Response to LACES in relation to Clinical Practice Guideline for Transcatheter Versus Surgical Valve Replacement in Patients with Severe Aortic Stenosis in Latin America

Resposta à LACES sobre a *Clinical Practice Guideline for Transcatheter Versus Surgical Valve Replacement in Patients with Severe Aortic Stenosis in Latin America*

Martín Alberto Ragusa^{1iD}, Pablo Lamelas^{2iD}, Iqbal Jaffer^{3iD}, Henrique Barbosa Ribeiro^{4iD}, Magaly Araís dos Santos^{5iD}, Ariel Izcovich^{6iD}

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Letter to: Latin American Association of Cardiac and Endovascular Surgery.

Dayan et al.¹, on behalf of the Latin American Association of Cardiac and Endovascular Surgery (LACES), expressed their concerns about the development and relevance of our clinical practice guideline for the use of transcatheter aortic valve implant (TAVI) or surgical aortic valve replacement (SAVR), in patients with severe aortic stenosis living in Latin America.² In this response, we address several points raised in their letter.¹

GUIDELINE VALIDITY IN LATIN AMERICA

This clinical practice guideline was conceived and designed to address this clinical problem in Latin America. All panelists, whether clinical cardiologists, cardiac surgeons, interventional cardiologists, and patients live and work in Latin America, and were commanded to build a recommendation specifically for Latin Americans. LACES position states that the guideline development group “explicitly disregarded Latin-American evidence under the assumption that the conclusions were erratic. Not including regional evidence is a significant flaw, and suggests serious selection bias in the evidence process.”¹ It also stated that “a guideline to help physicians and stakeholders decide the best course of action in Latin America must come from Latin-American effectiveness data. It is impossible to recommend something for our region when we do not know what is going on.”¹ This assessment is not aligned with fundamental principles of Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidance, which states that the body of evidence should encompass all studies providing the best available evidence for a given question.³ Although LACES positions state that “different centers from Latin America have generated essential data to produce high-quality effectiveness results”,¹ in our systematic review update, we did not identify randomized control trials that included patients treated in Latin America. We did not identify any compelling reasons to suspect effect modification in Latin America, in comparison to other regions, if the procedures assessed are appropriately instrumented reaching good quality standards. Considering the evidence on TAVI and SAVR peri-procedural mortality and complications in Latin America, the panel acknowledged this might not be the case in several centers within the region. As a consequence, we highlighted that “local expertise and results should be taken into account when applying these recommendations in Latin America”.²

¹ Internal Medicine, Hospital General de Agudos Dr. Juan A. Fernández, Buenos Aires, Argentina.

² Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina.

³ Cardiac Surgery, McMaster University, Hamilton, Ontario, Canada.

⁴ HCor, São Paulo, SP, Brazil.

⁵ Instituto Dante Pazzanese de Cardiologia, São Paulo, SP, Brazil.

⁶ Internal Medicine, Hospital Alemán, Buenos Aires, Argentina.

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Corresponding author:

Martín Alberto Ragusa
Avenida Cerviño 3356
Buenos Aires, Argentina
E-mail: martinalbertoragusa@gmail.com

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EVIDENCE SUMMARY AND APPRECIATION

The authors of LACES letter stated “the SOLACI/SIAC document implicitly assumes an equipoise between long-term outcomes of TAVI and SAVR, which has been challenged by recent evidence. In this way, the results of randomized controlled trials, meta-analyses, and national databases show the opposite”.¹ With “the opposite”, they assumed TAVI showed inferior results compared to SAVR, disregarding any degree of uncertainty. To support their statement, they selected one observational registry, in which patients treated with TAVI and SAVR had substantial baseline differences in age and surgical risk.⁴ They also mentioned one specific secondary analysis of an individual-data meta-analysis that, in consonance with our findings,² reported similar 60-month cumulative mortality between TAVI and SAVR treated patients (HR of 0.95; 95%CI 0.86-1.01; $p=0.3$).⁵

We did not implicitly assume equipoise between long-term outcomes of TAVI and SAVR. On the contrary, we explicitly expressed in different parts of the document that the very-long term effects of TAVI *versus* SAVR are uncertain. In the absence of certain estimates on patients’ values and preferences,⁶ the panel decided that possibly most elderly patients would prefer avoiding an open-heart surgery, even if the very-long term effects of TAVI *versus* SAVR are uncertain. We acknowledge LACES authorities did not agree with this decision, their assumption went the other way around, since they stated elderly patients would be more worried about uncertainty in very-long term effects, than the demonstrated short-term benefits of TAVI. We understand the manifested disagreement as this is a judgment matter, but we do not agree this makes the recommendation less real. Furthermore, users are encouraged to carefully revise panel judgments before implementing guideline recommendations, especially in the context of conditional recommendations.⁷

LACES also stated that we “have mentioned, but not analyzed, the role that costs have on TAVI implementation in Latin America”, and that “in times of extreme pressure on health resources, regardless of the countries’ economic situation, adopting a new technology that is five to 10 times more expensive than the existing standard, with inferior results, seems illogical and requires serious reflection.”¹ Dayan et al. seem to agree with our clinical practice guideline, *i.e.*, implementing TAVI may result in large costs, which was the main concern that led the guideline panel to make a conditional recommendation. Also, as we reported in the supplement, “access to high-cost health technology is markedly heterogeneous in Latin America. Even within the same health facilities, costs may or may not be considered a limiting factor for patients to have access to a TAVR procedure.”² LACES standpoint also declares the recommendation seems illogical, because TAVI is not only more expensive but has inferior results. We do not agree with the latter conclusion, since the results of our thorough systematic review, in consonance with those from other high-quality reviews and clinical practice guidelines showed the opposite.⁸⁻¹⁰

SELECTED AGE THRESHOLD OF 75 YEARS-OLD

The rationale and process of selecting 75-year-old individuals as a threshold are expanded in both the manuscript and in the appendix.² LACES position states “the recommendation for TAVI in patients aged over 75 years is unrealistic, given the life expectancy for men and women aged 75 is a further 11.18 and 12.97 years, respectively; therefore, the long-term benefit of the procedure would be adversely affected, cutting short late survival”.¹ These life expectancy estimates are based on the general population of the United States, born in 2019, not on the target population of our guideline, who was born 75 or more years ago, and currently has severe aortic stenosis. A prior systematic review demonstrated median survival in candidates who received SAVR, aged 75-85 years, is just seven years.¹¹ Moreover, we stated and referenced in our appendix,² that those born in Latin America would have 2 (for women) and 5 (for men) fewer years of life expectancy compared to the developed regions. Finally, we expressed in multiple parts of the manuscript that this age threshold is for guidance, and not determinant, and should be integrated with multiple other factors detailed in the clinical practice guideline.

MANAGEMENT OF CONFLICT OF INTEREST

Dayan et al. make it clear they disagree with the management strategy implemented for conflicts of interest.¹ Ideally, no members of the guideline development team should have any conflict of interest. However, this is something rarely achieved, since the best guideline panel candidates usually have some degree of conflict of interest.¹² Following Guidelines International Network principles, we pursued those who declared a conflict of interest represented a minority of the panel members, and clarified the reasons for including them. In our manuscript,² we expanded on the rationale of permitting TAVI proctoring to be part of the panel. Among others, the most important reason is that, virtually, all TAVI operators doing 50 or more TAVI implants per year (which is considered a quality standard) in Latin America do TAVI proctoring for, at least, one prosthesis. We acknowledge many professionals with low volume of implants in Latin America have an outstanding academic understanding of the evidence. Nonetheless, to better integrate the experience of advanced TAVI programs that concentrate most procedures in Latin America, we prioritized clinical over academic expertise for the panel. Similarly, the surgeons that participated in the panel also belong to high-volume centers in Latin America.

As a result of our strategy to manage conflicts of interest, the methods team was composed of four members of which the majority (75%) had no declared conflict, while the panel had 13 members, nine of which declared no conflict of interest (70%). All the methodological decisions were approved by the methods team, including evidence synthesis and appraisal. Although Dayan et al. strongly ma-

nifest that the inclusion of guideline team members with some degree of conflict of interest resulted in biased judgments,¹ they fail to specify which of those judgments are, and why they can so compellingly reach that conclusion.

LATAM SOCIETIES INVOLVEMENT

In response to our explanation related to *Sociedad Latino-Americana de Cardiología* (SOLACI) and *Sociedad Interamericana de Cardiología* (SIAC) endorsement, LACES stated that “the principal investigator (PI) is the coordinator of research in SOLACI, and one of the external reviewers, Oscar Mendiz (for whom the conflict of interest was not disclosed), is part of the counseling committee of SOLACI”.¹ For those interested, Mendiz’s declarations of interest are available in the latest version of the guideline.²

LACES also stated “despite the fact that surgeons have proficiently been treating aortic valve stenosis for more than 60 years, no cardiovascular surgical association was invited to take part in this document”.¹ Our main priority was to develop a high-quality, transparent and useful document. We followed rigorous guideline development methods and, in accordance with the RIGHT statement,¹³ the finalized manuscript underwent an independent external review, by cardiac surgeons, research methodologist, clinical and interventional cardiologists. Although important for dissemination and implementation, inclusion or endorsement of societies is not mandatory for high-quality evidence-based clinical practice guideline development. We made efforts to contact and include local cardiac surgery societies, and we included the same number of surgeons and interventional cardiologists in all guideline key roles. Therefore, the Heart Team was properly balanced during the clinical practice guideline development process. In the guideline supplement, we stated “at the time of this guideline development (November 2019), we contacted several cardiac surgeons from Latin America, and we could not find a society in which they would state they belong to or feel represented”.² With this statement, we aimed to explain why cardiac surgery societies were not involved, but meant no disrespect to LACES.

We hope this letter helps to clarify their concerns and promote credibility, acceptability, adoption, and implementation of the guideline, with the support of LACES and other societies.

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