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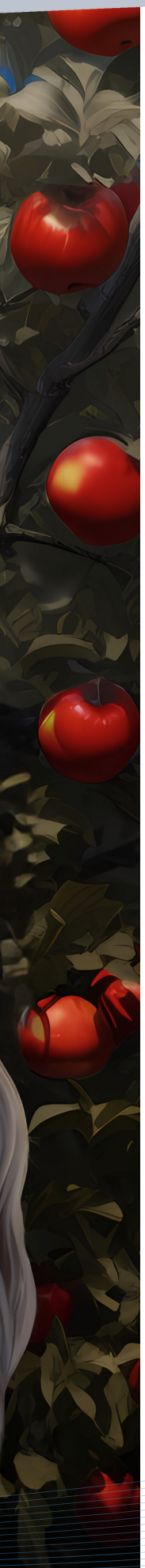
In transcatheter mitral valve replacement, InnovHeart aims to replicate surgical experience, including ease of delivery and the ability to fit more patients.

▶ MARY STUART



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InnovHeart: Multifunctional Mitral Valve Replacement in a Single Device

In 33 years of working in heart valve R&D, Giovanni Righini, the founder of InnovHeart (Milan, Italy), has come to respect the knowledge of cardiac surgeons. That's why he has set out to replicate that experience to the extent possible in the development of a transcatheter mitral valve replacement.

After spending the 1990s directing R&D at the surgical heart valve manufacturer Sorin, Righini wanted to join the revolution in transcatheter aortic valve therapy. In the 2000s, he joined Symetis (now part of **Boston Scientific** after a 2017 acquisition), the developer of the *Acurate* TAVR product line.

Ten years later, Righini says, he felt that transcatheter development on the aortic side had plateaued with the availability of several devices from Edwards Lifesciences, **Medtronic** (which had acquired CoreValve), Boston Scientific (after acquiring Sadra Medical), **JenaValve**, and Direct Flow Medical, so he turned his attention to the underserved mitral valve space. In November 2010, he filed his first patent application on the ideas that led to InnovHeart.

Righini believed that patients affected by mitral regurgitation would be better served by transcatheter mitral valve replacement than by repair. "A good cardiac surgeon can do an amazing repair by performing many surgical operations, and that is not possible with a transcatheter approach," he says. "You usually have to make one choice." That might be an edge-to-edge repair (with Abbott's *MitraClip* or the *PASCAL Precision System* from Edwards) or a transcatheter annuloplasty strategy (with *Carillon*, from Cardiac Dimensions), but it's either/or. "You have limited capability to repair a valve, and although it might result in a good acute result, you sometimes get poor long-term outcomes," he explains, that is, the recurrence of mitral regurgitation within a year.

Righini's goals for a TMVR device were many. It would be safe, that is, not prone to migration, well anchored, and it wouldn't interfere with critical structures like the LVOT. It would be effective in terms of the complete and durable elimination of regurgitation and it wouldn't interfere with systolic flow. Within a single valve system, it would achieve a multifunctional repair to address a pathology that is dilative due to the mutually destructive enlargement of the left ventricle and the mitral annulus. The size of the implant would suit the greatest number of patients while providing good hemodynamics, but also allow it to correct an enlarged annulus. Finally, for interventional cardiologists to adopt the device, it would need to be delivered simply and with minimal procedure time.

It's early in the product's journey to market, but so far, at least after a small human feasibility study, the design of InnovHeart's *Saturn TMVR* appears to meet these criteria.

A Peculiar Design

InnovHeart had an unconventional beginning for a medtech start-up. "It didn't start in the OR or the cath lab. It all started in my kitchen," where, Righini says, he built a TMVR prototype. Righini then put together a pitch deck and shopped around for funding. "It looked like nothing else out there. People were surprised by the peculiar design we were proposing, and in seven months of investor presentations, all we collected was feedback."

So, he took his shot; he made one valve, and then self-funded a chronic animal study at IMMR in Paris (now part of **Veranex**), well known for large-animal preclinical work in the cardiac space. Righini reports that outcomes at 60 days were good.

Thanks to his experimental work, in 2015 he was able to attract VC interest in the project, choosing to work with Genextra, a firm based in Milan. InnovHeart was officially founded in November 2015, with the completion of a €13.4 million Series A round, although, Righini emphasizes, the intellectual property has an earlier priority date.

Today, the company has operations in the Boston area and Italy and has raised €58 million. On the roster of investors is, as noted, Genextra, plus other Italian VCs—Panakes, Indaco Venture Partners, and CDP Venture Capital SGR—as well as East Ocean Ventures (Hong Kong) and Grand Pharma (a pharmaceutical company based in China).

In 2022, InnovHeart's €24.4 million Series C round was led by the latter, with the simultaneous signing of a licensing agreement granting Grand Pharma rights to the *Saturn TMVR* device in mainland China, Hong Kong, Macau, and Taiwan.

Experienced CEO David James Wilson joined soon after the Series C. Wilson's career in the medical device industry spans 30 years, with two decades spent at various operating companies within Johnson & Johnson, where he held a number of leadership positions including worldwide president of Cordis. "I came on at an important time to help the company move forward. We had some early success in transapical delivery; we now have two-year follow-up on the first three patients." InnovHeart is ready to turn its attention to its commercial product, which will be delivered by transseptal access.

Complicated Patients

Developing an effective treatment for functional mitral regurgitation presents many design challenges due to the complex anatomy of the mitral valve, as noted, and the proximity of functional structures—the aortic valve and the LVOT, with which the device mustn't interfere—and the ventricular wall and septum.

Figure 1
Saturn TMVR

Source: InnovHeart

The physiology of the valve, which experiences stress and pressures much higher than the aortic valve does, must also be taken into consideration. Finally, says Righini, "The pathology of functional mitral valve disease is dilative," that is, the dilation of the left ventricle and the mitral annulus in response to hemodynamic changes, which interfere with the ability of the mitral valve leaflets to coapt.

Developers here hope to achieve the same success as transcatheter aortic valve replacement devices, but in terms of valve design, not much can be leveraged from the TAVR field. The mitral valve requires its own solution. "If you used a traditional transcatheter aortic valve to treat a mitral valve you would be applying radial force and expanding something that already tends to dilate," says Righini, "and instead of reversing remodeling, you would be contributing to it." Further, he notes, "If you expand something inside the annulus, and if, because of the progression of the pathology, the annulus dilates, what happens to your prosthesis? You have the risk of recurrent paravalvular leaks and perhaps late migration as well."

Righini believes InnovHeart's solution meets the outlined criteria. The *Saturn TMVR* is modular. Once implanted, it is one integrated whole, but it is delivered in two components. The first component, a pair of annular segments, is designed to encircle and restrain the annulus, "because no matter what parts of the mitral valve surgeons repair, they always use an annuloplasty ring," Righini explains. The ring prevents the application of prosthetic radial force to the native mitral annulus and at the same time stabilizes the implant site, providing durable anchorage and sealing to the prosthesis (*see Figure 1*).

The other component, the central valve, has two connecting arms that attach the valve to the ring. One of the arms, oriented toward the anterior leaflet, immobilizes it so it can't move in front of the aortic valve. "There is no other technology for mitral replacement today, in preclinical or clinical use, with the same feature," states Righini, and that's important because it is designed to avoid systolic anterior motion (SAM), a problem of both surgical and transcatheter mitral valve treatments. SAM describes a situation where, during systole, the anterior leaflet is pushed into the LVOT, stopping forward flow. This increases cardiac afterload and can result in cardiac hypertrophy, dilation, and ultimately, failure of the left ventricle.

Because of this feature of *Saturn*, Righini believes the device would also be beneficial for treatment of primary mitral regurgitation, where flailing of the anterior leaflet is even more prevalent, whereas in functional MR, the tethering of the anterior leaflet reduces motion.

Finally, he notes, the dimensions of the *Saturn* valve are comparable to those of a surgical mitral prosthesis, which further prevent it from causing LVOT obstruction. Citing the company's five-patient human feasibility study, Righini reports: "With a 28-mm prosthesis we have treated an inter-commissure diameter up to 45 mm, with perfect apposition of the annulus to the native valve, without paravalvular leaks. That is common to all our experience, regardless of the annulus baseline." Because the ring component helps shrink the native annulus, "we have the possibility to undersize the prosthesis compared to the dilated annulus, in order to restore mitral anatomy to a more physiological size."

The company will offer two device sizes to cover most anatomies. Wilson adds, "Many patients have been screened out of other clinical studies because of the potential for LVOT obstruction, so we hope we'll have a solution for that."

Finally, Righini outlines a simple implant procedure, which in the company's five-patient experience, is possible to complete in 45 minutes from apex to apex.

The implantation process is based on the use of conventional guidewires, which act as a rail for the accurate positioning of the valve under the guidance of echocardiography, and Righini describes it as basically three steps, which are the same for both transapical (retrograde approach) and transseptal delivery (antegrade approach).

After the advancement of two standard guidewires (one for each side of the native valve), which encircle the native valve at the level of the sub-annular groove at the base of the ventricle, the operator delivers the two annular segments into the left ventricle, over the wire, to position them behind the native leaflets. The prosthetic valve is then introduced in the left ventricle, sliding over the same guidewires, which then allows the annular segment to be connected to the valve. The valve self-expands inside the mitral orifice to secure the native leaflets in between. The learning curve is short, according to Righini; in the five-patient human feasibility study, the first case took 80 minutes, and the last, 46 minutes.

The Product the Market Wants

In its transapical iteration, the *Saturn TMVR* has provided the experience InnovHeart needs to move forward with the transseptal TMVR; as noted, the procedural steps are similar. In the human feasibility study, there was 100% technical success, no residual MR at two years, and no LVOT obstruction. On average, the prosthesis was able to be undersized by approximately 40% compared with the baseline mitral annulus. According to David Wilson, "We have proven that we can deliver the valve transapically, and we have shown, albeit in a small cohort of five patients, that the valve is performing well."

Wilson notes that the transapical product needs to be implanted by a cardiac surgeon. "It is minimally invasive compared with open heart surgery, but you are penetrating the thoracic cavity and you need to suture the apical puncture you make." Although there are some geographic markets interested in transapical delivery, he adds, "Strategically that is not our primary focus; we are moving on to transseptal."

Wilson is now fundraising for a Series C extension, probably about €15 million to fuel the pilot phase of the transseptal product, before seeking approval for a global pivotal study. The company plans to enroll about 15 patients for early feasibility studies in Europe in Q4 2023. Early next year, InnovHeart will pursue early feasibility studies in the US. "We like the early feasibility model so we can demonstrate safety and device functionality en route to raising more money for the larger pivotal trial."

As stated, the patient population is complex, and Wilson says the company has the benefit of learning from what other companies have done in terms of inclusion and exclusion criteria, and why. "I think over time we will be able to manage a wider range of anatomies because of the design of our valve; it doesn't take up a lot of space, it is shorter in height, we capture the native leaflets ... and all the other things we've talked about that make us a better option for patients whose anatomy puts them at risk for LVOT obstruction. But we don't want to be niched, we want to be a mainstream player offering more solutions for patients." MTS

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