Influence of Closed-Loop Pacemaker Implantation on Patients' Quality of Life: RAPID Study Findings

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Summary

Unless carefully programmed, conventional open-loop rate-adaptive pacemakers may cause symptoms and impair quality of life (QOL) of the patients. Closed Loop Stimulation (CLS) systems regulate the pacing rate automatically based on the inotropic drive and allow the physician to program only the basic and maximum pacing rate. This study aimed to investigate the influence of automatic CLS rate adaptation on QOL of patients with different indications for pacing. Seventy-four patients from 14 clinical centers (mean age 71.5 ± 6.9 years, 36% female) with sick sinus syndrome (n = 37), atrioventricular block (n = 17), binodal disease (n = 16), and other indications for pacing (n = 4) filled out a QOL questionnaire before and at two instances (6-32 weeks) after implantation of a dual-chamber Inos² CLS pacemaker. Pacemaker application improved total QOL score by 14.7% ($p < 0.001$) in gross patient population and by 9.2%-20.8% in conjunction with different indications for pacing. QOL changes in gross population were highly significant ($p < 0.001$) in categories "Satisfaction" (+37.2%), "Mobility" (+29.1%) and "External activity" (+19.1%), significant ($p < 0.05$) in "Health" (+34.8%), "Moods" (+9.8%), "Social life" (+6.3%), "Appetite" (+15.8%) and "Housework" (+18.9%), and insignificant in "Self-confidence" (+5.9%), "Autonomy" (+3.9%), "Job performance" (+12.0%) and "Sleep" (-3.6%). Too fast pacing rates during night were reported by two patients (2.7%), which required a reprogramming of the maximum pacing rate to a lower value or changing the pacing mode to DDD. In conclusion, patients with different indications for pacing benefited from dual-chamber CLS pacing in terms of improved QOL.

Key Words

Pacemaker therapy, quality of life, Closed Loop Stimulation (CLS)

Introduction

Conventional open-loop rate-adaptive cardiac pacemakers use physical or physiological signals outside the cardiovascular control loop (body activity, acceleration, minute ventilation, QT-interval, etc.) to control the stimulation frequency [1-5]. The optimal combination of programmable rate adaptive parameters is

determined in each patient based on in-clinic exercise testing [1]. Suboptimal pacemaker programming by the physician can cause symptoms and impair quality of life (QOL) of the patients [6-9].

Closed Loop Stimulation (CLS) pacemakers from the Inos pacemaker family (Biotronik, Germany) regulate pacing rate according to the inotropic drive, which is estimated through intracardiac impedance measurements that take place during isovolumetric contraction and the beginning of the ejection phase [10-13]. Any mismatch between the cardiac output and current cardiovascular demands will result in a modified heart contractility, guiding pacing rates toward optimal values according to the "negative feedback" principle [14-23]. Conventional programmable rate-adaptive parameters, such as rate-responsive factor, rate acceleration/deceleration, degree of sensor sensitivity, sensor blending, etc., are made superfluous in CLS systems as they are controlled by natural cardiovascular control centers. The physician may influence CLS rate modulation only by programming the basic rate and maximum closed loop rate. There is a lack of information on how CLS influences QOL of patients with different indications for pacing.

Materials and Methods

Patients

A cohort of 102 patients with indications for dual-chamber pacing was enrolled in the international multicenter RAPID study (*R*ate Behavior of the *P*acing System *I*nos^2 CLS during *D*aily Life) from January 1998 to December 1999. Seventy-four patients who filled out a QOL questionnaire both prior and after pacemaker implantation are included in QOL data evaluation. Clinical characteristics of study patients are illustrated in Table 1. From 74 patients, 14 (18.9%) were diagnosed to have paroxysmal atrial arrhythmia before pacemaker implantation. The patients stemmed from 13 centers in Germany and one center in Poland (Clinical Investigators list is provided).

Pacemaker Description

Inos^2 DR, Inos^2 CLS, and Inos^{2+} CLS pacemakers (Biotronik, Germany) were inserted as the first implants in 92% of the patients and as an exchange unit in 8%. The pulse generators were connected to conventional tined or screw-in pacemaker leads from three manufacturers (Biotronik, Germany; Medtronic, USA;

(1) Health
- Self-perceived symptoms?
- Self-perceived well-being?
- Self-perceived state of health?

(2) Satisfaction
- How much are you satisfied with yourself?
- How much are you satisfied with your well-being?
- How much are you satisfied with your health?

(3) Moods
- How often do you feel satisfaction?
- How often do you experience inner peace and balance?
- How often do you feel tired?
- How often do you feel unrest?
- How often do you feel depression?
- How often do you feel fear?

(4) Social life
- How much do you enjoy social life?
- Do you manage to get on well with others?
- How often are you irritated or aggresive towards others?
- How often do you withdraw into isolation?
- How often do you experience problems in meeting friends?
- How often do you experience problems in your relationship with friends?
- How often do you experience problems in taking care about others?
- How often do you experience problems in other social activities?

(5) Sleep
- How often do you experience problems related to sleep?

(6) Appetite
- How often do you feel a lack of appetite?

(7) Self-confidence
- How often do you experience a lack of self-confidence?

(8) Autonomy
- How often do you experience problems in daily self-management (e.g., in getting dressed)?

(9) Housework
- How often do you experience problems in houskeeping activities?

(10) Mobility
- How troublesome for you is to climb stairs?
- How troublesome for you is to move around in your home?

(11) External activity
- How often do you experience problems in using public transport?
- How often do you experience problems in going shopping?
- How often do you experience problems in exercising sports?

(12) Work capability
- How often do you experience problems in being punctual?
- How often do you experience problems in coming to terms with your job tasks?
- How often do you make errors while working?
- How often do you experience problems with exhaustion?
- How often do you have problems with concentration?
- How often do you experience problems in your relationship with colleagues?
- How often do you have problems with motivation?

Table 1. The list of questions contained in the custom-designed questionnaire used in the RAPID study (after free translation from German to English). The questions were graded on a 3-point Likert scale, from 0 (the least favorable answer) to 2 (the most favorable answer). Scores for the indicated 12 major categories were obtained by averaging scores for individual questions belonging to the given category.

and Guidant, USA). All pacemakers were dual-chamber units using the same algorithm to translate changes in the contraction dynamics into pacing rate variation [13]. CLS requires ventricular pacing on all heart cycles to ensure stable morphology of the sensed signal. Dynamic atrioventricular (AV) delay should be programmed in a way to slightly overdrive eventual spontaneous AV conduction during rest and exercise. Naturally conducted ventricular beats are not taken into account and can cause gradual decrease of pacing rate toward basic rate. Upon resumption of ventricular pacing, pacing rate will gradually increase to the CLS-indicated rate. The atrium may be paced, sensed, or both. CLS rate modulation is automatic – only the basic rate and maximum closed loop rate can be programmed by the physician. Conventional mode-switching to the VDI mode is available to prevent ventricular tracking of atrial tachyarrhythmia.

Study Protocol

Following pacemaker implantation, DDD-CLS mode (i.e., CLS rate adaptation) was enabled. Other pacemaker parameters were programmed under physicians' discretion, except for the dynamic AV-delay which had to be about 30 ms shorter than the intrinsic AV conduction. In the absence of generally adopted and validated questionnaire for QOL evaluations in cardiac pacing (see Discussion), we used a single page custom-designed questionnaire depicted in Table 1. Patients filled out the QOL questionnaire before pacemaker implantation and in the period from 6 to 14 weeks (first follow-up) and from 5 to 7 months (second follow-up) after implantation. They completed the questionnaire independently with the opportunity to get additional explanations from the attending personnel upon request. Pacemaker diagnostic data were retrieved at each follow-up, to assess percent of paced and sensed events in the atrium and ventricle.

Data Analysis

Twelve QOL scores were derived from a single questionnaire in the way defined in Table 1; the total QOL score was then calculated as the mean value of the 12 scores. The scores for multi-item categories 1 – 4 and 10 – 12 were computed as the mean values of the related questions. QOL scores from the 1st and 2nd follow-up controls were averaged per category to generate mean after-implantation scores in each patient.

Before- and after-implantation QOL scores were compared to each other in the total population as well as in subpopulations formed from patients with AV block only, with sick sinus syndrome only, with binodal disease, and from patients under ß-blocker therapy. The ß-blocker group was included due to concerns of some physicians that ß-blockers may impair CLS rate modulation through suppression of the inotropic drive. Clinical characteristics of patients from different groups were similar with respect to patient age and NYHA functional class (Table 2).

Data for groups are presented as mean values (± standard deviations) and as mean percent of QOL improvement. Paired two-tailed t-tests were used for intraindi-

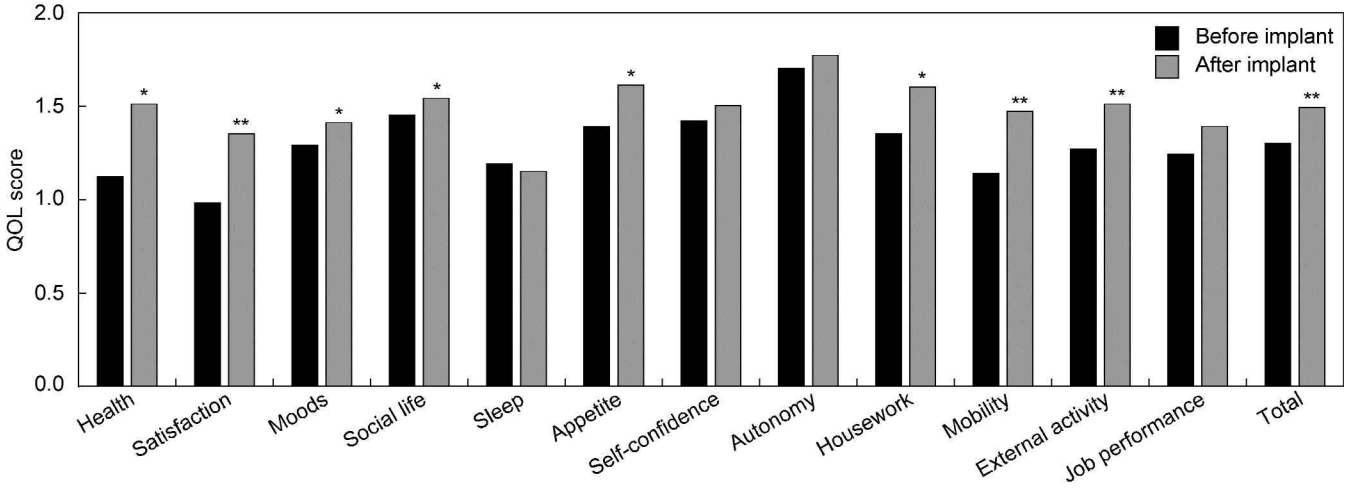

*Figure 1. Mean quality of life (QOL) scores before and after pacemaker implantation in gross population (n = 74). A higher score is more favourable. *p-value < 0.05, **p-value < 0.001.*

vidual comparisons of before- and after-implantation QOL scores. Differences in QOL scores between 1st and 2nd follow-up controls were analysed using unpaired two-tailed t-tests, in order to assess placebo effect of pacemaker implantation [24,25]. In all instances, p-values < 0.05 were considered significant and p-values < 0.001 highly significant.

Results

Follow-up Results

The mean programmed basic rate was 60 ± 3 beats/min and the mean maximum closed loop rate 121 ± 9 beats/min. Paced AV-delay was 166 ± 12 ms at the basic rate and 108 ± 16 ms at 130 beats/min (point of maximum AV-delay shortening). Sensed AV-delays were 30 ms shorter than the corresponding paced AV-delays. On average, ventricular pacing was achieved on 99.2% of heart cycles, indicating nearly continuous CLS rate adaptation. Atrial pacing (CLS guided heart rate) was present in 81% ± 17% of heart cycles. Fifty-six patients filled out QOL questionnaire at both follow-up controls, eight patients only at the 1st follow-up and ten only at the 2nd follow-up.

During the course of the study, two patients (2.7%) complained on relatively fast pacing rates during night, which was resolved by decreasing maximum closed loop rate to 80 beats/min or by pacemaker reprogramming to the DDD mode. Complications that could not be directly linked to CLS pacemaker function were within normal limits, which included one atrial lead revision (1.4%), coronary artery bypass graft in two patients (2.7%), symptomatic atrial fibrillation or flutter in four patients (5.4%, which was resolved by cardioversion or by drug administration), marked heart insufficiency in one patient (1.4%), a syncope caused by ventricular tachycardia (1.4%), and a decompensated liver in one patient (1.4%).

Mode-switching function was active in 48 (65%) of the patients, and 32 patients had at least one mode-switch episode during the study. The mean burden of atrial fibrillation in these patients was 6.9 ± 12.9% of total study time (range 0.01% – 60%, in 20 patients > 1%).

QOL Results

QOL scores are shown in Figures 1 and 2 and subjected to statistical analysis in Table 3. When ten patients with complications unrelated to pacemaker function were excluded, QOL findings remained substantially the same.

Comparison of QOL results from the 1st and 2nd follow-up controls in gross population revealed that only

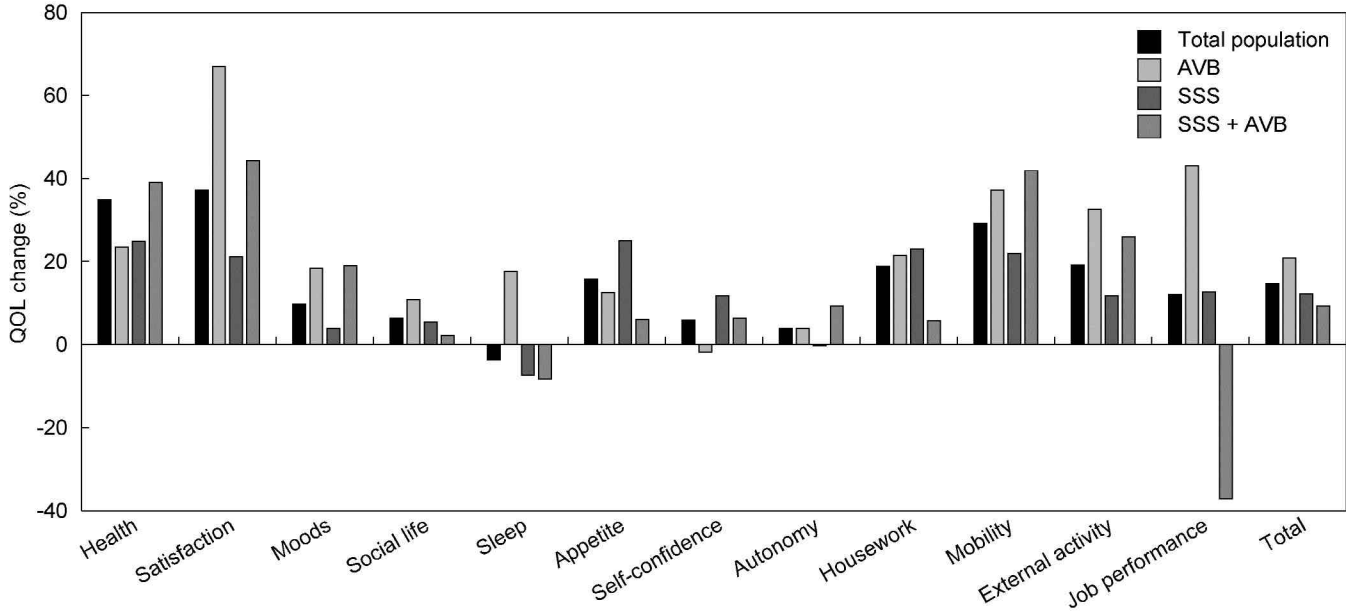

Figure 2. Percent of quality of life (QOL) improvement after pacemaker implantation, calculated as: (QOL_{after} - QOL_{before})/QOL_{before} in gross patient population (n = 74) and in patients with atrioventricular block (AVB) (n = 17), sick sinus syndrome (SSS) (n = 37), and SSS in the presence of AVB (n = 16).

	Number	Age (years)	Female	NYHA
Total	74 (100%)	71.5 ± 6.9	36%	1.8 ± 0.7
Indication for pacing				
AVB	17 (23%)	70.6 ± 6.4	29%	1.8 ± 0.7
SSS	37 (50%)	72.4 ± 6.6	50%	1.7 ± 0.8
Binodal disease	16 (22%)	70.1 ± 8.1	19%	1.9 ± 0.5
Other*	4 (5%)	72.5 ± 7.3	0%	1.8 ± 0.5
Use of ß-blockers	26 (35%)	71.8 ± 7.9	42%	1.7 ± 0.7

Table 2.Clinical characteristics of study patients. Patient age and pre-implantation New York Heart Association (NYHA) functional class are presented as mean value ± standard deviation. AVB = atrioventricular block. SSS = sick sinus syndrome. Binodal disease = AVB + SSS. Other (*) indications comprised paroxysmal atrial fibrillation with slow ventricular response (n = 2), hypersensitive coronary sinus (n = 1), and left bundle branch block (n = 1).

"Health" score was better at the 1st follow-up (by 16%, p = 0.27). Despite the tendency for better QOL scores at the 2nd follow-up, only a difference in "Self-confidence" reached statistical significance (higher by 8.2% at the 2nd follow-up, p = 0.04). Seemingly, a relatively low self-confidence level at the 1st follow-up examination gave rise to the insignificant difference between before- and after-implantation "Self-confidence" scores.

Discussion

Clinical performance of conventional open-loop pacemaker systems should be optimised by careful programming of a range of rate-adaptive parameters (rate-responsive factor, rate acceleration/deceleration, sensor sensitivity, sensor blending, etc.) by the physician [1,6]. Otherwise, the anticipated improvement of QOL due to augmented cardiac output with exertion may be compromised by insufficient heart rate increase or by interference of the sensor-guided rate with the sinus rate, potentially causing palpitations, dyspnea, and other symptoms that may result in even lower QOL score in rate-adaptive than in non-rate-adaptive pacing systems [6-9].

CLS pacemakers are guided by natural cardiovascular control centers and rate-responsive programming is simplified to the extent that only basic rate and maximum closed loop rate are externally adjustable. Several groups of authors indicated that CLS may improve not only choronotropic incompetence but also restore baroreceptor reflex, optimise heart rate variability and support patients with vasovagal syncope or cardiomyopathy [16,19,21-23,26-28]. There is a lack of information, however, on how CLS influences QOL of patients with different indications for pacing. The relevance of patients' perception of well-being over time is

	Total population (74)		AVB (17)		SSS (37)		Binodal disease (16)		ß-blocker users (26)	
	QOL increase (%)	p-value	QOL increase (%)	p-value	QOL increase (%)	p-value	QOL increase (%)	p-value	QOL increase (%)	p-value
Health	34.8	<0.05	23.5	ns	24.9	ns	39.1	<0.05	33.3	<0.05
Satisfaction	37.2	<0.001	67.0	<0.05	21.1	<0.05	44.3	<0.05	27.3	ns
Moods	9.8	<0.05	18.4	<0.05	3.9	ns	19.0	<0.05	4.7	ns
Social life	6.3	<0.05	10.9	ns	5.4	ns	2.2	ns	2.8	ns
Sleep	-3.6	ns	17.6	ns	-7.4	ns	-8.3	ns	-7.1	ns
Appetite	15.8	<0.05	12.5	ns	25.0	<0.05	6.0	ns	12.6	ns
Self-confidence	5.9	ns	-1.8	ns	11.8	ns	6.3	ns	2.8	ns
Autonomy	3.9	ns	3.9	ns	-0.3	ns	9.3	ns	2.1	ns
Housework	18.9	<0.05	21.4	ns	23.0	<0.05	5.8	ns	21.2	ns
Mobility	29.1	<0.001	37.2	<0.05	21.9	<0.05	41.9	<0.05	42.4	<0.05
External activity	19.1	<0.001	32.5	ns	11.7	ns	25.9	<0.05	16.4	ns
Job performance	12.0	ns	43.0	ns	12.7	ns	-37.2	ns	9.2	ns
Total	14.7	<0.001	20.8	<0.05	12.2	<0.05	9.2	ns	12.5	<0.05

Table 3. Improvement in quality-of-life (QOL) after pacemaker implantation. Number of patients is given in parentheses. AVB = atrioventricular block. SSS = sick sinus syndrome. Binodal disease = AVB + SSS. QOL increase was in all instances calculared as: (QOL_after_impl - QOL_before_impl) / QOL_before_impl.

of particular importance in automatic systems where a momentary observation of an objective parameter, e.g., exercise tolerance or hemodynamics, may have limited reproducibility due to continuous self-adjustment of pacemaker parameters.

Selection of QOL Questionnaire

Generally accepted health-related QOL questionnaires such as Short Form-36 (SF-36), Sickness Impact Profile, Nottingham Health Profile, and Minnesota Living with Heart Failure Questionnaire were considered inappropriate for our study due to their low sensitivity to effects of pacemaker therapy [8,25,29,30]. Although Karolinska and Hacettepe QOL questionnaires are occasionally utilised in pacemaker patients, they have not been fully validated and generally accepted [30]. Under these conditions, we created a QOL questionnaire illustrated in Figure 1. Our questionnaire differed from the custom-designed questionnaire previously published in Z Kardiol by Epperlein et al. [9] in the total number of questions (38 instead of 6) and in the scoring method (3-point instead of a 10-point Likert scale).

Study Findings in Gross Population

A highly significant ($p < 0.001$) improvement of QOL due to CLS pacemaker application was present in the total QOL score (14.7%) as well as "Satisfaction" (37.2%), "Mobility" (29.1%) and "External activity" (19.1%) (Table 3). While these findings can be attributed to the restoration of AV synchronisation and of physiologic heart rates, no previous study demonstrated as high significance of the improvement as our study did [6-9]. This is probably due to the largest number of patients participating in the study, allowing for sound statistical evaluation, and the fact that previous studies compared different pacing modalities rather than pacing versus no pacing. Significant improvements ($p < 0.05$) in "Health" (34.8%), "Moods" (9.8%), "Social life" (6.3%), "Housework" (18.9%) and "Appetite" (15.8%) appear to be a logical consequence of the increased patient stamina.

An insignificant overall improvement in "Self-confidence" is explainable by the relatively low score at the 1st follow-up. However, patient self-confidence significantly increased at 6 months as compared to 6 – 14 weeks after implantation. The "Autonomy" level was high before implantation (mean 1.7 points) and could not be substantially improved with pacing. Insignificant changes in "Job performance" were probably a consequence of patient age – the majority of patients were not professionally active and could not answer the related questions.

The only deteriorated QOL aspect after CLS application was "Sleep", where a 3.6% decrease did not reach statistical significance ($p = 0.73$). Elevated CLS rates during dreaming (Rapid Eye Movement Phase of sleep) and posture changes in bed are the likely reason [17,19]. To overcome this problem, the latest generation of CLS systems ($Inos^{2+}$ CLS with the "K"-software) offer an additional algorithm for pacing rate limitation during night.

QOL Results in Subpopulations

QOL improved clearly in patients with sick sinus syndrome (12.2%, $p < 0.05$) as well as in subjects with isolated AV block (20.8%, $p < 0.05$) (Table 2). While the latter finding is explainable by the restoration of AV synchrony offered by a dual-chamber unit, QOL improvement in sick sinus syndrome may be attributed to the effect of CLS. A slight overdrive of the intact AV conduction to allow CLS execution appears less important than the restoration of physiologic heart rate control. Moreover, CLS rate interference with the normal sinus function in patients with isolated AV block did not affect marked positive QOL change following pacemaker implantation, implying that CLS does not result in pacing rates discrepant from healthy sinus rates. High statistical significance of the improvement in the individual QOL categories in gross population could not be repeated in subpopulations with different indications for pacing due to a smaller number of patients.

In binodal disease, CLS was associated with a significant improvement in scores in five QOL categories, which is more than in any other indication for pacing. However, the 9.2% improvement in the total QOL score in this subpopulation failed to reach statistical significance ($p = 0.08$) due to a marked incidental decrease in "Job performance" (-37.2%, $p = 0.47$) in a few patients that answered the corresponding questions.

Favourable QOL scores in ß-blocker users (Table 2) suggest that administration of this drug did not exert negative influence on CLS performance. This may be explained by continuous adaptation of CLS to changing patient conditions, allowing for chronically limited variations of the inotropic drive to be translated into the full scope of pacing rates ranging from basic to maximum closed loop rate.

Study Limitations

Major limitation of the present study was a lack of randomised, blind study design in which the effect of CLS would be compared to the outcome of rate-adaptive pacing using conventional sensors or to DDD pacing. A fully validated and generally endorsed QOL questionnaire for evaluations in cardiac pacing would be also appreciated, to increase legibility of the findings and allow comparisons of the results from different investigator groups (30).

Conclusion

Implantation of a CLS pacemaker improved total QOL by 14.7% ($p < 0.001$) in gross patient population and by 9.2% – 20.8%, on average, in patient groups with sick sinus syndrome, isolated AV block, and binodal disease. The only deteriorated QOL aspect with CLS was "Sleep" (-3.6%, $p = 0.73$), pointing out to the need for additional rate limitation during night. The use of ß-blockers (in 26 patients) had no negative impact on QOL scores compared with gross patient population.

Clinical Investigators

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