Transfemoral Implantation of a Fully Repositionable and Retrievable Transcatheter Valve for Noncalcified Pure Aortic Regurgitation

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ABSTRACT

OBJECTIVES This study sought to evaluate the use of the Direct Flow Medical (DFM) transcatheter heart valve (Direct Flow Medical, Santa Rosa, California) for the treatment of noncalcific pure aortic regurgitation (AR).

BACKGROUND The treatment of noncalcific AR has remained a relative contraindication with transcatheter heart valves due to challenges in anchoring devices in the absence of calcium, concerns of valve embolization, and the high risk of significant residual paravalvular leak.

METHODS The study population consisted of patients treated for severe noncalcific pure AR with transfemoral implantation of a DFM transcatheter heart valve at 6 European centers. The primary endpoint was the composite endpoint of device success and the secondary endpoint was the composite early safety endpoint (according to the VARC-2 criteria).

RESULTS Eleven high-risk (STS score 8.84 ± 8.9, Logistic EuroSCORE 19.9 ± 7.1) patients (mean age 74.7 ± 12.9 years) were included. Device success was achieved in all patients. In 1 patient, the initial valve prosthesis was retrieved after pull-through, and a second valve was successfully deployed. The early safety endpoint was reached in 91% of the patients, with 1 patient requiring surgical aortic valve replacement secondary to downward dislocation of the prosthesis that was successfully managed with surgical aortic valve replacement. DFM implantation resulted in excellent hemodynamics with none or trivial paravalvular regurgitation in 9 patients and a transprosthetic gradient of 7.7 ± 5.1 mm Hg at 30-day follow up. All patients derived symptomatic benefit following the procedure, with 72% in New York Heart Association functional class I or II.

CONCLUSIONS This study reports the feasibility of treating severe noncalcific AR with the Direct Flow prosthesis via the transfemoral route. (J Am Coll Cardiol Intv 2015;8:1842–9) © 2015 by the American College of Cardiology Foundation.

Although transcatheter aortic valve replacement (TAVR) has become the standard of care for extreme- and high-risk patients with symptomatic aortic stenosis, pure AR is still generally considered a relative contraindication for TAVR (1–5). This is predominantly due to the fact that most pure AR patients can undergo surgical aortic valve replacement even in high operative risk situations; TAVR is still considered off-label for almost all transcatheter valves. This is due to the fact that TAVR valves were designed to anchor on the native annulus in the presence of valvular calcification. The absence of valvular calcification and the

presence of large annular anatomy have made the transcatheter treatment of pure AR a challenge mainly because of the risk of inadequate anchoring and sealing resulting in prosthesis dislodgment and residual paravalvular leak. Despite this, a number of TAVR devices designed for the treatment of calcific aortic stenosis, such as the CoreValve (Medtronic, Minneapolis, Minnesota), JenaValve (JenaValve Technology, Munich, Germany), and Acurate TA (Symetis, Eclubens, Switzerland), have been used off-label for treatment of pure AR, with the JenaValve having recently received CE-mark (Conformité Européenne) for this indication (6–9). These devices, however, have a number of limitations such as the risk of residual AR, the lack of repositionability and retrievability, the need for valve-in-valve implantation in up to 30% of the patients, or the requirement for transapical access (Acurate TA, JenaValve) for implantation.

There is currently an unmet clinical need to have a safe and efficacious transfemoral TAVR device for treatment of high surgical risk patients with non-calcific native pure AR. Thus, the purpose of the present study was to evaluate the off-label use of the fully repositionable and retrievable Direct Flow Medical (DFM) transcatheter aortic valve system (Direct Flow Medical, Santa Rosa, California) for this indication.

METHODS

STUDY POPULATION. Baseline characteristics, procedural and follow-up data from patients who underwent transfemoral implantation of the DFM valve for symptomatic and severe pure AR from May 2014 to April 2015 at 6 centers in Europe were retrospectively analyzed. Patients with mixed aortic valve disease or previous aortic valve replacement were excluded.

During TAVR work-up, all patients underwent multimodality cardiovascular imaging including transthoracic and/or transesophageal echocardiography, cardiac multislice computed tomography (CT), and when required, invasive cardiac catheterization. Multislice CT was used for the accurate assessment of aortic valve anatomy and calcification, subannular calcifications, aortic root size, height of coronary ostia from the aortic annular plane, and final valve sizing. Valve sizing was based on the perimeter-derived diameter on CT by using the largest annular diameter in systole or diastole with at least 3 mm of oversizing.

The indication for TAVR in every patient was thoroughly discussed and decided by a multidisciplinary heart team at each individual center, which included interventional cardiologists, cardiac surgeons, imaging cardiologists, cardiovascular radiologists, and cardiac anesthetists. The patient's or physician's preference alone was not considered reason enough for performing the procedure. All patients were considered as being at prohibitive or high surgical risk for surgical aortic valve replacement. Eligibility was based on available surgical risk scores (Logistic EuroSCORE and STS Score) and other clinical (e.g., frailty) or anatomic (e.g., porcelain aorta) variables not captured by these scores. Comorbidities not captured by traditional risk score (e.g., frailty or porcelain aorta) were defined according to the Valve Academic Research Consortium (VARC) II criteria (10).

All patients were informed about potential risks and benefits related to the off-label use of the DFM device. All patients signed informed consent for the procedure and for the anonymous and retrospective analysis of their data for scientific purposes as per local practice and ethics committee requirements at each center.

AR was defined according to the European Society of Cardiology guidelines (11). Post-procedural AR after initial implantation and at the end of the procedure was assessed by aortography according to the Sellers et al. (12) method, and by transthoracic or transesophageal echocardiographic assessment, according to VARC-2 criteria, at the end of the TAVR procedure, at hospital discharge, and at 30 days of follow-up. Echocardiographic assessment of post-procedural AR was carried out by a cardiologist experienced in TAVR echocardiographic evaluation. Clinical and echocardiographic follow-up were performed by clinical visits or telephone contacts according to each center's clinical practice. All events were site reported.

DEVICE AND PROCEDURE DESCRIPTION. The DFM transcatheter aortic valve system is a TAVR device composed of a nonmetallic bovine pericardial tissue

TABLE 1 Demographic and Clinical Features

Patient #	Age (yrs)	Sex	Previous CABG	Previous MI	NYHA Functional Class	Creatinine Clearance (ml/min)	STS Score (%)	Logistic EuroSCORE	Reason for TAVR
1	85	Female	No	Yes	2	25	7.9	17.8	Age
2	85	Female	No	No	2	30	8.2	17.8	Age
3	83	Female	No	No	3	45	7.5	19.5	High surgical risk
4	46	Male	No	Yes	4	58	3.8	27.3	Bridge to HTX
5	87	Female	No	No	4	45	9.6	31.0	Age
6	67	Male	Yes	Yes	3	50	3.8	17.5	High surgical risk
7	82	Female	No	No	3	91	3.7	9.1	Age
8	72	Female	No	No	3	80	5.4	13.7	IS
9	79	Female	No	Yes	3	18	8.9	15.7	Age, frailty
10	58	Male	No	No	4	23	9.4	30.8	Post-endocarditis
11	78	Male	No	Yes	4	46	3.5	18.3	Age, low EF

CABG = coronary artery bypass graft; EF = ejection fraction; HTX = heart transplantation; IS = immunosuppression; MI = myocardial infarction; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

leaflet aortic heart valve, a delivery system, and exchange system that can be implanted either via a transfemoral, subclavian, or direct aortic approach and has been described elsewhere in detail (13,14). In brief, the valve utilizes a formed-in-place support structure with independently inflatable ventricular (lower) and aortic (upper) rings, which encircle and capture the native valve annulus thereby ensuring positive anchoring of the bioprosthesis. After insertion into the left ventricular cavity, the inflatable rings are pressurized with saline and contrast solution, allowing for precise positioning, repositioning, and retrieval, if needed. The bioprosthesis is positioned at the native annulus using 3 independent positioning wires without hemodynamic compromise, because the DFM is fully functional during positioning. To decrease the risk of pull through in most cases, the valve is pulled from the left ventricular outflow tract to the native annulus more in a parallel fashion, different from the previously described "inner curve technique" applied in patients with aortic stenosis (14). The aortic ring is then pressurized and enables the evaluation of valve hemodynamics, residual AR as well valve stability. If residual AR is still present or the position is suboptimal, the aortic ring can be deflated to allow repositioning to achieve the best possible result. When an optimal final position is achieved and valve stability is confirmed by pulling and pushing the positioning wires, the contrast-saline mixture is exchanged for a polymer that solidifies to provide the permanent support structure to fixate the valve in position.

TABLE 2 Echocardiographic and MSCT Features

Patient #	Etiology of AR	AR	ST Junction (mm)	Sinus Valsalva (mm)	VC (mm)	PHT (ms)	Flow Reversal in Aorta	PAP (mm Hg)	EF (%)	EDD (mm)	MR Grade	Calcification	CT Min Diameter (mm)	CT Max Diameter (mm)
1	Degenerative	Severe	27	32	4.5	462	Yes	40	50	54	Moderate	None	22.0	24.5
2	Degenerative	Severe	24	28	7	130	Yes	35	55	55	Mild	Mild	19.2	25.3
3	Degenerative	Severe	25	32	6	458	Yes	45-50	70	50	Mild	None	17.1	29.2
4	Radiation-induced	Severe	27	35	NA	NA	Yes	40	20	72	Mild	None	21.3	31.6
5	Degenerative	Severe	26	34	7	110	Yes	60	33	55	Moderate	None	22.0	28.0
6	Traumatic lesion of LCC	Severe	31	36	NA	NA	Yes	25	36	78	Moderate	None	24.0	29.0
7	Degenerative	Severe	31	32	9	89	Yes	50	30	61	Severe	Mild	24.8	27.3
8	Degenerative	Severe	NA	NA	NA	NA	NA	NA	60	55	Mild	None	18.4	24.8
9	Radiation-induced	Severe	28	32	4.5	NA	Yes	45	45	53	Moderate	Mild	24.3	24.8
10	Post-endocarditis	Severe	23	31	NA	NA	Yes	30	58	58	Moderate	None	17.0	30.0
11	Degenerative	Severe	42	35	NA	NA	Yes	49	26	55	Mild	Mild	19.0	29.0

AR = aortic regurgitation; CT = computed tomography; EDD = end-diastolic diameter; EF = ejection fraction; LCC = left coronary cusp; MR = mitral regurgitation; MSCT = multislice computed tomography; NA = not available; PAP = pulmonary artery pressure; PHT = pressure half-time; SA = sinus Valsalva; ST = sinotubular junction; VC = vena contracta.

STUDY ENDPOINTS. All the study endpoints and clinical outcomes were assigned according to the VARC-2 criteria (10). The primary endpoint was the composite endpoint of device success, defined as: absence of procedural mortality, successful vascular access, delivery and deployment of the device, successful retrieval of the delivery system, correct final position of the device, proper functioning of the prosthetic heart valve (mean gradient <20 mm Hg, peak velocity <3 m/s, absence of moderate or severe AR), and no need for valve-in valve implantation or surgical conversion. Secondary endpoints were the early safety endpoints and post-procedural AR and at 30 days, respectively.

STATISTICAL ANALYSIS. Due to the observational nature of the study, only descriptive statistics has been performed. Categorical data are presented as frequency (percentages). Continuous variables are expressed as mean ± SD. Statistical analysis was performed using SPSS software version 21.0 (SPSS, Chicago, Illinois).

RESULTS

A total of 11 patients with pure AR underwent transfemoral implantation of the DFM valve. The mean age of patients treated was 74.7 ± 12.9 (range 46 to 87) years, and the majority were female (63.6%). Baseline clinical and echocardiographic characteristics are shown for each individual patient in **Tables 1 and 2**. All the patients treated were evaluated as being high risk with a mean STS score of 8.84 ± 8.90 and Logistic EuroSCORE of 19.9 ± 7.1. The main reason for TAVR was advanced age and frailty (defined by VARC II

FIGURE 1 Calcification in Multislice Computed Tomography
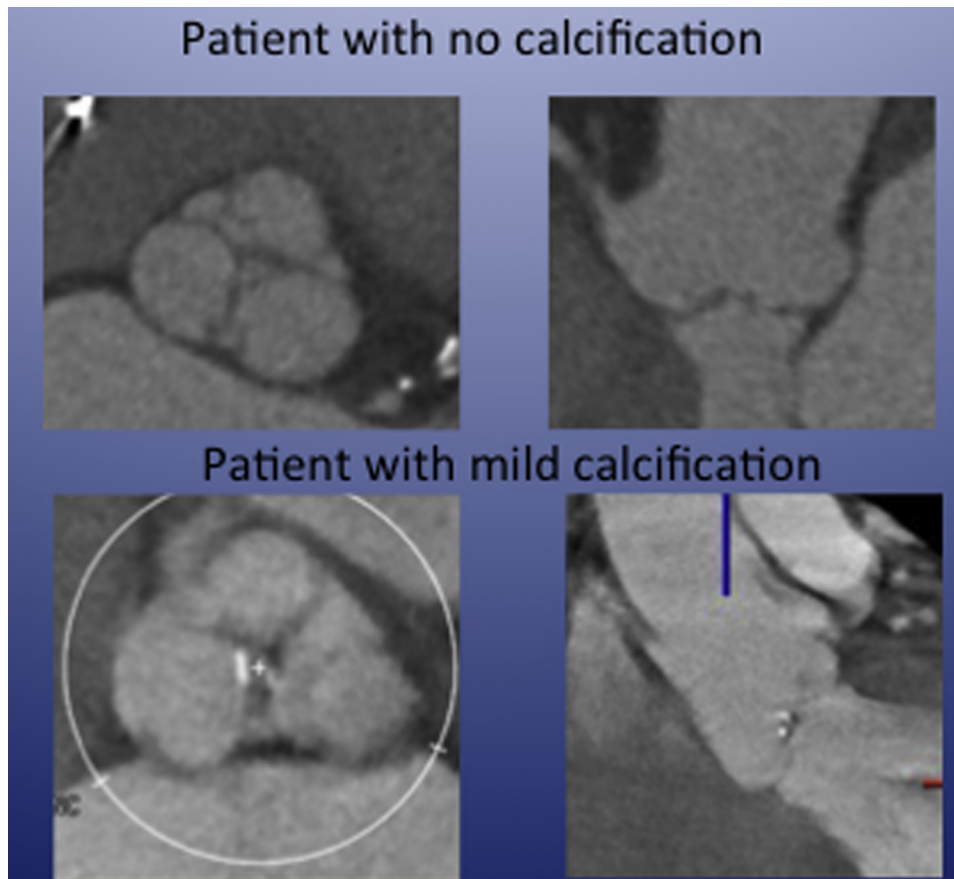
Multislice computed tomography of a patient with severe pure AR with a noncalcified aortic valve **(top)** and a patient with a very mild calcified aortic valve **(bottom)**.

TABLE 3   Procedural Features

Patient #	Perimeter-Derived Diameter (mm)	Direct Flow ~Valve (mm)	Intraprosthetic Regurgitation	Paravalvular Regurgitation	Reintervention
1	CT without contrast (GFR25), in TEE 24	27	No	No	No
2	22.7	25	Mild	Mild	Valve retrieval, 2nd DFM valve successfully implanted
3	23.9	27	Trivial	Trivial	SAVR after subacute valve embolization
4	27	29	No	No	No
5	27.5	29	Trivial	No	No
6	25.8	29	No	No	No
7	27.2	29	No	No	No
8	23	25	No	No	No
9	25.9	27	No	No	No
10	24.8	27	No	No	No
11	24.1	29	No	Trivial	No

AV = atrioventricular; CT = computed tomography; GFR = glomerular filtration rate; DFM = Direct Flow Medical; SAVR = surgical aortic valve replacement; TEE = transesophageal echocardiography.

achieved in all treated patients. The average procedural time and contrast volume were 74.8 ± 35.4 min and 95.8 ± 47.1 ml, respectively. None of the patients experienced acute kidney injury, major or life-threatening bleeding, or atrioventricular block during hospitalization.

The composite early safety endpoint was reached by 82% of the patients, with 1 patient requiring conversion to surgical aortic valve replacement, and 1 patient died of noncardiovascular causes.

One patient (Patient #3) had a recurrence of severe AR at 3 days after implantation and was found to have a downward dislocation of the prosthesis. This patient was successfully converted to surgical aortic valve replacement. This patient had a perimeter-derived diameter of 23.9 mm, and a 27-mm DFM was implanted with the final position of the valve slightly oblique to the native annular plane. Intraoperatively, the annulus diameter turned out to be larger, thus the downward displacement of the valve was probably related to insufficient oversizing and the suboptimal final position of the valve.

[10]), except for the 46-year-old patient who had radiation-induced aortic valve and coronary artery disease, where multivessel percutaneous coronary intervention and TAVR was performed as a bridge to heart transplantation. All patients treated had severe pure AR, and the majority (63%) had complete absence of valvular calcification on CT, with the remaining patients having mild calcification (**Figure 1**). The mean perimeter-derived diameter was 24.3 ± 2.8 mm.

All the TAVR procedures (**Table 3**) were performed transfemorally with percutaneous access (**Figures 2 and 3**). Pre-dilation was not performed in any patient. A 25-mm, 27-mm, and 29-mm valve was implanted in 2 patients (18%), 4 patients (36%), and 5 patients (45%), respectively. Device success was 100%. However, in 1 patient, the valve was pulled through the native annulus into the ascending aorta during positioning. In this case, the valve was successfully retrieved and another DFM of the same size was successfully implanted by switching from the inner curve to the parallel technique as described in the preceding text. Implantation of the DFM valve was associated with excellent hemodynamics with none or trivial paravalvular regurgitation in 10 of 11 patients and a transprosthetic gradient of 7.7 ± 5.1 mm Hg. Only 1 patient had mild paravalvular regurgitation. There were no cases of coronary obstruction, intraprocedural valve embolization, or vascular complications. Device and procedural success was thus

FIGURE 2   Echocardiography Case Example

(A) Aortic regurgitation (AR) at baseline. **(B)** AR after Direct Flow Medical valve placement.
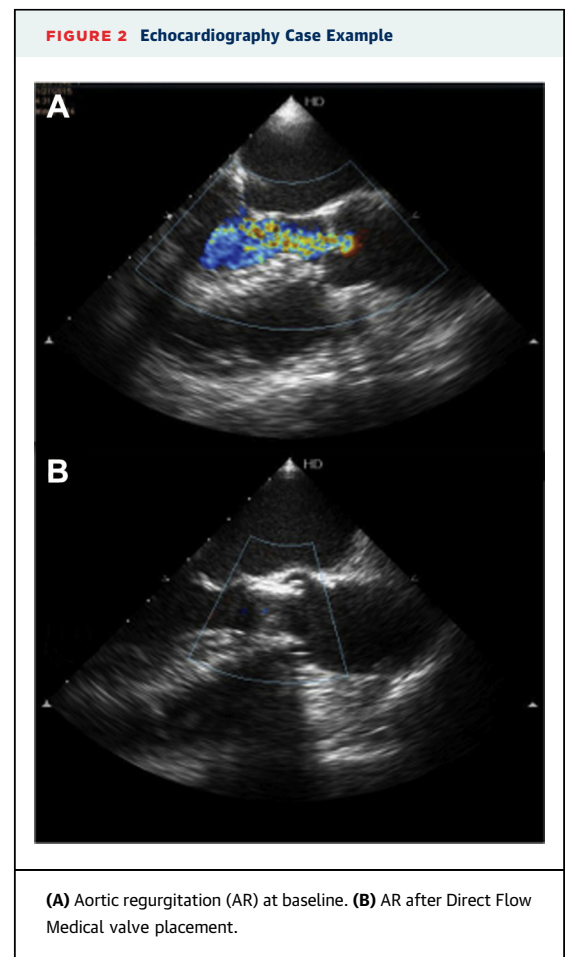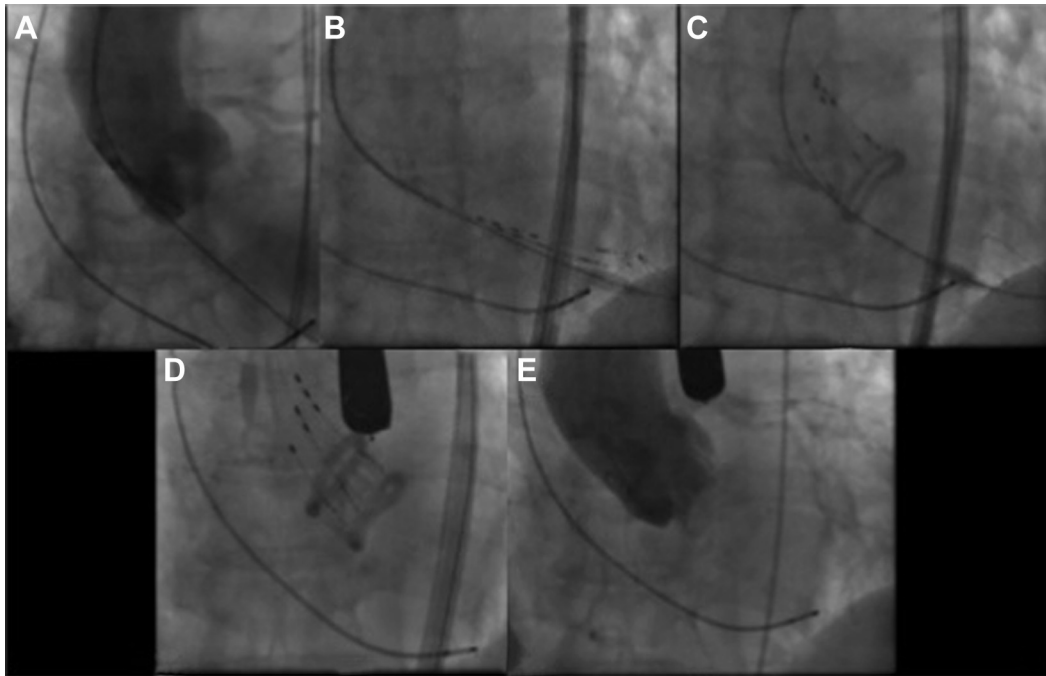
FIGURE 3 Case Example: Fluoroscopic Demonstration of Procedural Steps

(A) Aortography pre-procedural with aortic regurgitation (AR) grade III. (B) Release of the Direct Flow Medical valve in the left ventricle. (C) Positioning of the lower ring towards the aortic annulus. (D) Additional inflation of the upper ring. (E) Aortography after polymer exchange with no AR.

The 30-day all-cause mortality was 9% caused by a noncardiac death due to pneumonia and acute respiratory failure. There were no cerebrovascular events, and 1 patient underwent cardiac resynchronization therapy because of a severely depressed left ventricular function. Valve function remained stable with no change in post-procedural AR, that is, 8 of 9 patients had none or trivial paravalvular AR. All patients had derived symptomatic benefit from the procedure with 72% in New York Heart Association functional class I or II.

DISCUSSION

The present study reporting a preliminary multicenter experience confirms the feasibility of transfemoral implantation of the fully retrievable DFM for pure AR in high-risk patients, with excellent procedural success and with minimal residual paravalvular regurgitation. It also highlights the challenges of treating this subset of patients by transcatheter implantation of aortic prostheses that were designed for implantation in calcific aortic valves and the importance of sufficient oversizing to anchor the valve in the noncalcified aortic annulus. There are a number of other complexities of treating pure AR that differ from calcific aortic stenosis, such as the diverse etiologies of pure AR, associated dilation of the aortic root and ascending aorta, larger annular size, and instability of the TAVR valve during positioning due to the large regurgitant volume (9). Because the population of patients is perceived to be small, this has resulted in limited development of a pure AR–specific device, only the Helio docking system (Edwards Lifesciences, Irvine, California), which was investigated for this indication but meanwhile terminated (15).

The published clinical experience with transcatheter valves, as summarized in **Table 4**, has been with self-expanding valves because of the ability to significantly oversize the TAVR prosthesis without the risk of damage to the native annulus. The largest experience has been the Medtronic CoreValve that has been implanted retrogradely via the transfemoral, subclavian, and direct aortic approaches. The published data by Roy et al. (9) and Testa et al. (7) showed high rates of valve-in-valve (19% and 30%) and residual AR (21% and 88%, respectively). This was probably related to insufficient oversizing, the inability to

TABLE 4   Overview of Studies Performed on Transcatheter Treatment of Pure AR

First Author (Ref. #)	Valve	Access	n	Successful Implantation of a THV	Valve-in-Valve	Post-Dilation	Conversion to Surgery	None or Trace Residual AR	Moderate-Severe Residual AR	Valve Reintervention During Follow-Up
Roy et al. (9)	CoreValve	Transfemoral, subclavian, direct aortic, carotid	43	42	8	4	1	NR	9	0
Testa et al. (7)	CoreValve	Transfemoral, subclavian, direct aortic	26	26	5	3	0	NR	23	0
Wendt et al. (6)	Symetis Accurate	Transapical	8	8	0	2	0	8	0	0
Seiffert et al. (8)	JenaValve	Transapical	31	30	1	2	0	28	0	2
Present study	DFM	Transfemoral	11	10	0	0	0	9	0	1

AR = aortic regurgitation; DFM = Direct Flow Medical valve; NR = not recorded; THV = transcatheter heart valve.

accurately position the prosthesis requiring rapid pacing for valve stability, inability to reposition the valve and insufficient anchoring. The JenaValve appears to overcome many of these issues because of its unique clip fixation to the native leaflets and has shown good results with a reduced need for valve-in-valve (3%) and no patients with residual moderate or severe AR. Similarly, the Symetis has shown promising results albeit in only 8 patients. However, both of these valves were implanted transapically, which may be associated with increased risk of morbidity in high-risk or inoperable patients, particularly those with pure AR and a dilated left ventricle.

The unique design of the DFM offers some theoretical advantages for treating of pure AR, namely: fully functional during positioning improves hemodynamic stability; repositionability to fine tune the final result and decrease residual AR; and full retrievability if the position is unstable or there is significant residual AR. Anchoring of the valve does not necessarily need calcification but is ensured by adequate oversizing of at least 2 mm compared with the size of the native annulus. Furthermore, stability of the device can be checked by a push-and-pull test using the positioning wires before performing the polymer exchange and permanently fixing the device. Despite these advantages, in the early phase of this study (patient #3), we had 1 case of late ventricular displacement of the DFM valve, which provided important learning points; that is, the importance of oversizing the DFM valve at least 2 mm, optimal alignment of the rings parallel to the valve plane, and proof of stability of the position by the aforementioned push/pull test. Indeed, oblique positioning of the DFM does not take advantage of the largest diameter of valve and may be associated with prosthesis dislodgement.

The technique of positioning the DFM may need to be modified from that described and currently used for treating calcific aortic stenosis, that is, the inner curve technique (16). During this technique, the part of the DFM valve facing the inner curve of the ascending aorta is pulled to the annulus and used as a hinge point for pulling up the rest of the valve. However, the large regurgitant jet in patients with pure AR may result in the valve being pulled into the ascending aorta when using the inner curve technique as was seen in 1 patient. In cases where it is difficult to pull the valve up to the annulus, rapid pacing at 110 to 130 beats/min to decrease the regurgitant jet and a switch to the parallel technique may facilitate implantation.

In 72.7% (8 of 11 patients), no residual paravalvular leak was present after aortic valve implantation. Two patients (18.2%) had a trivial paravalvular regurgitation, only 1 patient (9.1%) had a mild aortic paravalvular regurgitation. The possible cause of paravalvular leak in this patient could be a lower implant to prevent a pull through, which happened during the first attempt.

Aortic paravalvular leaks were seen in particular in the early phase of the study. In the second half of the patient cohort, mostly the parallel technique was used, and care was taken to implant as high as possible. Using this technique, there was only 1 patient with trivial residual paravalvular leak. Thus, the difference in outcome may reflect a learning curve because compared with patients treated for aortic valve stenosis, the way to implant is slightly different.

There are no data available so far on other transfemorally implanted second-generation devices for the treatment of pure AR. Compared to other

second-generation repositionable and recapturable devices, the DFM valve has a unique anchoring mechanism with 2 inflatable ring balloons, which does not need the presence of calcium and may have a better sealing.

STUDY LIMITATIONS. The limitations of this study are those inherent to the retrospective design and the lack of an echocardiography and angiography core laboratory or an independent event adjudication committee. The small sample size and short follow-up time also limit any conclusions about long-term safety or stability of the valve in patients. However, this study does provide data on feasibility, technique, and sizing of the DFM that may facilitate the treatment of a larger group of high-risk or inoperable patients with pure AR.

CONCLUSIONS

This study reports the feasibility of treating pure native AR with the Direct Flow valve, which can be implanted transfemorally and has the advantages of a fully retrievable and repositionable valve. The acute results obtained here need to be confirmed in a larger study.

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PERSPECTIVES

WHAT IS KNOWN? The treatment of noncalcific AR has remained a relative contraindication with transcatheter heart valves.

WHAT IS NEW? This study reports the feasibility of treating severe noncalcific AR with the Direct Flow prosthesis via the transfemoral route.

WHAT IS NEXT? The data have to be confirmed by a larger study with longer follow-up.

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