

## STATE-OF-THE-ART REVIEW

# Echocardiography Core Laboratory Methodology for TAVR



## A Transatlantic Consensus

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### ABSTRACT

Inter-echocardiography core laboratory (ECL) harmonization is pivotal to consider data from different ECLs interchangeable. On the basis of the experience of the first trans-Atlantic harmonization of 2 established ECLs in the field of transcatheter aortic valve replacement (TAVR) trials, this review describes the harmonized ECL methodology in analyzing and adjudicating the post-TAVR echocardiographic endpoints according to Valve Academic Research Consortium 3 definitions. This review presents the feasibility and intra- and inter-ECL reproducibility, explains the root cause of potential important inter-ECL variability, and formulates ECL recommendations for optimal post-TAVR echocardiographic image acquisition. The implementation of inter-ECL harmonization may further define the best practice of ECLs and have logistic and regulatory implications for the realization of future TAVR trials. (J Am Coll Cardiol Img 2024;■:■-■) © 2024 by the American College of Cardiology Foundation.

Regulatory bodies and medical device manufacturers rely on echocardiography core laboratories (ECLs) to adjudicate the echocardiographic endpoints in transcatheter aortic valve replacement (TAVR) trials and registries. Ideally, an ECL should demonstrate clinical and academic leadership, methodologic robustness and standardization, management and logistical capabilities, data reliability and reproducibility, and long-term sustainability. Regulatory-compliant ECLs have the responsibility and obligation to ensure data consistency, validity, and reproducibility. In most randomized controlled trials (RCTs) and postmarket clinical follow-up studies, 1 single ECL is generally used,<sup>1-3</sup> with some exceptions where several (2-3) ECLs were involved such as the PARTNER 2 (Edwards

SAPIEN XT Transcatheter Heart Valve Therapy for Intermediate and High Risk Patients; NCT01314313)-SAPIEN 3 (Edwards Lifesciences) registry,<sup>4</sup> PARTNER 3 (Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis; NCT02675114),<sup>5</sup> and EARLY TAVR (Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis; NCT03042104). In some circumstances, the same ECL has been used for all subsequent trials for 1 given TAVR prosthesis, to facilitate the pooling of echocardiographic data from these trials.

Whether data from different ECLs can be considered interchangeable is unsettled, but it is desirable from a regulatory body and industry point of view.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Manuscript received November 7, 2023; revised manuscript received April 5, 2024, accepted April 15, 2024.

ISSN 1936-878X/\$36.00

<https://doi.org/10.1016/j.jcmg.2024.04.014>

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**ABBREVIATIONS  
AND ACRONYMS**

<b>AR</b>	= aortic regurgitation
<b>AVA</b>	= aortic valve area
<b>CWD</b>	= continuous-wave Doppler
<b>ECL</b>	= echocardiography core laboratory
<b>LVOT</b>	= left ventricular outflow tract
<b>PG</b>	= pressure gradient
<b>PLAX</b>	= parasternal long-axis
<b>PSAX</b>	= parasternal short-axis
<b>PWD</b>	= pulsed-wave Doppler
<b>RCT</b>	= randomized controlled trial
<b>RVOT</b>	= right ventricular outflow tract
<b>SV</b>	= stroke volume
<b>TAVR</b>	= transcatheter aortic valve replacement
<b>VTI</b>	= velocity time integral

ECLs typically use similar standardized analysis methodology, conforming to guidelines, recommendations,<sup>6-10</sup> and standardized definitions<sup>11-13</sup> published by medical societies. Nevertheless, guidelines/recommendations may differ in the respective consensus documents with regard to the methodology on measuring echocardiographic parameters. A good example is the measurement of left ventricular outflow tract (LVOT) diameter, which is a key parameter in calculating the aortic valve area (AVA) and an efficacy endpoint in TAVR trials. Furthermore, in the guidelines/recommendations, not all echocardiographic parameters are elaborated precisely enough to allow universal standardization of the analysis methodology. Finally, even if ECLs a priori use identical or very similar standardized analysis methodology, they may interpret and/or implement the methodology somewhat differently, and this variation may ultimately result in substantial

differences in reported data. To consider data from 2 or more ECLs interchangeable and to generalize data from 1 ECL to others, as addressed earlier, implementations of guidelines, definitions, and best practices<sup>14</sup> in 1 given ECL are not sufficient. It is pivotal to undertake inter-ECL harmonization efforts.

With currently limited published reports and recommendations in this endeavor, 2 major ECLs with sizable track records in the field of TAVR trials have undergone a rigorous inter-ECL harmonization process. In the consensus document, the harmonized ECL methodology in analyzing and adjudicating the post-TAVR echocardiographic endpoints according to the VARC-3 (Valve Academic Research Consortium-3)<sup>12</sup> ([Supplemental Table 1](#)) is elaborated with inter- and intra-ECL reproducibility after harmonization is presented and the root cause of inter-ECL variability is explained. Additionally, the ECL recommendations on optimal post-TAVR echocardiographic image acquisitions, particularly related to ECL assessments on the post-TAVR endpoints, are also specified because high-quality echocardiographic image acquisition (independent of the acoustic window quality) is a crucial prerequisite for accurate and reliable ECL assessments.

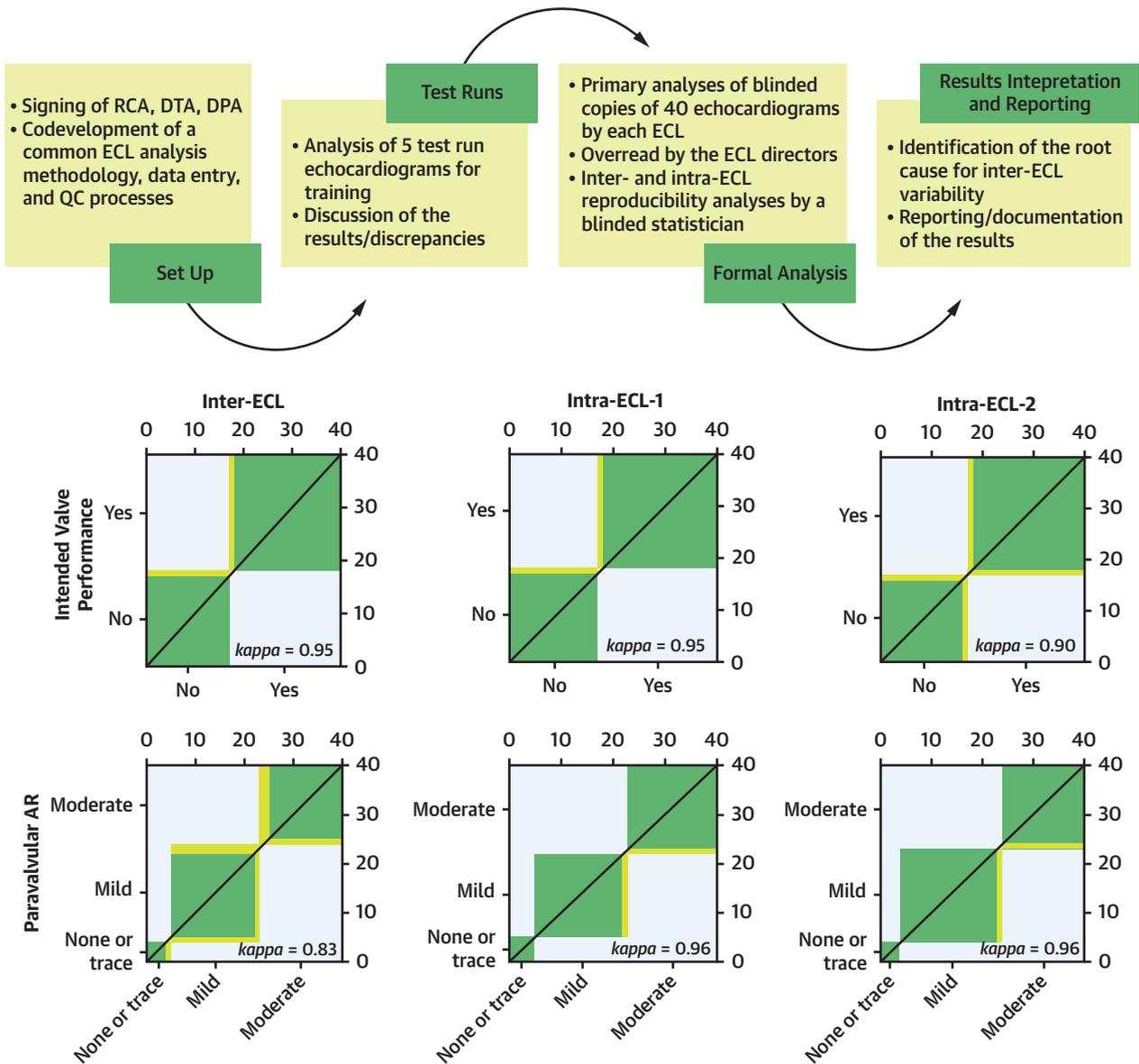
**INDEPENDENT ECHOCARDIOGRAPHY CORE LABORATORIES AND THE HARMONIZATION PROCESS**

The independence of ECLs prevents sponsor and/or investigator bias and ensures data integrity so the echocardiographic results of the 2 arms from an RCT can be compared. The inter-ECL harmonization aims for the following ambitious goals: 1) echocardiographic results from different ECLs involved in different development phases of 1 TAVR prosthesis can be pooled together; and 2) echocardiographic results from different ECLs in RCTs (on different investigational devices) can be compared.

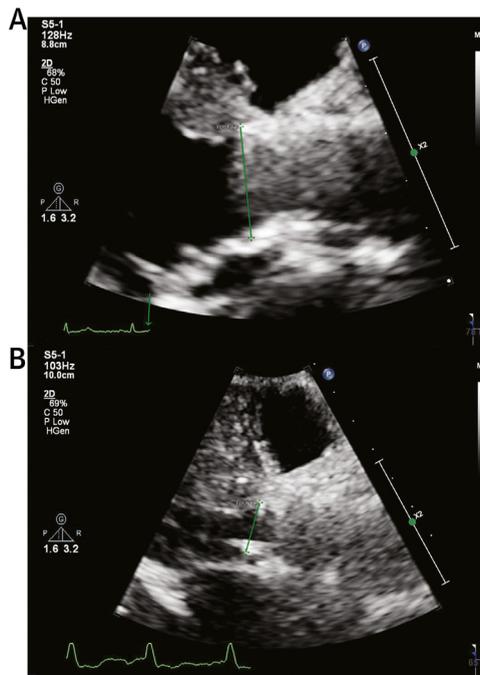
Inter-ECL harmonization is particularly relevant for high-volume, regulatory-compliant ECLs and for large TAVR trials that potentially require several high-volume ECLs. The present inter-ECL harmonization involved 2 major ECLs with well-established track records in the field of TAVR trials, the Québec Heart and Lung Institute (Laval University, Québec, Canada) and Cardialysis (Rotterdam, the Netherlands). To date, the Québec Heart and Lung Institute ECL has analyzed >25,000 echocardiograms in 18 TAVR trials, and the monthly volume is approximately 450 echocardiograms. The Cardialysis ECL has analyzed >19,000 echocardiograms in 14 TAVR trials in all phases of development, and the monthly volume is approximately 300 echocardiograms. Both ECLs are compliant with U.S. Food and Drug Administration regulatory requirements, as well as existing standards, to provide high-quality data that support device evaluation procedures.

The present inter-ECL harmonization was implemented in a 4-step approach ([Central Illustration](#)):

1. A uniform ECL analysis methodology was established in a first harmonization meeting of both ECLs. Thereafter, a common Core Laboratory Analysis Plan was drafted and reviewed by both ECLs.
2. Afterward, 5 test run echocardiograms were analyzed on the basis of the Core Laboratory Analysis Plan for training purposes. The results, especially the discrepancies, were extensively discussed and further aligned during the second harmonization meeting.
3. Thereafter, for the formal analysis, 2 analysts from each ECL analyzed 2 blinded copies of

**CENTRAL ILLUSTRATION** The Process and Key Results of Inter-ECL HarmonizationRen CB, et al. *J Am Coll Cardiol Img.* 2024;■(■):■-■.

This figure summarizes the process and main results of the first trans-Atlantic inter-ECL harmonization on post-TAVR echocardiographic endpoints according to VARC-3 definitions. (Top) The harmonization process, including the setup of the DTA, the DPA, the RCA, common ECL methodology, data entry (including study specific electronic case reporting forms) and QC, test run analysis, formal analysis, and result interpretation. (Middle) The main results demonstrate promising inter- and intra-ECL agreements on intended valve performance adjudicated according to the VARC-3 (all kappa  $\geq 0.90$ ). (Bottom) The results on paravalvular AR, 1 composite of the intended valve performance, are separately shown, where the inter- and intra-ECL agreement is considered good to excellent (kappa 0.83 and 0.96). The numbers 0, 10, 20, 30, and 40 on the agreement graphs indicate the number of cases. The area with dark green indicates the cases with concordant adjudications between the 2 ECLs or between 2 observations of the same ECL, and the area with light green indicates the discordant adjudication. (Middle) "Yes" and "No" indicate whether the intended valve performance is met adjudicated on the basis of the ECL assessments. (Bottom) "None or trace," "Mild," and "Moderate" indicate the 3-class grading scheme of paravalvular AR severity. AR = aortic regurgitation; DTA = data transfer agreement; DPA = data processing agreement; ECL = echocardiography core laboratory; QC = quality control; RCA = research collaboration agreement; TAVR = transcatheter aortic valve replacement; VARC-3 = Valve Academic Research Consortium 3.

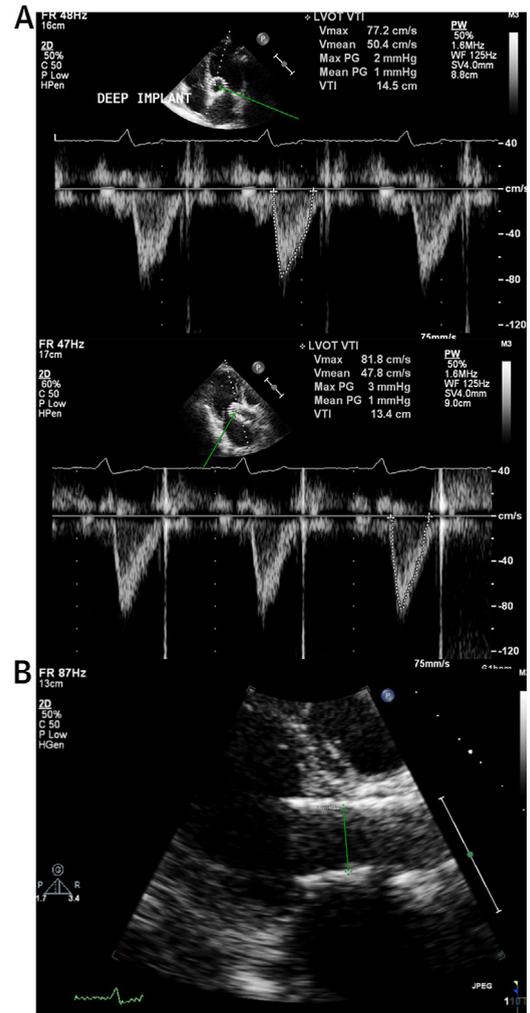
**FIGURE 1** Harmonized ECL Method in Measuring the LVOT Diameter

The LVOT diameter should be measured in midsystole (arrows on the electrocardiogram) (A) from the outer edge to outer edge at the prosthesis inflow edge, including (B) the scenario of a “free-hanging” prosthesis, provided the LVOT PWD sample volume is placed at the prosthesis inflow edge. 2D = 2-dimensional; ECL = echocardiography core laboratory; LVOT = left ventricular outflow tract; PWD = pulsed-wave Doppler.

40 post-TAVR echocardiograms as the primary analysis; the ECL director from each ECL overread the 2 copies of primary analyses. The results of the overread were taken into the statistical analysis of inter- and intra-ECL reproducibility (Supplemental Figure 1).

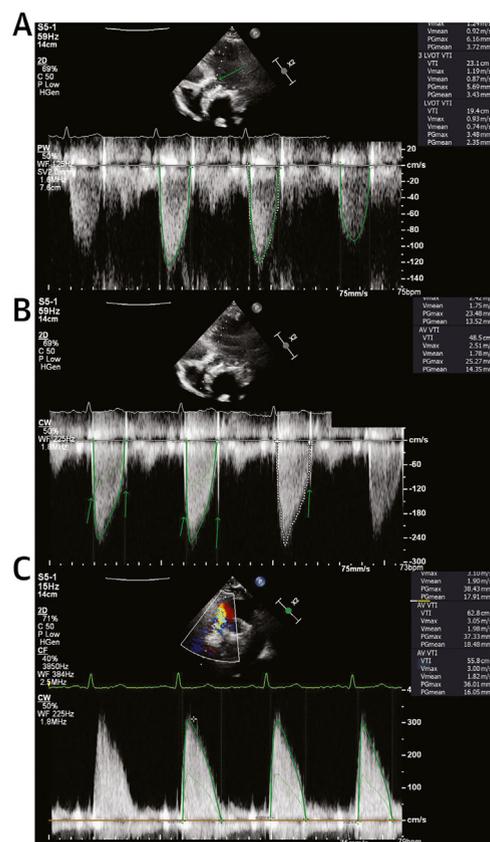
- Outliers identified in the inter-ECL variability were reviewed between the ECL directors during the third meeting to identify the root cause of the variability.

According to the study objective and design, the image analysis and reproducibility tests had not been performed before the harmonization (ie, the reproducibility of nonharmonized ECL analyses was not available). For future inter-ECL

**FIGURE 2** ECL Method in Measuring the LVOT Diameter for the Scenario of “Deep Implantation”

(A) If a prosthesis (typically self-expanding) is implanted too deep into the left ventricle and the LVOT PWD sample volume is placed in the prosthesis stent in both 5CH and 3CH views (arrows), (B) the LVOT diameter should then be measured from the inner edge to the inner edge. 3CH = 3-chamber; 5CH = 5-chamber; Max = maximum; PG = pressure gradient; Vmax = maximum velocity; Vmean = mean velocity; VTI = velocity time integral; other abbreviations as in Figure 1.

harmonization, it would be scientifically interesting to perform both preharmonization and postharmonization analyses and to observe to which extent the reproducibility is improved after harmonization.

**FIGURE 3** Harmonized ECL Method in Measuring the VTIs of LVOT and AV

The VTIs should be traced in the image with the best alignment between the ultrasound beam and the flow, along the compact contour of the Doppler envelopes in 3 to 5 cardiac cycles depending on the heart rhythm. (A) The PWD acquisition with correct LVOT PWD sample volume location (ie, on the prosthesis inflow edge during systole) is preferred for the ECL analysis (arrow pointing to the location of the PWD sample volume). (B) The tracing should exclude the fluffy edge and the 2 strong echogenic strips in the Doppler envelopes if visualized (arrows pointing to the strong echogenic strips at the beginning and end of systole). (C) The aortic valve (AV) VTI should be traced in the CWD image from the view with the highest aortic valve velocity, which is often the right parasternal view. AVA = aortic valve area; CWD = continuous-wave Doppler; SV = stroke volume; other abbreviations as in [Figures 1 and 2](#).

## ECHOCARDIOGRAPHIC MATERIAL FOR INTER-ECL HARMONIZATION

In the present harmonization, the 40 echocardiograms used were retrospectively selected from the

TAVR cohort from a high-volume academic center (Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands) on the basis of certain criteria ([Supplemental Methods](#)), and the transfer of fully anonymized imaging data sets was approved by the Institutional Review Board. For inter-ECL harmonization, it is important that the image data exchange follows applicable legal requirements, such as data transfer and processing agreements between participating ECLs. The ECLs were and should be blinded on prosthesis types, sizes, or any other clinical information. The case identifications of echocardiogram copies used in the harmonization should be recorded in all copies so that the ECL observers are properly blinded.

## HARMONIZATION OF ECL ANALYSIS METHODOLOGY

Post-TAVR echocardiographic endpoints, including typically the AVA, transaortic hemodynamics, transvalvular aortic regurgitation (AR), and paravalvular AR as defined by VARC-3,<sup>12</sup> are the main targets of the inter-ECL harmonization.

**EFFECTIVE AVA AND HEMODYNAMICS.** The post-TAVR effective AVA is calculated on the basis of the LVOT diameter, LVOT velocity time integral (VTI), and aortic valve (AV) VTI by using the continuity equation:

$$AVA = (LVOT \text{ diameter} / 2)^2 \times \pi \times LVOT \text{ VTI} / AV \text{ VTI}^7$$

Given the inevitable errors of the continuity equation (ie, the geometric assumption that the LVOT is circular<sup>15</sup> and the error in LVOT diameter is squared), the intraobserver variability and interobserver variability in calculating the AVA is mainly driven by the variability in the LVOT diameter measurement. Therefore, precision in the measurement itself is crucial. The aortic hemodynamics, typically the maximal and mean pressure gradient (PG), are derived directly from AV VTI tracing in continuous-wave Doppler (CWD) acquisitions on the transaortic outflow, which has a relatively straightforward methodology.

**LVOT diameter.** The LVOT diameter should be measured:

- In the parasternal long-axis (PLAX) view, preferably in the zoom mode because of the higher frame rate.<sup>6</sup>
- Where the delineation of the TAVR prosthesis outline is clearly visualized; off-axis view (eg,

**TABLE 1 Inter-ECL Reproducibility on AV Hemodynamic Parameters**

	ECL-1 (n = 40)	ECL-2 (n = 40)	P Value	Bias	LOA	ICC	r <sup>2</sup>
AVA, cm <sup>2</sup>	1.88 ± 0.36	2.02 ± 0.44	0.001	-0.14	0.47	0.78 (0.54-0.89)	0.91
Mean PG, mm Hg	9.9 ± 4.0	10.5 ± 4.1	<0.001	-0.65	2.25	0.95 (0.87-0.98)	0.98
Max PG, mm Hg	18.8 ± 7.3	18.7 ± 7.6	0.776	0.1	4.22	0.96 (0.92-0.98)	0.98
AV VTI, cm	40.3 ± 9.7	41.6 ± 10.0	0.025	-1.3	6.9	0.93 (0.86-0.96)	0.97
LVOT VTI, cm	22.0 ± 6.0	20.6 ± 4.9	<0.001	1.38	4.52	0.89 (0.72-0.95)	0.96
LVOT diameter, mm	21.0 ± 2.2	22.7 ± 2.1	<0.001	-1.63	2.27	0.66 (0.00-0.88)	0.94

Values are mean ± SD or mean (95% CI).

AV = aortic valve; AVA = aortic valve area; ECL = echocardiography core laboratory; ICC = intraclass coefficient; LOA = limits of agreement; LVOT = left ventricular outflow tract; Max = maximum; PG = pressure gradient; VTI = velocity time integral.

tricuspid or pulmonic valve in the view should be disregarded).

- In mid-systole in the second or best cardiac cycle, whichever offers the better visualization.
- At the location where the sample volume of the LVOT pulsed-wave Doppler (PWD) is placed during systole:
  - By default, the sample volume should be placed on the prosthesis inflow edge (stent ventricular end) (Video 1), and the LVOT diameter should be measured from the outer edge to the outer edge at the prosthesis inflow edge (Figure 1A).<sup>9</sup>
  - In cases where the only available LVOT PWD acquisition is with the sample volume placed inside the prosthesis (Figure 2A) (eg, typically when a self-expanding prosthesis is implanted too deep into the left ventricle, especially when the stent ventricular end is even lower than the anterior mitral valve leaflet) (Video 2), the LVOT diameter should then be measured from the inner edge to the inner edge (Figure 2B).<sup>9</sup>
- In the scenario of a “free-hanging” prosthesis in the LVOT (ie, the ventricular part of the prosthesis seems not to be in contact with the LVOT wall), the LVOT diameter is recommended to be measured from the outer edge to the outer edge (provided the LVOT PWD sample volume location was correct) (Figure 1B).

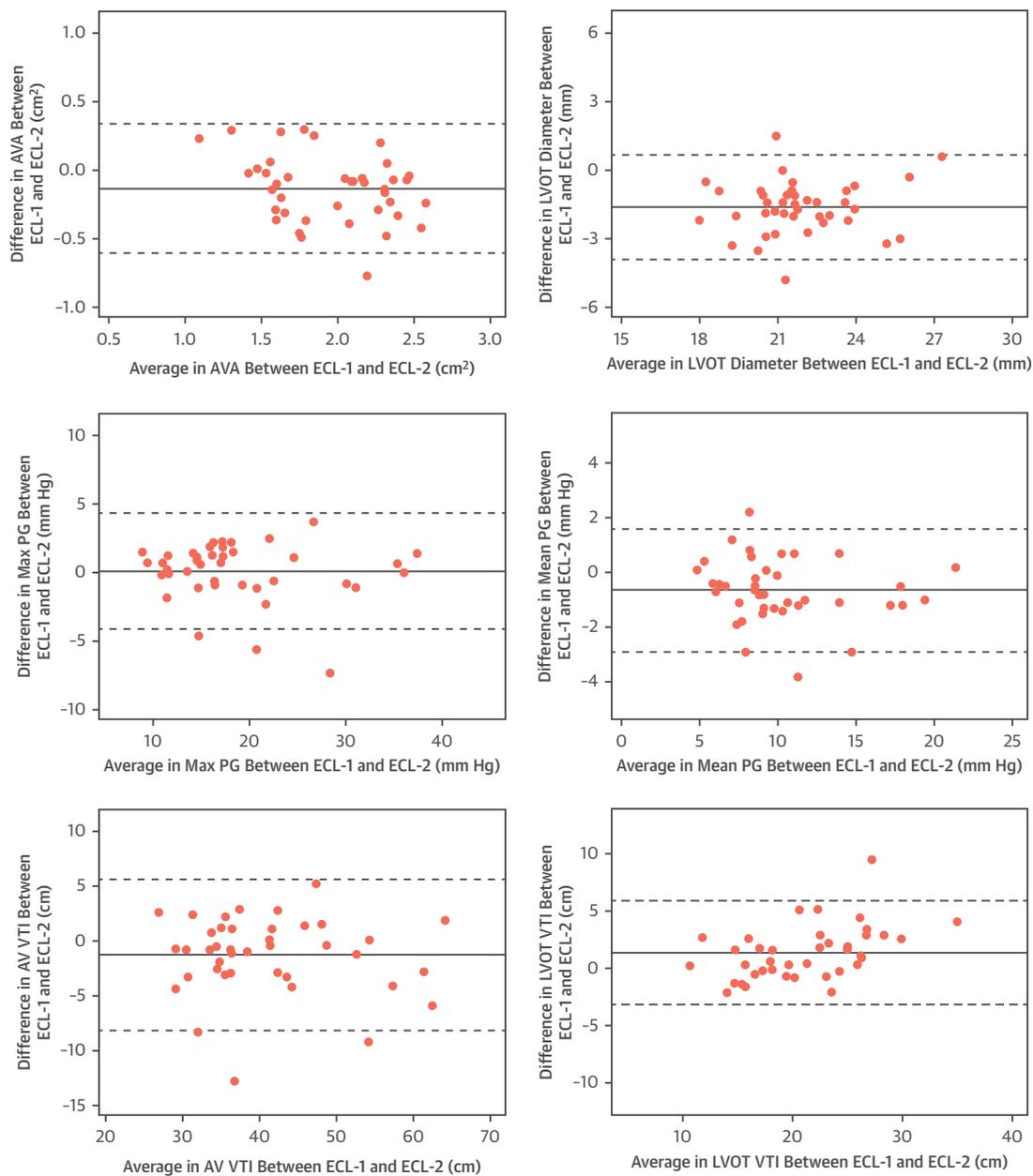
It is crucial that the LVOT PWD sample volume location is carefully inspected in both 5-chamber (5CH) and 3-chamber (3CH) view acquisitions before measuring the LVOT diameter. The PWD acquisition with correct LVOT PWD sample volume location (ie, located on the prosthesis inflow edge during systole) is preferred for ECL analysis (Figure 3A, Video 1). Additionally, the sample volume should not be placed too deep into the left ventricular cavity (Video 3) because the PWD profiles acquired do not represent

**TABLE 2 Intra-ECL Reproducibility on AV Hemodynamic Parameters**

	Intra-ECL-1 (n = 40)				Intra-ECL-2 (n = 40)			
	Bias	LOA	ICC	r <sup>2</sup>	Bias	LOA	ICC	r <sup>2</sup>
AVA, cm <sup>2</sup>	0.07	0.41	0.81 (0.67-0.90)	0.91	0.04	0.39	0.89 (0.80-0.94)	0.95
Mean PG, mm Hg	0.35	2.15	0.95 (0.91-0.98)	0.98	0.65	2.1	0.96 (0.88-0.98)	0.98
Max PG, mm Hg	0.91	3.28	0.96 (0.91-0.98)	0.99	0.54	3.71	0.97 (0.94-0.98)	0.99
AV VTI, cm	0.03	3.91	0.98 (0.96-0.99)	0.99	-0.93	5.9	0.96 (0.92-0.98)	0.98
LVOT VTI, cm	0.38	3.6	0.95 (0.91-0.97)	0.98	-0.33	2.88	0.96 (0.92-0.98)	0.98
LVOT diameter, mm	0.16	1.88	0.91 (0.84-0.95)	0.96	0.13	1.37	0.94 (0.89-0.97)	0.97

ICC is expressed as mean (95% CI).

Abbreviations as in Table 1.

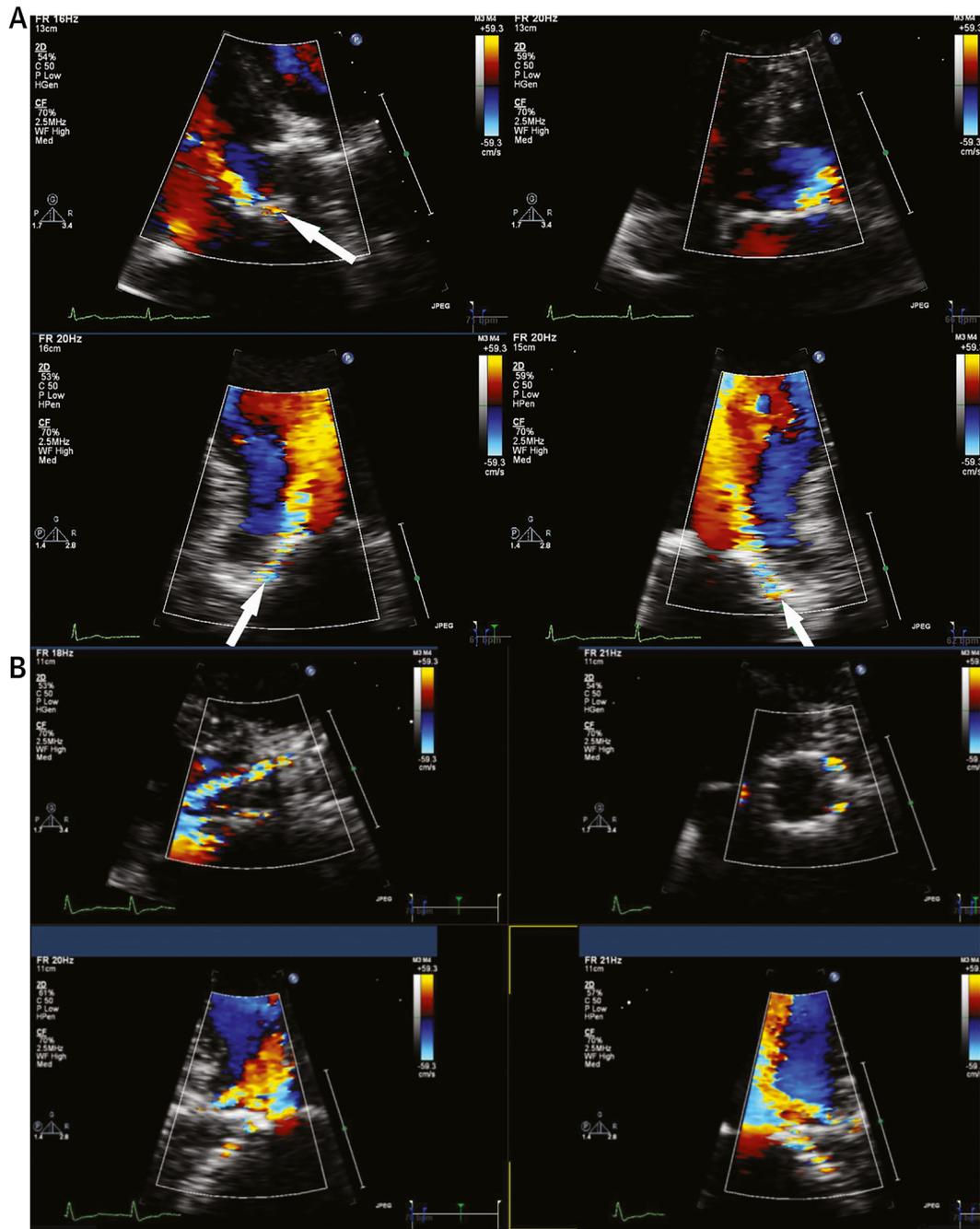
**FIGURE 4** Bland-Altman Plots of Inter-ECL Reproducibility on AVA and Hemodynamics Related Parameters

Abbreviations as in [Figures 1 to 3](#).

the flow pattern of the LVOT, but rather the left ventricular midcavity.

**VTI of the LVOT and AV.** The VTIs of both the LVOT and AV are derived from tracing the Doppler profiles ([Figure 3](#)):

- Trace in the Doppler image of the best quality (ie, the best alignment between the ultrasound beam and the flow among all views available).
- Trace along the compact contour of the Doppler envelopes, excluding the fluffy edge and the 2 strong echogenic strips at the beginning and end of systole, if visualized ([Figure 3B](#), arrows).
- Trace 3 cardiac cycles for sinus rhythm and 5 (or all) for irregular rhythms.
- For AV VTI, trace CWD profiles with the highest AV velocity, often the right parasternal view

**FIGURE 5** Harmonized ECL Method in Assessing the Qualitative Doppler Parameters of Paravalvular AR

The qualitative Doppler parameters, including jet origin, jet number, jet path, and jet flow convergence, are visually assessed in color Doppler images from the PLAX, PSAX, 5CH, and 3CH views if available. When paravalvular AR (single or multiple) is seen in 1 view, it is important to acquire and assess in all 4 views. (A) an example of 1 posterior paravalvular AR jet originating from 4 to 5 o'clock in the PSAX view with a slim jet path seen in the PLAX, 5CH, and 3CH views (arrows), without a wide jet origin or flow convergence zone. (B) An example of 2 paravalvular AR jets originating from 2 and 4 o'clock in the PSAX view, where the anterior jet (at 2 o'clock) is seen with a slim jet path seen in the PLAX view and the posterior jet (at 4 o'clock) is seen with a slim jet path in the 5CH and 3CH views; both jets are without wide jet origins or flow convergence zone observed. AR = aortic regurgitation; PLAX = parasternal long-axis; PSAX = parasternal short-axis; other abbreviations as in [Figures 1 to 3](#).

**TABLE 3** Harmonized ECL Analysis Methodology on the Semiquantitative Doppler Parameters for Paravalvular AR

	Echocardiographic Modality and View	ECL Methodology
E/A ratio	PWD with the sample volume at MV orifice in 4CH	Assess first whether the PWD sample volume is correctly positioned at the MV orifice level; measure on the compact contour of the Doppler peaks (Figures 6A to 6C); this is not feasible in atrial fibrillation as a result of missing of the A wave (Figure 6C).
Vena contracta width	Color Doppler (zoom mode preferred) in PLAX, 5CH, and 3CH	Measure on the jet neck on the "mosaic" color Doppler signal (indicating high velocity) perpendicular to the jet long axis, only if the jet path is clearly visualized (Figure 7). If multiple jets are present, each jet is measured separately in different frames if needed.
Jet width in LVOT	Color Doppler (zoom mode preferred) in PLAX	Measure on the jet body (being either laminar or turbulent flow) perpendicular to the jet long axis on the level of the prosthesis inflow edge (ie, the same location where the LVOT diameter is measured) (Figures 8A and 8B). For multiple jets, each jet is measured separately in different frames if needed. For radial flying jet, the same methodology applies (Figure 8B).
Jet density and PHT (and VTI)	CWD in 5CH and/or 3CH	Assess first in both 5CH and 3CH acquisitions the alignment between the ultrasound beam and the flow, and choose the one with the better alignment; AR velocity is generally high, about 4 m/s. Any velocity lower than that indicates suboptimal alignment between the ultrasound beam and the flow. Visually assess the CWD density of the jet and compare it with the CWD density of the forward flow (Figures 9A to 9C). If the Doppler profiles are complete with high AR velocity, trace along the compact contour of the Doppler envelopes, in 3 to 5 cardiac cycles (Figure 9A).
Diastolic flow reversal in proximal descending aorta	PWD with the sample volume at proximal descending aorta in SS	First assess whether the PWD sample volume is correctly positioned at the proximal level of the descending aorta; assess then whether the PWD velocity scale is optimal, adapting to the velocity of the flow reversal (Figure 10A showing an example of a suboptimal velocity scale where the flow reversal could be underestimated); assess visually the flow reversal profile (Figures 10B to 10E), and measure the end-diastolic velocity if it is clearly holodiastolic (Figure 10E).
Circumferential extent and vena contracta area (2D)	Color Doppler (zoom mode preferred) in PSAX	The prerequisites of measuring: <ul style="list-style-type: none"> <li>• Only on the mosaic color Doppler signal</li> <li>• Mosaic color Doppler signal lasts at least 2 consecutive frames</li> <li>• Frame rate at minimal 15 Hz</li> <li>• If multiple jets, each jet measured/assessed separately in different frames if needed (Figure 11)</li> </ul> The circumferential extent is expressed in a clock mode (1-12 o'clock) in both degrees (out of 360°) (Figure 11) and a visual assessment of the approximate coverage of the number of minutes (out of 60 minutes) (Video 15), whichever is feasible. The vena contracta area is measured along the mosaic color zone. For flying jet, these measurements are challenging; thus, they should either be avoided or measured with caution because they could lead to overestimation (Video 16).

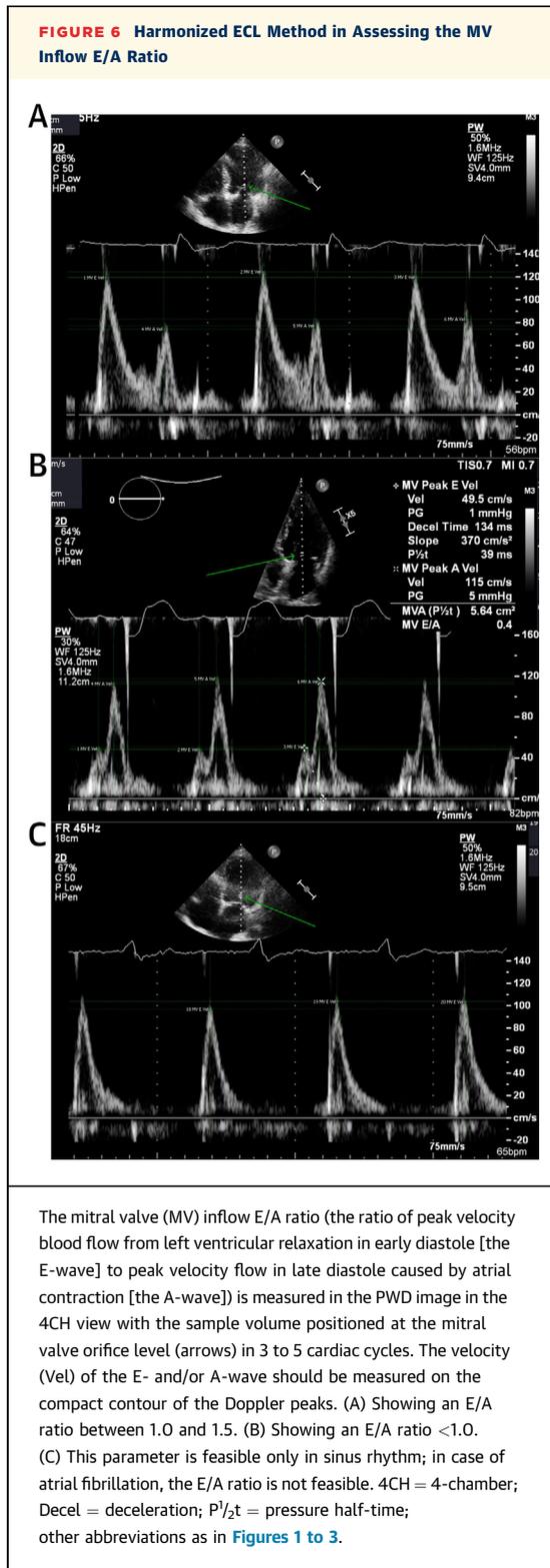
2D = 2-dimensional; 3CH = 3-chamber view; 4CH = 4-chamber view; 5CH = 5-chamber view; AR = aortic regurgitation; CWD = continuous-wave Doppler; E/A ratio = ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave); MV = mitral valve; PHT = pressure half-time; PLAX = parasternal long-axis; PSAX = parasternal short-axis; PWD = pulsed-wave Doppler; SS = suprasternal view; other abbreviations as in Table 1.

(Figure 3C), given the best alignment and the regions of interest in the near field of the ultrasound beam.

The inter- and intra-ECL reproducibility results on AVA and hemodynamics in the present harmonization are shown in Tables 1 and 2. The inter-ECL Bland-Altman plots are shown in Figure 4, and the intra-ECL Bland-Altman plots are shown in Supplemental Figure 2. As expected, the transaortic mean PG yielded excellent inter-ECL agreement (intraclass coefficient [ICC]:  $\geq 0.95$  and very small biases and limits of agreement), which is important and reassuring given that the PG is a commonly reported TAVR

endpoint. Potential pitfalls in tracing the VTIs are as follows: the tracings are performed on nonrepresentative cardiac cycles, especially in irregular heart rhythm, thus leading to overestimation or underestimation of the VTIs; the contours of the tracings are too wide, either exceeding the systole period (ie, outside the 2 strong echogenic stripes) or not following the most compact Doppler envelopes, both leading to overestimation of the VTIs. These pitfalls can be easily avoided if the ECL methodology is strictly followed.

The LVOT diameter, however, yielded higher inter-ECL variability (ICC: 0.66), leading to moderate to good inter-ECL reproducibility (ICC: 0.78) in



AVA. The sources of the variability in the LVOT diameter measurement can be summarized as follows:

- A suboptimal PLAX acoustic window, where the ventricular border of the prosthetic was not clearly visualized or distinguishable from adjacent tissue ([Video 4](#)).
- Unstable imaging plane during systole as a result of either the heart or respiratory motion, or both ([Video 5](#)), or an irregular heart rhythm, such as atrial fibrillation ([Video 6](#)). This may show different results depending on the frame selected. Depending on the heart rate and frame rate, midsystole occurs between the third and fifth frame from the onset of systole. It is likely that different analysts may use different frames, and this may translate into different LVOT diameter measurements if there is significant interframe variability.
- Noncoaxially implanted prosthesis, either because it is “free-hanging” (ie, the prosthesis not in complete contact with adjacent tissue in the LVOT) ([Figure 1B](#), [Video 7](#)), or because the long axis of the prosthesis is not in line with the long axis of the LVOT, thus adding to the challenge of identifying the ventricular edge of the prosthesis.

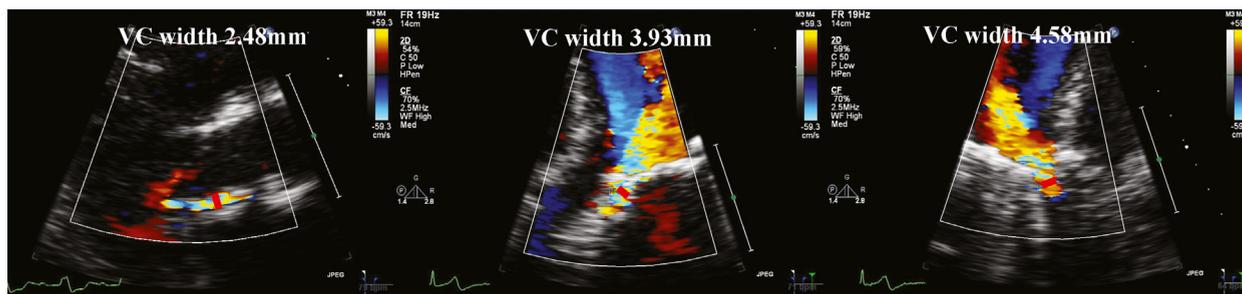
These sources of error or variability are difficult to resolve within the ECL procedures because they originate outside of the ECL methodology.

**PARAVALVULAR AR ANALYSIS.** Paravalvular AR analysis is based strictly on the VARC-3 definitions,<sup>12</sup> with a multiparametric approach, including the qualitative, semiquantitative, and quantitative Doppler parameters.

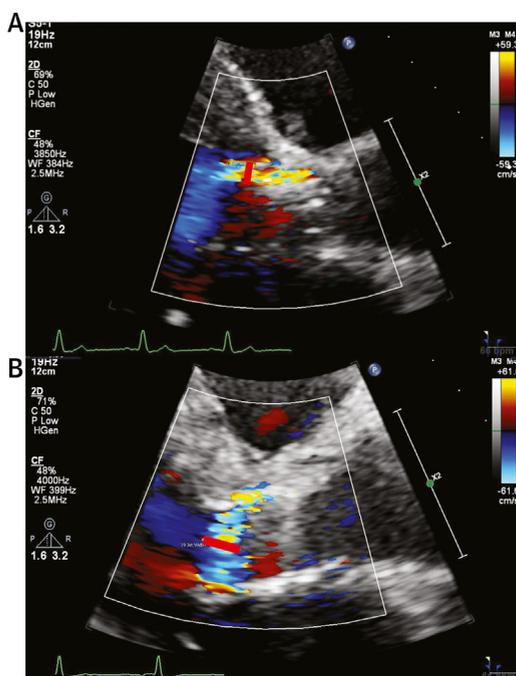
**Qualitative Doppler parameters.** The qualitative Doppler parameters of the jet features include the following:

- Jet origin
- Jet number
- Jet path
- Jet flow convergence

These parameters are visually assessed in color Doppler images from PLAX, parasternal short-axis (PSAX), 5CH, and 3CH views if available<sup>9</sup> ([Figure 5A](#), [Videos 8 to 13](#), showing multiple-view color Doppler images of different severity of paravalvular AR consented). If multiple jets are present, it is crucial to

**FIGURE 7** Harmonized ECL Method in Measuring the VC Width

The vena contracta (VC) width should be measured/attempted in the PLAX, 5CH, and 3CH views (zoom mode is preferred) when the jet path is clearly seen. It should be measured on the jet neck in “mosaic” color Doppler signal (indicating high velocity) perpendicular to the jet long axis (thick red line). This parameter is challenging because very high quality in acoustic window and acquisition is required. Caution is needed because the cutoffs in vena contracta width are very small in value. Abbreviations as in [Figures 1, 2, 3, and 5](#).

**FIGURE 8** Harmonized ECL Method in Measuring the Jet Width in the LVOT

(A) The jet width is measured in the PLAX view on the jet body (being either laminar or turbulent flow) perpendicular to the jet long axis on the level of the prosthesis inflow edge (ie, the same location where the LVOT diameter is measured). (B) For radial flying jet, the same methodology applies, while being aware of the angle in the long axis between the jet and the LVOT. Abbreviations as in [Figures 1, 2, 3, and 5](#).

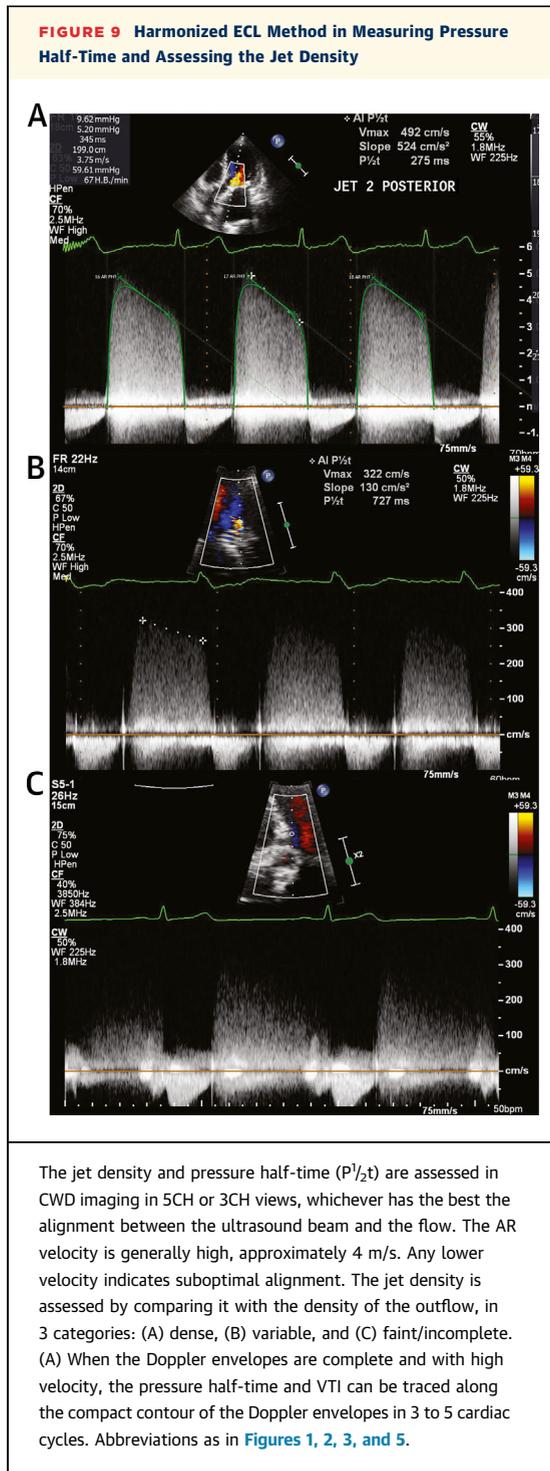
identify the number of the jets and the corresponding location of each jet.<sup>9</sup> ([Figure 5B](#), [Video 14](#)).

**Semiquantitative Doppler parameters.** The semiquantitative Doppler parameters need to be measured/assessed carefully on the basis of the image quality and reliability of the measurement because the cutoff values in the VARC-3 definitions on these parameters are small (eg, vena contracta width measures 2 to 6 mm across up to 5 grades), and thus any slight difference in measurement may lead to a large difference in adjudicated severity. The recommended methodology for measuring/assessing the semiquantitative Doppler parameters is shown in [Table 3](#) ([Figures 6 to 11](#), [Videos 15 and 16](#)).

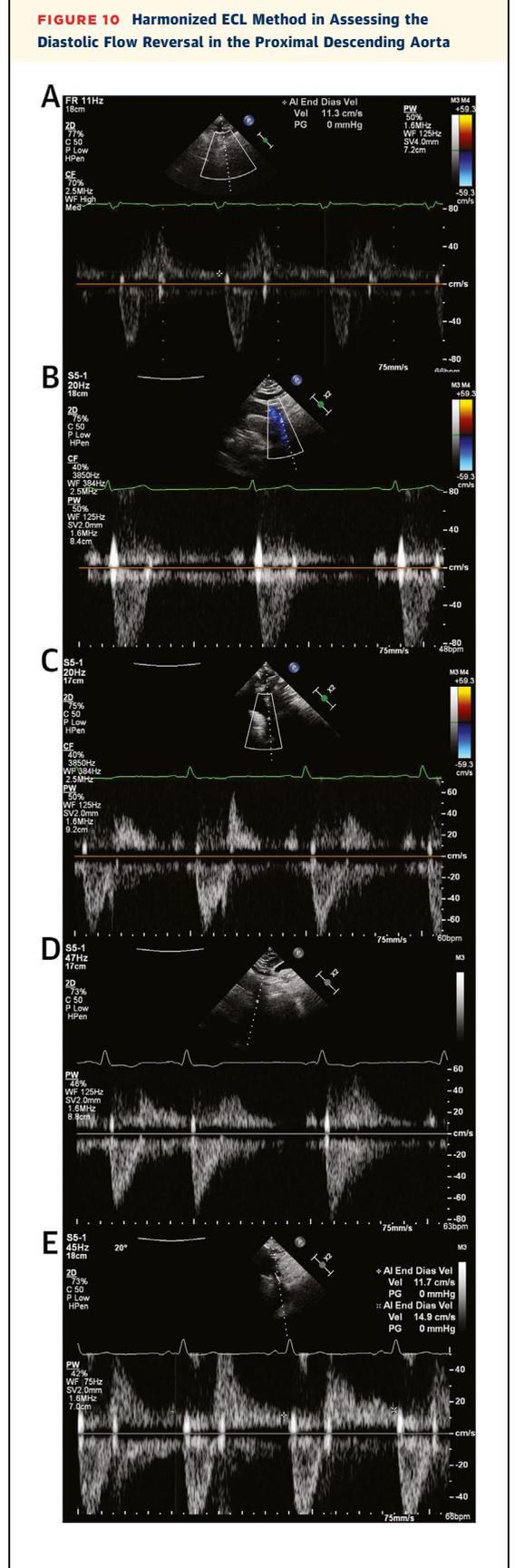
**Quantitative Doppler parameters.** The quantitative Doppler parameters, including the regurgitant volume, regurgitant fraction, and effective regurgitant orifice area, are calculated on the basis of the PWD method of calculating the difference in the stroke volume (SV) between the LVOT and the right ventricular outflow tract (RVOT). The LVOT SV was calculated on the basis of the LVOT diameter and LVOT VTI by using the following formula:

$$SV = \text{LVOT diameter}^2 \times 0.785 \times \text{LVOT VTI}$$

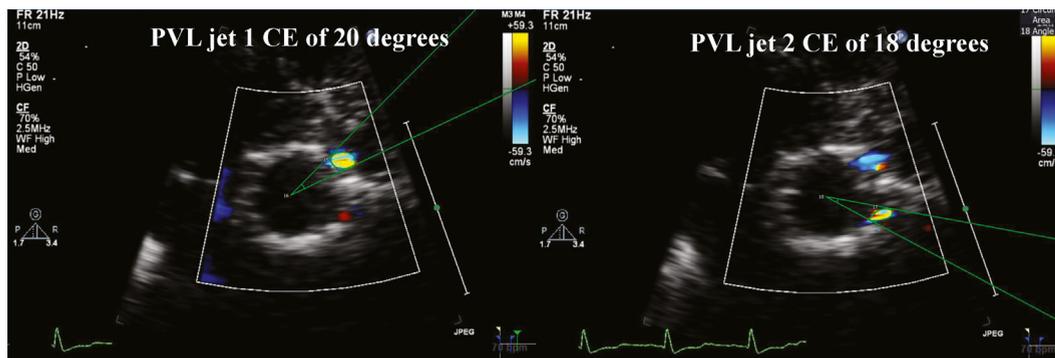
The RVOT SV, similarly, was calculated on the basis of the RVOT diameter and VTI by using the same formula. The methodology for measuring the RVOT diameter and VTI is similar to that used for the LVOT ([Figures 12A to 12C](#)): measure the RVOT diameter in the PSAX view focused on the RVOT with clear



visualization of the RVOT border, in midsystole in the second or best cardiac cycle, correct location of the RVOT PWD sample volume (just below the pulmonic valve), and the general rules for tracing the Doppler envelopes.



Continued on the next page

**FIGURE 11** Harmonized ECL Method in Measuring the Circumferential Extent and Vena Contracta Area

These 2 parameters are measured in the parasternal short-axis view with sufficient image quality (ie, high frame rate and clear mosaic color signal lasting at least 2 consecutive frames). If multiple jets are present, each jet should be measured separately in different frames. This figure shows an example of 2 jets at 2 o'clock with the circumferential extent (CE) of 5.6% (20°/360°) and at 4 o'clock with the circumferential extent of 5% (18°/360°). Because of the high requirement of the image quality, these parameters should be measured with caution. For flying jet, these parameters should be avoided because they easily lead to overestimation (Video 16). PVL = paravalvular leak; other abbreviations as in Figures 1 to 3.

Given the unavoidable limitations of the PWD method (ie, the geometric assumption that both the LVOT and RVOT are circular and the mathematical formula where the diameters are squared<sup>15,16</sup>) and the very good acoustic window needed for RVOT measurements, it is expected that the feasibility and reliability of these parameters are low.

**PARAVALVULAR AR ADJUDICATION.** The adjudication of the paravalvular AR severity is based on each Doppler parameter (qualitative, semiquantitative, and quantitative) according to the cutoffs proposed in the VARC-3 definitions.<sup>12</sup> Because of the clinical relevance of moderate or greater paravalvular AR,<sup>4,17</sup> in the present harmonization, each Doppler parameter

was individually adjudicated for gross severity into “mild or less” or “moderate or more.”

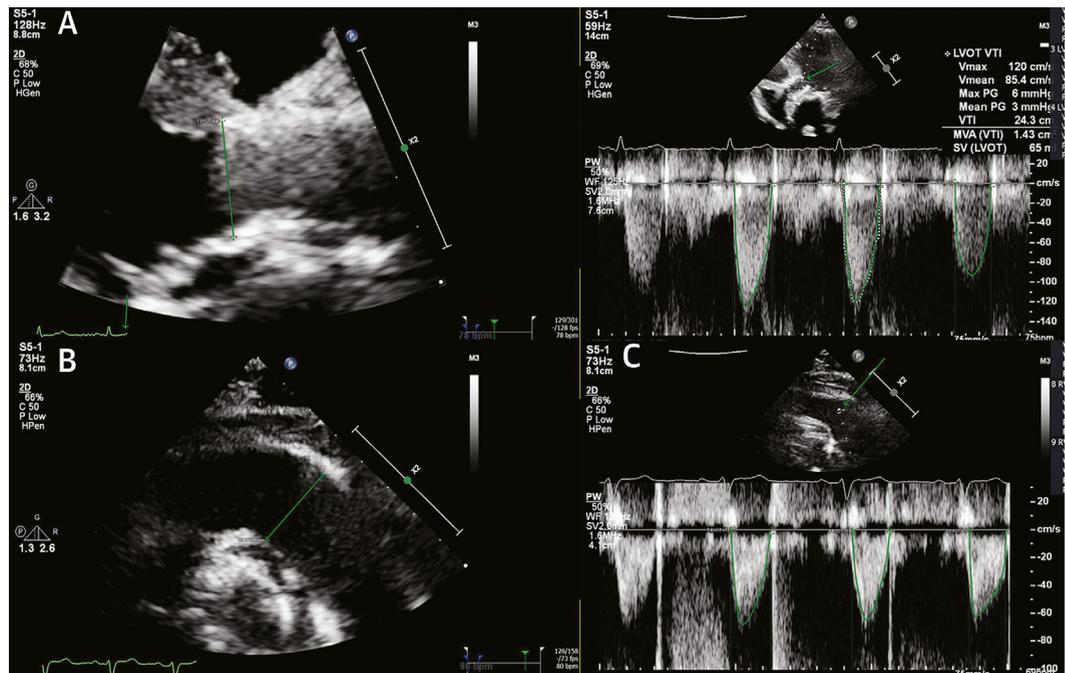
For adjudication of paravalvular AR severity, the assessment of reliability is important. One should use a measurement for adjudication only if it is deemed reliable (ie, sufficient acoustic window, the best visualization of the regions of interest, sufficient frame rate, and representative heart cycles). For the parameters measured/assessed in multiple views, (eg, the vena contracta width, measured in PLAX, 5CH, and 3CH views), the most reliable measurements/assessment deemed by the observer should be used for the adjudication. The adjudication of the final paravalvular AR severity is based on the adjudication of all parameters deemed reliable in the 5-class and 3-class grading scheme.<sup>12</sup>

The inter- and intra-ECL reproducibility of the final paravalvular AR severity in the current harmonization is shown in Table 4, and the feasibility and inter- and intra-ECL reproducibility of each Doppler parameter used in adjudicating the paravalvular AR severity are shown in Table 5. The kappa statistics yielded moderate to good agreement between the 2 ECLs in the paravalvular AR with the 5-class grading scheme (0.74), which became higher in the 3-class grading scheme (0.83) (Central Illustration).

Varied feasibility and important inter-ECL variability among these Doppler parameters were also

**FIGURE 10** Continued

The diastolic flow reversal pattern is assessed in a PWD image from the suprasternal view, where the sample volume is located at the proximal part of the descending aorta. The flow reversal is generally of low velocity; thus, the PWD scale and baseline position need to be adjusted accordingly to avoid underestimation. (A) An example showing a PWD scale that is too large. (B to E) Different diastolic flow reversal patterns of (B) no reversal, (C) brief reversal, (D) intermediate reversal, and (E) holodiastolic reversal. (E) When diastolic flow reversal is clearly holodiastolic, the end-diastolic velocity (End Dias Vel) can be measured. Abbreviations as in Figures 1 to 3.

**FIGURE 12** Harmonized ECL Method in Measuring the Quantitative Doppler Parameters Using the PWD Method

The quantitative Doppler parameters, regurgitant volume, regurgitant fraction, and effective regurgitant orifice area, are calculated on the basis of the PWD method of calculating the difference in the SV between the LVOT and the RVOT. (A) The methodology in measuring LVOT diameter and VTI is the same as elaborated in Figures 1 to 3. (B) The RVOT diameter is measured in the parasternal short-axis view focused on the RVOT with clear visualization of the RVOT border. (C) The RVOT VTI should be traced in the same view as where the RVOT diameter is measured in the PWD image with the sample volume placed just below the pulmonic valve (arrow). RVOT = right ventricular outflow tract; other abbreviations as in Figures 1 to 3.

seen. Expectedly in general, the more quantitative, the lower the feasibility was (ie, the qualitative or visual assessments on the jet features were highly feasible, provided sufficient acoustic window and acquisition quality), whereas the quantitative

parameters were much less feasible (eg, regurgitant orifice area was the least feasible parameter given that more parameters are needed in its derivation). In some Doppler parameters such as the vena contracta width and quantitative parameters in the PWD method, different feasibility was seen between the 2 ECLs. Despite the detailed methodology, there is still some latitude in the decision of the observer to perform the measurement or not. Moreover, measurements of the vena contracta width and RVOT diameter are intrinsically more challenging<sup>16</sup> because very high-quality images are requested, thus explaining the lower feasibility. Additionally, such challenging measurements (eg, vena contracta width) were also seen to be of low inter-ECL reproducibility, even for the 2 ECLs highly experienced in the TAVR analysis after a rigorous harmonization process. This finding could partly be attributed to the small cutoff values among different paravalvular AR severity grades proposed in VARC because even 1-mm difference in the

**TABLE 4** Inter- and Intra-ECL Reproducibility (kappa) on Paravalvular, Transvalvular, and Total AR

	Inter-ECL	Intra-ECL-1	Intra-ECL-2
Paravalvular AR			
5-class grading	0.74 (0.57-0.90)	0.80 (0.65-0.94)	0.97 (0.90-1.00)
3-class grading	0.83 (0.67-0.99)	0.96 (0.88-1.00)	0.96 (0.87-1.00)
Transvalvular AR			
Adjusted 5-class grading <sup>a</sup>	0.72 (0.36-1.00)	0.59 (0.22-0.96)	0.63 (0.25-1.00)
3-class grading	— <sup>b</sup>	— <sup>b</sup>	— <sup>b</sup>
Total AR 3-class grading	0.83 (0.67-0.99)	0.96 (0.88-1.00)	0.96 (0.87-1.00)

The kappa values are mean (95% CI). <sup>a</sup>None and trace were further differentiated on top of the 5-class grading scheme. <sup>b</sup>The kappa value could not be defined because of low incidences in higher grades.

Abbreviations as in Tables 1 and 3.

**TABLE 5 Feasibility and Agreement of the Doppler-Echocardiographic Parameters in Adjudicating the Paravalvular AR per VARC-3**

	Feasibility		Reproducibility		
	ECL-1	ECL-2	Inter-ECL	Intra-ECL-1	Intra-ECL-2
<b>Qualitative and semiquantitative</b>					
Extensive jet origin	40 (100)	40 (100)	$\kappa$ 0.32 (0.08-0.57)	$\kappa$ 0.83 (0.61-1.00)	$\kappa$ 0.63 (0.41-0.85)
Multiple jets	40 (100)	40 (100)	$\kappa$ 0.19 (-0.02 to 0.40)	$\kappa$ 0.34 (0.09-0.60)	$\kappa$ 0.44 (0.24-0.65)
Jet path visible along the stent	40 (100)	40 (100)	$\kappa$ 0.82 (0.65-0.99)	$\kappa$ 0.64 (0.41-0.87)	$\kappa$ 0.65 (0.47-0.82)
Proximal flow convergence visible	40 (100)	34 (85)	$\kappa$ 0.06 (-0.05 to 0.17)	$\kappa$ 0.64 (0.27-1.00)	$\kappa$ 0.26 (0.09-0.44)
E/A ratio	38 (95)	30 (75)	ICC 0.96 (0.92-0.98) $\kappa$ 0.82 (0.66-0.99)	ICC 0.97 (0.93-0.99) $\kappa$ 0.82 (0.66-0.99)	ICC 0.98 (0.96-0.99) $\kappa$ 0.91 (0.78-1.00)
Vena contracta width	21 (53)	35 (88)	ICC 0.18-0.60 <sup>a</sup> $\kappa$ 0.44 (0.13-0.75)	ICC 0.53-0.86 <sup>a</sup> $\kappa$ 0.65 (0.36-0.93)	ICC 0.01-0.83 <sup>a</sup> $\kappa$ 0.27 (0.05-0.48)
Jet width (% LVOT diameter)	30 (75)	33 (83)	ICC 0.14 (0.00-0.45) $\kappa$ 0.07 (0.00-0.27)	ICC 0.85 (0.69-0.93) $\kappa$ 0.64 (0.44-0.83)	ICC 0.53 (0.23-0.74) $\kappa$ 0.41 (0.16-0.65)
Jet density in CWD	35 (88)	36 (90)	$\kappa$ 0.65 (0.45-0.85)	$\kappa$ 0.57 (0.36-0.78)	$\kappa$ 0.53 (0.28-0.78)
Jet PHT in CWD	21 (53)	27 (68)	ICC 0.88 (0.70-0.95) $\kappa$ 0.47 (0.27-0.67)	ICC 0.89 (0.02-0.97) $\kappa$ 0.45 (0.26-0.65)	ICC 0.79 (0.59-0.90) $\kappa$ 0.47 (0.23-0.71)
Diastolic flow reversal in proximal descending aorta in PWD	28 (70)	37 (93)	$\kappa$ 0.69 (0.50-0.89)	$\kappa$ 0.66 (0.45-0.87)	$\kappa$ 0.28 (0.02-0.55)
Circumferential extent, %	33 (83)	37 (93)	ICC 0.29 (0.00-0.81) $\kappa$ 0.11 (0.00-0.32)	ICC 0.30 (0.00-0.84) $\kappa$ 0.59 (0.34-0.84)	ICC 0.59 (0.33-0.77) $\kappa$ 0.68 (0.47-0.90)
<b>Quantitative</b>					
Regurgitant volume	15 (38)	24 (60)	ICC 0.54 (0.00-0.90) $\kappa$ 0.17 (0.02-0.31)	ICC 0.40 (0.00-0.89) $\kappa$ 0.41 (0.17-0.66)	ICC 0.73 (0.23-0.90) $\kappa$ 0.40 (0.16-0.65)
Regurgitant orifice area	8 (20)	18 (45)	ICC 0.75 (0.00-1.00) $\kappa$ 0.12 (0.00-0.27)	ICC 0.53 (0.00-1.00) $\kappa$ 0.52 (0.21-0.84)	ICC 0.77 (0.22-0.93) $\kappa$ 0.48 (0.27-0.69)
Regurgitant fraction	15 (38)	24 (60)	ICC 0.23 (0.00-0.78) $\kappa$ 0.14 (0.01-0.28)	ICC 0.16 (0.00-0.82) $\kappa$ 0.43 (0.19-0.66)	ICC 0.46 (0.02-0.75) $\kappa$ 0.45 (0.22-0.69)
Values are n (%) or mean (95%CI). <sup>a</sup> Vena contracta width was measured in 3 views (PLAX, 5CH, and 3CH) when measurable; thus, the ICC is shown as a range of values calculated on the basis of the measurements from all views.					
VARC-3 = Valve Academic Research Consortium 3; other abbreviations as in Tables 1 and 3.					

measurement could lead to different grades, thus resulting in a low kappa agreement. Therefore, the measurements of such quantitative parameters should be interpreted with caution during adjudication, and the multiparametric approach incorporating all available parameters (instead of relying on a single parameter) is essential. Finally, because of the inevitable arbitrariness in the visual assessment and interpretation, with parameters showing high feasibility but low inter-ECL reproducibility, such as jet width (percentage of LVOT diameter), jet density, and flow reversal in the proximal descending aorta, cautions during adjudication are also warranted.

Interestingly, 2 Doppler parameters were identified with both high feasibility and high inter-ECL reproducibility: the jet path visible along the stent and the mitral E/A ratio (the ratio of peak velocity blood flow from left ventricular relaxation in early diastole [the E wave] to peak velocity flow in late diastole caused by

atrial contraction [the A wave]). This finding could indicate that among all Doppler features, the jet path, visible or not, is probably the most reliable in itself (yes or no) and in deriving at least gross severity of the paravalvular AR (if yes, then pointing to moderate or more; if no, then mild or less). In the scenarios of mild to moderate paravalvular AR where the jet path could be seen in 1 or more long-axis views, other parameters are mandated to differentiate whether it is indeed mild to moderate (which is eventually graded as mild in the 3-class grading scheme) or actually moderate. The E/A ratio, although yielding excellent inter-ECL agreement, should be interpreted with caution as elaborated in the VARC-3 document,<sup>12</sup> and it is also not assessable in patients with nonsinus rhythm, as is commonly seen in patients undergoing TAVR.

In summary, for reliable adjudication of the paravalvular AR severity, the multiparametric approach is essential, and cautions are needed in interpreting

**TABLE 6 ECL Recommendations on Optimal Image Acquisitions on Essential Post-TAVR Echocardiographic Parameters**

View and Modality		ECL Recommendations	Common Pitfalls
General	—	<ul style="list-style-type: none"> <li>Optimize the machine presets according to the acoustic window quality, (eg, [color] gain, compress, depth, filter)</li> <li>Optimize the ECG signal (ie, clear identification of at least the R wave)</li> <li>All acquisitions contain at least 3 cardiac cycles; in case of irregular heart rhythm, acquire 5 cardiac cycles</li> <li>"Clean" acquisitions (eg, without tracing the images)</li> <li>In case of paravalvular AR, sweep mode with multiple cardiac cycle acquisitions is highly encouraged (ie, continuous probe tilting/angulations sweeping through the stent to visualize the jet origin)</li> <li>In case of flying AR jet, off-axis imaging planes are encouraged to visualize the jet origin and path</li> <li>For PWD and CWD acquisitions, the Doppler scale, baseline, and velocity need to be constantly adjusted/optimized accordingly; avoid "1 setting fits all"</li> </ul>	<ul style="list-style-type: none"> <li>No ECG or poor ECG signal</li> <li>Acquisitions with only 1-2 cardiac cycles</li> <li>CWD and/or PWD settings (ie, scale, baseline position, and velocity are not optimized/adapted according to individual acquisition, leading to Doppler scale usually too large for low velocity)</li> <li>All images with sites' tracings/measurements</li> </ul>
LVOT diameter	PLAX, gray scale and zoom mode	<ul style="list-style-type: none"> <li>Clear visualization of the prosthesis outline (Video 18)</li> <li>Avoid off-axis view (eg, tricuspid or pulmonic valve in view) (Video 19)</li> </ul>	<ul style="list-style-type: none"> <li>Off-axis, tricuspid or pulmonic valve in view; imaging plane too low (3CH alike) or too high (too much ascending aorta in view)</li> <li>No zoom acquisitions</li> </ul>
LVOT VTI	5CH and 3CH, PWD	<ul style="list-style-type: none"> <li>Acquire in both 5CH and 3CH</li> <li>Do not use angle correction</li> <li>Place the PWD sample volume carefully at the stent inflow edge (ventricular end) during systole</li> <li>Acquire first in 2D gray scale; moving loops showing the sample volume position (Video 1);</li> <li>Afterward, acquire in PWD with 3-5 profiles in still image</li> <li>Optimize the Doppler scale, baseline, and velocity accordingly (Figure 13A)</li> </ul>	<ul style="list-style-type: none"> <li>Only 1 view acquisition available</li> <li>PWD sample volume placed too deep into the left ventricle (Video 2); this gives very low velocity (Figure 14)</li> <li>Ambiguous PWD sample volume position—cannot tell from the acquisition whether it is in or out of the stent</li> <li>&lt;3 PWD profiles available</li> <li>Doppler scale too large (Figure 13B)</li> </ul>
AV VTI	At least in 5CH, 3CH, and RPS, CWD	<ul style="list-style-type: none"> <li>Acquire in at least 5CH, 3CH, and RPS at each visit (Figures 15A to 15C)</li> <li>Do not use angle correction</li> <li>Optimize the alignment between the aortic outflow and the ultrasound beam with proper probe angulation</li> <li>Acquire in CWD with 3-5 profiles in still image</li> <li>Use proper probe angulation to obtain the highest velocity</li> <li>Optimize the Doppler scale, baseline, and velocity accordingly (Figures 15A to 15C).</li> </ul>	<ul style="list-style-type: none"> <li>Only 1 view acquisition available or no RPS view</li> <li>Inconsistent views among visits</li> <li>Large angle (&gt;30°) between the outflow and ultrasound beam</li> <li>&lt;3 CWD profiles available</li> <li>Doppler scale too large (Figure 15D).</li> </ul>
<b>AR-related</b>			
General color Doppler	PLAX, PSAX, 5CH, and 3CH, color Doppler	<ul style="list-style-type: none"> <li>Acquire in all 4 views: PLAX, PSAX, 5CH, and 3CH, regardless of the presence of AR</li> <li>Do not use color variance map</li> <li>If AR (paravalvular and/or transvalvular) is seen, use proper probe angulation to visualize the origin and path of jet</li> <li>Optimize the color sector size to cover the entire jet with the highest frame rate.</li> </ul>	<ul style="list-style-type: none"> <li>Not all 4 views are available</li> <li>Color variance map on</li> <li>Jet origin in mosaic color not visualized; cannot tell whether the AR is paravalvular or transvalvular</li> </ul>
Vena contracta width	PLAX, PSAX, 5CH, and 3CH, color Doppler Zoom mode	<ul style="list-style-type: none"> <li>Acquire in all 4 views: PLAX, PSAX, 5CH, and 3CH</li> <li>If AR (paravalvular and/or transvalvular) is seen, proper probe angulation to visualize the origin and path of jet</li> <li>Optimize the zoom color sector size to visualize the jet neck and jet path with the highest frame rate</li> <li>In case of flying AR jet, off-axis imaging planes are encouraged to visualize the jet path</li> </ul>	<ul style="list-style-type: none"> <li>Not all 4 views are available</li> <li>Color variance map on</li> <li>No Zoom acquisitions</li> <li>Jet neck/path in mosaic color not visualized</li> </ul>
Circumferential extent and vena contracta area (2D)	PSAX, color Doppler, and zoom mode	<ul style="list-style-type: none"> <li>If paravalvular AR is seen, use proper probe angulation to visualize the origin of jet, usually present with mosaic color Doppler signal</li> <li>Sweep mode with multiple cardiac cycle acquisitions (ie, continuous probe tilting/angulations, scanning from the valvular level (higher level of the stent) to the LVOT level (lower level of the stent) (Video 20)</li> </ul>	<ul style="list-style-type: none"> <li>Color variance map on</li> <li>Jet origin in mosaic color not visualized: imaging plane either too high for paravalvular AR or too low for transvalvular AR</li> <li>No zoom or sweep acquisitions</li> </ul>

Continued on the next page

TABLE 6 Continued

View and Modality		ECL Recommendations	Common Pitfalls
CWD density and PHT	5CH and 3CH, CWD	<ul style="list-style-type: none"> <li>If AR (paravalvular and/or transvalvular) is seen, acquire in both 5CH and 3CH</li> <li>Do not use angle correction</li> <li>Optimize the alignment between the AR jet and the ultrasound beam with proper probe angulation; AR velocity is usually high, about 4 m/s; any lower velocity indicates a suboptimal alignment</li> <li>Acquire in CWD with 3-5 profiles in still image</li> <li>Optimize the Doppler scale, baseline, and velocity accordingly</li> </ul>	<ul style="list-style-type: none"> <li>Only 1 view acquisition available</li> <li>Large angle (&gt;30°) between AR jet and ultrasound beam</li> <li>&lt;3 CWD profiles available</li> </ul>
Diastolic flow reversal in proximal descending aorta	SS, PWD	<ul style="list-style-type: none"> <li>Do not use angle correction</li> <li>Place the PWD sample volume carefully at the proximal location of the descending aorta</li> <li>Afterward, acquire in PWD with 3-5 profiles in still image</li> <li>Optimize the Doppler scale, baseline, and velocity accordingly; flow reversal is of low velocity, so the PWD scale needs to be decreased accordingly</li> </ul>	<ul style="list-style-type: none"> <li>Acquired in CWD</li> <li>PWD sample volume placed at the distal descending aorta</li> <li>Doppler scale too large (Figure 10A)</li> </ul>
RVOT diameter	PLAX and/or PSAX, gray scale and zoom mode	<ul style="list-style-type: none"> <li>ROI should focus on the RVOT with reduced depth</li> <li>Clear visualization of the RVOT border throughout the cardiac cycle (Figure 12B, Video 21)</li> </ul>	<ul style="list-style-type: none"> <li>ROI not on RVOT</li> </ul>
RVOT VTI	PLAX and/or PSAX (the same view where the RVOT gray-scale image is acquired (Figures 12B and 12C))	<ul style="list-style-type: none"> <li>Do not use angle correction</li> <li>Place the PWD sample volume carefully just below the pulmonic valve during systole (Figure 12C)</li> <li>Optimize the alignment between the RV outflow and the ultrasound beam with proper probe angulation</li> <li>Acquire in PWD with 3-5 profiles in still image</li> <li>Optimize the Doppler scale, baseline, and velocity accordingly</li> </ul>	<ul style="list-style-type: none"> <li>RVOT gray scale and PWD acquired from different views</li> <li>PWD sample volume placed above the pulmonic valve into the main pulmonary artery</li> <li>Large angle (&gt;30°) between the outflow and ultrasound beam</li> <li>Doppler scale too large</li> </ul>

ECG = electrocardiographic; ROI = region of interest; RV = right ventricular; RVOT = right ventricular outflow tract; TAVR = transcatheter aortic valve replacement; other abbreviations as in Tables 1 and 3.

each individual Doppler echocardiographic parameter on the basis of reliability.

**TRANSVALVULAR AND TOTAL AR ANALYSIS AND ADJUDICATION.** The methodology in analyzing and adjudicating the transvalvular AR is similar to that used for the paravalvular AR, excluding the parameters that do not apply (eg, the circumferential extent). A more granular approach (ie, adding none/trace to the 5-class grading scheme) is perhaps useful given the general observation of low incident and lower severity of transvalvular AR currently (Video 17). The total AR grade (ie, the sum of the paravalvular and transvalvular AR grades) is assessed subjectively, incorporating all measurements and assessments described earlier. Although subjective, as in the present harmonization, the inter-ECL agreement in the total AR with 3-class grading was high (kappa 0.83). The results of transvalvular and total AR severity in the present harmonization are shown in Table 4.

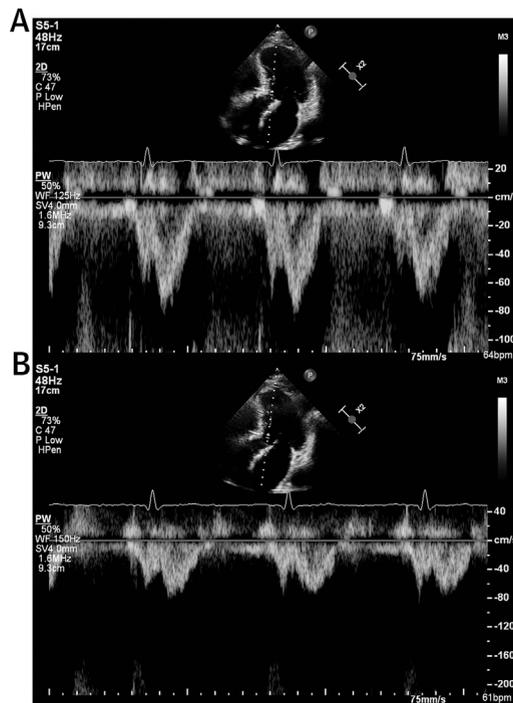
**ADJUDICATED INTENDED VALVE PERFORMANCE.** According to VARC-3 definitions, the composite endpoints include device success at 30 days, where the

intended performance of the valve is assessed with echocardiography on the basis of the following criteria:

- Mean PG <20 mm Hg
- Peak velocity <3 m/s
- Doppler velocity index  $\geq 0.25$
- AR less than moderate

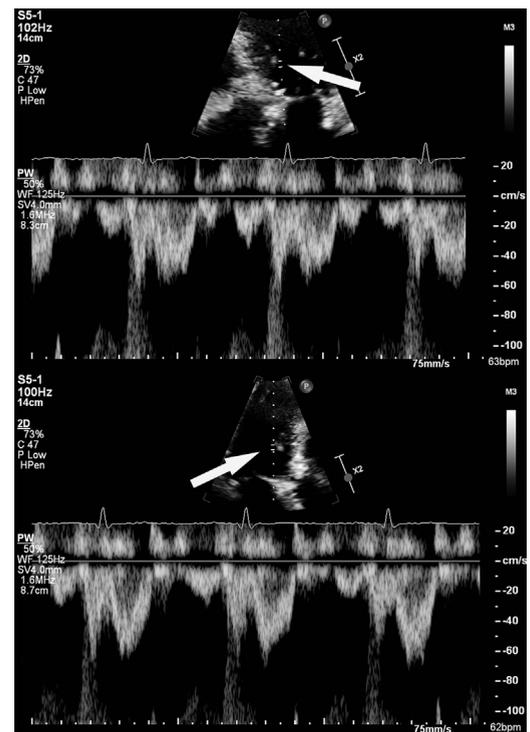
Although there is varied inter-ECL reproducibility in each individual surrogate, especially the LVOT diameter, the overall inter-ECL agreement in adjudicating the intended valve performance was seen to be very high: discrepancy was observed in only 1 of 40 cases (2.5%). The intra-ECL agreements were also similar, with discrepancy seen in 1 to 2 cases (Central Illustration). The (total) AR severity is 1 component of the intended valve performance where the 3-class grading scheme is applied. This is also supported by the higher inter-ECL agreement in paravalvular AR severity with the 3-class grading scheme. The 5-class grading scheme brings expectedly slightly higher inter-ECL variability, yet it can be easily collapsed/reported with the 3-class scheme, and this granular

**FIGURE 13** ECL Recommendations in Optimal Echocardiographic Acquisitions in the LVOT PWD Acquisitions: Doppler Scale



(A) Optimized PWD scale for LVOT PWD acquisition according to the recommendation of the ECL. (B) The PWD scale is too large, which can lead to errors in ECL measurements in the LVOT VTI. Abbreviations as in [Figures 1 and 2](#).

**FIGURE 14** ECL Recommendations in Optimal Echocardiographic Acquisitions in the LVOT PWD Acquisitions: Sample Volume Position



This figure shows a “wrong” PWD sample volume position because it is placed too deep into the left ventricle (arrows) in both 5CH and 3CH views, resulting in very low LVOT velocity. For ECL analysis, such acquisitions are disregarded, leading to an AVA that is not calculable. Abbreviations as in [Figures 1 to 3](#).

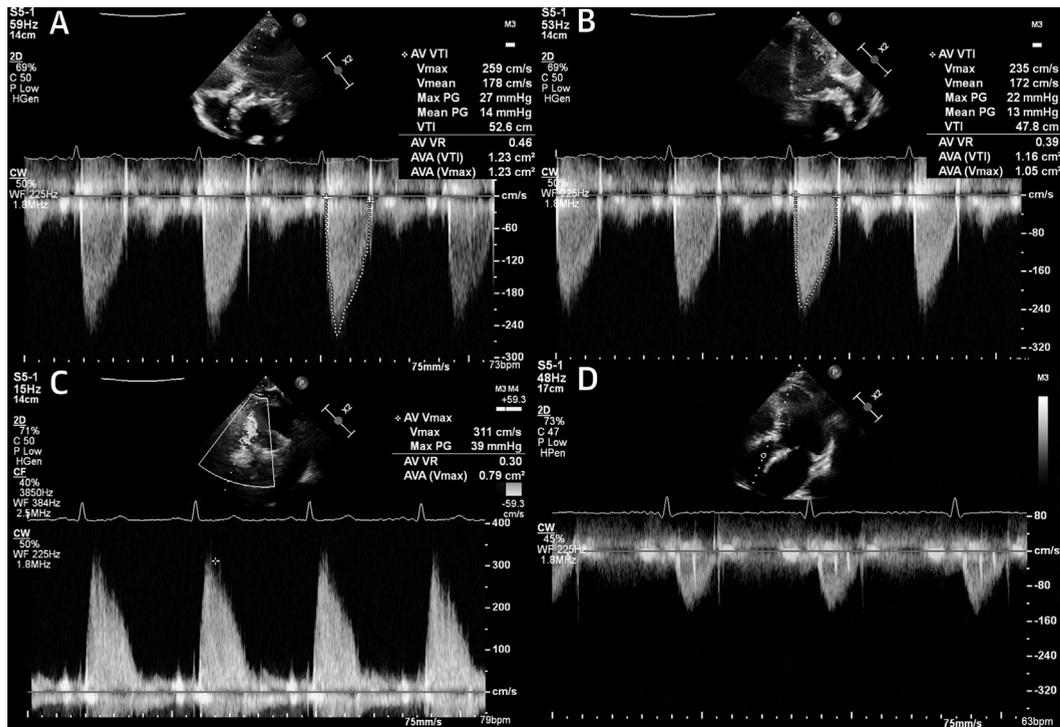
approach can derive benefits in clinical application.<sup>18</sup> In both ECLs, AR severity is reported routinely in both 5- and 3-class grading schemes.

#### OTHER SOURCES OF INTER-ECL VARIABILITY

Besides the ECL methodology, different ECL procedures could be another potential source of variability, including processes of data entry, overread, and data cleaning/quality check. For optimal inter-ECL harmonization, such processes should be aligned as much as possible. In the current harmonization, for pragmatic reasons, not all ECL processes between the 2 ECLs were fully harmonized because these would have required prohibitive additional resources. We expect even higher inter-ECL agreement than currently reported should all processes be fully harmonized.

#### INTRA-ECL REPRODUCIBILITY

Importantly, for the best practice of an ECL, the intra-ECL reproducibility should be assessed regularly (eg, annually). If outliers are identified, retrains and reassessments are warranted, until these features are no longer identified as outliers. High intra-ECL reproducibility is the prerequisite and foundation of inter-ECL harmonization. This is also particularly relevant when a new reader joins the ECL team. Inter-ECL harmonization can be used as an “intra-ECL harmonization” for sufficient internal training of the new team member to achieve similar reproducibility within an ECL.

**FIGURE 15** ECL Recommendations in Optimal Echocardiographic Acquisitions in the Transaortic CWD Acquisitions

The CWD acquisitions in transaortic outflow to determine the highest velocity and VTI *must* be acquired in multiple views with proper probe angulation to determine the highest velocity. This figure shows the CWD acquisitions in (A) the 5CH view with a maximum velocity (Vmax) of approximately 2.5 m/s, (B) the 3CH view with a maximum velocity of approximately 2.4 m/s, and (C) the right parasternal view with a maximum velocity of approximately 3.1 m/s. This clearly shows the importance of the right parasternal view. (D) The CWD scale is too large, which can lead to errors in ECL measurements in the AV VTI. Abbreviations as in [Figures 1 to 3](#).

### ECL RECOMMENDATIONS FOR OPTIMAL POST-TAVR TRANSTHORACIC ECHOCARDIOGRAM ACQUISITIONS

For an accurate and reliable ECL analysis on post-TAVR echocardiographic endpoints, consistent high quality in echocardiographic image acquisition is a must. Some important sources of the (inter- and/or intra-ECL) variability stem from suboptimal-quality echocardiographic acquisition (independent of the acoustic window quality). In current TAVR trials/registries, echocardiograms of multiple visits (typically including baseline and/or screening, discharge, 30-day, 6-month, 1-year, and yearly afterward up to 10-year follow-up) of the patient cohorts are sent for ECL analysis. The consistency in ECL data is also largely driven by the consistency in

echocardiographic acquisition quality across all visits. One typical example is the ECL measurement on the transaortic maximal velocity and PG, derived from tracing the transaortic CWD profiles. If in 1 follow-up visit the transaortic CWD profile is acquired in only apical views and in another follow-up visit it is also acquired in the right parasternal view, which offers much higher maximal velocity than from the apical views, the difference in the transaortic maximal velocity and PG between these 2 follow-up visits cannot be taken as a true change in the transaortic PG, a red flag for bioprosthetic valve dysfunction<sup>13</sup> but actually a “bias” caused by inconsistent echocardiographic acquisitions. Such errors/biases cannot be solved within the ECL system. Therefore, consistency in image acquisition at the trial sites is the key.

**HIGHLIGHTS**

- Inter-ECL harmonization may have regulatory implications on clinical trials and provide standards for the best practice of ECLs.
- Inter-ECL harmonization on the methodology and processes may improve inter-ECL reproducibility.
- Consistent and high quality of echocardiographic image acquisition is essential for accurate and reliable ECL assessments.
- Positive results of the current trans-Atlantic harmonization between 2 major ECLs will hopefully encourage other major ECLs to join this effort.

In current TAVR trials/registers aiming for regulatory submission, a predefined echocardiographic acquisition guideline/manual specified by ECLs must be in place before and during enrollment. In **Table 6 (Figures 13 to 15, Videos 18 to 21)**, the general recommendations from ECL perspectives for optimal echocardiographic image acquisition on the important post-TAVR echocardiographic endpoints are shown, with commonly seen pitfalls. It is of paramount importance that all site personnel involved in echocardiographic acquisitions of a given TAVR trial are trained on the ECL echocardiographic acquisition guideline/manual to ensure consistent and high-quality echocardiographic image acquisitions of all visits for accurate and reliable ECL assessments.

**IMPLICATIONS FOR CLINICAL ECHOCARDIOGRAPHY LABORATORIES**

Although this review mainly focuses on the harmonization process between regulatory-complied ECLs for adjudicating post-TAVR echocardiographic endpoints, some key learning points can be derived for clinical echocardiography laboratories for the assessment of post-TAVR echocardiograms:

**STANDARDIZATION OF MEASUREMENTS OF AVA AND HEMODYNAMICS.**

- Measure the LVOT diameter from the outer edge to the outer edge at the prosthesis inflow edge.
- Position the PWD sample volume just on the prosthesis inflow edge (stent ventricular end) and avoid signals with opening or closing clicks.

- Use the LVOT diameter measured at early follow-up after TAVR (eg, at 30-day follow-up) for all subsequent follow-ups in a given patient.
- Perform systematic multiview interrogation with CWD for transaortic flow velocity.
- Measure and report the Doppler velocity index.
- Use a multiparametric approach, including peak velocity, mean PG, AVA, AVA index, and Doppler velocity index, to assess the hemodynamic performance.

**STANDARDIZATION OF ASSESSMENT OF PARAVALVULAR AR.**

- Use multiview interrogation with color Doppler imaging to assess paravalvular AR, including the PLAX, PSAX, 5CH, and 3CH views.
- Quantitative measures, such as the proximal isovelocity surface area, are very rarely feasible for assessing paravalvular AR.
- One should not rely on a single parameter to adjudicate paravalvular AR severity because all qualitative and semiquantitative parameters have substantial limitations in terms of accuracy and reproducibility.
- Use a multiparametric approach, including qualitative parameters (jet path along the stent and jet number), jet width/LVOT, vena contracta width, circumferential extent, and pressure half-time to adjudicate the paravalvular AR severity. The other parameters appear to have limited value because of limited feasibility or reproducibility.

**CONCLUSIONS**

To consider data from different ECLs comparable, an inter-ECL harmonization process is needed. The present trans-Atlantic harmonization between 2 established ECLs in the field of TAVR resulted in good inter- and intra-ECL reproducibility in the essential post-TAVR echocardiographic endpoints. These results support the implementation of an inter-ECL harmonization process, which may have logistic and regulatory implications for the realization of TAVR trials.

**ACKNOWLEDGMENTS** The statistical and data management departments of Cardialysis are gratefully acknowledged for supporting this study.

**FUNDING SUPPORT AND AUTHOR DISCLOSURES**

This study was self-funded by the participating institutions. Dr Ren has received institutional contracts for echocardiography core laboratory analyses with Boston Scientific, Cardiawave, Edwards Lifesciences, and NVT/Biosensors, for which she has received no personal compensation; and has received speaker fees from Abbott. Dr Van

Mieghem reports institutional grant support from Abbott, Boston Scientific, Biotronik, Edwards Lifesciences, Medtronic, PulseCath, Daiichi Sankyo, Teleflex, AstraZeneca and scientific advisory fees from Siemens, Pie Medical, Abbott, Boston Scientific, Medtronic, PulseCath, Daiichi Sankyo, Amgen, Teleflex, Abiomed, JenaValve, Anteris. Dr Spitzer has received institutional contracts for which he has received no direct compensation with Boston Scientific, Cardia-wave, Edwards Lifesciences, Medtronic, Shanghai MicroPort Medical, NVT, Pie Medical Imaging, and Siemens Healthcare. Dr Pibarot has received funding from Edwards Lifesciences, Medtronic, Pi-Cardia, and Cardiac Phoenix for echocardiography core laboratory analyses and research studies in the field of transcatheter valve therapies, for which he has received no personal compensation; and has received

lecture fees from Edwards Lifesciences and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**KEY WORDS** aortic, core laboratory, echocardiography, harmonization, transcatheter

**APPENDIX** For an expanded Methods section as well as supplemental figures, a table, and videos, please see the online version of this paper.