# B-type natriuretic peptide-guided treatment for heart failure: is the GUIDE-IT trail the end of the road?

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In the last decades major advancements in the treatment of chronic heart failure (HF) have led to a significant reduction of mortality and morbidity. Optimized medical therapy, appropriate use of implantable device, like automatic implantable cardioverter defibrillators (AICD) or cardiac resynchronization therapy (CRT), and implementation of disease-management programmes, focused on tailored follow-up, patient education and counselling about appropriate style of life, account for this progress.

Despite these encouraging results, mortality and morbidity due to HF remain a major burden to patients and national health systems.

Neurohormonal control trough angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blocker (ARB), beta-blockers (BB) and mineral corticoid antagonist (MRA) is pivotal to improve survival in HF patients. Guidelines from major scientific societies (1,2) recommend that medical therapies should be up-titrated to achieve target or maximum tolerated doses, according to the design and the results of the major randomized clinical trials performed in the past years.

However, some unmet needs in treatment of HF-patients remain to be satisfied.

In real life clinical practice many patients are untreated or receive doses lower that those recommended (3).

Tailored, precision medicine, guided by pathophysiological targets, could optimize medical therapy in HF patients; biomarkers could help to identify patients who may benefit from more aggressive treatment, avoiding, on the other hand, over-treatment of other patients.

Since its discovery in the 1981 (4), natriuretic peptide (NP) system raised physician's interest for possible clinical applications.

Assay of Brain NP (BNP) or N-terminal pro-B-type NP (NT-proBNP) is a useful tool for the diagnosis of acute dyspnoea in emergencies department and HF in the community (5-6). Furthermore, NPs are powerful predictive variables in both acute and chronic HF (7-9).

According to American Heart Association (AHA)/ American College of Cardiology (ACC) guidelines, measurement of BNP or NT-proBNP is useful to support clinical decision making regarding the diagnosis of HF, and for establishing prognosis or disease severity in chronic and/or acutely decompensated HF, with an IIa class recommendation (1).

More recently, NPs system offered a target for innovative pharmacological treatment, by the blockade of neprilysin, the enzyme involved in NPs degradation, with the outstanding clinical results reported in the PARADIGM trial (10).

In the 2000 the first prospective study exploring the possibility of using NPs for guiding HF treatment was published (11). Patients randomized to NP-guided treatment had better clinical outcome in comparison with control group. However, only a little percentage of study subjects had an optimal neurohormonal blockade, due to inadequate use of BB and MRA.

Following studies explored the possibility of optimizing medical therapy, targeting pharmacological dosing to prespecified NP concentration, with conflicting results (12-14). While in some studies this approach demonstrated a benefit

in reducing mortality or mobility, no advantage was found in other studies; in some studies, a benefit was found only in younger patients.

Meta-analyses were successively published. One of the largest, published by Savarese (15) including twelve trials enrolling 2,686 participants, reported a significant reduction of HF-related hospitalization and mortality with NT-proBNP guided therapy.

Similar result was found in Troughton's meta-analysis (16), and however, limited the benefit of NP-guide therapy to patients younger than 75 years old. Comorbidities may explain the lower efficacy of this approach in elderly patients (17).

Eventually a Cochrane library systematic review concluded that "*low quality evidence showed a reduction of HF-hospitalization, and uncertain in the effect of NP—guided treatment for all-cause mortality or HF mortality*" (18).

On the whole, these evidences lead AHA/ACC guidelines to establish for BNP- or NT-proBNP guided HF therapy a class IIa (level of evidence B) recommendation for outpatients, and a class IIb recommendation for acutely decompensated HF patients (1).

European Society of Cardiology guidelines did not provide class of recommendation, but underscored the uncertain of the advantage of a NP-guided treatment (2).

So, further high quality clinical trials were required to provide stronger evidence about the clinical utility of tailoring therapy according to NP-levels.

The recently published GUIDE-It trial (19) is a randomized multicentre clinical trial, designed to evaluate the safety, efficacy, and cost-effectiveness of a strategy of adjusting therapy with the goal of achieving and maintaining a target NT-proBNP level of <1,000 pg/mL compared with usual care in high-risk patients with HF and reduced ejection fraction.

Eighty hundred and ninety-four patients were enrolled at 45 sites and randomized to receive biomarker therapy or usual care. Suggested intervention for reaching target levels of NT-proBNP were up-titration of medical therapy, increase of loop diuretic, prescription of digoxin, rate control for atrial fibrillation, optimization of CRT, exercise programme or repeated HF education regarding diet, sodium restriction.

Above all, investigators were encouraged to prioritize titration of neurohormonal antagonist over diuretics.

After a median follow-up of 15 months, when about 50% of planned primary end points events had occurred, the study was discontinued due to lack of evidence for the biomarker guided treatment in comparison with usual care. None significant difference was found for primary composite end point of first hospitalization for HF or death from cardiovascular cause (37% in both groups).

What are the reasons for this disappointing result?

Guidelines advice to up-titrate neurohormonal blockade therapy to the target dose; this approach guarantee the best outcome for HF patients. Unfortunately, only a small percentage of patients achieve maximum doses, especially in the real-life setting. ACEi/ARB therapy, betablockers or MRA may not reach the target dose due to adverse effects, like hypotension, worsening renal function and hyperkalaemia. Oldest and more compromised HF patients are frequently intolerant to medium/high doses of medical therapy.

In a NP-guided approach, poor tolerance to medical therapy may display before the predefined value of NP is reached, limiting the efficacy of this strategy.

Indeed, in the GUIDE-IT trial there were no significant differences in the percentage of patients reaching the target dose of BB, ACE/ARB and MRA, between the two groups that were comparable even for loop diuretic mean doses.

The achieved dosing of pivotal medical therapy was less in this study in comparison with previous reports; maybe because the trial recruited high risk patients, with elevated NPs and a HF hospitalization within the prior 12 months.

Interestingly in the NP-guided group, the target value of NT-proBNP less than 1,000 pg/mL was reached only by the 46% of enrolled patients, and was not statistically different from that of usual group (40%). Furthermore several factors can affect BNP level including age, gender, renal function, body mass, and the presence of atrial fibrillation. Whether these factors impact on the efficacy of NP-guided HF care is uncertain and requires further analysis.

In conclusion guidelines-driven approach remains the standard way to pursuit the target dose of life-savings drugs in HF patients.

The primary outcome of the study was a composite of time to first hospitalization or death from cardiovascular causes. However there are other outcomes, like improvement in functional capacity and quality of life (QoL), that are relevant for patients, but that were neglected by study authors. So, we don't know the impact of NP-guided therapy on these alternative end-points. There are alternative approaches in the use of NPs for clinical decision making for HF that deserve further investigations.

A different strategy is to use NT-proBNP to identify high risk patients for more intensive therapies or for prolonged specialized HF programme. This approach has been used in the North Star trial (20), but did not show

any advantage in term of mortality and hospitalization reductions.

Future studies should evaluate if allocation of patients to advanced therapies, driven by NPs measurements (or by multivariable risk scores including NPs measurements), could improve the clinical outcome.

A further strategy for the possible use of NP in clinical decision making is given by the availability of sacubitril/valsartan that in the PARADIGM trial (10) has been associated to a significant reduction of composite end-point in comparison to enalapril.

The increase of BNP and the concomitant reduction of proBNP levels are marker that could identify patients responding to therapy, allowing to select those who benefit from neprilysin inhibition.

Despite the result of GUIDE-IT trial, the path of tailoring medical decision according to clinical, plasmatic and instrumental biomarker should not be left.

Recently, the CHAMPION trial (21) demonstrated that pulmonary artery pressure (measured by remote monitoring of implantable device) guided management of patients with HF was able to reduce morbidity and mortality. A significant increase of ACEi/ARB, betablockers and vasodilators agents (nitrate and hydralazine) was observed in the treatment group, recalling the relevance of treating both neurohormonal and hemodynamic derangements in HF (22).

Among biomarker that have shown to be of prognostic value in HF, soluble sST2 (associated to inflammation, fibrosis and cardiac remodelling) and Galectin-3 (marker of fibrosis and extracellular matrix remodelling) are the most promising. However, there is lack of evidence that this prognostic value could translate into improved clinical decision making. Large prospective trials are needed to clarify this point, beside the cost-effectiveness of a biomarker guided treatment strategy.

Awaiting further studies, maximum effort should be spent in order to achieve guideline directed target dosing of therapies, being the percentage of patients, in which this result is obtained, the best process-of-care measure for disease management programmes for HF.

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