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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

1. Synopsis

Objectives:	Primary objective: To compare the influence of the treatment with Nebivolol following ECV with biphasic waveform shocks to the treatment with Nebivolol alone on the left ventricular end diastolic diameter (LVEDD). Secondary objectives: - Left ventricular end systolic diameter (LVESD) - Ejection fraction (EF). - Influence of the treatment on further echocardiographic parameters: a. Right atrial diameter (RAD) b. Right ventricular diameter c. Left atrial diameter d. Left ventricular end-systolic volume (LVESV) e. Left ventricular end-diastolic volume (LVEDV) f. Left ventricular end-systolic wall thickness g. Left ventricular end-diastolic wall thickness h. Relaxation disturbance (E wave/A wave ratio, Mitral E wave deceleration time, isovolumic relaxation time) i. Mitral inflow (peak early diastolic filling velocity/E-max, early filling deceleration time/Edec) - To assess the response to treatment (overall and response to cardioversion) - To compare the influence of the treatment with Nebivolol following ECV with biphasic waveform shocks to the treatment with Nebivolol alone on clinical parameters of heart failure - To compare the influence of the treatment with Nebivolol following ECV with biphasic waveform shocks to the treatment with Nebivolol alone on NT-proBNP (N-terminal-pro-B-type natriuretic peptide) - To assess the bioimpedance and energy load of electric cardioversion with biphasic wave shocks in dependence of weight (group A only)
Variables:	Primary efficacy variable: Changes of the LVEDD 4 weeks after start of treatment (visit 1 vs. visit 3). Secondary efficacy variables: - Changes of the LVESD 4 weeks after start of treatment. - Changes of the left ventricular EF 4 weeks after start of treatment. - Changes of the right atrial diameter 4 weeks after start of treatment. - Changes of the right ventricular diameter 4 weeks after start of treatment. - Changes of the left atrial diameter 4 weeks after start of treatment.

Variables (continued):	- Changes of the LVESV 4 weeks after start of treatment. - Changes of the LVEDV 4 weeks after start of treatment. - Changes of the left ventricular end-systolic wall thickness 4 weeks after start of treatment - Changes of the left ventricular end-diastolic wall thickness 4 weeks after start of treatment. - Changes of the relaxation disturbance 4 weeks after start of treatment: - Changes of the E wave/A wave ratio - Changes of the mitral E wave deceleration time - Changes of the isovolumic relaxation time. - Changes of the mitral inflow 4 weeks after start of treatment: - Changes of the peak early diastolic filling velocity (E-max) - Changes of the early filling deceleration time (Edec) - Overall responder rates: response was hereby defined as: no drop-out due to relapse of tachycardia and heart rate < 90 beats per minute (bpm) at the end of the study - Cardioversion responder rates: applied for treatment group A only: response was hereby defined as successful cardioversion (cardioversion to normal sinus rhythm) - Changes of clinical parameters of heart failure 4 weeks after start of treatment - Changes of the NT-proBNP levels after 4 weeks of treatment - Changes of bioimpedance and energy load of electric cardioversion with biphasic wave shocks in dependence of weight (group A only) - Safety variables: - Incidence and type of adverse events - Safety laboratory parameters - Vital signs - ECG
Method (primary variable only):	Transthoracic echocardiography (TTE) at baseline and after 4 weeks of treatment. The results will be evaluated blinded by a central Echo lab.

Clinical Trial Design:	- Randomized, prospective phase IV parallel-group trial comparing Nebivolol following ECV with biphasic waveform shocks to treatment with Nebivolol alone. All patients were hospitalized at Visit 1 and stayed at least until day 2. All patients received 5 mg Nebivolol daily for 4 weeks after randomization. Patients of group A received Nebivolol after cardioversion, irrespective of it being successful or not. - Normal Sinus Rhythm (NSR) was defined as a heart rate of between 60 and 100 beats per minute (at rest). - Tachycardia was defined as an abnormally rapid heart rate, above 100 beats per minute. Stopping rule for all patients: in case of refractory tachycardia (heart rate > 100 bpm) drop-out and alternative treatment. - Rate control was defined as heart rate < 100bpm.
Medical and Statistical Consideration leading to the Calculation of the Number of Patients:	Due to lack of knowledge with respect to the distributional properties of the primary efficacy variable and the expected treatment effects, no formal sample size calculation was carried out. It was assumed, however, that 25 patients in each group were sufficient to evaluate possible treatment differences.
Expected Drop out Rate:	25% (including screening failures)
Statistical Methods:	Two-sided significance tests comparing both treatment groups were performed for all efficacy variables. Because of the pilot character of the study, all tests were carried out on an exploratory basis. The Wilcoxon-Mann-Whitney test was applied for quantitative variables, dichotomous variables were tested by means of Fisher's exact test. The Wilcoxon signed rank sum test was used to investigate whether change in LVEDD between visit 1 and visit 3 was significantly different from zero.
Inclusion Criteria:	Inclusion criteria: - Age ≥ 18 years - Newly occurring supraventricular tachycardia with a heart rate > 130 bpm within the last three months and initial treatment with Metoprolol and/or digitalis i.v. - EF ≤ 50 % after i.v. rate control treatment with Metoprolol and/or digitalis i.v. - History of or new diagnosed arterial hypertension according to JNC - Complete heparinisation - Metoprolol and/or digitalis i.v.

Exclusion Criteria:	Exclusion criteria: - Acute myocardial infarction - Haemodynamic relevant heart valve disorders - Left atrium diameter ≥ 55 mm - Hyperthyroidism - Contraindication to heparin including low-molecular-weight heparins, oral anticoagulation, Metoprolol, Nebivolol, digitalis or to cardioversion - Concomitant treatment with antiarrhythmics - Concomitant treatment with other beta-blockers after randomization except for Nebivolol as study medication - Known hypersensitivity to Nebivolol or any of the ingredients of the trial medication or any known hypersensitivity to ß-blockers - Patients with known SGPT (ALAT) and SGOT (ASAT) levels exceeding three times the upper limit of the investigator's normal range, known serum bilirubin > 1.75 mg/dl (> 30 µ mol/l) or clinical evidence of severe hepatic disease or hepatic failure - Women of childbearing potential without adequate contraception - Pregnancy or lactation - Cardiogenic Shock - Peripheral arterial occlusive disease > IIa (PAOD) or Raynaud's syndrome - Severe cardiac decompensation as judged by the investigator and/or NYHA class IV - Sick-sinus-syndrome including heart blocks (SA node) and/or AV block 2nd and 3rd degree and/or significant arrhythmia and/or bradycardia < 50 bpm (in resting condition prior to treatment) - Bronchial hyperreagibility, bronchial asthma, or history of bronchospasm - Untreated pheocromocytoma - Metabolic acidosis - Prior or active malignancy in the previous 5 years except adequately treated basal cell/ squamous cell carcinoma of the skin or carcinoma in situ of the cervix - Hypotension with systolic blood pressure < 85 mmHg - Patients with psychiatric diseases - Patients with a history of alcohol and/or drug abuse - Patients who are currently participating in another clinical study or who have received an investigational drug within 30 days prior to entering the study - Patients who are unwilling or unable to provide informed consent or to participate satisfactorily for the entire trial period.

Disposition of patients	Randomized: N=31 (group A: 15; group B: 16) Safety analysis set: N=29 (group A: 15; group B: 14) - two patients did not receive any dose of trial medication. ITT analysis set: N=28 (14 per treatment group) PP analysis set: N=18 (group A: 7; group B: 11).
Efficacy evaluations	<u>Demographics and medical history</u> In the ITT analysis set (N=28), patient's age was 67.2 years, similar in the two treatment groups (65.8 years in group A and 68.6 in group B). There was a gender imbalance between groups, with 2 females in group A (14.3%) vs. 8 in group B (57.1%), all post-menopausal (in the PP analysis set (N=18), the number of female patients were 1 in group A and 7 in group B). Other demographic characteristics were similar between groups. The main concomitant diseases were hypertension (N=22; 78.6%), cardiac failure (N=19; 67.9%), mitral valve incompetence (N=10; 35.7%), hyperlipidaemia (N=12; 42.9%), diabetes mellitus (N=6; 21.4%), coronary artery disease (N=5; 17.9%), and chronic obstructive pulmonary disease (N=5; 17.9%). No major differences were shown between treatment groups in this regard. <u>Primary efficacy parameter</u> - LVEDD was similar at baseline in group A (52.65 mm on average) and in group B (49.00 mm on average), and increased on average by + 2.15 mm in group A, and +0.25 mm in group B (NS) at visit 3 (NS). - The analysis stratified by gender showed a significant difference in the LVEDD evolution from visit 1 to visit 3 in male patients only, with increase of +1.17 mm in group A and decrease by -4.96 mm in group B (p=0.034). - Changes observed in the PP analysis set (male subset) were +0.78 mm in group A and -8.67 mm in group B (p=0.036). <u>Secondary efficacy parameters</u> - The RAD showed a significantly larger decrease in group A (-8.27 mm) compared to group B (-0.50 mm) (p=0.007). - The Mean R-R interval increased by 423.2 ms in group B and by 187.2 in group B (p=0.061). - The EF increased in a similar manner in both groups. - The other TTE secondary efficacy parameters did not show differences in changes from baseline between groups. - All clinical parameters of heart failure improved over time; Killip class, and NYHA class showed a shift towards less severe classes. Sixteen patients improved by 1 NYHA class (from class III to class II, or from class II to class I), 6 patients improved by 2 NYHA classes (from class III to class I), and 6 patients stayed unchanged. NT-pro BNT levels were comparable between groups.

Safety evaluations	Exposure to study medication: The median exposure to the study medications was 28 days. The compliance criterion was satisfied by 12 patients from group A and 13 from group B. Adverse events experience: - No difference in adverse experience was evidenced between the two groups. - No patient died during the study. - The overall frequency of adverse events, their severity and outcome was similar between groups. Sixteen patients (55.2%) from the safety population had at least one adverse event, including 9 patients from group A (60.0%) and 7 from group B (50.0%). Most events were of mild or moderate severity. - Four patients from group A (23.5%) and 2 patients from group B (12.5%) had at least one serious adverse event (7 SAE were experienced by these 6 patients). No SAE was judged related to the study medication. All SAE were resolved (N=6) or resolving (N=1) at the last study visit. - Four patients had at least one adverse drug reaction (one patient in group A and 3 in group B): in group A, one patient (6.7%) suffered from bradycardia which led to withdrawal of study medication. In group B, 3 patients (17.6%) presented with ADR, including tachycardia, cough, and insertion of an implantable defibrillator (one each), respectively. The relationship of these events to the study medication was “unlikely”. - Patients treated with ECV plus Nebivolol presented slightly more cardiac events (7 patients from group A, 4 patients from group B). In the 4 patients from this group who experienced a SAE (1 patient in group B), three of these events were cardiac disorders (myocardial infarction, atrial fibrillation, ventricular arrhythmia). Vital signs, ECG parameters: Between visit 1 and visit 3, systolic and diastolic blood pressure dropped by approximately 10 mm Hg. The heart rate, which was on average 144.5 bpm at visit 1, dropped to 75.7 bpm at visit 2, and 81.9 bpm at visit 3. Minor changes were noted with respect to the duration of the QRS complexes. Compared to its duration at visit 1, the QT was prolonged at visit 3 by approximately 80 ms. All changes occurred in a similar manner in the two groups. Laboratory parameters: Patients from both treatment groups showed similar and minor changes in the safety laboratory parameters from visit 1 to visit 3. Bilirubin, comparable for both groups at baseline, decreased by –0.288 µmol/l in group A, and by –0.529 µmol/l in group B.

Discussion and Conclusions	In the present proof of concept randomized, monocenter study, Nebivolol 5 mg/day was administered for 4 weeks to patients suffering from recent-onset tachycardia and ejection fraction ≤ 50% after initial medical treatment, associated or not with initial ECV. The responder rate, that is, patients with a heart rhythm ≤90 bpm at the end of the study, was similar with both treatments, as was clinical improvement defined by decrease of symptoms of heart failure, and reduction of NYHA and Killip classes. Ejection fraction improved in both groups. The left ventricle end diastolic diameter (where the average values were within the limits of normal range at baseline) showed a minor and non statistically significant increase of 2.15 mm in group A and 0.25 mm in group B after 4 weeks of treatment. Actually, the analysis stratified by gender showed that it decreased by on average -5 mm in male patients treated by rate control, whereas it did not decrease in male patients from the other group, neither in females. This result is to be taken with caution, as it arises from a subset analysis. The other echographic parameters showed generally similar changes between groups, with the exception of the decrease of RAD in patients receiving ECV plus Nebivolol) and R-R interval, which tended to be more prolonged in the same group. These findings do not permit to favour one treatment strategy over the other one. However, it is to be noted that in terms of safety, cardiac adverse events were more frequent in the group receiving ECV. Study limitations include the small sample size, decreasing the power of the study to identify a true difference, the short follow-up duration, and the potential heterogeneity of the patient population. A larger scale study should permit to determine the best treatment strategy in presence of tachyarrhythmia-induced cardiomyopathy, with regard to reversibility of heart failure symptoms, and cardiac reverse remodelling.