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CURRENT OPINION

The year in cardiology 2014: valvular heart disease

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Preamble

Numerous articles have been published in 2014 regarding valvular heart diseases. Many papers focused on percutaneous interventions: transcatheter aortic valve implantation and percutaneous mitral valve repair. This article presents the most relevant articles published in 2014 in this important clinical setting.

Epidemiology

Valvular heart disease remains frequent but is subject to temporal and spatial epidemiological heterogeneity and this has important consequences on patient management. The predominance of degenerative aetiologies in industrialized countries accounts for the high burden of valve disease in elderly patients with comorbidities. Unfortunately, it is not possible today to accurately estimate the prevalence of chronic secondary mitral regurgitation (MR) from available population-based studies as they do not comprise an analysis of anatomical features and mechanisms of MR. This should be dealt with by running prospective registries with homogenous echocardiographic assessment.[1]

Guidelines

The recently issued ACC/AHA guidelines in 2014[2] are largely concordant, with respect to most recommendations, with the 2012 ESC/EACTS guidelines.[3] The rare discrepancies and the number of level C recommendations highlight the need for further randomized studies and large registries. Both documents stress the importance of risk assessment and shared decision-making emphasizing the need for an individualized approach.

Aortic stenosis

The Edinburgh group showed the relationship between high troponin concentration and left ventricular (LV) hypertrophy. Patients with high troponin levels had more advanced hypertrophy and myocardial fibrosis. There was also a relationship between the level of troponin I and outcome. These findings suggest the potential interest of this biomarker in the early stages when timing of surgery is discussed.[4]

The entity of patients with 'paradoxical low-flow low-gradient aortic stenosis and preserved ejection fraction' continues to solicit interest. Pibarot and coworkers performed a careful study measuring the weight of operatively excised valves and showed that, when corrected for gender and anatomic type, there is no difference in the weight of aortic valves from patients with normal flow and high gradient and those with paradoxical low flow, low gradient.[5] Similarly, there was no significant difference in the percentage of severe aortic stenosis between these two groups. Thus, these data provide further information for the characterization of this entity and support the use of multidetector computed tomography in the quantification of calcification to assess the severity of aortic stenosis in these patients.

A paper of major interest for practising cardiologists evaluated the risk of non-cardiac surgery in a large group of patients who underwent either intermediate- or high-risk surgery with contemporary practices.[6] There was no difference in survival but more major cardiac events were observed in patients with aortic stenosis especially due to heart failure. Most complications occurred when non-cardiac surgery was performed in an emergency. The presence of symptoms is very important in preoperative risk stratification since asymptomatic patients did very well.

Transcatheter aortic valve implantation (TAVI) is now widely used worldwide which increases the number of patients with severe aortic stenosis who receive intervention using either surgery or TAVI. However, a recent prospective registry conducted in several provinces in Spain showed that among octogenarians with severe symptomatic aortic stenosis too many patients (46%) are still managed conservatively which is associated with poor prognosis. This stresses the need for continuous education according to the guidelines.[7]

Transcatheter aortic valve implantation

Patient selection is one of the crucial steps of TAVI. Surgical risk scores, such as the STS PROM and EuroScore, have been shown to be sub-optimal for estimating the risk of surgery. However, decision-making also needs to be supported by evaluation of the risk of TAVI

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by 'TAVI risk scores'. The first attempt to develop a TAVI risk score was recently published by Iung *et al.* from the FRANCE 2 registry with the aim of predicting 30-day mortality. The authors developed and validated a multifactorial risk model including pre-procedural factors related to impaired cardiovascular status, non-cardiac co-morbidities, and one factor related to procedural strategy. Calibration of the score was good; however, the discrimination was only moderate. The reasons for this moderate prediction performance were probably multiple: the number of patients may be insufficient and the very high-risk patients included in this trial may have too many comorbidities to be captured in any score. In particular, there was no precise assessment of frailty[8]; peri-procedural complications were not taken into account even though they still occur frequently.[9] The PARTNER investigators developed a risk score predicting poor outcome at 6 months integrating quality of life with mortality. Here, again there was only moderate discrimination and a good calibration.[10]

Despite being imperfect, these TAVI risk scores may help to guide treatment choice and offer patients realistic expectations of outcome based on their presenting characteristics.

An interesting paper looking at patients judged to be surgically inoperable showed that patients who were inoperable for technical reasons (porcelain aorta, previous bypass, and hostile chest) had better survival and quality-of-life improvement after TAVI than those who were inoperable due to clinical co-morbidities.[11] In this regard, the decision to perform TAVI may be more 'futile than utile' in patients who were shown to have very poor outcome after TAVI such as those with advanced chronic kidney disease treated by dialysis who also had atrial fibrillation[12] or patients with chronic lung disease who are poorly mobile and/or oxygen dependent.[13]

For the first time, a randomized trial comparing TAVI, using a self-expanding transcatheter aortic valve bioprosthesis, with surgical valve replacement in 795 patients at high risk, showed significant survival benefit in favour of TAVI (mortality at 1 year 14.2 vs. 19.1%; $P = 0.004$) (*Figure 1*). It should be noted that a similar comparison in PARTNER A only showed non-inferiority for TAVI. However, patients included in PARTNER were at higher risk and PARTNER was conducted in 2007 when the TAVI technique, in particular valve sizing, was less mature.[14]

Several important registries [GARY ($n = 13\,860$), ADVANCE ($n = 1015$), extreme risk study ($n = 506$), TVT ($n = 6190$)][15–18] consistently showed that survival after TAVI improves over time. However, there remain concerns related to complications such as moderate-to-severe paravalvular leaks which carry a poor prognosis while the prognostic impact of mild paravalvular leak is still debated. This complication will decrease in the future due to better sizing using three-dimensional imaging and new technologies.[19] The recently published REPRISE 2 trial is promising in this respect showing an incidence of moderate-to-severe aortic regurgitation of 1%.[20] Stroke frequency after TAVI has been declining and is probably not higher than that of surgery.[14] This complication may decrease thanks to the use of protection devices.[21] Strokes remain an issue. Over time, it seems that stroke frequency after TAVI has been declining due to improvement in patient selection, use of lower profile catheters, more careful anti-coagulation and better prevention of atrial fibrillation. A recent randomized comparison, including a neurologic assessment, showed that the incidence of major stroke after TAVI is not superior to that of surgery.[22] In addition, protection devices have shown promising signs of efficacy in preliminary evaluation. There is still an ongoing debate on the long-term consequences of pacemaker implantation and the best strategy to use in patients with concomitant coronary artery disease,[23] and the consequences of new-onset persistent left bundle branch block.[24]

The first comparison between balloon-expandable vs. self-expandable valves was presented by the CHOICE trial. The

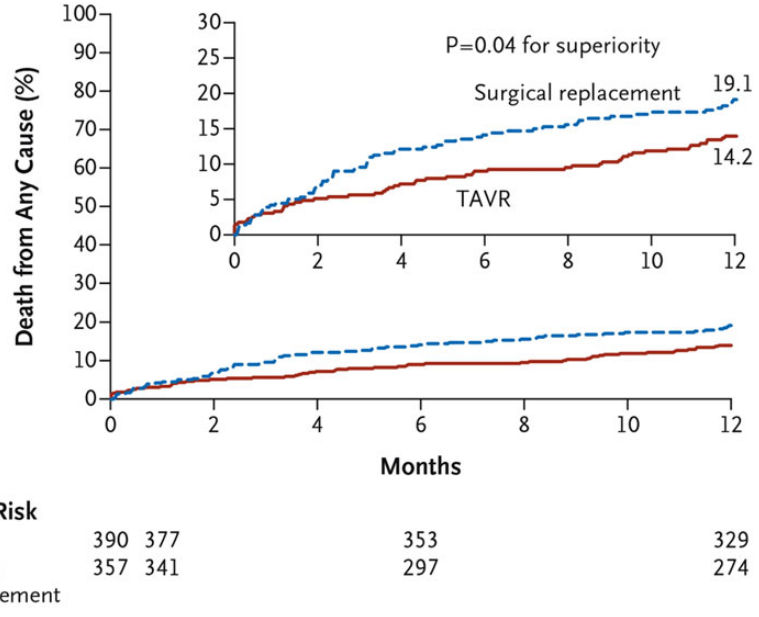

Figure 1 Kaplan–Meier cumulative frequency of death from any cause.

primary endpoint of this trial 'device success' was more frequent in the balloon-expandable valve (95.9 vs. 77.5%, $P < 0.001$) due to a significantly lower frequency of residual rather than mild aortic regurgitation (4.1 vs. 18.3%) and less frequent need for implantation of >1 valve. In addition, the need for permanent pacemaker was three times higher for patients treated with a self-expanding valve. This trial is important but a longer follow-up and a larger number of patients are needed to determine whether differences in device success will translate into clinically relevant overall benefit.[22] This trial opens the debate as to whether head-to-head comparisons between the two devices currently used and newcomers will be needed in the future.

The recommendations in the field of TAVI are similar in the ACC/AHA and the ESC guidelines limiting the use of TAVI to medico-surgical centres where a Heart Team selects high-risk or inoperable patients.

As a useful summary about the technique, a comprehensive review by Bax *et al*. addresses a number of issues which remain open in TAVI as regards patient selection, treatment strategy, procedural issues, and outcome after the procedure.[25,26]

Aortic regurgitation

A multicentre retrospective study looking at the progression of aortic dilatation in adults with bicuspid valve showed that tubular ascending aorta dilatation is the most common pattern and also has the fastest growing rate. Aortic dilatation progresses equally quickly in bicuspid valve at the level of the tubular segment and in Marfan patients at the level of the Valsalva sinuses but does not progress at all in a significant proportion of patients with bicuspid valve. In addition, baseline aortic diameter does not predict progression rate. Therefore, systematic follow-up is warranted in patients with bicuspid valve.[27] Four-dimensional cardiovascular magnetic resonance can assess flow and wall shear stress patterns in ascending aorta. Higher shear forces in patients with bicuspid aortic valve may influence the development of aortic dilatation and the follow-up of patients at risk for aortic dilatation.[28]

The results of TAVI in pure or predominant aortic regurgitation available so far are very limited and suggest that the procedure is feasible. However, the incidence of moderate-to-severe aortic regurgitation seems to be high and a second valve is frequently needed.[29] Indications are likely to be limited in industrialized countries where aortic regurgitation is mostly of degenerative origin and where dilatation/aneurysm of the ascending aorta requires treatment.

Mitral regurgitation

Patients with severe symptomatic MR and heart failure remain largely untreated as suggested years ago by the EuroHeart Survey, and confirmed by recent observations.[30] Accurate quantitative assessment of the severity of MR is essential. In primary MR, regurgitant fraction using LV volumes obtained by 3D echography is highly feasible and reliable for identification of severe MR.[31]

The recent AHA/ACC guidelines revised the definition of severe secondary MR from an effective regurgitant orifice area (EROA) of 0.4–0.2 cm^2 and from a regurgitant volume of 60–30 mL^2. This change has generated controversy. The measurement of EROA is imprecise and the determination of MR severity should consider the relationship between EROA and LV end-diastolic volume at different haemodynamic changes. Smaller LV volumes are associated with lower EROA thresholds and larger LV volumes with higher EROA thresholds. Careful integration of all echocardiographic data must be used to define severe secondary MR.

Surgery

Practice guidelines recommend surgery in patients with severe ischaemic MR, but do not specify whether to repair or replace the mitral valve, because of lack of evidence for indicating which intervention is superior. Many surgeons prefer to repair with an undersized complete ring. A randomized trial including 251 patients showed no significant difference in LV reverse remodelling or survival at 12 months between patients who underwent mitral valve repair and those who underwent valve replacement whereas replacement provided a more durable correction of MR.[32]

Mitral valve annuloplasty may cause functional mitral stenosis, especially during exercise and have been shown to be associated with lack of mitral valve opening reserve, elevated postoperative exercise systolic pulmonary arterial pressure compared with mitral valve replacement.[33]

ESC/EACTS guidelines indicate that surgery should be considered in patients with moderate MR who are submitted to coronary artery bypass grafting (CABG) (class IIa, level of evidence C).[3] A recent study randomly assigned 301 patients with moderated ischaemic MR to CABG alone or CABG plus mitral valve repair. Repair was performed using complete, downsized by two sizes, annuloplasty rings. At 1 year, the combined procedure did not result in a higher degree of LV reverse remodelling but was associated with a longer bypass time, a longer hospital stay after surgery and more neurologic events. No significant between-groups differences were foreseen in major adverse cardiac or cerebrovascular events, deaths, readmissions, functional status or quality of life. A longer follow-up is required to assess whether the lower prevalence of MR after combined surgery translates into a better clinical benefit.[34]

Percutaneous mitral valve repair

The current clinical experience of transcatheter mitral valve intervention is almost exclusively limited to the MitraClip system with which over 15 000 patients have been treated. The criteria for anatomic selection of patients has been addressed in a very comprehensive review by Wunderlich and Siegel (*Figure 2*).[35]

The follow-up results of the randomized clinical trial EVEREST II were reported up to 4 years[36] showing stable improvement in valve function and sustained clinical benefit after successful procedure from 30 days up to 4 years.

A large number of patients have been included in registries where the majority of patients did not fulfil the inclusion criteria for EVEREST as they were high-risk with secondary MR. These registries confirmed the safety of the procedure in expert hands and improvement of symptoms mid-term while the majority of patients still have mild-to-moderate residual MR.[37] Most patients in these registries

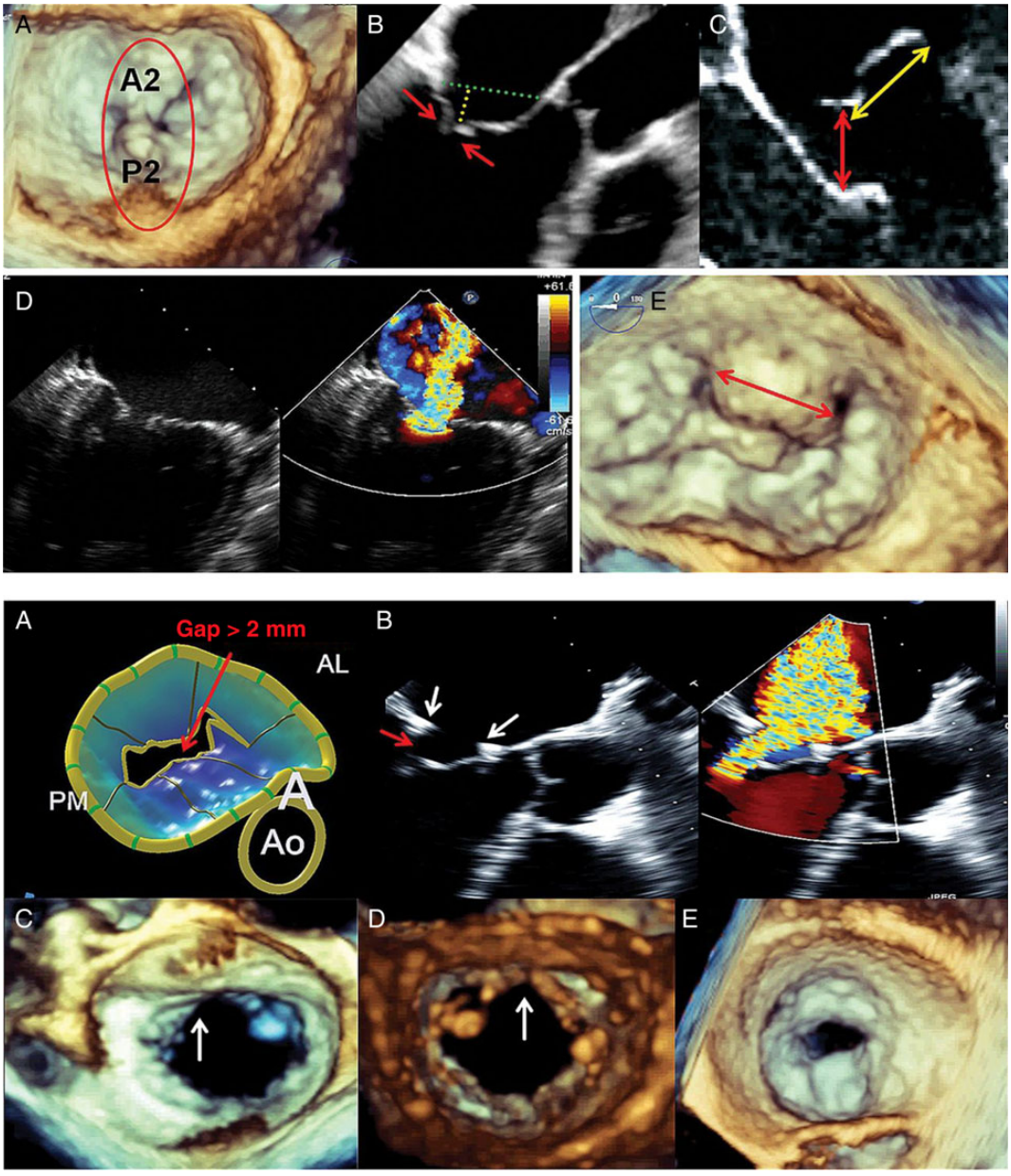

Figure 2 Ideal (upper panel) and unsuitable (lower panel) morphologies for a Mitraclip implantation. Ideal morphologies for a MitraClip implantation. The pathology should be located in the middle segments (*A* and *D*) with no calcification in the grasping area as shown in an intercommissural view in (*D*). (*B*) Some remaining degree of coaptation (red arrows, ideally at least 2 mm), the yellow line represents the coaptation depth (ideally $<$11 mm). The yellow arrow in (*C*) follows a posterior leaflet with enough tissue for grasping (ideally $\geq$10 mm) and the red arrow illustrates the measurement of a flail gap (ideally $<$10 mm). In (*E*), the flail width is marked with a red arrow (ideally $<$15 mm) (P2 prolapse in a non-surgical view). Unsuitable morphologies for a MitraClip implantation. In (A), a gap between the anterior and posterior leaflet is documented in a 3D reconstruction of the mitral valve (MVQ, Q-lab software, Philips). In (*B*), the white arrows point towards a surgically implanted mitral ring, the red arrow marks a gap as a result of a missing posterior leaflet (no tissue to grasp), the anterior leaflet is retracted in addition. An anterior cleft is illustrated in an *en face* view from the LA (*C*) and an *en face* view from the LV (*D*). In (*E*), an example of a severe mitral stenosis is shown in a 3D LA aspect. Ao, aorta; AL, antero-lateral; PM, postero-medial; LA, left atrium. With permission from Wunderlich and Siegel.[35]

have secondary MR. In this group, the outcomes are poor in patients treated at a too advanced stage of the disease reflected by a 'too large' left ventricle or very high levels of BNP.[38]

In patients with primary MR, some promising data[39,40] suggest that when performed by experienced teams, this treatment may provide satisfactory results in terms of safety and clinical outcome in high-risk patients. The mid-term results are closely related to MR severity at discharge. The mid-term outcome seems to be more favourable in patients successfully treated with primary MR than those with secondary MR.

Patients submitted to MitraClip procedure who have moderate–severe tricuspid regurgitation (TR) show impaired safety at 30 days. Moderate–severe TR independently predicted death and rehospitalization for heart failure at 12 months.[41]

The 2014 ACC/AHA recommendations on valvular heart disease state that this technique may be considered in severely symptomatic patients with chronic severe primary MR who have reasonable life expectancy but a prohibitive surgical risk due to severe comorbidity.[2] This recommendation is consistent with the ESC/EACTS guidelines as regards the need for comprehensive assessment by a heart team and limitation of the use of the technique to highly selected patients at high risk. However, they differ concerning the recommendations on the type of MR. This clearly mandates more clinical research trials such as COAPT, RESHAPE, and Mitra Fr in patients with secondary MR.

More anecdotal reports have been published on the use of transcatheter intervention after surgical failure, transcatheter 'valve-in-a-valve',[42] valve in a ring implantation,[43] or the first-in-man transcatheter mitral valve replacement in patients with calcified mitral annulus.[44] Finally, a review of the pre-clinical and early clinical evaluation of percutaneous transcatheter mitral valve replacement was provided by DeBaker.[45]

Mitral stenosis

Cardiac magnetic resonance has been shown to reliably measure planimetric mitral valve area.[46] A new scoring system including new quantitative echocardiographic parameters has been shown to improve the prediction of outcomes following percutaneous balloon commissurotomy.[47] This study confirmed however that anatomic parameters are only part of the prediction of the long-term results of the procedure which are also independently influenced by age, degree of MR, and post-procedural haemodynamic data.

Further analysis of the very long-term results after previous mitral commissurotomy has shown that almost half of patients remain free from surgery up to 20 years after a successful intervention. Repeat percutaneous intervention can be performed in 1 of 4 cases allowing postponement of surgery.[48] In patients who present restenosis after surgical commissurotomy, percutaneous commissurotomy can be performed; when the results are good, 1 in 3 patients remain free from surgery and 1 in 5 has good functional results up to 20 years.[49] The technique can also provide satisfactory long-term functional improvement in patients with mild calcification[50] or when calcification is localized to one commissure in patients with otherwise favourable clinical characteristics.[51]

Endocarditis

Antibiotic prophylaxis given before invasive dental procedures for infective endocarditis prevention is limited to patients at high risk according to the ESC guidelines.[52] In UK, the National Institute for Health and Clinical Excellence (NICE) recommended in 2008 complete cessation of antibiotic prophylaxis.[53] Prevention of infective endocarditis fell substantially after the introduction of the NICE guidance, but the number of cases of infective endocarditis in England increased significantly about the projected historical trend.[54] However, these data do not establish a causal association and large-scale prospective, randomized controlled studies are warranted.[55]

Conclusion

Many studies published in 2014 have important clinical implications. Some contrast with the most recent ESC/EACTS and AHA/ACC guidelines. The ESC/EACTS guidelines published in 2012 will probably require an update in the next future.

Conflict of interest: Prof A.V. is a member of the board of the European Society of Cardiology, he is a consultant for Edwards LifeSciences and Valtech and receives speaker fees from Abbott Vascular.

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