is to walk before it runs by establishing a "beachhead" through proving effectiveness on DRH patients first. In doing so, the company also plans to accumulate supporting clinical data on that and other potential applications for the *Symplivity* technology. Building a solid foundation of evidence-based data is also essential in convincing the hypertension community and particularly the company's initial physician customer group, interventional cardiologists, of the benefits of adopting this new technology. While interventionalists are perhaps the most eager adopters of new devices and techniques of any physician specialty, they also rely on evidence-based data more than other physicians in making product adoption decisions.

One thing Ardian is clear on with regard to potential future clinical applications for its technology is that they will all be served from within the same company. Cleeland eschews the approach adopted by other device entrepreneurs who choose to spin off different applications of a technology into separate companies to treat different conditions and serve different physician customers.

Cleeland acknowledges that Ardian will be faced with the challenge of selling to different physician specialties—most notably, heart failure specialists and nephrologists—in the future, but insists that can be done best through one company, thereby also maximizing the enterprise value of that company. He also points out that, even in hypertension, Ardian will need to call on the range of physician specialties who currently manage hypertension patients. These include a large number of primary care providers whom the company will need to convince of the benefits of the *Symlicity* procedure so that they will begin referring their patients to the interventional cardiologists for treatment.

The Cost of Clinical Trials

Perhaps the company's biggest challenge at this stage will be funding the clinical trials necessary to establish renal denervation as a safe and effective therapy in those various therapeutic areas beyond DRH and hypertension generally. The size and complexity of running clinical trials in heart failure alone is daunting, particularly for a start-up company. When you add in the continuing hypertension studies that Ardian will need to maintain, plus trials in kidney disease and perhaps diabetes, the question becomes what is manageable—and affordable—for a small company, while still focusing on rolling out its initial products for the DRH market?

Ardian is well aware of the potential risk that costly clinical trials can pose for start-ups, having seen another Foundry company, Xtent, ultimately brought down by that burden. Despite having an innovative drug-eluting stent technology and completing a successful IPO, the company was recently forced to dissolve because it could not afford to fund the additional DES clinical trials needed for FDA approval and to remain competitive in that market. (In fact, Ardian's CFO, Timothy Kahlenberg, joined the company after having held the same position with Xtent.) Cleeland acknowledges, "If we had \$100 million, we could be running five of these large studies in parallel, but at the moment, we don't, so we're focusing on running SYMPLICITY HTN-2 first, then carefully considering our other options."

Not that Ardian is crying poverty. In this current difficult financing climate, the company is one of the success stories among device start-ups, having raised a total of \$65 million, including \$47 million in its recently closed Series C round. The company's initial Series A funding of \$1.6 million in January 2003 came from Split Rock Partners and Morgenthaler Ventures, who finance all of The Foundry's projects. In January 2005, the company raised what Cleeland calls its Series B-1 round, which was led by Advanced Technology Ventures, which had originally brought this technology to The Foundry, and a year later, closed on its Series B-2 round with just inside investors, for a total from both tranches of \$16 million.

And despite the depressed financing environment, Ardian's \$47 million Series C round, which closed in March 2009, was done at a substantial step-up valuation to its prior rounds. Medtronic was the largest investor in this most recent fundraising, which also included a new investor, Emergent Medical Partners, along with the existing investors.

While some may question bringing on a strategic partner at this stage of Ardian's development, Cleeland is confident the relationship will provide significant value. He is quick to point out that Medtronic did not acquire any significant rights in exchange for its investment and that Ardian wasn't necessarily looking for a large company to invest in the most recent round. "We had been so far under the radar that no one knew anything about us, so we took the opportunity to introduce ourselves to a select number of large companies that we thought could potentially help us down the road," he says.

Ardian is acutely aware of the costs they are facing in contemplating future clinical trials, and company officials note that their only current competitor, CVRx, has raised a total of \$209 million, including strategic investments from **Johnson & Johnson** through its venture capital unit Johnson & Johnson Development. In addition to approaching several large device companies, Ardian also contacted a number of major drug companies with products such as anti-hypertensive agents that could benefit from being used together with the *Symplicity* system. According to Cleeland, Medtronic ultimately proposed the most attractive investment package. Interestingly, several years ago, Medtronic was working on developing its own device-based approach to treating hypertension, but ultimately discontinued the project.

For Ardian, the relationship with Medtronic may prove to bring more than just investment value. The large company agreed to have Richard Kuntz, MD, who is senior vice president and chief scientific, clinical, and regulatory officer, and a thought leader in device clinical trials, assume the board seat that came along with Medtronic's investment, which should prove valuable in crafting Ardian's future clinical trials strategy.

The company has already begun working with the FDA, resulting in two feasibility study IDEs being approved. Cleeland projects that Ardian's current funding will carry the company through completion of its US pivotal PMA trial and what he calls a "controlled market release" in Europe, both in 2011, to reach cash-flow positive.

In Europe, the company has already received CE Mark approval, but is holding off on commercializing the product immediately, preferring to wait until mid-2010 to accumulate more supporting clinical data. When Ardian begins its European sales effort, it will be with its own sales force. In Cleeland's view, "It's just like our clinical studies; we want to maintain ownership of the process, build customer relationships, and capture product feedback ourselves."

Ardian is also getting an early start on reimbursement activities. The company's view is that the *Symplicity* system is at least cost effective and potentially can reduce costs, but they acknowledge that this is something they'll need to demonstrate over time. There are current CPT codes for placing catheters in the renal artery that Ardian may be able to use to obtain reimbursement initially and still others for the old renal denervation surgeries, but the company is in the process of reviewing the reimbursement landscape to determine if existing codes

will apply or whether they will need to obtain new ones.

Competitively, too, Ardian is staking out new ground. Right now, the company has the interventional market to itself, and the only device-based competition for hypertension is CVRx with its surgical approach. CVRx, which is currently conducting its US pivotal study, is closer to US commercialization than Ardian. Given the potential size of the hypertension market, Cleeland does not believe that either company will have the field to itself for very much longer, but he acknowledges that for two small companies looking to change longstanding physician practice patterns from drug to device therapy, the best scenario would be for both companies to succeed, thereby validating the benefits of device-based therapy in this space. "This is the classic case where a rising tide does lift all boats," he says.

Getting Realistic Returns on Innovation

Conventional wisdom in the device industry holds that, despite the recent decline in M&A activity and the lack of an IPO market, there will always be an exit opportunity for truly disruptive technologies. While most device deals remain smaller transactions of under \$100-\$150 million, even in these tight economic times truly innovative companies are still being well-rewarded. Thus, in a hot space like percutaneous heart valves, for example, Medtronic's \$700+ million acquisition of CoreValve (now **Medtronic CoreValve LLC**) and **Abbott Laboratories Inc.**'s \$400+ million deal for **Evalve Inc.** belie the current overall state of device M&A and demonstrate that acquirers are still willing to pay a premium for innovative technologies. [\[200910024\]](#) [\[200910100\]](#)

Yet, as buyers become more cautious, clinical and regulatory hurdles get higher, and product development timelines lengthen, there are still dark clouds on the horizon that threaten the ability of innovative start-ups to develop their technology to the point where they become viable M&A candidates. When well-funded start-ups with experienced management and promising technology like Xtent and Northstar Neuroscience are forced to dissolve, there is reason for other emerging companies to be concerned. For Xtent, the burden proved to be the high cost of DES clinical trials; for Northstar, it was missing a clinical trial end point and not having the opportunity to develop other promising applications for its technology. In both cases, investors decided it was better to pull the plug rather than risk putting additional funds into what were already well-financed companies.

Those risks become even greater for any start-up whose technology represents a significant innovation, particularly one like Ardian that is looking to change current practice patterns. Today, the clinical trials burden alone for companies with truly novel technologies can easily force companies to raise in excess of \$100 million just to reach commercialization. The \$65 million that Ardian has raised to date looks impressive—until one considers that, as noted, rival CVRx has raised \$209 million and is still in the middle of its US trial. Each company already has a strategic investor, but the question remains as to whether, in this economic climate, these companies will be able to achieve the kind of returns investors

expect. Indeed, Hanson Gifford questions whether a company like Ardian would even be able to get funded as a start-up today.

For now, Andrew Cleeland insists that he and his management team are not focused on the vagaries of the current device M&A environment or Ardian's ultimate exit strategy, preferring instead to concentrate on executing the company's clinical trials strategy and bringing its technology to market as a stand-alone business. "Our vision as a leadership group is that, no matter what state the economy is in, you don't sell a company; a company gets bought," he argues.

Cleeland says that 21 years in the device industry has taught him that, no matter how novel Ardian's technology may be and no matter how large the markets that it could potentially serve are, he needs to run the company like any cash-conscious device start-up. Indeed, only in the past year did Ardian's payroll top 20 employees. "We are not going to anticipate success and build up the infrastructure in anticipation of hitting a milestone," he says. "We prefer to run lean and let our success guide our way."

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