Use of Natriuretic Peptides as a Guidance for Treating Patients with Chronic Heart Failure: Unresolved Issues and Novel Insights

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Abstract: Serial measurements of natriuretic peptides (NPs), i.e. B-type natriuretic peptide (BNP) or amino-terminal fragment of pro B-type natriuretic peptide (NT-pro BNP), may serve as an objective guide to modulate the intensity of drug treatment for individuals with chronic heart failure (CHF). However, considerable uncertainty remains about the alleged useful role of NP-guided therapy in this context. Particularly, which NP level should be assumed as optimal target level for therapy is still matter of debate. Actually, a too low predetermined cut off is encumbered with the risk of inducing a dose escalation perhaps not founded on solid rationale but provided with the potential of propitiating adverse medication effects that may be associated with higher doses. Conversely, a too high predetermined level for NP would entail a poor sensitivity, with the potential of excluding from higher doses of medications, that are proven to increase survival, just the patients who above all would have benefitted from this uptitration. Another much debated issue is constituted by possible age-related differences concerning the effects on clinical endpoints of NP-guided therapy. In addition, some Authors dispute about the possible advantages for the cardiovascular system arising from the functional activation of NPs in CHF patients, so denying that their increased levels have to be per se blamed for hemodynamic upheaval, especially in elder CHF patients.

After outlining the main RCTs carried out so far, the Authors stress the above reported issues and discuss the sometime contradictory results of the RCTs exploring NPs use as a guidance for therapy.

Keywords: B-type natriuretic peptides, natriuretic peptide-guided therapy, expert clinical assessment, chronic heart failure.

NATRIURETIC PEPTIDES AND HEART FAILURE: GENERAL CONCEPTS

Based on well-established cognitions of cardiovascular physiopathology, it is ascertained that in the setting of volume expansion or pressure overload, as typically found in heart failure, the resulting wall stress promotes synthesis of pre-pro- B-type natriuretic peptide (pre-pro- BNP) in the ventricular myocardium [1]. After synthesis, the peptide is cleaved first to proBNP, then to the biologically active B-type natriuretic peptide (BNP) and the inactive fragment, aminoterminal (NT) – proBNP (Figure **1**). The release of BNP induces improved myocardial relaxation and plays an important regulatory role in response to acute increases in ventricular volume by antagonizing the vasoconstriction, sodium retention, and antidiuretic effects of the activated renin–angiotensin– aldosterone system (RAAS) [2].

The identification of a threshold value of circulating natriuretic peptide, whose possible finding will prompt the physician to intensify the therapy even in the case of clinically stable chronic heart insufficiency, has been in recent years one of the paths more explored by clinical researchers in the cardiovascular field [3-5].

However, some difficulties have arisen during the attempts at achieving this objective. Actually both biologically active (BNP) and inactive (NTpro BNP) fractions have been shown to tend to rather wandering fluctuations in the blood. This high biological variability of natriuretic peptide (NP) levels, as evidenced by its changes unrelated to clinical alterations in cardiovascular status [6], has compromised the plans of those who were thinking to be able to easily codify or modulate the therapeutic behavior depending on variations of plasma NP concentrations. Also still at present state a consensus was not reached about the prognostic value and therapeutic implications to be attributed to changes (increases or decreases) in NP concentrations even for those regarded as statistically significant (i.e. > 25% from baseline) (5-6). Inter-pretation of NP levels requires an understanding of the variability of these peptides. As a result of both analytical and biological variabilities, reference change values (RCV) have been reported to be large for both BNP and NT-proBNP, varying from 40–130% [7-9]. Furthermore, in the opinion of several Authors [8], only large variations in the concentrations of these peptides should be believed to really mirror parallel variations in the clinical status. In fact, the biological significance of changes in concentrations less than 50% would be modest, because it was found inconsistently associated with detectable haemodynamic and clinical alterations worthy of change of therapy (dose adjustment of the

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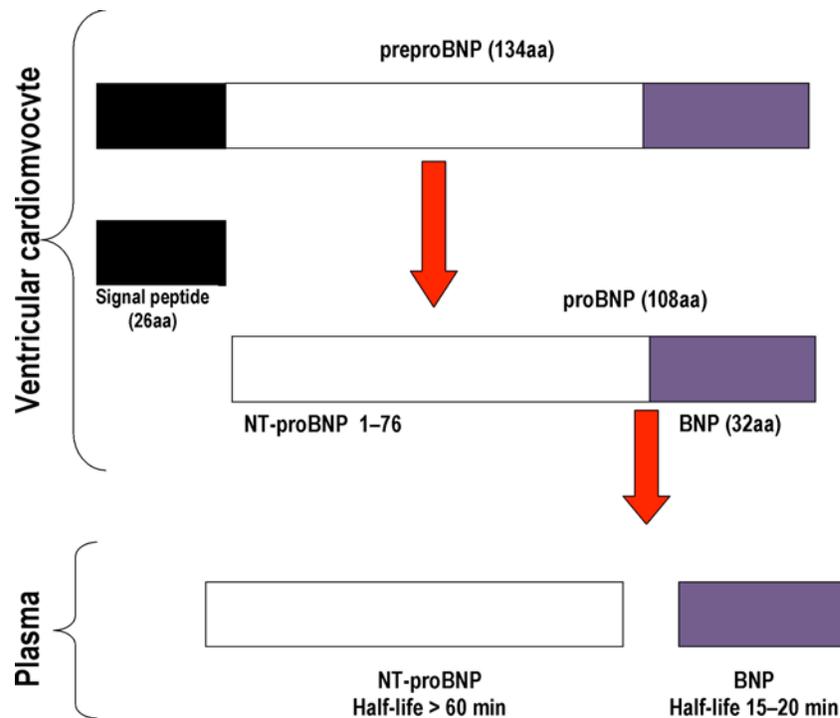
Figure 1: Schematic representation of BNP production and secretion.

diuretic, shift to more intense schemes of neuro humoral blockade by introduction of higher doses etc.) For instance, in the study by Miller *et al*. [10], where the prespecified cut point of 500 pg/ml for BNP was chosen, BNP increases from less than to more than the cutpoint of 500 pg/ml were associated with increased risk of events; on the contrary, only substantial natriuretic peptide decreases (>80%) reduced risk. Thus the Authors argue that only robust decreases in natriuretic peptide concentrations should be targeted to reduce mortality and heart failure– related hospitalizations.

When a change in a NP level is not accompanied by a change in clinical status, this might reflect biological variability or a change in cardiac or renal function that has not yet resulted in symptoms or signs. In the second case, for example, an increase in hormone level may announce in advance possible upcoming worsening of hemodynamic and clinical picture. However, there is also the possibility that through the massive recruitment of NP effects, the cardiovascular apparatus is able to realize a counterbalance -albeit transient - against vasoconstrictor and sodium-retentive systems known to be hyper-activated in acutely decompensated heart failure (ADHF). Therefore, in the case of rise in hormone levels that tends to remain over time, a subsequent clinical deterioration or a static condition of hemodynamic equilibrium can arise; the latter would be reached because functional status of NP system in advanced CHF is usually involved by a kind of "reset" towards higher levels of tonic secretory activity. In other words, in some patients with heart failure a hemodynamic balance would be painstakingly achieved only at the cost of a massive release of natriuretic peptides [5, 11]. Thus, in these patients the hemodynamic overload would be lightened and the pump function would be improved thanks to the marked activation of the natriuretic peptides. This would result in acceptable levels of pulmonary capillary wedge pressure (≤ 18 mm Hg) as well as of central venous pressure (≤ 10 mmHg), able to prevent the onset of pulmonary congestion, or the development of marked systemic venous stasis with related peripheral edema, respectively. Conversely, in other patients (probably the majority of patients), the counterbalance exerted by the natriuretic peptide system would fail: in this subset of patients, the high circulating levels of these hormones should be simply interpreted as a biohumoral index of hemodynamic imbalance that has generated a massive but ineffective counter-regulatory reaction.

The randomized controlled trials that have dealt with B-type natriuretic peptides as a guidance for treating heart failure: a brief outline

Several trials have broached the issue of NP-guided therapy in outpatients with CHF (Table **1**).

Table 1:   Study Design Overview for Included Trials

Studies	Troughton	STARS-BNP	TIME-CHF	Berger	BATTLESCARRED	PRIMA	SIGNAL-HF	STARBRITE	PROTECT
N°	69	220	499	278	364	345	252	137	151
Marker used	NT-proBNP	BNP	NT-proBNP	NT-proBNP	NT-proBNP	NT-proBNP	NT-proBNP	BNP	NT-proBNP
Length of follow up (months)	9.6	15	18	12	36	23.4 (IQR:16.3-24.3)	9	3	10
Primary end point	Death + cardiovascular hospitalization +outpatient heart failure event	Heart failure death + heart failure hospitalization	Death + all cause hospitalization	Death + HF-related rehospitalization	All-cause mortality	Days alive outside the hospital	Days alive and out of hospital + symptom score from the Kansas City Cardiomyopathy Questionnaire	Days alive outside the hospital	Total cardiovascular events (a composite outcome consisting of worsening HF, hospitalization for ADHF, clinically significant ventricular arrhythmia, acute coronary syndrome, cerebral ischemia, and cardiac death).
Target BNP/NT-Pro-BNP–Guided therapy	NT-pro-BNP level < 200 pmol/L (1692 pg/ml)	BNP<100 pg/ml	NT-proBNP < 400 pg/ml if age< 75 y, NT-proBNP < 800 pg/ml if age ≥75 y	NT-pro-BNP < 2200 pg/ml)	NT-pro-BNP < 150 pmol/L (1270 pg/ml)	Individual NT-pro-BNP target (lowest level during the first 2 weeks after treatment of HF) together with clinical assessment	At least a 50% reduction from baseline NT-proBNP was to be achieved, even if not indicated by the patient's clinical symptoms and signs.	BNP<2 x hospital discharge	NT-pro-BNP ≤ 1000 pg/ml
Target Control Group	Heart failure score* < 2 (based on Framingham criteria)	Based on PE +usual paraclinical + biological parameters	NYHA class ≤ II	Based on PE by primary care physicians (usual care arm)or by clinical expert assessment by HF specialists (multidisciplinary care)	Heart failure score* < 2 (based on Framingham criteria)	Clinical assessment	Clinical symptoms and signs	Congestion score calculated at the time of discharge	Clinical symptoms and signs
Age (y, mean)	70	66	77	71	76	72	78	59(IQR:50-70)	80.3 (3.9) if age is ≥75 y 57.6(11.2)if age is <75 y
Gender (% male)	76%	64%	66%	65%	62%	58%	71%	70%	84%
basal LVEF mean (SD) unless (%)	NP 28 / C 26	29.9(7.7) / 31.8(8.4)	29.8(7.7) / 29.7(7.9)	<40 / <40	37 / 37	31 / 35	<50 / <50	20(IQR:15-25) / 20(IQR:15-25)	31 if age ≥75 y 23 if age <75 y (median values) / 33 if age ≥ 75 y 27 if age <75 y (median values)

Abbreviations: BNP: type natriuretic peptide; **NT-pro-BNP:** amino-terminal fragment of pro-BNP; **IQR:** interquartile range; **PE:** physical examination; **NYHA:** New York Heart Association. **HF:** heart failure. **NP:** Natriuretic peptide-guided group; **C:** control group; **LVEF:** left ventricular ejection fraction; **SD:** standard deviation *Heart failure score based on Framingham data for diagnosis of HF with major criteria each scoring 1 point and minor criteria each scoring 0.5 point.

The main features and results of these trials are outlined as follows. This brief description is addressed to summarize several data concerning year reported, number of patients, patient age, type of biomarker used (whether BNP or NT-pro BNP), length of follow up, NP target values for BNP- or NT-Pro-BNP–guided therapies, clinical and/or hematochemical targets for clinically-guided therapy, primary and secondary end points for every selected study. However, it does not provide enough data about ethnicity or gender difference within each study or in the comparison between studies. This is a limitation for the generalizability of the reported findings.

In The Christchurch New Zealand pilot trial [12] by Troughton and coworkers, outpatients with symptomatic CHF (NYHA class II-IV) and impaired systolic function (left ventricular ejection fraction <40%) were randomized to two therapeutic strategies guided either by NT-proBNP levels or by a clinical score based on signs and symptoms of CHF. In the peptide – driven arm, the programmed target consisted in achieving a plasma NT-proBNP level < 200 pmol/L (1692 pg/ml). At the end of the study (median follow-up 9.6 months), the incidence of the composite primary end point of cardiovascular death, hospitalization, or outpatient heart failure event was significantly decreased in the group where therapy was driven by NT-proBNP periodic measurements compared with the group guided by clinical expert judgement (19 versus 54 events, P = 0.02). Thus, this study sparked great interest in a natriuretic peptide-guided approach to HF management and paved the way for subsequent trials.

In STARS-BNP trial [13], 220 participants with LVEF <45% and NYHA class II or III were randomly assigned to standard care (according to established guidelines) or standard care plus BNP reduction to <100 pg /ml. During a median follow-up of 15 months, the BNP-guided strategy was characterized by larger than 50% reduction in the incidence of HF-related death or hospitalization when compared with clinically-guided care (24% vs 52%, p <0.001). The mean doses of ACE inhibitors and β-blockers were significantly higher in the BNP group compared with the symptom-guided group, whereas the mean rise in furosemide dose did not significantly differ when comparing the two treatment arms during the first 3 months after randomization. Even though mean BNP levels were significantly decreased in the BNP-guided arm, only 33% of participants in the trial achieved their target BNP value of <100 pg/ml.

Despite the Christchurch and STARS-BNP trials gained promising results, some of the subsequent studies have not proven such a clear advantage from a natriuretic peptide-guided strategy for HF management.

Patients enrolled in the Battlescarred trial [14] were randomly assigned to one of three treatment arms— usual care, intensive clinical management, or NT-proBNP-guided strategy. After 12 months of follow-up, all-cause mortality was curtailed by 50% in patients assigned to intensive clinical care or NT-proBNP-guided strategy (P = 0.028 for both), when compared with usual care. After 2 and 3 years of follow-up, however, the two intensive therapeutical approaches were no longer significantly better than usual care in terms of mortality. In patients aged ≤ 75 years, mortality was consistently lower in the NT-proBNP-guided group after 1, 2, and 3 years follow up, as compared with the usual-care arm. There was no statistically significant benefit with any strategy in patients aged >75 years. In conclusion, although a trend toward fewer adverse events was noticed with NT-proBNP-guided therapy, there was no clear advantage with this approach compared to intensive clinical management.

The investigators of TIME-CHF trial [15], enrolled a total of 499 patients with symptomatic HF (NYHA class II–IV) plus a history of HF hospitalization during the previous year and randomized them to NT-proBNP-guided strategy or a clinically-guided care. For patients in the Nt-proBNP-guided arm, the predefined peptide target to be reached and/or kept during follow-up depended on age, since the study design provided for a NT-proBNP level <400 pg/ml to be applied to patients aged <75 years, while it prescribed a level of < 800 pg/ml for patients ≥75 years. On the contrary, in clinically-guided arm the researchers were instructed to simply up titrate therapy to reduce symptoms to the NYHA class I or II.

The composite endpoint of death plus hospitalization from all causes as well as the one of quality of life were chosen as primary end points, to be explored during a mean follow up of 18 months. Survival free of all-cause hospitalization did not significantly differ between the two groups (HR 0.91, 95% CI: 0.72–1.14, p = 0.39). Similarly, even though quality of life improved significantly from baseline in both arms, a statistically significant difference was not reached when comparing the two treatment arms.

Notably, an apparent interaction between patient age and the benefit of a BNP-guided strategy was noticed, as evidenced by the fact that NT-proBNP-guided strategy was found associated with a remarkable non significant trend towards the increase in proportion of patients alive and free from hospitalization (primary composite endpoint) only in patients younger than 75 years. Of note,the relative fall in NT-proBNP levels after 6 months was similar between treatment arms. Therefore, in despite of greater intensification of therapies in the NT-proBNP-guided arm, the decrease in its plasma level did not significantly differ between groups. Accordingly, the relation between prognosis and a reduction in NP concentration might not be as strong as previously thought and importantly, NP concentration might not always decrease in response to therapy intensification.

Berger and coworkers [16] randomized the 278 patients enrolled in their study to three arms: NT pro–BNP–guided intensive management (BM), multidisciplinary care and usual care. Multidisciplinary care included 2 consultations from an HF specialist who provided therapeutic recommendations and home care by a specialized HF nurse. In addition, BM included intensified up-titration of medication by HF specialists in high-risk patients. A total of 278 patients were randomized. After 12 months, NT pro–BNP–guided regimen reduced days of HF hospitalization (488 days) compared with the hospitalization for the multidisciplinary care (1,254 days) and usual care (1,588 days) groups (p <0.0001; significant differences among all groups). Moreover, the sum of deaths or HF rehospitalizations (primary combined end point of the study) was significantly lower in the NT pro–BNP–guided arm than in the two other groups considered in the study. So, in CHF patients after ADHF-related hospitalization, a significant improvement of clinical outcome was proven to be induced by NTproBNP – guided approach.

In the PRIMA study [17] 345 patients previously hospitalized for HF were enrolled if they had been shown to have elevated NT-proBNP levels (≥1,700 pg/ml) at hospital admission and if they had developed, during hospitalization, a fall in the value of NTproBNP > 10% of the value corresponding to the first measurement taken at admission, and equal to 850 pg / ml at least. All of the CHF patients with these features were randomly assigned to undergo NT-proBNP-guided or symptom- guided therapy. In the NP arm, an individualized target was chosen, corresponding to the lowest level of NT-proBNP in each individual patient, identified at discharge or during the 2 subsequent weeks, whichever value was lower. During follow-up (median 23 months)the number of days that patients were alive and free from hospitalization(primary composite end point) did not significantly differ between treatment arms (685 vs 664, p = 0.49). In PRIMA trial, alterations in pharmacologic dosing during follow up were more frequent in NTpro BNP-guided compared to clinically-guided arm in the case of loop diuretics, ACE-inhibitors and angiotensin receptor blockers; on the contrary, the doses of beta-blockers and ARAs were not more frequently modified (up- or down-titration) in NTpro BNP-guided arm. The predefined, individualized NT-proBNP target level was achieved in 80% of patients in the NT-proBNP arm, far more than in the STARS-BNP or the TIME-CHF trials, which had used a common NP target for all participants. However, this might have depended on remarkably high NP target concentration, such as that used as individualized reference within the NP-guided group of the PRIMA study.

In SIGNAL-HF trial [18] 252 patients were randomized to two arms, of whom the former followed up with NT-proBNP periodical measurements and the latter whose patients did not undergo NT-proBNP monitoring. All of the patients were treated with loop diuretics plus evidence-based drugs for CHF according to recommended guidelines. The eligibility criteria were CHF in NYHA class II–IV, left ventricular ejection fraction (EF) <50% and elevated NT-proBNP levels (>800 pg/ml for males and >1000 pg/ml for females). The primary outcome variable was the composite endpoint of days alive outside the hospital, and symptom score from the Kansas City Cardiomyopathy Questionnaire. Treatment doses of beta-blockers and blockers of the renin–angiotensin–aldosterone system were markedly increased towards target doses and to a similar extent in both groups. There were no differences between the two arms regarding either the primary endpoint (p = 0.28) or its components (cardiovascular death, p = 0.93; cardiovascular hospitalization, p = 0.88; or symptom score, p = 0.28). So, based on the SIGNAL-HF findings, NT-proBNP-guided treatment appears to not entail important improvements in clinical outcomes in patients with CHF in primary care above and beyond what could be achieved by education and structured CHF treatment according to guidelines.

The investigators of the STARBRITE trial [19] enrolled 130 patients with systolic dysfunction (LVEF
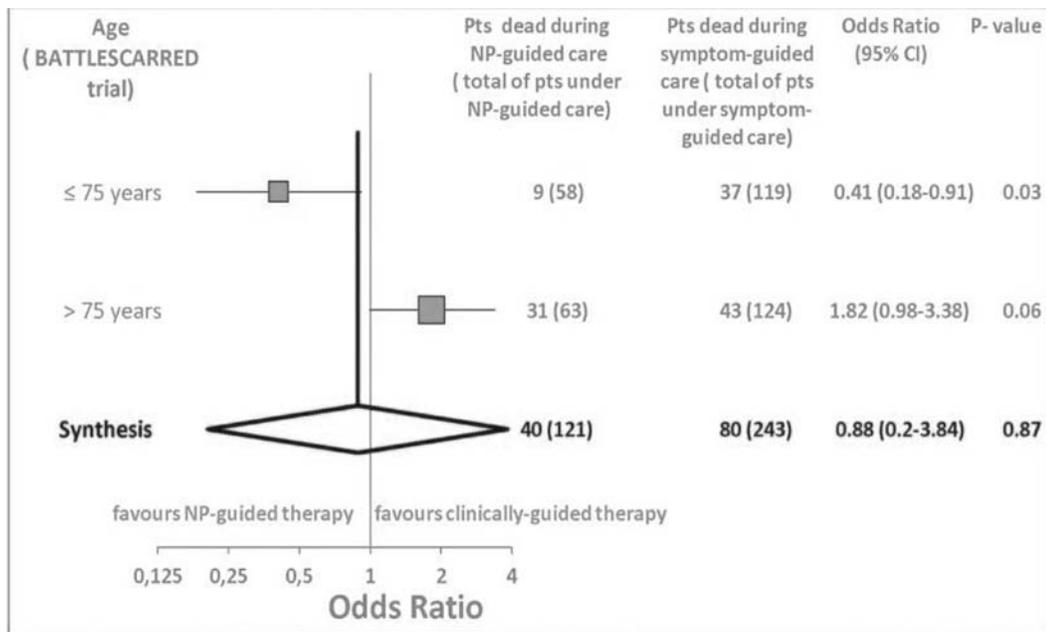
≤35%) and symptomatic HF (NYHA class III–IV). They were randomly assigned to therapy guided by symptoms versus that guided by BNP levels. For patients in the BNP-guided arm, clinicians were instructed to titrate diuretics to attain as their target a BNP level less than twice the value obtained at the time of hospital discharge or an alternate BNP target if believed appropriate by the clinician. For patients in the clinically-guided arm, the goal to be pursued was a value of congestion score equal to that calculated at the time of hospital discharge. After 90 days of follow-up, patients randomly assigned to the BNP-guided arm showed a non significant trend towards longer hospitalization-free survival (hazard ratio : 0.72, 95% CI 0.41–1.25, *p* = 0.25).

The PROTECT study [20] included 151 patients with HF resulting from left ventricular systolic dysfunction by randomizing them to two distinct treatments: HF treatment clinically guided or guided by NT-proBNP values (with a goal to lower NT-proBNP below 1000 pg/ml) during a follow up period of 10 months. The primary end point was total cardiovascular events in 2 age categories (<75 and ≥75 years). Elderly patients treated with clinically-guided management had the highest rate of cardiovascular events, whereas the elderly with NT-proBNP management had the lowest rate of cardiovascular events (1.76 events per patient versus 0.71 events per patient, p =0.03); the adjusted logistic odds for cardiovascular events related to NT-proBNP- guided care for elders (n° 38 pts) was 0.24 (p =0.008), whereas in those <75 years (n° 113), the adjusted logistic odds for events following NT-proBNP-guided care was 0.61 (*p*= 0.10). Thus, this study documented that NP-guided care induced in elders a substantial improvement in cardiovascular event rates. So, this study overtly contradicts the findings of previous studies, such as TIME-CHF and BATTLESCARRED, which found significant improvement in clinical outcomes exclusively involving younger patients (aged<75 years) undergoing NP-guided strategy.
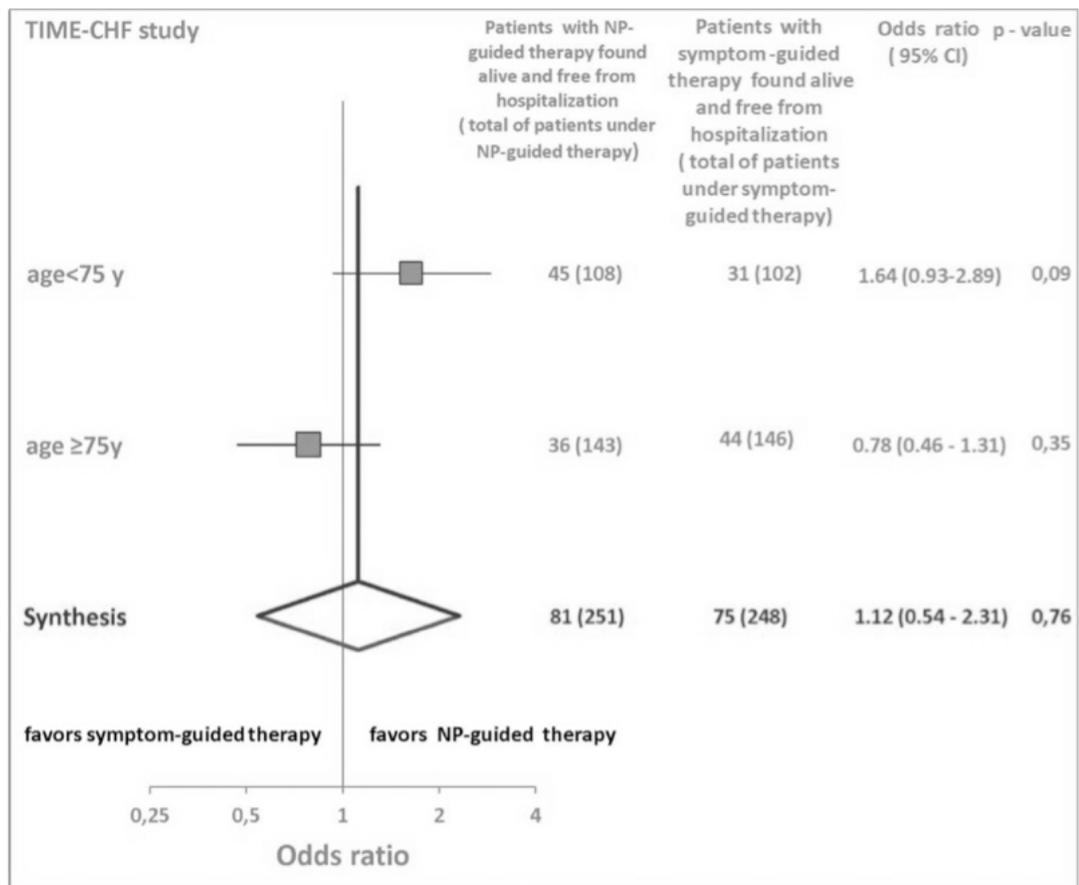
The age as an effect modifier of the relationship between clinical outcome and treatment of chronic heart failure guided by measurements of B-Type natriuretic peptide: contradictory results of the randomized controlled trials

The issue of the possible age-related differences concerning the effects of therapy B-type natriuretic peptide-guided has been extensively treated. It appears to be characterized by rather conflicting interpretations. Indeed, in some studies [14-15] there

are arguments in favor of greater effectiveness and safety of the NP-driven approach in the younger patient's category (that consisting of patients aged less than 75 years); in the same studies this finding is accompanied by concomitant evidence that the effectiveness of treatment in older patients (those aged more than 75 years) is indistinguishable from that obtained with conventional clinical criteria. On the contrary, other Authors have documented the favorable effect of NT pro BNP-guided therapy on clinical outcomes even in elder patients (aged more than 75 years) [20]. As regards the argument that advanced age would be an effect modifier, able to induce a disappearance or reversal of the favorable relation between clinical outcome and pharmacologic approach led by plasma BNP determinations, the data that support this thesis come mainly from BATTLESCARRED [14] and TIME-CHF [15] studies. In the following figures there are the forest plots depicting the data pertaining to the clinical primary and secondary endpoints, which were considered by these studies. In BATTLESCARRED study the interaction due to the advanced age is more pronounced since it appears to involve the primary endpoint represented by mortality (Figure **2**). On the contrary, in TIME-CHF trial as regards the effects on clinical outcomes by NP-guided strategy (Figures **3-5**), age-related differences have been reported to involve two secondary clinical endpoints, namely overall survival and probability of HF –related hospitalization during follow up (Figures **4-5**); whereas in the same trial the proportion of patients found alive and free from hospitalization at the end of 18 month follow-up (primary composite endpoint) has been shown to not differ in NP-guided vs. clinically guided arm in both age categories (namely in both CHF patients aged < 75 years and those aged ≥ 75 years) (Figure **3**). Indeed, a single-center randomized controlled trial has been recently published that contradicts and disclaims in full the results of the two trials cited above (20). Based on the results of this study, just in older patients (ie those aged ≥ 75 years) the programmed benefit related to natriuretic peptide-guided approach is clearly and significantly detectable (Figure **6**). In this study, the Authors assumed for NTpro BNP a "target" value of 1000 pg / ml, which is intermediate between the value adopted in the BATTLESCARRED trial (1270 pg / ml) and the maximum value (applying to elderly patients ≥ 75 years) chosen by TIME-CHF study (800 pg / ml). As primary clinical end point the mean number of cardiovascular events per patient during a follow-up of 10 months was selected. A sharp refutation of the

Age (BATTLESCARRED trial)		Pts dead during NP-guided care (total of pts under NP-guided care)	Pts dead during symptom-guided care (total of pts under symptom-guided care)	Odds Ratio (95% CI)	P-value
≤ 75 years		9 (58)	37 (119)	0.41 (0.18-0.91)	0.03
> 75 years		31 (63)	43 (124)	1.82 (0.98-3.38)	0.06
Synthesis		40 (121)	80 (243)	0.88 (0.2-3.84)	0.87

favours NP-guided therapy   favours clinically-guided therapy

0,125   0,25   0,5   1   2   4

Odds Ratio

Figure 2: Forest plot of Odds Ratios which appraises the effect of NP-guided therapy on mortality in patients aged ≤ 75 years compared with that found in patients older than 75 years. Notably, the protective effect by BNP-guided therapy in younger patients is reversed in patients aged >75 years. The data have been drawn from the BATTLESCARRED study [14].

TIME-CHF study		Patients with NP-guided therapy found alive and free from hospitalization (total of patients under NP-guided therapy)	Patients with symptom-guided therapy found alive and free from hospitalization (total of patients under symptom-guided therapy)	Odds ratio (95% CI)	p-value
age<75 y		45 (108)	31 (102)	1.64 (0.93-2.89)	0,09
age ≥75y		36 (143)	44 (146)	0.78 (0.46 - 1.31)	0,35
Synthesis		81 (251)	75 (248)	1.12 (0.54 - 2.31)	0,76

favors symptom-guided therapy   favors NP-guided therapy

0,25   0,5   1   2   4

Odds ratio

Figure 3: Forest plot of Odds Ratios evaluating the effect of NP-guided therapy on the number of patients alive and free from hospitalization during follow up (primary composite end point of the study) in the subgroup of patients aged <75 years compared to that consisting of patients aged ≥ 75 years. No significant differences were found as regards this clinical outcome in NP-guided arm compared to that assigned to clinically-guided therapy in both age categories. The data have been drawn from the TIME-CHF study [15].

results previously obtained by BATTLESCARRED and TIME- CHF studies can be inferred from PROTECT study. Various reasons have been proposed to explain the discrepancies with the two previous studies mentioned above. First, in contrast to PROTECT, where the magnitude of NT-proBNP-lowering in elders treated with biomarker guided care was considerable, neither the TIME-CHF or BATTLESCARRED studies appeared to achieve significant natriuretic peptide lowering in older subjects. Thus, it is reasonable to assert that in older patients care guided by NT-proBNP concentrations in the course of HF management may be effective if NT-proBNP-lowering below a threshold of risk occurs; the therapeutic approach to achieve this goal may need to be modified in elders in order to be successful [21]. Secondly,in PROTECT, older patients were seen more frequently, underscoring the importance of more gradual and careful drug therapy titration in this vulnerable patient subgroup. Additionally, the BATTLESCARRED study included HF patients with preserved LVEF. To date, no therapies have been conclusively proven to improve outcomes in HF with preserved LVEF and it remains unclear if biomarker -guided therapy will benefit this challenging patient population. In conclusion, the strong benefit of

NT-proBNP-guided HF management for older patients in this study paralleled successful lowering of the biomarker, which likely explains the finding. Reconsideration of assumptions that the older HF patient cannot benefit from this novel approach for HF care is necessary.

Conflicting interpretations of the elevated levels of NTproBNP. What is the most suitable cut-off level, if any, to be used as a target value during NP-guided approach for heart failure treatment?

Conflicting opinions are reported in the literature concerning the rationale for using NPs as an aid or a guidance for identifying optimal pharmacologic dosages in CHF outpatients. In particular, there is no general agreement about the reference values to be taken in account to determine in patient with already diagnosed CHF whether the current therapy deserves to be intensified on the basis of a NTpro BNP value judged to be off target - even in the presence of stable and / or not perceptibly altered cardiovascular status compared to the previous clinical evaluation [5]. Similarly, a cut-off value for elevation from baseline of plasma NP concentration (as a percentage) indicating the need to trigger an increase in daily oral diuretic
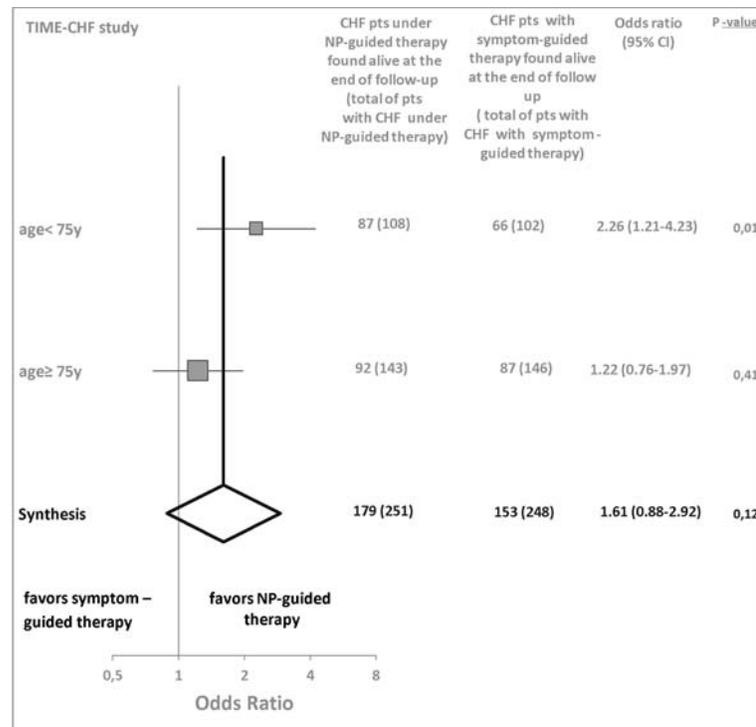
Figure 4: Forest plot of Odds Ratios evaluating the effects of NP –guided therapy on the overall survival (proportion of CHF patients who were found alive after 18 months of follow up) in the subset of patients aged <75 years compared to that composed of patients aged ≥ 75 years.Significantly higher Odds of survival was detected in patients treated with NP-guided approach belonging to the relatively young category (<75 years): OR=2.26 95% CI:1.21-4.23 p=0.01. On the contrary, no significant advantage for NP-guided approach was identified in the layer of older patients (aged ≥ 75 years). The data have been drawn from the TIME-CHF study [15].
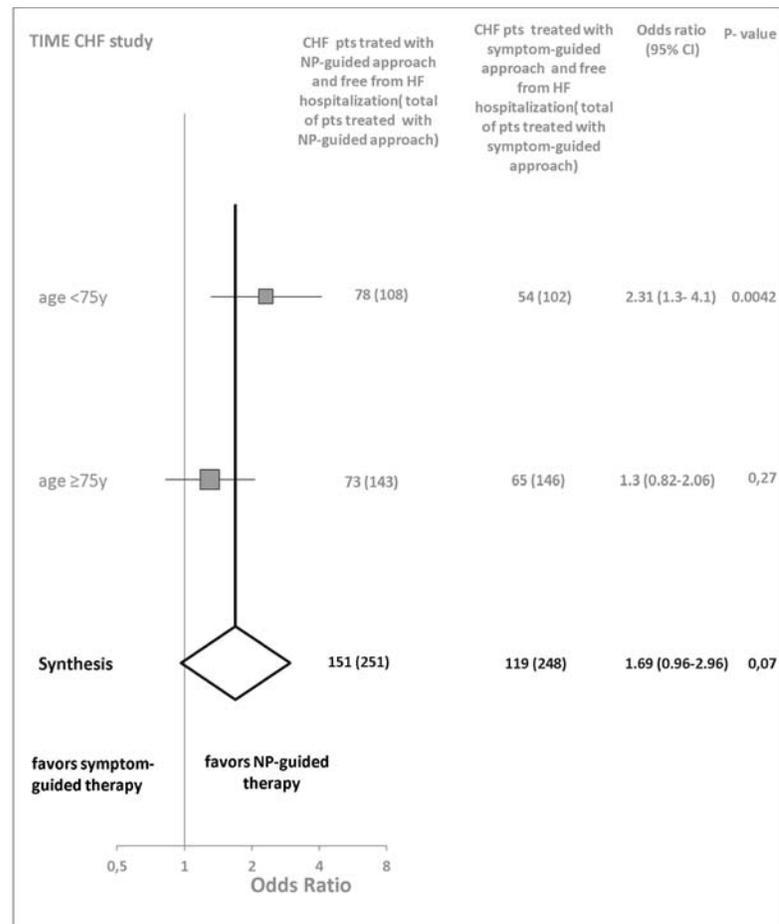
Figure 5: Forest plot of Odds Ratios evaluating the effects of NP –guided therapy on the HF hospitalization (proportion of CHF patients who were found free from hospitalization due to HF after 18 months of follow up) in the subset of patients aged <75 years compared to that composed of patients aged ≥ 75 years. Significantly higher Odds of freedom from hospitalization HF-related was detected in patients treated with NP-guided approach belonging to the relatively young category (<75 years): OR=2.31 95% CI:1.3-4.1 p=0.0042. On the contrary, no significant advantage for NP-guided approach was identified in the layer of older patients (aged ≥ 75 years). The data have been drawn from the TIME- CHF study [15].

dose, has never been defined clearly [22]. The still prevailing uncertainty about the NTpro BNP reference values that should be assumed in the management of CHF outpatients is evidenced by the lack of uniformity of the target values for NTproBNP which is seen by comparing the studies that have explored the effectiveness and safety of a peptide-guided approach (Table **1**). Indeed, there are studies that seem to affirm the feasibility of treatment protocols built depending on well-defined NP threshold- values [13, 14], which are sometimes broken down by age group [15]. Other studies [17-18] seem to want to exclude a specific predefined threshold value that applies to all patients with heart failure: the case of the trial PRIMA [17]. In this study, the target peptide concentration that has to be kept or to be achieved is defined by the lowest NTproBNP value, found in a stage of optimal presumed volume status - so- called optivolaemic or "dry" NP level [5] namely the relatively low NP value detected at

previous hospital discharge or during the two subsequent weeks. Indeed, some distinctive traits of the PRIMA study have been questioned [22]. Firstly, some objections have been raised about the criterion chosen for eligibility. Actually, the study provided for a NT-proBNP level of ≥1700 pg / ml in patients hospitalized for ADHF ("acute decompensated heart failure"), (that is a level higher than those adopted by other previous biomarker-guided studies), which should have been associated, during hospitalization, to a fall in the value of NTproBNP > 10% of the value corresponding to the first measurement taken at admission, and equal to 850 pg / ml at least (a requirement not prescribed by the previous studies). Then at discharge patients with this dynamics of plasma NP concentration during hospitalization were randomized to an arm using natriuretic peptide-guided strategy and another arm whose therapy was established in accordance with the conventional clinical

criteria. The choice of an individualized target (corresponding to the lowest level of NT-proBNP, identified at discharge) in the PRIMA has been strongly criticized because of the alleged lack of sensitivity of the cut-off calculated in this manner. The most common objection against the study design has consisted in criticizing the fact that the authors adopt as their NTpro BNP target level an unreasonably high concentration of peptide [20, 22]. Actually In the arm whose care was driven by NTpro BNP periodic determinations the median value was 2491 pg/ml, a value that differs greatly from the target values set out in other previous studies, which had adopted a fixed threshold (1692 pg / ml in the study of Troughton [12], 1270 pg / ml in BATTLESCARRED [14], 400 and 800 pg / ml -respectively in pts with age <75 and ≥ 75 years- in TIME CHF study [15]). In this manner the occasions in which an increase in the doses could have been prescribed were reduced compared to other trials using a predefined fixed target of NTpro BNP. The consequence of this approach is that the NTproBNP elevation (>850 pg / ml) needed to trigger an increase in the doses of diuretics or RAAS inhibitors would have implied the achievement of a concentration of 3341 pg / ml at least (2491+850 pg/ml) for half of the cohort, a level that is nearly 3 × higher than required in the biomarker-guided arm of BATTLESCARRED trial and between 4× and 8× higher than age stratified targets in TIME-CHF.
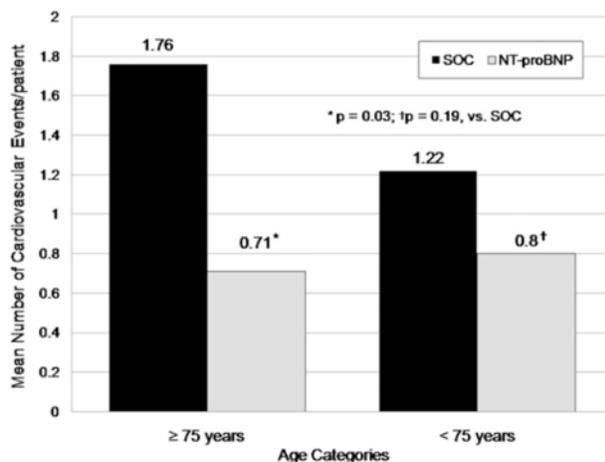
Figure 6: Number of cardiovascular events as a function of treatment allocation and age. Significantly fewer cardiovascular events were seen in the elderly patients treated with N-terminal pro-B type natriuretic peptide (NT-proBNP) guided care. SOC, standard of Care (reproduced with permission from Gaggin HK, *et al.* Heart failure outcomes and benefits of NT-proBNP-guided management in the elderly: results from the prospective, randomized ProBNP outpatient tailored chronic heart failure Therapy (PROTECT) Study. J Card Fail. 2012 Aug; 18(8): 626-34).

As a result, for many patients, this feature of the PRIMA study design may have further limited the opportunity to apply the treatment strategy, possibly diluting its effect. Actually, this study failed to demonstrate improvement in clinical outcomes, especially in specific primary endpoint represented by the number of days alive outside the hospital.

Thus in the opinion of the advocates of peptide-guided therapy, application of an absolute BNP or NT-proBNP level would be more appropriate compared to an individualized target, such as employed by PRIMA. The question of what target levels are to be pursued for NTpro BNP in CHF outpatient could perhaps be answered by data of observational studies, but this issue is controversial and deserves further basic and clinical research in the future.

The advantages for the cardiovascular system arising from functional activation of the natriuretic peptides in CHF patient: beyond the role of simple bystanders

According to several Authors [23] heart failure is consistently characterized by increased expression of the BNP mRNA in both the atrial and ventricle and increased plasma concentration of immunoreactive BNP. In some patients, BNP plays an important role in maintaining cardiorenal homeostasis in symptomatic left ventricular dysfunction resulting in preservation of sodium and water balance despite left ventricular dysfunction [11]. However, in severe symptomatic HF,there is sodium and water retention associated with increased systemic vascular resistance and high cardiac filling pressures despite an extremely high plasma concentration of immunoreactive BNP [11]. This may happen because an hormone-resistance might occur at this stage. Previous study [24] has reported that 2 major molecular forms of BNP are present in the plasma of patients with HF, a high molecular weight (HMW) form and low molecular weight (LMW) form. It has been demonstrated that the HMW form is the pro-BNP hormone and the LMW form is the active BNP 1-32 [24]. Importantly, using reverse-phase HPLC, very little detectable BNP 1-32 from the LMW fraction was found from some CHF patients [24]. Supporting these findings, Hawkridge et al. [25] failed to detect BNP 1-32, with mass spectroscopy techniques in plasma from patients with severe HF and high levels of immunoreactive BNP as measured by the Triage point of care assay (Biosite Inc., San Diego, California). Thus, based on these data and on other studies as well [26], it has been hypothesized that HF

is a state of relative deficiency of active BNP 1-32, thus accounting partially for the discrepancy between the high immunoreactive BNP levels and the lack of biological activity in severe HF. Moreover, according to some Authors, abnormal processing of pro BNP into less active forms may also factor into the state of relative BNP insufficiency [27]. However, it has to be pointed out that all of these studies used plasma from patients with New York Heart Association functional class IV severe HF and, therefore, cannot be extrapolated to all patients with HF. Further studies are needed to determine the molecular forms of BNP in patients with less severe HF, especially those with left ventricular dysfunction that do not have any symptoms (stage B HF). Both human severe HF and animal models of severe HF are characterized by an attenuated biological response to endogenous and exogenous natriuretic peptides [28]. Indeed, it has been suggested that the diminished response to the cardiac natriuretic peptides (so –called resistance to the NPs) play an important role in the pathophysiology of sodium retention and systemic and renal vasoconstriction observed in severe HF, thus contributing to disease progression [28-30].

As regards resistance to the action of both endogenous and exogenous NPs, Miller *et al.* [30] report the possibility of minimal or very slight reductions in NTpro BNP level after infusion of nesiritide, a synthetic analogue of BNP, even in the presence of clinical improvement. In this study, the circulating cGMP increased as a result of the stimulus with nesiritide. Moreover, all of the patients were deemed sufficiently improved to be discharged; but in most patients, NT-proBNP concentrations did not decrease substantially during nesiritide infusion, although statistically absolute values were lower at 24 h of infusion. The reason for NT-proBNP and BNP not consistently responding to nesiritide therapy is unclear. It has also been reported that conjoint congestive heart failure and renal dysfunction induce marked increases in the NTproBNP signal [31-32]. It may be as well that these patients were so ill that their response to therapy, although clinically beneficial, may have left many patients with substantially increased concentrations of NT-proBNP as a way of maintaining hemodynamic compensation. This might be expected more to occur in patients with chronic heart failure that is acutely exacerbated because there is very little storage of BNP and persistently elevated NP plasma concentrations are likely to be generated by even slight increases in myocardial wall strain [33]. Of interest, the mortality in

the subsequent 10 month posthospital follow-up was the same in the patients who were infusion responders (i.e. those who showed decrease in NTproBNP level during iv nesiritide infusion) and nonresponders, lending support to the concept that in very ill patients the inability to maintain high natriuretic peptide concentrations may be an adverse prognostic indicator as well [34].

Difficulties in the evaluation of trials with NT pro BNP- guided pharmacologic regimens: inconstancy in pursuing the achievement of NP target levels, inconsistency with the originally planned study design, lack of homogeneity of the NP target levels and clinical end- points in the comparison between studies.

In some studies, where it had been planned to reduce NP levels below well- defined cut- off values in every patient proven to be "off target "during folllow up, the optimal pre-determined plasma NP concentration was really obtained only in a relatively exiguous percentage, especially in the case of older patients (aged >75 years) [14-15]. Therefore, the disappointing outcome of the peptide-guided approach in the older CHF patients was later attributed by some scholars [20] not to the ineffectiveness of NP-guided strategy, but rather to the failure to follow the programmed study design, for which the investigators should have been more persevering in order to finally reach the NP target - value as originally planned. Nevertheless, these arguments could be easily countered by replying that sometime a frank intolerance to increases in diuretics and vasodilator drugs, evidenced by occurrence of symptomatic hypotension and prerenal hyperazotemia [35], might have prevented the investigators from achieving the predefined target and might have suggested them to avoid making further increases in the doses. Yet, in other cases, even a reduction in GFR, which is a frequent finding in heart failure [5, 36], may have contributed to the persistence of elevated circulating levels of NP by hindering its clearance and / or by propitiating the occurrence of hormone-resistance. By assessing and comparing the RCTs which have addressed the issue whether NP-guided therapy is superior to symptom-guided therapy in management of outpatient with CHF, lack of homogeneity inter-study for both NP-target values and predefined clinical end points is noticed. In addition, even the endpoints adopted in the various studies which have broached the issue of NP-guided therapy are not homogeneous. Actually, a rather striking number of different primary composite endpoints is

noticeable: death + cardiovascular hospitalization +outpatient heart failure event [12], death + HF-related rehospitalization [13, 16], all-cause mortality [14], proportion of patients found alive free from hospitalization [15], days alive outside the hospital [17, 19], days alive and out of hospital + symptom score from the Kansas City Cardiomyopathy Questionnaire [18], total cardiovascular events (a composite outcome consisting of worsening HF, hospitalization for ADHF, clinically significant ventricular arrhythmia, acute coronary syndrome, cerebral ischemia, and cardiac death) [20]. This might have contributed to make difficult and perhaps poorly reliable the meta-analyses made so far about the topic of NP-guided vs. symptom-guided treatment for managing outpatients with CHF [37-38].

CONCLUSIONS

Some strong uncertainties remain about the issue whether NP-guided therapy is able to significantly improve the clinical outcomes of all-cause death and heart failure - related hospitalization, compared with usual clinical care. Moreover, this approach remarkably influences the therapy for outpatients with CHF, by triggering or by propitiating more frequent and intense up-titration of the pharmacologic dosing of various agents for CHF management (especially diuretics and RAAS inhibitors). However, even though the pooling of data derived from the metaanalyses demonstrates an overall effect of slightly significant amelioration in clinical outcomes with NP-guided approach, some large studies remain [14-15, 17] which failed to document significant clinical improvement in terms of mortality and morbidity using NP-guided strategy. Thus, larger and well conducted trials addressed to the unresolved issues of NP- guided therapy are recommended in the future.

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