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Quantitative aortography assessment of aortic regurgitation. Insight into a novel technique

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Running title: Quantitative assessment of aortic regurgitation

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Abbreviations

AR = aortic regurgitaion

DSA = digital subtraction aortogram

LV = left ventricle

LVOT = left ventricle outflow tract

MSCT = multi slice computed tomography

PVL = paravalvular leak

TAVI = transcatheter aortic valve implantation

TEE = transesophageal echocardiogram

TTE = transthoracic echocardiogram

VD = Videodensitometry

Classifications: Imaging modalities; TAVI; Non-invasive imaging

Introduction

Transcatheter aortic valve implantation (TAVI) is undeniably invading the "surgical" space and expanding its indication. Over the last 5 years, there has been a real revolution in TAVI technology with the introduction of newer devices that aimed to simplify the procedure [1]. These swift advances have transformed the landscape in structural heart disease and culminated in a broader use of TAVI in clinical practice [2, 3]. The procedure is not only spreading worldwide but is also becoming less aggressive for the patient with the so-called "minimalist approach".

With the rise and consolidation of this minimally invasive era of TAVI procedures, precluding general anaesthesia, the use of transesophageal or transthoracic echocardiogram during the procedure becomes restricted. However, a thorough assessment for (paravalvular) aortic regurgitation (AR) is important immediately post TAVI, since more than mild AR affects short- and long-term clinical outcomes [4-6] and can be corrected during the procedure (e.g. with a valve-in-valve implant, balloon post dilatation or even snaring) or even in the chronic stage (percutaneous closure of paravalvular leak)[7]. Thus, aortography (re)emerges as a valuable tool for periprocedural AR assessment, as a surrogate technique of AR assessment, whenever transthoracic echocardiography is not available or doable in the interventional suite.

The low reproducibility of Sellers criteria[8], a subjective method to quantify aortic regurgitation, begets the need for an objective and precise quantification of aortic regurgitation such as that of video-densitometry. This objective method relies on aortography and can accurately quantify the transvalvular or paravalvular AR [9-11].

The quantitative AR assessment using the aortogram with videodensitometry was tested in vitro, in animal models and validated in clinical trial and real-world populations, either evaluated in comparison with echocardiogram or magnetic resonance imaging [9-15].

In this "insight" review we describe the evolution of this novel technique towards its complete validation in the clinical setting for TAVI, as well as the present and future application of the method in clinical trials and in assessment of regurgitation in other valve procedures, such as mitral and tricuspid.

History of videodensitometry

The use of the so called Roentgen videodensitometry was introduced in the 1960's by Earl H. Wood [16] from New York, USA and Paul H. Heintzen [17] from Germany. The simple method for the recording of radiopaque dilution curves during angiocardiography consisted in the amalgamation of the consolidated techniques of angiocardiography and dye-dilution method. The use of radiopaque angiographic contrast medium as the "indicator" and the continuous recording of the changes in the x-ray density of different heart chambers (or vessels) – provoked by the passage of the contrast media – could produce a refined quantitative evaluation of the images – e.g. regurgitation.

In the seventies, with the use of the cineangiography, Dr. Bernuth, together with Dr. Wood have undertaken an experimental procedure to test videodensitometry for the assessment of AR [18]. In 4 closed chest dogs (with provoked aortic insufficiency by valvotomy), the investigators injected radiopaque material in the aorta, recording the angiograms on magnetic tapes – producing time-density curves (videodensograms). The so-called aortic regurgitation index was calculated as the ratio of the area under the time-density curves of the aortic root

and left ventricle videodensograms. The results were then compared with the consolidated upstream-sampling dye-dilution technique, and with data from a simultaneous assessment with an electromagnetic aortic flow transducer, previously implanted in the dogs. After a series of assessments with different heart rates, the investigators found that videodensitometric assessment of regurgitation greatly correlated with the assessment of the electromagnetic flow meter (r=0.95) and with upstream-sampling dye-dilution technique (r=0.92). The authors concluded that "VD is a sensitive method for detection and estimation of the severity of AR presumably applicable in the clinical setting".

It was more than a decade later that the technique was applied with a computer-based analysis of the time-density curves in human. In 1986, Klein et al. tested the concept of videodensitometric assessment of AR in human using digital subtraction aortogram [19]. The authors performed aortograms in 17 patients with varying degrees of aortic regurgitation and in 4 control patients. After acquisition of the images, the computer generated a display, with time as a function of cardiac cycles from the start of the contrast injection in the x-axis and the summation of density within the two regions of interest (aortic root and left ventricle) on the y-axis (**Figure 1**). Then the computer generated a separate curve corresponding to the ratio of the two previous density curves from the left ventricle and aortic root; the ratio at the end of the injection was then the result of the videodensitometric assessment in this particular study (**Figure 2**). The authors could show the discrimination of quantitative videodensitometric regurgitation among the different categorical classes of regurgitation by blinded visual assessment of the cineangiographies, suggesting its potential clinical use. Since this correlation was made with (although blinded) subjective visual assessment, one year later Grayburn et al. compared the quantitative assessment of regurgitation in the angiography with the objective assessment of electromagnetic flow (EMF) [20]. For that, the authors used 6 dogs instrumented with an EMF probe in the ascending aorta and produced

varying degrees of regurgitation by a basket catheter. Applying the same methodology of time-density curves (**Figure 3**) the authors could show an excellent correlation between videodensitometry and EMF (r=0.94) – **Figure 4**. Based on that, the authors concluded that aortic regurgitation fraction could be accurately quantified by analysis of time-intensity curves generated from the aorta and left ventricle after digital subtraction angiography.

Rise of echocardiography and dethrone of aortography for regurgitation assessment

In the 1980's growing adoption of echocardiography and introduction of new parameters for non-invasive assessment of heart valves diseases, challenged the role of invasive angiography for the diagnosis and decision-making processof valvular heart disease. In a single centre experience of 305 patients that were operated in a year for either mitral or aortic valve disease, 184 did not undergo catheterization pre-surgery; there was no difference in surgical mortality, 2-year follow-up mortality nor in 2-year presence of symptoms [21]. Since the patients underwent non-invasive methods of assessment of disease severity and surgical planning, these results pointed out the lack of need for catheterization prior to valve replacement procedure [21]. Later, with Doppler echocardiogram, similar findings were observed in different studies confirming the non-requirement of catheterization for valve surgeries [22, 23].

Echocardiographic assessment of regurgitation post TAVI

Nowadays, TAVI has substantially spread worldwide and the introduction of new designs aiming to simplify the procedure, reduce complications and improve procedural outcomes. One of the main issues with the aortic prosthesis for TAVI is the AR, mainly represented by

the paravalvular regurgitation – which leads to a constant focus on the engineering of new devices.

Aortic regurgitation (central or paravalvular) is a common condition after the prosthetic valve implantation and can affect up to 70% of patients [24]. Regurgitation can be due to multiple factors related to the device, the patient or even to the operator. Among the most likely causes we can name the prosthesis type, degree of native valve calcification, implantation depth, annulus size (limited sizes of prostheses) and also the method of sizing the annulus (either with transthoracic [TTE] or transesophageal [TEE] echocardiogram or with multi-slice computed tomography [MSCT] scan) [25-27].

Not only AR is common following TAVI, but the severity of AR relates closely to clinical outcomes[24]. Aappropriate and accurate assessment of regurgitation becomes essential during the procedure.

AR assessment after the implantation of a bioprosthesis is more demanding and difficult than for a native valve evaluation [28] and is still the Achilles' heel of TAVI [29]. Several reasons are responsible for making this quantification of regurgitation a challenge with echocardiogram: (i) patient-specific aortic annular and/or leaflet geometry, especially in calcified and degenerated cusps; (ii) calcification that contributes to incomplete apposition of the device to the annulus, and ultrasound backscattering of the metallic struts of the device that may attenuate the ultrasound signal; (iii) paravalvular regurgitant jets may be single or multiple, and are often crescent and eccentric, following serpiginous trajectories, with an axis of flow that may not be well assessed through standard Doppler imaging windows and (v) the lack of a standardized reference to consistently define PVR severity, which is still a major issue [29, 30]. Thus, conventional methods applied to quantify regurgitation in the native valve such as

pressure half time, *vena contracta* location and jet width may not be reliable for post TAVI assessment.

In addition, the assessment is majorly influenced by the imaging plane and also the location of the regurgitant jet (**Figure 5**). As shown in the figure, jets in certain locations are not assessable in certain acoustic windows of the echocardiogram [31]. Another important aspect of the echocardiographic assessment of regurgitation after TAVI is its low reproducibility. It has been demonstrated that even between core laboratories, the agreement on AR assessment was weak. Hahn et al. [32] performed an analysis comparing the agreement in AR assessment between a consortium composed of three echocardiographic core laboratory directors and the Placement of Aortic Transcatheter Valves (PARTNER) IIB trial core laboratory. The authors documented that both for the 4-class grading of PVR (Kappa=0.48) and for the 7-class grading (Kappa=0.52) the agreement was considered weak [33] (**Figure 6**).

Lately, the Valve Academic Research Consortium 2 (VARC-2) proposed in their consensus document some approaches for assessing PVR post TAVI. However, these methods have yet to be validated and may be insufficient to overcome all of the specific limitations imposed on echocardiography in TAVI patients [34].

The minimalist TAVI era and the unmet need for AR assessment

In the early days, following Cribier's first-in-man report of a TAVI in 2002 [35], the procedure was performed worldwide mainly in inoperable patients, usually under general anaesthesia with the guidance of a TEE [36].

Currently, percutaneous transfemoral TAVI is the preferred treatment strategy for symptomatic aortic stenosis patients, even those at low surgical risk [2, 3]. With the

improvement in devices, growth of clinical experience and broader indication of TAVI, the procedure had to be majorly simplified [37], and the so-called minimalist TAVI became the mainstream. This simplified approach for TAVI has been shown to be safe and effective and is already the routine in many centres [38-40].

The minimalist TAVI comprises a series of simplification within the pre-procedure, intra-procedure and follow-up. For a TAVI to be considered minimalist, the most important changes during the procedure are the maximum use of transfemoral approach, the local anaesthesia (with or without patient sedation), the minimum restricted insertion of catheters and lines, the true percutaneous approach (meaning the use of vascular closure devices and percutaneous bailout management in case these devices fail) [37].

The use of local anaesthesia has some advantages, compared to the general anaesthesia: (i) the patient tends to maintain hemodynamic stability during the entire procedure, thus with less need for inotropic agent;, (ii) the operators are able to continuously assess neurological status of the patients as well as easily assess pain – which is a valuable marker for vascular complications; and (iii) it reduces the length of hospital stay which, combined with the other advantages, makes local anaesthesia a cost-effective alternative to TAVI with general anaesthesia [37, 41].

With the preclusion of general anaesthesia, TEE use in the procedure becomes limited, leaving the PVL assessment at a later stage – to post-procedure TTE. However, the use of a TTE-guided TAVI has shown major detection of intraprocedural PVL-related events, defined as a combination of mild PVL, need for intraprocedural post dilation and for second valve insertion [42]. Therefore the use of a simplified and intraprocedural assessment (angiographic) of post-implantation PVL is generally adopted in the minimalist approach [37].

Hemodynamic has been studied recently as an adjunctive assessment after TAVI as a surrogate for regurgitation. Namely we have: the aortic regurgitation index [43] and the diastolic pressure-time index [44]. These two methods take into account the pressures measured in the aorta and left ventricle after the procedure. Although not thoroughly validated and manly presented as a dichotomous information, they may be integrated with multimodality imaging for the decision-making process during the procedure.

Contrast angiography – from visual to objective evaluation of regurgitation

Sellers proposed the semi-quantitative method of AR grading in 1964 [8]. Originally this visual assessment method graded the severity of aortic insufficiency in "+", ranging from 1+ to 4+. More recently, Frick et al. adapted that assessment for a post-TAVI scenario [45]. The details of these visual peculiarities of each strata of regurgitation are shown in **Table 1.**

However, its somewhat subjective nature imposes bias on this assessment, mainly related to the reproducibility of the technique. An analysis involving 4 experienced interventional cardiologists blinded to any other type of AR assessment showed a poor agreement of assessment. The kappa coefficients from their assessment results ranged mostly from 0.47 to 0.60, which are considered weak agreements [33]. A quantitative objective way to assess regurgitation, precluding this reproducibility drawback was mandatory. Hence, we saw the revival of the aortographic assessment of regurgitation using videodensitometry.

Contemporary quantification of aortic regurgitation from aortogram – the Phoenix's rebirth from its ashes.

With adopted valve regurgitation assessment by the echocardiogram – aortogram was pushed back as a historical method of assessment. However, with the increase in TAVI procedures, and even more, with the rise of the minimalist TAVI approach, the use of aortogram to assess PVL became pervasive again. Quantification of aortic insufficiency using videodensitometry has evolved from the early days, with improvements, into what we use nowadays: the contemporary quantitative aortogram. Chronologically the assessment of post-TAVI PVL in the entire left ventricle (LV) by videodensitometry preceded the assessment restricted to the left ventricle outflow tract (LVOT) approach[11, 46].

From the left ventricle to the outflow tract. The LV videodensitometry was the first to be used in the contemporary analyses of AR aortography. The entire left ventricle represents the region of interest for the analyses[46]. From the aortogram images, the regions to be analysed are drawn including the contrast-filled aortic root and the entire left ventricle. The software (CAAS A-Valve, Pie Medical Imaging, Maastricht, the Netherlands) then stabilises the image by subtracting the permanently radiopaque images (static background) before producing five time-density curves derived from the reference area (aortic root), and from the left ventricular base, mid and apex and overall **(Figure 7)**. A great number of mathematical calculations with all data derived from the time-density curves were performed in that pilot study. Of note in the evolution of the technology, the investigators performed the ratio between the areas under the curves (RAUC) and the quantitative regurgitation analysis (qRA) index. The qRA index was calculated from the first three cardiac phases after the arrival of contrast in the aortic root by weighting the RAUC with increasing apical depth and longer duration of contrast within the LV (analogous to Sellers' grading method).

The authors showed a good correlation of the results of both the qRA index ($r=0.83$, $p<0.001$) and RAUC ($r=0.81$, $p<0.001$) with the Sellers' grade of AR assessed by 4 independent and

blinded observers. The most important findings of the study, however, were the reproducibility assessment of both methods: Sellers' and videodensitometry. The agreement on the analyses of the Seller's grade was weak [33], with a Kappa statistics ranging from 0.47 to 0.72 (**Table 2**). In contrast to that, the correlation between two observers for both qRA index assessment and RAUC was excellent, both $r=0.98$, $p<0.001$ – showing the great reproducibility of the technique.

Although the technique has shown to be highly reproducible and correlated with visual assessment of regurgitation, the weakness of the method was the feasibility of analysis – 69% of the aortograms in this particular study [46]. The basis of videodensitometry is to assess changes in density in two particular regions (i.e. left ventricle and aortic root) induced by opacification from the injected angiographic contrast medium. Thus, the overlapping of those regions with another region to be contrasted (e.g. the descending aorta) would compromise the isolated assessment of the density in the regions of interest, thus compromising the accurate assessment of regurgitation. This initial study by Schultz et al. had acquisition guidelines to avoid the overlap. However, specifying an overlap-free projection was not simple because of variability in patient anatomy – hence, the low feasibility of analysis. In order to overcome this overlapping issue, a new study using only the left ventricle outflow tract as the region of interest was planned, examining the feasibility and reproducibility of this approach, called LVOT-AR [11].

Using retrospective data from the Brazilian TAVI Registry [47], Tateishi et al. assessed 182 angiographies with both qRA and LVOT-AR. Briefly the LVOT-AR technique uses the same concept as the RAUC of the entire LV videodensitometry, but confined to the third basal part of the LV – the outflow tract [11]. The anatomical advantages of using LVOT-AR instead of qRA are shown in **Figure 8**.

For this analysis, since data was retrospectively assessed, no acquisition guidelines were followed. The feasibility of LVOT-AR was shown in comparison with the feasibility of qRA in the same cohort of patients. A total of 137 were analysed with both techniques (qRA and LVOT-AR). Only 54 cases (29.7%) were analysable using qRA, as opposed to 118 cases (64.8%) that could be analysed using LVOT-AR– showing the higher yield of LVOT-AR for the analyses. LVOT-AR was also shown to be highly reproducible. The inter-observer correlation coefficient was 0.95 ($p<0.0001$) and the intraobserver was 0.97 ($p<0.0001$) [11].

In vitro validation. Although not in a chronological order of events, the investigators performed the in vitro experiment following the experience acquired during the analysis of aortograms stemming from clinical practice. With the success of the method and the knowledge of the three modalities of videodensitometric evaluation of regurgitation, namely (i) RAUC or LV-AR, (ii) LVOT-AR and (iii) qRA, Abdelghani et al. sought to determine the accuracy of the results of videodensitometry in a controlled environment of regurgitation (a mock circulation system with a transcatheter heart valve) [12]. The mock circulation system (shown in **figure 9**) was set-up to simulate the left ventricle and the aortic root with a bioprosthetic valve in between. It consisted in an elastic silicone tube corresponding to the aortic root, heart valve module (a 25 mm diameter plastic tube in which a prosthetic valve was deployed), and a rigid polycarbonate tube including a servomotor-operated piston pump acting as the left ventricle. The system was kept warm (body temperature - 37 degrees Celsius) submerged in a 30-litre water bath. A pulsatile cardiac output of 5 L/min was generated at a rate of 75 cycles/min with a corresponding ISO 5840-compliant flow curve (35% systole and 65% diastole per cycle).

To create a paravalvular regurgitation observed after implantation of a prosthetic transcatheter valve, a radiolucent screw was inserted radially into valve module and advanced

to deform the stent of the valve (26 mm SAPIEN XT device - Edwards Lifesciences, Irvine, CA, USA) (**Figure 9 C and D**). Thus, a predicted regurgitation could be created, controlled by an operator with real-time visualization of the trans sonic measured regurgitation (Transonic 28 PAU, with TS 410 flowmeter; Transonic Systems Inc., Ithaca, NY, USA). A total of 12 experiments were performed with increasing degrees of regurgitation fraction [12]. For both LV-AR (regression line = 0.845x -6.011) and LVOT-AR (0.816x -3.049) the correlation with regurgitation fraction was strong (Spearman r^2=0.958 and 0.964, respectively) – **Figure 10**. Also, both methods (LV-AR and LVOT-AR) were considered not different (p=0.514) and were strongly correlated (r^2=0.992, p<0.001, y = 0.967x + 2.718), in the absence of any overlapping structures.

Establishment of number of cardiac cycles to analyse. Another important aspect of this controlled experiment was the determination of the number of heart beats to be used for a proper analysis of regurgitation with videodensitometry. Although even with a single cardiac cycle the correlation of videodensitometry with RF could be documented, there was a stepwise increase in the correlation coefficients from one to 4 cardiac cycles. With 3 cardiac cycles the correlation was already very strong (r^2 higher than 0.9) with no meaningful increment in accuracy with further increase in the number of heart beats (**Figure 11**).

In vivo validation – animal study. The investigators also sought to test the videodensitometry technique in vivo, with controlled increasing regurgitation. In order to conduct that experiment, Modolo et al. [48] used long peripheral Wallstents with increasing diameters (6, 7, 8 and 10 mm). The Wallstents were inserted across the aortic valve of an anaesthetised pig over a wire inserted in the LV and were partially deployed to induce a regurgitation – resulting in a fully unconstrained device across the valve, impeding the coaptation of the leaflets. After deployment, the Wallstents were re-sheathed and replaced by

a larger device to induce progressively more AR. The schematic representation of the procedure and the results of the quantitative assessment of regurgitation are shown in **Figure 12**. The authors could determine an increase in the quantitative amount of regurgitation related to the increase of the Wallstent diameter.

Clinical use and implications of videodensitometry

Prognostic value. It is known that paravalvular regurgitation following TAVI majorly influences clinical outcomes, especially mortality [4-6]. Thus, the use of quantitative aortogram to assess regurgitation post-TAVI was warranted. This work was performed by Tateishi et al. [11]. In an analysis of the Brazilian TAVI Registry [47], the investigators assessed the regurgitation post-TAVI evaluated by an academic core laboratory.

With a mean follow-up of 609 days and 112 patients with LVOT-AR assessed, the investigators could determine a cut-off value of 17% of regurgitation, by a receiver-operating characteristics curve, for best predicting all-cause mortality. In fact a time-to-event analysis could show a significant separation of survival curves (**Figure 13**). Even in a Cox regression adjusted model, LVOT-AR above 17% was considered an independent predictor of all-cause mortality (hazard ratio = 2.40, 95%CI 1.27 – 4.54, p=0.007). Similar results were found in a cohort of Japanese patients undergoing TAVI (n=51). Using the same cut-off point, the investigators identified higher 1-year all-cause mortality in those with LVOT-AR > 17% (59.5% versus 16.6%, p=0.03)[15] – **Figure 14**. These studies showed a close link between all-cause mortality after TAVI procedures and regurgitation assessed by the quantitative aortogram method.

With regard to the categorical ordinal assessment of regurgitation, even mild amounts of paravalvular regurgitation are associated with poor outcomes [5]. Nowadays, the impact of a mild regurgitation could be evaluated specifically in a sensitive way, in contrast to the past, when mild regurgitation was frequently mixed and merged with trace, none or in particular when a moderate AR was misclassified as mild. Thus, a more granular approach, such as the quantitative continuous method, given in percentage, might better assist physicians and more accurately discriminate within the trace / mild / moderate categories of regurgitation.

Validation and correlation with echocardiogram and MRI

Echocardiogram. Association of quantitative results of videodensitometry were made with both transthoracic and transesophageal echocardiogram. Using a cohort of 399 patients from the Brazilian TAVI Registry [47], Abdelghani et al. [10] were able to retrospectively evaluate 228 aortograms that were considered analysable for videodensitometry. Comparing the values of quantitative assessment of regurgitation (LVOT-AR) with the strata of regurgitation by pre discharge transthoracic echocardiogram, the investigators found that: LVOT-AR was 0.10 [0.04–0.16], 0.12 [0.06–0.19], and 0.25 [0.16–0.34] in none-trace, mild and moderate-severe AR (Figure 13). Applying the Receiver-operating characteristics curve statistics, the authors encountered a cut-off value of > 0.17 for defining echocardiographic moderate to severe regurgitation (**Figure 15 B and C**).

A cohort of 74 consecutive patients from a single centre (Yamaguchi University Hospital) was evaluated to investigate the association of transesophageal echocardiogram parameters with the quantitative assessment of regurgitation using the aortogram (LVOT-AR) [15]. From 51 patients that had a TEE performed, the investigators could discriminate different and crescent values of LVOT-AR in the strata of regurgitation assessed by circumferential extent

on the intraprocedural TEE (**Figure 16 A**). Also, an association of the continuous values of LVOT-AR and circumferential extent by TEE was observed (**Figure16 B**). These studies have shown that both TEE and TTE findings on aortic regurgitation post-TAVI greatly correlate with the continuous findings of regurgitation assessed using only the aortogram with LVOT-AR.

Cardiac Magnetic Resonance. Following the validation of videodensitometry (LVOT-AR) with both TTE and TEE, Abdel-Wahab et al. used the videodensitometry technique to compare its results with the findings of the quantitative and reproducible assessment of regurgitation with cardiac magnetic resonance (CMR) [9]. The investigators used a subset of 135 patients that underwent a TAVI procedure and in whom CMR was performed after the procedure. CMR data were analysed by two independent and experienced observers in imaging. The aortic regurgitation fraction by CMR (CMR-RF) was evaluated as a percentage value as follows: regurgitant volume divided by the total forward volume. Comparing the two continuous assessments of quantitative regurgitation (LVOT-AR and CMR-RF) the investigators found a reasonable correlation (Pearson statistics $r=0.78$, $p<0.001$) – as seen on **Figure 17**. Taken together with the findings of LVOT-AR validated against echocardiogram, these results showed a good correlation of LVOT-AR with both categorical (TTE and TEE) and continuous (CMR) classification of regurgitation. Following this publication, Samir Kapadia et al. wrote a nice editorial about the paper entitled "The pursuit of Perfection" referring to the implementation of videodensitometry to assess regurgitation post TAVI[49]. A brief comparison of the methods for assessing regurgitation after TAVI is shown in **Table 3**.

Application in clinical trials and clinical practice

Use of LVOT-AR in clinical trials. Following its extensive validation (i) in vitro, (ii) with echocardiogram and (iii) with CMR, LVOT-AR assessment was applied in the context of a

major clinical study. Modolo et al. conducted a post hoc analysis of 472 unselected patients of the multicentre RESPOND (Repositionable Lotus Valve System—Post-Market Evaluation of Real-World Clinical Outcomes) study [13]. Both evaluations of echocardiogram and LVOT-AR were performed by an independent academic core laboratory, blinded for the other method analysis, making these results unbiased for observational interferences. The investigators showed that here was a significant LVOT-AR difference across the different strata of PVR by transthoracic echocardiogram: (2.0% [0.0% to 4.0%] vs. 3.0% [1.0% to 7.0%] vs. 3.0% [1.75% to 9.25%] vs. 7.0%; $p < 0.001$) for none, trace, mild, and moderate PVR, respectively; as no severe regurgitation was observed. Its use in a major clinical study reinforced the previous findings and showed the feasibility of using it in the context of major clinical trials on TAVI. A previous work by Miyazaki and Modolo et al. has already shown the difference in quantitative regurgitation on different valve types (first versus second generation) [50] (**Figure 18**).

Possible use for guidance of post-dilatation. Although newer generation and new commercially available valves are designed with better paravalvular sealing features, balloon post-dilatation is still performed in up to 17% of TAVI procedures [51, 52]. However, with the minimalist approach for TAVI, without intraprocedural echocardiogram, the evaluation of PVR needs to be done by the angiogram. Miyazaki et al. evaluated the quantitative changes in paravalvular regurgitation resulting from post dilatation of the valves assessed by videodensitometry (LVOT-AR) [53].

Analysis of 61 patients from the Brazilian TAVI Registry – in whom balloon post-dilatation was performed – showed an improvement in LVOT-AR from 24 % (18% - 30.5%) to 12% (5.5% - 19%), $p<0.001$. Despite the small sample size, there was a clear numerical difference in 4-year all-cause mortality between those with final LVOT-AR > 17% (34%) and those

with LVOT-AR < 17% (19%), p=0.11 (**Figure 19**). This study evidenced the potential role of quantitative assessment of regurgitation with videodensitometry in evaluating the need for balloon post-dilatation after TAVI. Although the present "insight" document focused on quantitative aortogram for the assessment of regurgitation post-TAVI, the technique is feasible also in patients having undergone surgical implantation of aortic valves. Recently Teixeirense et al. demonstrated the feasibility of performing the analysis in a patient with a late paravalvular regurgitation more than 10 years after surgical aortic valve replacement. The authors showed a decrease in the regurgitation from 16% to 1% right after the closure of the paravalvular tunnel with a plug [7].

Of course, the evaluation of regurgitation after TAVI should not rely solely on videodensitometry, but on the consistency of multimodality assessment, such as visual angiographic assessment, echocardiography (when feasible and available, with an experienced operator) and even hemodynamic.

The feasibility caveats. The evolution of the videodensitometry assessment of aortic regurgitation, going from the analysis of the entire LV (qRA) to the analysis of only the left ventricle outflow tract (LVOT-AR) increased the feasibility of analysis, but did not solve the issue. Recent studies have shown that retrospective analysability of LVOT-AR are still moderate (still with overlap of the descending aorta with the LVOT), thus compromising the evaluation of the entire studied population. For example, the feasibility of analysis in the major RESPOND study was 57.5%. To overcome this issue, the investigators sought to determine whether a simple protocol for image acquisition would eliminate the overlapping of the region of interest (LVOT) and reference area (aortic root) with other contrasted segments such as the descending aorta (**Figure 20**).

Recently, a single centre experience showed that the retrospective feasibility of analysis improved from 57% to 100% after the implementation of a protocol for acquisition guided by pre-procedural computed tomography [54] - **Figure 21**. Subsequently, Modolo et al. conducted a multicentre registry to determine the feasibility of analysis with a predefined protocol of acquisition (the ASSESS-REGURGE[55]). The selection of the best projection for acquisition could be determined either from computed tomography, or based on a simple visual estimation of the position of the descending aorta made traceable by the radiopaque presence of the delivery system in the descending aorta – the so-called Teng's rule [56]. After enrolment of 354 consecutive patients, the investigators identified a high feasibility of analysis of 95.5% (95% CI from 93.2% to 97.5%). This showed that a simple acquisition protocol based on different pre-planning techniques (either CT or visual estimation) yielded a high feasibility of analysis (close to 100%), in a multicentre experience.

Future perspectives

Videodensitometry technique for analysing aortic regurgitation was introduced more than 50 years ago, but only recently had its relevant application in the clinical area. After intense validation both in vitro and in the clinical field, the next step will be to show its feasibility inside the cath lab, and not only as a retrospective core laboratory tool. With that goal in mind, we are currently conducting the OVAL (Online Videodensitometric Assessment of Aortic Regurgitation in the Cath-Lab) study (NCT04047082), which is evaluating the feasibility of the online assessment. The assessment is performed in real-time (online) with the procedure and the results will be compared with the results from the offline core laboratory experienced examiner (RM). The results from OVAL are eagerly awaited since they may usher videodensitometry into daily clinical practice for TAVI procedures. Together

with the clinical practice implications, videodensitometry could also be applied in major clinical trials to objectively compare the sealing feature devices of newer generation valves. In addition, it could be an adjunctive tool for assessing regurgitation in TAVI: (i) for aortic regurgitation patients, (ii) for novel bioengineered or biorestorative leaflets and (iii) for bicuspid aortic valve patients. Besides Amsterdam, other centres are implementing the online system in their cath labs, such as Toulouse, France and Galway, Ireland. The installation of the software for offline analysis is simple and a trained technician or an operator can perform the analysis in 2 to 3 minutes in average.

On-going work is aiming to validate the same technology for application in the mitral field, which is increasing after the development and introduction of novel devices for mitral regurgitation in interventional cardiology [57] – **Figure 22**.

Conflict of Interest Statement

Dr. Modolo received research grant from Biosensors and SMT outside the submitted work. Carl Schultz have received research grants and honoraria from Abbott Vascular unrelated to the this work. Jean-Paul Aben is an employee of Pie Medical Imaging B.V. Dr. Brito Jr is proctor for Medtronic and Edwards LifeSciences. Cherif Sayoun is a full-time employee of Philips Medical Systems. Prof. Van Mieghem received institutional research grants from Abbott, ACIST, Boston Scientific, Medtronic, Edwards and PulseCath BV and received advisory fees from Abbott, ACIST, Boston Scientific, Medtronic, and PulseCath BV. Prof. Serruys reports personal fees from Abbott Laboratories, personal fees from AstraZeneca, personal fees from Biotrinik, personal fees from Cardialysis, personal fees from GLG Research, personal fees from Medtronic, personal fees from Sino Medical Sciences Technology, personal fees from Société Europa Digital Publishing, personal fees from Stentys France, personal fees from Svelte Medical Systems, personal fees from Philips/Volcano, personal fees from St. Jude Medical, personal fees from Qualimed, personal fees from Xeltis, outside the submitted work

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T**able 1.** Adapted Sellers degrees of aortic regurgitation.

Grade of regurgitation	Description of the visual assessment of the aortogram
grade 0	absence of AR
grade 1	small amount of contrast entering the LV during diastole without filling the entire cavity and clearing with each cardiac cycle
grade 2	contrast filling of the entire LV in diastole, but with less density as compared to contrast opacification of the ascending aorta
grade 3	contrast filling of the entire LV in diastole equal in density to the contrast opacification of the ascending aorta
grade 4	contrast filling of the entire LV in diastole on the first beat with greater density as compared to the contrast opacification of the ascending aorta)

Adapted from Frick et al. [45]

Table 2. Agreement between different observers on grading of aortic regurgitation according to the method of Sellers. Observers 1 and 2 graded each aortogram independently and blinded to one another's results and the quantification methods. Observer 3 and 4 graded each aortogram independently but while viewing the same screen. After scoring all aortograms any discrepancies were reviewed by observers 3 and 4 and resolved by consensus.

Kappa ± SE	Observer 1	Observer 2	Observer 3	Observer 4	Observer 3 & 4 consensus
Observer 1	-	0.52±0.10	0.51±0.10	0.57±0.09	0.51±0.10
Observer 2	0.52±0.10	-	0.47±0.11	0.60±0.10	0.60±0.10
Observer 3	0.51±0.10	0.51±0.10	-	0.72±0.09	-
Observer 4	0.57±0.09	0.60±0.10	0.72±0.09	-	-
Observer 3 & 4 consensus	0.51±0.10	0.60±0.10	-	-	-

Table 3. Brief comparison among the methods for assessing regurgitation after TAVI. CMR: cardiac magnetic resonance.

	Visual - Sellers	Echocardiogram	CMR[58]	Videodensitometry
Reproducibility	Low (weak inter and intraobserver correlation)	Low (weak inter and intraobserver correlation)	Highly reproducible (high inter and intraobserver correlation)	Highly reproducible (high inter and intraobserver correlation)
Method of assessment	qualitative (subjective)	Qualitative / semi-quantitative	Quantitative	Quantitative
Disadvantages	Increase in contrast use	Operator dependent / less space in the minimalist TAVI	Cannot be performed within the procedure	Increase in contrast volume
Advantages	Easy, interventionist-friendly	Non-invasive, no contrast used	Quantitative	Quantitative. Use in the procedure

Figure legends

Figure 1. Computer-generated time-density curves of the aortic root (continuous line) and the left ventricle (dashed line) after injection of contrast in a patient with aortic regurgitation in whom digital subtraction aortogram was performed. Reproduced from Klein et al. [19]

Figure 2. Ratio at the end of injection (LV_D/Ao_D). The plateau at the end of the injection, defined as the time of the final peak of the aortic density curve is analysed. Reproduced from Klein et al. [19]

Figure 3. Calculation of regurgitant fraction with the use of videodensitometry (time-intensity curves). The left panel shows the processed, subtracted digital image of the aortogram in a severe regurgitation in dogs. Note the two white squares representing the areas of interest for creating the time-intensity curves. On the left panel, the curves generated for both areas of interest, aortic (grey line) and left ventricle (black line). Reproduced from Grayburn et al. [20]

Figure 4. Scatter plot with regression line showing the relation between regurgitant fraction calculated with digital subtraction aortography (DSA) and electromagnetic flow (EMF). Reproduced from Grayburn et al.[20]

Figure 5. Determinants of misinterpretation of paravalvular regurgitant jets by echocardiogram. Panel A shows a schematic representation of how the imaging plane can

influence the interpretation of the amount of regurgitation assessed by circumferential extent. Panel B exemplifies the location of paravalvular AR jets determined by Colour Doppler in parasternal short axis view and long axis views. Jets originating at the non-coronary sinus region (posterior location in apical 3-chamber view) are under-represented in parasternal short axis view. While 20% of jets seen in long axis views are present in that region, only 4% of those depicted on parasternal short axis view are located in the corresponding sector. A3C = apical 3-chamber, A5C = apical 5-chamber, PSAX = parasternal short axis, LAX = long axis, PLAX = parasternal long axis. Reproduced and modified from Abdelghani et al. [31]

Figure 6. Agreement between the Placement of Aortic Transcatheter Valves (PARTNER) IIB (PIIB) core laboratory and the consortium using Kappa statistics in the grading of aortic regurgitation. Left panel shows the agreement using the 4-grade scheme and the right panel shows the agreement using the 7-grade scheme. Reproduced with permission from Hahn et al. [32]. PVR: Paravalvular regurgitation.

Figure 7. Different degrees of aortic regurgitation assessed by LV-videodensitometry (qRA). The region of interest is drawn to include the contrast-filled aortic root and the entire left ventricle (left panel, dotted yellow lines). The base of the aortic root is indicated (left panel, purple line). The panels on the right show the 5 time-density curves generated by the qRA software, i.e., for the aortic root reference area (red), and for the left ventricle (LV) base (purple), mid-section (light blue), apex (green) and overall (yellow). Cumulative LV contrast density maps overlaid on the aortograms give a visual impression of the quantified severity of aortic regurgitation ranging from absent (0) to moderate to severe (3) in the examples shown. Reproduced with permission from Schultz et al. [46].

Figure 8. Representative images of the advantage of LVOT-AR in contrast with qRA. A) Regular analysis of qRA. However, the yellow arrows show the increase in density in the middle/apical part of the LV not related to regurgitation, but related to the contrast-filled descending aorta overlapping the LV (upper right panel), also detected on the time-density curves (lower panel). B) The contour of the ROI confined to the subaortic segment (LVOT-AR: yellow dashed line in upper left panel) and excluding the region of the descending aortic overlap so that the spurious increase in the contrast density can be corrected (upper middle and right, and the time-density curve in lower panel). C) Schematic representation of qRA index and LVOT-AR. Left panel: the ROI includes all three LV segments and the five TDCs are generated. qRA index algorithm is based on comparing the AUC of the three LV segments (basal - purple, mid - blue, and apical - green) versus the AUC of the reference region (aortic root - red). RAUC can also be computed for the whole ventricle by comparing the AUC of the entire ventricle (yellow) to that of the reference region. The calculation is made over three cardiac cycles (phases 1-3). Contrast-density values in the ROI are normalised to the peak density value in the reference region, which is given a value of 100. Right panel: the ROI is confined to the subaortic segment (basal segment), and the RAUC is the ratio between the AUC of the subaortic segment (yellow curve) and the reference region (red curve). AR: aortic regurgitation; LV: left ventricle; LVOT: left ventricle outflow tract; qRA: quantitative regurgitation analysis; RAUC: relative area under the curve; ROI: region of interest. Reproduced from Tateishi et al. [11].

Figure 9. In vitro validation experiment set-up. (A) Cath lab with the Mock circulation system mounted and captured by the C-arm. (B) The mock circulation system showing the

aortic and LV sides, divided by the prosthetic valve and the positioning of a trans sonic probe in the LV side. (C) Closer look at the circulation system showing how to externally compress the prosthetic valve with a white plastic screw, creating a controlled deformation in order to provoke a paravalvular regurgitation. White arrow highlights the "en-face" view of the prosthetic valve evidencing its controlled deformation created by the plastic screw. (D) Technician adjusting in real-time the amount of regurgitation by pressing the screw and checking the transducer-measured regurgitation on the screen. Reproduced and modified from Abdelghani et al.[12].

Figure 10. Representation of the three modalities of videodensitometric assessment of regurgitation: in vitro experiment. Below the three scatter plots with the line of best fit and the 95% confidence interval lines displaying the relation between the regurgitation fraction (RF; on the horizontal axis) assessed by the trans sonic probe and videodensitometric parameters of regurgitation severity on the vertical axis: qRA, LV-AR and LVOT-AR. Reproduced and adapted from Abdelghani et al.[12].

Figure 11. Correlation between LV-AR and LVOT-AR and regurgitation fraction (RF) using different numbers of cardiac cycles. Scatter plots with the lines of best fit displaying the correlations of LV-AR (left side) and LVOT-AR (right side) with RF when one (red), two (blue), three (purple), four (green) or five (black) cardiac cycle(s) is/are included in the analysis. With 3 cardiac cycles or more the best fit lines are visually superimposed and the Spearman r^2 are all above 0.9 for either method. Reproduced and adapted from Abdelghani et al.[12].

Figure 12. Induced regurgitation in vivo. Panel A shows the schematic representation of the procedure. After the positioning of the LV guidewire a Wallstent was inserted across the aortic valve and partially unsheathed and deployed (right side) up to its fully unconstrained diameter. The aortogram and quantitative assessment of regurgitation was then performed. Panel B shows the correlation of the multiple assessments of regurgitation with different diameters of Wallstent inserted. Study performed by Modolo et al[48].

Figure 13. Time-to-death curves using Kaplan Meier method and log-rank test of cumulative survival according to LVOT-AR categories (above 17% or 17% and below). Reproduced from Tateishi et al. [11].

Figure 14. Time-to-death curves using Kaplan Meier method and log-rank test of cumulative survival in a Japanese cohort of patients undergoing TAVI according to LVOT-AR categories (above 17% or 17% and below). Reproduced from Tateishi et al. [15].

Figure 15. Discrimination of LVOT-AR measures in different echocardiographic strata of regurgitation. A. The distribution of LVOT-AR across the echocardiographic grades of aortic regurgitation after TAVI. The box (interquartile range) and whiskers (95% confidence interval) plot shows a significant overlap of LVOT-AR between the none-trace and the mild grades of aortic regurgitation on echocardiography. **B.** Receiver operating characteristics curve of LVOT-AR corresponding to greater than mild AR as defined by echocardiography

after TAVI. **C.** Statistical details of the ROC curve. AUC: area under the curve. Reproduced from Abdelghani et al. [10].

Figure 16. Relationship between LVOT-AR and transesophageal echocardiographic severity of regurgitation. A. LVOT-AR according to echocardiographic post-TAVI aortic regurgitation as defined by percentage of circumferential extent (CE) on intra-procedural transesophageal echocardiography (n=51). **B.** Scatter-plot of the continuous assessment of CE (%) and LVOT-AR. Reproduced from Tateishi et al. [15].

Figure 17. Correlation of LVOT-AR with magnetic resonance imaging. The left panel shows the cumulative frequency distribution curves for both LVOT-AR results (blue) and CMR-RF (red) in 135 patients. The right panel shows a scatter-plot with a linear relationship between LVOT-AR and CMR-RF result for regurgitation after TAVI. Reproduced from Abdel-Wahab et al. [9].

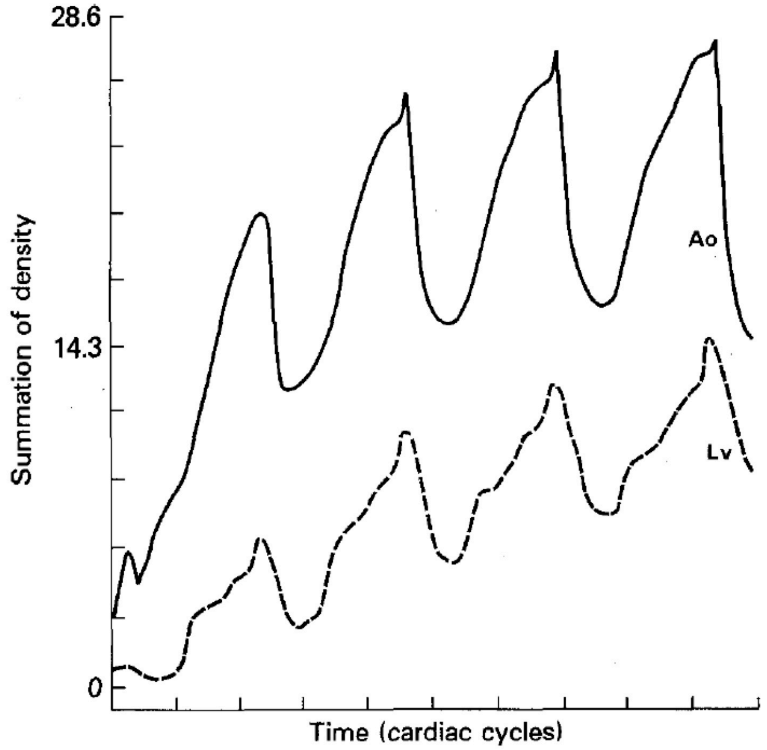
Figure 18. Cumulative frequency curves of LVOT-AR assessment in 1,184 patients receiving first (blue) or second (red) generation transcatheter aortic valves. The quantitative regurgitation is higher in patients after 1st generation TAVI, and the number of patients with a regurgitation above 17% is also higher among those receiving 1st generation aortic valves. Reproduced with permission from Miyazaki and Modolo et al. [50]

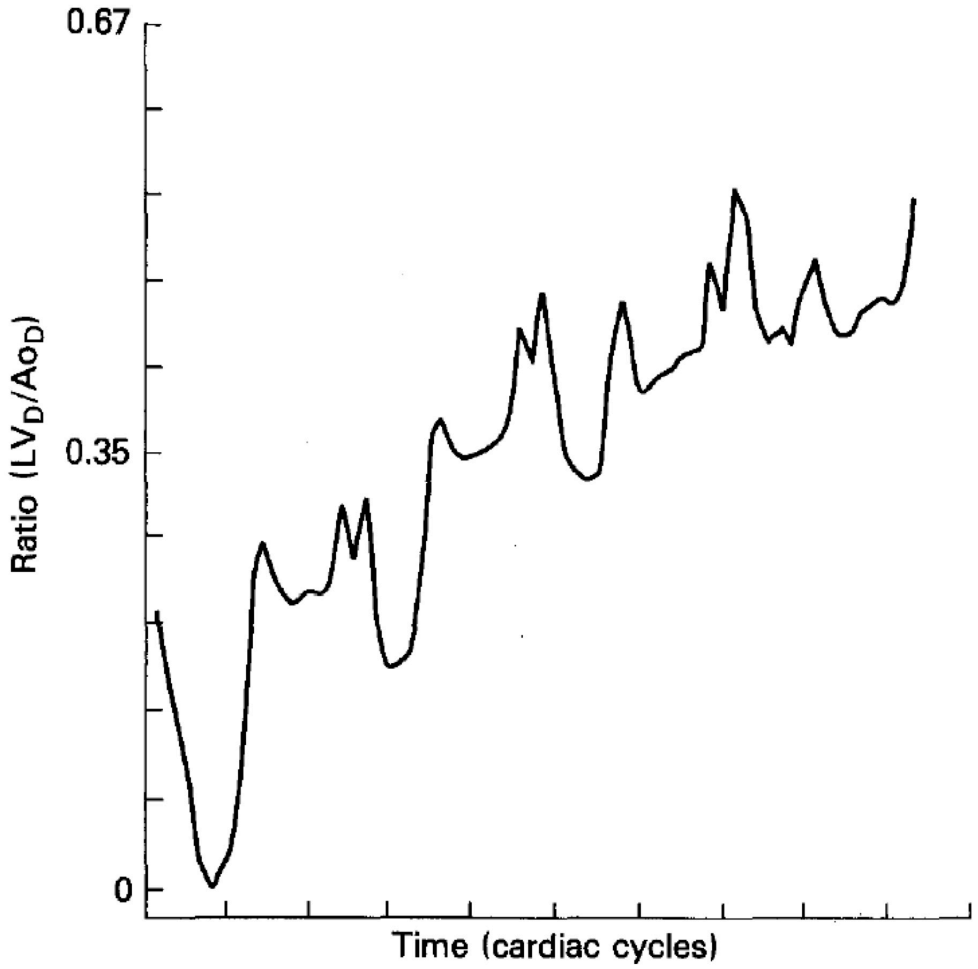
Figure 19. Serial changes of the LVOT-AR. Individual serial changes before and after balloon post-dilatation are shown in this figure (left panel). In patients with LVOT‑AR > 17%, 7 deaths (34%) occurred, whereas in patients with VD-AR ≤ 17%, 8 deaths (19%) were observed. Reproduced and adapted from Miyazaki et al. [53].

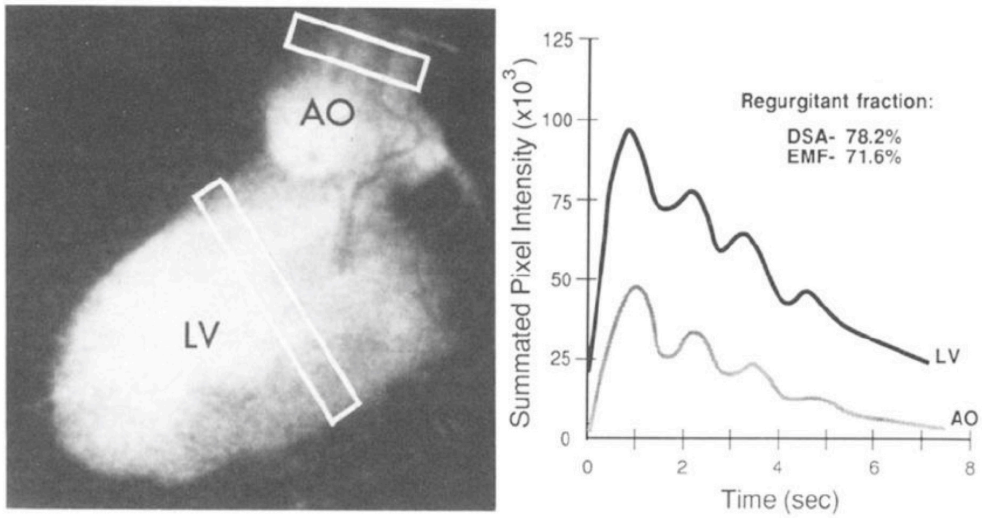
Figure 20. Three-dimensional CT reconstruction of the aorta (ascending and descending – in orange) and the LVOT (purple) - HeartNavigator, Philips Medical Systems. In this image we can see the location of the reference area (aortic root) and of the ROI (LVOT). In the left corner is a demonstration of the C-arm position and the angulation and rotation for this image acquisition during angiography. In this particular case, there is overlapping of the ROI with the descending aorta, thus making this projection unfeasible for a proper evaluation of LVOT-AR. CAUD: caudal; dAo: descending aorta; LVOT: left ventricle outflow tract; RAO: right anterior oblique; ROI: region of interest. Reproduced from Modolo et al. [13].

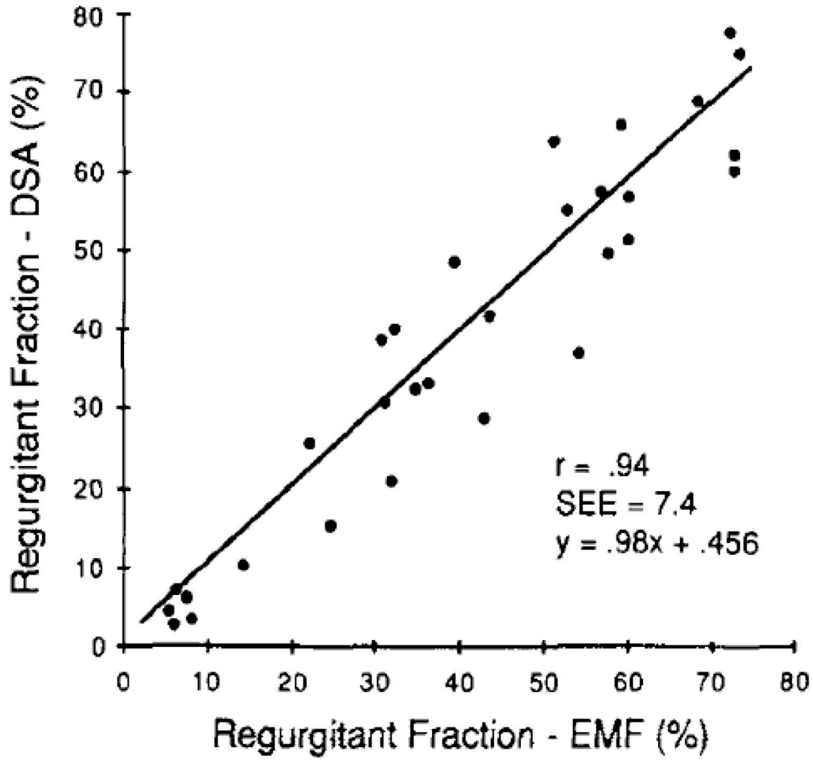
Figure 21. Single centre experience showing the impact of implementation of a protocol for image acquisition on LVOT-AR feasibility of analysis. Reproduced from Tateishi et al. [54].

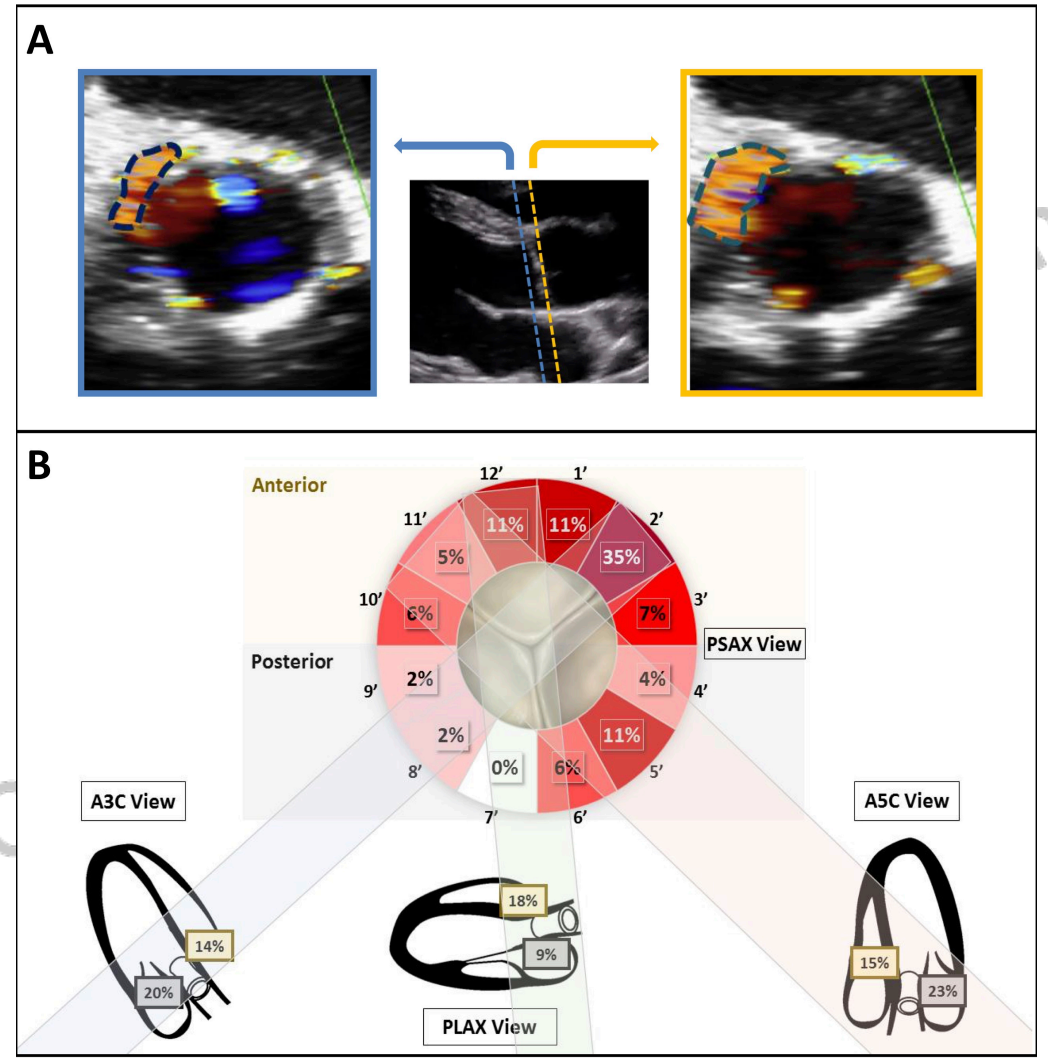
Figure 22. Left ventricle angiographic model showing the tracing of the region of interest (left atrium) and the reference area (left ventricle). Similarly to the quantitative assessment of aortic regurgitation using aortogram, the figure shows the quantitative assessment of mitral regurgitation using LV-gram. The appropriate angiographic view was selected from a prior computed tomography view as described by Pighi et al [59]. LV: left ventricle, LA: left atrium, RAUC: ratio area under the curve











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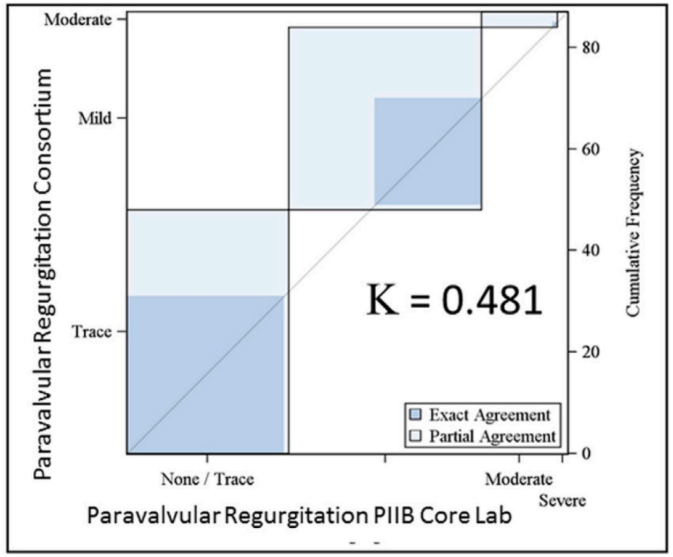

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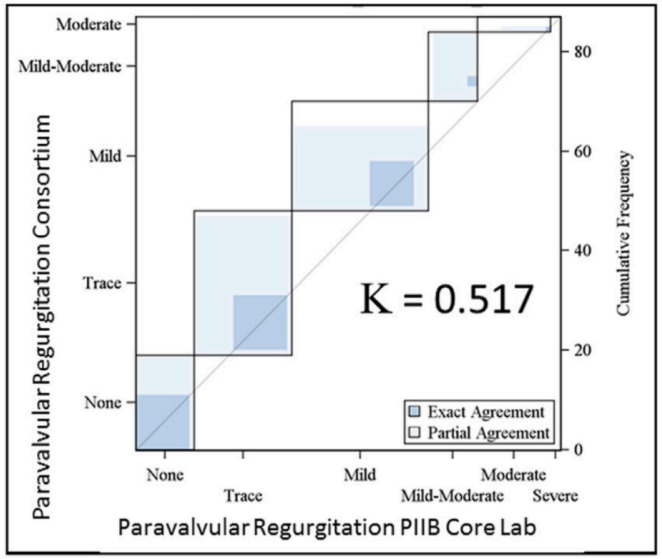
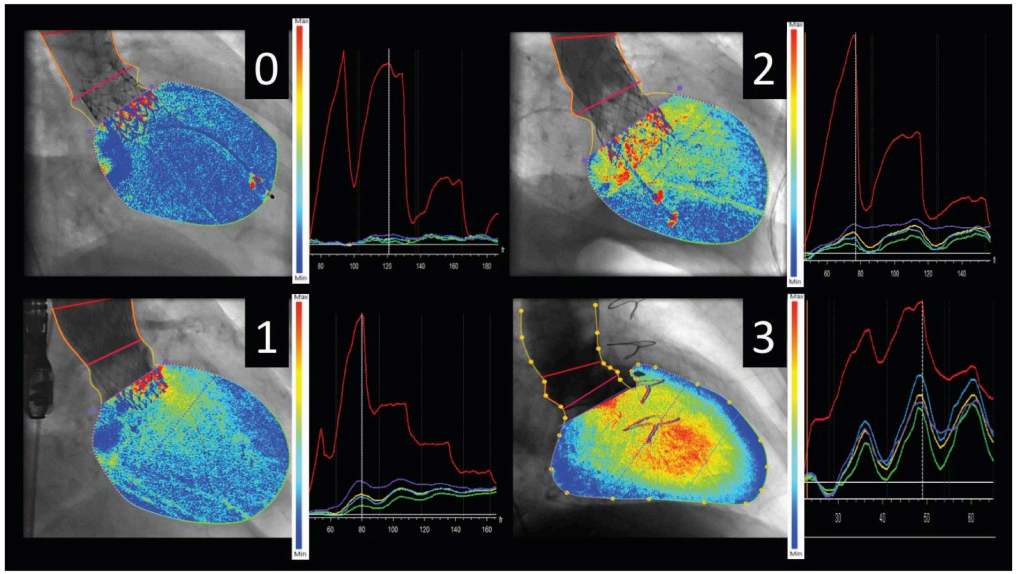
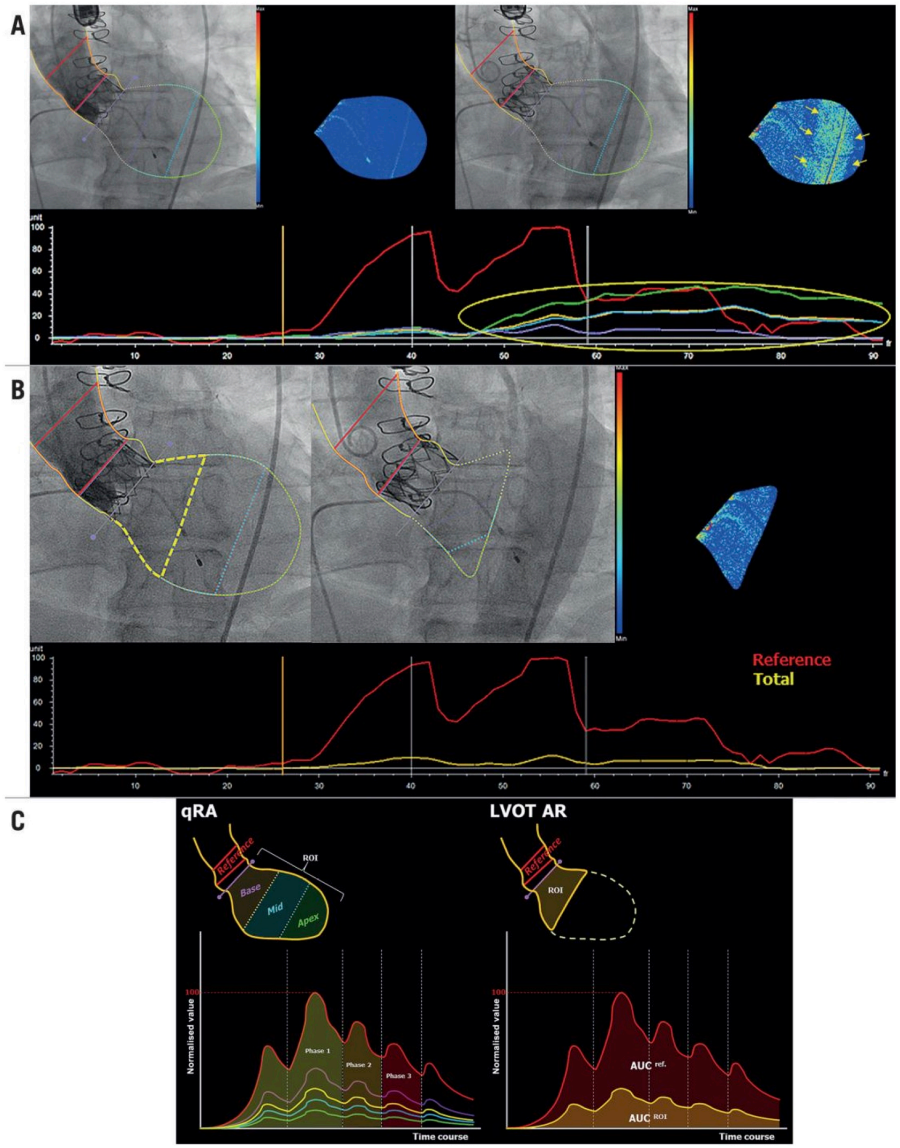
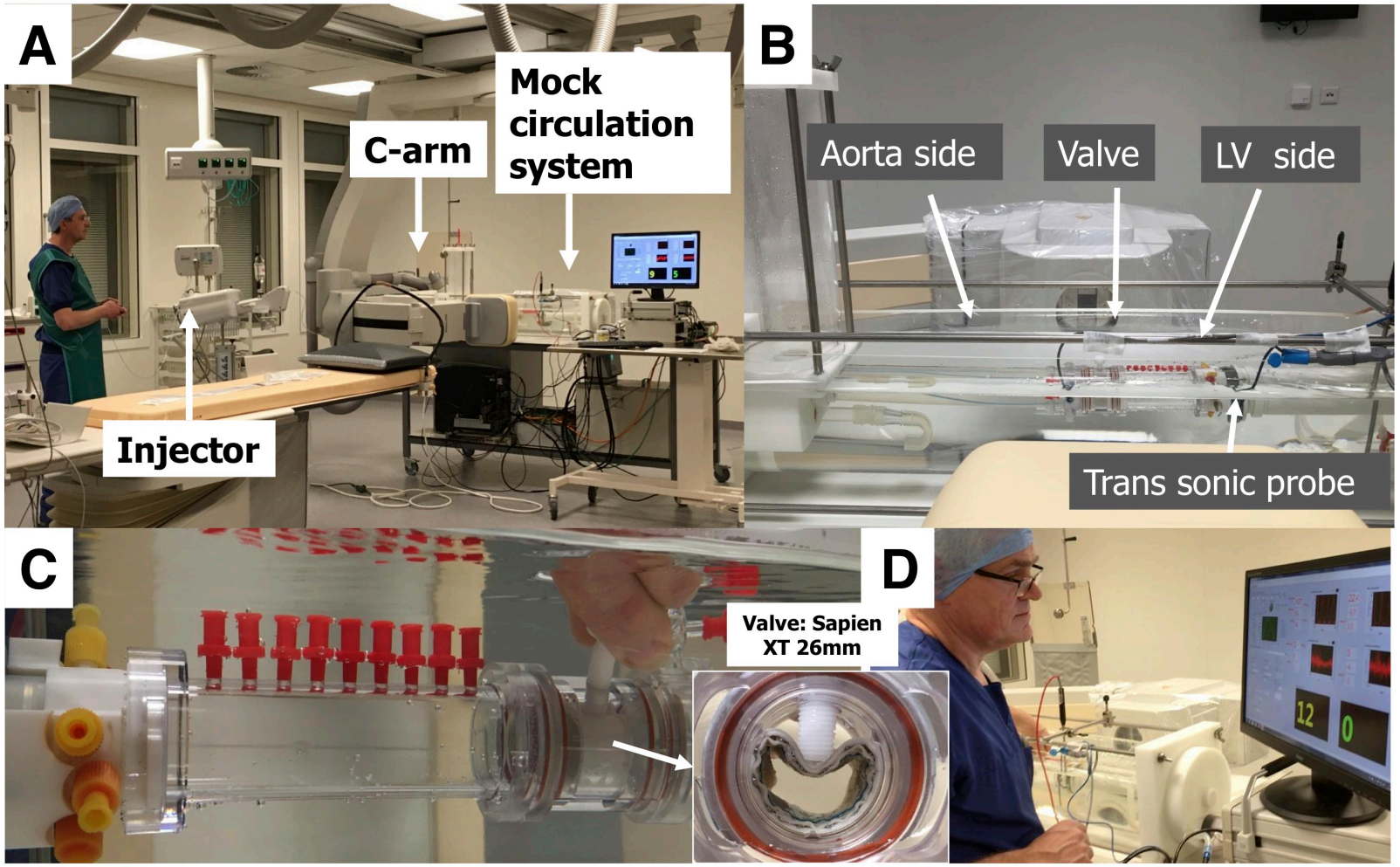
PVR 7-class agreement

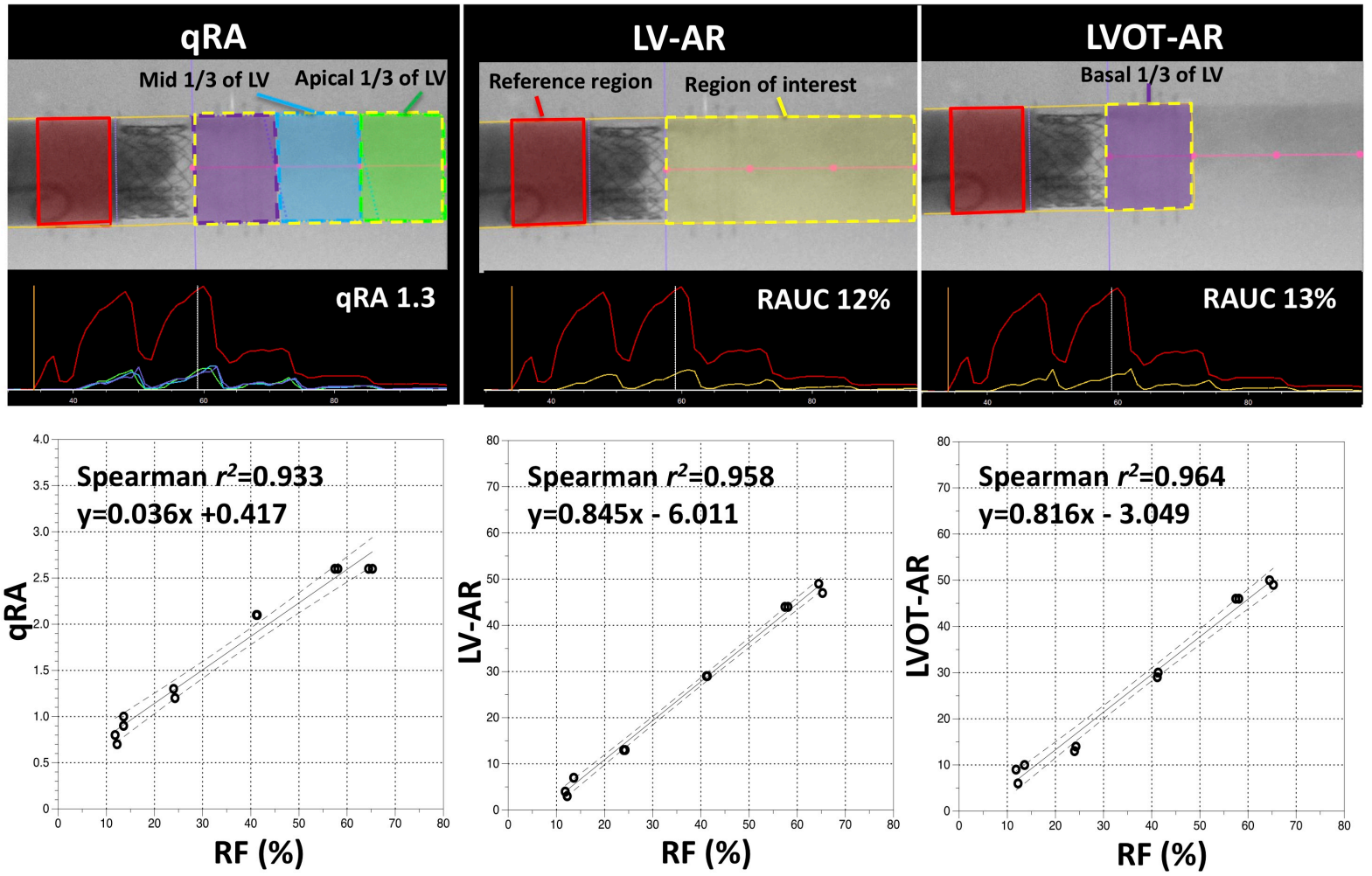


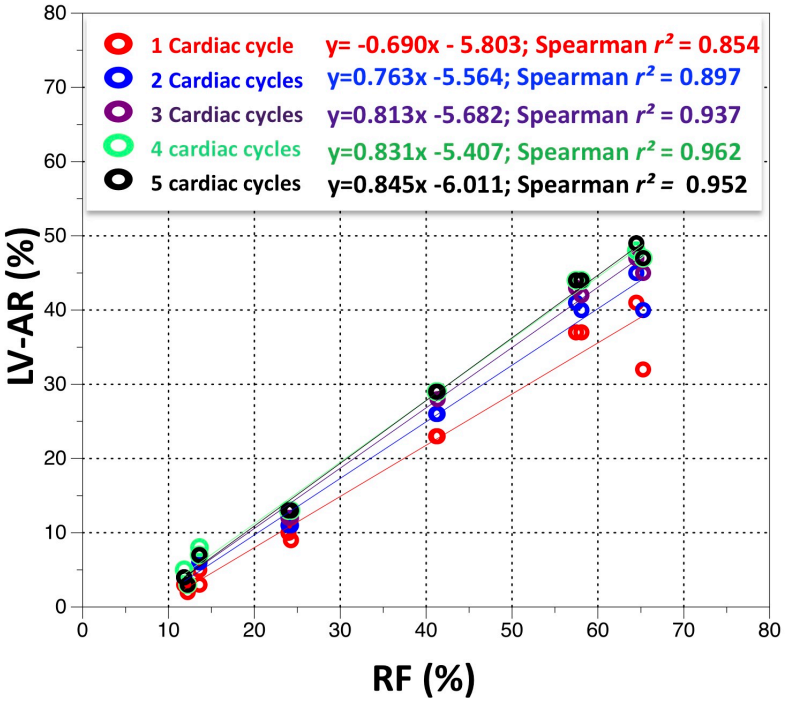
None / Trace / Mild /Mild to Moderate / Moderate / Moderate to Severe / Severe

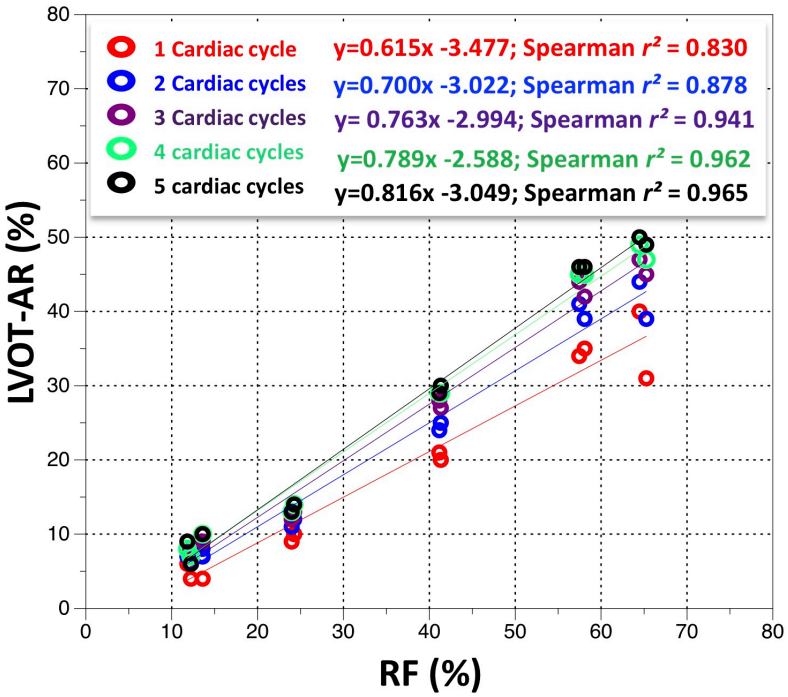


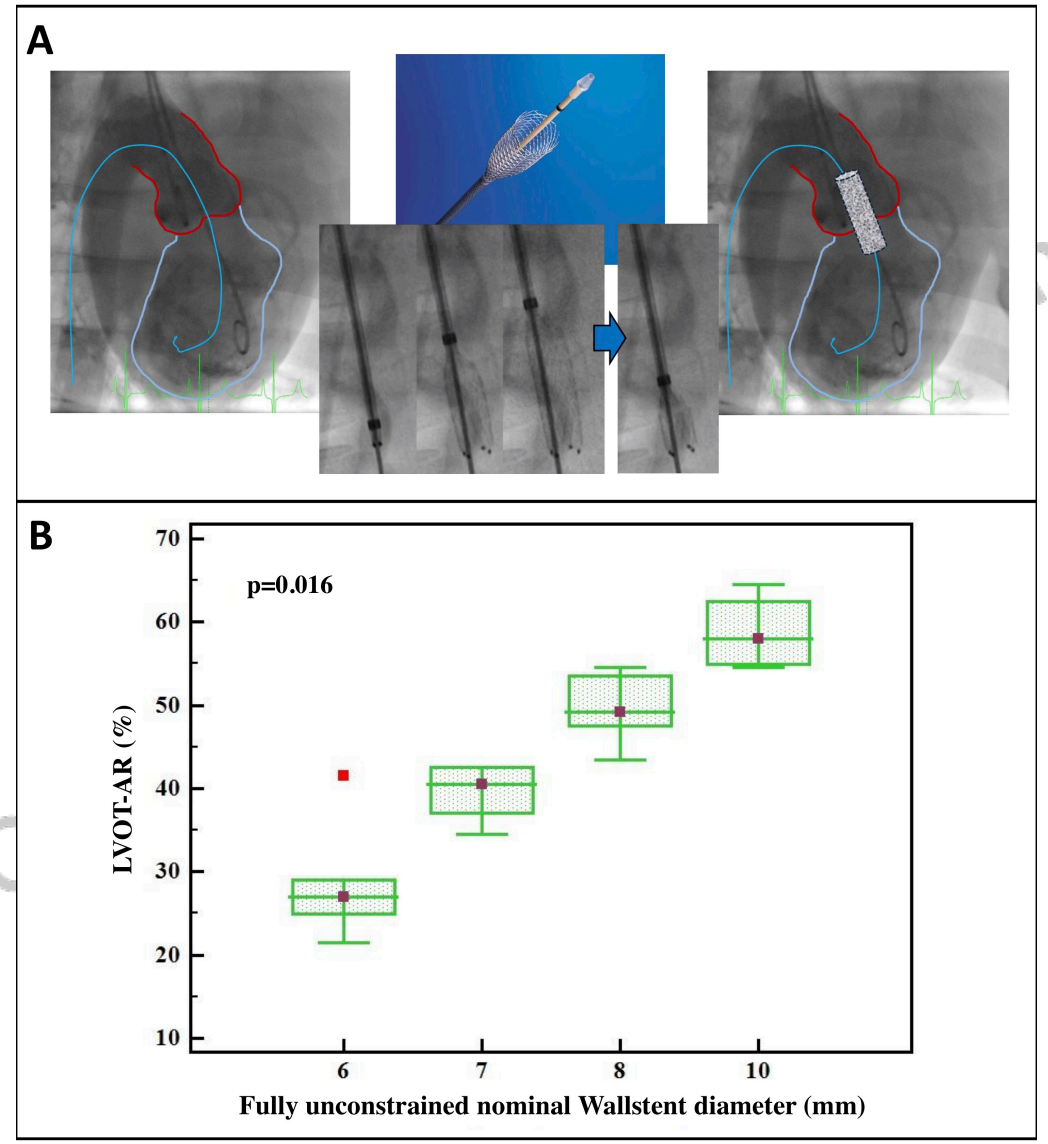


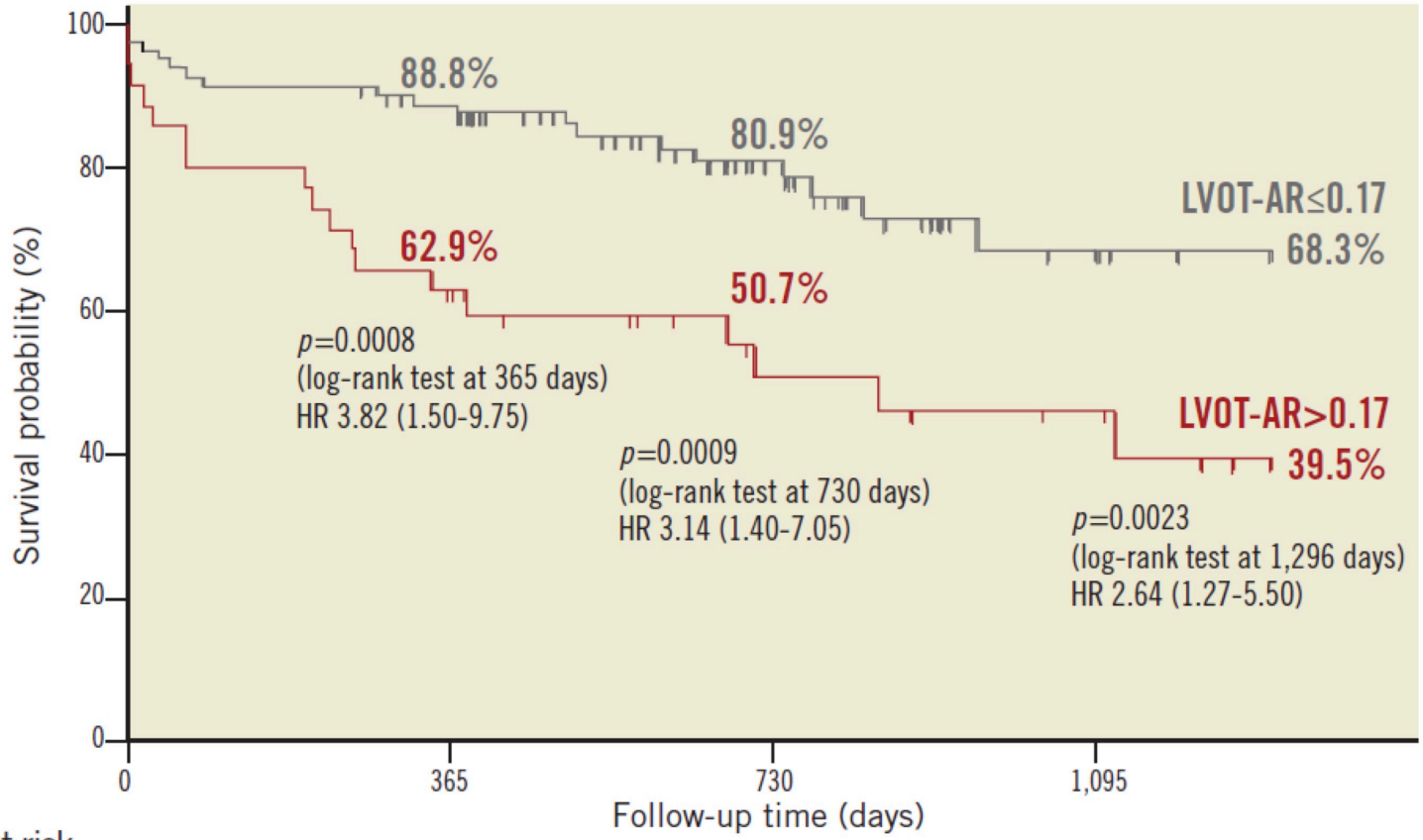




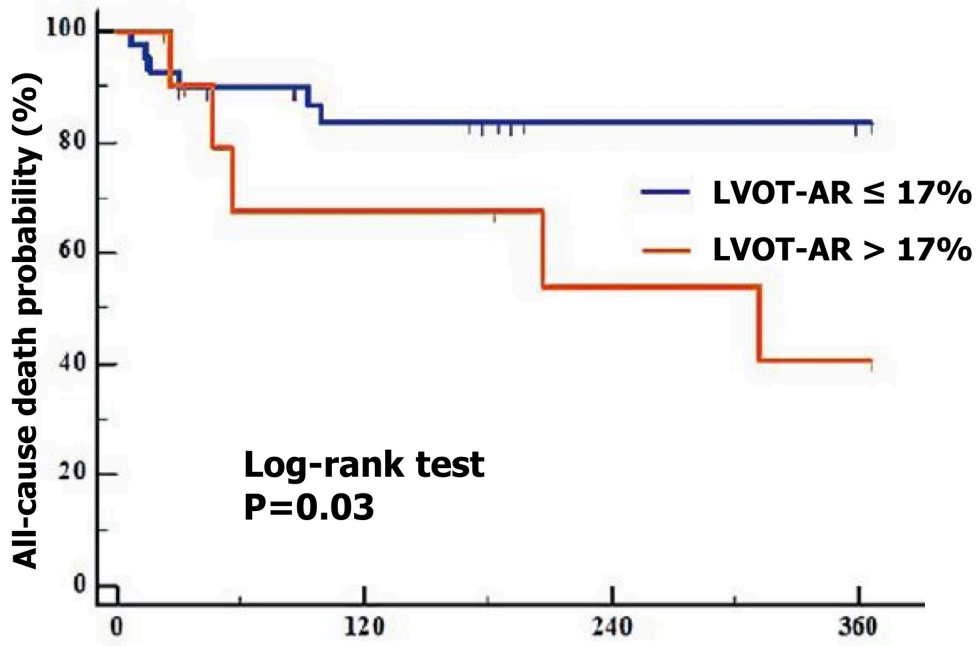




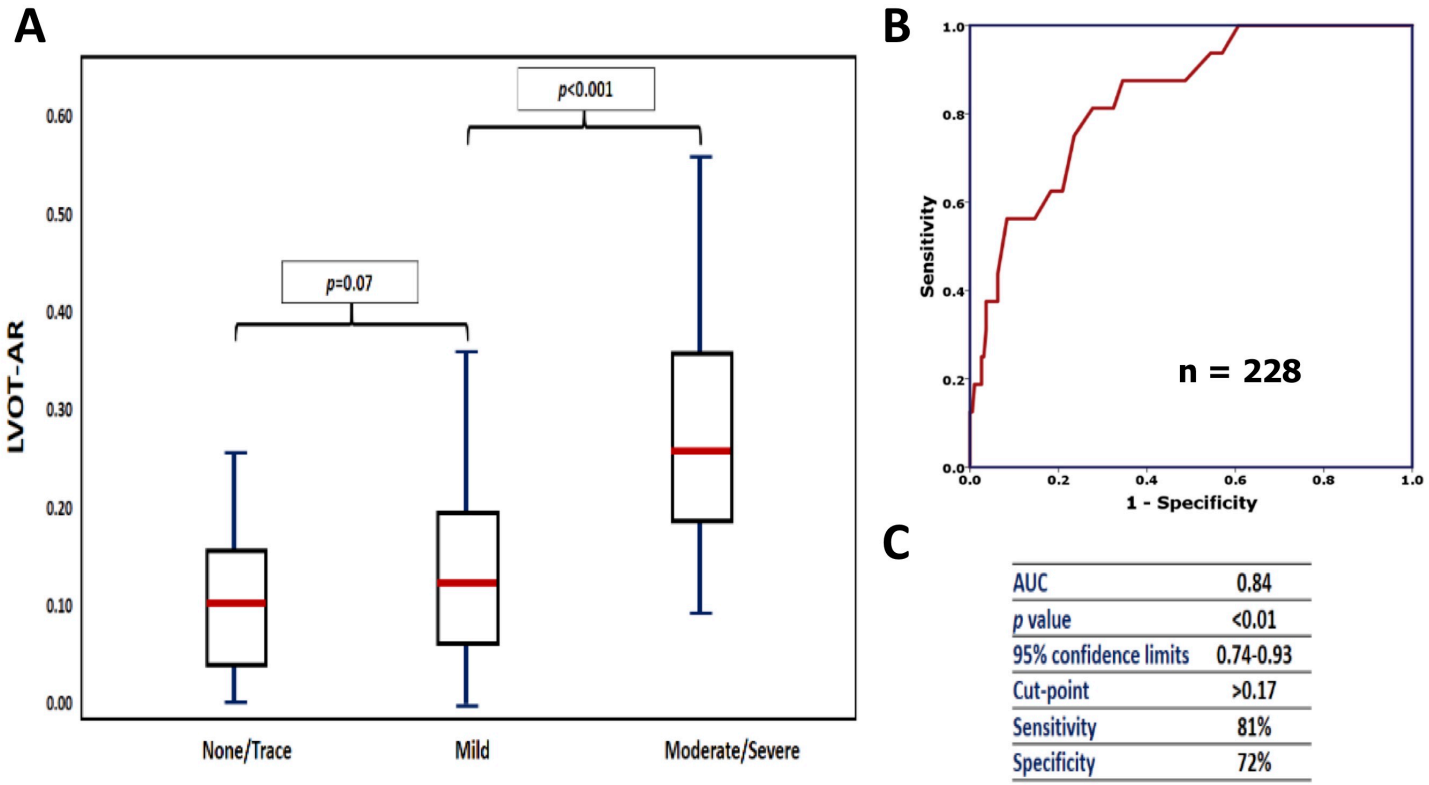


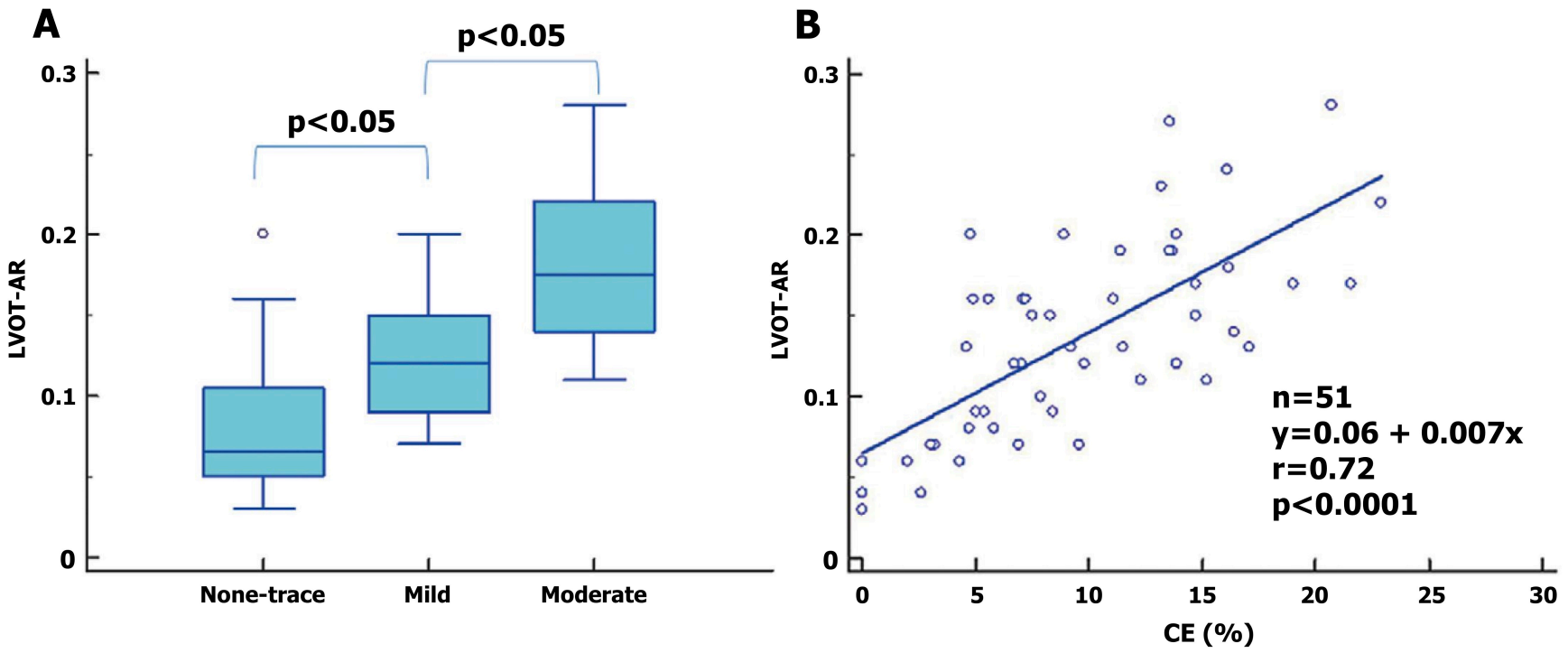


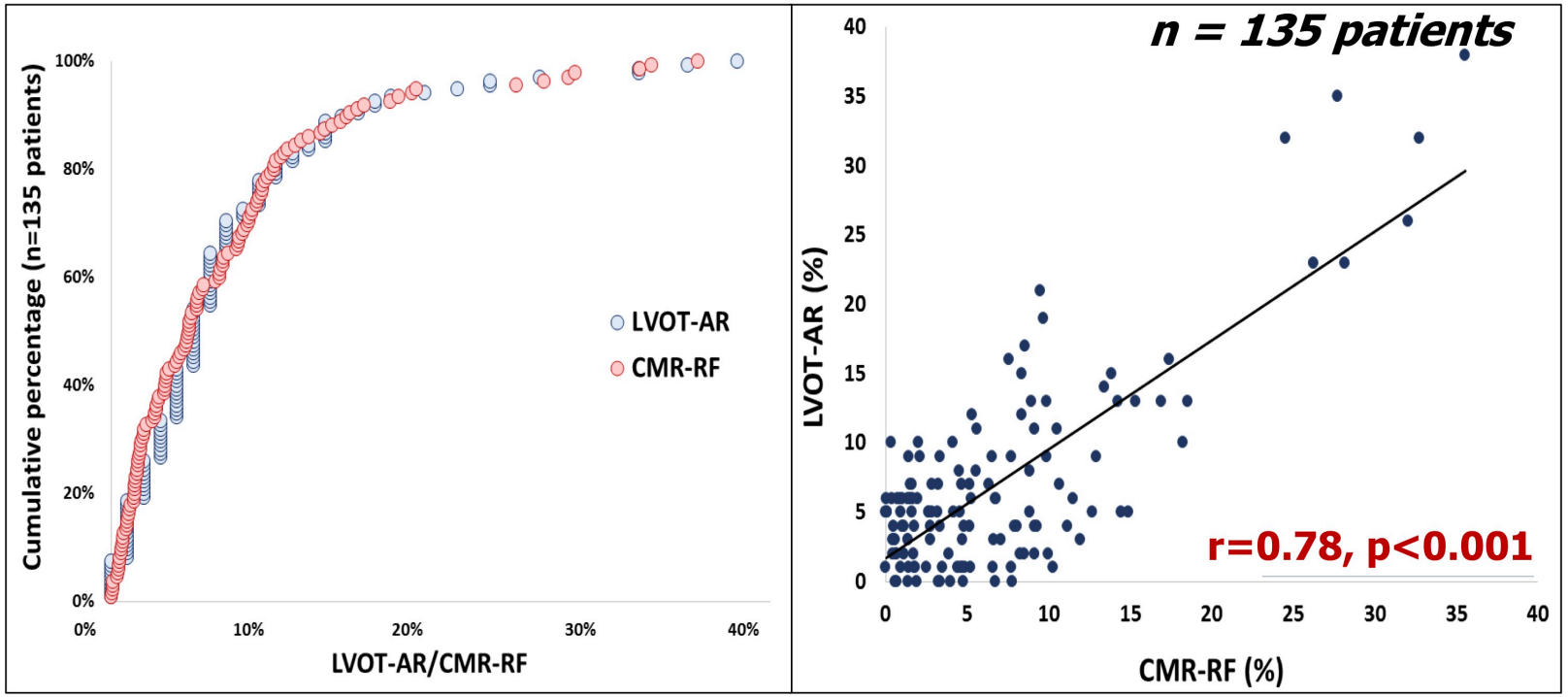
Number at risk				
LVOT-AR ≤0.17	79	69	35	14
LVOT-AR >0.17	33	21	11	8
TOTAL	112	90	46	22

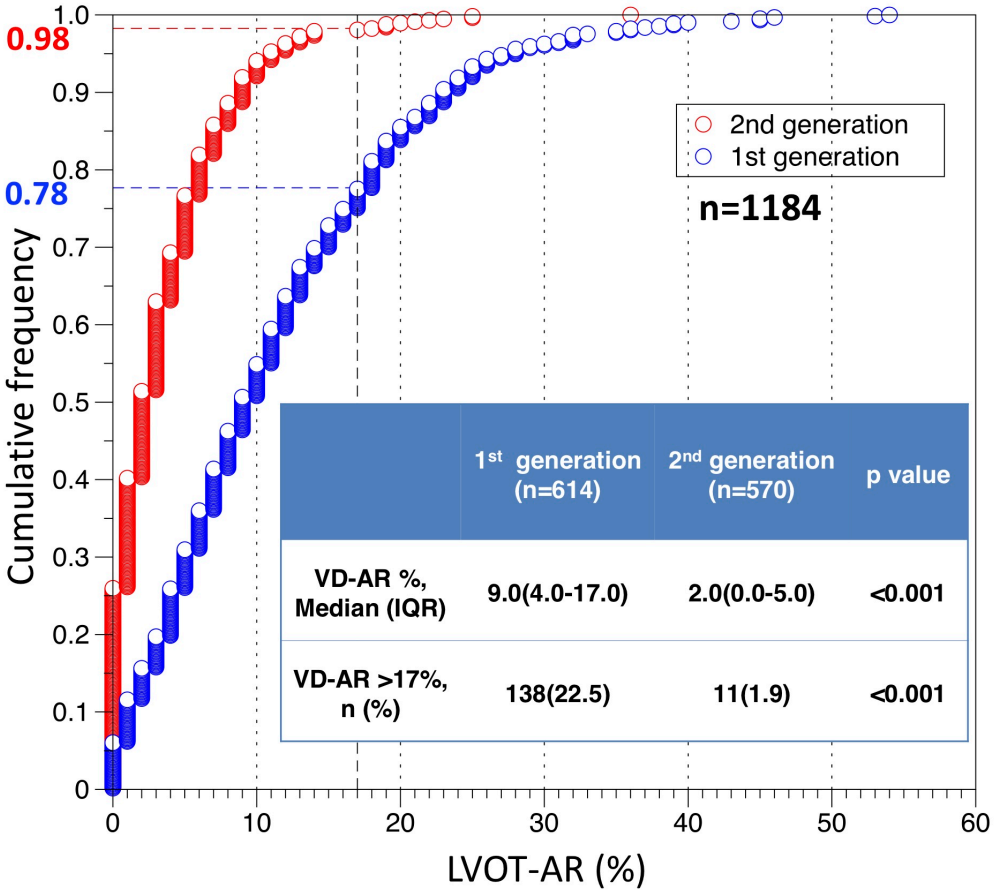


Number at risk				
LVOT-AR ≤ 17%	40	26	20	18
LVOT-AR > 17%	11	6	4	3

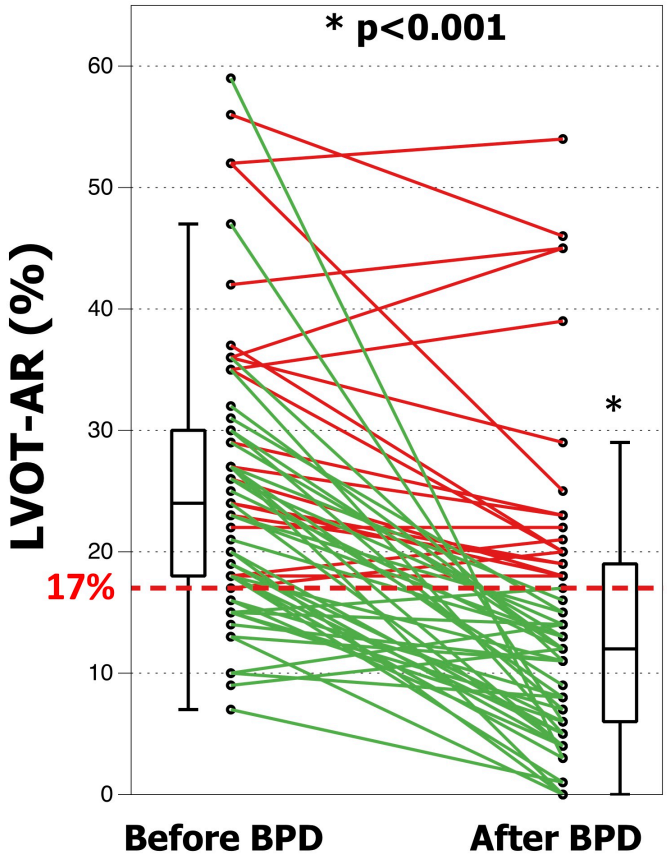








	1st generation (n=614)	2nd generation (n=570)	p value
VD-AR %, Median (IQR)	9.0(4.0-17.0)	2.0(0.0-5.0)	<0.001
VD-AR >17%, n (%)	138(22.5)	11(1.9)	<0.001



	Before BPD (n=61)	After BPD (n=61)
LVOT-AR (Median[IQR])	**24.0[18.0-30.5]**	**12.0[5.5-19.0]**
LVOT-AR>17%, n (%)	**47(77%)**	**19(31%)**
LVOT-AR≤ 17%, n (%)	**14(23%)**	**42(69%)**

	All-cause mortality¶ (4 years)
LVOT-AR>17%, n (%)	**7/19(34%)**
LVOT-AR≤ 17%, n (%)	**8/42(19%)**

¶ *p-value = 0.11*