ORIGINAL RESEARCH ARTICLE

Effect of Carillon Mitral Contour System on patient-reported outcomes in functional mitral regurgitation: an individual participant data meta-analysis

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Abstract

Aims The Carillon Mitral Contour System has been shown to reduce mitral regurgitation and left ventricular volumes in symptomatic heart failure patients with functional mitral regurgitation. We sought to evaluate the effects of the Carillon device on quality of life and functional capacity in these patients.
Methods and results An individual participant data meta-analysis was conducted utilizing data from REDUCE-FMR, TITAN, and TITAN II studies. The main outcomes assessed were changes from baseline in Kansas City Cardiomyopathy Questionnaire overall summary scores (KCCQ-OSS), 6 min walk test (6MWT) distance, and New York Heart Association (NYHA) classification at Months 1 and 12 after device implantation. Subgroup analyses were conducted for patients with severe functional mitral regurgitation (Grade 3 or 4). Pooled estimates were calculated using a random-effects model and are presented as weighted proportions or weighted mean differences along with 95% confidence intervals (CIs). Among 139 patients included in the analysis, Carillon device significantly improved the 6MWT distance (63.0 m; 95% CI 18.8–107.2, *P* = 0.0056) and KCCQ-OSS score (15.1; 95% CI 5.6–24.7, *P* = 0.0022) at 1 month from baseline. These benefits were sustained at 12 months (64.1 m; 95% CI 13.2–115.0, *P* = 0.0141, for 6MWT distance, and 12.3; 95% CI 4.7–19.8, *P* = 0.0019, for KCCQ-OSS score). More than 50% of the patients had improvements in KCCQ-OSS by ≥5 (60.4%; 95% CI 47.4–72.1) and 10 points (50.5%; 95% CI 34.9–66.0) at 12 months. Almost half of the patients experienced a ≥1 class improvement in NYHA class after implantation of the device at 1 month (67.9%; 95% CI 37.3–88.3) and at 12 months (48.8%; 95% CI 31.8–66.2). Results remained similar for KCCQ-OSS, 6MWT distance, and NYHA classification when only patients with Grade 3 or 4 mitral regurgitation were analysed. The pooled estimates of 30 day and 1 year all-cause mortality were 2.2% (95% CI 0.7–6.5) and 17.3% (95% CI 11.8–24.5), respectively.
Conclusions The Carillon Mitral Contour System significantly improved patient-reported quality-of-life outcomes in heart failure patients with functional mitral regurgitation.

Introduction

Functional mitral regurgitation is commonly seen in patients with heart failure with reduced ejection fraction (HFrEF) and is associated with poor prognosis.[1–6] Functional mitral regurgitation contributes to progressive adverse remodelling of the heart that worsens the progression of heart failure.[1–6] While many pharmacological and device-based therapies have shown to improve outcomes in heart failure, few interventions have explicitly targeted

functional mitral regurgitation.[7,8] Trial with MitraClip (Abbott Laboratories, Rockville, MD) in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial showed a significant reduction, while the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trial showed no benefit in terms of mortality or heart failure hospitalization in these patients.[9,10]

The Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, WA) is a percutaneous treatment of functional mitral regurgitation in which mitral annuloplasty is performed via coronary sinus. Carillon device has been shown to reduce left ventricular (LV) volumes and mitral regurgitant volumes in heart failure patients receiving optimal medical therapy in several studies.[11–14] However, clinical trials evaluating Carillon Mitral Contour System have been limited by small sample sizes and have not focused on health status outcomes.[11–13] Quality of life is increasingly becoming a focal point in treatment of heart failure with the Food and Drug Administration recognizing Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire as tools that can be used as clinical trial endpoints in evaluating heart failure medical devices.[15,16] In this individual participant data meta-analysis, we sought to evaluate the effects of the Carillon Mitral Contour System on patient-reported outcomes in heart failure patients with functional mitral regurgitation.

Methods

Overview

We conducted an individual participant data meta-analysis of three studies regarding the effect of Carillon Mitral Contour System in functional mitral regurgitation. The three studies included in the meta-analysis were REDUCE-FMR (Carillon Mitral Contour System for Reducing Functional Mitral Regurgitation), TITAN (Trans-catheter Implantation of Carillon Mitral Annuloplasty Device) I, and TITAN II. The results from the individual studies have been published previously.[11–13] The REDUCE-FMR was a sham-controlled trial, whereas TITAN I and II did not have a control group. All the three studies included similar patients. The REDUCE-FMR trial enrolled adults >18 years of age with an LV ejection fraction (LVEF) of <50%, an LV end-diastolic diameter more than 55 mm, and a functional mitral regurgitation grade of 2 or 3 or 4 despite the use of at least 3 months of guideline-directed medical therapy. In the TITAN studies, adults >18 years of age with LVEF of <40%, an LV end-diastolic diameter more than 55 mm, and an FMR grade of 2 or 3 or 4 despite the use of

at least 1 month of guideline-directed medical therapy were included. Both REDUCE-FMR and TITAN studies required patients to complete a 6 min walk distance of 150 to 450 m to confirm exercise limitations. All three studies excluded patients with severe mitral annular calcification, prior mitral valve surgery, and existing cardiac resynchronization therapy.

Outcomes

The pre-specified primary endpoint of the REDUCE-FMR trial was change in mitral regurgitant volume at 12 months. Secondary efficacy endpoints were changes in LV end-diastolic and end-systolic volumes and changes in 6 min walk distances, New York Heart Association (NYHA) functional class, and KCCQ scores at 12 months compared with baseline. In the TITAN studies, the primary endpoint was the rate of major adverse events at 30 days, defined as death, myocardial infarction, cardiac perforation necessitating intervention, device embolization, or the occurrence of surgery or percutaneous intervention related to the device. Secondary efficacy endpoints included NYHA classification and 6 min walk improvement over 12 months' follow-up. While KCCQ was assessed in TITAN, it was not evaluated in TITAN II. Patients were followed for 24 months in TITAN and for 12 months in REDUCE-FMR and TITAN II.

The outcomes of interest for this meta-analysis were changes from baseline in KCCQ overall summary scores (KCCQ-OSS), 6 min walk test (6MWT), and NYHA class at Months 1 and 12 after device implantation. The KCCQ is a 23-item, disease-specific measure intended for the assessment of heart failure patients' perspectives of how their disease impacts their health status.[17] The KCCQ has been shown to be valid, reliable, sensitive to clinical changes, and associated with death, hospitalization, and healthcare costs.[18–20] In the KCCQ-23, clinical summary score includes the physical function and symptoms domains, the total symptom score quantifies the symptom frequency and severity, and OSS is derived from the following domains (total symptom score, physical function, quality of life, and social function). Scores are transformed to a range of 0–100, where higher scores reflect better health status. For this analysis, KCCQ-OSS was used, and a 5-point change in KCCQ-OSS score was considered a clinically meaningful threshold.[21,22] KCCQ was filed using a paper–pen version via in person. The 6MWT was performed indoors along a flat, straight, walking course supervised by a trained researcher. Patients were allowed to stop and rest during the test but were instructed to resume walking as soon as they felt able to do so. Patients were provided with instructions about the 6MWT but received no encouragement during the test.

Statistical analyses

Categorical data from each trial are presented as frequencies and proportions. The proportions from each study were pooled using logit transformations and a random-effects model yielding an effect estimate with 95% confidence intervals (CIs). Continuous variables are presented as means and standard deviations. For continuous variables, weighted mean differences (WMDs) and 95% CIs were pooled by using a random-effects model. To assess the between-study heterogeneity, the estimated variances (τ^2) of the random study effects are reported; for binary outcomes, these are on the logarithmic odds scale. Analyses were based on all available data. Subgroup analyses were conducted for patients with severe FMR (Grade 3 or 4.) at baseline. All statistical analysis was carried out using SAS software Version 9.4 (SAS Institute Inc., Cary, NC, USA), and a P-value of <0.05 was considered significant in all cases.

Results

Patient characteristics

The characteristics of the REDUCE-FMR and TITAN study populations are shown in *Table 1*. In the REDUCE-FMR trial, 120 patients were randomized: 87 to treatment arm and 33 to sham control. Of the 87 patients randomized to the treatment arm, 73 had the device implanted. The most common reason for not having a device implanted was coronary impingement ($n = 8$). Among the 139 patients included in the analysis overall, majority were men (105, 75.5%), had NYHA Class III symptoms at baseline (96, 69.6%), and had an ischaemic cause of heart failure (94, 67.6%). The mean age was 68.0 (10.7) years. Almost half of the patients had Grade 3 or 4 mitral regurgitation (66, 49.3%). The mean LVEF, LV end-diastolic dimension, LV end-diastolic volume, and LV end-systolic volume at baseline were 31.1% (8.4), 6.6 (0.9) cm, 193.3 (62.7) mL, and 135.6 (54.6) mL, respectively. The mean KCCQ-OSS score at baseline was 50.4 (22.1) points, while the mean 6MWT at baseline was 307.2 (85.5) m. Majority of the patients were taking optimally tolerated doses of guideline-directed therapy, including beta-blockers, renin–angiotensin–aldosterone system blockers, and loop diuretics.

Kansas City Cardiomyopathy Questionnaire score

Carillon device improved the KCCQ-OSS score as early as 1 month by 10.8 (95% CI 4.7–17.0) points in the REDUCE-FMR and by 20.5 (95% CI 13.6–27.5) points in the TITAN (pooled estimate 15.1; 95% CI 5.6–24.7, $P = 0.0022$). These benefits were sustained during follow-up through 12 months. The mean change in KCCQ-OSS score at 12 months from baseline was 9.4 (95% CI 2.7–16.0) points

Table 1 Baseline patient characteristics

	REDUCE	TITAN	TITAN II	Pooled cohort
N	73	36	30	139
Men	57 (78.1)	27 (75.0)	21 (70.0)	105 (75.5)
Prior MI	38 (52.1)	20 (55.6)	15 (50.0)	73 (52.5)
Age (years)	70.0 (9.2)	61.9 (12.7)	70.3 (8.7)	68.0 (10.7)
Ischaemic cause	51 (69.9)	26 (72.2)	17 (56.7)	94 (67.6)
History of Afib	42 (57.5)	12 (33.3)	15 (50.0)	69 (49.6)
BMI	27.0 (5.3)	26.3 (4.6)	25.1 (5.5)	26.4 (5.2)
NYHA class				
2	35 (48.0)	0 (0.0)	1 (3.3)	36 (26.1)
3	36 (49.3)	33 (94.3)	27 (90.0)	96 (69.6)
4	2 (2.7)	2 (5.7)	2 (6.7)	6 (4.4)
Heart rate (b.p.m.)	70.1 (12.7)	78.3 (19.9)	76.5 (15.7)	73.5 (15.8)
Systolic BP (mmHg)	118.5 (19.6)	104.4 (14.7)	115.0 (18.5)	114.1 (19.0)
Diastolic BP (mmHg)	69.5 (10.9)	63.8 (10.9)	70.2 (9.3)	68.1 (10.9)
6 min walk test (m)	314.8 (92.1)	302.5 (73.6)	294.1 (82.6)	307.2 (85.5)
LVEF (%)	32.8 (8.6)	28.7 (7.5)	30.5 (8.7)	31.1 (8.4)
LVEDD (cm)	6.6 (0.9)	6.7 (0.8)	6.3 (0.8)	6.6 (0.9)
LVEDV (mL)	191.8 (65.9)	208.5 (62.0)	174.4 (51.2)	193.3 (62.7)
LVESV (mL)	131.8 (56.4)	151.8 (57.1)	119.9 (39.6)	135.6 (54.6)
Mitral regurgitant grade				
1	25 (34.3)	0 (0.0)	0 (0.0)	25 (18.7)
2	27 (37.0)	7 (19.4)	9 (36.0)	43 (32.1)
3	17 (23.3)	20 (55.6)	9 (36.0)	46 (34.3)
4	4 (5.5)	9 (25.0)	7 (28.0)	20 (14.9)
KCCQ	53.9 (23.0)	43.0 (18.0)	N/A	50.4 (22.1)

Afib, atrial fibrillation; BMI, body mass index; BP, blood pressure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; NYHA, New York Heart Association.

in the REDUCE-FMR and 17.3 (95% CI 7.1–27.5) points in the TITAN trial (pooled estimate 12.3; 95% CI 4.7–19.8, *P* = 0.0019) at 12 months (*Table 2*). More than 50% of the patients had improvements in KCCQ-OSS by ≥5 (60.4%; 95% CI 47.4–72.1) and 10 points (50.5%; 95% CI 34.9–66.0) at 12 months. Results remained similar when only patients with Grade 3 or 4 mitral regurgitation were analysed (*Table 3*).

Six minute walk test

The mean change in 6MWT at 1 months after device implantation was 22.8 m (95% CI 3.4–42.1) in the REDUCE-FMR, 93.7 m (95% CI 43.3–144.1) in the TITAN, and 77.3 m (95% CI 58.8–95.9) in the TITAN II (pooled estimate 63.0 m; 95% CI 18.8–107.2, *P* = 0.0056). Similar benefits were observed after 12 months of device implantation as well. The mean change in 6MWT at 12 months from baseline was 20.6 m (95% CI −4.2 to 45.4) in the REDUCE-FMR, 102.5 m (95% CI 31.6–173.5) in the TITAN, and 77.6 m (95% CI

39.4–115.9) in the TITAN II trial (pooled estimate 64.1 m; 95% CI 13.2–115.0, *P* = 0.0141) at 12 months (*Table 2*). Results remained similar when only patients with Grade 3 or 4 mitral regurgitation were analysed (*Table 3*). About two-thirds of the patients (67.3%; 95% CI 56.8–76.2) experienced a >20 m improvement in 6MWT after implantation of Carillon device.

New York Heart Association class

The number of patients who had a ≥1 class improvement in NYHA at 1 month was 28, 26, and 23 in REDUCE-FMR, TITAN, and TITAN II, respectively. On pooling, more than half of the patients (67.9%; 95% CI 37.4–88.3) experienced a ≥1 class in NYHA after implantation of Carillon. Similarly, the number of patients who experienced a ≥1 class improvement in NYHA at 12 months was 23, 18, and 17, respectively (pooled estimate 48.8%; 95% CI 31.8–66.2). Results remained similar

Table 2 Health status outcomes in overall cohort

Outcome	REDUCE (*n* = 73)	TITAN (*n* = 36)	TITAN II (*n* = 30)	Pooled cohort (*n* = 139)
KCCQ: change from baseline at 1 month	10.8 (4.7–17.0)	20.5 (13.6–27.5)	N/A	15.1 (5.6–24.7), *P* = 0.0022 (het. τ^2 = 33.7)
KCCQ: change from baseline at 12 months	9.4 (2.7–16.0)	17.3 (7.1–27.5)	N/A	12.3 (4.7–19.8), *P* = 0.0019 (het. τ^2 = 12.3)
KCCQ: improvement ≥5 points at 1 month (%)	55.9 (44.1–67.7)	86.7 (74.5–98.8)	N/A	72.9 (35.4–92.9) (het. τ^2 = 1.16)
KCCQ: improvement ≥5 points at 12 months (%)	55.9 (43.3–68.6)	69.6 (50.8–88.4)	N/A	60.4 (47.4–72.1) (het. τ^2 = 0.04)
KCCQ: improvement ≥10 points at 1 month	47.1 (35.2–58.9)	66.7 (49.8–83.5)	N/A	55.8 (36.6–73.4) (het. τ^2 = 0.23)
KCCQ: improvement ≥10 points at 12 months (%)	44.1 (31.0–56.7)	60.9 (40.9–80.8)	N/A	50.5 (34.9–66.0) (het. τ^2 = 0.11)
6MWT: change from baseline at 1 month (m)	22.8 (3.4–42.1)	93.7 (43.3–144.1)	77.3 (58.8–95.9)	63.0 (18.8–107.2), *P* = 0.0056 (het. τ^2 = 1247.4)
6MWT: change from baseline at 12 months (m)	20.6 (−4.2–45.4)	102.5 (31.6–173.5)	77.6 (39.4–115.9)	64.1 (13.2–115.0), *P* = 0.0141 (het. τ^2 = 1521.6)
≥1 class improvement in NYHA at 1 month (%)	39.4 (28.1–50.8)	83.9 (70.9–96.8)	76.7 (61.5–91.8)	67.9 (37.4–88.3) (het. τ^2 = 1.11)
≥1 class improvement in NYHA at 12 months (%)	33.3 (22.2–44.5)	56.3 (39.1–73.4)	60.7 (42.6–78.8)	48.8 (31.8–66.2) (het. τ^2 = 0.294)

6MWT, 6 min walk test; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association.

Table 3 Health status outcomes in patients with Grade 3/4 vs. 1/2 mitral regurgitation

Outcome	Pooled cohort (*n* = 139)
KCCQ: change from baseline at 1 month	15.3 vs. 15.1 (*P* = 0.975)
KCCQ: change from baseline at 12 months	13.5 vs. 10.8 (*P* = 0.643)
KCCQ: improvement ≥5 points at 1 month (%)	75.3 vs. 66.6 (*P* = 0.586)
KCCQ: improvement ≥5 points at 12 months (%)	58.6 vs. 63.8 (*P* = 0.653)
KCCQ: improvement ≥10 points at 1 month	54.1 vs. 58.1 (*P* = 0.717)
KCCQ: improvement ≥10 points at 12 months (%)	52.8 vs. 48.0 (*P* = 0.681)
6MWT: change from baseline at 1 month (m)	75.9 vs. 47.6 (*P* = 0.140)
6MWT: change from baseline at 12 months (m)	71.8 vs. 55.5 (*P* = 0.527)
≥1 class improvement in NYHA at 1 month (%)	63.0 vs. 74.0 (*P* = 0.254)
≥1 class improvement in NYHA at 12 months (%)	45.1 vs. 50.2 (*P* = 0.710)

6MWT, 6 min walk test; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association.

when only patients with Grade 3 or 4 mitral regurgitation were analysed (*Table 3*).

All-cause mortality

The 30 day all-cause mortality was low among all the studies (pooled cohort 2.2%; 95% CI 0.7–6.5). The 1 year all-cause mortality was higher in the TITAN studies (TITAN 22.2%; 95% CI 8.6–35.8, and TITAN II 20.0%; 95% CI 5.7–34.3) compared with the REDUCE-FMR trial (13.7%; 95% CI 5.8–21.6). The pooled 1 year all-cause mortality was 17.3% (95% CI 11.8–24.5).

Discussion

We report several key findings in this individual participant data meta-analysis. First, Carillon Mitral Contour System significantly improved the KCCQ-OSS score by clinically meaningful thresholds as early as 1 month, and these benefits were sustained at 12 months. Second, Carillon Mitral Contour System significantly improved the 6MWT at 1 and 12 months compared with baseline. Third, more than half of the patients experienced a ≥1 class in NYHA after implantation of Carillon device by 1 month suggesting an improvement in patient-reported and physician-assessed health status outcomes. Considering the increasing use and emphasis of patient-reported outcomes for regulatory device approvals, these results have important clinical implications for the management of heart failure patients with functional mitral regurgitation.

Improving health-related quality of life is a critical component of the management of heart failure.[23,24] Previous studies in HFrEF patients have suggested that minimal clinically importance differences threshold for KCCQ score is numerically lower than the threshold of 5-point change considered for clinical outcomes prognosis.[21,22] Carillon Mitral Contour System was shown to improve the KCCQ-OSS score by almost twice these thresholds at 1 and 12 months after device implantation. Moreover, in the responder analysis, more than 50% of the patients had improvements in KCCQ by ≥5 and 10 points at 12 months. These numbers compare favourably with several other heart failure interventions such as sodium–glucose co-transporter 2 inhibitors, angiotensin receptor neprilysin inhibition, and cardiac resynchronization therapy.[25–30] In the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF), 53% of the patients had ≥5 point improvement in KCCQ at 8 months, while with Carillon Mitral Contour System, almost two-thirds of the patients had ≥5 point improvement in KCCQ as early as 1 month.[26] Furthermore, in the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) study, treatment with cardiac resynchronization therapy resulted in only 2-point improvements in KCCQ among HFrEF patients with left bundle branch block.[29]

In the MITRA-FR trial, KCCQ values were not evaluated, and large amount of data on functional status outcomes were missing on follow-up.[9] In the COAPT trial, change in KCCQ score from baseline to 12 months was 12.5 points in the MitraClip group, which is comparable with what was observed with Carillon device.[10] No benefit was observed with MitraClip in regard to 6MWT (−2.2 m); however, in comparison with the control group (−60.2 m), relatively less significant decline occurred in 6MWT at 12 months (mean difference 57.9 m). Carillon was shown to improve the 6MWT by approximately 50 m at both 1 and 12 months. It is also important to highlight that MitraClip trials were conducted in centres with experienced operators who were certified, compared with Carillon Mitral Contour System studies that were performed at centres previously unfamiliar with the technology.

Carillon Mitral Contour System works differently from MitraClip and offers many advantages compared with other devices for functional mitral regurgitation. First, it does not require a trans-septal puncture like implantation of MitraClip. Second, instead of clipping the valve leaflets together, Carillon Mitral Contour System is implanted in the coronary vasculature to reshape the mitral annulus from the outside without contacting the mitral apparatus. Thus, Carillon device does not preclude the use of MitraClip or other surgical procedures in the future. Third, MitraClip mainly works by reducing the regurgitant volume from the left ventricle. Recent data show that in many of the functional mitral regurgitation patients, the left ventricle is relatively small and the left atrium plays an important role. This has been termed as atrial function mitral regurgitation, and Carillon device may be ideal for such condition. Fourth, Carillon device may especially be a good option in patients with small annular dimensions, in which other devices might lead to mitral stenosis or in very dilated annuli, which may prohibit the use of other devices. A few limitations of the Carillon device should also be considered. The Carillon Mitral Contour System does not have great efficacy if coronary sinus is not co-planar to the mitral annulus and is contraindicated in the presence of cardiac resynchronization therapy lead. Current ongoing trials (NCT03142152) will give us further insight in to the efficacy of Carillon Mitral Contour System on hard clinical outcomes compared with medical therapy and also compare the effect of the Carillon device on patient-reported outcomes with other interventional approaches, especially the MitraClip device.

There are some limitations that should be considered in this individual participant data meta-analysis. First, our results do not take in to consideration the 'placebo effect' as TITAN studies were not sham or placebo controlled. However, the patient-reported outcome benefits observed with

Carillon Mitral Contour System were considerably large, and thus, it is unlikely that all the benefits observed could have been due to placebo effect. Nonetheless, the lack of a randomized blinded comparator and lack of adjustment for baseline values in mean changes reported are limitations that must be acknowledged and may have caused bias. Second, the number of patients included in the studies was limited. Lastly, the follow-up durations were limited; hence, long-term safety and effectiveness cannot be gauged.

In conclusion, the Carillon Mitral Contour System has acceptable procedural success and improves patient-reported outcomes in heart failure patients with functional mitral regurgitation. Carillon Mitral Contour System substantially improved the quality of life (KCCQ) scores and 6MWT distance as early as 1 month, and these benefits were sustained at 12 months. Quality-of-life improvement in patients who were treated with the Carillon device was similar or better than other recently reported heart failure trials. Carillon Mitral Contour System represents an attractive new option for heart failure patients with typically poor prognosis and offers many advantages compared with other devices for functional mitral regurgitation.

Conflict of interest

S.D.A has received research support from Vifor International and Abbott Vascular and fees for consultancy and/or speaking from AstraZeneca, Bayer, Boehringer Ingelheim, Respicardia, Impulse Dynamics, Janssen, Novartis, Servier, and Vifor International. J.B. serves as a consultant for Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squib, CVRx, G3 Pharmaceutical, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, V-Wave Limited, and Vifor. T.F. reports personal fees for consultancies (including data monitoring committees) from Novartis, Bayer, Janssen, SGS, Roche, Boehringer Ingelheim, Daiichi Sankyo, Galapagos, Penumbra, Parexel, Vifor, Biosense Webster, CSL Behring, Fresenius Kabi, Coherex Medical, and LivaNova, all outside the submitted work. Other authors report no relevant disclosures.

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