Natriuretic peptide-guided therapy in high-risk heart failure patients, to be or not to be?

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The natriuretic peptides, B-type natriuretic peptide (BNP) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP), are biomarkers of neurohormonal activation related to heart failure (HF) severity and associated with adverse outcomes and poor prognosis in HF patients with rising levels (1-3).

In their work, Felker *et al.* investigated whether an NT-proBNP-guided treatment strategy was able to improve clinical outcomes as compared with usual care in high-risk patients with HF and reduced ejection fraction (HFrEF) (4). From January 2013 to September 2016 a total of 1,100 patients were planned to be enrolled at 45 sites in the United States and Canada, but only 894 patients were finally randomized because the study has been prematurely stopped for futility. Patients were randomized to either an NT-proBNP-guided strategy or usual care. Subjects randomized to guided strategy (N=446) had an HF therapy titrated to achieve a target of NT-proBNP <1,000 pg/mL while those randomized to usual care (N=448) had an HF therapy accordingly to the current guidelines with emphasis on titration of proven neurohormonal therapies. The NT-proBNP dosage was discouraged in the second group. The study enrolled high-risk HF patients, according to NYHA class (90% II or III class), mean left ventricular ejection fraction (mean value 25%) and elevated NT-proBNP (mean value 2,653 pg/mL). The primary endpoint was the composite of time-to-first HF hospitalization or cardiovascular (CV) mortality. Secondary endpoints included: all-cause mortality, total hospitalization for HF, days alive and not hospitalized for CV reasons, the individual components of the primary endpoint, and adverse events. With a median follow-up of 15 months, primary and secondary endpoints did not significantly differed between the two groups as well as the decreases in NT-proBNP levels, highlighting that in high-risk HF patients an NT-proBNP-guided strategy was not more effective than usual care in improving outcomes. Three important limitations of this trial were: the unblinded nature of the study, the non-study site or non-study clinician dosage of NT-proBNP in the usual care group that may have affected the type and dosage of administered drugs, and the higher number of follow-up visits of enrolled patients as compared with the normal clinical practice. Moreover, the therapy administered to the two groups of HF patients (NT-proBNP guided or controls) seemed to be quite similar, demonstrating a great attention by clinicians in treating according to the Guidelines (GLs) (93% of patients in both groups treated with beta-blockers, 77% with ACE-inhibitors and 50% treated with mineralcorticoid antagonist). In fact, the plasma level of NT-proBNP was similar in the NT-proBNP guided therapy *vs* usual care group at 12-month control, demonstrating that, independently to the knowledge of value of natriuretic peptide (NP), clinicians aimed to obtain the maximum dosage of anti-HF active drugs.

Other trials evaluated the role of natriuretic peptides and HF home monitoring to drive pharmacological therapy. The meta-analysis of Troughton *et al.* (5) based on 11 studies and including 2,000 HF patients, demonstrated a survival benefit from a NP-guided therapy only in younger (less then 75 years) (P=0.004) patients and not in older ones

(P=0.96). On the other hand, hospitalization due to HF was significantly lower (P=0.009) in patients followed with a NP-guided strategy. Based on these results, the neutral effect of the NP-guided obtained in the Felker's experience (4) (study concluded for futility) seemed to be quite disappointing and demonstrated than a close follow-up and an adequate therapy according to the GLs might be enough for treating adequately those patients.

Elderly patients with congestive heart failure (CHF) represent most of subjects (70%) admitted to hospitals for acute cardiac decompensation; the length of hospitalization lasts usually >2 weeks in geriatric wards and readmission is frequent (6). Recently, the OPTIMIZE–HF study (7) included more than 30,000 CHF patients discharged from 215 hospitals, described the short length of hospitalization (4 days) but a 21.3% of rate of readmission within 30-day. This study (7) evidenced as an early (one-week) outpatient clinical follow-up after discharged had lower probability to be readmitted within 30-day. In the IN-HF Outcome, an Italian nationwide registry, the 30-day mortality after discharging for an acute episode of HF proved to be 2.8% and hospital readmission 6.2% (8). Older age, longer in hospital stay, the necessity of inotrope use, worsening New York heart Association (NYHA) class identified HF patients discharged home who are at highest risk of death or readmission.

According to the huge number of HF patients discharged from our hospital, easy and practical prognostic parameters able to predict adverse outcome are mandatory in order to allocate correctly our resources and established tailoring specific follow-up (9). The bet for the future would be probably to stratify correctly our HF patients before discharging and decide a strict ambulatory follow-up treating them with the maximal tolerated drugs independently to NP-guided therapy, utilizing NPs for diagnosing/preventing acute decompensation of HF.

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