Cutoffs for Intervention for Asymptomatic Severe Aortic Stenosis

The report from Belgium (1) and the accompanying editorial from Sweden (2) complain, rightly, that the published indications for intervention for asymptomatic severe aortic stenosis are in conflict. American guidelines (3) require a valve area <1 cm² and a mean gradient >40 mm Hg, whereas Otto et al. (4) required a peak velocity >4 m/s that predicts a gradient of 64 mm Hg. The European guidelines (5) require a mean gradient >50 mm Hg.

The recent Belgian study used appropriate measures of outcome, event-free survival and hazard ratio, whereas Otto et al. (4) used aortic valve surgery as an end point in 48 patients and death in only 8. The former is clearly subject to selection bias, reflecting the investigators’ indication for surgery.

A 1965 publication from the same hospital (6) on this subject, coauthored by Alvin Merendino, a thoughtful surgeon, emphasized the limitations of what can be accomplished by commissurotomy for congenital aortic stenosis without producing severe aortic regurgitation. That report concluded that young patients with this condition would eventually develop calcification and require valve replacement, with or without early surgery, and that this justified a conservative approach in young patients. Furthermore, the investigators found that the peak systolic gradient was not sufficiently accurate as an indication for surgery, compared with valve area or the mean ejection gradient. (Ejection fraction is primarily of concern when aortic regurgitation is severe.)

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REFERENCES


Aortic Stenosis

New Classification

The report by Lancellotti et al. (1) concludes that “the use of the new proposed aortic stenosis grading classification integrating valve area and flow-gradient patterns allows a better characterization of the clinical outcome of patients with asymptomatic severe aortic stenosis.” However, there are several points to be interpreted with caution before applying this conclusion to patients.

First, after the multivariate analysis, the investigators stated in the text that peak aortic velocity (in meters per second) was independently associated with event-free survival (hazard ratio [HR]: 1.7; 95% confidence interval [CI]: 1.04 to 2.84; p = 0.035). In Table 4 (1), they report a different value (HR: 1.82; 95% CI: 1.13 to 2.9; p = 0.013). However, the interpretation is similar: peak aortic velocity is a risk factor for the development of events during follow-up, with higher risk at higher velocities. The investigators also found that the new proposed category of low flow/low gradient was an independent predictor (in the text [1]: HR: 5.26; 95% CI: 2.04 to 14.1; p = 0.001). Discordant data between the text and the table are also presented for the category of low flow/high gradient. The low gradient variable alone was also an independent predictor (HR: 2.4; 95% CI: 1.4 to 4.2; p = 0.003), as was the variable in its continuous format (mean pressure gradient). Peak aortic velocity and mean aortic gradient are closely and directly correlated. Therefore, it is difficult to conclude that those variables predict events in a contradictory fashion in the same patients.

Second, as the investigators cited as study limitations, there were just 11 patients in the category with worse evolution (low flow/low gradient) and 15 in the category of low flow/high gradient. Only a few events explained the very different evolution in both categories. Chance may explain these results.

Third, under “Clinical Implications,” Lancellotti et al. (1) stated that “early elective aortic valve replacement could represent a beneficial option in those with low comorbidities,” citing a report by Kang et al. (2). However, this study evaluated patients with “asymptomatic very severe aortic stenosis,” and mean aortic gradients were 59 and 65 mm Hg in the 2 groups of patients, so the results are not applicable to low-flow/low-gradient patients.

Finally, I agree with Flachskampf and Kavianpour (3) that “the first reflex in the presence of a surprising ‘paradoxic’ set of echo data should be critical review of the raw data.” I think that more data are needed before adopting as an everyday practice this new classification.
We would like to thank Drs. Guntheroth and Parras for their interest in our study, which underlined that the assessment of aortic stenosis (AS) severity should integrate the flow-gradient pattern to the classic measurement of aortic valve area (1). The reason is that most of the echocardiographic parameters used to assess the severity of AS are flow dependent. As a general rule, a low transvalvular gradient (<40 mm Hg) or velocity (<4 m/s) does not exclude the presence of a severe AS in patients with small aortic valve areas and preserved left ventricular (LV) ejection fraction. In addition, a preserved LV ejection fraction (>50%) does not exclude the presence of myocardial systolic dysfunction and low transvalvular flow in AS. Such rules are also applicable to congenital AS, particularly when concomitant aortic regurgitation exists (2).

In daily practice, the discrepancy between gradient and aortic valve area may potentially lead to an underestimation of AS and symptom severity and therefore to an inappropriate delay of aortic valve replacement (AVR). Unless related to concomitant valvular (mitral or aortic) regurgitation, potential causes for these discordances include: 1) measurement errors; 2) small body size; 3) paradoxical low-flow AS; and 4) inconsistent grading related to intrinsic discrepancies in guideline criteria. As a first step, the best rule of the thumb is to confirm the low-flow state using volumetric approaches (2- or 3-dimensional echocardiography). If the stroke volume measured by these independent methods is consistent with the stroke volume measured using the LV outflow tract, one can be reassured of the accuracy of the measurement of stroke volume. Such a low-flow state represents a witness of intrinsic myocardial dysfunction and a more advanced disease process. It could be associated with either high-gradient or low-gradient AS.

In our study, all patients were regularly followed in our outpatient heart valve clinic. Both soft and hard events were considered in a composite end point defined as cardiovascular death or need for AVR motivated by the development of symptoms or LV dysfunction. This eliminates bias related to the inclusion of AVR not dictated by symptoms. As mentioned by Dr. Parras, there are some discrepancies in the hazard ratios reported in the “Results” section of the report and in Table 4 [1]. Nevertheless, these differences did not affect the interpretation of the results. In fact, such differences are explained by different multivariate models used in the 2 sections. According to the statistical review, it was suggested, to avoid overfitting of the models, not to include variables with high degrees of collinearity. These changes were reported in Table 4 [1], but not in the text, in which the multivariate model including all variables was provided. Peak aortic velocity and mean aortic gradient are closely and directly correlated. Therefore, it may be difficult to admit that those variables predict events in a contradictory fashion. However, this reflects the statistical models used. The normal-flow low-gradient entity represented the referent group. This is the reason why the peak aortic velocity or the low-flow pattern predicted the outcome compared with the referent group. However, outcome prediction was more significant in the low-flow low-gradient entity. These results were obtained even if the incidence of the low-flow low-gradient AS pattern was low. Of note, 82% of patients in this category experienced cardiac events during follow-up. Furthermore, chance has no role to play in these results.

The outcomes of patients with low-flow high-gradient AS are nearly identical to those of patients with normal-flow high-gradient AS. When symptomatic, AVR is the only therapy that can significantly improve functional capacity, symptoms, and survival. Paradoxical low-flow low-gradient AS conveys the poorest outcome, even in asymptomatic patients. In this entity, though the benefit of surgery is not proven, AVR may probably be beneficial in selected patients. Of note, even if the data reported by Kang et al. (3) are not applicable to this category, they suggest that early AVR may improve survival. However, before considering surgery, symptoms should be matched to the severity of AS.

We thank Dr. Guntheroth for his interest in the paper by Lancellotti et al. (1) and our editorial (2). He emphasizes the use of mean gradient and aortic valve area, as opposed to peak gradient, in managing aortic stenosis. The cited report from 1965 (3), which Dr. Guntheroth coauthored, allows a fascinating glimpse into predigital cardiology using analog pressure tracings, when determining a mean as opposed to a peak transaortic gradient involved “special equipment” and considerable additional work. The investigators demonstrated that spikes in left ventricular