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PI-CARDIA: REPAIR RATHER THAN REPLACEMENT IN TAVR

While most of the focus in transcatheter aortic valve technology has been on replacement devices, Pi-Cardia is making a case for aortic repair, claiming it can be clinically better for many if not most patients.

▶ DAVID CASSAK

- Pi-Cardia executives recognize that transcather aortic valve replacement, one of the most dynamic market segments in medtech today, is not likely to slow down any time soon. But they believe some, if not many patients will fare better with a repair procedure before a replacement is called for, for reasons of both demographics and cost.
- A collaboration with Chinese TAVR leader Venus Medtech brought both investment dollars and access to one of the world's largest markets.
- The company has also developed a novel replacement device, at least in part an acknowledgment that repair is unlikely ever to supplant replacement.
- In short, facing much larger and well-established competitors, Edwards and Medtronic, Pi-Cardia's focus is less on an alternative valve device than on a new way to segment the market.

For much of the history of cardiovascular devices, the sheer power of innovation levelled the playing field for big and small companies. The market leading positions of much larger multi-nationals was never entirely safe because the appetite of physicians for new devices gave small companies open access to promising markets, provided they could demonstrate that their technology was better than anything big companies had to offer.

The rapid growth of transcatheter aortic valve replacement (TAVR) changed all that as multi-nationals **Edwards Lifesciences** and **Medtronic plc** quickly established what appear to be unassailable positions as market leaders—positions not likely to be eclipsed any time soon. Start-ups with novel technology thus can either pray that they're acquired by one of the multi-nationals or they must find a new path to market. Israel-based **Pi-Cardia Ltd.** believe it has found that new path, offering interventional cardiologists an alternative way to think about treating aortic stenosis, one focused on repair rather than replacement of stenotic valves. Erez Golan and Eyal Kolka, Pi-Cardia co-founders, believe that offering cardiac interventionalists an additional option makes sense for many patients and the healthcare system, in the process offering physicians not so much an alternative valve device than a new way to segment the market.

A Meaningful and Measurable Improvement

With backgrounds in both physics and mathematics, Golan and Kolka first met during their days in the Israeli military, working together in R&D for Israel's defense industry. Research is "a big part of the Israeli military," Erez Golan notes, and, in turn, there are close connections between the Israeli military and its rich medical device industry. Notes Eyal Kolka, "The combination, on the one hand, of physics, electronics, and mechanics, and on the other, biological variants makes things complicated but also challenging. And when you add to that the mission to save lives or improve the quality of life, it makes this much more satisfying than developing a quicker router or other things in communications and software. This is more like a mission."

In the late 1990s, Golan and Kolka began to work as serial entrepreneurs in medical devices, with a focus on cardiovascular. Their first effort together was intravascular MRI company TopSpin Medical, developers of a miniaturized MRI camera on the tip of a catheter to identify vulnerable plaque. (Golan has earlier worked at interventional cardiovascular pioneer Medinol.) TopSpin eventually received a CE mark and commercialized its technology in Europe

before going public on the Tel Aviv stock market. In the early 2000s, the company entered into a collaboration with **Johnson & Johnson** around its drug-eluting stent (DES). But concerns at the time about the relationship between DES and stent thrombosis scuttled the project. As a result, TopSpin changed direction to focus on urology, and Kolka and Golan left the company in 2007.

Contemplating their next project, the two knew they wanted to stay in medical devices, but instead of launching one new company, they founded two. One, called Clear Cut Medical, focused on intra-operative assessments of breast cancer, which evolved based on expertise in MRI gained from their experience at TopSpin. Clear Cut developed a microwave-sized MRI for performing intra-operative margin assessment, a machine that was easily portable from one operating room to another, or could even be used in a physician's office to analyze tissue taken in surgery or in a biopsy. (The device now has a CE mark and is commercialized in Europe.)

The other company was Pi-Cardia. The idea, says Erez Golan, came out of a discussion with a cardiac surgeon with a high volume in surgical aortic replacement procedures at one of the biggest hospitals in Israel. "One of the lessons we learned from TopSpin is that interventional cardiologists really want [devices] that create a meaningful and measurable, acute improvement for the patient," he says.

Repair, Don't Replace

From their days focusing on vulnerable plaque, Kolka and Golan gained an insight that would shape their future entrepreneurial efforts. In the late 1990s, there was an early and somewhat premature view that the true source of acute myocardial infraction (AMI) wasn't occlusion of arteries, but the buildup of plaque on the artery wall—friable or fragile plaque that could break off at any moment, sending emboli into the heart, causing an infarction. People didn't get heart attacks, the thinking went, because of too many cheeseburgers that clogged their arteries; even otherwise healthy people could be at risk if their plaque was vulnerable to rupture or displacement.

But the targeting of vulnerable plaque never really took off, and Golan and Kolka saw firsthand that exciting new and radically different strategies for the treatment of a medical problem didn't always have as long a shelf life as their early enthusiasts expected. Interventionalists "want to see that the patient came into the lab with a problem and came out without it," says Kolka. "With vulnerable plaque, that was hard to see" if only because measuring the degree of calcification or occlusion was no longer definitive. Vulnerable plaque was, he says, "a theoretical and prophylactic exercise" because treatment was all about anticipating a problem that might occur in the future "and how do you convince people that a certain area of the coronary artery could potentially be a problem in the future? That's difficult to understand."

The notion, moreover, that vulnerable plaque was more a systemic condition than a focal buildup *per se* made treatment strategies particularly elusive, because unlike with an occlusion, the assigning of a specific time to treat was flexible. With systemic conditions, Kolka goes on, "How do you know where to treat? What are you really trying to treat? Who's the enemy? It was just too vague for interventional cardiologists." Eventually, the treatment of vulnerable plaque, "went into the pharma space," he says.

It was around the time of Pi-Cardia's launch in late 2009 that transcather aortic valve replacement (TAVR) was taking off. "Everybody was talking about treating valves percutaneously, replacing the valve," Golan says. "But as physicists, we saw that when you look at calcified leaflets, the calcium grows into the leaflets and starts slowly but surely to hinder their motion or mobility. Now, a patient can live with that condition for decades, until there is a clinically meaningful stenosis or severe narrowing of the valves. So we thought instead of implanting a new valve, maybe you could just treat the calcification issue."

Pi-Cardia's device does just that by cracking or scoring the calcification, leaving the native valve in place and addressing the buildup. "For patients who will live until 75 or 85, the best approach is to continue to live with their own valve," Golan goes on. "I mean, why would you put an implant into that patient unless that was the last resort? If you look at every field of medicine, putting in an implant is the last resort. It didn't seem right to us that people were just skipping over the step of trying to fix the valve and going directly to an implant."

Moreover, there were strategic as well as clinical considerations. TAVR differed from the kinds of cardiovascular device innovations of a decade earlier. While small companies like Advanced Cardiovascular Systems (ACS) and Arterial Vascular Engineering (AVE) could, in angioplasty and coronary stents, challenge and win against much larger, well-established companies in the 1990s, by the time TAVR came along two large multinationals, Edwards Lifesciences and Medtronic, had built formidable franchises in transcatheter valves, franchises that would resist the kind of small-company leapfrogging of a decade earlier. Notwithstanding their confidence in repair, Pi-Cardia's founders saw early on that "replacement was going to become very well-established," says Golan. Instead of entering the competitive fray with another replacement device, "we were always about finding ways to keep the native valve because to compete with the big companies on just another platform didn't seem possible to us."

A Whole New Space

To be sure, Pi-Cardia believes there is a compelling clinical case to repair. "You'd always prefer to repair a native valve than replace it as long as that repair is safe, effective, and durable," Golan goes on. Pi-Cardia's strategy is to offer interventionalists an alternative—not so much an alternative (replacement) valve, but an alternative way of thinking about addressing aortic stenosis.

Pi-Cardia's first device is called the *Leaflex* and is designed, as the name implies, to make the valve leaflets more flexible via a scoring mechanism. (A second product, introduced about a year ago, is called the *ShortCut*, and is designed to be used by interventionalists who had earlier opted for replacement by creating a full cut through the leaflet to limit the risk of coronary obstruction that can occur in replacement procedures.)

Though development of *Leaflet* started in 2016, Golan notes that the company began work on the concept of repair before having any idea about what the device might look like. "One of the things about Pi-Cardia is that we really started with the basic science," he says. "We collected thousands of valve leaflets taken from patients over 10 years to study calcification patterns and mechanical properties." Pi-Cardia wanted to understand how calcium grows and what its mechanical properties look like. The company also explored different ways of cracking or fracturing the calcification, such as laser, ultrasound, and lithotripsy. "We didn't start with a particular technology," Golan goes on. "Instead, we looked at this very broadly, trying to understand the target of calcified leaflets."

That effort around basic research alone took several years. "The reason is, this [i.e., repair] was really uncharted territory," he says. While surgeons routinely do valve replacements, Pi-Cardia reasoned, interventionalists would be less familiar with valves and valve repair. "Many of the cardiologists, when they started to go into this space, were not very familiar with how the calcium grows into the valve, and what's the morphology of the calcification, how you can potentially crack it. We needed to invent a whole new space of effective repair, non-implant-based repair of the aortic valve that we think can be no less significant than the TAVR market."

In a *Leaflex* procedure, an interventional cardiologist uses a transfemoral approach, snaking a guidewire to the spot in the valve where the calcification or stenosis has taken hold. There are two elements to the device: an expander that sits just below the valve and a frame that sits above it. Once at the spot of calcification, the guidewire is then pulled back to measure the pressure within the ventricle and, at the same time, within the aorta. The interventionalist continuously monitors the gradient across the valve, "an important index for how much of an improvement has to be made in the mobility of the valve" during the scoring, says Golan.

Pi-Cardia's strategy is to offer interventionalists an alternative—not so much an alternative (replacement) valve, but an alternative way of thinking about addressing aortic stenosis.

Once in place, the expander is brought into the valve, pushing the leaflets against the frame and the scoring elements. The frame has sharp struts facing the calcification that score the plaque as the expander enlarges. "That's key," says Golan. *Leaflex* doesn't simply push the plaque to the side with the stenosis radially outwards, as a balloon would. Rather, the frame struts "create real fracturing and segmentation of the calcium," he explains. "The key point is that the calcium that originally was one long arc, preventing the motion of the leaflet, is now segmented into much shorter segments," freeing the motion of the leaflet.

"The scoring makes that very stiff leaflet turn into a much more flexible leaflet," Golan continues, "and unlike balloon valvuloplasty, which just simply pushes everything to the side, [*Leaflex*] addresses the real issue, which is the calcification." Indeed, he argues that the reason balloon valvuloplasty has pretty much disappeared from clinical practice is that "it doesn't deal with the plaque, it just dilates the valve," which often gives way due to a quick elastic recall of the annulus. "People pretty much gave up on using balloons because they don't work in a calcified valve," Golan says, adding, "We've studied this for years and looked at thousands of valves, and eventually found out that the right way to treat it is really to cut through the calcification."

Just as important, *Leaflex* fractures the calcification without compromising the natural elasticity of the leaflets themselves. And the mechanism of action is entirely mechanical, with no energy-based or biological approach that might alter the patient's anatomy. "It's a very predictable and fairly simple mechanism," Golan says. And the interventionalist doesn't

have to worry about scoring too much or too little because the device controls and delivers the appropriate amount of scoring. "The device itself actually makes sure that the tissue is cut right, without harming the native," he adds. "It's rather simple to operate."

A Shift to Execution

In effect, *Leaflex* restores the native function of the valve, neutering the impact of the calcium buildup and giving the patient back the natural function of the valve. Moreover, the procedure is simple and quick, around 20 minutes, and improvements are realized immediately. "The goal is to have something that gives the patient and the physician a very clear improvement that can be measured during the procedure," he says.

Early clinical trials of the *Leaflex* device were initiated in 2018 and 2019. By 2020, Pi-Cardia had enough evidence from its trials to raise a significant round of capital, a $27 million raise led by Paris-based Sofinnova Partners. (The money raised will be used, at least initially, to fund a long-term durability study of *Leaflet*; the fund-raise also coincided with the start of the development of the *ShortCut* device.)

Before this latest round, Pi-Cardia had raised a little over $10 million in the early 2000s from an Israeli venture firm, largely during its research phase; that was followed by a $15 million round in 2016 led by an unnamed strategic.

The most recent, $27 million round coincided with a deal struck with **Venus Medtech**, a Chinese leader in transcatheter valves, which will see Venus help take Pi-Cardia into China and includes a separate investment in the company. The funding, says, Eyal Kolka, will likely take the company through the next two to three years and, importantly, marks a shift for Pi-Cardia from its research-focused phase to execution. "Right now, our focus is on execution, on proving the value and compiling clinical data. We don't, in the near term, have to worry about fundraising."

Based in Israel, Pi-Cardia has a team in Europe that runs clinical trials and supports and trains physicians. The company also has a small team in the US, which will support efforts there, expected to begin soon, as the firm starts an early feasibility study. And, as noted, it has started to build a business in China with the help of Venus. Both the US and China initiatives are, to date, focused on conducting clinical trials to support regulatory approval before any commercial launch.

Venus is China's leader in TAVR technology with a market share that Pi-Cardia estimates at around 70%. About the collaboration, Golan says, "China is a very interesting opportunity, given that TAVR is still in the very early days there. There's no reimbursement for TAVR in China, and there's a large population of bicuspid valve patients, so they need a good solution for those patients. And since patients pay out of pocket [for the procedure], *Leaflex* can be a perfect solution for them because it may be a lower-cost therapy that is affordable for the majority of the population."

The collaboration with a Chinese leader in TAVR, as well as the investment from a strategic, make sense because Pi-Cardia isn't arguing that repair should supersede replacement as a treatment for aortic stenosis; rather it argues that repair should be one of the options that physicians and patients consider and may be part of a multi-pronged approach to treatment. Golan notes that even with replacement, protocols and device approvals moved through a series of differently triaged patients, starting with inoperable patients who weren't candidates for a surgical replacement. Early clinical studies showed that TAVR was a viable alternative for these patients over the standard of care at the time. "That was a very successful trial, and led to looking at [TAVR] for patients at high surgical risk, then intermediate risk, and now low surgical risk," he says, "pretty much going down the surgical risk scale."

Different Options for Different Patients

In the late 2000s, as Pi-Cardia was getting started, it wasn't entirely clear that you could do a replacement safely or that it really offered a benefit for most patients. "Now it's not a question anymore," says Golan. "There's no question about the usefulness or safety of replacement, which is why it's such a big market today and is expected to continue to grow exponentially over the next few years. But the question is, is it the right thing for the patient?"

But Eyal Kolka notes it's not a matter of whether repair or replacement is always the right approach. "It's about having alternatives for the cardiologist for different patients," he says. He compares transcatheter valve therapy to coronary revascularization. "You have [bare-metal] stents, drug-eluting stents, drug-eluting balloons, atherectomy devices, even the *Shockwave* [lithotripsy] device," he continues. "It's about different options for different patients. What we wanted to do is to create options." In other words, it's not so much about different patient niches or population groups, he goes on, but different options for all stenosis patients. "For some patients, [replacement] may be the optimal solution," he concedes. "We're not eliminating TAVR; it's a great technology and very important for many patients." But, he adds, there are also large patient populations for whom repair is a better option (see *Figure 1*).

Moreover, say the Pi-Cardia executives, the choice should not be about the physician's preference for one procedure or another, but about what's best for the patient. Erez Golan points to a concept that has caught on recently—the lifetime management of aortic stenosis—which, he says, "fits nicely" with Pi-Cardia's strategy. When TAVR first began to be adopted, he says, it was all about whether the physician could actually perform a transcatheter replacement; now, it's about how to manage a patient over his or her lifetime. "Say you have a patient who is 85 years old," he says. By virtue of age alone, and factoring in other possible morbidities, that patient may not have long to live. "If you can show that you can repair the valve and get a good enough result hemodynamically, to give the patient another one to two years without symptoms, that may be all they need." For that particular patient, he goes on, TAVR may actually be "overkill." "They don't need to get their valve replaced; they just need to have a couple of years without symptoms and with good valve function, that's it."

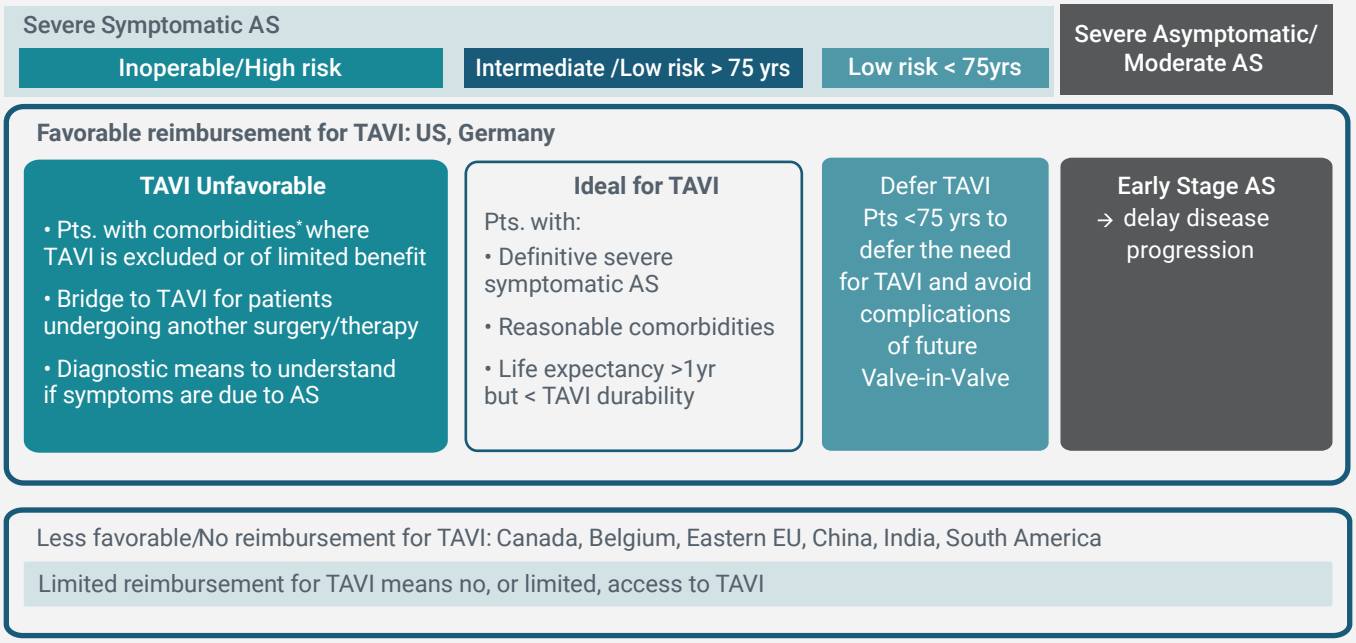
Plus, repair is safe, and by eliminating the replacement device, less costly, making more sense for the healthcare system. Indeed, Eyal Kolka says the cost of the *Leaflex* device will be "a fraction of the cost of a valve implant, making it more affordable not just in developing countries, but in the US and Europe as well."

On the opposite end of the age spectrum, he notes that repair may also be better for younger patients—at least as a stopgap to a later replacement. "We know today that a biological valve lasts about 10 to 15 years at the most," he says. "Think about a 60-year-old patient. If you put a heart valve in that patient, by the time they're 70 or 75, they'll need another replacement valve." At that point, putting in a second valve in "is definitely suboptimal," he argues. There are a lot of issues around putting a second replacement valve inside an existing one. "The annulus starts to become smaller, you have a higher gradient across the valve, and you have a lot of potential complications," says Kolka. "It's not the best option for the patient. If you can defer the need to put in a replacement, that's always better." Moreover, for younger patients, repairs can be done a number of times, so a replacement can be put off time and again.

And when you do a follow-on replacement, he says, "about 35% of the patients are at risk for a coronary obstruction," because when you push back the leaflets of the previous implant, you can block the flow of blood into the coronaries. And those patients have a 50% mortality rate of obstructed blood flow into the coronaries. "In the early days of TAVR, nobody thought about this," says Kolka. "But now, there is a concern. It can be fatal."

Figure 1

Leaflex Creates Treatment Options



*Short life expectancy, COPD, acute pulmonary edema, infection, LFLG

Source: Pi-Cardia

A Device for Replacement, Too

As noted, it's not a choice between replacement or repair, but rather a matter of under which circumstances one is better for the patient than the other. Kolka argues that if a physician can do a durable, effective repair, "that should be the first choice for most patients because they may be too old" to benefit from a replacement or too young to risk having multiple replacements in their lives.

He says he can even see where repair might be preferred for patients in the 75 to 85 age range, but the real goal isn't to argue against replacement but rather to create "a more balanced [treatment] map." Given the clinical success of TAVR, Pi-Cardia executives don't expect cardiologists to choose repair over replacement in all or even most cases. "I assume eventually there's going to be a sweet spot for TAVR where patients can fully benefit from the valve and the healthcare system benefits as well. But for all of the others, *Leaflex* can actually be a very good first choice," says Kolka.

In addition, by eliminating the need to deliver an implant, Pi-Cardia hopes eventually to reduce the size of the catheter, making the procedure simpler to perform. "We're not there yet," says Kolka, who notes that *Leaflex* is about the size of a TAVR catheter. "But the potential is there, and it's one thing interventional cardiologists prefer."

"Really, the goal is to make [aortic repair] like a PCI [percutaneous coronary intervention] procedure because eventually we'd like this to be the first choice," says Erez Golan. "If a patient is suspected to have stenosis or some degree of calcification, [the cardiologist] won't have to think much about it; he can just score the calcification and give [the patient] a few more years" without TAVR. In some cases, the patient may, in fact, never actually need a replacement. And for hospitals, Golan envisions a procedure so quick and simple, and done in a cath lab, "that you don't need a big TAVR center with a surgical team."

Still, Pi-Cardia's development of its *ShortCut* device underscores the founders' ready acceptance that replacement will continue to be a force in treating stenosis. Golan notes that, at least for now, the replacement valves used in TAVR aren't designed to be retrievable if they eventually fail. *ShortCut* is, as noted, designed to be used in patients who've previously had a replacement valve implanted where there's a risk of coronary obstruction when a new implant is placed over the previous one.

Introduced last year, the development time for *ShortCut* was much shorter than *Leaflex*'s because Pi-Cardia was able to leverage some of the latter's development efforts. "It's "pretty much the same platform—the same catheter, a similar handle" as the one developed for *Leaflex*, Golan explains. "All of the benefits of being able to center the catheter in the valve and to use different orientations to land on the valve were taken from *Leaflex*." Only the distal part is different, featuring a splitting tool, rather than a scoring mechanism. The splitting tool creates a puncture in the leaflet at a spot determined by the cardiologist; when the tool is drawn back, the leaflet splits allowing for blood flow to the coronary. By doing so, *ShortCut* is actually enabling a follow-on replacement procedure.

Golan notes that splitting the leaflets isn't a new concept—it's actually an established procedure. The current approach, the Basilica procedure, uses a guidewire to deliver electrocautery to puncture and cut the leaflet. "We didn't need to prove the concept," he says. But that approach is "an extremely complex, two- to three-hour procedure," he adds, performed now on "maybe a couple of hundred patients and by maybe a handful of physicians," all of whom, he says, agree on how difficult the procedure is even as they endorse splitting. *ShortCut* enables a reduction in procedure time from hours to minutes (see *Figure 2*).

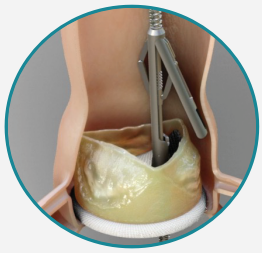
As of mid-2021, Pi-Cardia had done five compassionate care cases with *ShortCut*, all in Israel

Figure 2

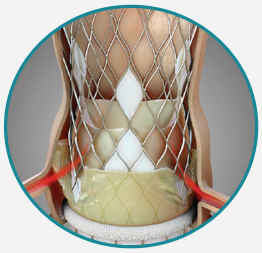
ShortCut Catheter

First dedicated transcatheter leaflet splitting device

Designed to enable coronary access and prevent coronary obstruction during TAVI



Complete control over positioning and leaflet splitting location



Allows for safe, simple, splitting of single or double leaflets, with short procedural times

Source: Pi-Cardia

and all of which, says the company, were done "safely and successfully." Golan says, "We managed to show that we are splitting the leaflets very successfully. In some patients, only one leaflet needed to be cut; others needed two but all showed very nice [blood] flow into the coronaries, and the patients are doing fine." The cases were done both with Edwards and Medtronic TAVR valves and with some previously surgically implanted valves.

Pi-Cardia's goal: to start a clinical trial in the US as soon as possible, and to be the first to market with the only dedicated leaflet-splitting device. And a better leaflet-splitting procedure is of great value not just to physicians, says Pi-Cardia, but to the TAVR companies as well. "Think of it," says Golan. "If you're a physician who has a young patient, right now there's no good option in the future" if the valve needs to be replaced "This is a roadblock" to replacement for that patient. A viable way to address coronary obstruction resulting from a valve-in-valve procedure would alleviate any concerns on the part of physicians.

A Game Changer

And it's not just of value to today's TAVR leaders. Golan says that Pi-Cardia has had discussions with both TAVR companies and also those "who don't have plans" for TAVR. As for the former, he says, "Even the major TAVR players appreciate that TAVR may not be the first choice for all patients and simply pushing TAVR for all patients is wrong. They understand why this completes the portfolio of choices for patients and physicians."

Even if the major TAVR players don't see the opportunity, Pi-Cardia officials believe *Leaflex* and *ShortCut*, by representing essentially another PCI procedure, could prove of value to an interventional cardiology company that doesn't itself have a TAVR platform *per se*, a way to tap into the enormous TAVR market with getting into TAVR itself by offering valuable additions to their sales reps' bag. "We're getting interest from companies that recognize they're never going to be a big player in TAVR," says Eyal Kolka, "but this could be potentially an entry ticket in this phenomenal space without competing head-to-head with the leading platforms."

Again, Pi-Cardia hopes to have it both ways, repair and replacement, with a wide array of options, regardless of the way the TAVR market evolves. Golan notes that much of the focus on TAVR now is on bringing the procedure to a younger, less acutely ill patient population than that the procedure was originally approved for. *ShortCut* clearly addresses the trend by giving cardiologists and patients an option should a second or third replacement likely be needed in the future. And *Leaflex* is also relevant because it offers both an option to do a repair and defer a replacement until a future time. Pi-Cardia clearly believes doing a replacement on a younger patient is suboptimal. But should physician and patient decide to do an implant early, in about one-third of these cases, there's a high risk of blockage in the arteries because of the existing valve. "*ShortCut* can be an enabler for doing TAVR earlier," Golan says. "Whether physicians decide to use *Leaflex* and defer a replacement, or do a replacement earlier and use *ShortCut*, either way we have both [procedures] covered."

Eyal Kolka says *ShortCut* could likely come to market before *Leaflex*, but also gain traction quicker because with TAVR growing in popularity, "it addresses a current unmet need that, if successful, can be proven quite quickly," while *Leaflex*'s repair is "a revolutionary, disruptive technique and may need more time to demonstrate the durability of the therapy."

Despite the traction replacement has gained over the last decade, Erez Golan argues that Pi-Cardia's triage approach is consistent with standard of care in other areas of medicine. "If a patient comes to a doctor with a problem, the first thing the doctor usually says is, 'You need to change your lifestyle' or 'You need to do more exercise or have a better diet.' Or he prescribes medicine. Then he might escalate to a small, local intervention. But you don't start with major surgery." In treating aortic stenosis, implanting a valve should be the last resort, he says, not the first.

That's not only the appropriate clinical strategy, says Pi-Cardia, it's the way healthcare, generally speaking, has long been delivered. Golan notes that in most countries today, TAVR is not reimbursed. "There are a lot of financial incentives for healthcare systems to try to offer something that's lower cost." Eventually, he says, there are reimbursement codes that will cover *Leaflex* at a higher price than typical angioplasty balloons, but lower than a TAVR device.

Pi-Cardia's first clinical trial was performed in Poland in 2017 and showed that "the device works really well," says Golan. "We saw very substantial improvement in the mobility of the leaflets, and we saw that it was safe, with nice scoring and no damage to the leaflets." A second, transfemoral feasibility study, done in 2019 at six sites in Europe, was conducted on 16 patients who were about to undergo TAVR. "Just prior to implanting a valve, we performed the *Leaflex* procedure," says Golan. The idea was to have a fallback TAVR procedure if something went wrong and the repair didn't take. But the trial was, in the end, "extremely successful," proving *Leaflex* is "a very short and safe procedure."

Pi-Cardia currently has other studies underway (see *Figure 3*). One in Europe, currently enrolling, will look not just at safety

and efficacy but also at longer-term durability. A second trial, being done in China in collaboration with Venus Medtech, is a feasibility study. And there's the US early feasibility study that was initially approved for 15 patients; Pi-Cardia hopes to include an additional 15, for a total of 30.

With each of the trials, echo studies are performed pre- and post-*Leaflex* and patients are followed at three-month intervals, to look for any progression of the stenosis, with safety andimproved hemodynamics the endpoints of the study. "Obviously, our goal is to show that we can do the procedure safely, easily, and get a significant acute result and that the result is sustained throughout the course of the study," says Golan. "If we can show that, this really is a game changer."

But a game changer can be a good thing or a bad thing. Golan notes the clinical trial data is important because physician reaction to *Leaflex* can be guarded at first. "Sometimes in our discussions, it takes them a while to understand." Eventually, he says, most physicians come around. But, he adds, "It's fair to say that it all depends on the clinical data. In today's evidence-based world, it's all about data. As long as we can bring good data on both products and can show, especially with *Leaflex*, that this is safe, effective, and durable, this will be a game changer."

Durability, rather than the concept of repair *per se*, seems to be a critical issue. And Pi-Cardia acknowledges that, of course, the stenosis could grow back. "No one's expecting that the treatment will hold for 50 years," Golan remarks. But the effect doesn't need to be good for decades, "only a couple of years, and if it's sustainable for even more than a couple of years—for three to five years," he says, physicians will embrace it.

A New Competitive Model

Working with its KOLs, Pi-Cardia designed *Leaflex* to score calcification in the aorta, before coming up with *ShortCut* and the idea of developing a tool that fully splits the leaflet. In short, while *Leaflex* argues for doing a repair as a first option to treat stenosis, *ShortCut* is designed for cases where cardiologists prefer to replace the valve. Either way—whether the physician chooses to do a repair or a replacement—Pi-Cardia wins.

It all goes back to the company's strategy not to challenge TAVR or TAVR's large market leaders directly, but rather to develop new tools and alternative approaches where appropriate. "We're never going to compete with TAVR," says Erez Golan. "We're not going to develop another valve platform." Today, even larger, more mature companies have difficulty competing with Edwards and Medtronic in TAVR. "If you don't have significant market share, it's very hard to compete against the major platforms," he says. "For a small start-up out of Israel to think we can develop a valve platform better than Edwards' or Medtronic's is too ambitious." Where Pi-Cardia hopes to make its mark is by providing cardiologists with a new option,

Figure 3

Leaflex Clinical Program

Intra-Operative Study	Transfemoral Feasibility Study	EU Standalone Study Exploratory	US Early Feasibility Study	China Feasibility Study
✓Completed	✓Completed	Enrolling	Expected 2021	Expected 2021
5 pts	16 pts	50 pts	15 + 15 pts	20 pts
1 site in EU	6 sites in EU	13 sites in EU	7 sites in US	1-8 sites in China
Safety and acute performance of *Leaflex* in severe AS patients undergoing SAVR (Intra-operative)	Safety, feasibility and acute performance of *Leaflex* in severe AS patients undergoing TAVI	Safety and performance of *Leaflex* as standalone treatment of severe AS		

Source: Pi-Cardia

an alternative therapy that will defer a replacement valve when it's in the patient's interest to do so.

What's interesting in Pi-Cardia's case is that it also presents an alternative model in innovation in cardiovascular devices. Twenty years ago, when big companies like **Cordis** or **Boston Scientific Corp.** held the market in coronary stents, small companies sought to leapfrog their market leadership by essentially bringing out new, improved versions of the same technology. Developer of the first bare-metal stent, Johnson & Johnson saw its market leadership in coronary stents almost totally disappear when smaller, new competitors came to market with their versions.

TAVR seemed likely to follow the same model, with start-ups like Israel-based PVT and France's CoreValve playing early roles as challengers. But the willingness of Edwards and Medtronic to disrupt their own heart valve businesses by scooping up, respectively, the two pioneers gave the large strategics a foot up in building and sustaining their leadership. This, in turn, made it extremely difficult for start-ups, even those with next-generation technologies, to gain market traction, let alone leapfrog their much larger rivals. That's why for years, many venture capitalists resisted investing in TAVR start-ups, notwithstanding the size and dynamism of the market opportunity.

In effect, Pi-Cardia has found a way to capitalize on aortic stenosis without necessarily challenging the big guys head on. Pi-Cardia, says Eyal Kolka, "is trying to disrupt the aortic valve space not by creating the next-generation TAVR system, but by creating more alternatives for physicians" than simply replacing a damaged valve. "This is a very disruptive approach, but in a different way than developing a new TAVR device."

How far-fetched is this notion of disrupting TAVR by making repair a first-line therapy for some patients? Golan notes that in transcatheter mitral valve (TMVR), there are companies focused on both replacement and repair. "I see no reason why you can't have a similar situation on the aortic side. For some patients, replacement is preferred, for others, repair is preferred. And having a repair [procedure] does not preclude doing another repair or a replacement at another time."

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