The year in cardiology 2015: valvular heart disease

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Received 6 October 2015; revised 2 November 2015; accepted 9 December 2015; online publish-ahead-of-print 3 January 2016

Preamble
Valvular heart disease is a subject of growing interest due to its prevalence and difficult issues in decision-making in the rapidly moving field of percutaneous interventions. During this year, a number of interesting articles addressed the topic of valvular heart disease with a special emphasis on imaging, interventions, and the publication of the new European Society of Cardiology (ESC) guidelines on the management of infective endocarditis (IE). We present here a selection of the most recent and particularly relevant papers.

Aortic stenosis
A population study was performed to explore the hypothesis that a link may exist between aortic stenosis (AS) and psoriasis due to shared inflammatory pathways.1 The study comprised the entire Danish population aged >18 years followed up until diagnosis of AS or death. The overall incidence rates for AS were 8, 16, and 20 per 10 000 person-years for the reference population, mild psoriasis, and severe psoriasis, respectively. The results indicate a disease severity-dependent increased risk of new-onset AS in patients with psoriasis. This association with increased risk of AS was independent of age, gender, comorbidity, and socioeconomic status. These findings expand the current knowledge of psoriasis as a clinically relevant risk factor for a range of cardiovascular diseases such as coronary artery disease or heart failure.

The evaluation of the severity of AS remains a challenge. The largest source of error in the measurement of aortic valve area (AVA) is the variability in the measurement of left ventricular outflow tract (LVOT) area and the assumption that LVOT is circular whereas it is elliptical. The group from Leiden studied 191 patients who underwent transcatheter aortic valve implantation (TAVI) with indexed AVA (AVAi) < 0.6 cm²/m² and left ventricular ejection fraction (LVEF) ≥ 50%.2 Patients were classified according to flow (stroke volume index < 35 or ≥ 35 mL/m²) and gradient (mean transaortic pressure gradient ≤ 40 or > 40 mmHg). The left ventricular outflow tract area was measured by planimetry on multi-detector computed tomography (MDCT) (Figure 1) and combined with Doppler haemodynamics on continuity equation to obtain the fusion AVAi.

By using the fusion AVAi, 52% of patients with normal flow–low gradient would have been reclassified into moderate AS, whereas this was the case in only 12% of patients with low flow–low gradient. This reclassification may have important therapeutic implications since patients with normal flow–low gradient severe AS and preserved LVEF had comparable survival to that of patients with moderate AS, whereas patients with low flow–low gradient have worse survival. This study suggests the potential interest of fusion imaging, besides the evaluation of valve calcification, when there is discordance in the assessment of the severity of AS especially in the entity of low flow–low gradient AS with preserved LVEF.

The ‘success story’ of TAVI is further reinforced by the publications of several large registries and the extended follow-up of the existing randomized trials.

The publication of 5-year outcomes of the PARTNER trials confirmed the initial observations. In inoperable patients, TAVI provided a 22% survival benefit over medical management, which translated, importantly for this patient population, into a significant improvement in quality of life.3 However, 5-year mortality in the TAVI-treated patients was still 71.8% with a large proportion of non-cardiac deaths and 48% of patients were readmitted to hospital, which underlines the need for better avoiding performing the procedure in patients where it is more ‘futile than futile’ because of co-existing comorbidities. In high-risk patients, outcomes for TAVI and surgery were similar in terms of mortality and functional improvement and there was no continuous risk of stroke.4 In both studies, there was at least equivalent or even better valve function for TAVI and no prosthetic dysfunction occurred. These encouraging data, which are in line with the 2-year outcomes observed with the self-expandable device,5 may well lead TAVI to be considered as the gold standard in high-risk patients even more so, because accumulated experience in patient selection, procedural performance, and technology further improve the results of TAVI.

Paravalvular leak (PVL) after TAVI is considered ‘the Achilles’ heel’ of TAVI. The PARTNER group published the largest single study to examine severity of PVL in 2553 patients and association with outcomes after TAVI with the Edwards Sapien valve.6 Echocardiograms were assessed by a core lab. Paravalvular leak was graded as none/trace in 53.1%, mild in 38.1%, and moderate to severe in

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

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Undersizing of the prostheses was associated with higher PVL se-

Quantifying PVL, which may be improved in the future by the use

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• Patients’ characteristics, such as presence of AR before TAVI, may

• Undersizing of the prostheses was associated with higher PVL se-

Fortunately, the new TAVI prostheses with sealing or inflatable cuffs

Stroke is also a feared complication after TAVI. In the study by

Three-vessel cerebral coverage was achieved in 88.9% of cases. The primary in-hospital procedural safety end-

• Undersizing of the prostheses was associated with higher PVL se-

Growing experience with valve repair for AR may be an incentive

Aortic regurgitation

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A recent study reported that subclinical thrombosis of TAVI pros-

A careful and comprehensive follow-up and reporting is neces-

Aortic regurgitation

8.8%. Multivariate analysis indicated that the presence of moderate/

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Figure 1 Measurements of left ventricular outflow tract. (A) Left ventricular outflow tract diameter using transthoracic echocardiography.

(A) Left ventricular outflow tract diameter using transthoracic echocardiography. (B) Left ventricular outflow tract area using multi-detector computed tomography. Reproduced with permission from Kamperidis et al.2

Few patients. Some complications are similar to those observed after

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valve-sparing surgery in 21 of them. Ten-year overall survival did not differ between the two
groups (91 ± 4 vs. 89 ± 5%, respectively, P = 0.87). Patients who

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10-year overall survival than patients with no regular cardiologic follow-up. These findings do not support earlier indications for surgery in AR than those in the guidelines and highlight the need for regular cardiologic follow-up when asymptomatic patients are conservatively managed.

**Mitral regurgitation**

The quantitation of the severity of mitral regurgitation (MR) requires an integrative approach, in which quantitative criteria play an important role. Quantitative echocardiography was compared with cardiac MRI in a prospective series of 103 patients with a majority (82%) of primary MR. Agreement between the two methods was moderate (correlation for regurgitant volume \( r = 0.6 \)). In particular, 45 out of 58 patients with severe MR according to echocardiography were reclassified as mild or moderate when using MRI. In the 26 patients who had MRI after surgery, the correlation between reverse left ventricular (LV) remodelling and indices of MR severity was much higher for MRI than for echocardiography (\( r = 0.85, P < 0.0001 \) vs. \( r = 0.32, P = 0.10 \), respectively), which tends to support the accuracy of MRI.

The management of patients with severe secondary MR and LV dysfunction is a topic where the data currently available on the impact of different treatments are somewhat discordant. The study by Samad et al. merged two large databases from Duke University putting together a record of 1441 patients with moderate to severe functional MR and LV dysfunction. This study confirmed that in current practice, medical management, which was used in 75% of patients, is the most popular strategy while coronary artery bypass grafting (CABG) plus mitral valve surgery was performed in only 7% and finally mitral valve surgery in isolation in 4% of cases. Follow-up was up to 5 years and based on a clinical endpoint combining death, transplantation, or implantation of LV assist. Medical management carried only a dismal prognosis since the survival rate was only 40% at 5 years. This was not a randomized study, but a propensity adjustment showed that the use of mitral valve surgery was associated with better event-free survival than medical management. Among patients with coronary artery disease, CABG or CABG plus mitral valve surgery was associated with a better event-free survival. On the other hand, mitral valve surgery in isolation was not associated with a significant survival benefit compared with medical therapy. Among patients with coronary artery disease, mitral valve surgery offered better event-free survival over no mitral valve surgery. Among patients who underwent CABG, the combined use of mitral valve surgery showed no survival benefit. Finally, in patients without coronary artery disease, mitral valve surgery did not significantly improve outcomes when compared with medical therapy even if there was a favourable trend. These results contrast with findings in the STICH trial, but are in accordance with the CTSN trial in which, however, clinical endpoints were not a primary endpoint. The present study supports the benefit of revascularization in these patients with poor LV. These conclusions also support the current recommendations, which state that mitral valve surgery can be combined in selected patients with CABG and has few indications in the absence of CABG.

The 2012 ESC/European Association for Cardio-Thoracic Surgery (EACTS) guidelines on the management of valvular heart disease stated that percutaneous MitraClip therapy may be considered, after heart team discussion, in high-risk patients with either primary or secondary MR. This led in current practice, in the countries where the cost of treatment is reimbursed, to a large use of the device in high-risk patients with secondary MR. Conversely, the use of MitraClip therapy is not currently recommended in secondary MR in the American Heart Association (AHA)/American College of Cardiology guidelines following US Food and Drug Administration (FDA) advice. To help answer the debate, the efficacy of this therapy, on top of optimal medical management, is being studied in three ongoing randomized trials: COAPT in the USA, MITRA-FR and RESHAPE II-HF in Europe.

Newcomers in interventional cardiology such as direct mitral annuloplasty and, in a more distant future, transcatheter mitral valve replacement (Figure 2) will also play a role.

In the rapidly moving field of interventions on MR, a joint position paper from the ESC Working Groups on cardiovascular surgery and valvular disease recently addressed the indications and limitations of surgical and percutaneous treatment of MR. Surgery remains the reference treatment for primary MR, while percutaneous edge-to-edge repair is an alternative in symptomatic patients at high-risk or contra-indicated to surgery. Unlike in primary MR, interventions should be considered in secondary regurgitation only in patients who remain symptomatic despite optimal medical therapy.

**Mitral stenosis**

Degenerative mitral stenosis is frequent in the elderly and mostly results from extensive annular calcification. The absence of commissural fusion makes it not amenable to percutaneous mitral commissurotomy. Preliminary experience has suggested that transcatheter valve implantation may be considered in symptomatic patients if the anatomy is suitable. Such indications require comprehensive imaging and a cautious heart team evaluation (Figure 3).

**Tricuspid regurgitation**

The diameter of the tricuspid annulus is important in decision-making for combining tricuspid valve repair with left-sided valve surgery, but the method of measurement is not clearly stated. Tricuspid annulus diameter was measured using four transthoracic 2D views in 282 patients, 3D transoesophageal echocardiography (TOE) in 183, and the apical four-chamber view in 66 healthy controls. Transthoracic apical four-chamber view was the most feasible and reproducible measurement, while TOE gave larger annular diameters (mean 4 mm). The comparison with controls suggested a threshold for dilated tricuspid annulus of 42 mm or 23 mm/m² with the apical four-chamber view.
Many patients with severe tricuspid regurgitation, especially after previous left heart surgery, are considered inoperable or at very high risk for surgery, which was an incentive in the search for interventional techniques. The experience was previously limited to case series of valved stent implantation in the vena cava. This year the first in man percutaneous tricuspid valve repair was...
successfully performed and demonstrated feasibility in addition to some preliminary efficacy data. The principle here is to ‘bicuspidize’ the tricuspid orifice reproducing the Kay operation.39

**Anticoagulant therapy in native heart valve diseases**

At the present time, direct oral anticoagulants (DOACs) are labelled for use in patients with non-valvular atrial fibrillation (AF). Subgroup analyses of two trials are now available to assess the safety and efficacy of DOACs in patients with valvular disease. Rivaroxaban was compared with vitamin K antagonists (VKA) in 1992 patients with AS (11%), AR (25%), or MR (90%).28 There was no difference in the annual rate of stroke or systemic embolism between rivaroxaban and VKA (2.01 vs. 2.43%; HR, 0.83; 95% CI, 0.55–1.27). However, the annual rate of major or clinically relevant bleeding was higher with rivaroxaban than with VKA (19.8% vs. 16.8%; HR, 1.25; 95% CI, 1.05–1.49), while no significant difference was observed in the 12 179 patients without valvular disease.

Another paper reported on 4808 patients with AF and valvular heart disease (MR in 73%) who were treated using apixaban.29 These 4808 patients were compared with 13 389 patients without valvular disease. In patients with valvular disease, the rate of stroke or systemic embolism was lower with apixaban than with VKA (HR, 0.70; 95% CI, 0.51–0.97). Major bleeding tended to be less frequent with apixaban than with VKA (HR, 0.79; 95% CI, 0.61–1.04). Differences between apixaban and VKA were consistent in the 13 389 patients without valvular disease.

These findings support the possibility of using certain DOACs in patients with AF who have AS, AR, and MR. This will contribute to clarify the debate on how so-called non-valvular AF should be interpreted in the light of patient particularities.30,31

**Valvular surgery**

The choice of heart valve prosthesis is characterized by an increase in the percentage of bioprostheses. A retrospective analysis of 4253 patients aged between 50 and 69 years undergoing aortic valve replacement between 1997 and 2004 in the USA compared 15-year outcome according to the type of prosthesis. An analysis of two propensity-matched subgroups of 1001 patients found no difference in survival.32 Patients with a mechanical prosthesis experienced more frequent severe bleeding (13.0 vs. 6.6%; HR, 1.75; 95% CI, 1.27–2.43), less frequent reoperations (6.9 vs. 12.1%; HR, 0.52; 95% CI, 0.36–0.75), and no difference in stroke (8.6 vs. 7.7%; HR, 1.04; 95% CI, 0.75–1.43). Another comparison of the type of prosthesis was recently reported in 4545 patients aged between 50 and 69 years who underwent an isolated aortic valve replacement between 1997 and 2013 in Sweden.33 The comparison of two propensity-matched subgroups of 1099 patients showed a significantly higher 15-year survival in patients who received a mechanical prosthesis than a bioprosthesis (59 vs. 50%; HR = 1.34; 95% CI, 1.09–1.66; P = 0.006). This difference remained significant in patients aged between 50 and 59 years but not in those aged between 60 and 69. As in the previously mentioned study, there was no difference in the incidence of stroke, higher rates of major bleeding, and lower rates of aortic valve reoperation in patients with a mechanical prosthesis.

The discrepancies in survival between these two studies using the same methodology and targeting the same population illustrate the usefulness of replicating such studies. In contrast with the American study, the Swedish study does not support a further extension of indications for aortic bioprostheses under the age of 60.

The main reasons for the decreased use of mechanical prosthesis are the constraints and hazards related to the need for lifelong anticoagulant therapy. Since DOACs are contra-indicated in this indication, the optimization of the modalities of VKA therapy remains a relevant goal. Recent series suggested the possibility to further downgrade the target International Normalized Ratio (INR) for mechanical prosthesis, in particular with the use of INR self-monitoring.34 This strategy was tested in a trial including 1571 patients who were randomized to low INR with self-monitoring or very-low INR with self-monitoring combined with telemedicine-guided dose adjustment.35 Patients with very-low target INR, i.e. [1.6–2.1] in aortic and [2.0–2.5] in mitral position, had a significantly lower 2-year rate of major bleeding than those with low target INR, i.e. [1.8–2.8] in aortic and [2.5–3.5] in mitral position, with no difference in the thromboembolic risk.

Current knowledge and remaining gaps in evidence on anticoagulant therapy after valve replacement have been detailed in a recent review in the *European Heart Journal*, encompassing long-term and post-operative anticoagulation, bridging, and specificities of bioprostheses and TAVI.34

**Infective endocarditis**

Although there has been a consistent trend for restricting indications for antibiotic prophylaxis during the last decade, the prevention of IE remains a debated issue.

A recent analysis of the National Inpatient Sample (NIS) database in the USA reported an increase in the incidence of IE between 2000 and 2011, with a statistically significant slope increase for *Streptococcus viridans* after the restriction of antibiotic prophylaxis on AHA guidelines in 2007.36 Temporal association does not prove a causal relationship, but raises concerns as to the justification to reduce indications for antibiotic prophylaxis. The same concerns were raised following a report of an increase in the incidence of IE in England after the release of NICE guidelines in 2008, which abandoned any antibiotic prophylaxis.37 These findings from administrative databases should, however, be analysed with caution, since a number of other factors may account for the increased incidence of IE. Moreover, the temporal relationship with guideline changes is debatable since statistical testing for slope changes was also significant at all points in time between April 2003 and May 2010 in the English series.38 The results of the analysis of the American NIS database are discordant with the previous analysis of another large American database39 and with another analysis of the same NIS database.40 Finally, IE incidences reported in both recent studies were discordant with the estimations from specific population-based series. Discrepancies in analyses of the evolution of the incidence of IE after guidelines changes underline the need for specifically designed prospective surveys to strengthen the level of evidence of future guidelines.
The new ESC guidelines on IE were recently published.41 In the absence of any major breakthrough in the pro and contra for antibiotic prophylaxis, the 2015 issue of the ESC guidelines maintains the principle of antibiotic prophylaxis restricted to the highest risk patients undergoing the highest risk dental procedures. These new guidelines emphasize even more the importance of oral and cutaneous hygiene and non-specific aseptic measures for all healthcare procedures. Advances in diagnosis integrate non-cardiac imaging for the detection of embolic events and cardiac nuclear imaging for difficult diagnosis (Figure 4). Indications for curative antibiotic therapy and surgery have been refined. New ESC guidelines emphasize the importance of the evaluation of patients with IE in ‘endocarditis teams’ comprising all resources in cardiac and non-cardiac imaging, microbiology, and surgery.

Indications for surgery during acute IE often raise problems since surgery carries a higher risk during acute IE. Data from the large International Collaboration on Endocarditis database were used to determine if patients had an indication for surgery and if they actually underwent surgery. As many as 74% of patients had an indication for surgery during the acute phase of IE.32 Surgery was performed in 57% of patients and 76% of those who had an indication. Non-operated patients with an indication for surgery had a particularly high mortality at 6 months. These findings highlight the difficulties of the analysis of risk and benefits of surgery for acute IE and support an early evaluation of patients with acute IE in specialized medico-surgical teams.41

Authors’ contributions

B.I. and A.V. selected the papers reviewed and drafted the manuscript. S.H.R. reviewed the content of the manuscript.

References


