OPINION ARTICLE

Analysis of the National Board of Health Technology Assessment Report on Transcatheter Aortic Valve Implantation

Análisis del informe de la Comisión Nacional de Evaluación de Tecnologías de Salud sobre el implante transcatéter de la válvula aórtica

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The National Ministry of Health and Social Development published the "Transcatheter aortic valve implantation in severe aortic stenosis" document developed by the National Board of Health Technology Assessment [Comisión de Evaluación de Tecnología de Salud (CONETEC)]. In its conclusion, it declares that transcatheter aortic valve implantation (TAVI) should be reserved for inoperable patients, and does not recommend it for high, moderate or low-risk patients, based on not sufficiently strong scientific evidence (both in the quality and magnitude of the benefit) for this recommendation.

The document suggests adhering to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology, whose most relevant aspects are its reproducibility and transparency compared with other forms of summarizing evidence and generating clinical practice recommendations. (1) However, the CONETEC recommendation is opposed to that of the McMaster University -that uses the same GRADE methodology- and recommends transfemoral TAVI as an indication independent from surgical risk: strongly in favor of prioritizing TAVI in patients above 85 years of age and weakly in favor of prioritizing it in patients between 75 and 85 years. (2, 3) Nevertheless, from 75 years onwards, TAVI should be selected over surgical replacement as a first option regardless of the surgical risk. The weak recommendation, but in favor of TAVI, from 75 to 85 years, should be interpreted considering that most patients should receive TAVI, except for specific situations in which a conventional aortic valve replacement surgery would be recommended, such as bicuspid aortic valve, associated multi-vessel coronary artery disease, patient's preference or local results. (1)

The 2016 publication is previous to low surgical risk publications which were also favorable for TAVI. The aim of this article was thus to evaluate the CONETEC document based on the GRADE clinical guidelines

It is not clear in the CONETEC bibliographic search why this document is solely based on systematic reviews with meta-analyses instead of primary randomized studies as recommended by the GRADE guidelines. The bibliographic review used to report a new clinical guideline on the efficacy and safety of an intervention should be centered on a systematic review where primary randomized studies and not meta-analyses are the focus of the search.

In addition, the document ignored the McMaster systematic review with meta-analyses published in 2016 (4) and a 2019 systematic review reporting reduced mortality, stroke, atrial fibrillation, renal dysfunction and major bleeding, among other relevant events in patients with TAVI, independently of surgical risk. (5)

The selection of studies for the report was not performed with rigorous criteria. The application of the PRISMA ckecklist can give an idea of the quality of the report derived from the systematic reviews found, but not of the quality of the content or the conclusions as suggested in Annex II of the CONETEC report.

Although a study selection flow diagram is provided, it does not follow the accuracy suggested by PRISMA on the degree of detail and rationales for the exclusion of studies, and neither does it provide detail on how many are primary studies versus systematic reviews. The report mentions that a systematic review with meta-analyses was chosen in each risk stage to evaluate the efficacy and safety of TAVI, but it does not mention the reason for selecting these systematic reviews. This is a key step that goes against the GRADE principle on the transparency and reproducibility of the recommendations using this methodology (1)

The report refers the meta-analysis of Liu (6) which "at 5 years of follow-up of the PARTNER 1A study (699 patients) and the CoreValve U.S. Trial (795

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patients), found no differences both in all-cause mortality (HR: 0.97; 95% CI 0.83-1.12; p=0.19) as in cardiovascular mortality, though in the latter it tended to favor surgery (RR: 1.21; 95% CI 1.00-1.45; p=0.05)". When evaluating the original Liu article, we found that this estimator of effect that seems to be at the statistical limit against TAVI was based only on the 5-year follow-up of the PARTNER 1A study, and did not include the CoreValve U.S. trial at 5 years as suggested in the CONETEC report (Liu included the CoreValve U.S. trial at 3 years, and the 5-year estimators only derive from the PARTNER 1A study). The analysis of the PARTNER 1A study showed that the p value was not 0.05, but 0.67 (far from the statistical limit). (7)

The reason for this marked discrepancy is that Liu et al. analyzed raw data events using relative risk, an estimator of effect that does not take into account censoring during follow-up, as well as potential interactions with time that can be substantially different given the high mortality rate or the imperfect follow-up of high-risk patients at 5 years. On the other hand, the study by Liu et al. (May 2018) was the basis of the CONETEC report to generate TAVI recommendations versus surgery at 5 years. However, it did not include the CoreValve U.S. trial data at 5 years, which represents half of all the information available for this population. (8)

For intermediate-risk the report selects only the meta-analysis by Lazkani et al. (9) which also includes observational studies. When the GRADE methodology is applied, randomized study results are always prioritized. and observational studies are used in case randomized studies do not provide evidence of sufficient quality. (1)

For low-risk, the CONETEC report chose the meta-analysis by Saleem et al.; (10) yet, there are meta-analyses of randomized studies which report lower overall and cardiovascular mortality with TAVI in low-risk patients. (11-13)

The CONETEC report stratified and analyzed results in subgroups according to the surgical risk of patients, since it was interpreted that the technology analyzed could have a different impact. However, the McMaster GRADE TAVI guidelines recommend guiding the decision for TAVI according to age instead of surgical risk, as its long-term durability is the missing information to recommend TAVI as first option for all the range of patients. (3)

Among other relevant aspects, all the tables have a problem with the marks in the quality of evidence, where all have 4 crosses. All the data in Table 2.3 of intermediate risk mention that events only come from randomized trials. However, this is incorrect, since when reviewing the original reference these estimators of effect include observational studies. (9) It is not clear why quality of life and stroke are considered "important" instead of "critical" events, as they are usually critical for decision-making in GRADE guidelines.

Regarding the economical evidence, we consider that a dedicated economical study was not performed and that the text content is very poor. It is striking that the price of one TAVI module (excluding the prosthesis) is higher than a surgical module, and that the cost of cardiovascular rehabilitation, rehospitalizations and conventional surgery comorbidities are not taken into account. It is also necessary to consider that the price in pesos/dollars of the TAVI prosthesis that appears in the report is much higher than that of the current PAMI contract, and that the politics to reduce taxes of TAVI prosthesis could solve a great part of this economical problem.

With respect to the health coverage politics of other countries, the reason why patients at intermediate and low risk have no support in international clinical guidelines, depends on the date these guidelines were written and the evidence was published (for example, for low risk, March 2019). The report mentions, among others, France, as a country that endorses the use of TAVI; however, French social security covers TAVI in high-risk patients since 2012 and patients at intermediate risk have been added since 2019.

In conclusion, to our best understanding, the CONETEC report has methodological failures that could be summarized in the use of systematic reviews with meta-analyses, unnecessary inclusion of observational studies in intermediate and low risk patients, and fragmentation of the research question by risk strata. Other relevant aspects were ignored, as the reality of cardiac surgery perioperative mortality in Argentina, which in many cases is greater than that of countries with high economic income. (14) In addition, to perform its analysis, the CONETEC has summoned, among others, medical professionals representing prepaid medical insurance companies, which could give rise to a biased view, and conversely, has not requested the opinion of scientific societies involved in the specialty.

Conflicts of interest

The Argentine College of Interventional Cardioangiology is a scientific and union organization that groups interventional cardiologists of Argentina.

Diego Grinfeld is Proctor of Medtronic and Boston Scientific; Pablo Lamelas is Proctor of Boston Scientific; Rubén Kevorkian, Ruth Henkin y Alejandro Cherro declare no conflicts of interest.

(See authors' conflicts of interest forms on the website/ Supplementary material).

REFERENCES

1. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. 2013.

2. Siemieniuk RA, Agoritsas T, Manja V, Devji T, Chang Y, Bala MM, et al. Transcatheter versus surgical aortic valve replacement in pa-

tients with severe aortic stenosis at low and intermediate risk: Systematic review and meta-analysis. BMJ 2016;354; i5130. https://doi.org/10.1136/bmj.i5130
3. Vandvik PO, Otto CM, Siemieniuk RA, Bagur R, Guyatt GH, Lytvyn L, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: A clinical practice guideline. BMJ 2016;354: i5085. https://doi.org/10.1136/bmj.i5085
4. Siemieniuk RA, Agoritsas T, Manja V, Devji T, Chang Y, Bala MM, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. BMJ 2016;354:i5130. https://doi.org/10.1136/bmj.i5130
5. Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: An updated meta-analysis. Eur Heart J 2019;40:3143-53. https://doi.org/10.1093/eurheartj/ehz275
6. Liu Z, Kidney E, Bem D, Bramley G, Bayliss S, De Belder MA, et al. Transcatheter aortic valve implantation for aortic stenosis in high surgical risk patients: A systematic review and meta-analysis. PLoS One 2018;13. https://doi.org/10.1371/journal.pone.0196877
7. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): A randomized controlled trial. Lancet 2015;385:2477-84. https://doi.org/10.1016/S0140-6736(15)60308-7
8. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, et al. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. J Am Coll Cardiol 2018;72:2687-96. https://doi.org/10.1016/j.jacc.2018.08.2146
9. Lazkani M, Singh N, Howe C, Patel N, Colón MJ, Tasset M, et al. An updated meta-analysis of TAVR in patients at intermediate risk for SAVR. Cardiovasc Revascularization Med 2019;20:57-69. https://doi.org/10.1016/j.carrev.2018.04.001
10. Saleem S, Younas S, Syed MA. Meta-Analysis Comparing Transcatheter Aortic Valve Implantation to Surgical Aortic Valve Replacement in Low Surgical Risk Patients. Am J Cardiol 2019;124:1257-64. https://doi.org/10.1016/j.amjcard.2019.07.029
11. Kolte D, Vlahakes GJ, Palacios IF, Sakhuja R, Passeri JJ, Inglessis I, et al. Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients. J Am Coll Cardiol 2019; 74:1532-40. https://doi.org/10.1016/j.jacc.2019.06.076
12. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019; 380:1695-705. https://doi.org/10.1056/NEJMoa1814052
13. Popma JJ, Michael Deeb G, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med 2019; 380:1706-15. https://doi.org/10.1056/NEJMoa1816885
14. Lowenstein D. Realidad de la cirugía cardíaca en la República Argentina. Registro CONAREC XVI. Revista del CONAREC2015;130:184-9.