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ORIGINAL ARTICLE

Twelve-month follow-up results from the SIRONA 2 clinical trial

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Abstract

Aims In the SIRONA 2 trial, the safety and efficacy of pulmonary artery (PA) pressure (PAP)-guided heart failure (HF) management using a novel PAP sensor were assessed at 30 and 90 days, respectively, and both endpoints were met. The current study examines the prespecified secondary endpoints of safety and accuracy of the PA sensor along with HF hospitalizations and mortality, HF symptoms, functional capacity, quality of life, and patient compliance through 12 months.

Methods and results SIRONA 2 is a prospective, multi-centre, open-label, single-arm trial evaluating the Cordella™ PA Sensor System in 70 patients with New York Heart Association (NYHA) functional class III HF with a prior HF hospitalization and/or increase of N-terminal pro-brain natriuretic peptide within 12 months of enrolment. Sensor accuracy was assessed and compared with measurements obtained by standard right heart catheterization (RHC). Safety was defined as freedom from prespecified adverse events associated with use of the Cordella PA Sensor System and was assessed in all patients who entered the cath lab for PA sensor implant. HF hospitalizations and mortality, HF symptoms, functional capacity, quality of life, and patient compliance were also assessed. At 12 months, there was good agreement between the Cordella PA Sensor System and RHC, with the average difference for mean PAP being 2.9 ± 7.3 mmHg. The device safety profile was excellent with 98.4% freedom from device/system-related complications. There were no pressure sensor failures. HF hospitalizations and mortality were low with a rate of 0.33 event per patient year. Symptoms as assessed by NYHA ($P < 0.0001$) and functional capacity as measured by 6 min walk test ($P = 0.02$) were significantly improved. Patients' adherence to daily transmissions of PAP and vital signs measurements was 95%.

Conclusions Long-term follow-up of the SIRONA 2 trial supports the safety and accuracy of the Cordella PA Sensor System in enabling comprehensive HF management in NYHA class III HF patients.

Keywords Remote patient monitoring; Heart failure; GDMT; Pulmonary artery pressure

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Introduction

The clinical course of chronic heart failure (HF) is characterized by episodes of decompensation with worsening signs and symptoms and is associated with poor quality of life, increased risk of HF hospitalizations (HFHs) and death, and high economic cost.[1] Preventing HFH is a cornerstone of HF treatment, and it has been shown that decompensated HF in both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) patients is preceded by a significant increase in pulmonary artery (PA) pressure (PAP).[2] PAP-guided HF management using an implantable PAP sensor has been shown to reduce HFH in New York Heart Association (NYHA) functional class III patients in both randomized and

post-market studies[3–6] and has recently obtained a class IIb recommendation in both the European and American HF guidelines.[1,7]

The Cordella™ HF management system (Cordella) (Endotronix Inc, Chicago, IL, USA) provides comprehensive clinical information, including PAP, blood pressure (BP), heart rate (HR), body weight, blood oxygen saturation (SpO_2), and symptoms from HF patients to their clinical team (*Figure 1*). This comprehensive approach allows for proactive HF management and has been shown to enable safe and accurate monitoring of PAP.[8,9] The Cordella sensor is percutaneously implanted in the right PA,[10] enabling PAP readings in the supine or seated position via a unique handheld patient reader placed on the anterior chest, with the sensor data read wirelessly and transmitted automatically to the clinical team from patients at home.

SIRONA 2 is a prospective, multi-centre, open-label, single-arm trial evaluating the safety and efficacy of the Cordella PAP sensor and Cordella HF system in NYHA class III HF patients in Europe with HFH and/or an increase in natriuretic peptides in the previous 12 months.[9] The primary efficacy endpoint was the accuracy of the PA sensor mean PAP (mPAP) measurement compared with the fluid-filled catheter during right heart catheterization (RHC) at 90 days.

Figure 1 (A) Cordella Pulmonary Artery Sensor System. (B) Pulmonary angiogram depicting sensor deployment in the right pulmonary artery. (C) Depiction of patient using the handheld myCordella Patient Reader to measure seated pulmonary artery pressure (PAP) in the home environment. (D) Cordella Patient Kit with vital sign peripherals. (E) Cordella PAP system trend waveforms as seen by the clinician through the patient management portal. The red vertical lines represent clinician notes. (Inset) Daily reading of mean PAP. Respiratory fluctuations and secondary features such as the dicrotic notch are evident.

The primary safety endpoint was freedom from adverse events (AEs) associated with use of the Cordella PA Sensor System through 30 days post-implant. SIRONA 2 met the primary safety and accuracy endpoints and, building on these findings, the current study reports the 12 month outcomes.

Methods

Study design and participants

SIRONA 2 (clinicaltrials.gov Identifier: NCT04012944) is a pilot trial to evaluate the safety and efficacy of the Cordella PA Sensor System in NYHA class III HF patients implanted with the PA sensor and discharged to home with the Cordella HF system and has been previously described.[9] Briefly, SIRONA 2 was a prospective, multi-centre, open-label, single-arm trial evaluating the safety and efficacy of the Cordella PAP sensor and Cordella HF system in 70 NYHA class III HF patients in Europe with either HFH or an increase in natriuretic peptides in the previous 12 months.

The study was undertaken in accordance with the Declaration of Helsinki (GCP-ICH, ISO14155:2020) and approved by the relevant competent authorities and independent ethics committees. All patients provided written informed consent. Eligible patients for SIRONA 2 were men or women over 18 years of age with a diagnosis of NYHA class III HFrEF or HFpEF for at least 6 months treated for a minimum of 3 months and stable for at least 1 month prior to enrolment. Patients had to have at least one HF-related hospitalization, HF treatment in a hospital day-care setting, or unplanned outpatient clinic HF visit within 12 months prior to consent and/or increase of brain natriuretic peptide (BNP) or N-terminal pro-BNP at time of screening.

Follow-up and endpoints

Safety endpoints included the incidence of prespecified AEs, device/system-related complications (DSRCs), and PAP sensor failure rate through 12 months post-sensor implant. The accuracy endpoint includes accuracy of the PA sensor at 12 months as determined by assessing the agreement of the PA sensor measurements with standard-of-care fluid-filled catheter mPAP measurements obtained by standard RHC. Additional endpoints reported include frequency of HFHs, HF treatments in a hospital day-care setting, or urgent outpatient clinic HF visits (HFH), quality of life and functional changes, and patient compliance with data transmission. An amendment was introduced to the trial protocol requiring daily supine measurements along with daily seated measurements. Using these data, differences in seated and supine Cordella PA measurements are also reported. A survey was carried out to evaluate subject experience with both the Cordella HF system and seated and supine PAP measurements. The survey was optional and administered to patients longitudinally through 12 months. The survey consisted of 11 multiple choice questions that were asked via the Cordella patient tablet.

Statistical analysis

Descriptive statistics were used to evaluate baseline clinical and demographic characteristics. Results are reported as mean ± standard deviation (SD) for continuous variables and as percentage (count/sample size × 100) for binary variables. D'Agostino and Pearson's tests were used for normality assessment. Normally distributed variables were compared with paired samples *t*-tests, and non-normally distributed variables were compared with the Wilcoxon signed-rank test.

Several tests of PA sensor accuracy were conducted. Using the Bland–Altman method, supine Cordella PA Sensor System PAP measurements were assessed for agreement with PAP measured using standard-of-care fluid-filled invasive catheters. The limits of agreement (LOAs) in the Bland–Altman analyses were constructed using the SD of the differences between the two measurements, with the mean difference ± 1.96 SD representing the 95% LOA (i.e. the range within which 95% of the data points were expected to lie). Correlations between PAP measurements were assessed with Pearson's correlation coefficient. Differences between PAP measured by Cordella PAP sensor and RHC were examined at both 90 days and 12 months, and change in these differences between the two timepoints was tested using a paired sample *t*-test. Additionally, Levene's test for equality of variance was used to compare the variance of measurement differences between the PA sensor and RHC at 90 days and at 12 months. A P-value < 0.05 was considered significant for all tests.

HFHs/events and HFHs or death through 12 months was evaluated using the Anderson–Gill proportional hazards model. Comparison between HFHs prior to implant and HFHs after implant was assessed using the χ^2 test with $P < 0.05$ considered significant.

Results

Between 21 June 2019 and 16 July 2021, 70 patients were implanted with the Cordella PA Sensor System at seven sites. Two subjects (2.9%) withdrew from the study prior to reaching 12 months post-implant. Of the 70 patients, 50 (71.4%) were men, 66 (94.3%) were White, mean age was 71.0 years, and mean body mass index (BMI) was 28.9 kg/m^2. As required, all patients were NHYA class III. Twenty-two (31.4%) had a preexisting implantable cardioverter-defibrillator device, and 13 (18.6%) had a cardiac

resynchronization therapy (CRT) or CRT-defibrillator device. Twenty (28.6%) patients had left ventricular ejection fraction (LVEF) $\geq$ 50%, and differences between patients with LVEF $\geq$ 50% and LVEF $<$ 50% are reported with LVEF $\geq$ 50% patients being significantly older with higher baseline mPAP (*Table 1*).

Safety

AEs were assessed in the intent-to-treat population (*N* = 75). The implant was aborted in 5 patients, and the PA sensor was successfully implanted in 70 subjects. At 12 months, there were no pressure sensor failures, and one (1.3%) subject experienced a DSRC. Notably, there were no DSRCs reported following the 30 day primary safety endpoint. Overall, there were 10 predefined AEs in 9 (12.0%) subjects as adjudicated by the clinical events committee (*Table 2*).

Pulmonary artery pressure sensor accuracy

PAP sensor accuracy at the 12 month follow-up visit was assessed in 48 of the 70 implanted subjects via concurrent Cordella and fluid-filled RHC measurements, with a median follow-up time of 368 days (interquartile range: 357–382). In the 22 subjects for whom the 12 month assessment was not performed, 15 subjects did not undergo RHC (5 deaths,

Table 1 Baseline characteristics

Characteristic	Implanted (*N* = 70)	LVEF $\geq$ 50 (*N* = 20)	LVEF $<$ 50 (*N* = 50)	*P*-value
Demographics				
Age (years), median (IQR)	71.0 (10.0)	76.0 (7.3)	68.9 (10.3)	0.006
Male, *n* (%)	50 (71.4%)	11 (55.0%)	39 (78.0%)	0.103
White, *n* (%)	66 (94.3%)	19 (95.0%)	47 (94.0%)	0.296
Body mass index (kg/m^2), mean (SD)	28.9 (5.8)	29.4 (4.4)	28.7 (6.3)	0.668
Medical history				
CRT or CRT-D device, *n* (%)	13 (18.6%)	0 (0%)	13 (26.0%)	0.029
ICD device, *n* (%)	22 (31.4%)	0 (0%)	22 (44.0%)	0.001
Diabetes mellitus, *n* (%)	32 (45.7%)	11 (55.0%)	21 (42.0%)	0.471
Hypertension, *n* (%)	51 (72.9%)	16 (80.0%)	35 (70.0%)	0.581
Stroke, *n* (%)	9 (12.9%)	2 (10.0%)	7 (14.0%)	0.955
Atrial fibrillation, *n* (%)	46 (65.7%)	16 (80.0%)	30 (60.0%)	0.189
Chronic obstructive pulmonary disease, *n* (%)	8 (11.4%)	0 (0%)	8 (16.0%)	0.138
Chronic kidney disease, *n* (%)	30 (42.9%)	9 (45.0%)	21 (42.0%)	1.000
Laboratory				
Left ventricular ejection fraction (%), mean (SD)	36.7 (14.1)	55.0 (3.9)	29.4 (9.1)	$<$0.001
N-terminal pro-brain natriuretic peptide (pg/mL), median (IQR)	2608.3 (4629.8)	1655.8 (1227.7)	2985.4 (5386.2)	0.293
Creatinine (mg/dL), mean (SD)	1.4 (0.4)	1.3 (0.4)	1.5 (0.5)	0.232
Haemodynamics				
Systolic blood pressure (mmHg), mean (SD)	123.3 (19.6)	135.6 (21.4)	118.3 (16.6)	0.001
Diastolic blood pressure (mmHg), mean (SD)	70.2 (12.7)	72.2 (14.8)	69.5 (11.9)	0.429
Heart rate (b.p.m.), mean (SD)	74.3 (15.5)	78.8 (21.5)	72.5 (12.1)	0.130
Right atrial pressure (mmHg), mean (SD)	7.5 (5.6)	9.6 (5.2)	6.8 (5.6)	0.074
Pulmonary capillary wedge pressure (mmHg), mean (SD)	15.6 (7.5)	17.3 (7.7)	14.8 (7.3)	0.213
Cardiac output (L/min), mean (SD)	4.9 (1.5)	5.0 (1.8)	4.8 (1.4)	0.764
Cardiac index (L/min/m^2), mean (SD)	2.8 (3.2)	2.5 (1.0)	3.0 (3.8)	0.672
Supine systolic pulmonary artery pressure (mmHg), mean (SD)	15.5 (8.0)	19.4 (8.3)	13.9 (7.3)	0.008
Supine diastolic pulmonary artery pressure (mmHg), mean (SD)	26.1 (11.1)	33.1 (12.9)	23.2 (9.0)	0.001
Supine mean pulmonary artery pressure (mmHg), mean (SD)	44.5 (19.4)	57.8 (24.3)	39.2 (14.1)	$<$0.001
Medications				
Agents acting on the renin-angiotensin system, *n* (%)	54 (77.1%)	13 (65.0%)	41 (82.0%)	0.224
Angiotensin receptor–neprilysin inhibitor	26 (37.1%)	2 (10.0%)	24 (48.0%)	0.007
Angiotensin II receptor blocker	9 (12.9%)	4 (20.0%)	5 (10.0%)	0.463
ACE inhibitor	19 (27.1%)	7 (35.0%)	12 (24.0%)	0.524
Beta-blocker, *n* (%)	54 (77.1%)	13 (65.0%)	41 (82.0%)	0.224
Loop diuretic, *n* (%)	59 (84.3%)	18 (90.0%)	41 (82.0%)	0.640
Aldosterone antagonist, *n* (%)	38 (54.3%)	3 (15.0%)	35 (70.0%)	$<$0.001
SGLT2 inhibitor, *n* (%)	12 (17.1%)	1 (5.0%)	11 (22.0%)	0.176
Functional class and quality of life				
NYHA functional class III, *n* (%)	70 (100.0%)	20 (100.0%)	50 (100.0%)	1.000
6 min walk test (m), mean (SD)	287.3 (133.4)	242.8 (165.3)	306.6 (113.6)	0.074
Kansas City Cardiomyopathy Questionnaire Overall Summary Score (points), mean (SD)	55.7 (24.4)	53.0 (25.3)	56.9 (24.2)	0.553

ACE, angiotensin-converting enzyme; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillator; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation; SGLT2, sodium–glucose cotransporter 2.

Table 2 Incidence of adverse events through 12 months

Adverse event	Device related *n* (%)	Procedure related *n* (%)
Acute kidney injury	0 (0.0)	1 (1.3)
Renal dysfunction	0 (0.0)	0 (0.0)
Bleeding (life threatening or disabling)	0 (0.0)	1 (1.3)
Arrhythmias	0 (0.0)	2 (2.7)
Stroke	0 (0.0)	0 (0.0)
Device/system-related complication[b]	1 (1.3)	1 (1.3)
Haemoptysis[ab]	1 (1.3)	1 (1.3)
Vascular access site-related complications	0 (0.0)	3 (4.0)
Vessel trauma[ab]	1 (1.3)	1 (1.3)
Total	10 (13.3)	

[a]Same patient.
[b]Event is both device and procedure related.

2 withdrawals, 2 patients cancelled due to patient condition, 3 patients refused RHC, 2 patients had left ventricular assist device, and 1 patient had faulty cath lab equipment). Seven underwent RHC but were excluded (six due to their readings being impacted by electromagnetic interference from cath lab equipment and one due to not having concurrent Cordella readings).

Tests of PA sensor accuracy indicated agreement between Cordella PA Sensor System and RHC PAP measurements at 12 months. Correlation and the Bland–Altman plots for 12 month measurements are shown in *Figure 2*. In the Bland–Altman plots, 4.2% of readings fell outside the 95% LOA. At 12 months, Cordella PA Sensor System and RHC PAP measurements were strongly correlated for mPAP (r = 0.74) and systolic PAP (sPAP) (r = 0.88), and there was good correlation for diastolic PAP (dPAP) (r = 0.60) (all P-values $<$ 0.0001) with average differences of 2.9 ± 7.3, 3.2 ± 8.1, and 3.0 ± 6.8 mmHg, respectively. Correlation and the Bland–Altman plots for 12 month measurements are shown in *Figure 2*. Differences between Cordella PA Sensor System and RHC readings were statistically identical at 90 day and 12 month measurements for mPAP (1.4 ± 6.7 vs. 3.0 ± 6.8 mmHg, P = 0.12) and dPAP (2.3 ± 7.7 vs. 2.9 ± 7.3 mmHg, P = 0.39), though the difference increased for sPAP from 90 days to 12 months (−0.3 ± 7.4 vs. 3.2 ± 8.1 mmHg, P = 0.001) (*Table 3*). Levene's test for equality of variance showed that the variance in measurement accuracy (i.e. measurement error) of the Cordella PA Sensor System, compared with RHC, did not change from 90 days to 12 months (all P-values $>$ 0.05).

Heart failure medication changes

In the 12 months following implant, diuretics were adjusted most often (average monthly changes = 0.29) followed by beta-blockers (0.12), mineralocorticoid receptor antagonists (0.10), angiotensin receptor–neprilysin inhibitors (0.10), angiotensin-converting enzyme inhibitors (0.04), angiotensin II receptor blocker (0.03), and sodium–glucose cotransporter 2 inhibitors (0.03) for a total monthly change rate of HF medications of 0.71.

Heart failure hospitalizations

Fourteen patients (20.0%) experienced 18 HFH events (defined as in-hospital, hospital day-care setting, or urgent outpatient clinic HF visits) through 12 months. This translated into an event per patient year (EPPY) of 0.27. When examining the composite HFH plus death (N = 5 deaths), there were 23 events with an 0.33 EPPY. While not a prespecified outcome, when compared with the 12 months prior to implantation, the rate of HFH decreased by 78.6% (1.26 vs. 0.27 EPPY, $P < 0.0001$) in the 12 months post-implantation (*Figure 3*). Patients with LVEF $<$ 50% had a higher cumulative rate of HFH/death than patients with LVEF $\geq$ 50% (0.44 vs. 0.05, P = 0.031) (Supporting Information, *Figure S1*).

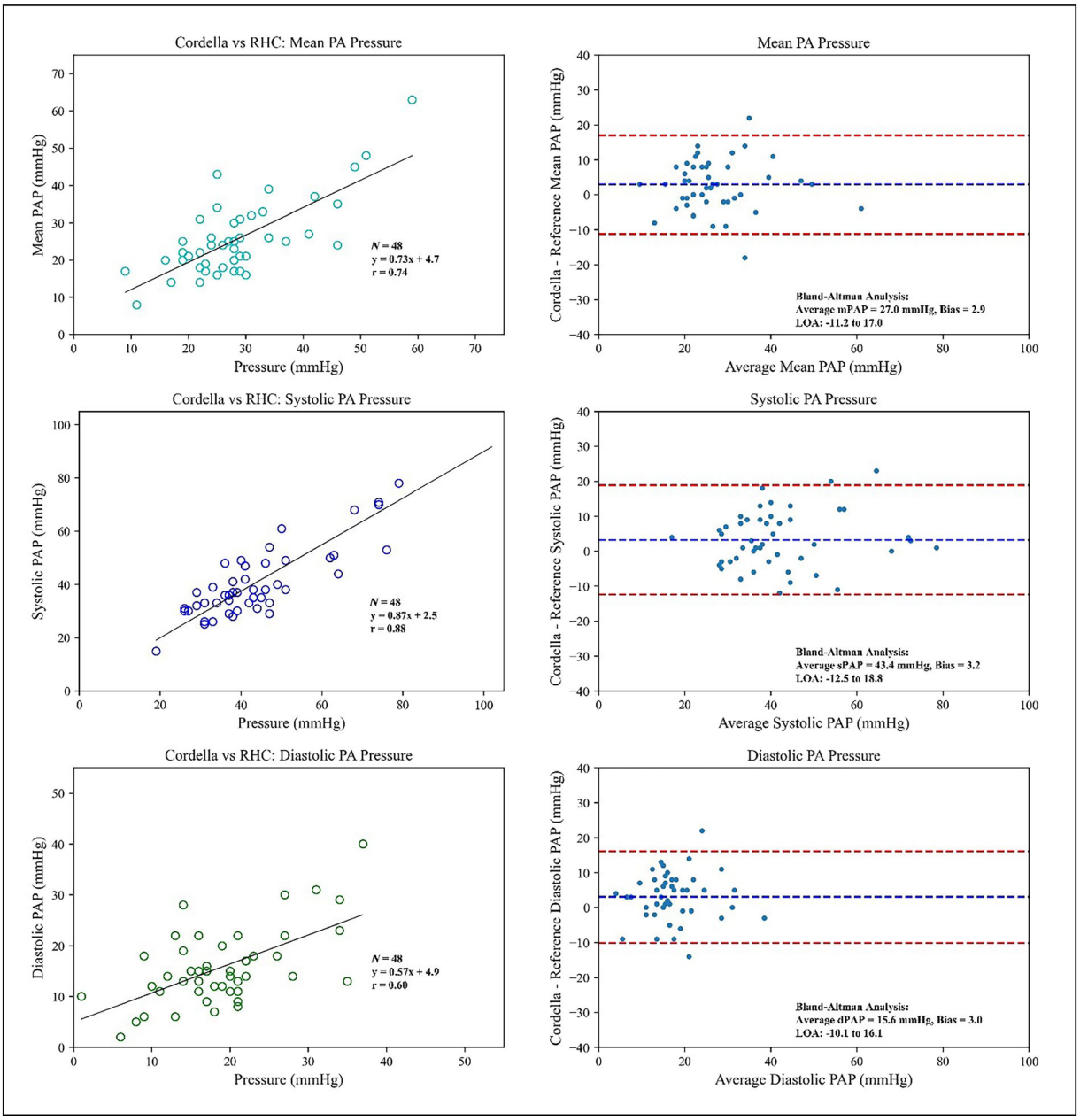
Quality of life and functional capacity

Significant improvement in NYHA functional classification was demonstrated in 41 of 59 subjects (69.5%, $P < 0.001$) (*Figure 4A*). There were no differences in improvement between LVEF $<$ 50% and LVEF $\geq$ 50% patients (Supporting Information, *Figure S2* and *Table S1*). Exercise capacity as measured by the 6 min walk test (6MWT) distance was significantly longer (301.2 ± 140.3 vs. 324.7 ± 116.1, P = 0.005) for those subjects with measures at both baseline and 12 months (*Figure 4B*). Patients with LVEF $<$ 50% had significantly longer 6MWT at both 3 and 12 months (Supporting Information, *Figure S3* and *Table S1*). Quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score was unchanged from baseline through 12 months (60.4 ± 24.2 vs. 59.4 ± 23.8 points, P = 0.82) for those subjects who had measures at both timepoints (*Figure 4C*). There were no differences KCCQ between LVEF $<$ 50% and LVEF $\geq$ 50% patients (Supporting Information, *Figure S4* and *Table S1*).

Patient compliance and satisfaction

Patient compliance was excellent with 95% of patients being compliant (data transmission $\geq$ 5 out of 7 days) at 1 month, 94% at 3 months, and 95% at 12 months (*Figure 4D*). Results of the patient survey show that 97% of respondents find the Cordella HF system easy to use, 82% notice and monitor their daily measurements (as opposed to leaving it to their clinician), and over half (51%) make changes to their lifestyle based on their daily readings.

Figure 2 Correlation (left) and the Bland–Altman (right) plots for mean (mPAP), systolic (sPAP), and diastolic (dPAP) pulmonary artery (PA) pressures (PAPs). LOA, limit of agreement; RHC, right heart catheterization.



Seated and supine pulmonary artery pressures

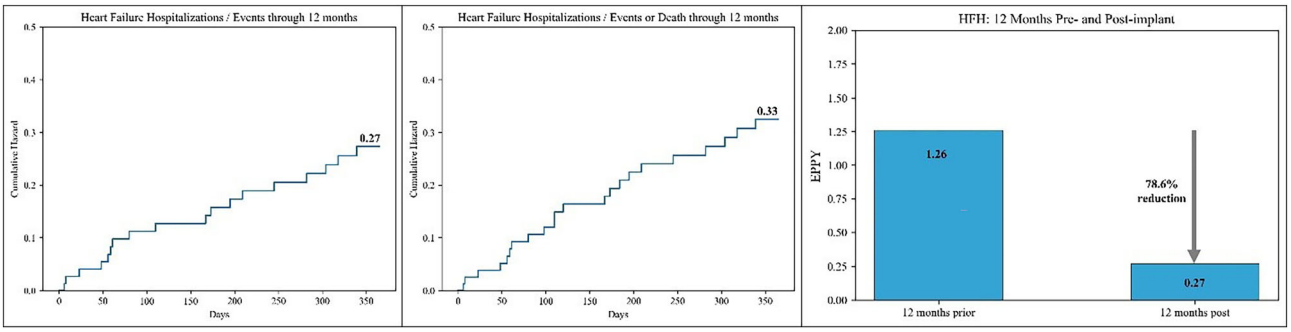
An amendment was introduced to the trial protocol requiring daily supine measurements along with the daily seated measurements, which have been reported above. Over 16 000 paired seated and supine measurements were transmitted by patients from home. The average differences were as follows: for mPAP, it was 6.8 ± 5.7 mmHg; for dPAP, it was 4.9 ± 4.6 mmHg; and for sPAP, it was 8.7 ± 7.3 mmHg (*Figure 4E*). Patients with LVEF < 50% had lower overall mPAP throughout the study but larger differences in seated and supine (Supporting Information, *Figure S5*). When subjects were surveyed on their postural preference for taking their home PAP readings, 87% of respondents preferred to take their PAP readings in the seated position (*Figure 4F*).

Table 3 Comparison of 90 day and 12 month pulmonary artery pressure measures by both pulmonary artery sensor and right heart catheterization

Timepoint	PAP parameter (mmHg)	PAP measurement method	Average ± SD (mmHg)	Levene's test *P*-value	Δ (RHC − PA sensor)	Δ *P*-value
90 days	mPAP	RHC	26.1 ± 10.4	0.13	1.4 ± 6.7	0.12
		Cordella	27.6 ± 12.1			
12 months	mPAP	RHC	25.6 ± 10.0	0.77	3.0 ± 6.8	
		Cordella	28.5 ± 10.0			
90 days	dPAP	RHC	15.8 ± 7.4	0.13	2.3 ± 7.7	0.39
		Cordella	18.1 ± 9.0			
12 months	dPAP	RHC	15.6 ± 7.4	0.49	2.9 ± 7.3	
		Cordella	18.6 ± 7.7			
90 days	sPAP	RHC	44.7 ± 18.4	0.5	−0.3 ± 7.7	0.001
		Cordella	44.4 ± 19.4			
12 months	sPAP	RHC	41.8 ± 18.3	0.7	3.2 ± 8.1	
		Cordella	45.0 ± 16.3			

dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PAP, pulmonary artery pressure; RHC, right heart catheterization; SD, standard deviation; sPAP, systolic pulmonary artery pressure.

Figure 3 (A) Hazard curve for heart failure hospitalizations (HFHs). (B) Hazard curve for HFHs/death. (C) Heart failure events per patient year (EPPY), 12 months pre- and 12 months post-implant.



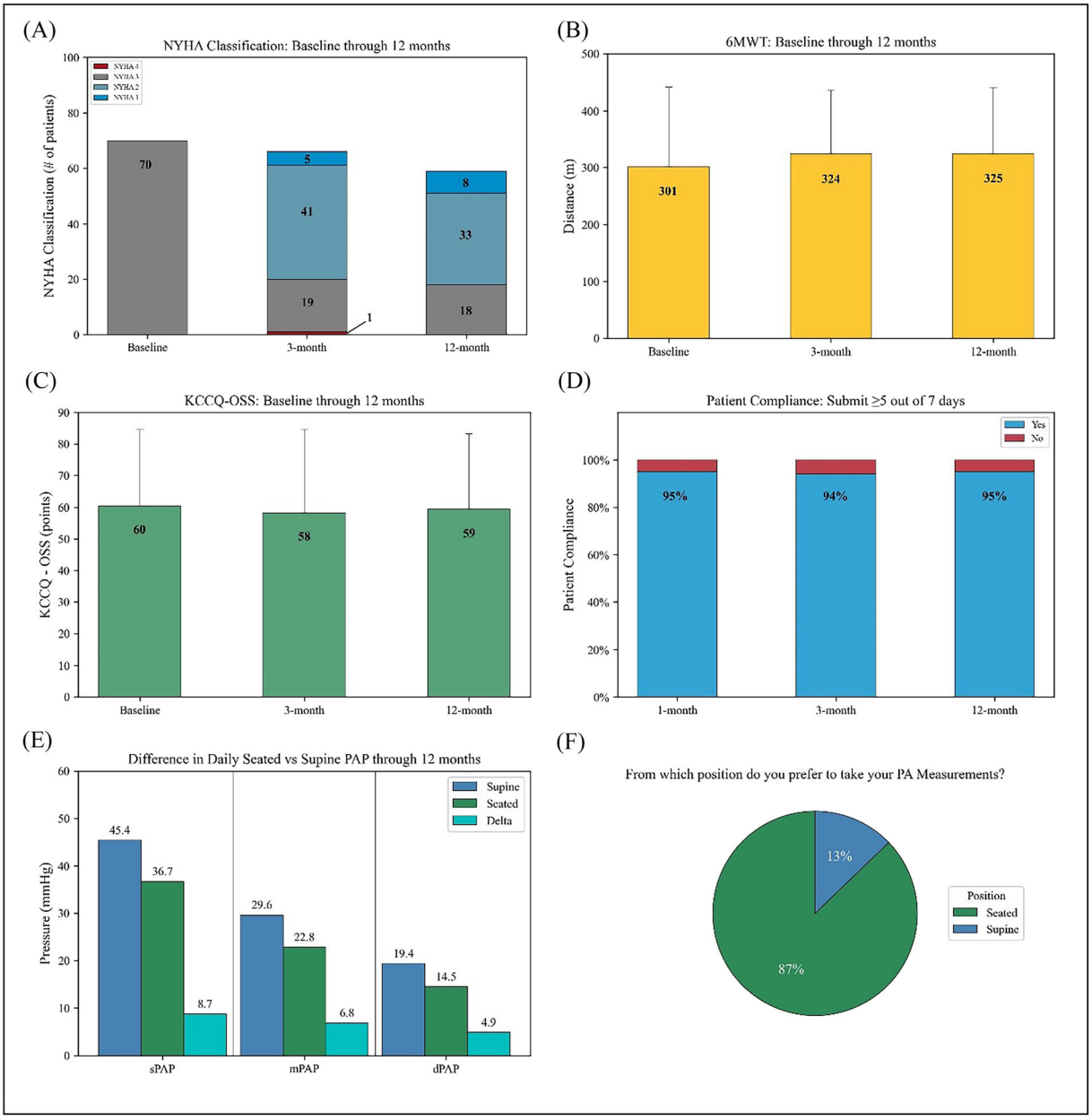
Discussion

SIRONA 2 a prospective, multi-centre study demonstrating that implantation of the Cordella PA Sensor System was feasible and safe, PAP measurements were equivalent to RHC, and patients' adherence to daily transmissions was excellent through 90 days.[9] The current report extends that analysis through 12 months, continuing to show an excellent safety profile with only one patient experiencing a DSRC related to the procedure (left ventricular lead dislodgment), high patient compliance (95% at 12 months), and low rates of HFH and death.

This is the first report on long-term (i.e. >90 days), prespecified accuracy of an implantable PA sensor. PAP measurements of the PA sensor, on average, showed a mean difference from the RHC of 2.9 mmHg for mPAP, 3.2 mmHg for sPAP, and 3.0 mmHg for dPAP 12 months after implant. Long-term accuracy is one of the primary challenges when developing implantable sensors. Signal drift can develop due to both sensor material aging and mechanical fatigue and due to the dynamic *in vivo* environment (i.e. tissue encapsulation).[11] Furthermore, the reference measurements, taken with fluid-filled catheter, are also prone to several sources of error such as improper calibration and levelling, differences between digital measurements and pressure waveforms, respiratory artefact, and patient-specific cardiac disease and anatomy.[12] Comparison of the 12 month differences in PA sensor and RHC measures with those previously reported at 90 days showed no significant change in average mPAP and dPAP differences and a small but significant change in the sPAP difference. As a reminder, the Cordella system utilizes seated mPAP in assessing patient trends over time. Additionally, measurement error of the PA sensor relative to RHC was not significantly different between 90 days and 12 months, suggesting excellent long-term stability of the sensor.

The SIRONA 2 clinical trial did not include a consistent medication management guideline based on PAP to guide remote adjustment of guideline-directed medical therapy (GDMT), and the rate of monthly HF medication changes is slightly lower than a contemporary report deploying similar technology.[6]

Figure 4 (A) New York Heart Association (NYHA). (B) Six-minute walk test (6MWT). (C) Kansas City Cardiomyopathy Questionnaire-Overall Summary Score (KCCQ-OSS). (D) Patient compliance. (E) Seated vs. supine. (F) Seated vs. supine survey. dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PAP, pulmonary artery pressure; sPAP, systolic pulmonary artery pressure.



The PROACTIVE-HF trial (ClinicalTrials.gov Identifier: NCT04089059) in the United States recently completed enrolment and incorporates prespecified PAP-based medication management guidelines, providing clinically actionable information to drive adherence to GDMT.[13]

Despite well-established guidelines and improvements in both pharmacological and device-based HF management over the past 20 years, HF remains a leading cause of hospital admission in the United States with HF admission accounting for almost 6.5 million hospital days annually.[14] Moreover, the number of HFH has been shown to be a strong predictor of all-cause death, with the median survival after the first, second, third, and fourth hospitalizations to be 2.4, 1.4, 1.0, and 0.6 years, respectively.[15] Both non-invasive (protocolized phone calls, vital sign measurement, and symptom monitoring) home telemonitoring and monitoring of PAP using a wireless haemodynamic monitoring system are recommended in the most recent European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF to reduce the risk of recurrent hospitalization and to improve

clinical outcomes.[1] While results using non-invasive home monitoring only are mixed, there is some evidence that certain telemedicine programmes may reduce HF-related mortality.[16] PAP-guided HF management has been shown to reduce HFH.[3–6] The CHAMPION trial showed a rate of 0.32 HFH per patient per 6 months,[3] the MEMS-HF trial showed that 27.8% of patients had HFH within 6 months of implant with an EPPY of 0.60,[5] and GUIDE-HF found that 42.9% of patients had one or more HFH within 12 months with an EPPY of 0.47 and a composite HFH plus death in 50.9% of patients with an EPPY of 0.56.[4] The most recent randomized controlled trial in Europe, the Monitor-HF trial, reported an HFH rate of 0.38 EPPY and a composite HFH plus death rate of 0.52 EPPY.[6] In the present study, utilizing both non-invasive and PA monitoring, there were 18 HFH in 14 patients (20.0%) through 12 months, with an EPPY of 0.27. For composite HFH plus death, there were 23 events in 19 patients (27.1%) through 12 months, with an EPPY of 0.33. Five patients (7.1%) died prior to 12 months. Furthermore, when we examine the EPPY of HFH in the 12 months prior to implant and compare it to the 12 month following implant, there was a significant reduction of 78.6%, further demonstrating the efficacy of the Cordella platform in reducing HFH events.

Besides preventing HFH and reducing mortality, proper treatment of HF aims to optimize patient health status, namely, their symptoms, function, and quality of life.[1] In this study, severity of symptoms, as classified by NYHA, significantly improved in 69.5% of cases (N = 33 went from NYHA class III to II, and N = 8 went from NYHA class III to I; N = 4 subjects did not have NYHA at 12 months). Functional capacity, as measured by 6MWT, also significantly improved for subjects who performed 6MWT at both baseline and 12 months. There was no statistically significant improvement (nor decline) in quality of life as measured by KCCQ through 12 months. However, given the proportion of patients who had fair to excellent KCCQ Overall Summary Scores (50–100) at baseline, this may represent a ceiling effect.[17]

While patients in this study were remotely managed by their clinicians using PAP, vital signs, and self-reported symptoms via the patient portal, it is important to note that subjects had access to their vital sign data in the SIRONA 2 trial. Due to this, a survey was carried out to evaluate the patients' experience with the Cordella HF system, and results show that 97% of respondents find the system easy to use, 82% notice and monitor their daily measurements (as opposed to leaving it to their clinician), and over half (51%) make changes to their lifestyle based on their daily readings. The most recent European HF guidelines state that HF patients who report more effective self-care have a better quality of life, lower readmission rates, and reduced mortality and that improving patients' knowledge of their condition is fundamental for development of self-care skills.[1] Strong patient engagement with their clinical data as shown by both the survey findings and patient compliance, along with low rates of HFH, suggests that providing HF patients access to their health data on a daily basis is an important step in improving knowledge of their condition.

The design of the Cordella PAP Reader enables patients to take their readings in either seated or supine posture and, at the onset of SIRONA 2, patients were instructed to take their PAP readings in the seated posture as seated pressures may be more reflective of a patient's pressure as they go about their daily activities.[18] An amendment was later added to the trial protocol instructing patients to take supine readings along with their seated readings in order to better understand the postural differences in PAP. Several small observational studies reported mPAP decrease from lying to sitting in normal subjects and in those with left heart dysfunction ranging from 2.6 to 5.2 mmHg.[19,20] While the postural differences outlined above were smaller than those reported herein (a mean mPAP decrease of 6.8 mmHg), most of subjects studied previously were healthy whereas the SIRONA 2 cohort includes relatively older, sicker HF population. Patients were also surveyed on their preferred posture for taking their readings, and patients largely preferred to take their readings in the seated posture (87%).

The Cordella platform is the only PAP-guided HF management platform to provide both ESC guideline-recommended telemonitoring modalities, invasive (PAP) and non-invasive vitals (BP, weight, HR, and SPO_2), from the patients' home. Allowing patients access to their clinical data, an easy-to-use patient and clinician interface, and a small handheld patient reader facilitated engagement and drove high compliance throughout the study. These results build on the results reported in the primary endpoint analysis[9] and provide evidence that remote PAP monitoring with an implantable sensor is safe, accurate, and may facilitate clinical benefits and position both clinicians and patients to achieve guideline-directed goals for at least 1 year after implant in NYHA class III HF patients.

Limitations

This prospective, multi-centre, open-label, single-arm trial has associated limitations that must be acknowledged, and several of the findings herein must be viewed as hypothesis generating only. First, the major methodological limitation is the lack of a control group under standard HF care management. Second, comparison between HFHs prior to sensor implant and after sensor implant may be affected by a lack of robust study definition of HFH prior to sensor implant. Finally, 9 months after SIRONA 2 began enrolment, the COVID-19 pandemic began. HF events were reduced in the general HF population during the COVID-19 pandemic[21,22] and norms around in-person clinic visits were altered,[23] which may have had an effect on reducing inpatient visits at the 12 month timepoint.

Conclusions

Use of a novel wireless implantable PAP sensor system, incorporating comprehensive vital signs and PAP monitoring, along with high levels of patient engagement, enables long-term safe and accurate monitoring of HF status in NYHA class III HF patients.

Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Comparison between HFH and HFH/D.
Figure S2. Comparison between NYHA.
Figure S3. Comparison between 6MWT.
Figure S4. Comparison between KCCQ-OS.
Table S1. Statistics for 6MWT, KCCQ-OS, and NYHA.
Figure S5. Comparison between seated and supine mPAP.

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