NEXT-GENERATION TAVR

A look at the future of percutaneous valve replacement.
Direct Flow Valve

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Transcatheter aortic valve replacement (TAVR) has become the standard of care for symptomatic patients with severe aortic stenosis who are not suitable for surgical aortic valve replacement (SAVR). Additionally, among high-risk patients with symptomatic aortic stenosis, TAVR and SAVR have similar outcomes with respect to mortality, reduction of symptoms, and improved valve hemodynamics. Thus, TAVR is an alternative to SAVR in well-chosen patients. However, TAVR patients had more vascular complications and strokes when compared to those treated with SAVR or medical therapy. Recently, TAVR has been associated with a significant incidence of paravalvular regurgitation compared to SAVR in high-risk patients, which is associated with late mortality.

Since 2008, the predominant worldwide experience with TAVR has been with the balloon-expandable Sapien valve (Edwards Lifesciences, Irvine, CA) and the self-expanding CoreValve device (Medtronic, Inc.).

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Minneapolis, MN). These early-generation devices have demonstrated impressive results and have a large effective orifice area, good securement, favorable intermediate-term durability, minimal incidence of coronary obstruction, and an acceptable delivery profile (18 F outside the United States, 22 and 24 F within the United States).

There is, however, opportunity for improvement, such as enhanced sealing to minimize paravalvular regurgitation, better flexibility and trackability for superior deliverability, and the ability to predictably and precisely position, reposition, and, if necessary, retrieve the valve. Furthermore, the need for permanent pacemakers and postballoon dilatation are unsolved clinical issues with the first-generation devices. These are all important design goals of the next generation of valves. Furthermore, development of a device that allows the physician the ability to assess valve function by measuring the transvalvular gradient and evaluate aortic insufficiency with echo-Doppler and angiography prior to final deployment is highly desirable.

DIRECT FLOW MEDICAL TRANSCATHETER AORTIC VALVE SYSTEM

The Direct Flow Medical (DFM) transcatheter aortic valve system (Direct Flow Medical, Inc, Santa Rosa, CA) is a next-generation device that is composed of bovine pericardial tissue. The system includes a heart valve (“bioprosthesis”), delivery system, and accessories. It is designed to reduce procedural and implant-related complications with several novel design features. This bioprosthesis is available in two sizes (25 and 27 mm), with two additional sizes to be added in the near future (23 and 29 mm). Depending on the bioprosthesis diameter, the height of the valve is approximately 18 to 19 mm. The bioprosthesis (Figure 1) has three bovine pericardial leaflets that are pre-treated with anticalcification technology and attached to a tubular, inflatable support structure that is covered with polyester fabric. The covered frame has two circular rings (upper aortic and lower ventricular) that are connected with vertical tubular supports, and there is a one-way ball valve between the aortic and ventricular ring.

During delivery, the bioprosthesis is attached to three positioning wires, two of which are used to inflate/deflate the bioprosthesis, as well as to precisely position the bioprosthesis (Figure 2). These two positioning wires have a channel that allows fluid to inflate and deflate the balloon frame, and they have a threaded connection to a one-way ball valve (Figure 3). The other positioning wire has a threaded connection for attachment but no channel. On the ends of the two inflation wires, there are special stopcocks for attachment to the indeflator and polymer exchange system.

The delivery system is an over-the-wire, catheter-based system. The bioprosthesis is loaded into the delivery system and is constrained by an outer polymer sheath. The body of the nylon catheter shaft is 16 F tapering to 12 F at the proximal handle (Figure 4). Inside the delivery system, there is a multilumen catheter that has channels for the three positioning wires and a central lumen for the guidewire tube (0.035 inch), which is connected to a soft, flexible nose cone. The positioning wires have radiopaque markers and corresponding markers on the back end to facilitate orientation and bioprosthesis placement. The delivery system is introduced through an 18-F sheath with a hemostatic valve.

The DFM bioprosthesis is positioned and secured in place with a saline contrast solution under 12 atm of pressure. When the bioprosthesis appears to be in its optimal position, the functionality is assessed with hemodynamics, aortography, and echo-Doppler. If the position and functionality are acceptable, the saline contrast is replaced with a solidifying polymer followed by detachment of the positioning wires. The proprietary polymer is an epoxy-based liquid material that solidifies within hours to provide a permanent support structure that maintains the position of the bioprosthesis in the native aortic valve annulus. The polymer in the liquid form is water-soluble and is nonembolic if it is inadvertently released into the blood stream.

Should removal of the bioprosthesis be necessary, a separate retrieval system is available that contains a braided nitinol basket that can be introduced over the multilumen catheter through the 18-F sheath and into the descending aorta.

VALVE IMPLANTATION PROCEDURE

The DFM bioprosthesis is rinsed in three saline baths before being attached to the delivery system and loaded. After balloon valvuloplasty (23-mm Z-Med II balloon [B. Braun Interventional Systems, Inc., Bethlehem, PA] or equivalent for a 25-mm valve and 25-mm balloon for 27-mm valve), the DFM delivery system is advanced over an extra-stiff Amplatz guidewire (Cook Medical, Bloomington, IN) into the left ventricle. The bioprosthesis...
is then unsheathed in the left ventricle, and the outer polymer sheath is retracted into the ascending aorta near the arch. Saline contrast is infused into the bioprosthesis, which is unfurled in the left ventricle. The upper aortic ring is deflated, and the lower ventricular ring remains inflated, at which time, the bioprosthesis is precisely positioned using the wires with the lower ring in the left ventricular outflow tract placed against the annulus. During positioning, the bioprosthesis is functioning as it is manipulated into position, and rapid pacing is not needed. The upper ring is then inflated, which mechanically secures the bioprosthesis in place with both rings encircling the annulus (Figure 5).

At this time, functionality of the bioprosthesis can be assessed by aortography, echo-Doppler, or by removing the guidewire and using the guidewire lumen in the delivery system to measure the left ventricular pressure while aortic pressure is monitored with a pigtail catheter positioned in the aorta. Aortography to check for adequate clearance of the coronary arteries is also possible prior to final deployment, as is a full assessment for aortic regurgitation using echo-Doppler. Depressurization by removing the saline contrast from the bioprosthesis allows for repositioning, and if necessary, the bioprosthesis can be completely withdrawn from the patient using the retrieval system. If the valve is functioning well and an adequate position is verified, the saline contrast is exchanged for the polymer under constant pressure. The positioning wires are then detached by unscrewing them from the bioprosthesis, and the delivery system is removed (Figures 6 and 7).

**DEVELOPMENT OF THE DFM TRANSCATHETER AORTIC VALVE**

The concept of a novel, inflatable prosthetic heart valve, which is initially percutaneously deployed in the collapsed configuration and subsequently inflated to an operative configuration, was conceived in the early 1990s. Direct Flow Medical further developed and validated the concept of this unique valve design using an inflatable support structure via extensive bench and preclinical testing. Early human investigations assessing the technical feasibility, safety, and performance were conducted at the Hospital Privado Frances in Asuncion, Paraguay. Extensive laboratory testing has validated the design, performance, and durability of the DFM transcatheter aortic valve. Accelerated wear testing has exceeded 5-year simulated use and meets the ISO 5840 surgical valve durability requirements. Pulsatile flow testing has verified the hydrodynamic performance of the DFM bioprosthesis.

A first-in-man feasibility and safety study was conducted in Germany from 2007 to 2008 and was reported in 2008. The early version of the DFM transcatheter aortic valve was available in two sizes (23 and 25 mm) and was endovascularly introduced via the femoral artery using a 22-F introducer sheath. Patients enrolled in the study had to be 70 years of age or older with symptomatic valvular
aortic stenosis and an aortic valve area \( \leq 0.8 \text{ cm}^2 \), a mean transvalvular gradient of \( \geq 35 \text{ mm Hg} \), annular dimension of 19 to 23 mm, contraindication to surgery because of concomitant comorbidities, logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) \( \geq 20\% \), and valvular and peripheral anatomy appropriate to accommodate the study device and its delivery system.

In this small series of 15 patients, the acute procedural success rate was 80\%, and there was a significant reduction of the transvalvular gradient. No patient exhibited hemodynamically significant aortic insufficiency, either central or paravalvular. One patient had displacement of aortic wall plaque that interfered with the coronary ostium, which was successfully treated with a coronary stent. There was one stroke and one cardiac death (13\%), which is similar to other first-in-man, stent-based percutaneous valve prostheses. There was significant improvement in functional class and improvement in left ventricular ejection fraction. The 2-year follow-up data were published in 2011 and confirmed stability of the device’s position, shape, and hemodynamic performance, with no aortic regurgitation in most patients. The first patient has remained asymptomatic nearly 5 years after implantation.

Recognizing the importance of a lower-profile delivery system (\( \leq 18 \text{ F} \)), a new iteration has been developed and tested that has improved radial force and a larger effective orifice area, leading to lower gradients while maintaining the excellent sealing results of the 22-F device to minimize paravalvular insufficiency. In addition, there have been significant enhancements to improve the ease of use of the device to allow predictable and precise positioning and to simplify the overall procedure. The European CE Mark trial is currently enrolling and should be completed by the end of 2012.

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**Figure 4.** The DFM valve components. The valve loaded in the delivery system (A). The valve unsheathed (B). The valve in the retrieval basket (C).

**Figure 5.** Positioning of the bioprosthesis is demonstrated with the lower ventricular ring inflated and manipulation of the positioning wires to place the ring in the left ventricular outflow tract against the aortic valve annulus. The upper aortic ring is then inflated to mechanically secure the bioprosthesis in position and provide sufficient sealing.

**Figure 6.** The DFM bioprosthesis in a cadaver heart demonstrating proper position and sealing with conformability of the lower ventricular ring in the left ventricular outflow tract.
SUMMARY

The DFM transcatheter aortic valve system is a nonmetallic transcatheter heart valve system with a fabric-covered, balloon-support frame supporting a trileaflet bovine pericardial valve with excellent performance characteristics, including a large effective orifice area and minimal-to-no transvalvular gradient. Apposition of the conformable lower ventricular ring to the left ventricular outflow tract under the aortic annulus and mechanical securement with the upper aortic ring pushes the native aortic valve leaflets into the sinus of Valsalva and out of the landing zone for valve deployment. This contributes to an excellent circumferential seal for minimizing or eliminating perivalvular aortic insufficiency.

Aortic insufficiency after TAVR is associated with increased mortality, although the nature of this relationship needs clarification. The very flexible and trackable delivery system is low profile (16 F) and is inserted through an 18-F sheath. Positioning of the valve is precise and predictable with step-by-step control using the three positioning wires. The bioprosthesis is immediately functional with stable hemodynamics during positioning/deployment, and rapid pacing is not needed. The DFM transcatheter aortic valve system is unique in that it allows for the assessment of flow dynamics prior to final device deployment. This design intends to improve clinical outcomes compared to first-generation TAVR devices by providing improved placement and a tight seal to the native valve anatomy, facilitating a more controlled implantation procedure, and reducing trauma caused during delivery, deployment, and valve replacement.

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Figure 7. The DFM bioprosthesis in position immediately after polymer exchange and deployment (A). Final aortography demonstrating coronary flow and no aortic insufficiency (B).