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Original Article

Interventions in the diagnosis and adoption of pacemaker therapy in sinus node dysfunction patients: Results from the IMPROVE Brady study

Rishi Sethi [a], Fazila Tun Nesa Malik [b], Ajay Naik [c], Nadeem Afroz [d], Dwight W. Reynolds [e], Yogesh Kothari [f], Vijayachandra Reddy [g], Vinayakrishnan Rajan [h], Tracy Bergemann [i], Alexandra Dedrick [i], Ulhas M. Pandurangi [j], Kaiswer Nasrullah Khan [k], Calambur Narasimhan [l, *]

[a] King George's Medical University, Lucknow, Uttar Pradesh, India
[b] National Heart Foundation Hospital and Research Institute, Dhaka, Bangladesh
[c] Care Institute of Medical Sciences, Ahmedabad, Gujarat, India
[d] The Mission Hospital, Durgapur, Kolkata, India
[e] University of Oklahoma Health Sciences Center, Oklahoma City, USA
[f] RajaRajeswari Medical College and Hospital, Bangalore, Kamataka, India
[g] Apollo Hospital, Chennai, India
[h] India Medtronic Pvt. Ltd. Mumbai, India
[i] Medtronic Plc, Mounds View, MN, USA
[j] The Madras Medical Mission, Chennai, India
[k] United Hospital Limited, Dhaka, Bangladesh
[l] Department of Cardiology, AIG Hospital, Hyderabad, India

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ABSTRACT

Aims: IMPROVE Brady assessed whether a process improvement intervention could increase adoption of guideline-based therapy in sinus node dysfunction (SND) patients.
Methods: /Results: IMPROVE Brady was a sequential, prospective, quality improvement initiative conducted in India and Bangladesh. Patients with symptomatic bradycardia were enrolled. In Phase I, physicians assessed and treated patients per standard care. Phase II began after implementing educational materials for physicians and patients. Primary objectives were to evaluate the impact of the intervention on SND diagnosis and pacemaker (PPM) implant. SF-12 quality of life (QoL) and Zarit burden surveys were collected pre- and post-PPM implant.
A total of 978 patients were enrolled (57.7 ± 14.8 years, 75% male), 508 in Phase I and 470 in Phase II. The diagnosis of SND and implantation of PPM increased significantly from Phase I to Phase II (72% vs. 87%, $P < 0.001$ and 17% vs. 32%, $P < 0.001$, respectively). Pacemaker implantation was not feasible in 41% of patients due to insurance/cost barriers which was unaltered by the intervention. Both patient QoL and caregiver burden improved at 6-months post-PPM implant ($P < 0.001$).
Conclusions: A process improvement initiative conducted at centers across India and Bangladesh significantly increased the diagnosis of SND and subsequent treatment with PPM therapy despite the socio-economic constraints.

1. Introduction

Sinus node dysfunction (SND), also known as sick sinus syndrome, is the inability of the sinoatrial node to achieve an adequate heart rate that meets the physiologic needs of the individual. The

* Corresponding author. Department of Cardiology, AIG Hospital, Survey No 136, Plot No 2/3/4/5, 1, Mindspace Rd, Gachibowli, Hyderabad, Telangana, 500032, India
E-mail address: calambur1@gmail.com (C. Narasimhan).

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Abbreviations

BPM	beats per minute
PPM	permanent pacemaker
QoL	quality of life
SF-12	short-form health survey
SND	sinus node dysfunction

prevalence of SND in the US is approximately 1 per 1000 patient years, with higher rates among those >65 years of age.[1] With increased life expectancy, it is anticipated the incidence of SND may nearly double in the next 50 years.[2] Although these trends may be mirrored in India and Bangladesh, epidemiological data are not available. For patients with permanent symptomatic SND, the established treatment is implantation of a permanent pacemaker (PPM), which is a Class I indication for treatment under both US and European guidelines.[3,4]

Several randomized trials have demonstrated quality of life and functional status benefits of PPM therapy in this patient population.[5,6] In addition, reductions in the incidence of atrial fibrillation and stroke have been demonstrated in patients receiving dual chamber or atrial based pacing versus single chamber pacing.[7] Despite these benefits and international guideline recommendations on usage, adoption of this therapy remains low in developing countries.[8]

The aim of the IMPROVE Brady study was to improve the diagnosis of SND and adoption of guideline-indicated therapy using a practice-specific process improvement intervention to educate health care providers and patients in India and Bangladesh. The results of Phase I examined the care pathway of patients presenting with symptoms of suspected SND and their respective diagnosis and treatment rates.[9] During this phase, 72% of patients were diagnosed with SND and 17% were treated with a pacemaker with reasons for non-treatment included subject refusal or deferred decision and lack of affordability. After the completion of Phase I, physicians attended an educational workshop and were provided an algorithm for identifying patients indicated for PPM implantation. The focus of this report is to measure the impact of this process improvement intervention on diagnosis and treatment rates compared with the baseline Phase I.

2. Methods

2.1. Study design

The design of the IMPROVE Brady study has previously been reported.[9] Briefly, the IMPROVE Brady study was a multicenter, prospective, interventional, quality improvement clinical study. The goal of this study was to use a practice-specific process improvement intervention consisting of education, diagnostic algorithms, and documentation tools that aimed to improve the quality of care for patients with SND through advocating and reinforcing adherence to consensus treatment guidelines.

After the completion of Phase I (control period), investigators completed an educational workshop, were given access to the IMPROVE Brady toolkit and encouraged to adapt tools from this kit to create a practice-specific process improvement implementation. The toolkit included: a physician training seminar, a diagnostic algorithm, patient education materials, a list of available therapy options, and/or information regarding the benefits and risks associated with the therapy options. The aim of Phase II was to assess the effect of critical care pathways, education, and comprehensive disease state management on the adoption of ACC/AHA/HRS and ESC indications and therapies for sinus node dysfunction.[10,11] Phase II of the study was conducted at tertiary care centers in India and Bangladesh in accordance with the Declaration of Helsinki. The study was sponsored by Medtronic and registered on clinicaltrials.gov (NCT01643707).

2.2. Patients and procedures

Both Phase I and II of the study recruited patients presenting with symptomatic bradycardia. Patients enrolled in this study were enrolled with symptoms and prior to physician diagnosis. If no diagnosis was obtained after enrollment and after study follow-up for that phase was complete, the patient was exited from the study. The key patient inclusion criteria were as follows: (1) over 18 years of age, (2) a sinus rate $\leq$50 beats per minute (BPM) or a junctional escape rhythm no faster than 50 BPM or a history of exercise intolerance, and (3) symptoms attributed to bradycardia (general fatigue, shortness of breath/dyspnea, shortness of breath with exertion, syncope, light headed dizziness, palpitations, lethargy, or malaise) within 30 days of enrollment that are not related to other medical causes (such as untreated hypothyroidism or anemia). Patients with known high degree atrioventricular block or history of chronic atrial fibrillation were excluded. Detailed inclusion/exclusion criteria have previously been published.[9]

All patients were provided written informed consent to the study protocol that was reviewed and approved by the ethics committee of each participating institution. Patients implanted with a Medtronic market-released PPM completed the SF-12 Health Survey at implant and at 6-months post-implant (Phase II only).[12] Additionally, primary caregivers of these patients completed the Zarit Burden Interview at implant and 6-months post-implant.[13] For subjects enrolled during Phase II, collection of diagnostic assessment data was completed 6 months after last enrollment. At that time, any patients without a diagnosis were exited from the study. Collection of implant data was completed 6 months after the last Phase II diagnosis. Any patients not implanted by the end of the 6 months were exited from the study.

2.3. Objectives

There were two primary objectives in the IMPROVE Brady study. Primary objectives were as follows: (1) to assess the impact of the intervention on the diagnosis of SND and (2) to evaluate the effect of the intervention on implantation of PPM among patients diagnosed with SND. Details on secondary objectives are described in Supplementary Methods.

2.4. Quality of life measurements

To assess QoL data from both caregivers of and patients receiving Medtronic PPM implants, two different surveys were utilized to compare pre-implant and 6 months post-implant (Phase II patients only). The Short-Form Health Survey (SF-12) consisted of two domains: the physical component score (PCS) and the mental component score (MCS).[12] The Zarit Burden Interview was utilized to measure burden on caregivers associated with the extent to which a caregiver perceives emotional, physical health, social life, and financial consequences that impair the ability to provide care.[13]

2.5. Sample size and statistical analysis

The proportion of SND diagnoses in bradycardia subjects was unknown in India at time of study start. The PANARM HF study of 2000 subjects found that 146 out of 331 bradycardia subjects (44%)

had symptomatic SND and that 15 (10%) of SND subjects opted for PPM therapy.[14] The power calculations thus conservatively assumed that the SND diagnosis would be 20% at six months of follow-up and that 10% of SND patients would be implanted with a PPM at three months post-diagnosis. If 500 subjects were collected in Phase I and 1000 subjects were collected in Phase II, assuming a type I error of 0.05 and power of 0.90, a chi-square test would detect an increase in SND diagnosis of at least 8% and an increase in PPM therapy of at least 16%. The Phase II sample size was recalculated once Phase I data collection was complete based on pre-specified rules for determination. It was observed that the study attrition rate during accrual was 3% of the study population and therefore the final sample size for Phase I was 515 subjects. Since the proportion of SND diagnoses in Phase I was higher than expected at 72%, there were 368 SND patients available in Phase I for the analysis of primary objective 2. Therefore, the Phase II sample size was reduced to an equal number of patients, another 515 patients, as were recruited in Phase I.

Reasons for declining an indicated PPM were characterized in both phases. The analysis of primary objective 1 used a Chi-square test to compare the proportion diagnosed with SND between Phases. The analysis of primary objective 2 used a Fisher's Exact test with a mid-P adjustment to the *p*-value to compare the proportion of SND patients subsequently treated with a PPM between Phases. Counts and percentages were used to characterize the proportion of patients diagnosed and treated within equally spaced time intervals and the reasons to decline implant. A multivariable logistic regression was used to examine variables that may be associated with the primary objective endpoints. The variables study phase, gender and age were included in the model regardless of the significance of the association. Other baseline variables were included in the models for both diagnosis and implant outcomes if they obtained statistical significance (with $p < 0.05$) in either of the two models. Paired t-tests evaluated the change in QoL scores and Zarit burden scores over time. Statistical analysis was performed using SAS version 9.4 (SAS Institute).

3. Results

3.1. Patient demographics and enrollment

A total of 515 patients were enrolled in Phase I of the study at 10 centers in India and Bangladesh from July 2012 to June 2014. Subjects in these centers were primarily seen by interventional cardiologists (60%) and electrophysiologists (39%).[9] Seven patients were excluded from analysis either because they did not meet inclusion/exclusion criteria or because they had no follow-up data. Of these 10 centers participating in Phase I, 8 continued on to Phase II by conducting educational workshops for physicians, setting up diagnostic algorithms, and implementing documentation tools. The 2 centers that did not participate in Phase II only contributed 21 patients to Phase I. In Phase II, 484 patients were enrolled from August 2015 through July 2018. Fourteen patients were exited based on inclusion/exclusion criteria, leaving 470 patients from Phase II for inclusion in the final analysis (Fig. 1). Patient characteristics across the two phases were similar, with patients being mostly male, mean age of approximately 58 years, and most having a college degree or higher. Mean follow-up duration was 9.6 ± 12.9 months in Phase II with a total average follow-up of 8.9 ± 10.7 months across both phases. Presenting symptoms (reported within 30 days prior to enrollment) are reported (Table 1). In Phase I, the most commonly reported symptom was dyspnea. Pre-syncope was the most commonly reported symptom in Phase II. Additionally, fewer patients presented with symptoms of chest pain in Phase II compared to Phase I.

3.2. SND diagnosis and treatment

In Phase I, 368 of 508 patients (72%) received an SND diagnosis. The percentage of patients with an SND diagnosis significantly increased to 87% ($P < 0.0001$) in Phase II (Fig. 2). Similarly, the proportion of patients diagnosed with SND and subsequently implanted with a PPM significantly increased from Phase I to Phase II ($P < 0.0001$). Both pre-specified study primary objectives were

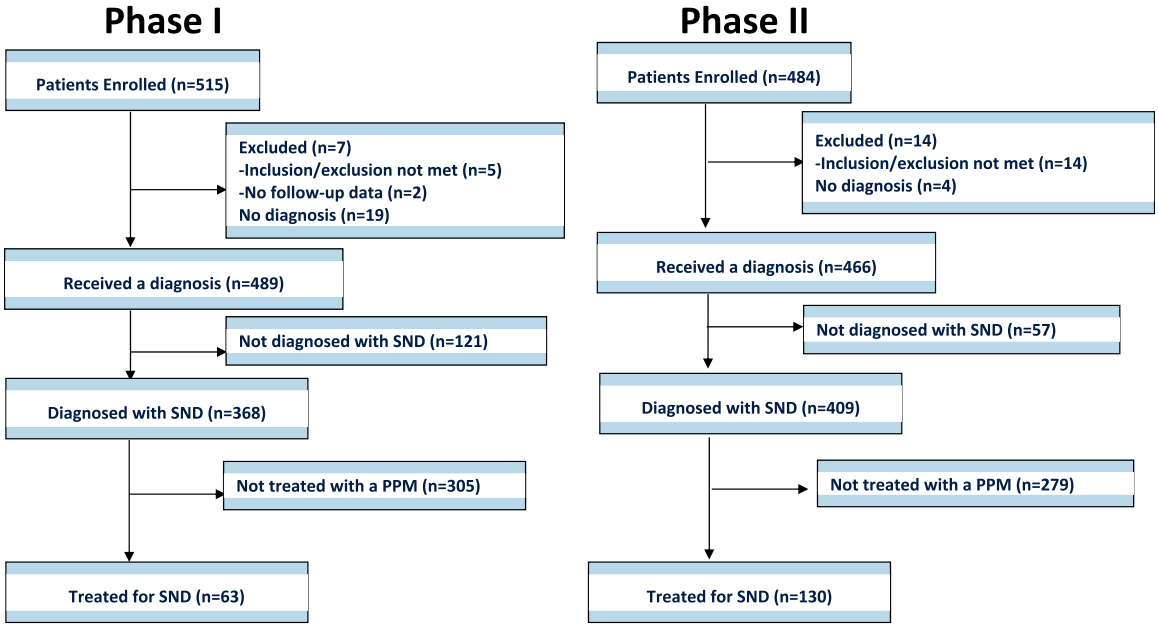

Fig. 1. Study flow diagram for Phase I and Phase II. Flow diagram depicting patient disposition for Phase I and Phase II of the study. PPM: permanent pacemaker; SND: sinus node dysfunction.

Table 1
Patient baseline characteristics and symptoms.

Characteristic	Phase I N = 508	Phase II N = 470	Total N = 978
Age	57.6 ± 14.8	58.0 ± 14.9	57.7 ± 14.8
Male gender	77.6%	72.8%	75.3%
Heart rate	55.7 ± 14.0	56.3 ± 16.5	56.0 ± 15.2
BMI	24.1 ± 4.6	24.9 ± 4.0	24.5 ± 4.3
Education			
None	9.1%	7.0%	8.1%
Primary	29.9%	18.1%	24.2%
Secondary	22.4%	29.8%	26.0%
College or higher	38.6%	43.6%	41.7%
Follow-up in months	8.3 ± 8.0	9.6 ± 12.9	8.9 ± 10.7
Symptoms			
Syncope	16.7%	12.1%	14.5%
Presyncope	28.5%	49.1%	38.4%*
Chest pain	35.4%	21.7%	28.8%*
Dyspnea	52.6%	33.4%	43.4%*
Edema	0.4%	0.9%	0.6%
Exercise intolerance	27.8%	30.6%	29.1%
Fatigue	24.4%	23.8%	24.1%
Malaise	1.0%	0.9%	0.9%
Palpitations	14.6%	12.1%	13.1%

Abbreviations: * = P < 0.05. Abbreviations: BMI = body mass index.

therefore met. The primary objective results were similar when excluding the 2 centers that did not participate in Phase II (Phase I SND diagnosis proportion 74% and PPM implanted 17%, P < 0.0001 in comparison to Phase II, still meeting both primary objectives).

The majority of patients in both phases were diagnosed within the first month of enrollment (79.9% and 94.8% for Phase I and Phase II, respectively), although more patients were diagnosed at enrollment in Phase II (56.7% vs. 34.2%). Pacemaker implant most frequently occurred within 1 month of enrollment in both phases (93.6% and 96.9% for Phase I and Phase II, respectively) (Supplementary Fig. 1).

In both phases, the predominant reason for declining an implant was related to insurance or cost barriers (43% in Phase I and 39% in Phase II) (Supplementary Fig. 2). In Phase II the second most common reason for declining an implant was the patient opted for continued follow-up and/or medical management (38%), while in Phase I, the second most common reason was the patient did not agree that the condition warranted implant or had aversion to the procedure (29%).

3.3. Multivariable analysis

Multivariable regression analysis was performed to identify factors associated with an SND diagnosis. There was an increase in the probability of receiving an SND diagnosis in Phase II vs. Phase I (Table 2). Syncope/pre-syncope symptoms at baseline also significantly predicted the probability of an SND diagnosis. Both factors remained significantly associated with SND diagnosis, even after adjusting for other risk factors.

Multivariable regression analysis was also performed to identify variables associated with PPM implant among patients diagnosed with SND. The presence of syncope/pre-syncope symptoms at baseline increased the odds of PPM implant (P < 0.001). Notably, even after adjusting for other factors, phase of the study (Phase II vs. Phase I) increased the odds of PPM (P < 0.01) (Fig. 3). Contributing to the household financially and age were also significantly associated with the odds of being implanted with a PPM among diagnosed patients (Table 2). Summary statistics for the variables included in the regression analysis are provided for patients with or without SND and with or without a PPM implant in Supplementary Table 1.

3.4. Quality of life following PPM implant

To address the impact that PPM therapy had on QoL, we surveyed patients using the SF-12 survey and primary caregivers using the Zarit Burden Interview at pre-implant (N = 75) and six months post-implant (N = 69). Following paired analysis over 6 months, patient QoL improved by 35% (11.7 points) in physical components (PCS; P < 0.0001) and 25% (10.2 points) in mental measure (MCS; P < 0.0001) at 6 months. Additionally, the burden on caregivers was reduced following pacemaker implantation by 56% (14.7 points) as measured by the Zarit Burden Interview (P < 0.0001) (Fig. 3).

4. Discussion

In this multicenter study of 978 patients from 10 centers in India and Bangladesh, a practice-specific process-improvement

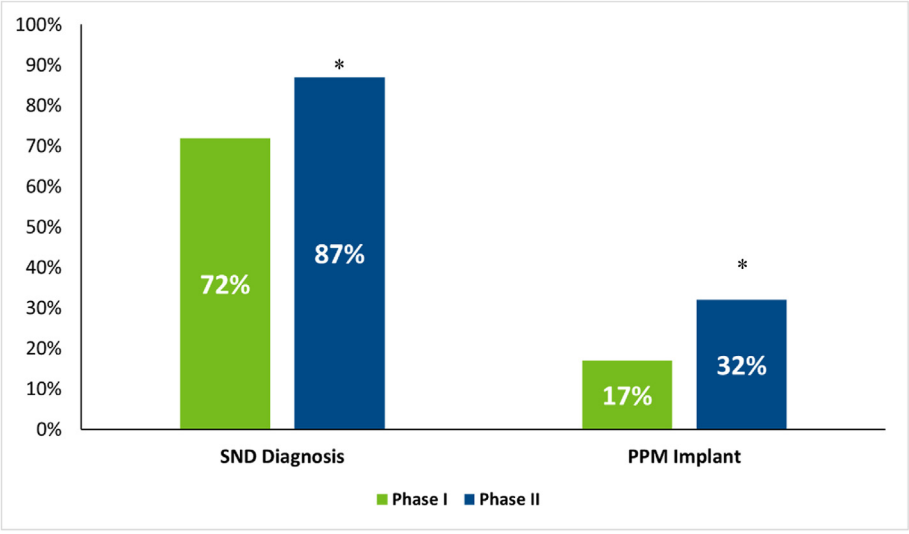

Fig. 2. Proportion of SND Diagnosis and PPM Implant by Study Phase: Proportion of SND diagnosis (left bars) and subsequent PPM implant (right bars) pre- and post-intervention. Green bars represent Phase I, blue bars represent Phase II.

Table 2
Multivariable analysis of factors affecting probability of SND diagnosis and PPM implant.

Effect	Reference Category	SND Diagnosis		PPM Implant	
		Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Phase	Phase I	3.54 (2.27, 5.53)	<0.001	1.88 (1.30, 2.74)	<0.001
Age	1 year increment	1.0 (0.99, 1.01)	0.887	1.03 (1.02, 1.04)	<0.001
Gender	Male	1.43 (0.83, 2.46)	0.198	1.44 (0.95, 2.18)	0.089
Adjusted HR	5 bpm increment	0.70 (0.65, 0.74)	<0.001	0.99 (0.93, 1.06)	0.752
Syncope or Pre-syncope	No	2.30 (1.45, 3.67)	<0.001	3.99 (2.64, 6.05)	<0.001
Beta Blockers	Not Used	0.32 (0.19, 0.55)	<0.001	0.78 (0.31, 1.95)	0.593
Education Level	No Formal Education	0.64 (0.51, 0.81)	<0.001	1.06 (0.87, 1.29)	0.569
Contributes Financially	No	1.73 (1.08, 2.77)	0.023	0.52 (0.34, 0.79)	0.002

Abbreviations: BPM = beats per minute; HR = heart rate; PPM = permanent pacemaker; SND = sinus node dysfunction.

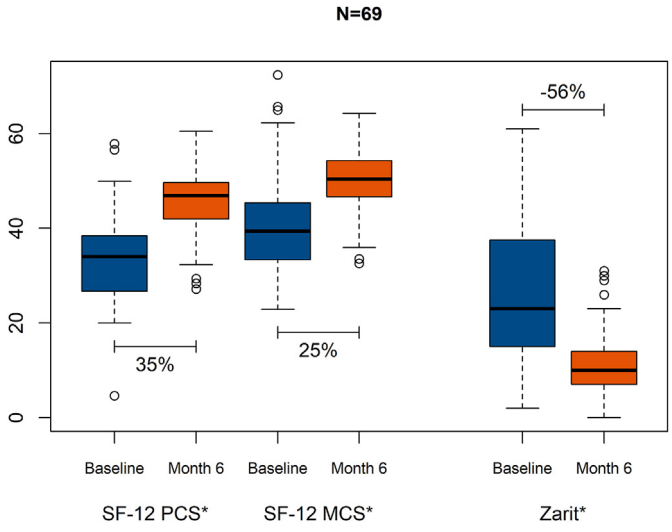

Fig. 3. Patient Quality of Life and Caregiver Burden Following PPM Implant: Box plot shows the distribution of quality of life and caregiver burden scores for patients implanted with a Medtronic-family PPM having paired data at implant and six months (N = 69). The average value is the center of the box, the black line represents median; the edges of the boxes denote the 95% confidence interval and the whiskers show the minimum and maximum values. Blue boxes are implant values and orange boxes are 6-month post PPM implant values. Boxes on the left represent the physical component score of the SF-12, middle boxes represent the mental component score of the SF-12, and boxes on the right represent caregiver burden scores from the Zarit Burden Interview. (For SF-12 scores, a positive change indicates an improvement in status; for Zarit scores, a negative change indicates an improvement in status).

intervention through education, diagnostic algorithms, and documentation tools significantly improved the diagnosis of SND and subsequent use of PPMs. Phase I of the study characterized the care pathway, diagnosis and treatment rates and barriers for PPM adoption.[9] In this report covering Phase II of the study, physicians were provided with comprehensive resources to address the adoption barriers, which included patient educational materials, diagnosis and treatment rates, and an algorithm for identifying patients indicated for PPM implantation. To our knowledge, this is the first comprehensive study characterizing and evaluating the impact of process improvement initiatives in the diagnosis and management of patients with SND.

The study successfully achieved the primary objectives of increasing the rate of SND diagnosis and improving the rate of guideline-indicated PPM implant. Implementation of process improvement interventions resulted in a 3.5-fold increase in the odds of a patient SND diagnosis and an approximate 2-fold increase in the odds of PPM implantation from Phase I to Phase II, after adjusting for other confounding factors. Barriers to therapy continued to exist during Phase II of the study. One of these barriers was affordability, which continued to be a major concern for patients refusing the therapy (43% in phase I and 39% in phase II). This problem is common in India and Bangladesh where a signification portion of the patient population lack health care insurance, necessitating out-of-pocket expenditure for healthcare.[15,16] These findings emphasize the importance of healthcare policies to address cost barriers for patients to access guideline indicated interventional therapies. Though financial constraints remained a barrier during Phase II, there was still a significant increase in the use of guideline-indicated PPM therapy, confirming the benefit of the educational intervention.

A multivariable analysis showed study phase was the strongest predictor of SND diagnosis. Physicians were more narrowly focused on recruiting patients with a symptom profile increasingly aligned with SND in Phase II, including an increasing number with pre-syncope symptoms. Syncope/pre-syncope symptoms within 30 days was correlated with a 4-fold increase in the odds of PPM implant across phases. While more patients had syncope/pre-syncope symptoms in Phase II, the multivariable statistical analysis adjusts for presence of pre-syncope symptoms and study phase still increased the odds of implant above and beyond the presence of those symptoms. Study phase significantly increased the odds of receiving a PPM implant by nearly 2-fold after accounting for other predictors of PPM implant. This further highlights the significance of the implementation of the practice-specific process improvement intervention.

Following PPM implant, the quality of life for patients improved by 35% in the physical component and 25% in the mental component scores as measured by the SF-12 survey. These findings are consistent with previous research demonstrating that PPM implantation can improve patient quality of life.[6,17–19] Although there is evidence to suggest that anxiety and depression are elevated in patients with a PPM, in the current report, the benefits of PPM implantation led to an improvement in the overall mental health of patients with SND.[20] While prior studies have addressed patient quality of life, this is the first report examining the impact of PPM implant on caregiver burden. Congruent to the patient quality of life improvement, there was a 56% reduction in the burden on caregivers of SND patients implanted with a PPM. This suggests that not only does appropriate intervention with a PPM increase the quality of life among patients, it also reduces the caregiver burden.

4.1. Limitations

There were several limitations to this non-randomized observational study. Unobserved confounding factors that may have differed between Phase I and Phase II cannot be ruled out as a cause for increase in diagnosis and treatment in Phase II. The Hawthorne effect also cannot be ruled out as a cause for the increase of diagnosis and treatment in Phase II. These data were collected in a

limited region with 10 specialized centers with the ability to implant pacemakers in India and Bangladesh over a relatively brief period of time; therefore, the patient population included within this study may not be reflective of the general sinus node dysfunction population. As discussed in the Results, 2 centers did not continue participation in Phase II; however, the primary objectives were still met even when excluding these centers from the analysis. Assumptions on the effect of pacemaker therapy affordability were limited because patients were not asked direct questions about their socioeconomic status and income. The quality-of-life increases were not compared to an age and gender-matched control group and so a placebo effect on quality-of-life cannot be ruled out.

5. Conclusions

A practice-specific process improvement intervention conducted at centers across India and Bangladesh significantly increased both the diagnosis of SND and subsequent use of guideline-indicated PPM therapy. Both patient QoL and caregiver burden significantly improved following PPM implant. Importantly, diagnosis of SND and pacemaker implantation improved over time despite similar insurance and cost constraints. These findings confirm the benefit of education and awareness across the entire care pathway of patients with SND. They also highlight the importance of addressing socio-economic issues which appear to play a major role in both appropriately diagnosing and optimally managing these patients in this important geography.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: DWR: Advisor/Consultant: Medtronic; VR: Employee and shareholder: Medtronic; TB: Employee and shareholder: Medtronic; AD: Employee and shareholder: Medtronic; All other authors report no disclosures.

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Appendix A. Supplementary data

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