VALVULAR DISEASE IN 2010

Evolution and revolution in risk stratification and therapy

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During 2010, several landmark studies, including the PARTNER trial, have made huge advances in the field of transcatheter aortic valve implantation. Other studies have made major contributions to the therapeutic management of young adult patients with severe aortic valve disease and of patients with asymptomatic severe mitral regurgitation.

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Key advances

- The severity of organic mitral regurgitation can change with exercise, and exercise stress echocardiography can thus provide important incremental prognostic value beyond that obtained with echocardiography at rest[1]
- The left atrial volume is a powerful predictor of risk of cardiac events in patients with mitral regurgitation and should be integrated in the routine Doppler-echocardiographic evaluation of these patients[2]
- Implantation of a pulmonary autograft can achieve complete restoration of life expectancy in young adult patients with severe aortic valve disease, whereas an aortic homograft does not seem to be a durable valve substitute[3]
- The 'valve-in-valve' procedure—the transcatheter implantation of a valve within a bioprosthesis—is an efficient and safe alternative to surgery in patients with structural failure of bioprostheses[4]
- Transcatheter aortic valve implantation markedly improves survival and symptoms in patients with severe aortic stenosis who are considered to be at prohibitive risk for surgical aortic valve replacement[5]

The year 2010 has been particularly prolific in the field of valvular heart disease. Selecting a few among the numerous outstanding studies published this year was thus a difficult and certainly imperfect exercise. The five articles highlighted in this overview provided important novel insights that are likely to change the diagnosis and treatment of mitral regurgitation[1,2] and aortic valve disease.[3–5]

> "At 1 year, mortality was 31% with TAVI and 51% with standard therapy..."

A controversy currently exists regarding the timing of mitral valve surgery—that is, on whether to perform prophylactic surgery or adopt a 'watchful waiting' strategy—in patients with asymptomatic severe mitral regurgitation. In a study by Magne and colleagues,[1] 78 consecutive asymptomatic patients with preserved left ventricular systolic function and moderate or severe organic mitral regurgitation were submitted to both resting and exercise echocardiography. Among the patients included in this series, 15% had pulmonary hypertension both at rest and during exercise and 32% had normal pulmonary arterial pressure at rest but developed pulmonary hypertension during exercise. The presence of pulmonary hypertension during exercise was related to the severity of mitral regurgitation during exercise and was associated with a 3.4-fold increase in the risk of development of mitral regurgitation symptoms during follow-up. Pulmonary hypertension during exercise was more accurate than pulmonary hypertension at rest in predicting the development of symptoms. The best cut-off value of exercise systolic pulmonary arterial pressure for predicting symptoms was 56 mmHg,[1] which is close to the empiric threshold of 60 mmHg recommended by current practice guidelines for risk stratification of patients with asymptomatic mitral regurgitation.[6] Before the publication of the study by Magne and colleagues,[1] no data existed to support the relevance of this 60 mmHg cut-off value. Of note, in another study by the same team,[7] organic mitral regurgitation was shown to be a highly dynamic lesion whose severity can change (increase or decrease) substantially with exercise. Furthermore, these changes were shown to influence clinical outcomes, independent of the severity of mitral regurgitation at rest.[7] These novel findings[1,7] demonstrate that exercise stress echocardiography provides important incremental prognostic information in patients with organic mitral regurgitation. This information could be used to select the most appropriate therapeutic strategy—prophylactic surgery or watchful waiting—in individual patients.

In a large prospective study that included 492 patients with sinus rhythm who had moderate to severe organic mitral regurgitation, Le Tourneau *et al.* reported that, compared with patients with left atrial (LA) volume index <40 ml/m^2, those with LA volume index ≥60 ml/m^2 had a 2.8-fold increase in mortality and a 5.2-fold increase in the risk of all cardiac events when treated medically.[2] Furthermore, mitral valve surgery resulted in improved outcomes in this population, particularly among patients with an LA volume index ≥60 ml/m^2. This study, therefore, reveals that, besides accurate quantification of mitral regurgitation severity *per se,* to assess the size of the chamber containing the mitral regurgitation jet is also important in disease prognosis. The powerful prognostic value of the LA volume index could be explained by the fact that this index is a composite marker of both resting and exercise-induced components of mitral regurgitation, as well as being a marker of the chronicity of the disease. These findings highlight the LA volume index as an important tool to add to the Doppler-echocardiographic armamentarium available for risk-stratification and clinical decision-making in patients with organic mitral regurgitation.

The implantation of a pulmonary autograft—the Ross operation—is the only surgical procedure that provides continued long-term viability to the valve tissue. In an elegant randomized trial, 228 adult patients (median age 39 years) were randomly assigned to receive aortic root replacement with a pulmonary autograft or with an aortic homograft.[3] Perioperative mortality, 13-year survival, and the 13-year reoperation rate were 1%, 95%, and 94%, respectively, in the autograft group, and 3%, 78%, and 51% in the homograft group. Notably, survival in the autograft group was similar to that in an age-matched and sex-matched group of individuals from the general British population. This study demonstrates that the implantation of a living valve can achieve complete restoration of life expectancy in young adult patients with severe aortic valve disease, whereas the aortic homograft does not seem to be a durable valve substitute in this population.[3] In another randomized study published by the same group, root replacement with a stentless bioprosthesis was also superior to use of an

aortic homograft in terms of freedom from reoperation.[8] The outcomes achieved with pulmonary autografts remain to be compared with those of other valve substitutes, such as stentless or stented bioprostheses, mechanical valves, and, in the future, transcatheter-implanted valves.

The Achille's heel of bioprostheses or homografts used for valve replacement is their limited durability, especially when employed in the young population. Reoperation has been the standard treatment for structural valve failure; however, repeat surgery carries a high operative risk.[6] In a multicenter study by Webb and colleagues,[4] transcatheter valve implantation within failed bioprostheses—that is, the 'valve-in-valve' procedure—was successfully performed in a series of 24 patients. No procedural deaths occurred, the 30-day mortality was 4.2% and, at the end of follow-up (median of 135 days), survival was 92% and 88% of patients were in NYHA functional class I or II. This pioneer study demonstrates that transcatheter valve-in-valve implantation is a safe and efficient alternative to surgical reoperation in the setting of bioprosthetic valve failure in high-risk patients. These findings might eventually change practice with regard to selection of type of prosthesis for surgical valve replacement. Having the potential to treat structural failure of bioprostheses using the valve-in-valve procedure might, in the future, incline surgeons to more frequently opt for a bioprosthesis rather than a mechanical valve, and to implant bioprostheses in patients younger than those who are currently receiving these valves.

> "...the implantation of a living valve can achieve complete restoration of life expectancy..."

One highlight of 2010 in the field of valve disease was the publication of the results of the PARTNER-B trial.[5] The cohort B of the PARTNER trial was composed by a total of 358 patients with severe aortic stenosis who were considered unsuitable candidates for surgery and who were randomly assigned to transfemoral transcatheter aortic valve implantation (TAVI) or standard treatment (medical treatment with or without balloon valvuloplasty). At 1 year, mortality was 31% with TAVI and 51% with standard therapy ($P<0.001$). Among the survivors at 1 year, 75% were in NYHA functional class I or II in the TAVI group, versus 42% in the standard therapy group. On the other hand, compared with standard therapy, TAVI was associated with higher incidence of major strokes (5% versus 1%, $P=0.06$) and major vascular complications (16% versus 1%, $P<0.001$). However, the rate of the composite of major stroke or death was still significantly lower in the TAVI group (33% versus 51% with standard therapy, $P<0.001$).[5] In the whole history of cardiovascular trials, very few of the therapies assessed have achieved a 20% reduction in absolute risk and 40% reduction in relative risk of mortality over a period of 1 year. The momentous results of the PARTNER-B trial[5] have major implications in terms of both clinical practice (Figure 1) and health-care costs. According to current estimates,[9] at least 30% of patients with a class I indication for aortic valve replacement are denied surgery because operation is considered to carry a high or prohibitive risk. A large proportion of these patients are amenable to TAVI and, in light of the results of the PARTNER-B trial,[5] not offering this alternative therapy has become ethically unacceptable unless the patient's short-term life expectancy is compromised by severe comorbidities.

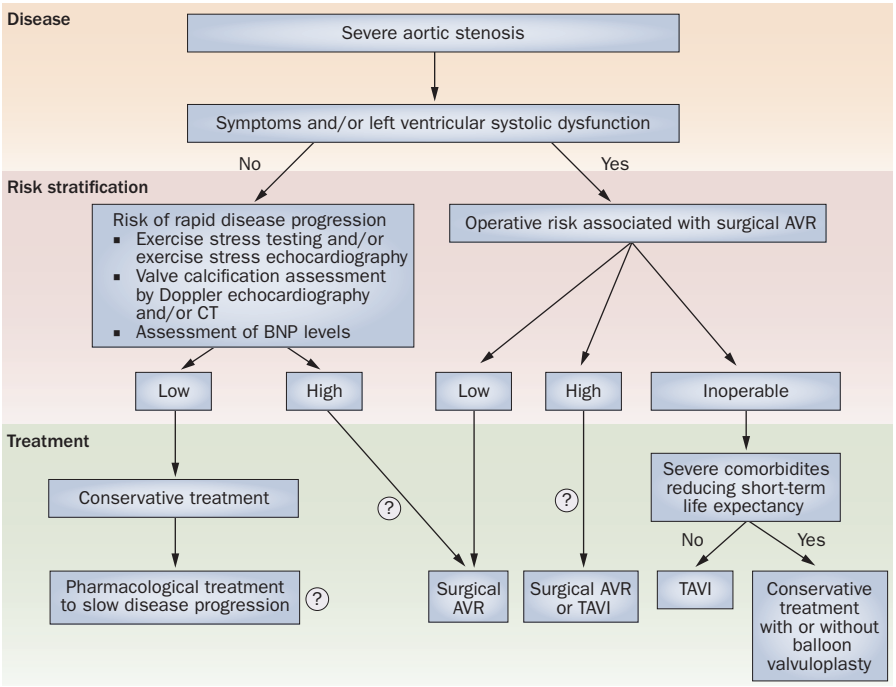

Figure 1 | The evolving therapeutic management of aortic valve stenosis. Question marks indicate no or not enough evidence to support the selection of a given treatment and, therefore, the urgent need for more research studies in the field. Abbreviations: AVR, aortic valve replacement; BNP, brain natriuretic peptide; TAVI, transcatheter aortic valve implantation.

The results for cohort A of the PARTNER trial, which will be presented in spring 2011, will address the next crucial question in this rapidly evolving field: is TAVI a viable alternative to surgery in patients considered at high operative risk? In this regard, the observation of a 30-day mortality of only 5% in the TAVI arm of PARTNER-B, which included only inoperable patients, is encouraging. In PARTNER-A, surgical aortic valve replacement is compared with TAVI and, unlike in PARTNER-B, includes both transfemoral and transapical approaches. In the Multicenter Canadian Experience (MCE) cohort,[10] in which patients had a baseline risk profile that was intermediate between those of PARTNER cohorts A and B, the 1-year survival was 78% for the transfemoral approach and 75% for the transapical approach. On the basis of the findings of PARTNER-B[5] and MCE,[10] we can anticipate a 30-day mortality inferior to 5% and a 1-year survival close to 80% in the TAVI arm of PARTNER-A, which could equate or even surpass the results of the surgical arm.

The results of PARTNER-B[5] also underline the importance of reducing both the risk of stroke associated with TAVI—by using, for example, devices for protection of carotid arteries during the procedure—and the risk of vascular complications—by developing, for example, smaller femoral access sheaths and catheters. Another important aspect associated with this emerging technology that remains unknown is how the durability of the transcatheter bioprostheses compares with that of surgical bioprostheses.

In 2010, major progresses have been made in the risk stratification and transcatheter therapy of valvular heart diseases. Strikingly, however, and as opposed to other cardiovascular diseases, no pharmacological treatment is available that can halt or slow the progression of valvular disease (Figure 1). Hopefully, the articles that will be published in 2011 and beyond will reveal novel therapeutic targets that will, in turn, pave the way for the development of efficient pharmacotherapy for these frequent and serious diseases.

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Competing interests
The author declares associations with the following companies: Edwards Lifesciences, Medtronic, and Sorin Medical; and with the following organization: PARTNER trial. See the article online for full details of the relationships.

1. Magne, J., Lancellotti, P. & Piérard, L. A. Exercise pulmonary hypertension in asymptomatic degenerative mitral regurgitation. *Circulation* **122**, 33–41 (2010).
2. Le Tourneau, T. *et al.* Impact of left atrial volume on clinical outcome in organic mitral regurgitation. *J. Am. Coll. Cardiol.* **56**, 570–578 (2010).
3. El-Hamamsy, I. *et al.* Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. *Lancet* **376**, 524–531 (2010).
4. Webb, J. G. *et al.* Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. *Circulation* **121**, 1848–1857 (2010).
5. Leon, M. B. *et al.* Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N. Engl. J. Med.* **363**, 1597–1607 (2010).
6. Bonow, R. O. *et al.* ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* **114**, e84–e231 (2006).
7. Magne, J., Lancellotti, P. & Piérard, L. A. Exercise-induced changes in degenerative mitral regurgitation. *J. Am. Coll. Cardiol*. **56**, 300–309 (2010).
8. El-Hamamsy, I. *et al.* Late outcomes following freestyle versus homograft aortic root replacement: results from a prospective randomized trial. *J. Am. Coll. Cardiol*. **55**, 368–376 (2010).
9. Iung, B. *et al.* A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur. Heart J.* **24**, 1231–1243 (2003).
10. Rodés-Cabau, J. *et al.* Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J. Am. Coll. Cardiol.* **55**, 1080–1090 (2010).