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EDITORIAL COMMENT

Paving the way for the treatment of the sickest aortic stenosis patients - transcatheter aortic valve implantation for all?

Construção do caminho para o tratamento dos doentes mais graves com estenose aórtica – válvula aórtica percutânea para todos?

Cláudio Guerreiro

Departamento de Cardiologia, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal

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With increasing experience and technology and the widespread use of transcatheter aortic valve interventions (TAVI), a broader range of patient phenotypes have been treated. It is already the standard of care for most elderly patients with severe symptomatic aortic valve stenosis (AS).[1] As the body of solid evidence in a broad risk population grows, including intermediate and low surgical risk patients, this therapeutic approach has assumed a determinant role in the current and future of AS treatment.[2,3] National data show that prognosis after TAVI has improved over time, most deaths being unrelated to major periprocedural complications, which have low prevalence nowadays, but instead due to baseline clinical status, patient comorbidities and access route.[4]

A particularly challenging subset of patients are those with low-flow low-gradient (LF-LG) severe AS, characterized by advanced disease stages, and frequently with late diagnosis and worse prognosis. In these patients mortality rates stand at over 30-50% at two years after treatment.[5] In these patients TAVI is a particularly relevant topic of research, first because the correct diagnosis of the hemodynamic phenotype of AS can be challenging, and secondly because appropriate patient selection for percutaneous treatment is not clear cut in this context. Symptom relief and quality of life improvement are of utmost importance; however, we also aim for prognosis enhancement. These patients frequently have multiple comorbidities that can impact their prognosis on the one hand, and on the other, there are data showing that specific AS hemodynamic patterns derive different benefits from the intervention.

The clinical outcomes of LF-LG AS after TAVI have not been specifically studied in large patient cohorts, unlike classical high gradient (HG) AS. Sub analyses of randomized multicenter or single-center studies show that long-term clinical benefit can be limited in the former patients.[6] Nevertheless, solid data on outcomes for the different subtypes of LF-LG are still missing. When thinking about LF-LG we must bear in mind that they concern different patient profiles. Classic LF-LG AS involves heart failure (HF) with reduced ejection fraction (EF) patients, while paradoxically LF-LG patients are in the preserved EF spectrum, having high afterload and impaired filling due to left ventricle (LV) remodeling, which generates a low-flow state.[7]

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E-mail address: claudioeguerreiro@gmail.com

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In the current issue of the Journal, Castelo A et al. provide interesting data on TAVI in LF-LG AS, comparing the outcomes with HG AS.[8] They analyzed 480 consecutive patients who underwent TAVI between 2008 and 2020, of whom 81 (16.9%) had a diagnosis of LF-LG AS. As expected, these patients had a worse clinical profile and higher surgical risk and significant coronary artery disease (CAD), including previous percutaneous and surgical revascularization, higher levels of natriuretic peptide and right ventricle (RV) dysfunction, translating into advanced stages of the disease. After propensity score-matching, and despite the heterogeneous follow-up duration, when comparing LF-LG and HG AS, the former had worse short- and long-term prognosis, particularly the subgroup with LVEF<40%, increased global and cardiovascular mortality and HF hospitalizations. The prognosis worsened as patients progressed to lower EF when compared to preserved EF LF-LG and HG AS. Interestingly, 56.4% of the patients with reduced LVEF saw an improvement in LV function to >=40%. These results must be interpreted with caution because of the limited number of analyzed patients with classic LF-LG (n=42) and on top of that, only a very reduced number of patients underwent a dobutamine stress echocardiography (n=5) to assess contractile reserve. A sub study of the TOPAS-TAVI registry that included 293 patients with LF-LG AS, of whom 44% had very low LVEF (<30%) and 56% low EF (30-40%), showed that there were no significant differences between groups in terms of hard outcomes such as early and late mortality, and patients in the lower spectrum of LVEF saw a greater improvement in LV function at one-year follow-up. The absence of contractile reserve had no relation to clinical outcomes or change in LVEF over time.[9] Steffen J et al., in a large retrospective study of 1,776 patients undergoing TAVI, showed that LF-LG and HG AS had similar short-term complications, however the former presented higher three-years all-cause and cardiovascular mortality, particularly the classic phenotype. The latter were patients with a predominance of other comorbidities, higher rates of CAD, prior myocardial infarction and percutaneous coronary intervention, chronic kidney disease, more dilated atria and ventricles and reduced RV function. Clinical success rates were, nevertheless, similar between groups, with improvement in clinical symptoms in all subsets of patients.[10]

Data suggest there is a benefit derived from aortic valve replacement surgery for LF-LG AS patients, compared with medical treatment alone.[11] Although in the study of Castelo et al. there was no comparison between different treatment strategies (medical therapy and surgery), which would have provide a more solid background regarding the best therapeutic choice for these specific patients, evidence seems to build up regarding the benefit of TAVI in classic LF-LG AS.

Other factors may, however, compromise these patients' clinical evolution, including myocardial disease, as stated by the authors, which is an important and frequently overlooked factor when selecting the proper patient for the right treatment, while avoiding futility.

In fact, if in most HG patients, AS is the key prognosis-limiting pathology, LF-LG patients tell us a different story, in which very adverse left ventricular remodeling, AV valves regurgitations, atrial fibrillation and other cardiovascular comorbidities have strong influence on further clinical evolution. Considering that we are dealing with patients with a dismal short- and long-term prognosis, it is urgent to add data regarding the best selection of patients for intervention, probably including also fragility profiles and functional capacity. A recent study from Ludwig et al. assists us in this task, although it was based on retrospective data. Analyzing 718 patients with classic LF-LG AS who underwent TAVI at five German centers, the authors put forward a new risk prediction in patients with low ejection fraction (RELiEF TAVI) score. It was based on multivariable Cox regression for all-cause mortality, ranging from 0 to 12 points (risk of one-year mortality: 13-99%). The c-index of the RELiEF TAVI score was 0.62 (95% confidence interval (CI): 0.59-0.68) for all-cause mortality, 0.66 (95% CI: 0.61-0.75) for cardiovascular mortality and 0.64 (95% CI: 0.55-0.70) for HF rehospitalization, which is superior to EuroSCORE II for all-cause mortality (0.57 (95% CI: 0.52 to 0.61)), and HF rehospitalization (0.58 (95% CI: 0.48 to 0.66)), although not for cardiovascular mortality (0.70 (95% CI: 0.63 to 0.77)). The included variables which were independent predictors of mortality were male gender, being underweight, chronic obstructive pulmonary disease, pulmonary hypertension, atrial fibrillation, stroke volume index, non-transfemoral access and low aortic valve calcification density on cardiac CT. A high RELiEF TAVI score (>4 points) demonstrated a rate of 46.1% for all-cause mortality and 53.4% for the combined endpoint of all-cause mortality or HF rehospitalization after one year. This score has the advantage of relying on simple baseline clinical, echocardiographic and CT parameters and could therefore be of assistance in decision-making in this complex context.[12]

To conclude, the study by Castelo et al. gives us interesting information regarding the clinical outcomes of patients with LF-LG AS, comparing different phenotypes, and showing that, while LF-LG AS is associated with worse prognosis, particularly the classical subtype, they also derive improvement in LVEF and clinical status, which is in line with the literature. Further studies specifically concerning this patient subgroup are urgently needed and should search, in a randomized manner, for the best way to select patients that are still eligible candidates for intervention. As the number of patients referred for TAVI will not stop growing in the near future, proper patient selection (is already and) will be of utmost importance, offering symptom improvement and favorable prognostic impact in a timely fashion to those in need. Future randomized prospective trials will help select optimal treatment options such as the ROTAS (NCT03667365) and REBOOT-PARADOX (NCT03863132) trials which will study the prognostic impact of aortic valve intervention in paradoxical LF-LG AS, as will the prospective observational TOPAS Study Phase III in classical LF-LG AS (NCT01835028). The importance must be highlighted of focusing not only on the technical aspects of TAVI, but also on HF optimal medical therapy for these patients, which is an established pillar and needs to be properly addressed at the core of the heart team. Further reflections will be made on this topic, as more robust data are still needed to provide definitive answers.

Conflicts of interest

The author has no conflicts of interest to declare.

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