

AN INTERVIEW WITH...

Thomas Modine, MD, PhD, MBA

Dr. Modine shares his thoughts on TAVI access approaches, evolving technology, and durability, as well as transcatheter mitral interventions and the expanding possibilities of valve-in-valve procedures.



With transfemoral access as the current gold standard for transcatheter aortic valve implantation (TAVI), where do we stand in terms of the safety of various alternative approaches for those who are not suitable candidates for femoral access?

Significant peripheral vascular or descending aortic disease are some of the anatomic challenges that render the iliofemoral pathway unfeasible for access. Despite the progress in miniaturization of new-generation transcatheter heart valves, comorbidities and unfavorable anatomy preclude transfemoral access in 15% to 20% of patients, according to contemporary registries. Nevertheless, there is an apparent increase over time in the proportion of patients eligible for the transfemoral approach. However, alternative access approaches are still needed in up to one-fifth of patients undergoing TAVI in contemporary registries, due to the risk of vascular complications that could occur in nearly 6%, as shown by latest randomized trials.¹⁻³

Newer, less invasive pathways have since been proposed and developed, namely transcarotid, transaortic, transsubclavian/transaxillary, and transcaval. However, the relative “invasiveness” of one alternative approach compared to another is subject to debate. Invasiveness relates to the need for a surgical cutdown, general anesthesia, vascular or heart lesion required for delivery system crossing, and potential impact on the other major systems such as the cerebral, respiratory, and renal systems.

No randomized trial has directly compared the different alternative approaches, and these are more or less subject to a learning curve. Also, patient anatomy and comorbidities often determine the eligibility to different alternative pathways. Indeed, general anesthesia for

transapical or transaortic access may be contraindicated in patients with chronic respiratory insufficiency, and the transsubclavian (surgical and percutaneous) pathway may be precluded by vascular anatomy, such as tortuosity, stenosis, or angulation. Patients who have previously undergone a coronary artery bypass may be unsuitable for the transaortic pathway if they received venous grafts or for the transsubclavian pathway if they received mammary artery grafts. Alternative access that is easily achievable under local anesthesia (eg, transcarotid) might have a great advantage and should be considered.

The majority of new TAVI devices are moving away from the balloon-expandable design to the self-expanding design. What is causing this shift?

The balloon-expandable Sapien 3 device (Edwards Lifesciences) currently offers excellent results. Nevertheless, the majority of manufacturers have or are developing self-expanding devices. In my opinion, the main reason is that this technology has the capability of offering the recapturability and repositionability features, with the intention of reducing the risk of paravalvular leak and coronary occlusion intraoperatively. This is an advantage that would be important for optimizing delivery and positioning at the level of the annulus, especially now that we are moving to younger and lower-risk patients. In this population, TAVI results must be near perfect. In addition, self-expanding devices avoid annulus rupture.

With durability being one of the main questions remaining in the TAVI data, do you know of any current or upcoming trials that are specifically aimed to fill this knowledge gap?

It took the surgical literature more than 25 years to show that the durability of biological prostheses could

(Continued on page 88)

(Continued from page 90)

go that far. However, with increasing interest in moving toward lower-risk and younger patients, it is important to distinguish that these are often separate cohorts.

A patient could be considered low risk and be 82 years old. More than 70% of surgical aortic valve replacement patients today are > 75 years. Do we need to implant a valve that has durability of more than 15 years in this category of patients, to which would surpass the average life expectancy in Western world? So far, data from PARTNER trials, and lately the FRANCE-2 registry, have demonstrated more than 5-year durability. We should continue to follow up on these implanted patients and see where it goes.

Furthermore, durability interpretation is subject to bias and is multifactorial. Age, comorbidities, the geometry of the valve once expanded, need for postdilatation, and other factors may play major roles. Also, the interpretation of valve degeneration should be redefined, as the current definition of durability is based on the surgical literature, which has major limitations. In this regard, the European Association of Percutaneous Cardiovascular Interventions consensus statement on standardized definitions of valve deterioration and failure is a step forward, and the suggested evaluation criteria have been validated by a group of experts including both interventionalists and surgeons.⁴

What are your tips for achieving comprehensive preprocedural imaging for transcatheter mitral valve replacement (TMVR)?

Preprocedural imaging for TMVR is extremely important. It needs to combine echocardiographic findings of the left ventricle (leaflet morphology, annulus shape and dimensions, aortic-mitral curtain, papillary muscles, myocardial function), left atrium, and importantly, the right heart beyond pulmonary pressure and ejection fraction. A CT scan is also helpful in providing more precise measurement of annular dimensions, angulation of the mitral valve and aortic valve, and calculation of left ventricular outflow tract (LVOT) obstruction risk, allowing estimation the neo-LVOT area. However, LVOT obstruction is a hemodynamic parameter and a CT scan alone is not enough. We need to develop and assess new imaging tools that allow the assessment of this risk on echocardiography also. A CT scan is mandatory for assessment before a surgical procedure (for access, catheter orientation, intercostal space, coronary vessels).

I will summarize with three crucial points. First, one must evaluate the disease and its status, as all cases of secondary mitral regurgitation are not the same, and every patient is different. Second, one must have a comprehen-

sive knowledge of the mitral anatomic complex (ie, valve, submitral apparatus, surrounding environment). Third, the LVOT must be thoroughly evaluated.

Can you give us a brief overview of the main limitations and challenges of TMVR at this time and possible options or techniques to overcome these difficulties?

First, we lack strong scientific data. The surgical literature does not provide enough elements to fully understand the disease, valve, and prognosis. We are still speculating and interpreting and that is not enough to address unmet clinical needs. The devices are not yet optimal, but this does not mean that percutaneous treatment will not succeed. We have to gather clinical, anatomic, imaging, and engineering information and ask for ambitious development of devices. I expected many devices to fail in the field in the past and that has happened.

Today's challenge is personalizing the indication. In the era of artificial intelligence, we must not continue thinking that all disease is at the same level of severity and all patients should be treated in the same way. Practically, the guidelines do not give enough space for this new therapy to develop, and conceptual conflicts of interest are a threat. Indeed, our best practice is based on evidence-based medicine, but to get there, we need the evidence. However, this is not easy to obtain when guidelines are so restrictive, especially when level of evidence is extremely low and no previous evaluations were conducted. The need for independent studies, not funded by industry, will be mandatory to assess, evaluate, and recommend disruptive therapies. Technically, at present, end-stage patients with a large annulus (beyond valve and annulus sizes), altered ventricular function, altered right heart function, and LVOT anatomy are current and temporary limitations.

What are the main differences between valve-in-valve (ViV) procedural considerations in the aortic, mitral, and tricuspid valves, respectively?

All of the considerations vary today except the devices we are using for ViV procedures. The anatomy, device size required, patient characteristics, and risk profiles of the individuals and the procedures are all different. There are completely unique anatomic challenges between aortic, mitral, and tricuspid valves (in terms of access, skills, coronary obstruction, LVOT obstruction, and thrombosis). For aortic ViV procedures, both self-expanding and balloon-expandable valves could be used, whereas for mitral ViV, only balloon-expandable devices are used. Mitral ViV can be achieved transapi-

cally or transseptally. Tricuspid ViV is still extremely rare, mainly because few tricuspid replacements have been surgically achieved; however, it should be easy from a technical standpoint, as the surgical valves used are usually larger than devices available today.

Can you provide some background on the hypothesis that procedural time of day for cardiovascular interventions may have an impact on outcomes and any findings you've observed at your center?

It is well-known that cardiovascular diseases exhibit a diurnal variation, with higher incidence of acute pulmonary edema, myocardial infarction, or stroke in the early morning as opposed to the evening. In 2010, myocardial tolerance to ischemia reperfusion was demonstrated to be dependent on time of day in mice. While studying a closed chest coronary artery occlusion model in wild-type mice, researchers showed 3.5-fold larger infarct sizes at the sleep-to-wake versus wake-to-sleep transition and that this was related to the cardiomyocyte circadian clock.⁵

With these elements in mind, we chose to study patients undergoing standard on-pump aortic valve replacement to assess the existence of a biorhythm in ischemia reperfusion (IR) tolerance in the human heart.⁵ Indeed, on-pump cardiac surgery provokes a predictable perioperative myocardial IR injury because of the aortic cross-clamping and cardioplegia during the cardiopulmonary bypass. In line with studies in mice, we observed that perioperative myocardial injury is highly influenced by the time of day. Moreover, we provided proof-of-concept evidence that antagonism of the clock gene *Rev-erb α* limits IR injury at the time of sleep-to-wake transition in an ex vivo Langendorff mouse heart model; that is a potent new cardioprotective strategy. This approach could be very interesting for personalized medicine in daily practice.

What led you to seek education and now a professorship position in Shanghai, China? What similarities and differences exist between practicing in Asia versus Europe?

I had been approached by Chinese colleagues as well as a Chinese medical device company (MicroPort Scientific Corporation) seeking educational, clinical, and research and development support. I then started collaborating on a TAVI study. I felt a great interest coming from this country and was very attracted by the history and culture there. You also understand and sense the huge potential that exists in China when you start working there. The professorship position was suggest-

ed by Jiao Tong University colleagues with the aim to provide educational support and develop collaborative training and research work between France and China.

Everything is different between Asia and Europe. Medical techniques are more advanced in Europe, so there is a great need for further education in China. The health system covers a wider population in Europe, but there has been a lot of progress in China over the years in this regard. The relationship is also different between physicians and patients. In China, patients are very well informed of their disease and potential treatments. They expect their doctors to give them the best treatment and use the latest technology, but don't take into consideration the training and learning curve involved in being able to provide such quality of treatment. From my perspective, the physicians I've met in China are extremely respectful and eager to learn. In large centers, the level of equipment is just amazing and our Chinese colleagues are highly skilled.

Apart from the clinical differences of practicing in these locations, which aspects of daily life you most enjoy in each location?

The human factor is extremely important in my opinion. Discovering new ways of thinking is an impelling challenge and practice. Being open-minded offers new perspectives and makes personal development a reality. Every time I travel to operate or teach, I feel that I am sharing a humanity legacy, which is a wonderful treasure: treating patients and saving lives because heart valve disease kills. ■

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