Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 57, No. 9, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.11.019

CLINICAL RESEARCH — Interventional Cardiology

The Valve-in-Valve Technique for Treatment of Aortic Bioprosthesis Malposition

An Analysis of Incidence and 1-Year Clinical Outcomes From the Italian CoreValve Registry

Gian Paolo Ussia, MD,*† Marco Barbanti, MD,* Angelo Ramondo, MD,‡ Anna Sonia Petronio, MD,§ Federica Ettori, MD,‖ Gennaro Santoro, MD,¶ Silvio Klugmann, MD,# Francesco Bedogni, MD,** Francesco Maisano, MD,†† Antonio Marzocchi, MD,‡‡ Arnaldo Poli, MD,§§ Massimo Napodano, MD,‡ Corrado Tamburino, MD, PHD*†

Catania, Padova, Pisa, Brescia, Florence, Milano, Bologna, and Legnano, Italy

Objectives We appraised the incidence and clinical outcomes of patients who were treated with the valve-in-valve (ViV) technique for hemodynamically destabilizing paraprosthetic leak (PPL).

Background Device malpositioning causing severe PPL after transcatheter aortic valve implantation is not an uncommon finding. It occurs after release of the prosthesis, leading to hemodynamic compromise. It can be managed successfully in selected cases with implantation of a second device inside the malpositioned primary prosthesis (ViV technique).

Methods Consecutive patients (n = 663) who underwent transcatheter aortic valve implantation with the 18-F CoreValve ReValving System (Medtronic, Inc., Minneapolis, Minnesota) at 14 centers across Italy were included in this prospective web-based registry. We identified patients treated with the ViV technique for severe PPL and analyzed their clinical and echocardiographic outcomes. Primary end points were major adverse cerebrovascular and cardiac events and prosthesis performance at the 30-day and midterm follow-up.

Results Overall procedural success was obtained in 650 patients (98.0%). The ViV technique was used in 24 (3.6%) of 663 patients. The 30-day major adverse cerebrovascular and cardiac event rates were 7.0% and 0% in patients undergoing the standard procedure and ViV technique, respectively (p = 0.185); the mortality rates were 5.6% versus 0% in patients undergoing the standard procedure and ViV technique, respectively (p = 0.238). There was an improvement in the mean transaortic gradient in all patients without significant difference between the 2 groups (from 52.1 ± 17.1 mm Hg and 45.4 ± 14.8 mm Hg [p = 0.060] to 10.1 ± 4.2 mm Hg and 10.5 ± 5.2 mm Hg, respectively [p = 0.838]). At 12 months, the major adverse cerebrovascular and cardiac event rates in the standard procedure and ViV technique groups were 4.5% and 14.1%, respectively (p = 0.158), and the mortality rates were 4.5% versus 13.7%, respectively (p = 0.230).

Conclusions This large, multicenter registry provides important information about the feasibility, safety, and efficacy of the ViV technique with the third-generation CoreValve ReValving System. The clinical and echocardiographic end points compare favorably with those of patients undergoing the standard procedure. The ViV technique offers a viable therapeutic option in patients with acute significant PPL without recourse to emergent surgery. (J Am Coll Cardiol 2011;57:1062–8) © 2011 by the American College of Cardiology Foundation

Transcatheter aortic valve implantation (TAVI) has matured into a viable treatment alternative for patients with severe aortic stenosis at high-risk for conventional aortic valve replacement (1,2). Large registries have indicated that TAVI can be accomplished successfully with acute and midterm clinical outcomes that compare favorably with those of aortic valve replacement (1,2).

TAVI is technically a challenging procedure even for experienced operators. A careful assessment of the anatomic features of the aortic apparatus is an integral part of the

From the *Ferrarotto Hospital, University of Catania, Catania, Italy; †ETNA Foundation, Catania, Italy; ‡University of Padova, Padova, Italy; §AOU Pisana, Pisa, Italy; ‖Spedali Civili, Brescia, Italy; ¶Careggi Hospital, Florence, Italy; #Niguarda Ca'Granda Hospital, Milano, Italy; **Clinical Institute S'Ambrogio, Milano, Italy; ††S. Raffaele Hospital, Milano, Italy; ‡‡Policlinico S. Orsola-Malpighi, Bologna, Italy; and the §§Ospedale Civile, Legnano, Italy. Drs. Ussia, Ramondo, Petronio, Ettori, Santoro, and Bedogni are proctors for Medtronic Incorporation. All other authors have reported that they have no relationships to disclose.

Manuscript received May 13, 2010; revised manuscript received October 29, 2010, accepted November 8, 2010.

procedure (3). Accurate positioning of the device with respect to the aortic annulus is critical for ensuring a successful procedure, whereas suboptimal deployment can result in significant hemodynamic compromise that is poorly tolerated and portends a poor procedural and clinical outcome.

It is almost impossible to reposition fully the current commercially available devices after initial deployment. Several percutaneous techniques have been described to manage suboptimal prosthesis deployment without recourse to surgical bailout therapy (4,5).

Paraprosthetic leak (PPL) is a common finding after device deployment (1,2). It is usually mild and well tolerated (1,2). Rarely, it is severe and induces hemodynamic instability (1,2). The mechanism of PPL in cases of suboptimal deployment of the CoreValve ReValving System (CRS) (Medtronic, Inc., Minneapolis, Minnesota) already has been described (4). Moreover, the feasibility of implanting a second prosthesis inside the first malfunctioning CRS device with the valve-in-valve (ViV) technique has been reported (4,5).

In the present multicenter prospective study, including a cohort of patients undergoing TAVI with the 18-F CRS device, we analyzed the incidence and characteristics of PPL requiring a second device with the ViV technique and report clinical and echocardiographic outcomes at 1 year of follow-up.

Methods

Consecutive patients (n = 663) undergoing TAVI with the 18-F CRS at 14 centers across Italy were enrolled prospectively in a dedicated web-based database. Patient eligibility criteria, registry design, features of the third-generation CRS, and technical details of the procedure have been described elsewhere (1,6).

Abbreviations and Acronyms

CRS = CoreValve ReValving System

MACCE = major adverse cardiovascular and cerebrovascular event(s)

PPL = paraprosthetic leak

TAVI = transcatheter aortic valve implantation

ViV = valve-in-valve

End point definitions. Procedural success was defined as device deployment with fall of transaortic peak-to-peak gradient, without any periprocedural major adverse cardiovascular and cerebrovascular event (MACCE) within 24 h of prosthesis implantation.

MACCE were defined as the composite of death resulting from any cause, myocardial infarction, stroke, or conversion to open heart surgery. Myocardial infarction was defined as creatinine kinase-MB enzyme elevation 3 times the upper limit of the normal value. Major access site complication was defined as vascular rupture with fatal bleeding or need for urgent vascular surgery or transcatheter repair. Major bleeding was

Table 1 Baseline Characteristics

	Overall Population (n = 663)	No ViV Group (n = 639)	ViV Group (n = 24)	p Value
Age, yrs	81.0 ± 7.3	81.0 ± 7.3	80.3 ± 6.2	0.656
Female	371 (56.0)	358 (56.0)	13 (54.1)	0.857
Diabetes mellitus	175 (26.4)	171 (26.7)	4 (16.6)	0.271
Coronary artery disease	320 (48.3)	306 (47.9)	14 (58.3)	0.315
Prior acute pulmonary edema	213 (32.1)	203 (31.8)	10 (41.7)	0.308
Prior balloon valvuloplasty	113 (17.0)	111 (17.4)	2 (8.3)	0.193
Prior myocardial infarction	143 (21.6)	138 (21.6)	5 (20.9)	0.929
Prior stroke	48 (7.2)	45 (7.0)	3 (12.5)	0.248
Prior bypass graft surgery	104 (15.7)	100 (15.6)	4 (16.7)	0.535
Prior percutaneous coronary intervention	189 (28.5)	181 (28.3)	8 (33.3)	0.594
Peripheral vascular disease	127 (19.2)	123 (19.2)	4 (16.7)	0.500
Chronic obstructive pulmonary disease	141 (21.3)	136 (21.3)	5 (20.8)	0.958
Cirrhosis Child class A or B	13 (2.0)	11 (1.7)	2 (8.3)	0.077
Prior neoplasia	84 (12.7)	79 (12.4)	5 (20.8)	0.176
Renal insufficiency*	154 (23.2)	149 (23.3)	5 (20.8)	0.777
Atrial fibrillation	109 (16.4)	106 (16.6)	3 (12.5)	0.424
Prior pacemaker	42 (6.3)	41 (6.4)	1 (4.2)	0.542
Porcelain aorta	72 (10.9)	72 (11.3)	0 (0.0)	0.060
NYHA functional class III and IV	434 (71.5)	415 (64.9)	19 (79.2)	0.486
Logistic EuroSCORE, %	23.0 ± 13.7	22.9 ± 13.7	23.6 ± 14.3	0.803
Baseline echocardiographic parameters				
Left ventricular ejection fraction, %	52.1 ± 25.5	52.2 ± 25.9	49.3 ± 15.1	0.581
Peak pressure gradient, mm Hg	83.7 ± 25.2	83.9 ± 25.2	79.0 ± 22.4	0.359
Mean pressure gradient, mm Hg	51.8 ± 17.0	52.0 ± 17.1	45.4 ± 14.8	0.062
Annulus diameter, mm	22.2 ± 2.2	22.1 ± 2.1	23.6 ± 2.7	0.010†
Aortic regurgitation 3+ or 4+	35 (5.3)	33 (5.1)	2 (8.3)	0.365

Values are mean ± SD or n (%). *Defined as serum creatinine >1.5 mg/dl. †Significant differences between patients who underwent standard procedure and those who underwent 2-valve implantation. NYHA = New York Heart Association; ViV = valve-in-valve.

defined as severe bleeding associated with transfusion of 5 U or more of packed red blood cells.

Statistical analysis. Continuous variables are presented as mean ± SD and were compared with the use of the paired *t* test or the Wilcoxon signed-rank test, as applicable. Categorical variables are presented as counts and percentages and compared with the use of the Fisher exact or chi-square test, as appropriate. A 2-sided p value <0.05 was considered statistically significant. MACCE and mortality rates and actuarial freedom from adverse events were estimated by using the Kaplan-Meier method, and differences between the groups were evaluated with the log-rank test. All data were processed using the Statistical Package for Social Sciences version 18 (SPSS, Inc., Chicago, Illinois).

Results

A total of 663 patients (mean age, 81.0 ± 7.3 years; mean logistic EuroSCORE, 23.0 ± 13.7%) who underwent TAVI were included in this analysis. No statistically significant difference was observed in terms of baseline clinical characteristics between patients who underwent the standard procedure (non-ViV group) and those requiring an additional prosthesis with the ViV technique (ViV group) (Table 1). The mean annulus diameter measured by transthoracic echocardiogram or transesophageal echocardiogram was larger in the ViV group (22.1 ± 2.12 mm vs. 23.6 ± 2.7 mm; p = 0.010). Transfemoral access was the preferred route for implantation used in a large majority of patients (n = 599; 90.3%). Subclavian access was used as an alternative in cases with unfavorable ileofemoral anatomic characteristics (n = 54; 8.1%). Implantation of the 26-mm CRS prosthesis was more frequent (n = 394; 59.4%) than implantation of the 29-mm device (n = 269; 40.9%).

Procedural outcomes. In the following paragraph, presentation style for parameter results is XX/XX/XX for overall/non-ViV/ViV groups (p value for non-ViV group vs. ViV group). Procedural outcomes are reported in Table 2. The ViV technique was associated with longer procedural time (p = 0.001) and fluoroscopy time (p < 0.001).

Overall procedural success rate was high: 98%/97.9%/100% (p = 0.616). Intraprocedural mortality (0.9%/0.9%/0%; p = 0.801) and MACCE (2.7%/2.8%/0%; p = 0.510) were similar in all groups. No significant differences were observed in the treatment groups in the occurrence of other important complications such as major access site complications (2.0%/3.7%/4.2%; p = 0.348) or cardiac tamponade (1.2%/1.2%/0%; p = 0.743).

Prosthesis underexpansion was managed in all cases with post-implant balloon dilation, whereas prosthesis migration occurred in 4 cases and was managed successfully with implantation of 2 (in-series) Corevalve prostheses (Medtronic, Inc.) (n = 2), 1 conversion to surgery, and 1 balloon aortic valvuloplasty.

Of all the patients in ViV group (n = 24), the 26-mm CRS was implanted as the primary device in 15 patients (62.4%) and the larger 29-mm prosthesis was implanted in 9 patients

Table 2 Procedural Outcomes

	Overall Population (n = 663)	No ViV Group (n = 639)	ViV Group (n = 24)	p Value
Procedural variables, min				
Procedure time	79.1 ± 33.6	78.0 ± 33.4	101.3 ± 30.8	0.001*
Fluoroscopy time	21.3 ± 13.3	20.6 ± 12.2	35.9 ± 25.5	<0.001*
Approach				0.306
Transfemoral	599 (90.3)	576 (90.1)	23 (90.4)	
Transsubclavian	64 (9.7)	63 (9.9)	1 (9.6)	
Device†				0.898
CRS 26 mm	394 (59.4)	379 (59.3)	15 (62.5)	
CRS 29 mm	269 (40.6)	260 (40.7)	9 (37.5)	
Ratio CRS diameter/aortic annulus‡	1.23 ± 0.1	1.23 ± 0.1	1.21 ± 0.9	0.397
Post dilation	68 (10.2)	56 (8.8)	12 (50)	<0.001*
Procedural success	650 (98.0)	626 (97.9)	24 (100)	0.616
Valve embolization	4 (0.6)	4 (0.6)	0 (0.0)	0.831
Death	6 (0.9)	6 (0.9)	0 (0.0)	0.801
Myocardial infarction	0 (0)	0 (0)	0 (0.0)	1.000
Stroke	8 (1.2)	8 (1.2)	0 (0.0)	0.743
Conversion to open heart surgery	5 (0.8)	5 (0.8)	0 (0.0)	0.831
MACCE	18 (2.7)	18 (2.8)	0 (0.0)	0.510
Major access site complications	13 (2.0)	12 (3.7)	1 (4.2)	0.384
Cardiac tamponade	8 (1.2)	8 (1.2)	0 (0.0)	0.743

Values are mean ± SD or n (%). *Significant differences between patients who underwent standard procedure and those who underwent 2-valve implantation. †Refers to the first prosthesis implanted. ‡Aortic annulus measured by transthoracic echocardiogram.

CRS = CoreValve Revalving System; MACCE = major adverse cardiovascular and cerebrovascular event(s); ViV = valve-in-valve.

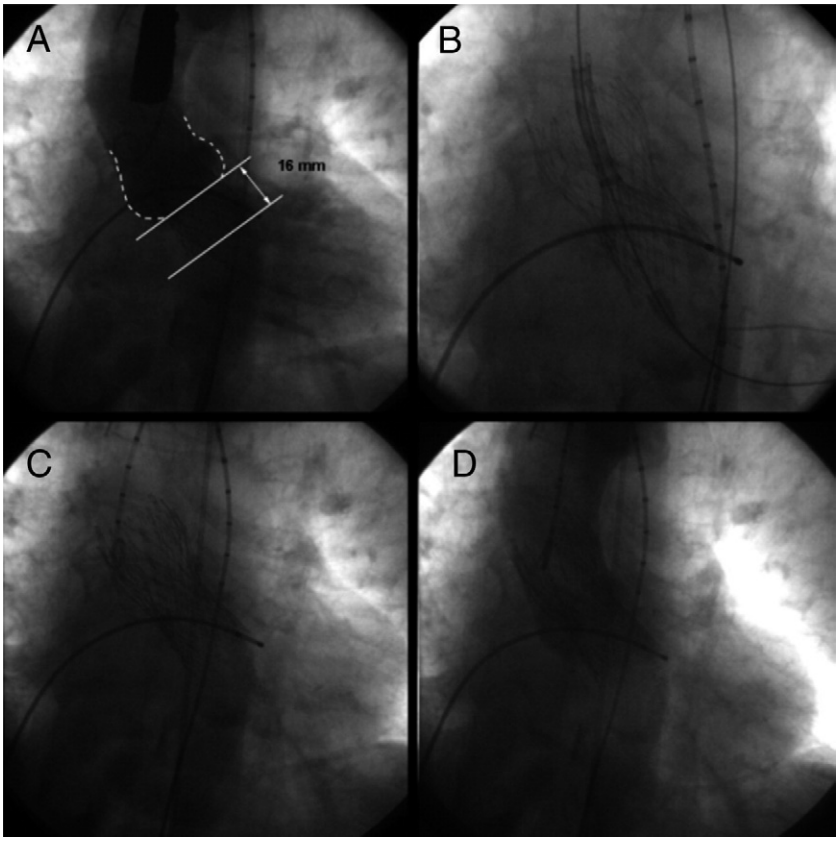

Figure 1 **Example of Low Implantation of CoreValve ReValving System Device Causing Severe Paraprosthetic Leak**

The **dotted line** indicates the sinuses of Valsalva contour, the **upper white line** designates the aortic annulus level, and the **lower white line** indicates the distal part of the frame.

(37.6%). Suboptimal deployment causing hemodynamically significant PPL was characterized by lower deployment inside the left ventricle in 75.0% (n = 18) (Fig. 1) and by higher deployment above the annulus level in 25.0% (n = 6) (Fig. 2). In 13 patients (54.1%), a balloon dilation was performed to optimize device expansion after implantation.

There were no reports of impingement or jailing of coronary ostia or damage to structures in the aortic root and mitral valve after deployment of the second device. No significant gradient was measured across the 2 CRS devices in any patient in the ViV group.

Clinical and echocardiographic outcomes. The median follow-up duration for the entire population was 10.5 months (interquartile range: 6.5 to 16.7 months). Overall 30-day mortality was 5.4%; 30-day mortality was 5.6% in the non-ViV group and 0% in the ViV group (p = 0.238). Mortality remained relatively low and statistically similar in both groups at the 12-month follow-up (13.7% vs. 4.5%, respectively; p = 0.230). No significant difference in the rate of MACCE (14.1% vs. 4.5%; p = 0.158) was observed between groups at both follow-up intervals. Incidence of all-cause mortality and MACCE are reported in Figures 3 and 4. New York Heart Association functional class III/IV at discharge was virtually absent in both groups (2.0% vs. 0%; p = 0.446). This benefit was sustained at 30 days (5.6% vs. 0%; p = 0.890) and 1 year (4.7% vs. 4.1%; p = 0.671). A higher incidence of definitive pacemaker implantation in the ViV group was reported at 30 days (14.4% vs. 33.3%; p = 0.020).

At 12 months, no differences were noted between 2 groups in terms of echocardiographic outcomes (mean transaortic gradient, 10.1 ± 4.2 vs. 10.5 ± 5.2; p = 0.838). No cases of central aortic regurgitation were observed. PPL of 2+ or more was observed in 26 (11.7%) and 1 (4.2%) patients in the non-ViV and ViV groups, respectively (p = 0.675). There were no instances of structural valve deterioration, valve thrombosis, new PPL, cases of impairment of anterior mitral leaflet in case of low deployment or thromboembolic events in any patient in the ViV group.

Discussion

TAVI is a challenging procedure that is associated with a significant learning curve. Procedural success is >90% in experienced centers (1,2). It is essential for operators to develop

JACC Vol. 57, No. 9, 2011
March 1, 2011:1062–8

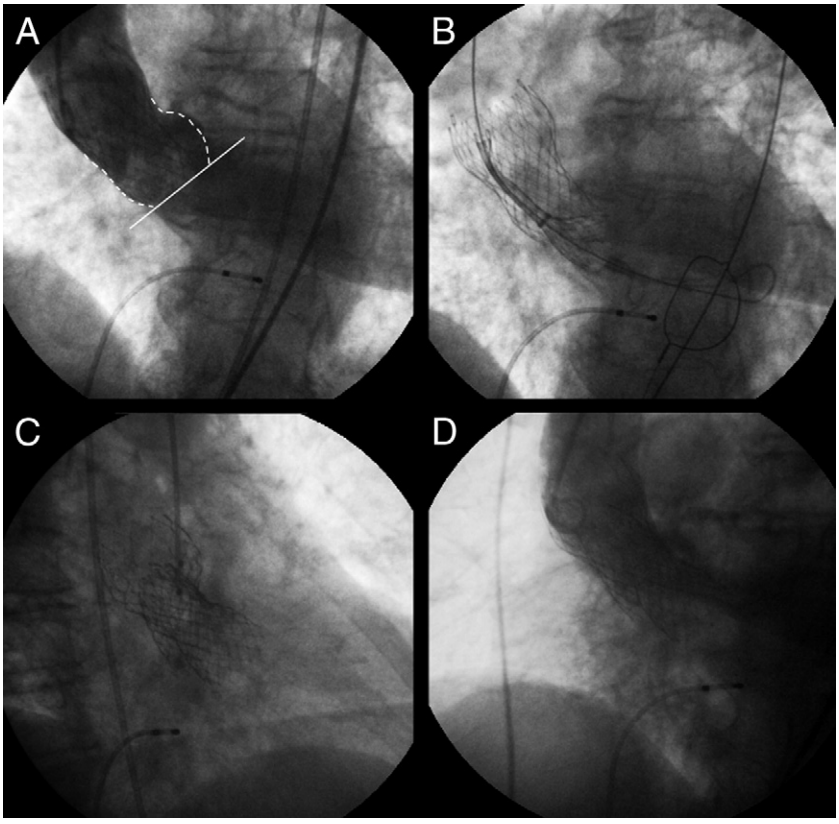

Figure 2 **Example of High Implantation of CRS Device Conditioning Severe PPL**

The **dotted line** indicates the sinuses of Valsalva contour, and the **white line** designates the aortic annulus level. Abbreviations as in Figure 1.

a strategy to manage prosthesis malposition in the catheterization laboratory, trying to avoid bailout cardiac surgery, because commercially available devices are extremely limited in their ability for repositioning after initial deployment (4,5).

Several percutaneous bailout strategies have been developed to address failed implantation, but few attempts have been made to estimate the frequency and to discuss the follow-up outcomes of these procedural issues (4). The ViV technique is one of the most interesting interventional options to manage device malposition that can occur during TAVI (4,5). To date, the literature provides only a few anecdotal cases that demonstrate the feasibility of this approach and show its midterm effectiveness in isolated patients (5). In this study, we compared acute and up to 12-month outcomes of patients undergoing the standard procedure and those who had a second prosthesis implanted inside the first one with the ViV technique as a result of severe PPL.

A number of important messages emerge from this multicenter registry. First, implantation of the CRS device was performed with a very high success rate (98%) across different centers, suggesting increasing operator familiarity and confidence with the CRS device. The ViV technique was used in 24 patients (3.6%); among them, 62.5% received a 26-mm CRS and 37.5% received a 29-mm CRS as their primary device. The most common type of device malposition was deployment that was too low inside the LVOT (75% of cases), whereas a higher implantation relative to the aortic annulus occurred less frequently. In more than one half of cases, balloon dilation was necessary to optimize the expansion of the second device. This was accomplished without any damage to the leaflets or aortic root structures.

Second, the procedural, 30-day, and 12-month outcomes of the ViV group are not different from the outcomes of those who underwent the uneventful procedure. Procedural success was obtained in 100% of the ViV patients, with no periprocedural death. Overall survival as well as freedom from MACCE at 1 and 12 months were not statistically different between the 2 groups, with high 12-month survival (86.3% vs. 95.5%, non-VIV vs. ViV group, respectively). Midterm prosthesis performances were good. No cases of valve deterioration or new onset of central or perivalvular regurgitation were observed. In addition, there were no reports of thrombotic or embolic events in the ViV group, which reflects well on the design features and the endothelialization of the CRS device. The initial clinical and echocardiographic successes were maintained for up to 1 year in all patients.

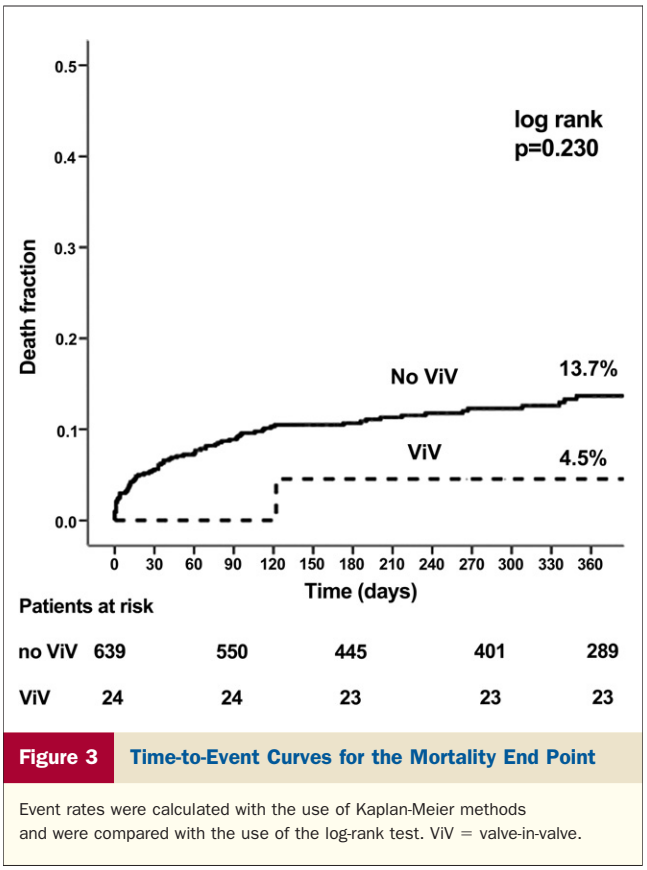

Figure 3 Time-to-Event Curves for the Mortality End Point

Event rates were calculated with the use of Kaplan-Meier methods and were compared with the use of the log-rank test. ViV = valve-in-valve.

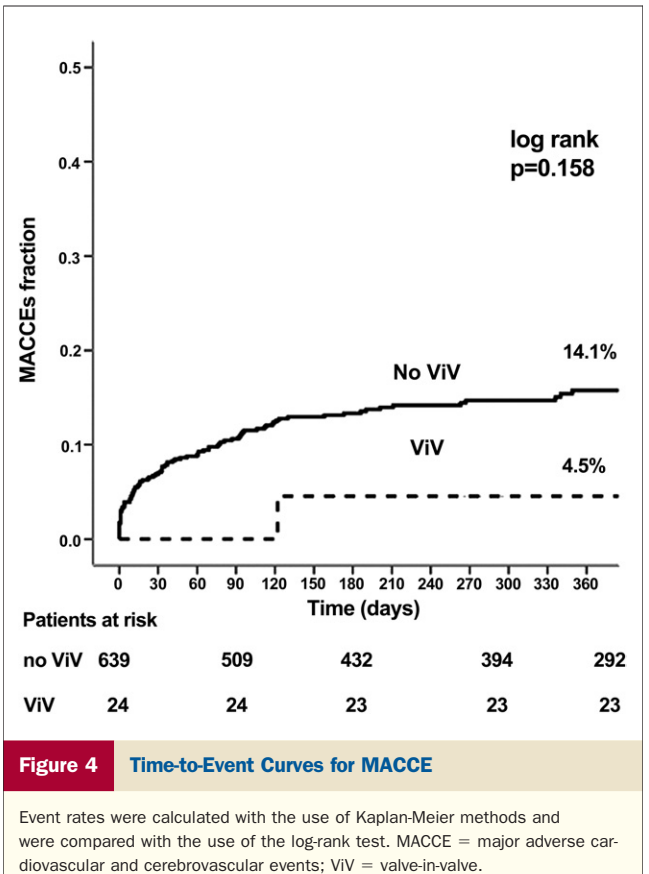

Figure 4 Time-to-Event Curves for MACCE

Event rates were calculated with the use of Kaplan-Meier methods and were compared with the use of the log-rank test. MACCE = major adverse cardiovascular and cerebrovascular events; ViV = valve-in-valve.

Finally, there was no impingement on the coronary ostia or restriction of mitral valve leaflets in the ViV group. The incidence of atrioventricular block requiring definitive pacing was higher (33.3% vs. 14.5% in the non-ViV group; p = 0.020). This correlates with the fact that nearly 80% of patients undergoing the ViV procedure had placement of the first prosthesis that was too low into the left ventricle, which exposed them to the risk of developing permanent conduction disorders (7).

The demonstration of the effectiveness of the ViV technique at midterm follow-up in a large number of cases performed at different institutions has implications. The ViV technique can be used readily in the catheterization laboratory as bailout therapy for a failed implantation resulting from a malpositioned valve with severe PPL when the attempt of reposition with the snare technique fails, preventing conversion to emergency open-heart surgery (5). The availability of a bailout provides a margin of safety and enhances operator confidence. This is important for a nascent technology like TAVI to gain widespread clinical acceptance.

However, 2 main potential concerns associated with this technique still remain. It is unknown whether the presence of 2 valves could impact on the long-term durability of the prosthesis, and the feasibility of cannulating the coronary ostia after the ViV procedure needs to be carefully assessed.

Conclusions

This analysis from the Italian CoreValve Registry demonstrates that the ViV technique is an effective percutaneous approach that may be accomplished with encouraging acute and midterm outcomes when severe PPL occurs after TAVI. This technique can be performed safely as a bailout procedure to avoid surgical conversion. Larger series and longer follow-up are warranted to determine the safety, efficacy, and durability of this technique.

Acknowledgment

The authors wish to thank Kunal Sarkar, MD, for his assistance in manuscript preparation.

Reprints requests and correspondence: Dr. Gian Paolo Ussia, Division of Cardiology, Ferrarotto Hospital, University of Catania, Via Citelli 1, 95100 Catania, Italy. E-mail: gpussia@hotmail.com.

REFERENCES

1. Piazza N, Grube E, Gerckens U, et al. Procedural and 30-day outcomes following transcatheter aortic\valve implantation using the third generation (18 Fr) CoreValve ReValving System: results from the multicentre, expanded\evaluation registry 1-year following CE mark approval. EuroInterv 2008;4:242–9.
2. Thomas M, Schymik G, Walther T, et al. Thirty-day results of the SAPIEN aortic bioprosthesis European outcome (SOURCE) Registry.

JACC Vol. 57, No. 9, 2011
March 1, 2011:1062–8

A European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2010;122:62–9.
3. Vahanian A, Alfieri O, Al-Attar N, et al. Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2008;11:1463–7.
4. Piazza N, Schultz C, de Jaegere P, Serruys PW. Implantation of two self-expanding aortic bioprosthesis valves during the same procedure? Insight into valve-in-valve implantation ("Russian doll" concept). Catheter Cardiovasc Interv 2009;73:530–53.
5. Ussia GP, Barbanti M, Immè S, et al. Management of implant failure during transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2010;76:440–9.
6. Petronio AS, De Carlo M, Bedogni F, et al. Safety and efficacy of the subclavian approach for transcatheter aortic valve implantation with the CoreValve Revalving System. Circ Cardiovasc Interv 2010;3:359–66.
7. Piazza N, Onuma Y, Jesserun E, et al. Early and persistent intraventricular conduction abnormalities and requirements for pacemaking after percutaneous replacement of the aortic valve. J Am Coll Cardiol Intv 2008;1:310–6.

Key Words: aortic stenosis ■ bailout ■ transcatheter aortic valve implantation.