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ORIGINAL RESEARCH ARTICLE

Functional outcomes with Carillon device over 1 year in patients with functional mitral regurgitation of Grades 2+ to 4+: results from the REDUCE-FMR trial

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Abstract

Aims The objective of this study was to compare functional outcomes through 1 year in patients with core-lab verified moderate to severe (Grades 2+ to 4+) functional mitral regurgitation (FMR) treated with the Carillon device or control in the blinded sham-controlled REDUCE-FMR (Carillon Mitral Contour System for Reducing Functional Mitral Regurgitation) study.

Methods and results The main outcomes of this analysis were the change in 6 min walk test (6MWT) distance, incidence of heart failure hospitalization or death, change in New York Heart Association (NYHA) class, and change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score through 1 year of follow-up. The minimum clinically important difference (MCID) was defined as a ≥30 m increase in 6MWT distance, an NYHA decrease in ≥1 class, and a ≥3 point increase in KCCQ score. The proportion of patients achieving the MCID in each treatment group was compared using Fisher's exact test, and the number needed to treat (NNT) with the Carillon device was calculated. Among 83 patients (62 Carillon and 21 sham), no statistically significant group differences were observed in the baseline characteristics. All outcomes at 1 year numerically favoured the Carillon group, including MCID for the 6MWT distance (59% vs. 23%, P = 0.029; NNT = 2.8), NYHA class (48% vs. 33%, P = 0.38; NNT = 6.9), KCCQ score (69% vs. 47%, P = 0.14; NNT = 4.5), and freedom from heart failure hospitalization or death (60% vs. 48%, P = 0.45; NNT = 8.3).

Conclusions REDUCE-FMR was the first blinded sham-controlled trial to report outcomes with percutaneous therapy for the treatment of FMR. Trends towards improvement in mean 6MWT distance, KCCQ score, and NYHA class were observed with the Carillon device. A substantially higher number of patients achieved MCID for all patient-centred outcomes with the Carillon device compared with the sham procedure.

Keywords Heart failure; Secondary mitral regurgitation; Quality of life; Percutaneous device

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Introduction

Functional mitral regurgitation (FMR) is commonly observed in patients with heart failure (HF) and is associated with poorer symptoms, clinical outcomes, and haemodynamics compared with patients with HF without FMR.[1–3] Catheter-based percutaneous treatment represents an attractive option for such patients especially considering the uncertain mortality benefit of surgical repair.[4,5] Unlike MitraClip, the Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, WA) is a percutaneous treatment of FMR in which mitral annuloplasty is performed via the coronary sinus and does not require trans-septal puncture. The REDUCE-FMR (Carillon Mitral Contour System for Reducing Functional Mitral Regurgitation) trial was the first blinded sham-controlled trial of mitral valve (MV) repair. The primary

endpoint was the improvement in regurgitant volume associated with the Carillon device at 12 months, relative to the control population. The primary endpoint was met as the Carillon device significantly reducing mitral regurgitant volume as well as left ventricular (LV) volumes compared with the sham procedure.[6]

Patients with HF often have considerable symptom burden, leading to impaired physical functioning and quality of life (QoL). Thus, improving patient-centred outcomes is one of the major goals of HF management.[7,8] This has been reflected by the recent Food and Drug Administration (FDA) guidance statement, which has recognized Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) as tools that can be used as clinical trial endpoints for medical devices in HF.[7–9] Previous analyses of the REDUCE-FMR trial have not specifically focused on the proportion of patients achieving the minimally clinically important difference (MCID) threshold of patient-centred outcomes, nor have they assessed the magnitude of the clinical benefit of Carillon device by estimating the number needed to treat (NNT) to achieve such MCIDs. The proportion of patients achieving MCID for QoL is important to assess as it can provide valuable insights whether aspects of health that are most important in terms of patients' perspectives are being impacted by the device.[10,11] To the best of our knowledge, none of the previous studies of catheter-based percutaneous treatment of FMR have systemically evaluated these parameters.

Moreover, previous results from REDUCE-FMR trial included some patients with FMR grade of +1, who may not receive the device in real-world clinical practice and may also not derive the intended benefits of Carillon device. The aim of this study was to assess patient-centred outcomes such as KCCQ score, 6 min walk test (6MWT) distance, and New York Heart Association (NYHA) class after implantation of Carillon device in patients with FMR Grades +2 to +4 and investigate the proportion of patients achieving MCID for these outcomes, in comparison with patients who were allocated to the sham procedure.

Methods

Study design

The REDUCE-FMR trial (NCT02325830) was a multicentre, randomized, double-blinded, proof-of-concept, sham-controlled trial of the Carillon Mitral Contour System in patients with HF with reduced ejection fraction and secondary mitral regurgitation. The design and primary results of the trial have been published previously.[12] In brief, the study population comprised patients with a left ventricular ejection fraction (LVEF) of $<$50%, an LV end-diastolic diameter $>$ 55 mm, symptoms of NYHA functional class II, III, or IV, and an FMR grade of 2+, 3+, or 4+, despite the use of stable ($\geq$3 month) guideline-directed medical therapy. In addition, patients had to have the capacity to finish a 6MWT of 150–450 m to exercise limitation and confirm their ability for serial 6 min walk testing. Patients with significant organic MV pathology, prior MV surgery, severe mitral annular calcification, percutaneous coronary intervention in the last 30 days, or any indication for cardiac resynchronization therapy were excluded.

After a decision was made about patients' suitability for the REDUCE-FMR trial, a baseline echocardiogram was acquired, and patients underwent a 6MWT and KCCQ. Participants were then randomized in a 3:1 ratio to receive either coronary sinus-based mitral annular reduction approach for FMR or sham. In those procedures not performed under general anaesthesia, measures such as headphones and patient draping were used to ensure the patient was unaware of treatment group allocation during the procedure. Subsequently, patients were evaluated for 6MWT distance, KCCQ, and LV structure and function at 1, 6, and 12 months of follow-up after the procedure. All echocardiograms were interpreted in accordance with established guidelines blinded to allocation and time point. Particularly in the evaluation of mitral regurgitation, a quantitative and multiparametric approach was applied to classify FMR into four grades (+1, +2, +3, or +4). The present analysis is restricted to patients with +2 to +4 FMR, the intended patient cohort of the study. A pragmatic design attempting to reflect (future) clinical practice meant that patients were entered into the study based on local echo assessment of FMR severity. On core-lab review, 29.7% were classified as only mild MR (Class 1+) and thereby outside the intended entry criteria for the study.

The trial was conducted according to the Declaration of Helsinki. An independent ethics committee/local competent authority or institutional review board approved the clinical protocol at every participating centre. All the patients provided written informed consent before study entry.

Outcomes

The pre-specified outcomes of this analysis included change in 6MWT distance, NYHA class, and KCCQ and the incidence of HF hospitalization or death through 1 year of follow-up. 6MWT distance, NYHA, and KCCQ at 1 year of follow-up were compared with baseline. The MCID was defined as a $\geq$30 m increase in 6MWT distance, a $\geq$1 class decrease in self-reported NYHA-assessed symptoms, and a $\geq$3 point increase in the KCCQ score.[9,10] The change in 6MWT distance is the preferred and most commonly used tool to assess functional status of patients.[13–15]

The 6MWT was performed on straight, flat, hard-surfaced walking course that was at least 25 m long. The patients were asked to wear comfortable shoes and clothing and to attend

having taken their usual medications. The supervisor noted the baseline heart rate, Borg scale rating for dyspnoea and fatigue, oxygen saturation, and brachial arterial blood pressure. After the instructions were understood by the patient, he or she was instructed to begin the test. The corridor was marked, and a cone was placed to denote the turnarounds. During the test, the participants were allowed to slow down or stop and resume walking as soon as possible. All participants were encouraged to walk at a rate suitable to their condition, and the supervisor was present throughout. Words of encouragement were not allowed. After the test was complete, the supervisor again noted the heart rate, Borg scale rating for dyspnoea and fatigue, oxygen saturation, and brachial arterial blood pressure. The number of laps and additional distance were also noted, and the 6MWD was calculated.

Kansas City Cardiomyopathy Questionnaire incorporates 23 items that map seven domains: symptom burden, symptom frequency, symptom stability, social limitations, physical limitations, QoL, and self-efficacy.[9] These domains are combined to create an overall summary score. All scores are represented on a 0 to 100 point scale and are summarized in 25 point ranges with scores representing health status as follows: 0–24, very poor to poor; 25 to 49, poor to fair; 50 to 74, fair to good; and 70 to 100, good to excellent. For the purpose of this analysis, KCCQ overall summary score was considered. Patients were categorized on the NYHA class according to the American Heart Association/American College of Cardiology guidelines.[16]

Statistical analysis

The results of change in 6MWT distance were classified into (i) increase in ≥20 m; (ii) increase in ≥30 m; and (iii) increase in ≥40 m. The results of change in KCCQ were classified into (i) increase in ≥3 points; (ii) increase in ≥4 points; and (iii) increase in 5 points. Patients were placed into groups based on whether the change in their 6MWT distance or KCCQ score was above or below the cut-off point. Subsequently, NNTs were calculated for each of the categories. NNTs are widely useful to estimate the risk–benefit ratio of an intervention or as a guidance tool to compare the efficiency of different therapeutic strategies. Over the years, NNTs have also been proven their usefulness in guiding regulators and other stakeholders to make decisions on drug/device regulation.[17] NNT is the number of patients that need to be treated to prevent one additional negative outcome. It is the inverse of absolute risk reduction (ARR) that was calculated as follows: ARR = Event rate in the sham cohort − Event rate in the Carillon device cohort. A relatively low NNT would suggest potential benefit on a population level. A high NNT would mean that widespread adoption could lead to excess and futile procedures. The proportion of patients achieving the MCID in each treatment group was also compared using Fisher's exact test. A *P*-value < 0.05 was considered significant in all cases. As a pilot study, REDUCE-FMR was not formally powered to assess differences in clinical event rates or outcomes, although exploratory analyses were pre-specified in the study protocol. Statistical analysis was performed with SAS Version 9.4 software (SAS Institute, Cary, NC).

Results

Patient population

Among the 83 patients included in this analysis, 62 (75%) were randomized to the Carillon device group, while 21 (25%) were randomized to the sham procedure group. Baseline demographic characteristics were well balanced between the two groups (*Table 1*). The mean age of the included patients was 70 years, 72% were male, and the aetiology of HF was ischaemic in 69%. Atrial fibrillation was present in 59% of the patients. At baseline, the 6MWT distance and KCCQ scores were 303 ± 93 and 299 ± 96 m and 53 ± 23 and 46 ± 23 in the Carillon and control groups, respectively.

Outcomes

Six minute walk test

A majority of the patients (Carillon device = 66% vs. sham group = 38%, *P* = 0.11) had a >20 m increase in 6MWT distance at 1 year of follow-up compared with their baseline. The mean change in 6MWT distance over 1 year in the Carillon device cohort ranged from −5 to 52 m (mean = 24 m), whereas it ranged from −43 to 62 (mean = 9 m) in the sham procedure group. The proportion of patients who achieved MCID in the 6MWT at 1 year of follow-up from baseline was significantly higher in the Carillon device group compared with the sham group (59% vs. 23%, respectively; *P* = 0.029). The NNT for a ≥30 m increase in 6MWT distance with the Carillon device was 2.8, and the NNT for a ≥20 m increase in 6MWT distance was 3.6 (*Table 2*).

Kansas City Cardiomyopathy Questionnaire

The majority of the patients (Carillon device = 69% vs. sham control = 47%) had a >3 point increase in KCCQ score at 1 year of follow-up compared with their baseline. The mean change in KCCQ score over 1 year in the Carillon device cohort ranged from 5 to 19 (mean = 12), whereas it ranged from −8 to 17 (mean = 5) in the sham procedure group. The number of patients who achieved MCID for KCCQ was numerically higher in the Carillon device group compared with the sham procedure group (69% vs. 47%, respectively; *P* = 0.14). The NNT for a ≥3 point increase in KCCQ score with the Carillon

Table 1 Baseline patient characteristics

Characteristic	Carillon (n = 62)	Sham (n = 21)	P-value
Demographics			
Age (years)	70 ± 10	70 ± 10	0.99
Male sex	73% (45/62)	71% (15/21)	1.00
Body mass index (kg/m^2)	26 ± 5	26 ± 4	0.98
Medical history			
Ischaemic cardiomyopathy aetiology	71% (44/62)	62% (13/21)	0.57
Atrial fibrillation	56% (35/62)	67% (14/21)	0.45
Myocardial infarction	47% (29/62)	48% (10/21)	1.00
Functional assessment			
New York Heart Association classification			0.40
II	40% (25/62)	57% (12/21)	
III	56% (35/62)	43% (9/21)	
IV	3% (2/62)	0% (0/21)	
6 min walk test (m)	303 ± 93	299 ± 96	0.85
KCCQ	53 ± 23	46 ± 23	0.20
LV parameters			
LV ejection fraction (%)	33 ± 9	36 ± 8	0.25
LV end-diastolic diameter (cm)	6.6 ± 0.9	6.4 ± 0.9	0.47
LV end-diastolic volume (cc)	194 ± 62	188 ± 78	0.73
LV end-systolic volume (cc)	133 ± 54	124 ± 62	0.55
Mitral valve parameters			
Regurgitant volume (mL)	48 ± 22	51 ± 20	0.72
Vena contracta (cm)	0.42 ± 0.09	0.43 ± 0.13	0.63
Effective regurgitant orifice area (cm^2)	0.31 ± 0.13	0.32 ± 0.11	0.73
MR grade			0.38
2	55% (34/62)	38% (8/21)	
3	37% (23/62)	52% (11/21)	
4	8% (5/62)	10% (2/21)	

KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; MR, mitral regurgitation.
Values are mean ± standard deviation (n) or percentage (n/N).

Table 2 Key functional outcomes over 1 year of follow-up

Outcome	Carillon	Sham	P-value	NNT[a]
6 min walk test increase ≥20 m	66% (29/44)	38% (5/13)	0.11	3.6
6 min walk test increase ≥30 m	59% (26/44)	23% (3/13)	0.029	2.8
6 min walk test increase ≥40 m	50% (22/44)	23% (3/13)	0.12	3.7
6 min walk test mean change over 1 year (m)	24 (−5 to 52)	9 (−43 to 62)	0.63	—
KCCQ increase ≥3 points	69% (33/48)	47% (7/15)	0.14	4.5
KCCQ increase ≥4 points	67% (32/48)	47% (7/15)	0.23	5.0
KCCQ increase ≥5 points	63% (30/48)	47% (7/15)	0.37	6.3
KCCQ mean change over 1 year (m)	12 (5 to 19)	5 (−8 to 17)	0.29	—
Freedom from HFH/death	60% (37/62)	48% (10/21)	0.45	8.3
NYHA decrease ≥1 class	48% (23/48)	33% (5/15)	0.38	6.9
NYHA decrease[b] ≥1 class	40% (23/58)	29% (5/17)	0.57	9.8

HFH/death, heart failure hospitalization or death; KCCQ, Kansas City Cardiomyopathy Questionnaire; NNT, number needed to treat; NYHA, New York Heart Association.
Values are percentage (n/N) or mean (95% confidence interval).
[a]Denotes the number of patients that must be treated with the Carillon device in order to avoid one 'failure'.
[b]For patients who died within 12 months, NYHA was set to 5.

device was 4.5, whereas the NNT for a ≥5 point increase in KCCQ score was 6.3 (*Table 2*).

New York Heart Association and freedom from heart failure hospitalization or death

From baseline to follow-up at 1 year, ≥1 class change in NYHA (48% vs. 33%, respectively; P = 0.38) and freedom from HF hospitalization or death (60% vs. 48%, respectively; P = 0.45) numerically favoured the Carillon group compared with the sham procedure group (*Table 2*).

Safety

No major complications such as intra-procedural ischaemic event, cardiac perforations, or device embolization or fracture were observed.

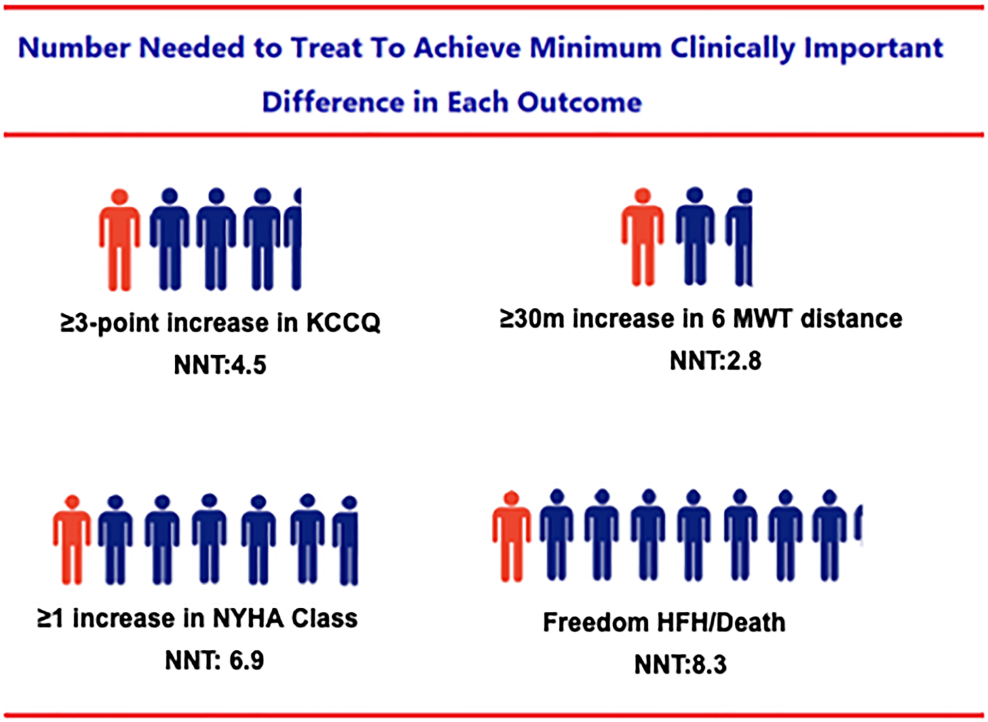
Discussion

In this analysis of REDUCE-FMR, we show several key findings. First, a trend towards improvement in mean 6MWT distance, KCCQ score, and NYHA class was observed with the Carillon device compared with the sham control. Second, a substantially higher number of patients achieved MCID for all patient-centred outcomes with the Carillon device compared with the sham procedure control. Third, the NNTs for achieving MCID of patient-centred outcomes and freedom from HF hospitalization or death were low, indicating a favourable absolute magnitude of benefit that might be observed with the Carillon device (*Figure 1*).

Currently, the only non-surgical treatment for FMR in patients with HF approved by the US FDA is the transcatheter MV leaflet edge-to-edge percutaneous repair with the MitraClip device (Abbott Vascular, Abbott Park, IL).[18] Both trials [Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) and Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR)] designed to assess the use of MitraClip in patients with FMR have yielded different conclusions.[19,20] While the COAPT trial showed improvements in mean 6MWT distance, QoL, and NYHA class, the MITRA-FR trial did not show significant improvement in these patient-centred outcomes.[20,21]

Inconsistency in findings from the two MitraClip trials has been attributed to the differences in patient populations.[22,23] Compared with the MITRA-FR trial, the COAPT trial included a more selective population with a smaller average LV diastolic diameter (LVDD; 62 vs. 69 mm) and a greater average effective regurgitant orifice area (EROA; 0.41 vs. 0.31 cm^2).[20,21] In other words, the COAPT trial only included patients with less, possibly more recoverable LV remodelling and greater valve involvement. Based on this evidence, the current expert opinion is that only a small subset of patients with FMR with larger EROA and smaller LVDD are candidates for the MitraClip procedure.[24] The patient population in this subgroup of those enrolled in REDUCE-FMR (EROA, 0.31 cm^2; LVDD, 66 mm) resembles that of the MITRA-FR trial and is more generalizable to patients with HF and moderate to severe FMR. However, unlike the MITRA-FR trial, our results show a trend towards improvement in patient-centred outcomes with the Carillion device. In fact, the low NNT for all patient-centred outcomes suggests that the Carillon device is likely to provide benefit in a large proportion of patients with FMR, rather than just a small subset. Furthermore, unlike the COAPT and MITRA-FR trials, the REDUCE-FMR trial used a sham procedure in the control group, which increases the reliability of its results by minimizing placebo and nocebo effects.

Figure 1 Number needed to treat to achieve minimum clinically important difference in each outcome. 6MWT, 6 min walk test; HFH/D, heart failure hospitalization or death; KCCQ, Kansas City Cardiomyopathy Questionnaire; NNT, number needed to treat; NYHA, New York Heart Association.



There are important reasons why the Carillon maybe more widely applicable in patients with FMR than the MitraClip device. First, Carillon implantation involves placement of the device via the coronary sinus and therefore does not interrupt the mitral apparatus. Second, in contrast to MitraClip, the Carillon device does not require trans-septal puncture. Third, the Carillon device might be a better option in patients with small annular dimensions, in which other interventional devices might induce mitral stenosis. Finally, the trial showed that the device was safe in a wide range of patients.

Although the low power of the study necessitates that the findings are considered exploratory rather than confirmatory, the low NNT values have important implications. NNT calculated from small trials and pilot studies has traditionally been used to determine the threshold of clinical significance for larger trials and assess their likelihood of being feasible.[25] Specifically, small NNTs provide justification for conducting larger trials on relatively complex, risky, expensive, or otherwise burdensome treatments.[26] Thus, we reason that findings from this analysis support the need for a larger trial to evaluate patient-centred outcomes using the Carillon device. The ongoing CARILLON trial (NCT03142152) will enrol 352 participants and evaluate the device for impact on mortality and hospitalization in patients with FMR.[27] Approximately 60 million patients have HF globally, and 70% of these patients may have concomitant FMR.[28] Following possible confirmatory evidence of benefit, widespread adoption of the Carillon device could potentially result in improved outcomes at a population level given the vast number of eligible patients.

Limitations

Our findings should be interpreted in the light of several limitations. First, this analysis was not adequately powered to evaluate clinical endpoints. Second, the duration of follow-up was limited to 1 year; therefore, it is not possible to assess the long-term safety and efficacy of this device. Lastly, these data encompass some of the early experience with the Carillon device and therefore may not reflect the current skill of device users.

Conclusions

In conclusion, a trend towards improvement in mean 6MWT distance, KCCQ score, and NYHA class with the Carillon device was observed. A substantially higher number of patients achieved MCID for all patient-centred outcomes with the Carillon device compared with the sham control. The NNTs for achieving MCID of patient-centred outcomes and freedom from HF hospitalization or death were low, indicating the absolute magnitude of benefit that may be observed with the Carillon device.

Conflict of interest

J.B. reports consulting fees from BI, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave Ltd., and Vifor. K.W. held a National Institute for Health Research (NIHR) (UK) Clinician Scientist Award 2012–2017; has received speaker fees and honoraria from Medtronic, Cardiac Dimensions, Novartis, Abbott, Bristol-Myers Squibb, Pfizer, and Bayer; and has received unconditional research grants from Medtronic UK (managed by the University of Leeds) for a PhD fellowship program. He has also acted as a proctor for Cardiac Dimensions. T.F. reports personal fees from Novartis, Bayer, Janssen, SGS, Roche, Boehringer Ingelheim, Daiichi-Sankyo, Galapagos, Penumbra, Parexel, Vifor, BiosenseWebster, CSL Behring, Fresenius Kabi, Coherex Medical, and LivaNova. A.J.S.C. reports honoraria and/or lecture fees from AstraZeneca, Bayer, Menarini, Novartis, Nutricia, Servier, Vifor, Actimed, Cardiac Dimensions, CVRx, Enopace, Faraday, Gore, Impulse Dynamics, Respicardia, Stealth Peptides, V-Wave, Corvia, Arena, and ESN Cleer. W.C.L. is a consultant for Abbott and Medtronic. EBR Systems, Baim Institute, Respicardia, PharmIN, and Cardiac Dimensions. J.L. has been a proctor for Cardiac Dimensions. H.S. has received grants from Cardiac Dimensions and has received grants, fees, and non-financial support from 4tech Cardio, Abbott, Ablative Solutions, Ancora Heart, Bavaria Medizin Technologie GmbH, Bioventrix, Boston Scientific, Carag, Celonova, Comed BV, Contego, CVRx, Dinova, Edwards, Endologix, Hemoteq, Hangzhou Nuomao Medtech, Lifetech, Maquet Getinge Group, Medtronic, Mitralign, Mokita, Occlutech, pfm Medical, Recor, Renal Guard, Rox Medical, Terumo, Vascular Dynamics, Vectorious Medtech, Venus, and Vivasure Medical. All other authors have no conflicts of interest to declare.

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