CONTROVERSY

Natriuretic Peptide-guided Therapy Should be Used in Heart Failure Patients

Agonist

EDUARDO R. PERNA[1]

INTRODUCTION

Chronic heart failure (CHF) therapy is currently at a stage in which strong evidence has derived in numerous guidelines and consensuses where, save exceptions, there is global agreement regarding adequate drug prescription, doses, opportunity and type of patient. (1, 2) However, the transfer of these recommendations to the individual subject is suboptimal. (3) Numerous reasons may explain this situation, including limitations associated to the patients, as well as the predisposition and conviction of the treating physician.

CARDIOMETABOLIC DISEASES AND THE NEED FOR GUIDED THERAPY

The usual management of highly prevalent diseases, as for example cardiometabolic diseases such as hypertension and diabetes, is aided by simple parameters which allow establishing a diagnosis based upon standardized numerical values. These indicators, in turn, become therapeutic targets used to estimate whether the intervention has been appropriate or define its refractoriness, implying the need to step up or titrate the treatment (Table 1). That is, a guided therapy based on therapeutic objectives is routinely applied.

THERAPEUTIC OBJECTIVES IN HEART FAILURE

Conversely, the normal diagnosis of heart failure is based on the concept that it is a clinical syndrome, where myriad signs and symptoms are used to confirm or reject its presence; that is, findings compatible with clinical congestion, leaving aside subclinical hemodynamic congestion. (4) From this perspective, the diagnosis is difficult, with an erratic monitoring that can derive in an erroneous interpretation of a good response to a deficient therapy. Therefore, the availability of a simple tool, as a biomarker (BM), which is measurable and adequately responds to interventions, becomes essential. In this sense, the B-type natriuretic peptide (BNP) and the amino-terminal portion of pro-brain natriuretic peptide (NT-proBNP) are supported for diagnostic purposes with strong recommendation in the most recent guidelines. (1, 2)

As corollary, the use of the same BM to guide therapy is the transfer to CHF of a common practice in other heart diseases. Different methods emerge as possible candidates for this purpose, including noninvasive methods as echocardiography, acoustic cardiography, bioimpedance and thoracic ultrasound, or invasive ones as transthoracic impedance and left atrial or pulmonary artery implantable devices. (4, 5)

REQUIREMENTS TO ACCEPT NATRIURETIC PEPTIDES AS GUIDES

The best known and studied natriuretic peptides (NP) are the atrial natriuretic peptide (ANP), the B-type (BNP) with a fast synthesis and without accumulation, so that its secretion depends on pressure and volume overloading conditions, and some less known peptides as CNP, DNP and urodilatin. (5, 6) Type B natriuretic peptide is released as a much larger molecule, the preproBNP, of 134 aminoacids, which is then cleaved to NT-proBNPType, with 108 aminoacids. At the myocyte level, this separates in BNP, which constitutes the active hormone with vasodilating and natriuretic properties and the amino-terminal portion or NT-proBNP, which is biologically inactive (1, 2, 5, 6)

Their diagnostic value and their role in the prognostic evaluation of different chronic and acute HF scenarios have led to assume that they could be used to guide treatment. This argument, according to expert opinion, should be supported on four principles: NP help to identify patients at risk, the reduction of their levels is associated with clinical improvement, therapies with established benefits in CHF reduce NP levels and their increase helps identify patients who derive more benefit with these interventions. (7) Moreover, an objective value for each patient should be easily defined, establishing therapeutic strategies that allow adjusting their levels and considering that this treatment improves clinical outcome; finally it should provide more benefits than the usual treatment.

Numerous published studies have assessed the value of NP-guided therapy in CHF, the most relevant of which are detailed in Table 2. (8-19)

Natriuretic peptide and risk of heart failure

The value of BNP and NT-proBNP to stratify risk in HF and patients admitted for acute heart failure

Rev Argent Cardiol 2013;81:484-496. http://dx.doi.org/10.7775/rac.v81.i6.3422

[1] Heart Failure and Pulmonary Hypertension Division- Instituto de Cardiología "Juana F. Cabral". Corrientes
e-mail: pernaucic@hotmail.com

Condition	Prevalence	Diagnostic criteria	Therapeutic target
Hypertensiom	33%	Clinic: BP ≥ 140/90 mm Hg ABPM 24 h: BP ≥ 125-130/80 mm Hg SBPM: <BP 130-135/85 mm Hg	BP < 140/90 mm Hg
Diabetes mellitus	8.3%	HbA1c ≥ 6.5% Blood glucose ≥ 126 mg/dl Blood glucose 2 h OGTT ≥ 200 mg/dl	HbA1c < 7.0%
Hypercolesterolemia	13.8%	Total cholesterol ≥ 240 mg/dl	Total cholesterol < 200 mg/dl
	25.3%	LDL cholesterol ≥ 160 mg/dl	LDL cholesterol < 100-130 mg/dl
Heart failure	2.1%	Self-questionnaire Framingham score BNP/NT-proBNP	¿? ¿Congestion?

BP: Blood pressure. ABPM: Ambulatory blood pressure monitoring. SBPM: Self- blood pressure monitoring. HbA1c: Glycosylated Hemoglobin A1c. OGTT: Oral glucose tolerance test.

Table 1. Cardiometabolic diseases, diagnosis and therapeutic target

syndromes (AHFS) has been extensively demonstrated. (5, 6, 20) They have independent prognostic significance and add relevance to other clinical and paraclinical markers with linear correlation between NP and risk.

Modification in natriuretic peptide levels and outcome

Although there are numerous reasons for NP elevation, HF is the major determinant through changes in wall stress and ensuing hemodynamic state. The higher its value, the worse the clinical condition. As increased NP is associated with CHF progression, their reduction is an indicator of improved outcome. In hospitalized patients with AHFS, a favorable outcome was found in patients with NT-proBNP reduction ≥ 30% compared with those without changes or even more than 30% increase. (21) In ambulatory patients, the persistently low or reduced NT-proBNP pattern at four months showed lower event rates compared with constant elevation or increased values. (22)

Effects of therapy on natriuretic peptide levels

Different interventions with favorable effects on CHF have demonstrated reduction of NP levels. (5) Diuretics, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and mineralocorticoid-receptor antagonists (MRA) are among the drugs used. Betablockers have shown a dual effect, with a slight increase at the beginning and posterior reduction. Resynchronization therapy and heart rate control in atrial fibrillation and exercise are among non-pharmacological interventions.

Therapeutic response according to the magnitude of natriuretic peptides

Although the magnitude of NP release is an expression of the seriousness of the disease, there is no consistent evidence favoring the intensity of an intervention based on its levels, and only the interaction between carvedilol and baseline NT-proBNP levels has been reported. It could be dangerous to assume that patients with low levels of these BM do not require maximum dose optimization, so the concept of titration based on clinical tolerance remains intact.

The individualized natriuretic peptide

Even though the cut-off points for BNP (125 pg/ml) and NT-proBNP (1000 pg/ml) under which the prognosis is more favorable have been identified, (5) in an individual case the best value that can be obtained under optimal treatment will depend on various conditions including the seriousness of the heart disorder, associated factors and hemodynamic response. This individualized value, known as “dry” NP should be available for each subject, so that a significant increase in its value allows inferring a risk condition.

The biological change of these BM, that is, the changes in physiological steady state, may reach up to 40% for BNP and 25% for NT-proBNP. A greater modification is considered relevant to identify clinical impairment. A time interval of at least 2 weeks is recommended to attain steady NP levels after an intervention.

ANALYSIS OF AVAILABLE EVIDENCE: CONSISTENCY AND FLAWS

Studies evaluating the efficacy of NP-guided therapy (NPGT) have used various intervention strategies, with different BM and cut-off points, achieving dissimilar impact on the targeted objective (Table 2). (8-19) Therefore, they could be grouped in those with negative or neutral results and those with positive results (Table 3). Moreover, two meta-analyses have assessed the impact of NPGT. The expectations of this strategy are based on looking for answers to different questions we will evaluate in the next section.

Table 2. Study characteristics evaluating natriuretic peptide-guided therapy strategy in heart failure. [Modified from Savarese et al (26)]

Study	N	NP type	Women (%)	Age (years)	Ischemic etiology	HTN (%)	DM (%)	FC	LVEF (%)	ACEI/ARB (%)	BB (%)	MRA (%)	Diuretics (%)	Follow-up (years)
Troughton (8)	69	NT-proBNP	23.2	70.1	73.9	65.2	13.0	2.0	27.0	NA	NA	NA	NA	0.79
Beck-da-Silva (9)	41	BNP	65.9	65.0	41.5	NA	NA	2.5	22.4	NA	NA	NA	NA	0.33
STARS-BNP (10)	220	BNP	42.3	65.5	46.8	NA	NA	2.3	30.9	99.1	98.2	23.2	100	1.25
TIME-CHF (11)	499	NT-proBNP	34.5	76.5	57.5	70.9	34.5	0.0	29.8	94.8	78.6	40.5	93.4	1.5
BATTLESCARRED (12)	364	NT-proBNP	36.0	75.7	59.1	43.7	17.9	2.1	38.7	NA	NA	NA	NA	3.0
SIGNAL-HF (13)	250	NT-proBNP	28.8	77.5	NA	54.8	20.0	2.4	32.0	93.6	77.6	20.0	68.4	0.75
PRIMA (14)	345	NT-proBNP	42.9	72.2	21.2	NA	NA	2.1	35.8	56.5	55.9	18.6	62.3	2.0
Anguita (15)	60	BNP	NA	NA	NA	NA	NA	0.0	NA	NA	NA	NA	NA	1.33
Berger (16)	278	NT-proBNP	35.3	71.3	69.4	72.3	45.0	0.0	NA	NA	NA	NA	NA	1.0
STARBRITE (17)	130	BNP	30.0	61.0	40.8	NA	NA	0.0	20.0	90.8	NA	67.7	93.8	0.5
UPSTEP (18)	279	BNP	27.2	70.9	NA	28.0	31.2	2.8	NA	100.0	93.9	57.0	89.2	1.0
PROTECT (19)	151	NT-proBNP	15.2	63.3	56.3	52.3	41.1	0.0	26.9	81.5	96	41.7	91.4	0.83

HTN: Hypertension. DM: Diabetes mellitus. FC: Functional class (New York Heart Association). LVEF: Left ventricular ejection fraction. ACEI/ARB: Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers. BB: Betablockers. MRA: Mineralocorticoid receptor antagonists.

Natriuretic peptide-guided treatment has a positive impact on therapeutic optimization

All the studies have demonstrated adequate drug titration, not only of diuretics, but specifically ACEI, ARB, betablockers and MRA, with an increase in the rate of use, dose, and attainment of 50% objective dose or maximum dose. It is interesting that although this finding occurred both in the intervention and control arms of some neutral studies (9, 13, 15, 18) it was observed in greater proportion in the NPGT arms, both in neutral studies (11, 12, 14, 17) and positive studies (8, 10, 16, 19) (see Table 3).

In the STARS-BNP study, the group guided by BNP had to change treatment more times than the control group (134 vs. 66 times; $p < 0.05$). (10) In addition, the PROTECT study evidenced that the guided adjust could also include the withdrawal of diuretics. (19) Moreover, in the Berger et al. study, (16) NPGT was better than multidisciplinary intervention and standard care.

Evidence favors natriuretic peptide monitoring of the events associated with heart failure

In the studies, the control arm showed variations from the clinical evaluation of congestion according to the physician´s experience, or adjusted to a score; or there were changes between two arms, where one was submitted to standard management and the other to a multidisciplinary one (see Table 2). The primary end point was also different among studies; in some cases overall events were considered (death and hospitalizations) while in others hospitalizations due to HF and mortality (overall, cardiovascular or for HF) were evaluated.

Four studies showed a positive effect, especially of events associated to HF, with a reduction in the primary end point and its components (see Table 3) (8, 10, 16, 19) This result was not obtained in the studies with neutral effect. However, four meta-analyses communicated consistent and robust reduction of all-cause mortality, with RR 0.738 (95% CI 0.596-0.913) (table 4) (23-26) It is important to point out that an intervention directed to improve the outcome of patients with CHF or after AHFS must show as main positive effect reduced need of hospital admissions associated with the condition, and if feasible, that this decrease translates into decreased mortality. The effect of NPGT has not been shown in overall hospitalizations or in the combined end point with mortality.

According to data of the PROTECT study, it is necessary to treat 1.8 patients to reduce one event and 4.8 to prevent a hospitalization for HF.

The differences can be explained by the variable effect of the intervention

One of the most relevant considerations for NPGT is to evaluate whether the intervention aimed to decrease the BNP/NT-proBNP values has effectively achieved the objective in the active arm, with correlation between the magnitude of change and the study results. This has been clearly observed in positive studies. In the study by Troughton et al., NT-proBNP decreased 34% in the guided therapy group and 1% in the control group at 6 months. (8) In the active arm of the STARS-BNP study, BNP decreased from 352 ± 260 pg/ml in baseline to 284 ± 180 pg/ml at 3 months ($p = 0.03$), with 16% to 33% ($p = 0.04$) increase in the number of patients with values below 100 pg/ml. (10) In the study of Berger et al. the group guided by BNP showed a higher reduction than the multidisciplinary

Study		HFPEF (%)	Target NP concentration	Active arm with < NP at the end	Active arm with different treatments
NEUTRAL	STARBRITE	No	BNP at discharge ≈ 450 pg/ml	No	Yes
	TIME-CHF	No	NT-proBNP < 400 pg/ml (< 75 years) or < 800 (≥ 75 years)	No	Yes
	BATTLESCARRED	Yes	NT-proBNP < 1270 pg/ml	No	Yes
	PRIMA	Yes	Individual NT-proBNP at discharge	No	Yes
	SIGNAL-HF	No	NT-proBNP < 50% on admission	No	No
	Beck-da-Silva	No	BNP < 10% of previous visit	No	No
	Anguita	Yes	BNP < 100 pg/ml	Yes	No
	UPSTEP	No	BNP < 150 ng/L (< 75 years) or < 300 (≥ 75 years)	Unknown	No
POSITIVE	Troughton	No	NT-proBNP 1735 pg/ml	Yes	Yes
	STARS-BNP	No	BNP < 100 pg/ml		Yes
	Berger	No	NT-proBNP < 2200 pg/ml	Yes	Yes
	PROTECT	No	NT-proBNP < 1000 pg/ml	Yes	Yes

HFPEF: Heart failure with preserved ejection fraction.

Table 3. Summary of studies evaluating natriuretic peptide-guided therapy strategy in heart failure. [Modified from Januzzi et al (5)]

group, while with the standard care no differences were found. (16) The PROTECT study indicated that the reduction in the NT-proBNP group was 52% vs. 5.2% in the control group (p = 0.03), with a proportion of 44.3% vs. 35.6% of cases that reached the objective < 1000 pg/ml. (19) Conversely, only one neutral study showed BM reduction in the intervention arm.

Natriuretic peptide guided therapy was also associated with effects on ventricular remodeling. The PROTECT echocardiographic substudy showed that the NT-proBNP-guided group evidenced more increased left ventricular (LV) ejection fraction, with LV end-systolic and diastolic volume improvement. (19) In addition, NPGT treatment has been referred to reduce hospital stay for HF (from 1588 to 488 days; p < 0.001).

Independently of the outcome, all studies have consistently demonstrated that the NP-guided strategy is well tolerated, without excessive adverse events.

Age is not a limitation to implement a natriuretic peptide-guided therapy strategy

One of the major criticisms to NPGT is its role in aging patients. The TIME-CHF study demonstrated a different effect in subjects younger and older than 75 years of age, with benefits in the former and without impact in the latter. These data were later confirmed in meta-analyses, where the composite end point of overall mortality and hospitalization for HF was reduced in younger (OR 0.499; 95% CI 0.207-0.973), but not in >75 year-old patients (OR 0.800; 95% CI 0.423-1,513). (26) However, this analysis was performed only considering three studies (11, 12, 18). In contrast, the PROTECT study showed similar NT-proBNP reduction in old and young patients (47% vs. 45%), in agreement with a favorable effect on ventricular remodeling in both groups.

RESPONDERS TO NATRIURETIC PEPTIDE-GUIDED THERAPY

As in any intervention that implies a cost, responders may help in the rapid selection of candidates with greater expected benefit. In the UPSTED study, responders prospectively defined as those with > 30% decrease at 48 weeks compared with baseline value, represented 60% of cases. (18) In the multivariate analysis for the primary end point of death, hospitalization or CHF worsening, responders presented a significantly lower risk (HR 0.45; 95% CI 0.29-0.70; p< 0.0005), with similar results in the secondary end points.

Recently, a posterior analysis of the PROTECT and BATTLESCARRED studies evaluated the response to guided therapy, defined as NT-proBNP ≤ 1000 pg/ml. (27) Non-responders were older, with a more serious clinical condition, more congestion and worse renal function. The incidence of events was lower in responders, with an even greater benefit when the response was more premature and sustained. Moreover, increased values after a favorable initial response

Table 4. Meta-analysis results evaluating natriuretic peptide-guided therapy vs. standard care

Characteristics	Felker M, et al. 2009 (23)	Parapakkham P, et al. 2010 (24)	Li P, et al. 2013 (25)	Savarese G, et al. 2013 (26)
Patients (studies)	1627 (6)	1726 (8)	2414 (11)	2686 (12)
Mortality	0.69 0.55-0.86	0.76 0.63-0.91 0.003	0.83 0.69-0.99 0.035	0.738 0.596-0.913 0.005
Hospitalization for HF			0.75 0.62-0.91 0.004	0.554 0.399-0.769 0.000
All-cause hospitalization		0.82 0.64-1.05 0.12		0.803 0.629-1.024 0.077
Overall survival free of hospitalization		1.07 0.85-1.34 0.58		

HFPEF: Heart failure with preserved ejection fraction.

identified a group with worse prognosis. Non-response predictors were: NT-proBNP levels of 1000-5000 and > 5000 pg/ml, heart rate < 60 beats/min, functional class III-IV and history of atrial fibrillation, with a validated score system based on these parameters.

These results show that the use of simple tools allows identification of patients who do not respond to HF therapy. When all the attempts to optimize therapy have been tried and NP levels remain elevated, there is a high probability of adverse outcome and these cases should be referred to specialized services in the management of advanced HF.

LIMITATIONS OF NATRIURETIC PEPTIDE-GUIDED THERAPY

In order for NPGT to be effective it is necessary to interpret the different additional information required, including knowledge of the pathophysiology, biological changes, reasons for the response and influence of different circumstances on NP. Furthermore, it is crucial to accept that BNP/NT-proBNP reduction will be the final objective to achieve. Hence, a trained team in the management of CHF is required. Also, cost, especially in our country, is a limitation for its generalized application.

CONCLUSIONS

Chronic heart failure is a prevalent and devastating condition, in which, different to other disorders, available monitoring elements are insufficient. This demands the urgent need of a key and sensitive element to assess the response to treatment. BNP and NT-proBNP have clearly shown their usefulness in the diagnostic and prognostic evaluation of this syndrome. Current evidence suggests that adequate application of a monitoring strategy based on NP levels, in indicated patients, reduces the incidence of events of particular interest in this condition: mortality and hospitalizations for HF. Therefore, natriuretic peptide-guided therapy should be used in patients with heart failure.

Conflicts of interest:
None declared.

REFERENCES

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803-69. http://doi.org/pwr

2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al; ACCF/AHA Task Force Members. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239 http://doi.org/f2mtdx

3. Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the registry to improve the use of evidence-based heart failure therapies in the outpatient setting (Improve HF). Circulation 2010;122:585-96. http://doi.org/ddt775

4. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail 2010;12:423-33. http://doi.org/dwbzs4

5. Januzzi JL Jr. The role of natriuretic peptide testing in guiding chronic heart failure management: review of available data and recommendations for use. Arch Cardiovasc Dis 2012;105:40-50. http://doi.org/fx3f5f

6. Perna ER. Utilidad de los marcadores serológicos en el diagnóstico y estratificación de riesgo de la insuficiencia cardíaca. Insuficiencia Cardíaca 2007;2:55-61.

7. O'Donoghue, M, Braunwald E. Natriuretic peptides in heart failure: should therapy be guided by BNP levels? Nat Rev Cardiol 2010;7:13-20. http://doi.org/b5zsp9

8. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000;355:1126-30. http://doi.org/dzw94w

9. Beck-da-Silva L, de Bold A, Fraser M, Williams K, Haddad H. BNP guided therapy not better than expert's clinical assessment for beta-blocker titration in patients with heart failure. Congest Heart Fail 2005;11:248-53. http://doi.org/c45656

10. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, et al. Plasma brain natriuretic peptide-guided therapy to improve

outcome in heart failure: the STARS-BNP Multicenter Study. J Am Coll Cardiol 2007;49:1733. http://doi.org/c697fg

11. Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIMECHF) randomized trial. JAMA 2009;301:383-92. http://doi.org/d9xz2f

12. Lainchbury JG, Troughton RW, Strangman KM, Frampton CM, Pilbrow A, Yandle TG, et al. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. J Am Coll Cardiol 2009;55:53-60. http://doi.org/c73k3g

13. Persson H, Erntell H, Eriksson B, Johansson G, Swedberg K, Dahlström U. Improved pharmacological therapy of chronic heart failure in primary care: a randomized study of NT-proBNP Guided Management of Heart Failure–SIGNAL-HF (Swedish Intervention study– Guidelines and NT-proBNP AnaLysis in Heart Failure). Eur J Heart Fail 2010;12:1300-8. http://doi.org/dq3xmc

14. Eurlings LW, van Pol PE, Kok WE, van Wijk S, Lodewijks-van der Bolt C, Balk AH, et al. Management of chronic heart failure guided by individual N-terminal pro-B-type natriuretic peptide targets: results of the PRIMA (Can PRo-brain natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study. J Am Coll Cardiol 2010;56:2090-100. http://doi.org/b6twkz

15. Anguita M, Esteban F, Castillo JC, Mazuelos F, López-Granados A, Arizón JM, et al. Usefulness of brain natriuretic peptide levels, as compared with usual clinical control, for the treatment monitoring of patients with heart failure. Med Clin (Barc) 2010;135:435-40. http://doi.org/csnb63

16. Berger R, Moertl D, Peter S, Ahmadi R, Huelsmann M, Yamuti S, Wagner B, et al. N-terminal pro-B-type natriuretic peptide-guided, intensive patient management in addition to multidisciplinary care in chronic heart failure a 3-arm, prospective, randomized pilot study. J Am Coll Cardiol 2010;55:645-53. http://doi.org/csnb63

17. Shah MR, Califf RM, Nohria A, Bhapkar M, Bowers M, Mancini DM, et al. The STARBRITE trial: a randomized, pilot study of B-type natriuretic peptide guided therapy in patients with advanced heart failure. J Card Fail 2011;17:613-21. http://doi.org/chsgjk

18. Karlström P, Alehagen U, Boman K, Dahlström U; UPSTEP-study group. Brain natriuretic peptide-guided treatment does not improve morbidity and mortality in extensively treated patients with chronic heart failure: responders to treatment have a significantly better outcome. Eur J Heart Fail 2011;13:1096-103. http://doi.org/dnv6c2

19. Januzzi JL Jr, Rehman SU, Mohammed AA, Bhardwaj A, Barajas L, Barajas J, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. J Am Coll Cardiol 2011;58:1881-9. http://doi.org/fv49bd

20. Masson S, Latini R, Anand IS, Vago T, Angelici L, Barlera S, et al. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. Clin Chem 2006;52:1528-38. http://doi.org/chqhx3

21. Bettencourt P, Azevedo A, Pimenta J, Friões F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004;110:2168-74. http://doi.org/bthgt5

22. Masson S, Latini R, Anand IS, Barlera S, Angelici L, Vago T, Tognoni G, et al. Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). J Am Coll Cardiol 2008;52:997-1003. http://doi.org/dmn6xf

23. Felker GM, Hasselblad V, Hernandez AF, O'Connor CM. Biomarker guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials. Am Heart J 2009;158:422-30. http://doi.org/df7r64

24. Porapakkham P , Porapakkham P, Zimmet H, Billah B, Krum H. B-Type natriuretic peptide-guided heart failure therapy. A meta-analysis. Arch Intern Med 2010;170:507-14. http://doi.org/bscq4t

25. Li P, Luo Y, Chen YM. B-type natriuretic peptide-guided chronic heart failure therapy: A meta-analysis of 11 randomised controlled trials. Heart Lung Circ 2013 Apr 17. [Epub ahead of print] http://doi.org/pws

26. Savarese G, Trimarco B, Dellegrottaglie S, Prastaro M, Gambardella F, Rengo G, et al. Natriuretic peptide-guided therapy in chronic heart failure: a meta-analysis of 2,686 patients in 12 randomized trials. PLoS One 2013;8:e58287. Epub 2013 Mar 5. http://doi.org/pwt

27. Gaggin HK, Truong QA, Rehman SU, Mohammed AA, Bhardwaj A, Parks KA, et al. Characterization and prediction of natriuretic peptide "nonresponse" during heart failure management: Results from the ProBNP Outpatient Tailored Chronic Heart Failure (PROTECT) and the NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) Study. Congest Heart Fail 2013;19:135-42. http://doi.org/pwv

Antagonist

JORGE THIERER[MTSAC]

Let us start at the end. Two recent meta-analyses confirm that NP-guided therapy improves the prognosis of HF. The meta-analysis of Li et al. (1) on 11 randomized studies shows 17% reduction in overall mortality (RR 0.83, 95% CI 0.69-0.99) and 35% in hospital readmission due to HF (RR 0.65, 95% CI 0.50-0.84). The meta-analysis of Savarese et al. (2) on 12 randomized studies arrived to similar conclusions: OR 0.74, 95% CI 0.60-0.91 for overall mortality and OR 0.55, 95% CI 0.40-0.77 for hospital readmission due to HF.

A priori, it seems hard to oppose the meta-analysis conclusions, which all the clinical practice guidelines consider as the highest level of evidence. In this sense, the Heart Failure European Guideline 2012 (3) establishes a class IIa, level of evidence C indication for natriuretic peptide dosage to facilitate differential diagnosis and help prognosis. However, it does not assign the peptide-guided therapy a defined indication, claiming that it is uncertain that it is better to simply follow the guidelines. The publication of the European Guideline is prior to the mentioned meta-analyses, though the most recent AHA-ACC Guideline (4) establishes a class I, level of evidence A for this practice.

Nonetheless, we are going to introduce a series of arguments regarding the significance of natriuretic peptides in the context of heart failure, with the design of the studies cited in the meta-analyses, and in general, with the idea of a biomarker-guided therapy, to assert that the subject is far from being closed, and that lot of water still has to flow under the bridge before adopting this strategy.

NATRIURETIC PEPTIDES AND HEART FAILURE

Natriuretic peptides appear as the surrogate end point of the seriousness of heart failure and as prognostic markers. (5)

[MTSAC] Full Member of the Argentine Society of Cardiology

a) Relationship with filling pressures

The worse the left ventricular echocardiographic parameters, the higher the natriuretic peptides: the worse the left ventricular ejection fraction, (LVEF), the higher the BNP elevation. (6) The strongest relationship is between end-diastolic wall stress and peptide level. Elevated peptides are a strong marker of increased left ventricular end-diastolic wall stress. (7) Conversely, the relationship with left ventricular filling pressures is less clear. Although higher peptide levels are found with higher filling pressures, the diagnostic certainty is lower. Why? Because several factors participate in peptide secretion: BNP is not only released by the left ventricle, but is also influenced by atrial and right ventricular secretion as well as geometry. Thus, a single value is not reliable, and a negative predictive value is very important. (8) If BNP is low, filling pressures will hardly be increased. If BNP is elevated, filling pressures may be high, but we do not know how much because of the influence of the above-mentioned factors and others we will examine in the next section. Thus, if a patient has a known cardiomyopathy, probably the echo-Doppler will be better than BNP to estimate pressures. In patients without history of heart disease, with no cardiomyopathy and in whom no right atrial or ventricular abnormality might be assumed a priori, BNP could be preferred as an initial method of screening to assume elevated filling pressures. (9)

b) Diagnostic usefulness: correlation with the clinic

The diagnostic usefulness of peptide measurement was strongly supported by the publication of the BNP study (10) in 1586 patients presenting at emergency services with dyspnea. Median BNP was significantly different in heart failure patients compared to those with ventricular dysfunction without heart failure and mainly with respect to those with dyspnea of different origin. Moreover, the BNP levels were significantly different according to the patients' typical functional class. For the diagnosis of heart failure, the area under the Framingham criteria ROC curve was 0.75 and for BNP it was 0.91.

The PRIDE study, (11) with a study design similar to the BNP study, used NT-proBNP measured in 599 patients who consulted at emergency services for dyspnea. A point of interest is the cut-off value suggested by study results: patients with a value > 900 pg/ml almost certainly suffer from heart failure, while patients with NT-proBNP < 300 pg/ml hardly present the disease. There is a grey area between 300 and 900 pg/ml in which the diagnostic ability of NT-proBNP is lower. (12) Furthermore, the cut-off value considered to make the diagnosis changes with age. In patients < 50 years the cut-off value was 450 pg/ml and in those >50 years it was 900 pg/ml. Also, it was later established that if the patient is > 75 years, the optimal cut-off value is 1800 pg/ml. (13) This means that at the moment of considering the diagnostic NT-proBNP value, and hence of decision-making, age has to be taken into account since the cut-off value changes. This study also explored the correlation between NT-proBNP and clinical judgment. Clinical judgment presented an area under the ROC curve of 0.90 while that of NT-proBNP was slightly enhanced, with a value of 0.94. The combination of clinical judgment and NT-proBNP resulted in an area under the ROC curve of 0.96. Therefore, in this study, NT-proBNP alone or associated with clinical judgment seemed superior to clinical judgment alone. However, the differences were not so marked as in the BNP study: the use of natriuretic peptide for diagnosis, even in subjects who had consulted for dyspnea at emergency services, scarcely improved the diagnostic benefit. Thus, it should be considered whether it is justified to measure it in all patients or only in those who pose doubts. Conversely, in the IMPROVE study, (14) NT-proBNP was superior to clinical judgment alone. The areas under the ROC curve for NT-proBNP and clinical judgment were similar. The combined use of clinical judgment and NT-proBNP was, effectively, better than clinical judgment alone.

Beyond the context of emergency consultation, it is worthwhile to consider its usefulness for the diagnosis of heart failure in patients with a non-acute condition. In a Dutch study (15) 721 ambulatory patients who consulted for a condition suggestive of heart failure underwent interrogation, physical examination, ECG, spirometry, laboratory tests and NT-proBNP dosage. The end point was diagnosis of heart failure. A model considering interrogation data and physical examination attained an area under the ROC curve of 0.83. The addition of ECG elevated the area under the ROC curve to 0.84 and with chest X-ray it reached 0.85. If NT-proBNP was incorporated into the model, the area under the ROC curve increased to 0.86. This shows that among all complementary studies, natriuretic peptide dosage offers the greatest diagnostic gain, though we consider that the scarce difference in the area under the ROC curve again brings into the open the fundamental significance of interrogation and physical examination.

c) Clinical significance: conditions affecting elevated values beyond heart failure

The higher the NT-proBNP values, the greater the prevalence of cardiovascular disease. (16) However, it may also be easier to make the diagnosis of heart failure simply by clinical judgment when the prevalence of cardiovascular disease is higher and the patient is sicker.

In the Olmsted County study, BNP and NT-proBNP were measured in 1869 subjects > 45 years without apparent illness. (17) The aim was to determine the accuracy of diagnosing the presence of LVEF ≤ 40% and LVEF ≤ 50%. NT-proBNP had > 85 % sensitivity and specificity to diagnose LVEF ≤ 40 %, but its accuracy for diagnosing LVEF ≤ 50 % was lower. The di-

agnostic yield was higher in men than in women with LVEF ≤ 40% or LVEF ≤ 50%. This explains another point: not only age but also gender are involved in the degree of diagnostic certainty of natriuretic peptides. In the general population the stronger determinants of NT-proBNP values were age, responsible for nearly 30% of the difference, left atrial volume, responsible for 7.7% difference and female gender responsible for just over 7% variation. The most important determinants and their specific weight were similar in healthy and sick subjects, also influenced by renal function and body mass index. The higher the body mass index and obesity, the lower the BNP and NT-proBNP values. All these data should be taken into account when deciding whether a single value of NT-proBNP is abnormal in our patient.

Furthermore, natriuretic peptides not only vary depending on heart failure. (18) Natriuretic peptides mainly express pressure and volume overload and are strongly correlated with wall stress. It can then be understood that different valve and heart diseases may increase BNP and NT-proBNP levels. In patients suffering from chronic atrial fibrillation with atrial dilation, these values are high. Anemia can be linked to elevated concentration of natriuretic peptides, either because it generates ischemia or because it is associated with volume overload. Different critical illnesses, sepsis and burns generate BNP and NT-proBNP elevation, probably because there is myocardial depression. Values also rise in stroke and pulmonary vascular disease. Therefore when a patient comes to emergency services with dyspnea and elevated BNP values, diagnosis may be heart failure, but also lung embolism or decompensated chronic obstructive pulmonary disease, with increased right ventricular wall stress. Finally, it is known that BNP and NT-proBNP are higher in patients with renal impairment due to reduced clearance. (19) However, patients with renal failure often have risk factors for developing heart failure. Even in the context of renal dysfunction, elevated NT-proBNP or BNP have prognostic value.

To conclude: we should not forget biological variability, for which we can only consider variations over 25% for NT-proBNP and 40% for BNP as clinically significant. (20)

d) Conclusions

The marked elevation of natriuretic peptides generally indicates heart failure, and this is indisputable. Much more so is the fact that low values exclude heart failure. As described, age, gender, weight, cardiac and noncardiac conditions and testing variability influence the individual value in a given patient. Finally, generalized measurement in all patients, apparently does not add much to a thorough interrogation and clinical examination for the presence of heart failure. In the next section we will discuss whether analyzing any of the peptides is useful to adopt actions that improve the prognosis.

GUIDED THERAPY STUDIES

According to results, studies have been divided into positive and neutral (21)

a) Positive Studies

There are four positive studies, all in patients with low LVEF and a fixed target of BNP reduction

Troughton et al.'s pioneering study, (22) included patients with LVEF <40 %, FC II-IV, in post hospitalization or outpatient follow-up, treated with angiotensin converting enzyme inhibitors (ACEI) and diuretics with or without digoxin. In the clinically-guided group (n = 36) the target was to achieve a Framingham score < 2, and in the peptide-guided group (n = 33) the target was to achieve a value of NT-proBNP < 200 pmol/L (1735 pg / mL). The primary end point was hospitalization or death from cardiovascular causes. After a median follow-up of 9.5 months, the peptide-guided group presented a significant reduction in the incidence of cardiovascular events (19 vs. 54) and a tendency to lower mortality (1 vs. 7). What were the differences in treatment that can account for these results? The NT-proBNP group received a significantly higher final dose of ACEI (mean 20.1 mg vs. 14.3 mg daily) and a strong tendency to higher doses of furosemide and additional visits. The NT-proBNP value decreased 79 pmol/L in the BNP group and only 3 pmol/L in the control group. However, some remarks can be made: There was a certain initial imbalance (patients in the BNP group were four years younger, their LVEF was slightly higher and their NT-proBNP value was lower), the number of patients included was low and, above all, the study was performed prior to the widespread use of beta-blockers.

The STARS-BNP (23) study included 220 patients with FC II-III, and LVEF ≤ 45%, who were stable in the last month, randomized to BNP-guided treatment (with the aim of achieving a value < 100 pg./mL) or to clinically-guided treatment without BNP measurement. The primary end point was hospitalization or death for heart failure. At follow-up there was no significant difference in the increase of furosemide administration, but there was a significant difference in the dose of ACEI (an increase of 94% to 98% of the recommended dose in the control group and of 94% to 106% in the BNP group) and of beta blockers (an increase of 57% to 67% in the control group and of 56% to 77% in the BNP group). There were also more changes for all drugs in the BNP group. At a median follow-up of 15 months, the primary end point was attained by 24% of patients in the BNP group versus 52% in the control group. There was no difference in all-cause death or hospitalization. In the peptide-guided group, the BNP drop was 352-284 pg/mL, with 33% of patients reaching a BNP < 100 pg / mL at 3 months.

Among the controversial points, we can mention that only 22% of patients initiated the study receiving aldosterone. What would have happened in case of a

more widespread use? Regarding medication changes in the first 3 months, there were 134 changes in the BNP group compared to 75 in the clinical control group. However, only 28 out of 134 changes in the BNP group were attributed to clinical reasons. Why? If the groups were comparable, it would be expected that the number of changes for clinical reasons was similar in both groups. In the control group the event rate related to heart failure was 27% at 6 months. It seems to be a higher than expected value. Mean heart rate at baseline was close to 70 beats/min; was it necessary to measure BNP to raise the beta-blocker?

The Berger et al study (24) included patients hospitalized for heart failure with cardiomegaly on chest X-ray or LVEF <40 %, who were randomly assigned to three groups: a) standard care, b) multidisciplinary care, with the intervention of a specialized nurse at 1, 3, 6 and 12 months and visit to a specialist in heart failure at 10 days and 2 months, with additional visits if necessary, c) peptide -guided treatment , where if NT-proBNP was > 2200 pg/ml, monitoring by a specialist every 2 weeks was established, for up to 3 or 6 months if necessary. At a minimum follow-up of 12 months, there were more visits and higher doses of beta blockers and renin-angiotensin system antagonists were administered in the b) and c) groups, with more pronounced differences in the last group, which also received a lower final dose of furosemide. Mortality was similar in both groups of more intensive treatment (22 % vs. 39 % with standard care), but the rate of rehospitalization was significantly lower in the c) group: 28% vs. 40% in the b) group and 60 % in the a) group.

The proportion of patients with NT-proBNP was about 55%, similar in the three groups. However, if only the patients in the peptide-guided group were followed-up by specialists for at least 3 months, with an option to 6 months if there was no improvement, what is the best performance attributed to? To BNP or to more experienced staff intervention? If, as happened, at baseline, mean heart rate was about 80 beats/min, and mean systolic blood pressure was 120 mm Hg, was it really necessary to measure BNP to increase the beta blocker?

The PROTECT (25) study included 151 patients with EF ≤ 40 % assigned to standard or NT-proBNP-guided therapy, with the purpose of lowering it down to < 1000 pg/ml in the latter group. Only 21.9 % of patients were over 75 years. The end point was a composite of worsening or hospitalization for heart failure, acute coronary syndrome, ventricular arrhythmia, stroke or death. At baseline there was a tendency to increase the use of aldosterone in the guided-treatment group (49% vs. 34%, p = 0.10). At mean follow-up of 10 months the average number of visits was slightly higher in the guided-treatment group (6 vs. 5, p = 0.05). This group also received higher aldosterone administration (62% vs. 44%) with a barely significant value (p = 0.05), a lower dose of loop diuretics, and a greater increase of beta-blockers. At the end of the study the desired NT-proBNP < 1000 pg/ml was achieved in 44% of patients compared to 35% with standard treatment. The primary end point was significantly lower in the guided-treatment group, and the difference was due to worsening or hospitalization for heart failure; there was no difference in mortality. The smaller the value of NT-proBNP attained, the better the outcome.

This study is considered by some as the ultimate confirmation of the utility of peptides in heart failure treatment. However, the study was not blind (treating physicians knew which group the patient belonged to) and, moreover, in the light of current treatment guidelines, administration of aldosterone antagonists is indicated in patients with low EF and FC II.

b) Neutral studies

The Beck -da- Silva et al. study (26) with only 41 patients, sought to define whether it was useful to use BNP values instead of standard clinical criteria to achieve higher doses of beta blockers. As opposed to other studies, a lower dose was reached, perhaps because onset of treatment initially produces an increase of BNP levels which prevents further titration.

The TIME-CHF (27) study enrolled 499 patients aged 60 years or older, with EF ≤ 45%, hospitalized for heart failure in the last year, with NT-proBNP > 400 pg/ml in patients between 60 and 74 years and > 800 pg/ml in the eldest patients. They were assigned to NT-proBNP-guided therapy (in order to decrease it below age cut-off values) or clinically-guided treatment (in order to achieve FC II or less). Mean age was 77 years, heart rate was 75 beats / min and systolic blood pressure was 120 mm Hg. The primary end point was all-cause hospitalization or death. Only 40 % received aldosterone. Baseline NT-proBNP was higher in the clinically-guided group: 4657 vs. 3998 pg/ml. It must be taken into account that in the Troughton study, a differential decrease of approximately 640 pg/mlwas associated with better prognosis.

Once more, guided-treatment resulted in increased use of neurohormonal antagonists and greater rate of dose change. There was no difference in the primary end point: all-cause hospitalization-free survival was only 40% at 18 months in both groups (the average advanced age should be considered), nevertheless, heart failure hospitalization-free survival was 72% with guided treatment vs. 62% with regular follow-up (p = 0.01). This demonstrates the high rate of hospitalization not due to heart failure in this population, and a fact we will underline: although, there was no difference in the overall primary end point, the division of patients according to age showed a clear benefit of peptide-guided therapy in those < 75 years, ensuring significant less mortality and hospitalization. In contrast, in the eldest patients (in which, as seen, higher values of NT-proBNP should be expected) no difference was significant. The TIME- CHF study then in-

troduced into the discussion the age issue: possibly, guided treatment is more useful in younger patients because these higher values of NT-proBNP speak of heart failure, whereas in the elderly it is clear that the peptide value is influenced by other factors, and outcome is strongly marked by the presence of concomitant pathology. In fact, the increased dose of neurohormonal antagonists had a stronger effect in those less than 75 years than in older patients.

The BATTLESCARRED (28) study considered 364 patients hospitalized for heart failure, with NT-proBNP > 400 pg/ml, randomly assigned at discharge to: a) standard treatment by a primary care physician), b) intensive treatment, guided by a specialist, in order to achieve low congestion score, and c) NT-proBNP-guided therapy, also in charge of a specialist, with the dual objective of achieving a low congestion score and NT-proBNP < 1200 pg/ml. There was no LVEF criterion to enter the study. The primary end point was death from any cause, and a composite of death or hospitalization for heart failure was also considered. The NT-proBNP was assessed every 3 months in groups b) and c), but it was only used to adopt treatment conduct in group c).

Once more, it can be reported that, despite baseline randomization, there were differences in favor of the guided treatment: initial prevalence of NT-proBNP > 150 pmol / L (1267 pg/ml) was 79% in group b) compared to 66% in group c). Mean LVEF was between 37% and 40%.

At follow-up, the dose of furosemide and beta-blockers increased similarly in groups b) and c), and the dose of spironolactone dropped in group c). NT-proBNP decreased in groups b) and c), although the prevalence of elevated NT-proBNP remained high in group b).

What about outcome? While groups seen by specialist doctors at 1 year had better outcome, at 3 years there was no difference among the three groups , except in the multivariate analysis (is it correct to do it in a randomized study?), perhaps because at 2 years all patients were transferred to standard treatment. As in the previous study, subject age was not irrelevant. Again, the benefit of guided-therapy focused on patients < 75 years: in them, the 3-year period was significantly better with this strategy than with either of the other two. However, the counterpart of the work not mentioned by the authors is that, mirroring these results, the BNP group had the worst outcome in patients > 75 years with 49% mortality vs. 35% in the other groups. As we see, older age clearly linked to age-dependent comorbidities, again played a leading role.

The PRIMA (29) study considered 345 patients hospitalized for heart failure with NT-proBNP > 1700 pg/ml on admission and a fall of ≥ 10% and ≥ 850 pg/ml at discharge. There was no LVEF criterion to enter the study (mean value of 35%). Patients were either assigned to a clinical monitoring group or to a NT-proBNP-guided group (although the peptide was assessed in both groups, it was considered for decision-making in the guided-treatment group) in which the objective was to maintain the discharge value or that achieved at two weeks after discharge. If the value of the peptide rose 10% or 850 pg/ml, the patient was treated; otherwise, no modifications were made. It is worth noting that the discharge NT-proBNP in both groups was slightly above 2900 pg/ml, i.e., a high value. The primary end point was days alive and out of hospital and follow-up was 2 years.

There was no outcome difference between the two groups, even though in the guided-group the use of inhibitors / antagonists of the renin- angiotensin system and the increase in the dose of diuretics were greater, with a higher tendency in the use of beta-blockers. Interestingly, the decrease in NT-proBNP was similar for both strategies, and although in 79% of cases with high values there was medical intervention, it was not enough to change the outcome. Perhaps the failure of this study can be attributed to a very high expected NT-proBNP value.

The SIGNAL-HF (30) study included stable patients with LVEF <50% and NT-proBNP > 800 pg. / mL in men and> 1000 pg/ml in women treated in primary care centers by physicians who received 2-3-hour training by cardiologists. There was a clinically-guided arm and a clinical and BNP-guided arm. In the latter group the aim was to lower the NT-proBNP value at least 50%, even though it was not a clinical indication. The decrease in NT-proBNP was similar in both groups: 10%. Approximately 20% of patients in both groups lowered the NT-proBNP value more than 50%. As expected, changes were similar in treatment and outcome.

The Anguita et al. study (31) included 60 patients, clinically assigned to follow-up in order to maintain a low congestion score or to BNP-guided monitoring, with a desired value of < 100 pg/ml. At mean follow-up of 16 months, although the peptide-guided group achieved a significantly lower BNP value compared to the other group, there was no difference in clinical score or outcome.

The STARBRITE (32) study included 122 patients hospitalized for heart failure with LVEF ≤ 35%, randomized to guided treatment by the presence of congestion or BNP-guided therapy, aiming to keep the discharge BNP with possible variation between half and twice this value. Follow-up was short: 90 days. Median visits in both groups were 3. At the end of the study there was a tendency in the peptide-guided group to increase the use of inhibitors / antagonists of the renin -angiotensin system and significantly greater use of beta-blockers: 93 % vs. 77 %. However, perhaps due to the low number of patients, the short follow-up or because the BNP target was achieved during hospitalization, there was no significant outcome difference.

The UPSTEP (33) study enrolled 279 patients with LVEF <40%, unstable or hospitalized in the last

month, with BNP >150 pg/ml in those under 75 years and BNP > 300 pg/ml in older patients. They were randomly assigned to treatment with a single BNP value at baseline, or BNP-guided therapy to decrease it to less than 150 or 300 pg / mL depending on age. The primary end point was all-cause death or hospitalization for heart failure. Patients were competently treated in both groups, and changes in treatment were similar. Accordingly, there were no differences in the outcome. Patients in the BNP group were either classified as responders (> 30% decrease in the BNP value at week 48) or not. Sixty percent of patients were responders, corresponding to younger subjects with better renal function.

c) General comments on the studies

No study by itself defines the issue. A meta-analysis is needed to find a significant reduction in mortality, and it is clear that the quality of the studies and differences in treatment groups may influence the outcome.

In some trials, for example, the ratio of baseline therapy used is currently considered too low. The most notable examples are the Troughton and STARS-BNP studies. Would guided-therapy have the same result if the patients had been treated according to current guideline indications?

In some of them, and although the difference did not reach statistical significance, there were initial imbalances that generally favored the guided-therapy group. The Troughton, TIME-CHF and BATTLESCARRED studies are prominent examples.

In others, design defects established different approximations favoring the guided-therapy group: Berger's study, in which the NT-proBNP group was simultaneously seen by the most experienced physicians, is the most flagrant example.

The TIME-CHF and BATTLESCARRED studies clearly expose the age issue. Guided-therapy appears to be associated with better outcome in younger patients. Should it be reminded that higher peptide values are expected in the older population, or that heart failure in younger patients has worse ventricular function and more frequent cardiovascular events, while among the elderly the LVEF is higher, the role of concomitant diseases (many of which are responsible for increased peptides) more significant, and the proportion of deaths from non-cardiac origin higher? (34) In fact, in Li et al.'s meta-analysis (1) guided-therapy significantly reduced rehospitalization in patients under 70 years (RR 0.45, 95% CI, from 0.33 to 0.51) but not in older patients (RR 0.84, 95% CI, from 0.69 to 1.01). Compared to that, the 33 patients over 75 years of the PROTECT study do not appear to be enough to change the sense of all said.

THE IDEA OF GUIDED THERAPY

We will now discuss the idea of guided therapy itself, its theoretical bases.

The presented trials established the comparison between two strategies: a standard monitoring (focused most of the time in reducing signs of congestion and stick to guidelines) and a follow-up guided by serial peptide measurement. Let us look at the weaknesses of this model.

a) Standard follow-up

In our daily practice, we have learned to appreciate examination findings that are beyond congestion. In the Framingham score, tachycardia (with a value greater than 100 beats / minute!) only represents 0.5 points. In any of the studies with a primary end point score <2, the presence of tachycardia would be perfectly tolerated, if it had reached that value. Is that what we do? Does the congestion score consider blood pressure values? The premise of achieving absence of overt signs of fluid overload looks insufficient for the current clinical practice.

But beyond that, do we practice strategy only based on clinical evidence? Surely not: we periodically evaluate laboratory data related to renal function, hemoglobin, nutritional parameters, and electrolytes. We order an echocardiogram to assess significant changes in the diameters and volumes, significant changes in LVEF, filling parameters, and evolution of valve pathology. The Holter ECG contributes to indicate potentially lethal ventricular arrhythmia or supraventricular arrhythmia which can further deteriorate the clinical condition. We assess exercise capacity, at least with one 6-minute-walk. All these studies contribute to our decision making.

b) Peptide-guided therapy

Where does guided therapy lead us? Towards a greater number of visits, changes in the dose of furosemide and increased use of neurohormonal antagonists.

Do we need a high peptide value to see patients more often? And, conversely, by the mere fact that it is not, should we defer the visit? Is it a high or low value the only fact that determines the frequency at which we follow-up the patient? Where do changes in heart rate, renal function, blood pressure, titration of a drug or a recent hospitalization stand as reasons for closer monitoring whatever the value of the peptide?

Regarding diuretics, in some studies with guided therapy the dose increased and in others it decreased. Should we decide the diuretic dose only based on peptides? I think not. In general, the presence of congestive signs alone is reason enough to increase diuretics. In the absolute absence of congestive signs, is a high value of BNP sufficient reason to raise the dose? Should we focus our therapy in a stubborn effort to lower BNP independently of blood pressure, physical examination, and the rest of the lab tests? Higher doses of diuretics may increase the risk of electrolyte imbalance and renal dysfunction. We have seen that in patients with heart disease echo-Doppler gives us a better estimate of LV filling pressures.

And, once more, in absolute absence of congestive

signs, is it not feasible to indicate a gradual decrease in the diuretic dose in order to achieve, as recommended, the lowest useful dose? Do we need to dose BNP to lower furosemide from 40 to 20 mg daily and see the outcome?

Let us look at neurohormonal antagonists. It is true that the doses in many of the studies ended up being higher in the guided group. But, with some exceptions, they were not higher than doses recommended by practice guidelines. Is it then really necessary to know the peptide value to achieve them? Beta blocker and ACEI doses should be the maximum tolerated, and when they are the maximum tolerated (for symptoms, heart rate, blood pressure, renal function), there is no peptide value worth changing them.

If in everyday practice we "forget" to adjust the referred doses and optimize treatment, do we really believe that we will remember it because we see the BNP value? Does this mean that we should "remember" to periodically ask a natriuretic peptide assessment so that at its sight we "remember" we must do what we already know? Remember to remember!

And finally, and beyond the academic discussion, is it possible to implement in our country a measurement strategy routine in all patients with heart failure several times a year? For just over 41 million inhabitants and a conservative estimate of 2% heart failure, and four measurements per year per capita, about 3280000 measurements per year should be performed. To educate primary care physicians and clinicians in the proper approach to pathology, an ongoing record of what is done in the public and private sectors, ensuring at least one echocardiogram and access to regular monitoring and elementary medication for all patients seem most urgent needs, and certainly much more cost-effective.

FINAL IDEAS

Elevated natriuretic peptides are an expression of heart failure. Numerous factors influence the individual value of each patient. No decisions automatically based on their value should be taken, without interpreting it in terms of other cardiac and noncardiac conditions. To put into practice what we know we must do, routine natriuretic dosage several times a year does not seem necessary in all patients. A more judicious use, as with the rest of the diagnostic and prognostic array, seems a more appropriate choice.

Conflicts of interest

None declared.

REFERENCES

1. Li P, Luo Y, Chen YM. B-type natriuretic peptide-guided chronic heart failure therapy: a meta-analysis of 11 randomised controlled trials. Heart Lung Circ 2013;22:852-60. http://doi.org/pws

2. Savarese G, Trimarco B, Dellegrottaglie S, Prastaro M, Gambardella F, Rengo G, et al. Natriuretic peptide-guided therapy in chronic heart failure: a meta-analysis of 2,686 patients in 12 randomized trials. PLoS One 2013;8:e58287. http://doi.org/pwt

3. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847. http://doi.org/pwx

4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240-319. http://doi.org/pwz

5. Motiwala SR, Januzzi JL Jr. Using biomarkers to "guide" heart failure management: current perspectives and future directions. Cardiol Rev 2013;21:127-34. http://doi.org/pw2

6. Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol 2007;50:2357-68. http://doi.org/b9822t

7. Iwanaga Y, Nishi I, Furuichi S, Noguchi T, Sase K, Kihara Y, et al. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. J Am Coll Cardiol 2006;47:742-8. http://doi.org/fr4qzn

8. Maisel A, Mueller C, Adams K Jr, Anker SD, Aspromonte N, Cleland JG, et al. State of the art: using natriuretic peptide levels in clinical practice. Eur J Heart Fail 2008;10:824-39. http://doi.org/dh8bg5

9. Troughton RW, Richards AM. B-type natriuretic peptides and echocardiographic measures of cardiac structure and function. JACC Cardiovasc Imaging 2009;2:216-25. http://doi.org/dzhtgx

10. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161-7. http://doi.org/drqfww

11. Januzzi JL Jr, Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005;95:948-54. http://doi.org/ck4gsw

12. van Kimmenade RR, Pinto YM, Januzzi JL Jr. Importance and interpretation of intermediate (gray zone) amino-terminal pro-B-type natriuretic peptide concentrations. Am J Cardiol 2008;101:39-42. http://doi.org/bn3899

13. Januzzi JL Jr, Chen-Tournoux AA, Moe G. Amino-terminal pro-B-type natriuretic peptide testing for the diagnosis or exclusion of heart failure in patients with acute symptoms. Am J Cardiol 2008;101:29-38. http://doi.org/ch4sbj

14. Moe GW, Howlett J, Januzzi JL, Zowall H. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation 2007;115:3103-10. http://doi.org/dptgqm

15. Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. Circulation 2011;124:2865-73. http://doi.org/bxsvgt

16. Galasko GI, Lahiri A, Barnes SC, Collinson P, Senior R. What is the normal range for N-terminal pro-brain natriuretic peptide? How well does this normal range screen for cardiovascular disease? Eur Heart J 2005;26:2269-76. http://doi.org/d27jhd

17. Costello-Boerrigter LC, Boerrigter G, Redfield MM, Rodeheffer RJ, Urban LH, Mahoney DW, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction. J Am Coll Cardiol 2006;47:345-53. http://doi.org/dcgskm

18. Baggish AL, van Kimmenade RR, Januzzi JL Jr. The differential diagnosis of an elevated amino-terminal pro-B-type natriuretic peptide level. Am J Cardiol 2008;101:43-8. http://doi.org/d4gqv2

19. DeFilippi C, van Kimmenade RR, Pinto YM. Amino-terminal pro-B-type natriuretic peptide testing in renal disease. Am J Cardiol 2008;101:82-8. http://doi.org/b6tw3z

20. Wu AH. Serial testing of B-type natriuretic peptide and NTpro-BNP for monitoring therapy of heart failure: the role of biologic variation in the interpretation of results. Am Heart J 2006;152:828-34. http://doi.org/bjwwmx

21. DeBeradiis B, Januzzi JL Jr. Use of biomarkers to guide outpatient therapy of heart failure. Curr Opin Cardiol 2012;27:661-8. http://doi.org/pw3

22. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000;355:1126-30. http://doi.org/dzw94w

23. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. J Am Coll Cardiol 2007;49:1733-9. http://doi.org/c697fg

24. Berger R, Moertl D, Peter S, Ahmadi R, Huelsmann M, Yamuti S, et al. N-terminal pro-B-type natriuretic peptide-guided, intensive patient management in addition to multidisciplinary care in chronic heart failure a 3-arm, prospective, randomized pilot study. J Am Coll Cardiol 2010;55:645-53. http://doi.org/csnb63

25. Januzzi JL Jr, Rehman SU, Mohammed AA, Bhardwaj A, Barajas L, Barajas J, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. J Am Coll Cardiol 2011;58:1881-9. http://doi.org/fv49bd

26. Beck-da-Silva L, de Bold A, Fraser M, Williams K, Haddad H. BNP-guided therapy not better than expert's clinical assessment for beta-blocker titration in patients with heart failure. Congest Heart Fail 2005;11:248-53; quiz 54-5. http://doi.org/c45656

27. Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 2009;301:383-92. http://doi.org/d9xz2f

28. Lainchbury JG, Troughton RW, Strangman KM. N-Terminal Pro B Type Natriuretic Peptide-guided treatment for chronic heart failure. Results from the BATTLESCARRED (NT-pro BNP-assisted treatment to lessen serial cardiac readmissions and death) trial J Am Coll Cardiol 2010;55:53-60. http://doi.org/c73k3g

29. Eurlings LW, van Pol PE, Kok WE, van Wijk S, Lodewijks-van der Bolt C, Balk AH, et al. Management of chronic heart failure guided by individual N-terminal pro-B-type natriuretic peptide targets: results of the PRIMA (Can PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study. J Am Coll Cardiol 2010;56:2090-100. http://doi.org/bdtrwr

30. Persson H, Erntell H, Eriksson B, Johansson G, Swedberg K, Dahlstrom U. Improved pharmacological therapy of chronic heart failure in primary care: a randomized Study of NT-proBNP Guided Management of Heart Failure--SIGNAL-HF (Swedish Intervention study--Guidelines and NT-proBNP AnaLysis in Heart Failure). Eur J Heart Fail 2010;12:1300-8. http://doi.org/dq3xmc

31. Anguita M, Esteban F, Castillo JC, Mazuelos F, López-Granados A, Arizón JM, et al. [Usefulness of brain natriuretic peptide levels, as compared with usual clinical control, for the treatment monitoring of patients with heart failure]. Med Clin (Barc) 2010;135:435-40. http://doi.org/b6twkz

32. Shah MR, Califf RM, Nohria A, Bhapkar M, Bowers M, Mancini DM, et al. The STARBRITE trial: a randomized, pilot study of B-type natriuretic peptide-guided therapy in patients with advanced heart failure. J Card Fail 2011;17:613-21. http://doi.org/chsgjk

33. Karlstrom P, Alehagen U, Boman K, Dahlstrom U. Brain natriuretic peptide-guided treatment does not improve morbidity and mortality in extensively treated patients with chronic heart failure: responders to treatment have a significantly better outcome. Eur J Heart Fail 2011;13:1096-103. http://doi.org/dnv6c2

34. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. Circ Heart Fail 2008;1:91-7. http://doi.org/d9tqtt

AGONIST'S REPLY

Let us end at the beginning, paraphrasing Dr. Thierer, where we agree that the concept of applying natriuretic peptide-guided therapy (NPGT) in patients with heart failure (HF) has solid evidence, supported primarily by the results of meta-analyses, to reduce total mortality and rehospitalization for heart failure. While some antagonist arguments were analyzed placing natriuretic peptides in a different context from the topic of discussion, many of them are valid and have been discussed in my presentation. Among them are the differences and limitations in clinical trials. In economic terms, its applicability in our country is a matter of concern. Therefore, a strategy with demonstrated evidence and of high cost should be used rationally and not indiscriminately. Hence the importance of selecting the best candidates to receive it, and in this evaluation the concepts set forth by Dr. Thierer questioning its use to improve what doctors should routinely do, actually represent the origin of TGPN.

If physicians who see patients with HF devoted the necessary time and effort to assess the state of congestion, heart rate, blood pressure, ECG, chest X ray and echocardiography, considering that frequent visits of ascending and descending drug titration are necessary and thinking in adequately implementing what the guidelines suggest, I agree that TGPN is not justified, and moreover, probably it would have never been developed. But the reality is different, and considering that the perfect biomarker does not exist, so does not the perfect doctor. Therefore, the availability of new techniques can help us be a little more efficient perhaps combining all available evidence, increasing complexity and incorporating TGPN when we fail to achieve our target.

Dr. Eduardo R. Perna

ANTAGONIST'S REPLY

Some comments on Eduardo Perna's excellent presentation.

If "a trained team in the management of CHF is required" to adequately perform guided therapy that is useful in "indicated patients", we may infer that it is not a strategy we should apply in all cases; particularly if "cost, especially in our country, is a limitation for its generalized application".

If my patient has a clear clinical manifestation of heart failure, do I need BNP as a guide? If my patient has no symptoms and standard control parameters (clinical and echocardiographic stability, heart rate, blood pressure, sodium, creatinine, albumin, and exercise capacity) are within desired values, do I need BNP to guide me?

Heart failure does not fit in a drop of blood.

And let us leave this phrase for the end: "*One reason for negative trials in this area was that the control arm received high quality care* with parallel suppression of the BNP or NT pro BNP, frequently comparable to the unblinded arm. Thus, a low post treatment natriuretic peptide concentration is desirable, *whether as a consequency of guided therapy or simply excellent care*". The italics belong to me; the phrase, to one of the most important advocates of guided therapy, James Januzzi. (1) With admission of parties, no proof is required...

Dr. Jorge Thierer[MTSAC]

REFERENCES

1. Januzzi JL Jr. The role of natriuretic peptide testing in guiding chronic heart failure management: review of available data and recommendations for use. Arch Cardiovasc Dis 2012;105:40-50.