Current definitions of hemodynamic structural valve deterioration after bioprosthetic aortic valve replacement lack consistency

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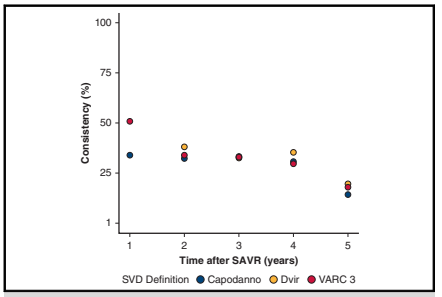
ABSTRACT

Objective: New echocardiographic definitions have been proposed for hemodynamic structural valve deterioration. We aimed to study their consistency in classifying structural valve deterioration after surgical aortic valve replacement.

Methods: Data were used of patients undergoing surgical aortic valve replacement in a multicenter, prospective cohort study with a 5-year follow-up. All patients received the same stented bioprosthesis. Echocardiographic parameters were assessed by an independent core laboratory. Moderate or greater stenotic hemodynamic structural valve deterioration was defined according to Capodanno and colleagues, Dvir and colleagues, and the Valve Academic Research Consortium 3; regurgitation data were not considered in this analysis. Consistency was quantified on the basis of structural valve deterioration classification at subsequent time points.

Results: A total of 1118 patients received implants. Patients' mean age was 70 years, and 75% were male. Hemodynamic structural valve deterioration at any visit was present in 51 patients (4.6%), 32 patients (2.9%), and 34 patients (3.0%) according to Capodanno, Dvir, and Valve Academic Research Consortium 3. A total of 1064 patients (95%) were never labeled with structural valve deterioration by any definition. After the first classification with structural valve deterioration, 59%, 59%, and 65% had no subsequent structural valve deterioration classification according to Capodanno, Dvir, and Valve Academic Research Consortium 3, respectively.

Conclusions: The current definitions of hemodynamic structural valve deterioration are strong negative predictors but inconsistent positive discriminators for the detection of stenotic hemodynamic structural valve deterioration. Although the diagnosis of structural valve deterioration may be categorical, echocardiographic indices lack this degree of precision in the first 5 years after surgical aortic valve replacement. The inconsistency of current structural valve deterioration definitions impedes the detection of true valve degeneration, which challenges the clinical usefulness of these definitions. (JTCVS Open 2024;19:68-90)



The consistency, represented on the y axis, was evaluated by calculating how many patients who were classified with hemodynamic SVD at 1 time point were also classified with SVD at the subsequent time point. *SAVR*, Surgical aortic valve replacement; *SVD*, structural valve deterioration; *VARC*, Valve Academic Research Consortium.

CENTRAL MESSAGE

After the first classification of hemodynamic SVD by recently proposed definitions, up to 65% of patients were not classified with SVD at the subsequent visit.

PERSPECTIVE

Current definitions are inconsistent positive discriminators for the detection of stenotic hemodynamic SVD. Although the diagnosis of SVD may be categorical, echocardiographic indices lack this degree of precision in the first 5 years after SAVR. The observed inconsistency impedes the detection of true valve degeneration, which challenges the clinical usefulness of these definitions.

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Abbreviations and Acronyms

AVR = aortic valve replacement
BVF = bioprosthetic valve failure
DVI = Doppler velocity index
EOA = effective orifice area
HALT = hypo-attenuated leaflet thickening
MPG = mean pressure gradient
SAVR = surgical aortic valve replacement
SVD = structural valve deterioration
VARC = Valve Academic Research Consortium

A main concern for bioprosthetic heart valves is durability. Irreversible damage to structural elements of the prosthesis, a process called "structural valve deterioration" (SVD), can eventually lead to hemodynamic dysfunction, symptoms, and the potential need for reintervention. Original clinical definitions of SVD after aortic valve replacement (AVR) were based on reoperation or death and identified only the most severe cases of hemodynamic dysfunction, whereas subsequent hemodynamic definitions did not distinguish between structural and nonstructural causes.[1] To overcome these shortcomings, new definitions have been proposed for hemodynamic SVD by Capodanno and colleagues,[2] Dvir and colleagues,[3] and the Valve Academic Research Consortium (VARC) 3.[4] These definitions slightly differ but are all partially based on an increase in mean pressure gradient (MPG) compared with a reference echocardiogram obtained after surgery.

Echocardiographic parameters such as MPG may vary over time due to factors unrelated to bioprosthetic valve performance, such as biological fluctuations (eg, circadian patterns, volemia, heart rate, irregular rhythms) and measurement error. Inevitably, these factors are part of clinical practice and could complicate consistent classification of SVD. Moreover, even small variations in measurements could result in dramatic changes when using strict categories such as the presence or absence of SVD. Thus, the aim of this study was to assess the consistency of the contemporary definitions of hemodynamic SVD after bioprosthetic AVR. Our secondary aim was to study longitudinal variability in MPG during follow-up.

MATERIAL AND METHODS

Study Data

Data from the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial for the Avalus valve (www.clinicaltrials.gov, NCT02088554) were used. The PERIGON Pivotal Trial is a single-armed, prospective, observational follow-up study to examine the safety and performance of the Avalus bioprosthesis (Medtronic). The design of the trial was formerly outlined in detail.[5,6] In short, patients with aortic stenosis or regurgitation and a clinical indication for surgical aortic valve replacement (SAVR) were enrolled. Several concomitant procedures were allowed, including coronary artery bypass grafting, left atrial appendage closure, and ascending aortic aneurysm or dissection repair not requiring circulatory arrest. The study was conducted at 38 centers across North America and Europe, at which local institutional review boards or ethics committees provided study approval (see supplementary files in Klautz and colleagues[7] for approval number and date per center). All patients provided written informed consent for publication of study data. All deaths and valve-related events were adjudicated by an independent clinical events committee (Baim Institute for Clinical Research), and study oversight was kept by an independent data and safety monitoring board (Baim Institute). A single core laboratory (MedStar Health Research Institute) assessed all echocardiographic parameters. After implant, patients were scheduled for follow-up at hospital discharge (up to 30 days), 3 to 6 months, 1 year, and annually through 5 years. A flowchart that depicts the number of patients who completed each visit and the reasons for dropout is provided in Figure E1. MPG and effective orifice area (EOA) were determined using the simplified Bernoulli equation and the continuity equation, respectively. By dividing the velocity-time integral of the left ventricular outflow tract by the velocity-time integral across the aortic valve, the Doppler velocity index (DVI) was derived.

Hemodynamic Structural Valve Deterioration Definitions

The definitions of hemodynamic SVD that were studied were proposed by Capodanno and colleagues,[2] Dvir and colleagues,[3] and the VARC 3.[4] These hemodynamic SVD definitions are abbreviated throughout the article as Capodanno-SVD, Dvir-SVD, and VARC3-SVD. Moderate or greater stenotic SVD was studied because we hypothesized there would be potential variability in quantitative echocardiographic parameters for hemodynamic obstruction. For this reason and because moderate or greater regurgitation was present in only 0.2% at 5-year follow-up,[7] regurgitation data were not considered in this analysis. The exact definitions as examined in this study are reported in Figure 1. To determine the change in echocardiographic parameters, values during follow-up were compared with a reference echocardiography performed at hospital discharge up to 30 days. In a subanalysis, values during follow-up were compared with a reference echocardiography performed at the first outpatient clinic visit between 3 and 6 months postsurgery.

Statistical Analyses

Numeric data were presented as mean ± SD or median [interquartile range] depending on their distribution, and categorical data were presented as counts (percentages). Missing echocardiographic data are presented in Table E1. A complete case analysis was performed in all analyses except for graphical representation of longitudinal data. Therein, patients with missing data at 1 or more time points were not omitted.

The consistency of each hemodynamic SVD definition was evaluated by calculating how many patients who were classified with SVD at 1 time point were also classified with SVD at the subsequent time point. Furthermore, heatmaps were generated for each patient who was classified with SVD at least once during follow-up to illustrate whether SVD was present or absent at each follow-up visit. If SVD classification was inconsistent, we evaluated which specific condition in the definition was not met anymore (eg, the increase in MPG). In addition, the agreement between the 3 SVD definitions was expressed in Cohen's kappa coefficients. In a subanalysis, patients with reintervention, endocarditis, or valve thrombosis were excluded to eliminate established clinical causes of hemodynamic alteration.

To assess longitudinal variability in MPG, patients who did not undergo reintervention were selected to guarantee that the same prosthetic valve was present at each time point. A 95% prediction interval was calculated for the change in MPG within individuals by subtracting their MPG value at discharge from their MPG value at 5-year follow-up. Furthermore, the change in MPG between 2 consecutive time points was repeatedly calculated for deciles of MPG at the start of the first time point. For example,

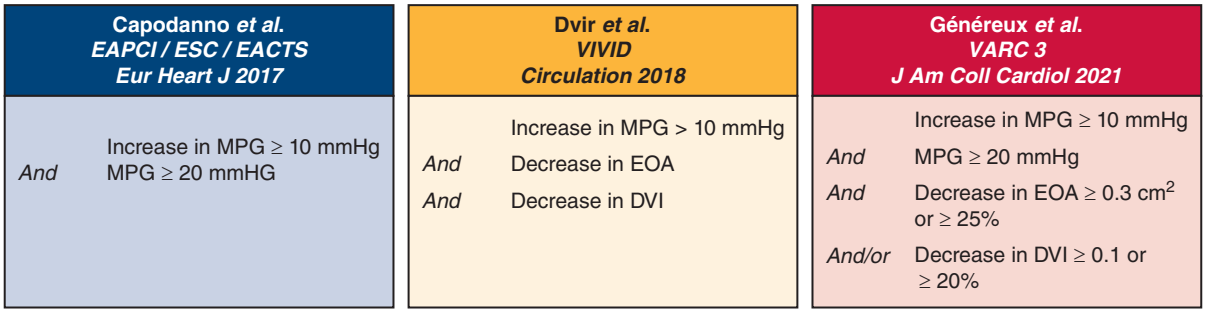

FIGURE 1. Contemporary definitions of moderate or greater stenotic hemodynamic SVD.[2-4] *EAPCI*, European Association of Percutaneous Cardiovascular Interventions; *ESC*, European Society of Cardiology; *EACTS*, European Association for Cardio-Thoracic Surgery; *MPG*, mean pressure gradient; *VIVID*, Valve-in-Valve International Data; *EOA*, effective orifice area; *DVI*, Doppler velocity index; *VARC*, Valve Academic Research Consortium.

for the change in MPG between 1-year and 2-year follow-ups, deciles were created based on the values of MPG at 1 year.

Although the data underlying this analysis are owned by the study sponsor, the analyses were proposed and performed by the authors, and the article was written by the author group. All analyses were performed using the R software (R Foundation for Statistical Computing, www.r-project.org).

RESULTS

A total of 1118 patients underwent successful valve implantations, and all were included in this analysis. The mean age of the study population was 70 years, 75% were male, and the median Society of Thoracic Surgeons predicted risk of mortality was 1.60 (Table 1). At discharge up to 30 days, the average MPG was 13.1 ± 4.7 mm Hg, the EOA was 1.54 ± 0.36 cm^2, and the DVI was 0.49 ± 0.10. By using the initial discharge echocardiogram as the reference, 51 patients were classified with Capodanno-SVD at least once during follow-up, 32 patients were classified with Dvir-SVD, and 34 patients were classified with VARC3-SVD (Table E2). A total of 1064 patients (95%) were never labeled with SVD by any definition.

Consistency of Hemodynamic Structural Valve Deterioration Definitions

Of the patients who were classified with Capodanno-SVD at 2 years, 33% were also classified with Capodanno-SVD at 3 years. The consistency during this interval was also 33% for the definitions by Dvir and colleauges[3] and the VARC 3.[4] Likewise, for all intervals, the consistency per definition is reported in Table 2 and illustrated in Figure 2.

The consistency of hemodynamic SVD classification within individuals is demonstrated in heatmaps in Figure E2 (Capodanno and colleagues[2]), Figure E3 (Dvir and colleagues[3]), and Figure 3 (VARC 3[4]). The heatmap for VARC3-SVD is presented in the main article because this definition is the most recent and the most comprehensive.

After the first classification of Capodanno-SVD, 59% had absent SVD, 16% had present SVD, and 25% had missing SVD (Figure E2). The reason for inconsistent Capodanno-SVD classification was an increase in MPG less than 10 mm Hg in 20% and not exceeding the increase threshold as well as the absolute threshold of 20 mm Hg anymore in 80%.

After the first classification of Dvir-SVD, 59% had absent SVD, 22% had present SVD, and 19% had missing SVD (Figure E3). Inconsistent Dvir-SVD classification was in 89% due to an increase in MPG 10 mm Hg or

TABLE 1. Patient characteristics at baseline and echocardiographic parameters at discharge for patients who underwent surgical aortic valve replacement

Patient characteristics	N = 1118
Age (y)	70.2 ± 9.0
Male	840 (75%)
Body surface area (m^2)	2.0 ± 0.2
Body mass index (kg/m^2)	29.4 ± 5.4
STS PROM (%)	1.60 [1.05-2.44]
Diabetes mellitus	298 (27%)
Hypertension	852 (76%)
Chronic obstructive pulmonary disease	130 (12%)
Left ventricle ejection fraction (%)	59 ± 10
Coronary artery disease	487 (44%)
NYHA class III/IV	472 (42%)
Previous stroke	45 (4%)
Peripheral vascular disease	81 (7%)
Renal dysfunction/insufficiency	119 (11%)
Echocardiography at discharge up to 30 d	
MPG (mm Hg)	13.1 ± 4.7
EOA (cm^2)	1.54 ± 0.36
DVI	0.49 ± 0.10

Numerical data are expressed as mean ± SD or median [interquartile range], and categorical data are expressed as count (percentage). *STS PROM*, Society of Thoracic Surgeons predicted risk of mortality; *NYHA*, New York Heart Association; *MPG*, mean pressure gradient; *EOA*, effective orifice area; *DVI*, Doppler velocity index.

TABLE 2. Consistency of contemporary definitions for hemodynamic structural valve deterioration after bioprosthetic aortic valve replacement

	3-6 mo to 1 y	1-2 y	2-3 y	3-4 y	4-5 y
Capodanno and colleagues[2]	1/3 (33%)	4/12 (33%)	4/12 (33%)	4/13 (31%)	1/7 (14%)
Dvir and colleagues[3]	1/2 (50%)	3/8 (38%)	2/6 (33%)	4/11 (36%)	1/5 (20%)
VARC 3	1/2 (50%)	3/9 (33%)	3/9 (33%)	3/10 (30%)	1/6 (17%)

Data indicate the percentage of patients labeled with hemodynamic SVD who were also so labeled at the subsequent follow-up visit. *VARC*, Valve Academic Research Consortium.

less, in 5.5% due to no decrease in EOA anymore, and in 5.5% due to an increase in MPG 10 mm Hg or less in combination with no decrease in EOA or DVI.

After the first classification of VARC3-SVD, 65% had absent SVD, 20% had present SVD, and 15% had missing SVD (Figure 3). The reason for inconsistent VARC3-SVD classification was in 23% an increase in MPG less than 10 mm Hg, in 9% related to the MPG increase in combination with EOA/DVI decrease criteria, in 41% not exceeding both the increase and absolute MPG threshold, in 23% not fulfilling both MPG criteria and the EOA/DVI criterium, and in 4% related to the EOA/DVI decrease criteria only.

The agreement on classification during follow-up between Capodanno-SVD and Dvir-SVD, expressed in Cohen's kappa coefficients, ranged between 0.60 and 0.92 (Table E3). For Capodanno-SVD and VARC3-SVD, the coefficients ranged between 0.80 and 0.91, and for Dvir-SVD and VARC3-SVD, these ranged between 0.70 and 1.00.

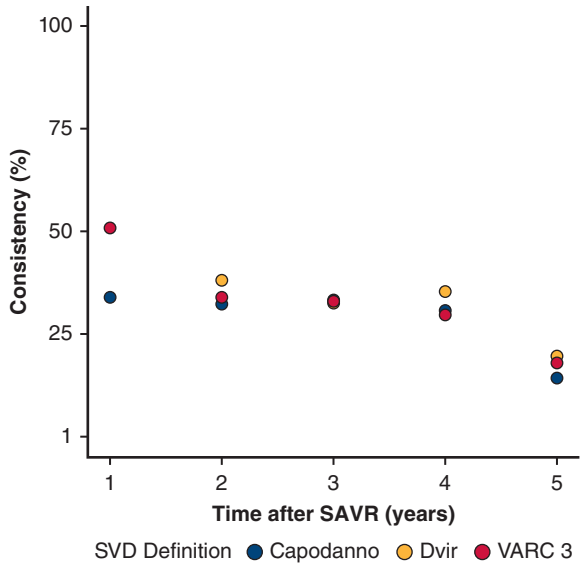

FIGURE 2. Consistency of contemporary definitions of hemodynamic SVD after bioprosthetic AVR. The consistency, represented on the y axis, was evaluated by calculating how many patients who were classified with hemodynamic SVD at 1 time point were also classified with hemodynamic SVD at the subsequent time point. *SAVR*, Surgical aortic valve replacement; *SVD*, structural valve deterioration; *VARC*, Valve Academic Research Consortium.

Longitudinal Variability in Mean Pressure Gradient

The average MPG at discharge was 13.1 ± 4.7 mm Hg (Table 1), and the change in MPG throughout 5-year follow-up was on average −1.1 mm Hg. The corresponding 95% prediction interval for the change within individuals ranged between −9.6 and 7.5 mm Hg. To give an example of variability during follow-up, the course of MPG is plotted for 5 randomly sampled patients with complete data (Figure 4). The change in MPG between consecutive time points is demonstrated per decile in Figure 5 and Table E4. At each interval, the MPG increased most in the lowest decile, whereas the MPG decreased most in the highest decile. For the deciles with lowest MPG, the average increase ranged between 1.2 and 2.3 mm Hg. For the deciles with highest MPG, the average decrease ranged between 1.0 and 5.9 mm Hg.

Subanalysis: Reference Echocardiogram at First Outpatient Clinic Visit

When the echocardiogram at the first outpatient clinic visit instead of discharge was used as reference, 65 patients were classified with Capodanno-SVD at least once during follow-up, 31 patients with Dvir-SVD, and 42 patients with VARC3-SVD (Table E5). The consistency of the SVD definitions is reported in Table E6, and the between-definition agreement is shown in Table E7. The heatmaps demonstrated within-patient inconsistency for all 3 definitions of SVD that was comparable to the observation with the discharge echocardiogram as the reference (Figures E4-E6).

Subanalysis: Patients Without Reintervention, Valve Thrombosis, or Endocarditis

For patients without reintervention, valve thrombosis, or endocarditis, the number of subjects who were classified with SVD are presented in Table E8. The consistency of the SVD definitions is reported in Table E9, and the between-definition agreement is shown in Table E10. After the first classification of present Capodanno-SVD, 25 patients (63%) had absent SVD (Figure E7). After the first classification of present Dvir-SVD and VARC3-SVD, 17 patients (65%, Figure E8) and 20 patients (71%, Figure E9) had absent SVD, respectively.

DISCUSSION

In this analysis of 1118 patients who underwent SAVR with core laboratory–adjudicated echocardiography data,

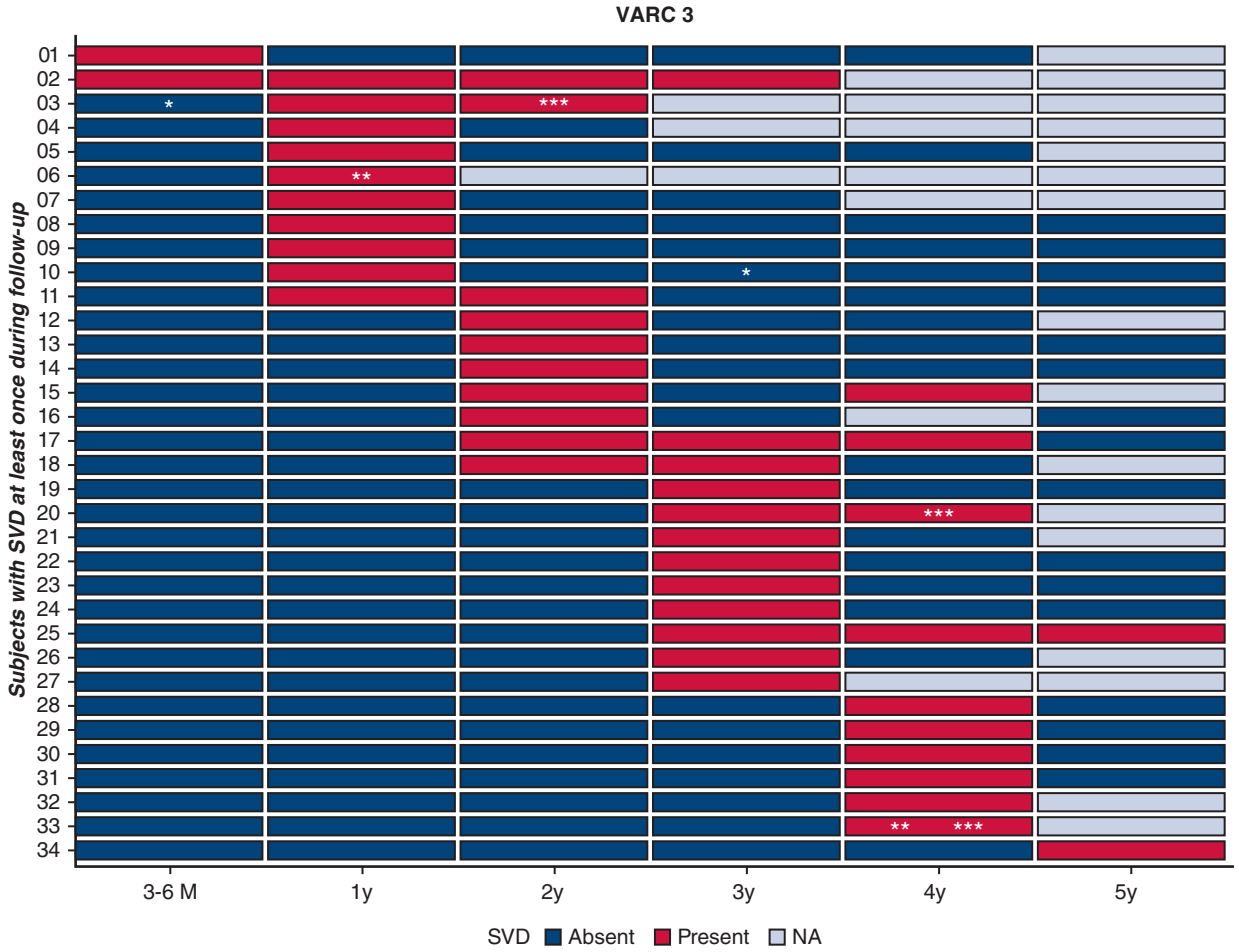

FIGURE 3. The consistency of hemodynamic SVD within patients who have been labeled with SVD at least once during follow-up according to the definition of the VARC 3. Each row represents 1 patient. *Endocarditis. **Valve thrombosis. ***Reintervention. *VARC*, Valve Academic Research Consortium; *SVD*, structural valve deterioration; *NA*, Not available.

the consistency of the classification of hemodynamic SVD using contemporary definitions was poor (Figure 6). After the first classification of hemodynamic SVD, up to 65% of patients were not classified with SVD at the subsequent visit.

Accurate diagnosis of SVD is challenging. Definitions based on clinical outcomes fall short in detecting dysfunction at times that are relevant to patients and may underestimate the occurrence of SVD.[1] Although hemodynamic definitions seem to offer a solution to these problems, these could also capture nonstructural dysfunction and noise variation due to imprecise measurements or due to natural variation. Capodanno and colleagues[2] proposed to include a change in MPG to distinguish between structural and nonstructural causes like prosthesis-patient mismatch. Thereafter, Dvir and colleagues[3] and the VARC 3[4] suggested incorporating additional parameters to prevent capturing noise: An increase in MPG should be accompanied by a decrease in EOA or DVI. Whether these new echocardiographic definitions of SVD correspond with adverse clinical outcomes is undetermined. One recent analysis suggests that the definitions of hemodynamic SVD by Capodanno and colleagues[2] and the VARC 3,[4] after additional verification of all potential cases by a panel of clinical experts, are associated with increased mortality.[8]

The underlying hypothesis of SVD is that prosthetic valve performance declines over time due to structural degeneration of the prosthesis caused by mechanical wear or immunological mechanisms. These irreversible processes do not resolve without reintervention and are assumed to be progressive over time. Therefore, a solid definition of SVD should consistently classify a patient with SVD after the initial diagnosis. In the current study, our aim was to test whether new echocardiographic definitions fulfill this requirement. However, because up to 65% of patients initially diagnosed were classified inconsistently over time, we conclude that none of the hemodynamic definitions of SVD capture structural degeneration of the

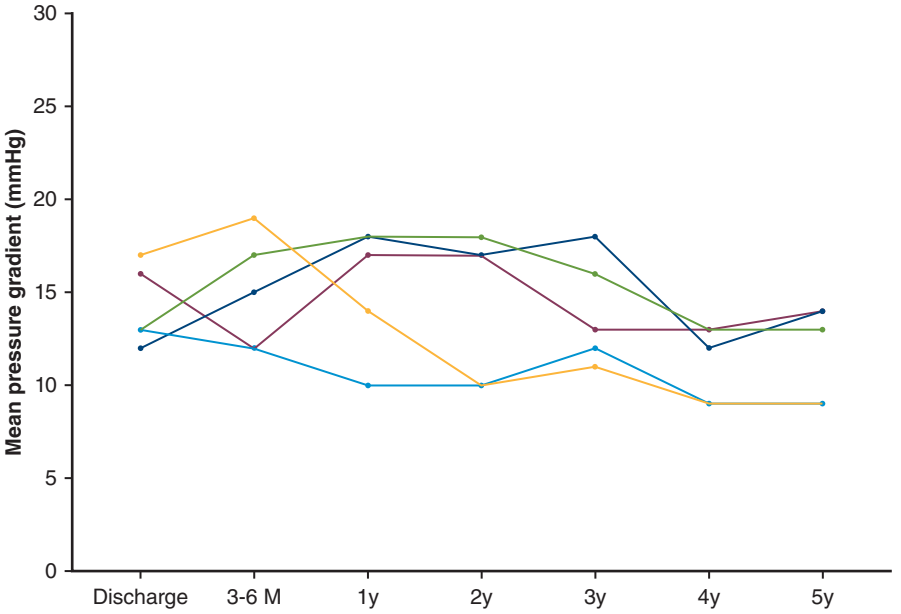

FIGURE 4. Change in MPG for 5 randomly sampled patients who did not undergo reintervention.

prosthesis accurately. Surprisingly, the amount of inconsistency was largely equal between definitions even though Dvir and colleagues[3] and the VARC 3[4] proposed more comprehensive definitions including EOA and DVI in addition to MPG. For these reasons, the results of the current study do not justify recommending any of these definitions as the most accurate one.

A potential explanation for inconsistent classification is within-patient variability in echocardiographic parameters. These parameters are proxies for prosthetic valve performance but are also affected by patient characteristics, for example, through blood flow and biological mechanisms such as circadian patterns, and by (random) measurement error. As a result, extreme echocardiographic values are likely to be followed by less extreme values during follow-up. This phenomenon, called "regression toward the mean,"[9] at least partially explains our results (Figure 5). Transient clinical events such as successfully treated endocarditis, valve thrombosis, or hypo-attenuated leaflet thickening (HALT) could also temporarily bring about abnormal echocardiographic parameters. However, inconsistency remained after excluding the first 2 sources

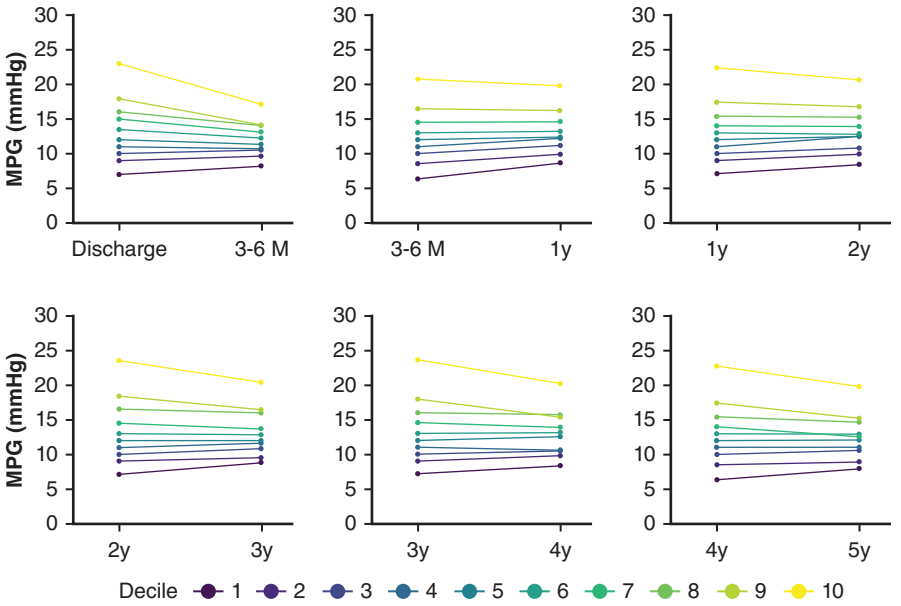

FIGURE 5. Change in MPG between subsequent follow-up visits stratified by deciles of MPG at the start of each period. *MPG*, Mean pressure gradient.

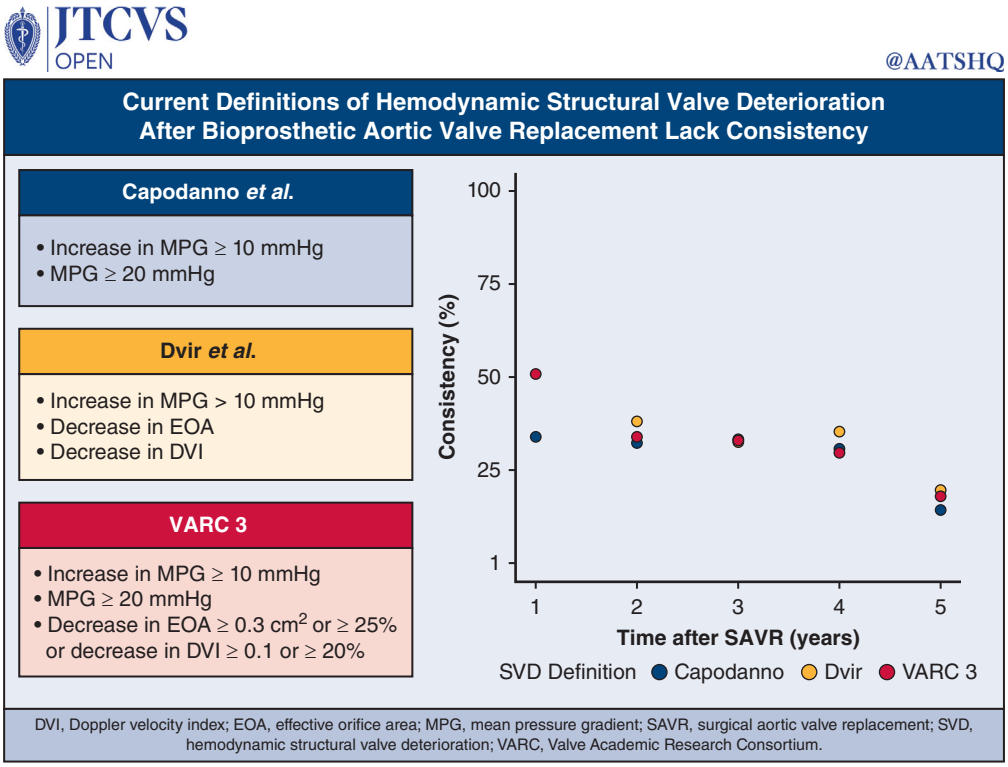

FIGURE 6. Current definitions of hemodynamic SVD after bioprosthetic AVR lack consistency. The consistency, represented on the y axis, was evaluated by calculating how many patients who were classified with SVD at 1 time point were also classified with SVD at the subsequent time point.[2-4] *MPG*, Mean pressure gradient; *EOA*, effective orifice area; *DVI*, Doppler velocity index; *VARC*, Valve Academic Research Consortium; *SAVR*, surgical aortic valve replacement; *SVD*, structural valve deterioration; *VARC*, Valve Academic Research Consortium.

in a subanalysis. Information on HALT was not available because the PERIGON trial lacked protocolized computed tomography examinations, but HALT is unlikely to explain such a large inconsistency in SVD classification.[10,11] In this analysis, inconsistent classification of SVD by any definition was predominantly related to not exceeding the increase and absolute thresholds for MPG anymore and to a lesser extent related to the criteria for EOA or DVI.

In this study, we focused on consistency of present SVD classification because this was considered clinically most relevant and aligns with the underlying hypothesis about SVD that is described above. Moreover, in daily practice, hemodynamic SVD definitions are used to identify those patients who might benefit from a reintervention. Thus, we did not focus on the consistency of absent SVD because we believe that it will hardly ever occur that a patient with a structurally degenerated valve would have normal echocardiographic parameters. As expected, the consistency of absent SVD was high, that is, 1064 of the 1118 were never classified with SVD by any definition throughout 5-year follow-up.

In theory, inconsistent SVD classification could lead to unnecessary reinterventions. However, because the decision to reoperate is predominantly based on clinical symptoms, we do not expect this to occur often. In addition, the VARC 3[4] states that "a definite diagnosis of SVD should not rely on the measurement of a single hemodynamic parameter, and preferably should incorporate evidence from at least 2 serial echocardiograms." Furthermore, this consortium recommends distinguishing bioprosthetic valve dysfunction, such as hemodynamic SVD, from bioprosthetic valve failure (BVF), which is the relevant and clinically meaningful variant for the patient. We demonstrated that dysfunction can be highly unreliable; thus, it is crucial to repeat measurements, assess valve leaflet morphology, and investigate the burden for the patient when considering reintervention.

For the research setting, hemodynamic SVD is proposed by the VARC 3 as an appropriate end point for durability of prosthetic valves.[4] However, this setting lacks the important nuances mentioned above because researchers generally can rely only on numerical values of echocardiographic parameters to adjudicate SVD. Considering our results, hemodynamic SVD, as currently defined, will be an unreliable end point for prosthetic valve durability in scientific research.

To develop more robust definitions, future research should investigate which definition of hemodynamic SVD corresponds best with clinically relevant outcomes such as BVF, valve-in-valve reinterventions, or redo

surgery. Although this sounds like a suggestion to return to previous clinical definitions, it is not. Revised definitions should still be based on hemodynamic criteria, although altered to correspond best to clinical events and not based on the events themselves. Such revised definitions would not be applicable to only the most severe cases because BVF is included, which is independent of eligibility for reinterventions. For example, BVF is present in case of new-onset or worsening symptoms, pathologic left ventricle remodeling, or secondary pulmonary hypertension.[1] Furthermore, accumulating experience and developments with valve-in-valve procedures and redo surgery have boosted treatments options for patients formerly unfit for reinterventions. Last, by adhering to hemodynamic criteria, revised definitions keep the advantage of detecting bioprosthetic dysfunction at times that are relevant to patients. We consider echocardiography to be the appropriate primary imaging modality to assess prosthetic valve performance. Any red flags detected during echocardiographic screening should be confirmed with other modalities, such as computed tomography or cardiac magnetic resonance.[1]

Study Strengths and Limitations

The current study has several potential limitations. The follow-up duration is relatively short. As follow-up progresses, the classification of SVD based on hemodynamic parameters could become more stable due to progressive degeneration of the bioprostheses. Furthermore, longer follow-up would lead to more clinical events, which would enable us to study the association between hemodynamic SVD and clinical outcomes. Although adverse event information was present, the study lacked information on specific patient-reported symptoms related to SVD. Another limitation is missing data. The main reason for missing data is that not all patients had completed the 5-year follow-up visit at the time of this analysis, which we consider as missing completely at random. Loss to follow-up could bias our results, because this may not be random. Because only 15 patients were lost to follow-up at 5 years, we consider this impact to be minimal. More complete information would increase the reliability of our findings on SVD consistency. Data imputations were deemed to obscure the interpretation of the results and therefore not applied. Last, the results could be less generalizable to populations of intermediate or high surgical risk because the study population was restricted to relatively low-risk patients. On the contrary, the study has several strengths. All patients received the same stented bioprosthesis, and longitudinal data were gathered in a prospective manner. An independent clinical events committee adjudicated all valve-related events, and a single core laboratory assessed all echocardiograms. Moreover, the international, multicenter setting and the allowance of concomitant procedures such as coronary artery bypass grafting boost the generalizability of the results.

Only moderate or greater stenotic hemodynamic SVD was studied in the current analysis. Thus, no conclusions can be drawn about the consistency of hemodynamic SVD due to regurgitation.

CONCLUSIONS

The current definitions of hemodynamic SVD are strong negative predictors but inconsistent positive discriminators for the detection of stenotic hemodynamic SVD. This inconsistency may be explained by large within-patient variability in echocardiographic parameters. Although the diagnosis of SVD may be categorical, echocardiographic indices lack this degree of precision in the first 5 years after SAVR. The observed inconsistencies obscure the detection of true valve degeneration, which is important to consider for clinicians and researchers applying this concept. For clinical usefulness and reliability of research findings, consistency of SVD classification is key.

Conflict of Interest Statement

Dr Velders: institutional research grant and speaker's honorarium paid to his department by Medtronic. Dr Vriesendorp: institutional research grant and reimbursement of travel expenses from Medtronic. Dr Asch: no personal conflicts of interest, but his organization receives grants or research contracts from Medtronic, Abbott, Edwards Lifesciences, Boston Scientific, Biotronik, Corcym, and HLT Medical. Dr Reardon: consultant to Medtronic, Abbott Medical, Boston Scientific, Gore Medical, and Transverse Medical; the fees are paid to his department. Dr Dagenais: proctor and speaker for Medtronic and COOK Medical. Dr Moront: trainer and consultant for Medtronic, trainer and speaker for AtriCure, and speaker and consultant for Haemonetics. Dr Sabik: Principal Investigator, PERIGON Pivotal Trial for Medtronic. Prof Klautz: research support, consultation fees, and Principal Investigator, PERIGON Pivotal Trial for Medtronic. All other authors reported no conflicts of interest.

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Key Words: bioprosthetic aortic valve replacement, echocardiography, hemodynamic structural valve deterioration

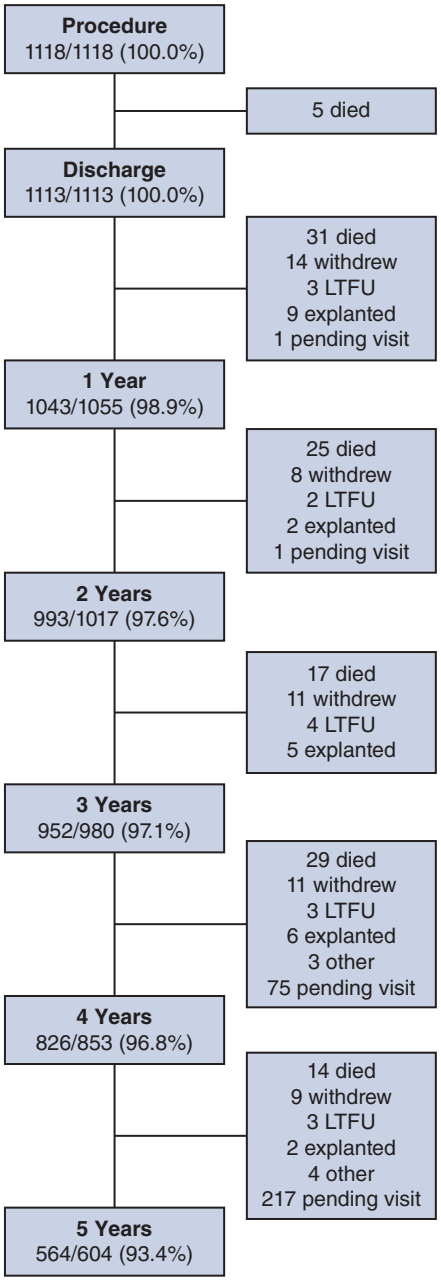

FIGURE E1. Patient follow-up through 5 years. *LTFU*, Loss to follow-up. Reproduced from Klautz and colleagues.[7]

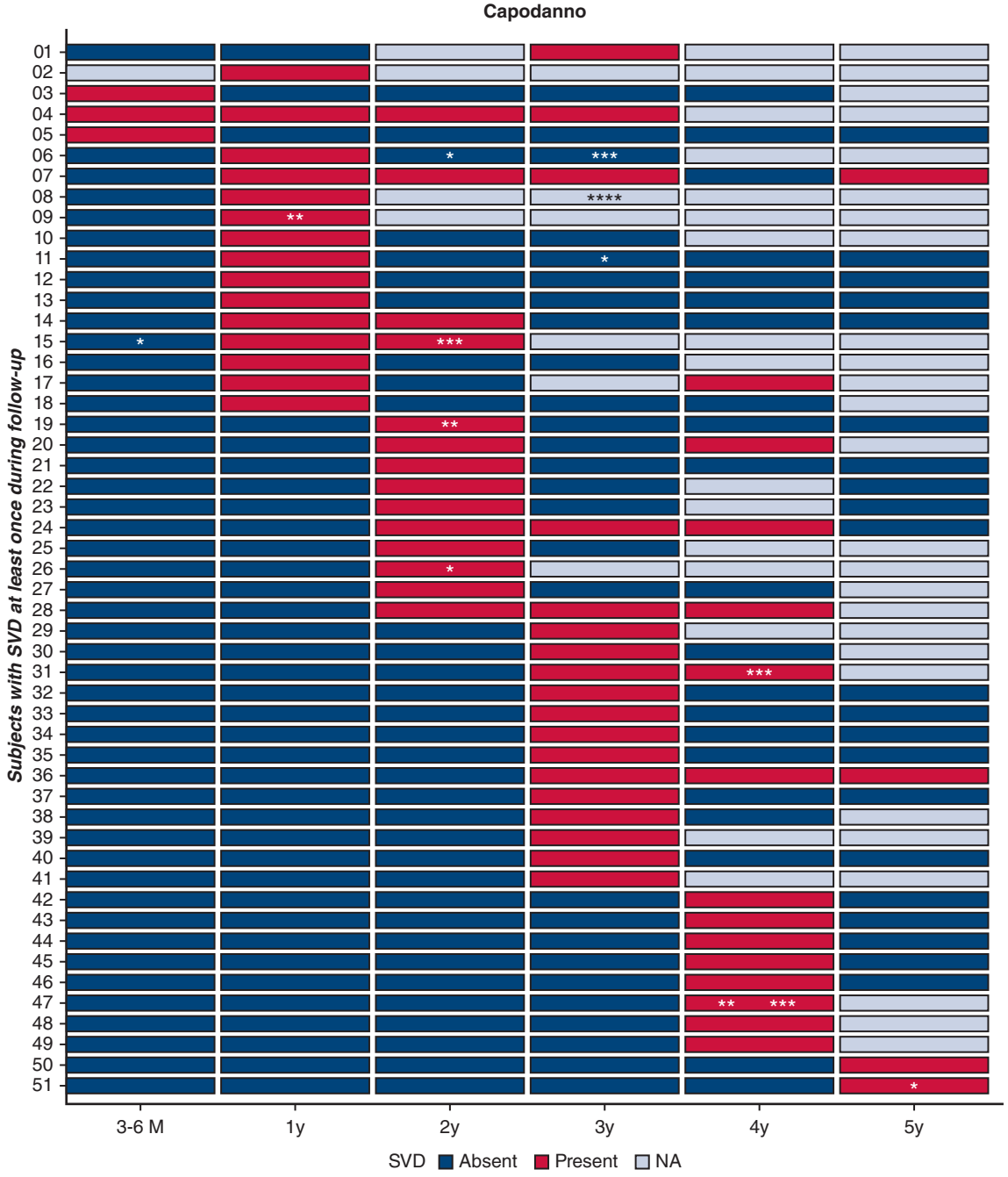

FIGURE E2. Consistency of hemodynamic SVD within patients who have been labeled with SVD at least once during follow-up according to Capodanno and colleagues' definition.[2] Each row represents 1 patient. *Endocarditis. **Valve thrombosis. ***Reintervention. ****Death. *SVD*, Structural valve deterioration; *NA*, not available.

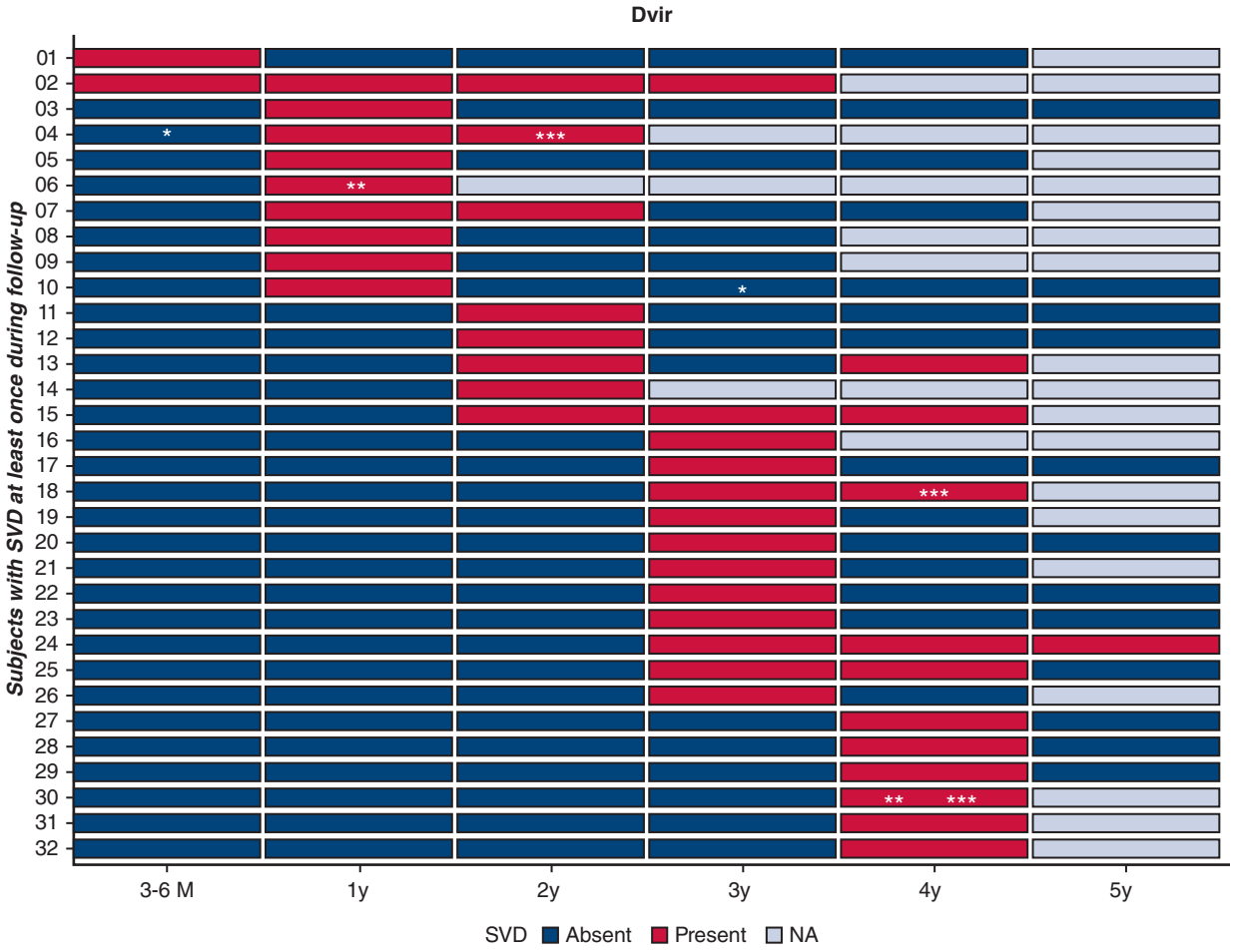

FIGURE E3. The consistency of hemodynamic SVD within patients who have been labeled with SVD at least once during follow-up according to Dvir and colleagues' definition.[3] Each row represents 1 patient. *Endocarditis. **Valve thrombosis. ***Reintervention. *SVD*, Structural valve deterioration; *NA*, not available.

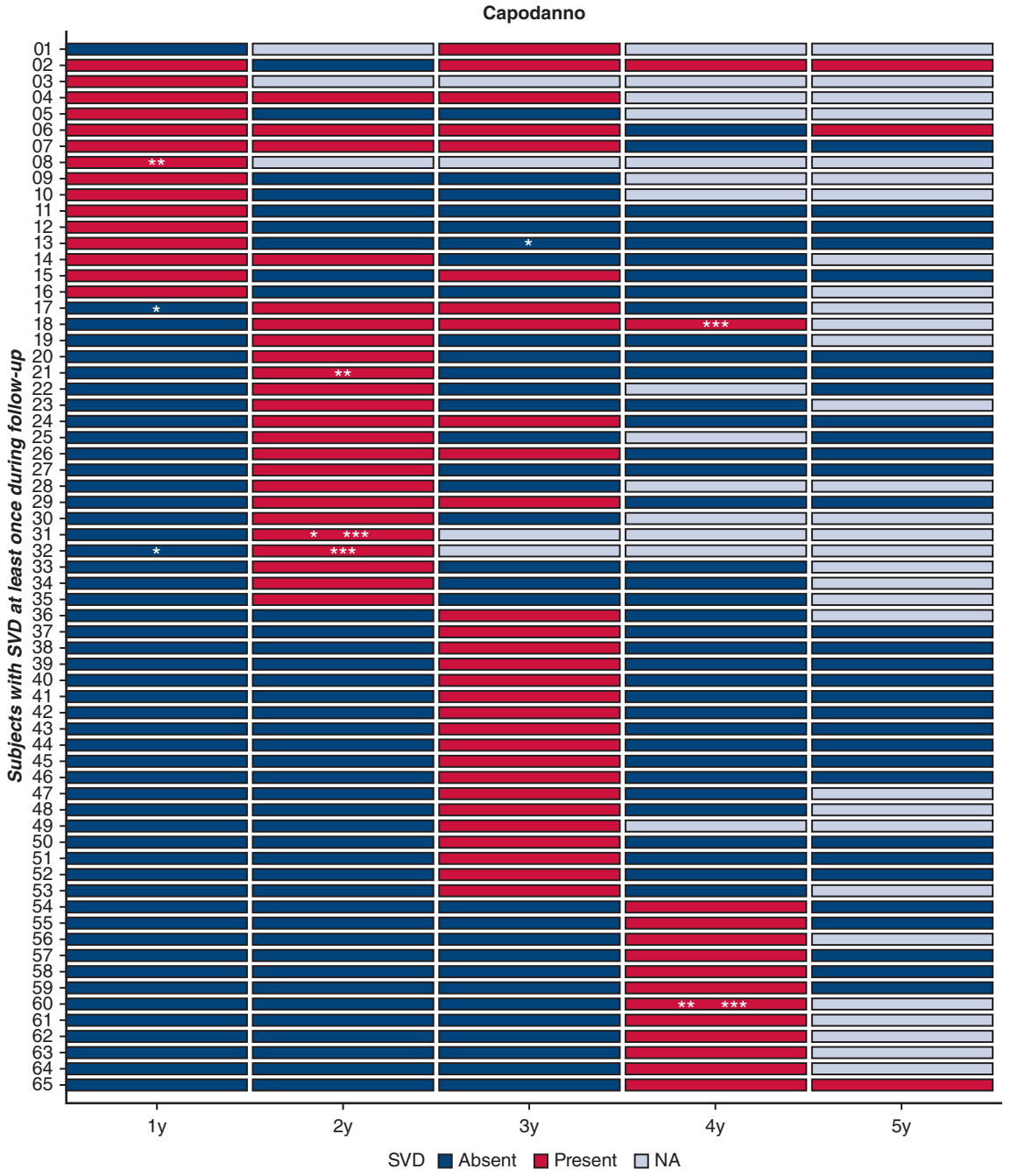

FIGURE E4. Consistency of hemodynamic SVD according to Capodanno and colleagues[2] within patients who have been labeled with SVD at least once during follow-up when the echocardiogram from the first outpatient visit is used as the reference. Each row represents 1 patient. *Endocarditis. **Valve thrombosis. ***Reintervention. *SVD*, Structural valve deterioration; *NA*, not available.

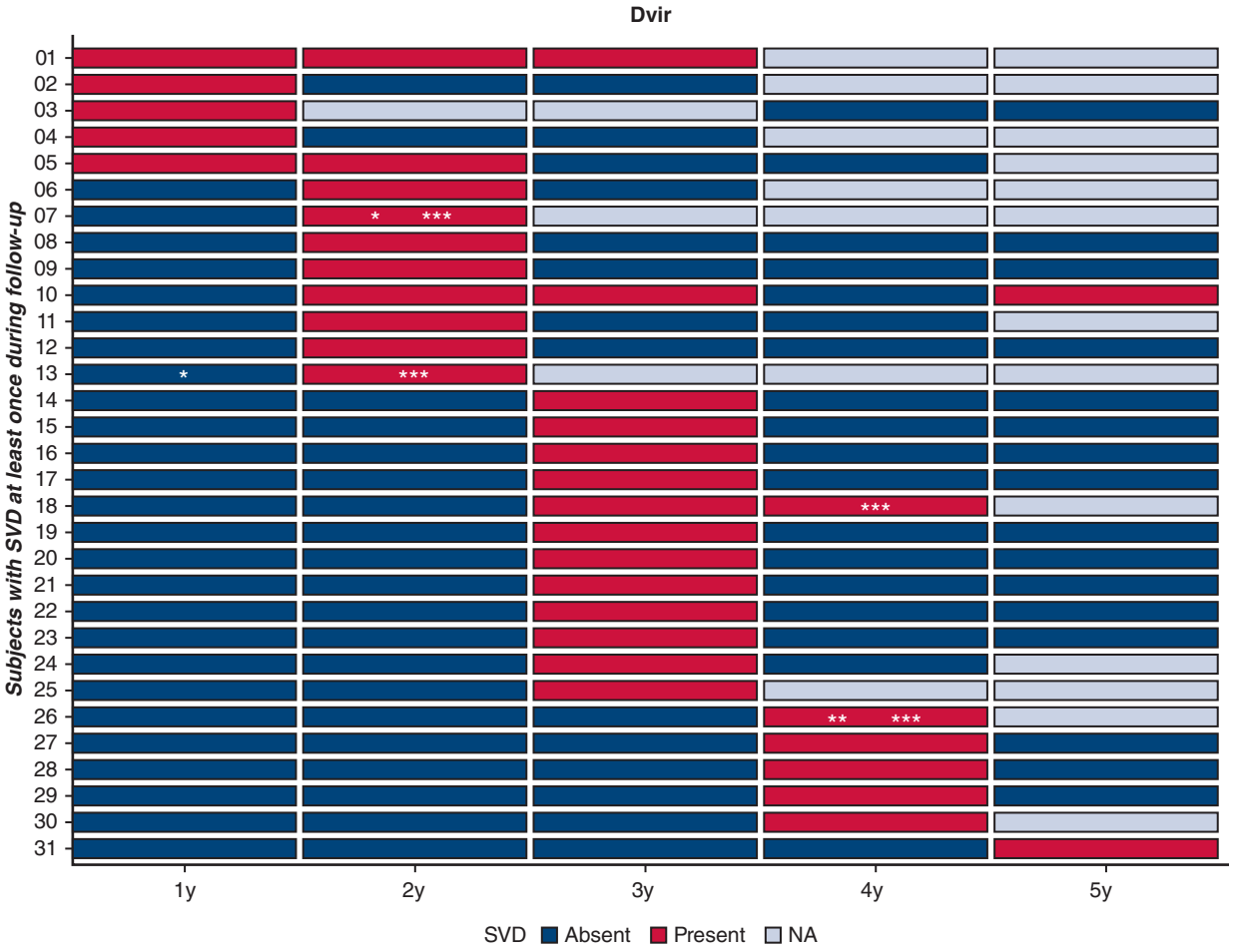

FIGURE E5. Consistency of hemodynamic SVD according to Dvir and colleagues[3] within patients who have been labeled with SVD at least once during follow-up when the echocardiogram from the first outpatient visit is used as the reference. Each row represents 1 patient. *Endocarditis. **Valve thrombosis. ***Reintervention. *SVD*, Structural valve deterioration; *NA*, not available.

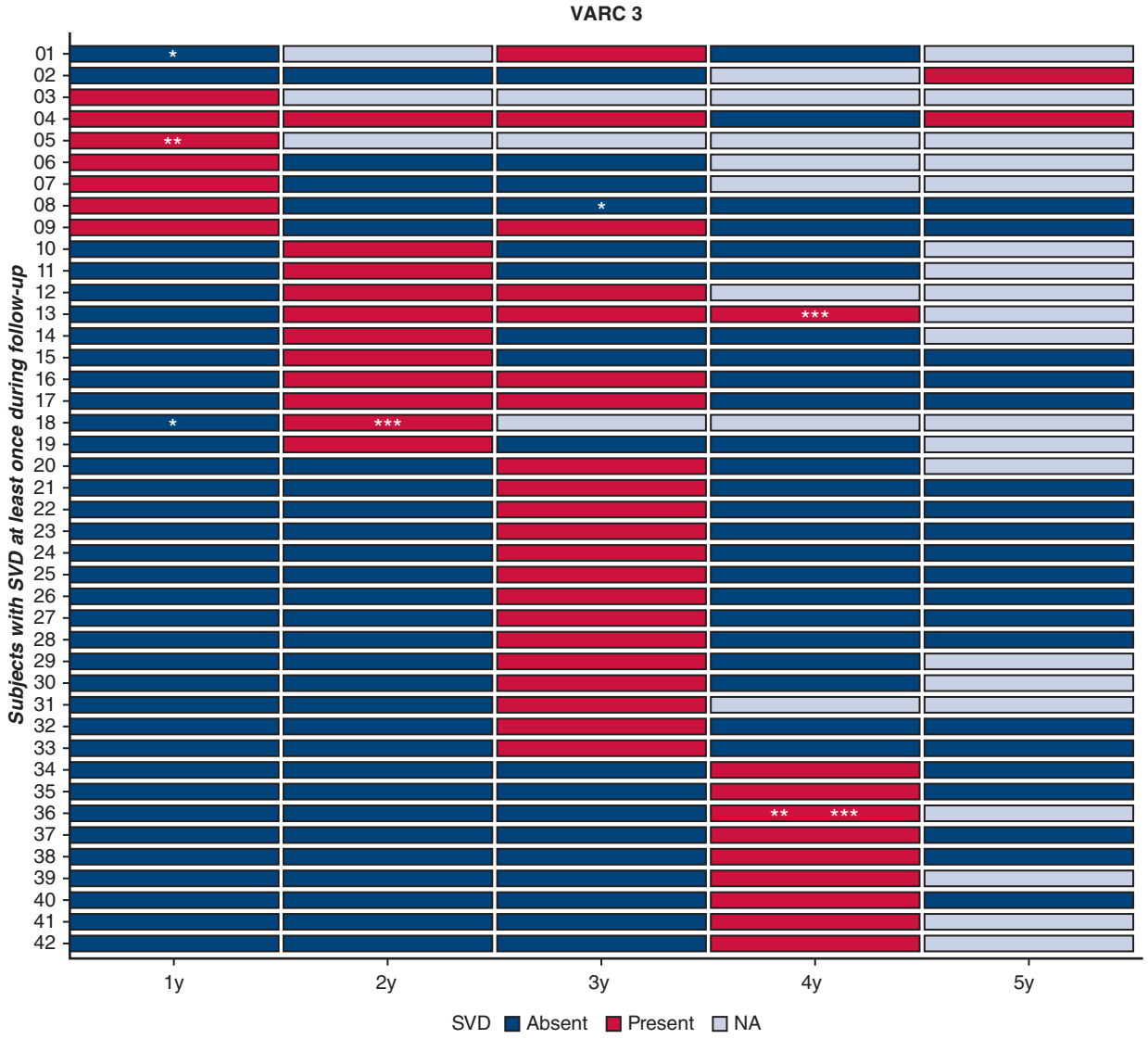

FIGURE E6. Consistency of hemodynamic SVD according to the VARC 3 definition within patients who have been labeled with SVD at least once during follow-up when the echocardiogram from the first outpatient visit is used as the reference. Each row represents 1 patient. *Endocarditis. **Valve thrombosis. ***Reintervention. *SVD*, Structural valve deterioration; *NA*, not available; *VARC*, Valve Academic Research Consortium.

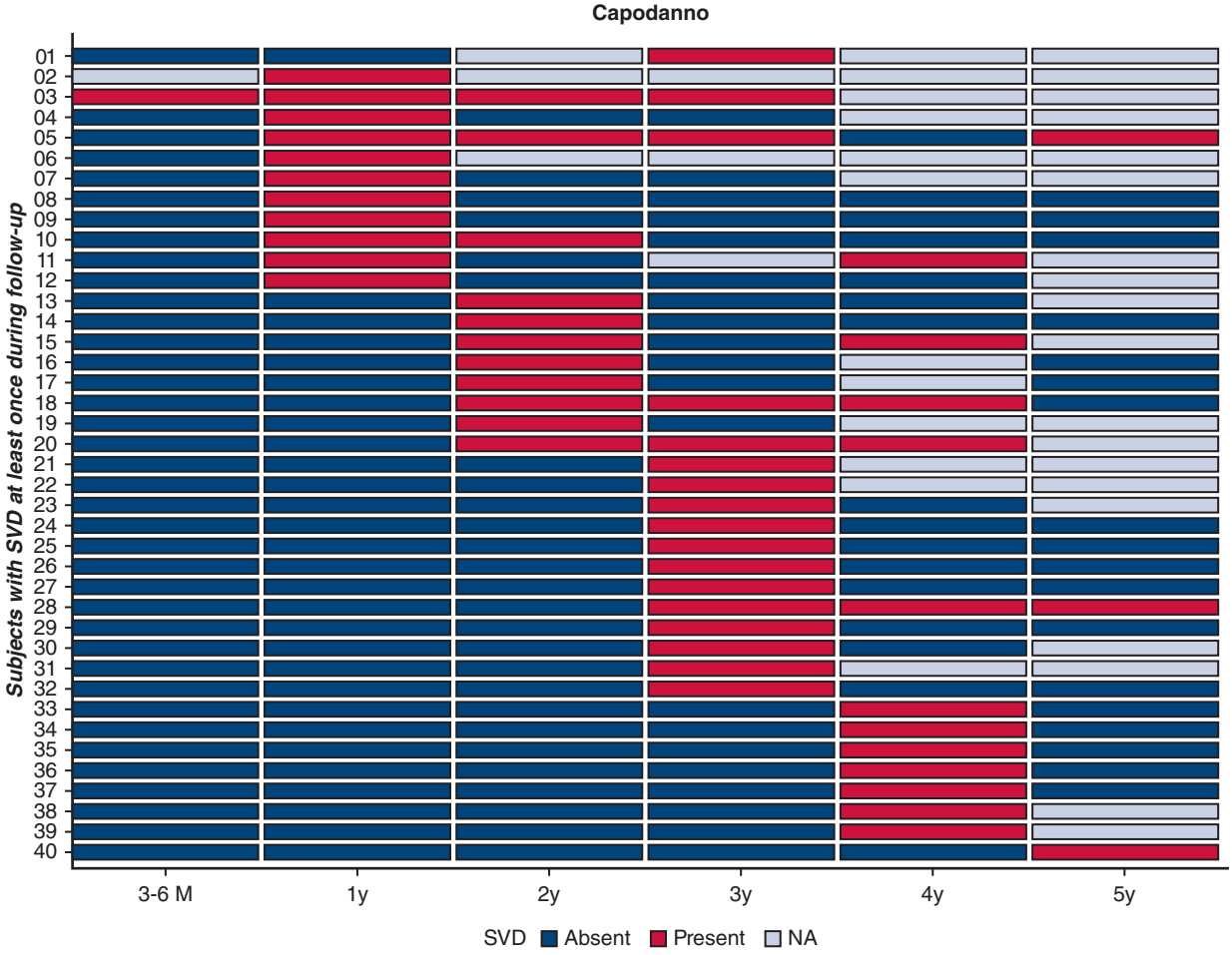

FIGURE E7. Consistency of hemodynamic SVD according to Capodanno and colleagues[2] within patients who have been labeled with SVD at least once during follow-up and did not have a reintervention, valve thrombosis, or endocarditis. Each row represents 1 patient. *SVD*, Structural valve deterioration; *NA*, not available.

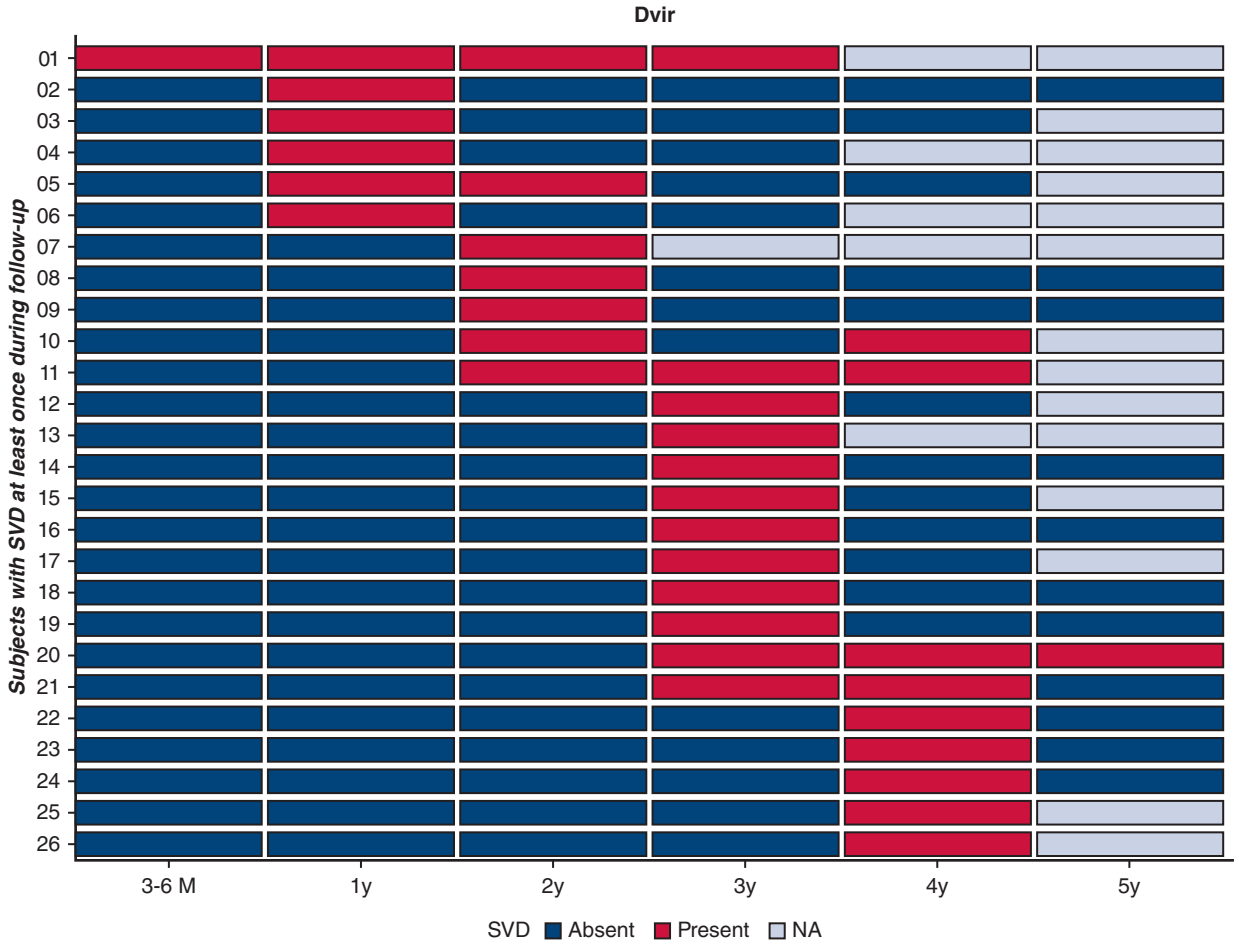

FIGURE E8. Consistency of hemodynamic SVD according to Dvir and colleagues[3] within patients who have been labeled with SVD at least once during follow-up and did not have a reintervention, valve thrombosis, or endocarditis. Each row represents 1 patient. *SVD*, Structural valve deterioration; *NA*, not available.

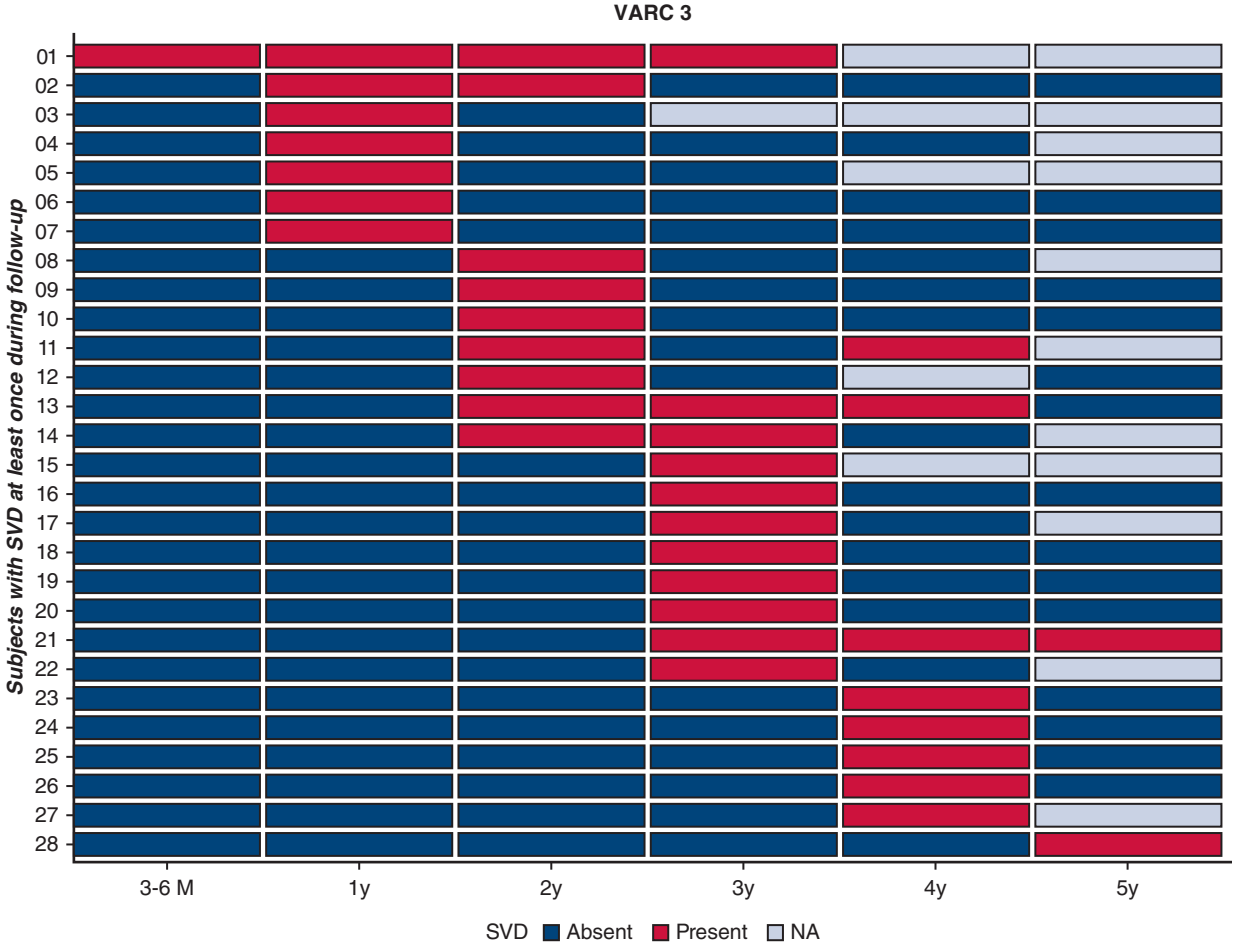

FIGURE E9. Consistency of hemodynamic SVD according to the VARC 3 definition within patients who have been labeled with SVD at least once during follow-up and did not have a reintervention, valve thrombosis, or endocarditis. Each row represents 1 patient. *SVD*, Structural valve deterioration; *NA*, not available; *VARC*, Valve Academic Research Consortium.

TABLE E1. Missing echocardiographic data for the current analysis

	Baseline	Discharge	3-6 mo	1 y	2 y	3 y	4 y	5 y
MPG	29 (2.6%)	44 (3.9%)	70 (6.3%)	104 (9.3%)	162 (14.5%)	250 (22.4%)	391 (35.0%)	689 (61.6%)
EOA	106 (9.5%)	169 (15.1%)	122 (10.9%)	140 (12.5%)	208 (18.6%)	312 (27.9%)	490 (43.8%)	762 (68.2%)
DVI	61 (5.5%)	83 (7.4%)	88 (7.9%)	121 (10.8%)	193 (17.3%)	293 (26.2%)	458 (41.0%)	736 (65.8%)

The number of patients at baseline (ie, 1118) was used as denominator to calculate all percentages. An important reason for missing data is that only 564 patients completed their 5-year visit at the time of the data snap for this analysis (Figure E1). *MPG*, Mean pressure gradient; *EOA*, effective orifice area; *DVI*, Doppler velocity index.

TABLE E2. Hemodynamic structural valve deterioration occurrence per definition during follow-up after aortic valve replacement

	Ever	3-6 mo	1 y	2 y	3 y	4 y	5 y
Capodanno and colleagues[2]	51	3 (0.3%)	15 (1.5%)	14 (1.5%)	18 (2.1%)	14 (1.9%)	4 (0.9%)
Dvir and colleagues[3]	32	2 (0.2%)	9 (0.9%)	8 (0.9%)	13 (1.5%)	11 (1.6%)	1 (0.2%)
VARC 3	34	2 (0.2%)	10 (1.0%)	10 (1.1%)	12 (1.4%)	10 (1.4%)	2 (0.5%)

VARC, Valve Academic Research Consortium.

TABLE E3. Agreement between contemporary definitions of hemodynamic structural valve deterioration for patients who underwent bioprosthetic aortic valve replacement

	Cohen's kappa coefficient (95% CI)					
	3-6 mo	1 y	2 y	3 y	4 y	5 y
Capodanno-Dvir	0.80 (0.41-1.00)	0.69 (0.48-0.91)	0.60 (0.34-0.85)	0.77 (0.60-0.94)	0.92 (0.80-1.00)	0.67 (0.05-1.00)
Capodanno-VARC 3	0.80 (0.41-1.00)	0.87 (0.72-1.00)	0.91 (0.78-1.00)	0.80 (0.64-0.96)	0.91 (0.78-1.00)	0.80 (0.41-1.00)
Dvir-VARC 3	1.00 (1.00-1.00)	0.73 (0.51-0.96)	0.70 (0.46-0.95)	0.96 (0.88-1.00)	0.85 (0.69-1.00)	1.00 (1.00–1.00)

VARC, Valve Academic Research Consortium.

TABLE E4. Change in mean pressure gradient over time for deciles of mean pressure gradient at start of each interval

Decile	30 d to 3-6 mo	3-6 mo to 1 y	1-2 y	2-3 y	3-4 y	4-5 y
1	1.2 ± 2.5	2.3 ± 2.5	1.3 ± 2.4	1.8 ± 2.6	1.2 ± 2.5	1.6 ± 1.8
2	0.6 ± 2.9	1.7 ± 2.6	1.0 ± 2.7	0.5 ± 1.9	0.8 ± 2.4	0.4 ± 1.9
3	0.5 ± 2.7	1.1 ± 2.7	0.8 ± 2.9	0.8 ± 3.1	0.5 ± 2.3	0.6 ± 2.4
4	−0.3 ± 2.8	1.2 ± 2.9	1.4 ± 4.3	0.6 ± 2.5	−0.3 ± 2.3	0.1 ± 2.5
5	−0.7 ± 2.9	1.2 ± 3.2	0.5 ± 3.7	0.0 ± 2.8	0.5 ± 3.5	0.1 ± 3.7
6	−1.3 ± 3.1	0.4 ± 3.0	−0.2 ± 3.3	−0.2 ± 3.2	0.2 ± 3.5	−0.1 ± 2.4
7	−1.9 ± 3.9	0.2 ± 3.4	−0.1 ± 3.5	−0.7 ± 2.1	−0.6 ± 3.0	−1.5 ± 2.2
8	−1.9 ± 4.0	0.2 ± 3.8	−0.2 ± 3.7	−0.5 ± 3.9	−0.3 ± 3.3	−0.8 ± 3.3
9	−3.8 ± 4.0	−0.3 ± 3.9	−0.7 ± 3.1	−2.0 ± 4.2	−2.6 ± 3.1	−2.2 ± 3.4
10	−5.9 ± 5.3	−1.0 ± 5.2	−1.8 ± 5.3	−3.2 ± 5.9	−3.4 ± 5.1	−3.0 ± 5.2

Reported are the mean change ± SD in mm Hg. Decile 1 had the lowest average MPG, and decile 10 had the highest average MPG at the start of each interval.

TABLE E5. Hemodynamic structural valve deterioration occurrence per definition during follow-up after aortic valve replacement when the echocardiogram from the first outpatient visit is used as reference

	Ever	1 y	2 y	3 y	4 y	5 y
Capodanno and colleagues[2]	65	15 (1.5%)	23 (2.4%)	29 (3.3%)	14 (1.9%)	3 (0.7%)
Dvir and colleagues[3]	31	5 (0.5%)	10 (1.1%)	14 (1.6%)	6 (0.8%)	2 (0.5%)
VARC 3	42	7 (0.7%)	11 (1.2%)	21 (2.4%)	10 (1.4%)	2 (0.5%)

VARC, Valve Academic Research Consortium.

TABLE E6. Consistency of contemporary definitions of hemodynamic structural valve deterioration after bioprosthetic aortic valve replacement when the echocardiogram from the first outpatient visit is used as reference

	Consistency of hemodynamic structural valve deterioration diagnosis			
	1-2 y	2-3 y	3-4 y	4-5 y
Capodanno and colleagues[2]	31%	33%	8%	29%
Dvir and colleagues[3]	50%	25%	9%	0%
VARC 3	20%	50%	5%	0%

Data indicate the percentage of patients labeled with hemodynamic SVD who were also so labeled at the subsequent follow-up visit. *VARC*, Valve Academic Research Consortium.

TABLE E7. Agreement between contemporary definitions of structural valve deterioration for patients who underwent bioprosthetic aortic valve replacement when the echocardiogram from the first outpatient visit is used as reference

	Cohen's kappa coefficient (95% CI)				
	1 y	2 y	3 y	4 y	5 y
Capodanno-Dvir	0.50 (0.23-0.77)	0.64 (0.43-0.85)	0.69 (0.53-0.86)	0.66 (0.41-0.92)	0.67 (0.05-1.00)
Capodanno-VARC 3	0.63 (0.40-0.87)	0.76 (0.58-0.93)	0.87 (0.77-0.97)	0.91 (0.78-1.00)	1.00 (1.00-1.00)
Dvir-VARC 3	0.33 (0.00-0.67)	0.49 (0.22-0.76)	0.78 (0.63-0.94)	0.75 (0.51-0.99)	0.67 (0.05-1.00)

TABLE E8. Hemodynamic structural valve deterioration occurrence per definition during follow-up after aortic valve replacement in patients without reintervention, valve thrombosis, or endocarditis

	Ever	3-6 mo	1 y	2 y	3 y	4 y	5 y
Capodanno and colleagues[2]	40	3 (0.3%)	11 (1.1%)	11 (1.2%)	17 (2.0%)	12 (1.7%)	3 (0.7%)
Dvir and colleagues[3]	26	2 (0.2%)	6 (0.6%)	7 (0.8%)	12 (1.5%)	9 (1.3%)	1 (0.2%)
VARC 3	28	2 (0.2%)	7 (0.7%)	9 (1.0%)	11 (1.3%)	8 (1.1%)	2 (0.5%)

VARC, Valve Academic Research Consortium.

TABLE E9. Consistency of contemporary definitions of hemodynamic structural valve deterioration after bioprosthetic aortic valve replacement for patients without reintervention, valve thrombosis, or endocarditis

	Consistency of hemodynamic SVD diagnosis				
	3-6 mo to 1 y	**1-2 y**	**2-3 y**	**3-4 y**	**4-5 y**
Capodanno and colleagues[2]	33%	33%	36%	25%	14%
Dvir and colleagues[3]	50%	33%	33%	30%	20%
VARC 3	50%	29%	33%	22%	17%

Data indicate the percentage of patients labeled with hemodynamic SVD who were also so labeled at the subsequent follow-up visit. *SVD*, Structural valve deterioration; *VARC*, Valve Academic Research Consortium.

TABLE E10. Agreement between contemporary definitions of structural valve deterioration after bioprosthetic aortic valve replacement for patients without reintervention, valve thrombosis, or endocarditis

	Cohen's kappa coefficient (95% CI)					
	3-6 mo	**1 y**	**2 y**	**3 y**	**4 y**	**5 y**
Capodanno-Dvir	0.80 (0.41-1.00)	0.62 (0.34-0.90)	0.58 (0.30-0.86)	0.75 (0.58-0.93)	0.90 (0.76-1.00)	0.67 (0.05-1.00)
Capodanno-VARC 3	0.80 (0.41-1.00)	0.87 (0.70-1.00)	0.95 (0.84-1.00)	0.78 (0.61-0.95)	0.89 (0.73-1.00)	0.80 (0.41-1.00)
Dvir-VARC 3	1.00 (1.00-1.00)	0.61 (0.30-0.93)	0.66 (0.39-0.94)	0.96 (0.87-1.00)	0.82 (0.62-1.00)	1.00 (1.00-1.00)

VARC, Valve Academic Research Consortium.