

One-Year Outcomes After Transcatheter Insertion of an Interatrial Shunt Device for the Management of Heart Failure With Preserved Ejection Fraction

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Background—Heart failure with preserved ejection fraction has a complex pathophysiology and remains a therapeutic challenge. Elevated left atrial pressure, particularly during exercise, is a key contributor to morbidity and mortality. Preliminary analyses have demonstrated that a novel interatrial septal shunt device that allows shunting to reduce the left atrial pressure provides clinical and hemodynamic benefit at 6 months. Given the chronicity of heart failure with preserved ejection fraction, evidence of longer-term benefit is required.

Methods and Results—Patients (n=64) with left ventricular ejection fraction $\geq 40\%$, New York Heart Association class II–IV, elevated pulmonary capillary wedge pressure (≥ 15 mmHg at rest or ≥ 25 mmHg during supine bicycle exercise) participated in the open-label study of the interatrial septal shunt device. One year after interatrial septal shunt device implantation, there were sustained improvements in New York Heart Association class ($P < 0.001$), quality of life (Minnesota Living with Heart Failure score, $P < 0.001$), and 6-minute walk distance ($P < 0.01$). Echocardiography showed a small, stable reduction in left ventricular end-diastolic volume index ($P < 0.001$), with a concomitant small stable increase in the right ventricular end-diastolic volume index ($P < 0.001$). Invasive hemodynamic studies performed in a subset of patients demonstrated a sustained reduction in the workload corrected exercise pulmonary capillary wedge pressure ($P < 0.01$). Survival at 1 year was 95%, and there was no evidence of device-related complications.

Conclusions—These results provide evidence of safety and sustained clinical benefit in heart failure with preserved ejection fraction patients 1 year after interatrial septal shunt device implantation. Randomized, blinded studies are underway to confirm these observations.

Clinical Trial Registration—URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT01913613.

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Key Words: heart failure ■ hemodynamics ■ physiology ■ therapeutics

Epidemiological and observational studies have demonstrated that approximately half of the current heart failure (HF) burden is represented by patients who have preserved ejection fraction (HFpEF).^{1–3} The pathophysiologic basis that underpin the symptoms of HFpEF are complex, including both central hemodynamic and peripheral vascular and

muscular mechanisms.^{4,5} In particular, elevated left atrial (LA) pressure is considered a key driver of symptoms in HF,⁶ and in HFpEF, this may be particularly evident during physical activity.^{7–10}

See Clinical Perspective

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The influence of a range of pharmacological approaches on morbidity and mortality in HFpEF has been examined in large randomized trials with the limited effect.^{11–14} Many of these agents were tested based on previous evidence of efficacy in patients with HF with reduced ejection fraction. These include the use of renin–angiotensin–aldosterone antagonists to notionally reduce myocardial fibrosis and hypertrophy and β -blockers. The effectiveness of vasodilators including nitric oxide donors and cyclic GMP modulators has also been examined with variable effects.^{15–18}

On the basis of the limited success of pharmacological management of HFpEF to date, an interatrial shunt device (IASD; Corvia Medical Inc., Tewksbury, MA) was developed to reduce the LA pressure in HFpEF. The REDUCE LAP-HF study (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure) was designed to evaluate device performance and safety of the transcatheter, transvenous interatrial shunt device in symptomatic patients with HFpEF.^{19,20} Specifically, the device was engineered to reduce elevated LA pressure, particularly associated with exertion, while avoiding excessive left to right shunting.^{19,20} At 6 months, this approach was associated with improved functional and exercise capacity, with reduced exercise normalized pulmonary capillary wedge pressure, whereas modest increases in right heart cardiac output and right atrial pressure were observed.²¹ In this context, we sought to establish the longer-term effects of the interatrial shunt device. This report describes the clinical and echocardiographic outcomes 1 year after IASD implantation, together with detailed rest and exercise hemodynamic data in a subset of patients.

Methods

The REDUCE LAP-HF study is a multicenter prospective, nonrandomized, open-label, single-arm study designed to investigate the safety and performance of a novel transcatheter interatrial shunt device. The study design and primary results have been described in detail elsewhere.^{21,22} We report here the 1-year outcomes of the cohort of implanted patients (n=64), with particular regard to device performance, safety, and the durability of clinical and hemodynamic effects. All patients provided written informed consent, and the study was conducted with the approval of competent authorities and institutional ethics review committees. Interpretation of the results and preparation of the article was the responsibility of the steering committee and principal investigators. The study was monitored by an independent Clinical Events Committee and Data Safety Monitoring Board. The sponsor played no role in the collection, analysis, or interpretation of the data.

Patient Population

We report here the 1-year outcomes of the cohort of patients who underwent successful IASD implantation, as described previously.²¹ Briefly, HFpEF was defined as symptomatic HF (New York Heart Association class II-ambulant class IV), a left ventricular ejection fraction >40%, and an elevated pulmonary capillary wedge pressure (PCWP) at rest (>15 mmHg) or during supine bicycle exercise (>25 mmHg) measured by right heart catheterization.²² Exclusion criteria included patients with moderate or greater right heart dysfunction and patients with significant valvular disease including >grade 2+mitral regurgitation, \geq grade 2+tricuspid regurgitation, \geq grade 2+aortic regurgitation, or \geq moderate aortic stenosis (aortic valve area \leq 1.1 cm²).

One-Year Follow-Up

Twelve months after device implantation, patients underwent clinical and echocardiographic assessment per protocol. Clinical parameters included 6-minute walk distance, New York Heart Association class,

and quality of life evaluation using the Minnesota Living with Heart Failure questionnaire. Transthoracic echocardiography was performed at the 12-month visit and as appropriate technically adequate images were analyzed at an independent core laboratory located at the University of Pennsylvania (PA). Parameters measured included left and right heart chamber sizes, tricuspid annular plane systolic excursion, and E/e'.

A subset of patients (n=18) underwent repeat right heart catheterization at 12 months according to individual site capacity and patient willingness at 8 of 21 participating sites. Assessment of cardiac output and central hemodynamics (right atrial pressure, pulmonary artery pressure, and PCWP) was performed at rest and during supine bicycle exercise. The exercise protocol was as previously used, comprising symptom-limited supine bicycle exercise commenced at 20 W with 20-W increments every 3 minutes until the patient achieved maximum effort. To account for the hemodynamic effect of differences in workload, we also calculated the workload corrected PCWP, as previously described.⁷ Blood samples were collected from the pulmonary artery and vena cavae at baseline and follow-up study to measure oxygen saturation and to evaluate left to right shunting as reflected by the Q_p:Q_s ratio. Hemodynamic records were analyzed by an independent core laboratory (PVLoops LLC, NY).

Statistical Methods

Normally distributed data are presented as mean \pm SD and non-normal data as median and 25th–75th percentile range. Between-groups and within-subject comparisons were performed using an unpaired or paired Student *t* test, respectively. Nonparametric tests were performed using a Mann–Whitney or signed-rank test as appropriate (for unpaired or paired data). Repeated-measures ANOVA with post hoc testing performed using Bonferroni testing for normally distributed data. Repeated-measures analysis of non-normal data was performed using Friedman test. Data provided for specific parameters represent only those cases in which measurements were available at all time points (baseline, 6 months, and 12 months). The null hypothesis was rejected at *P*<0.05. Statistical analysis was conducted using SPSS version 22.

Results

Clinical Outcomes, Quality of Life, and Functional Capacity

Of the 64 patients who underwent successful implantation all survived to 6 months as previously reported.²¹ During the period 6 months to 1 year, 3 patients died representing an overall 1-year survival of 95%. One patient died of combined pneumonia and renal failure, 1 patient had a fatal stroke (in an individual with CHA₂DS₂-VASc score of 6) and the cause of death in the third patient was undetermined (no previous adverse events had been reported). One patient did not return for the 12-month follow-up. There were a total of 17 HF hospitalizations, occurring in 13 patients over the first year. Of these, 10 HF hospitalizations events occurred within the first 6 months, in 10 patients. At 12 months, there were sustained significant improvements in New York Heart Association class and quality of life (Minnesota Living with Heart Failure) score as shown in Figure 1. Similarly, a sustained improvement in 6-minute walk distance was observed at 12 months compared with baseline (363 \pm 93 versus 331 \pm 90 m; *P*=0.001; Figure 1; n=55), and the 12-month 6-minute walk distance was similar to that seen 6 months after device implantation.

Echocardiography

Color flow Doppler imaging confirmed the presence of ongoing left to right shunting at 12 months post device

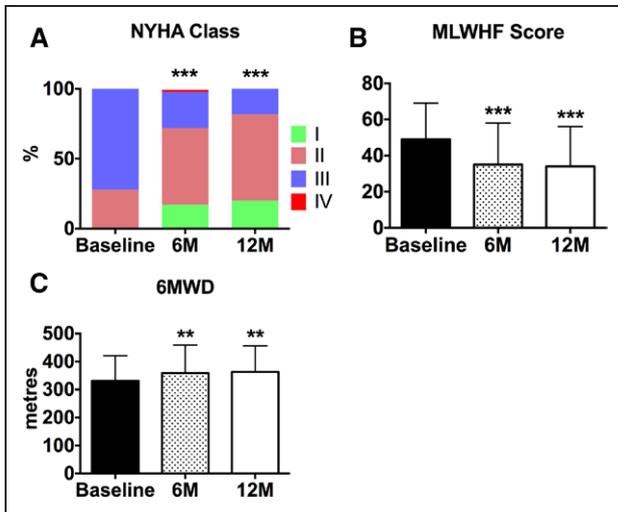


Figure 1. A, Bar graph represents the effects of interatrial septal shunt device implantation on New York Heart Association (NYHA) class (n=60), (B) Minnesota Living with Heart Failure Score (MLWHF; n=60), and (C) 6-min walk distance (6MWD; n=55). ** $P < 0.01$, *** $P < 0.001$ vs baseline. B and C, Data represent mean \pm SD.

implant, in all patients with adequate image quality and technique (n=48). At 12 months, left ventricular ejection fraction was unchanged, whereas right ventricular ejection fraction remained significantly elevated as observed at the 6-month follow-up (Figure 2A and 2B). In conjunction,

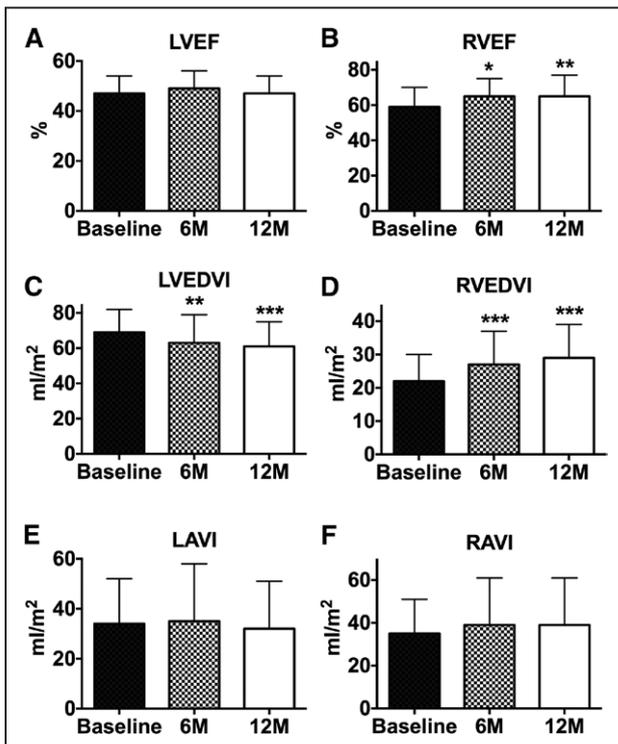


Figure 2. Bar graphs representing (A) left ventricular ejection fraction (LVEF; n=53), (B) right ventricular ejection fraction (RVEF; n=47), (C) left ventricular end-diastolic volume index (LVEDVI; n=53), (D) right ventricular end-diastolic volume index (RVEDVI; n=48), (E) left atrial volume index (LAVI; n=53), and (F) right atrial volume index (RAVI; n=47). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs baseline. Data are mean \pm SD.

there were modest but stable reductions in the left ventricular end-diastolic volume index with a concomitant rise in the right ventricular end-diastolic index (Figure 2C and 2D). By contrast, there were no progressive changes in the left or right atrial volume indexes between 6 and 12 months (Figure 2E and 2F). The E/e' remained stable from baseline to 6 and 12 months: 13.4 ± 5.5 , 13.1 ± 7.6 , and 12.2 ± 4.2 (n=36), respectively. Of interest, although tricuspid annular plane systolic excursion was unchanged from baseline to 6 months (2.0 ± 0.4 versus 2.0 ± 0.4 cm), it was significantly increased at 12 months to 2.2 ± 0.4 cm ($P < 0.05$ versus baseline and 6 months; n=36).

Invasive Hemodynamics and Exercise Testing

To further evaluate the longer-term influence of the IASD, rest and exercise right heart catheterization was conducted optionally in a subset (n=18) of patients at 12 months, thereby providing serial hemodynamic measures from baseline to 6 and 12 months. Patients undergoing cardiac catheterization at 12 months did not differ statistically from those who did not undergo catheterization with regard to demographic, clinical, or echocardiographic features (Table I in the Data Supplement). Within this cohort, exercise time increased significantly from baseline to 6 months (8.2 ± 3.4 versus 9.7 ± 3.2 minutes; $P < 0.05$), and this increase was sustained at 12 months (10.4 ± 4.2 minutes; $P < 0.05$ versus baseline). Similarly, there was an increase in the supine cycling peak work capacity from baseline to 6 months (48 ± 19 versus 60 ± 16 watts; $P < 0.01$; n=17), and this increase was sustained at 12 months (55 ± 15 watts; $P < 0.01$ versus baseline). The increase in supine exercise cycling peak workload was achieved without an increase in PCWP.

Over the course of follow-up, there were no significant changes in resting or exercise systemic blood pressure (data not shown). As shown in the Table, there were no significant changes in the right atrial pressure, pulmonary artery pressure, or PCWP at rest or during exercise in the cohort of subjects who underwent cardiac catheterization at each time point. Implantation of the shunt device reduced the pressure gradient between the left and right atrium, as assessed by the PCWP to RA pressure gradient (Table), and this reduction was sustained through to 12 months. As shown above, there was a significant increase in the workload capacity, and this occurred in the absence of a change in the peak PCWP. In keeping with previous studies, we calculated the workload indexed PCWP.⁷ As shown in Figure 3, IASD placement was associated with a sustained significant reduction in workload indexed PCWP >12 months. There was a significant increase in total right-sided cardiac output after IASD implantation, as measured by thermodilution, and this continued through 12 months (Table). Left-sided cardiac output, measured by oximetry, was unchanged (Table). The Qp:Qs ratio in patients undergoing cardiac catheterization at 12 months was 1.25 ± 0.25 , which was unchanged from that at 6 months (1.27 ± 0.24). Among the patients undergoing cardiac catheterization, assessment of the Qp:Qs confirmed the presence of continued left to right shunting in 6 patients in whom echocardiographic assessment was not possible. The pulmonary vascular resistance was also unchanged (data not shown).

Table. Serial Hemodynamic Measurements

	Baseline	6 mo	12 mo
RAP rest, mm Hg	8±3	11±6	10±4
RAP exercise, mm Hg	17±6	20±9	21±8
PAm rest, mm Hg	25±8	23±7	26±8
PAm exercise, mm Hg	45±12	45±11	45±13
PCWP rest, mm Hg	19±6	16±8	17±6
PCWP exercise, mm Hg	36±9	33±9	33±10
PCWP-RAP gradient rest, mm Hg	10±5	6±2†	7±4‡
PCWP-RAP gradient exercise, mm Hg	20±7	14±4‡	13±5*
Right-sided CO rest, L/min	5.2±1.3	6.3±1.4‡	6.7±1.8*
Left-sided CO rest, L/min (n=10)	4.5±1.3	4.9±1.5	5.8±1.4
Right-sided CO exercise, L/min	8.9±2.3	10.3±2.2*	11.3±2.9‡

Data are mean±SD (n=18 patients). CO indicates cardiac output; PAm, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; and RAP, right atrial pressure.

* $P<0.05$, † $P<0.001$, and ‡ $P<0.01$ vs baseline.

Discussion

To directly alleviate the contribution of impaired diastolic function and the consequent exertion mediated rise in the LA pressure, the effect of an iatrogenic interatrial shunt has recently been studied by 2 groups including our own.^{21,23} Computer modeling indicated that an 8-mm shunt opening could effectively reduce LA pressure in simulated HFpEF at rest and during exercise.¹⁹ The short-term, nonrandomized studies demonstrated significant positive effects on quality of life and functional capacity that were accompanied with modest reductions in pulmonary capillary wedge pressure either at rest or during exertion.^{21,23}

In the current report, we demonstrated the presence of sustained and meaningful clinical benefit as reflected by continued positive changes in quality of life score, 6-minute walk distance, and New York Heart Association class. In conjunction, echocardiographic and oximetric studies confirmed the presence of ongoing IASD patency with evidence of left to right shunting and a reduction in the pressure differential between left and right atrium, similar in degree to that observed at 6 months. At the 6-month time point, there was evidence of small but significant increases in right ventricular end-diastolic volumes, but these remained stable at 12 months. In parallel, there was a small, stable reduction in the left ventricular end-diastolic volume. Left and right atrial volumes were not changed, and LV mass remained stable (data not shown). Serial echocardiographic parameters could not be assessed by the core laboratory in a minority of the subjects because of inadequate image quality, potentially limiting our ability to detect subtle changes in chamber volumes. Taken together, however, these data suggest that there was no evidence of adverse remodeling after IASD placement, in keeping with the small size of the shunt.

We also performed rest and exercise hemodynamic follow-up in a limited cohort to address the potential concern that chronically increased right-sided blood flow could adversely

affect pulmonary pressures and to investigate whether IASD placement continued to favorably affect LA pressure dynamics. The PCWP to RA pressure gradient reduction was sustained through to 12 months. The Qp:Qs ratio at 12 months was unchanged from that at 6 months. There was a sustained increase in right-sided cardiac output, with no change in resting left-sided cardiac output as measured by oximetry. The apparent absence of a reduction in left-sided cardiac output could potentially be explained by volume retention although body weight was unchanged. The present data do not indicate any evidence of increased pulmonary pressure or pulmonary vascular resistance. Although there was no evidence of an effect of pulmonary capillary wedge pressure at rest or exercise, there was evidence of a sustained beneficial effect on bicycle exercise duration, workload, and on the workload corrected wedge pressure. This latter parameter has been shown to be an important prognostic factor.²⁴

Although the degree of functional impairment and impact on survival is similar across both HF with reduced ejection fraction and HFpEF, the pathophysiology of HFpEF differs in many ways from HF with reduced ejection fraction. Patients are typically older and comorbidities including atrial fibrillation, hypertension, obesity, frailty, chronic lung disease, and chronic kidney disease are all more frequent. The underpinning myocardial biology is also probably more complex than in HF with reduced ejection fraction and likely more problematic in regard to the potential for reverse remodeling.²⁵ Together, these factors may provide an explanation for the lack of a convincing long-term effects of pharmacological interventions to date in HFpEF patients.²⁶ Within this context, a safe and effective device-based therapy provides a possible advantage. The maintained positive effect on clinical status and functional capacity coupled with evidence of sustained shunt patency and improved central hemodynamic also confirms the key role of elevated filling pressures as a driver of symptoms in HFpEF. Furthermore, by the nature of the mechanism of action of the shunt device, it would be unlikely that the results observed relate to an effect on the peripheral circulation.

The current study has some important limitations. First, the trial was a nonrandomized open-label study, and the key clinical outcome variables, while important for this patient population, were of a subjective or effort-dependent nature. As such, we cannot exclude the possibility of a placebo effect; however, it is of note that the early effects observed within the first 6 months were sustained to the same extent at the 12-month observation period. Second, although stroke

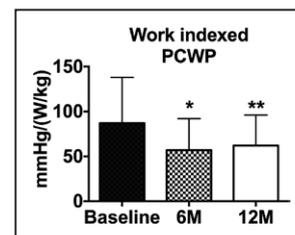


Figure 3. Bar graph showing workload indexed peak exertion wedge pressure before and after interatrial shunt device placement (n=16). * $P<0.05$, ** $P<0.01$ vs baseline. Data are mean±SD. PCWP indicates pulmonary capillary wedge pressure.

occurred in 1 individual at high preexisting risk for a cerebrovascular event, it is not possible to definitively exclude a potential device-related event although it was not adjudicated as device-related by the Clinical Events Committee. Third, in some cases, information at each observation point was not available, potentially leading to bias; however, the number of complete within-subject data sets across time was minimally reduced. Finally, only a subgroup of patients underwent hemodynamic assessment at 12 months, preventing reporting of longitudinal changes in the entire cohort.

Taken together, this study provides the longest experience with an interatrial shunt device specifically developed for the management HFpEF. The data provide additional longitudinal support for the safety and efficacy of this approach. Randomized trials, with blinded patients and physician assessors, are currently underway and are required to validate the utility of this novel therapy.²⁷

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Disclosures

None.

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CLINICAL PERSPECTIVE

Approximately half of all patients with heart failure are found to have a preserved left ventricular ejection fraction. The pathophysiology of heart failure with preserved ejection fraction is complex, and treatment remains a major therapeutic challenge. Elevated left atrial pressure, particularly during exercise, is a fundamental contributor to morbidity and mortality. Based on this pathophysiologic mechanism, an interatrial shunt device was developed to decompress the left atrium as a therapy for heart failure with preserved ejection fraction. Preliminary studies illustrated the potential clinical and hemodynamic benefit of this approach. The current open-label study in symptomatic patients with left ventricular ejection fraction >40% demonstrates the presence of sustained improvements in New York Heart Association class, quality of life, and 6-minute walk distance, 1 year after device implant. Invasive hemodynamic studies performed in a subset of patients demonstrated a sustained reduction pulmonary capillary wedge pressure at a given workload. Randomized, blinded studies are underway to confirm these observations.

One-Year Outcomes After Transcatheter Insertion of an Interatrial Shunt Device for the Management of Heart Failure With Preserved Ejection Fraction

David M. Kaye, Gerd Hasenfuß, Petr Neuzil, Martijn C. Post, Robert Doughty, Jean-Noël Trochu, Adam Kolodziej, Ralf Westenfeld, Martin Penicka, Mark Rosenberg, Antony Walton, David Muller, Darren Walters, Jorg Hausleiter, Philip Raake, Mark C. Petrie, Martin Bergmann, Guillaume Jondeau, Ted Feldman, Dirk J. van Veldhuisen, Piotr Ponikowski, Frank E. Silvestry, Dan Burkhoff and Christopher Hayward

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SUPPLEMENTAL TABLE 1.**Subject profile according to 12 month hemodynamic study**

	HD Study	No-HD Study
Age	69±8	69±9
Baseline BMI (kg/m ²)	31±6	33±6
12 Months BMI (kg/m ²)	31±6	31±5
Baseline NT-Pro BNP (pg/mL)	551 (262-909)	377 (156-1098)
12 Months NT-Pro BNP (pg/mL)	419 (224-637)	509 (216-1008)
Baseline 6MWD (m)	338±94	325±101
12 Months 6MWD (m)	376±86	352±98
Baseline MLHFQ score	51±19	47±20
12 Months MLHFQ score	29±21	36±21
Baseline NYHA Class	2.8±0.4	2.6±0.5
12 Months NYHA Class	2.0±0.6	1.9±0.7
Baseline LVEF (%)	47±7	45±7
12 Months LVEF (%)	48±7	46±5
Baseline RVEF (%)	54±9	61±12
12 Months RVEF (%)	62±9	66±13
Baseline LVEDVI (mL/m ²)	73±15	66±11
12 Months LVEDVI (mL/m ²)	63±15	58±14
Baseline PCWP (mmHg)	19±6	17±5
Baseline CO (L/min) at rest	5.3±1.2	5.6±1.7

Data are mean±SD, except for NT-proBNP (median, 25th-75th percentile).

Subject numbers: HD Study (n=18); No-HD Study (n=46 at baseline; n=42 at 12 months).