Preclinical Testing of Transcatheter Heart Valves

Introduction

Prosthetic heart valves are life-saving devices that improve diseased heart-valve function, which has been critical to improving the patient’s quality of life and increasing lifespans. These devices have consisted predominantly of mechanical and bioprosthetic surgical valves, with a smaller but critical market occupied by transcatheter valve replacements.

Requirements for preclinical *in vitro* and *in vivo* testing of heart valve substitutes are presented in International Standards Organization (ISO) 5840. No FDA guidance currently exists for this technology; however, ISO 5840 is an FDA-recognized standard. FDA has alluded to requiring the same testing for heart valves that for as surgical valves, in addition to evaluating the durability and hydrodynamics of noncylindrical shapes, delivery system performance, valve migration/embolization, valve-in-valve placement, and the need for additional device-specific testing. Ultimately, the test program should include verification and validation of the design and manufacture of the transcatheter heart valve device from the perspective of risk management.

Minimally invasive transcatheter heart valves are a rapidly evolving technology, and valve manufacturers must tailor their preclinical test programs to each unique aortic or mitral valve design. In developing this article, Exponent scientists collaborated with authors from Surpass, a contract research organization (CRO) specializing in preclinical services.

Hydrodynamic Performance Testing Considerations

Hydrodynamic tests provide information on the real-time performance of the deployed valve under steady and pulsatile flow conditions. Testing considerations should include the device sizes (smallest and largest), deployment shapes, and reference valves. To evaluate the relative performance of the test valves, an equivalent sized reference valve with a known clinical history, such as surgical heart valves,
can be evaluated for each valve size tested. In addition, the ISO standard recommends that the transcatheter valves be tested under ideal deployment conditions that produce a circular deployed configuration, as well as worst-case conditions with irregular deployed shapes (e.g., non-circular, under- or over-deployed) as anticipated from a risk assessment of the device.

Under steady forward flow conditions, it is recommended that the pressure difference across the test valves, as well as the effective orifice area (EOA) over a range of steady forward flow rates, be measured to determine whether the hemodynamic behavior is acceptable compared to the chosen reference valves. Similarly, the valves should be tested under various steady backflow pressures, to determine the leakage rate and the device’s capacity to prevent clinically significant transvalvular leakage during diastole. The standard also recommends that the performance of the transcatheter heart valve be assessed under pulsatile flow conditions, where the pressure difference and EOA are measured under various clinically relevant cardiac outputs. Under the same conditions, the transvalvular and paravalvular regurgitant volumes should also be measured using various clinically relevant back pressures and heart rates. The test device should perform in a manner similar to the reference valve and meet the minimum device performance requirements provided in ISO 5840 for EOAs and regurgitant fractions for both mitral and aortic valve devices. As part of the hydrodynamic pulsatile testing, the standard recommends characterizing the flow fields, including flow velocity and shear rates, in and around the transcatheter heart valve, using for example, a validated computational fluid dynamics model.

**Durability Testing Considerations**

Durability testing is an important subset of the preclinical *in vitro* tests, which aim to evaluate the performance of the prosthetic valve over its anticipated lifetime. The wear patterns observed during and resulting from these tests aid in identifying the valve regions most prone to wear and the modes in which the valve may eventually fail.

Similar to hydrodynamic testing, testing considerations should include the device sizes, shapes, and reference valves. The standard recommends testing of the smallest, medium, and largest sizes deployed under best-case (e.g., circular shape) or worst-case (e.g., irregular) conditions, and compared against commercially available reference heart-valve devices of equivalent size with known clinical performance. Test duration, as recommended by the FDA, is 200-million cycles for flexible valves (bioprosthetic, TAVR, etc.) and 600-million cycles for rigid replacement valves. ISO standards mirror the FDA for flexible valves but recommend 400-million cycles for rigid replacements.
ISO 5840 recommends that prosthetic heart valves be subjected to population-averaged transvalvular pressure gradients observed in the adult or pediatric population. Because prosthetic valves can be designed for differing positions within the heart, standards and guidance documents recommend selecting the worst-case hydrodynamic conditions.

During the testing, the defined target peak differential pressure across the closed valve should be maintained for 95% or more of the test cycles, and the minimum peak differential pressure should be maintained for at least 5% of each cycle. The system is tuned so that the valves experience the full range of motion. The design of the test fixture ensures that it is representative of the implant site. The interval analysis conducted at every 50-million cycles or less should examine the extent and modes of device damage/failure in comparison to the reference valves, with the acceptance criteria being established through a risk assessment. On completion of the durability test, the samples should be examined for excessive structural damage and tested for functional impairment under pulsatile flow conditions, to determine whether the device meets the minimum EOA and regurgitation fractions specified in ISO 5840.

Durability tests are typically performed at rates that far exceed the tachycardic rates observed clinically. ISO 5840-3 recommends cyclic rates to be justified based on the valve design, anticipated failure modes, and the behavior of time-dependent materials. Cyclic rates are additionally influenced by the ability to achieve full opening and closure of the valve under the defined hydrodynamic conditions. The conditions for durability testing for different valve types should be modified such that the total valve loading forces, and not just the transvalvular pressure, are maintained under physiologic and accelerated conditions. This aspect poses unique challenges to accelerated wear tester design, operation, and adjustability over the defined test program.

Preclinical Animal Studies

Preclinical in vivo testing is an essential step in taking a new heart valve to market. Tests in animal models provide critical information on biocompatibility (described in ISO 10993 but not discussed in this article), vascular response, device performance, and pharmacokinetics and can help mitigate potential risks around using the device in humans. Surpass is a leading contract research organization and a trusted partner for conducting preclinical research of medical devices, pharmaceuticals, and biotechnologies; their scientists have proven experience performing in vivo studies on transcatheter heart valves. Below, the Surpass team highlights common in vivo tests performed for assessing heart valves. As you freeze the design, safety data—in the form of a good laboratory practice (GLP) study—will need to be collected in all the areas discussed. Keep in mind the guidelines outlined in the FDA Cardiovascular Guidance Document and ISO 5840. For these later-stage studies, the device will need to be fully characterized to support the GLP requirements. See Surpass’s blog post on Test Article Characterization for Combination Product and Medical Device GLP studies.
Vascular Response Testing Considerations

*Species/Breed:* Preclinical studies to assess the safety and efficacy of heart valves have typically been performed in pigs or sheep due to the size of their anatomy with respect to humans. The best species/breed combination depends on the device’s intended indication, size of the device and delivery system, proposed study time points, and availability of scientifically relevant historical data with any particular species. Each model has its advantages and shortcomings; therefore, the right model should be chosen based on the specific study goals. For more information, see Surpass’s recent blog posts on comparative anatomy for transcatheter aortic valves and transcatheter mitral valves.

*Imaging:* Imaging is an essential part of heart valve studies, which look at vascular response and often will be used for assessing a primary or secondary study endpoints. Preclinical studies are intended to gather safety and efficacy information to support clinical trials and ultimate use of the device, so imaging used during the study should be similar to that used in the clinical setting. However, it is also important to keep in mind that the preclinical environment does not always fully mimic the clinical environment, so adjustments may be warranted. The Surpass research team can assist in making a determination about how best to proceed.

Prescreen imaging helps to ensure that the prosthetic valve to be implanted is appropriately sized to the native annulus. Follow-up imaging can help assess the success of the implant or treatment, as well as provide insight into early and long-term results. For transcatheter aortic valves, an aortogram is typically performed before and after implantation, in addition to just prior to euthanasia to assess valve placement. For transcatheter aortic and mitral valves, pre-implant echo is typically performed to help size the device to the native anatomy, and post-implant echo is used to confirm successful deployment and valve function (leaflet motion and valve insufficiency), and to acquire baseline hemodynamic parameters. In addition, echo is also performed every 30 days and just before euthanasia to assess hemodynamics and valve function. During necropsy, Faxitron images can be used to evaluate the explanted valve for evidence of calcification and device integrity issues (fractures).

*Histopathology:* Histopathology is typically a primary endpoint for heart-valve studies. Common histology endpoints include all or a subset of the following: thromboembolic events, calcification, and thrombosis, as well as pannus formation/tissue ingrowth, healing, inflammation, signs of erosion caused by cavitation, and bacterial vegetation within the valve and adjacent structures. For GLP studies, the FDA will also want to understand the downstream effects and impact on nontarget major organs. In addition, structural valve deterioration and non-structural dysfunction should be evaluated as well. Specific refinement of components of a valve, such as the cage or leaflets, may cause the study endpoints to be more focused on one or more of the above histopathology parameters.
Acute Performance Testing

The goal of acute performance testing is to assess the ease of interventional or surgical handling of the device during delivery to the target site, valve implantation, and removal of the delivery system. Often, this testing can be performed during the chronic vascular response study to reduce the number of animals used. Depending on the limitations of the animal model and need to diverge from the intended clinical delivery method, acute performance may be better evaluated in other models such as the human cadaver.

Pharmacokinetic (PK) Studies

Although many heart valves on the market and in development today do not have a pharmaceutical component, the future potential of this technology is great. PK studies for combination products are typically carried out in species to those used in the vascular response testing. Prior to finalizing the species for a PK study, it must be determined whether appropriate extraction methods and analytical assays are in place to avoid delays to the project.

Conclusions

Exponent and Surpass have the expertise to support the design and in vitro and in vivo testing of transcatheter heart valves. More information about Exponent’s cardiovascular device expertise can be found here, and Exponent’s Biomedical Engineering Lab capabilities, including the DuraPulse™ heart-valve durability tester from TA Instruments (Figure 1), can be found here.

More information about Surpass’s preclinical expertise and testing services can be found on the Surpass website. For insights and advice on preclinical in vivo studies, be sure to check out Surpass’s preclinical blog.

For further information, please contact:

Jasmine Patel, Ph.D.
Manager, Biomedical Engineering, Exponent
jpatel@exponent.com
(215) 594-8912

Mark R. Cunningham, Ph.D.
Chief Scientific Officer, Surpass
mark.cunningham@surpassinc.com
(715) 294-1266