

Commentary

Why Does the NOTION Trial Show Poorer than Expected Outcomes in the Surgical Arm?

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Abstract: The NOTION trial compares transcatheter aortic valve implantation versus surgical aortic valve replacement in low-risk patients. Looking carefully at the outcomes of this trial, there is no doubt that the transcatheter aortic valve implantation results were outstanding. The same thing cannot be said for the results of the surgery. We tried to understand the reason for that.

Keywords: transcatheter aortic valve implantation; surgical aortic valve replacement; patient prosthesis mismatch; structural valve deterioration



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1. Introduction

The indications of transcatheter aortic valve implantation (TAVI) in patients with aortic valve stenosis is still open for debate. Proof of that debate, are the differences in terms of modes of intervention recommended by the ACC/AHA [1] and ESC/EACTS guidelines [2]. The former [1] recommends TAVI over surgical aortic valve replacement (SAVR) in octogenarian patients or in patients whose lifespan is <10 years. In younger patients, aged between 65 and 80 years, either TAVI or SAVR are recommended. According to the ESC/EACTS guidelines TAVI is recommended in patients ≥ 75 years, or in those with STS-PROM/EuroSCORE II >8%, while SAVR is recommended in patients <75 years and with STS-PROM/EuroSCORE II <4%.

The publication of the 8-year results of the NOTION trial [3] has enriched the debate with new interesting data: in patients with low surgical risk, no differences were detected between TAVI and SAVR in terms of composite outcome of long-term risk for all-cause mortality, stroke, myocardial infarction and in terms of bioprosthetic valve failure. In our opinion, the NOTION trial [3] shows results in terms of incidence of severe patient prosthesis mismatch (PPM) and structural valve deterioration (SVD) in the surgical arm which may deserve a deeper analysis.

2. Patient Prosthesis Mismatch and Structural Valve Deterioration: A Matter of Definitions?

Two aspects of the surgical arm of the NOTION trial [3] have caught our attention: a severe PPM rate of 28.2% and a SVD cumulative incidence of 28.3%.

Severe PPM is a fearsome clinical entity, as it has been identified as an independent risk factor for mortality after AVR [4,5]. Several strategies can be adopted to avoid it, such as the selection of the appropriate size of a standard prosthesis, aortic root enlargement or use of sutureless prosthesis [6] (these last two options were not allowed in the NOTION trial [3]). In most cases, the availability of high-quality reference effective orifice area (EOA) values for valvular prosthesis makes possible, in the pre-operative phase, to predict the

risk of PPM and, consequently, to choose the appropriate size of the prosthesis in order to avoid PPM [4]. For this reason, severe PPM after SAVR is not a frequent entity. In one of the largest meta-analyses on mismatch comprising 27,186 patients undergoing SAVR, severe PPM, defined as indexed effective orifice area (IEAO) $\leq 0.65 \text{ cm}^2/\text{m}^2$, was detected in 9.8% of the sample population [7].

Recent data from the Finnish valve registry on 4097 patients who underwent SAVR with a stented bioprosthesis [8], showed a severe PPM rate, using the same IEAO cut-off value of 7.2%.

The severe PPM rate at three months reported by the NOTION trial [3], which used the same definition, exceeds this value by almost four times.

The surgical arm of the NOTION presents a large proportion (40%) of patients receiving 19 mm and 21 mm prosthesis [3]. This proportion doubles that one of the surgical arms of the PARTNER 3 trial [9] which has randomized, as the NOTION trial [3], low risk patients with aortic valve stenosis.

Even if it is well known that the smaller the prosthesis the lower the EOA [4], an appropriate selection of the valve prosthesis makes it possible to avoid severe PPM in most cases, even when dealing with small aortic annuli. The exclusion by the NOTION trial protocol of the aortic root enlargement procedure and of the use of sutureless prosthesis can explain the high incidence of severe PPM only to a small extent. For this reason, it could be interesting to know whether the NOTION investigators used measured or predicted EOA values for PPM diagnosis and which prostheses were associated with it.

Similarly, the literature offers very different SVD rates compared with those reported by the NOTION trial [3]. Anyway, we have to admit that most of the studies analyzing SVD in surgical prostheses use as the primary outcome “freedom from reoperation for SVD” [10] (which should not always be considered a good marker of SVD itself). There are exceptions, of course: Flameng, in his milestone study on SVD [11], analyzed six different bioprostheses implanted in 564 patients. At a maximum follow-up time of 16.4 years, SVD rate was 7.1%. This percentage is one fourth of that reported by the SVD original definition of the NOTION at 8 years [3]. In the Flameng’s study [11], very sensitive criteria were used to diagnose two SVD types: stenosis-type, identified by any grade of leaflet calcification (without requirement of any trans-prosthetic gradient) and regurgitation type defined by an increase of at least 1 degree of severity of regurgitation during follow-up.

Rodriguez-Gabella et al. [12], reported on a population of 672 patients undergoing SAVR with a bioprosthesis 10-year clinically relevant SVD rate (increase $>20 \text{ mm Hg}$ in mean transvalvular gradient + decrease $>0.6 \text{ cm}^2$ in valve area and/or new-onset moderate-to-severe aortic regurgitation) of 6.6%.

In the NOTION trial [3], a fixed trans-prosthetic gradient and the detection of worsening moderate regurgitation were used for SVD diagnosis. These SVD criteria were obtained from a solid consensus statement [13], which has codified two entities: hemodynamic SVD and morphological SVD. According to this consensus document [13], hemodynamic SVD, in fact, in its pure form (isolated hemodynamic dysfunction) does not need any morphological evidence of prosthesis deterioration. In our opinion, the exclusive use of a fixed trans-prosthetic gradient cut-off by the NOTION trial [3], could have overestimated SVD in the surgical arm. As mentioned above, small aortic prostheses ($\leq 21 \text{ mm}$), were implanted in 40% of the surgical arm and in no patient of the TAVI arm. It is well known that mean trans-aortic gradients in patients with small aortic surgical stented bioprosthesis can easily reach and exceed 20 mm Hg without representing SVD [14]. Notably, the largest difference in terms of SVD rates between TAVI and surgical prostheses is shown in the NOTION trial [3], when SVD was defined by a fixed cut-off mean trans-prosthetic gradient $\geq 20 \text{ mmHg}$: 8.5% and 26.8%, respectively. In other terms, according to the NOTION trial [3], aortic valve surgical prostheses deteriorate three time faster than TAVI.

SVD is a progressive, irreversible, multifactorial process mediated by the activation of inflammation pathways which can lead to the calcification of the connective tissue and consequent prosthesis dysfunction [10].

Over time, prosthesis deterioration can produce a decrease of EOA values and, consequently, an increase of trans-prosthetic gradients in the stenosis type SVD (40%) [10]. Alternatively, progressive tears or perforations of prosthesis leaflets lead to detectable morphological changes of the prostheses in the regurgitation type SVD (30%). Both processes, combination of stenosis and regurgitation, can be observed at the same time (30%) [15].

In our opinion, in trials comparing prostheses of very different sizes, such as those implanted percutaneously vs. surgically in the NOTION [3], a fixed trans-prosthetic gradient cut-off should not be used for SVD definition, because it cannot identify any dynamic process. An increase in trans-prosthetic gradients and a contemporary decrease in EOA values are much clearer indicators of a progressive stenosis type SVD. These concepts have been elegantly exposed by Rodriguez-Gabella et al. [15] who propose a dynamic definition of possible SVD (“an increase in mean transvalvular gradient of >10 mm Hg with a concomitant decrease in EOA > 0.3 cm² and/or new onset of at least mild intraprosthetic regurgitation or an increase by at least 1 grade of pre-existent intraprosthetic regurgitation”) and clinically-relevant SVD (“increase in mean transvalvular gradient >20 mm Hg with a concomitant decrease in the EOA > 0.6 cm², and/or new occurrence or increase of at least 1 grade of intraprosthetic AR leading to a moderate-to-severe or severe AR”).

Of course, the use of a hemodynamic criteria should always be accompanied by a morphological analysis of the prosthesis in all cases where higher gradients are expected, such as PPM (which alarming incidence in the surgical arm of the NOTION trial has already been discussed).

Even the modified definition of SVD provided by the NOTION trial [3] (which study protocol [16] was published before the updated SVD definition by Rodriguez-Gabella et al. [15]), “to avoid that PPM would impact the classification of SVD” is independent of data concerning the morphological examination of the prosthesis or the modification of the EOA.

We agree with Højsgaard Jørgensen et al. [3] that the use of the Mitroflow (Sorin Group Inc., Arvada, CO, USA) and Trifecta bioprosthesis (Abbott, Abbott Park, IL, USA) in the NOTION trial, which were implanted in 34% of the surgical sample population, could partially explain the very high SVD and PPM rates. In fact, SVD and PPM have been reported to be two interrelated phenomena [11,17]. A possible mechanism of this interaction is that PPM increases hemodynamic shear stress in the prosthesis promoting the calcification process of a specific segment of the prosthetic leaflets [18]. When this process involves the commissure, it could result in reduced mobility and stenosis. Calcification in the belly of the cusp could result in tears or perforation and regurgitation.

Because of the interaction between PPM and SVD, it would be interesting to know from the NOTION investigators the type of prosthesis that failed and those that presented a mismatch. Still, this would only partially explain the high deterioration rate.

Importantly, as suggested in the previously mentioned consensus document [13], severe SVD was considered by the NOTION trial [3] to be one of the three components of bioprosthetic valve failure (BVF) (the other two components were valve-related death and aortic valve re-intervention). Because of the above-mentioned reasons, possible overestimation of SVD may have been reflected on the overestimation of BVF.

We think that the incorrect SVD definition in patients that underwent TAVI adds a confusion factor to a treatment that, despite being an established procedure, is still up for debate as shown by recent publications which cast doubts on their mid- and long-term results [19,20].

3. Conclusions

In conclusion, PPM rate in the surgical arm of the NOTION trial seems higher than expected. Moreover, in our opinion, the use of a fixed trans-prosthetic gradient cut-off for SVD diagnosis could have resulted in an overestimation of the rate of prosthesis deterioration. For this reason, we think that applying pure hemodynamic SVD diagnostic criteria for comparing groups of prostheses with very different sizes, such as those analyzed in the two arms of the NOTION trial, may have produced misleading conclusions. NOTION

is the one of the SAVR vs. TAVI trials with a longer follow-up, and although the mean age of the patients at the time of the procedure was 79 years, it included patients with different risk profiles. Hence, it is considered an important trial in the subject. Nevertheless, the poorer than expected outcomes in the surgical arm may undermine its relevance.

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