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Clinical Investigation

Feasibility and Association of Neurohumoral Blocker Up-titration After Cardiac Resynchronization Therapy

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) improves mortality and morbidity on top of optimal medical therapy in heart failure with reduced ejection fraction (HFrEF). This study aimed to elucidate the association between neurohumoral blocker up-titration after CRT implantation and clinical outcomes.

Methods and Results: Doses of angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and beta-blockers were retrospectively evaluated in 650 consecutive CRT patients implanted from October 2008 to August 2015 and followed in a tertiary multidisciplinary CRT clinic. All 650 CRT patients were on a maximal tolerable dose of ACE-I/ARB and beta-blocker at the time of CRT implantation. However, further up-titration was successful in 45.4% for ACE-I/ARB and in 56.8% for beta-blocker after CRT-implantation. During a mean follow-up of 37 ± 22 months, a total of 139 events occurred for the combined end point of heart failure admission and all-cause mortality. Successful, versus unsuccessful, up-titration was associated with adjusted hazard ratios of 0.537 (95% confidence interval 0.316–0.913; $P = .022$) for ACE-I/ARB and 0.633 (0.406–0.988; $P = .044$) for beta-blocker on the combined end point heart failure admission and all-cause mortality. Patients in the up-titration group exhibited a similar risk for death or heart failure admission as patients treated with the maximal dose (ACE-I/ARB: $P = .133$; beta-blockers: $P = .709$).

Conclusions: After CRT, a majority of patients are capable of tolerating higher dosages of neurohumoral blockers. Up-titration of neurohumoral blockers after CRT implantation is associated with improved clinical outcomes, similarly to patients treated with the guideline-recommended target dose at the time of CRT implantation. (*J Cardiac Fail 2017;*■■*:*■■–■■)

Key Words: Cardiac resynchronization therapy, neurohumoral-blockers, quality of care, outcome.

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Numerous randomized controlled trials have consistently demonstrated a reduction in mortality and morbidity in patients with heart failure with reduced ejection fraction (HFrEF) treated with the use of angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs; jointly termed renin-angiotensin system (RAS) blockers)[1–3] and beta-blockers.[4–6] In addition, cardiac resynchronization therapy (CRT) has become an established treatment option for HFrEF patients with electrical dyssynchrony and persistently decreased ejection fraction despite optimal neurohumoral blocker treatment.[7] The Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) and a recent European survey, illustrate that real-world CRT patients are often treated with the use of lower doses than used in randomized controlled trials.[8,9] Indeed, only 18% and 30% of IMPROVE-HF

patients undergoing CRT received the guideline-recommended target doses for beta-blockers and RAS blockers, respectively. This is an important observation, because treatment with higher doses of neurohumoral blockers has been consistently linked to reduced morbidity and mortality.[10,11] Although CRT is often considered as a step-on option after optimal medical treatment, its beneficial effect regarding reverse remodeling, improved cardiac output, higher blood pressure and protection against bradycardia could allow for further up-titration of neurohumoral blockers. Yet the feasibility and association of neurohumoral up-titration with outcomes after CRT remain insufficiently elucidated.

Methods

Study Population and Follow-Up

Consecutive HFrEF patients undergoing CRT implantation at a single tertiary care center (Ziekenhuis Oost-Limburg, Genk, Belgium) from October 2008 to August 2015 were evaluated. CRT indications were in compliance with the European Society of Cardiology guidelines.[7,12] All patients underwent scheduled visits in a dedicated heart failure clinic to assure maximally tolerated up-titration of neurohumoral blockers before CRT implantation. Therefore, all patients included in the analysis were on an individual maximally tolerated dose at the time of CRT implantation. After implantation, all patients underwent a similar prespecified follow-up and dedicated post-implantation CRT optimization protocol, as previously published.[13] Aside from echocardiographic device optimization, all patients underwent further efforts to up-titrate their RAS blockers and beta-blockers. Up-titration was started the day after implantation in an inpatient setting and continued on an ambulatory basis. Systematic follow-up appointments were scheduled after 6 weeks and 6 months. This protocol strived to achieve maximal up-titration within 6 months after implantation. Up-titration of RAS blockers was halted in case of a drop in estimated glomerular filtration rate (eGFR) by >15%, serum potassium levels >5.5 mmol/L, or persistent symptomatic orthostatic hypotension. Beta-blocker up-titration was halted in case of bradycardia or debilitating Raynaud phenomena, impotence, chronotropic incompetence, or symptomatic hypotension. Of importance, drug up-titration was performed by the same physician before and after CRT implantation (M.D. or W.M.), so incremental changes in drug dosage after CRT are reflective of the capability to tolerate higher doses and are not reflective of a change in treating practice of a different physician. The present study was in compliance with the Declaration of Helsinki. Institutional Review Board approval was granted, but the need for written informed consents was waived owing to the retrospective study design. The manuscript was drafted according to the STROBE statement for observational studies.[14]

Data Acquisition and Patient Stratification

Demographics, clinical data, duration of HFrEF, and medical therapy were retrospectively collected from the electronic medical record. Dosing of guideline-advised medical therapy was uniformly registered as the percentage of the guideline-recommended target dosages for RAS blockers and beta-blockers. A conversion table with target doses is available in Supplemental Table 1. Individual dose changes of both RAS blockers and beta-blockers were assessed as the difference in dosage between baseline and 6 months after implantation. The choice to evaluate up-titration at 6 months followed from the rationale that reverse remodeling (and thus capability to tolerate higher dosages) occurs mostly in the first 6 months after CRT. Patients who were on maximal dosages at implantation and maintained this at 6-month follow-up or patients who had a formal and irreversible contraindication for RAS blockers or beta-blockers at baseline were excluded from the calculation of up-titration success, because no change in dosage would occur. The submaximally treated group at baseline was further stratified into 3 groups based on post-implantation dosing kinetics: (1) up-titration (increase in target dose >1%); (2) no up-titration (no change in dose was tolerated using the current up-titration protocol); and (3) down-titration (patients who necessitated down-titration after CRT implantation were deemed to be a unique and sicker population and were not classified into the no up-titration group).

Echocardiography Data

Comprehensive 2-dimensional transthoracic echocardiography examinations were performed (iE33w; Philips Medical Systems) by experienced cardiac sonographers at the time of device implantation and after 6 months of follow-up. All reported echocardiography measurements were averaged from 3 consecutive cycles or 5 cycles in case of atrial fibrillation and assessed as recommended by the American Society of Echocardiography.[15] Left ventricular ejection fraction (LVEF) was obtained by means of the modified Simpson biplane method in the apical 2- and 4-chamber views.

Outcome Analysis

Clinical outcome was analyzed as a primary combined end point of heart failure hospitalization and all-cause mortality. Heart failure hospitalizations were defined as any hospitalization lasting >24 hours with ≥2 signs or symptoms of congestion and necessitating the use of intravenous diuretics. Vital status was retrieved from the electronic medical record. Secondary end point analysis consisted of heart failure admission and mortality separately.

Statistics

Normally distributed continuous variables were expressed as mean ± SD. Normality was checked by means of the Shapiro-Wilk statistic. Categoric data were expressed as percentages and compared by means of the Pearson χ^2 test when a large sample size was present or Fisher exact test when a small sample size was present. Continuous variables were