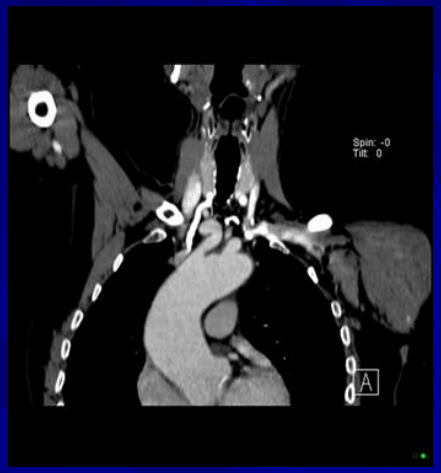
GCA

- Giant Cell Arteritis is associated with an increased risk of **aortic aneurysm**, which is usually a late complication and may lead to dissection and death



BNP-Guided vs Symptom-Guided Heart Failure Therapy

(JAMA, January 28, 2009 – Vol 301, No. 4)

BNP

- B-type natriuretic peptide (BNP) was first described in 1988 after isolation from porcine brain
- The major source of BNP synthesis and secretion is the ventricular myocardium
- With the primary site of synthesis localized to the cardiac ventricular myocytes, the term “B-type” natriuretic peptide is now favoured

BNP - History

1988 Sudoh et al. isolate BNP from porcine brain tissue

1991 Mukoyama et al. demonstrate that BNP is a normal cardiac hormone secreted primarily by the ventricles

1993 Shionogi & Co, Ltd. develop the first commercial BNP assay (RIA) in Japan

1994 Davis et al. provide the first report suggesting that BNP is useful in diagnosing HF in dyspnoeic patients

1994 Multiple reports of elevated BNP levels in HF

1995 Hunt et al.—first report of NT-proBNP circulating in human plasma

1997 Cowie et al. show that BNP has high accuracy to diagnose CHF in the primary care setting

1998 McDonagh et al. demonstrate that BNP is reliable in the detection of left ventricular dysfunction

2000 Biosite, Inc. introduces the BNP point-of-care assay

2001 Maisel et al. publish the first point-of-care BNP in the ED and hospital settings

2002 Breathing Not Properly Study published

2003 Lainchbury et al.—first report of NT-proBNP in the diagnosis of HF

2003 Central lab assays become available: Bayer Healthcare, LLC, Diagnostics Div., ADVIA Centaur, ShionoRIA BNP assay in US (central lab) and Roche Elecys

2004 BASEL trial showing reduction in morbidity and treatment cost with BNP published

2005 Beckman central lab (Biosite antibody) and Abbott Diagnostics, AxSYM BNP assay (central lab) becomes available

2005 PRIDE study on NT-proBNP in AHF published

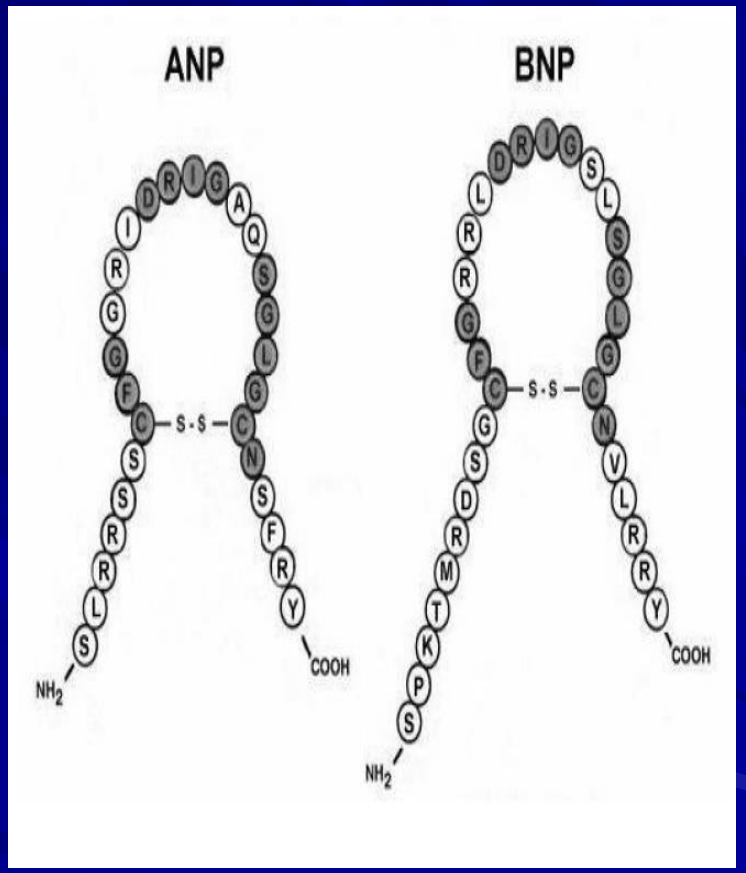
2005 ESC Guidelines for acute and chronic Heart Failure Endorse BNP

2006 Biosite Triage BNP Test receives CLIA waiver for whole blood use. AHA/ACC Guidelines for Heart Failure Endorse Class II a recommendation for NPs. (Level of evidence A)

BNP - Physiology

- BNP belongs to the natriuretic peptide family together with other structurally similar peptides, namely, atrial natriuretic peptide (ANP) and C-type natriuretic peptide (CNP)
- They all have a typical 17 amino-acid ring residue structure and they all also exist as a pro-hormone which is further cleaved into N-terminal peptide and C-terminal active hormone

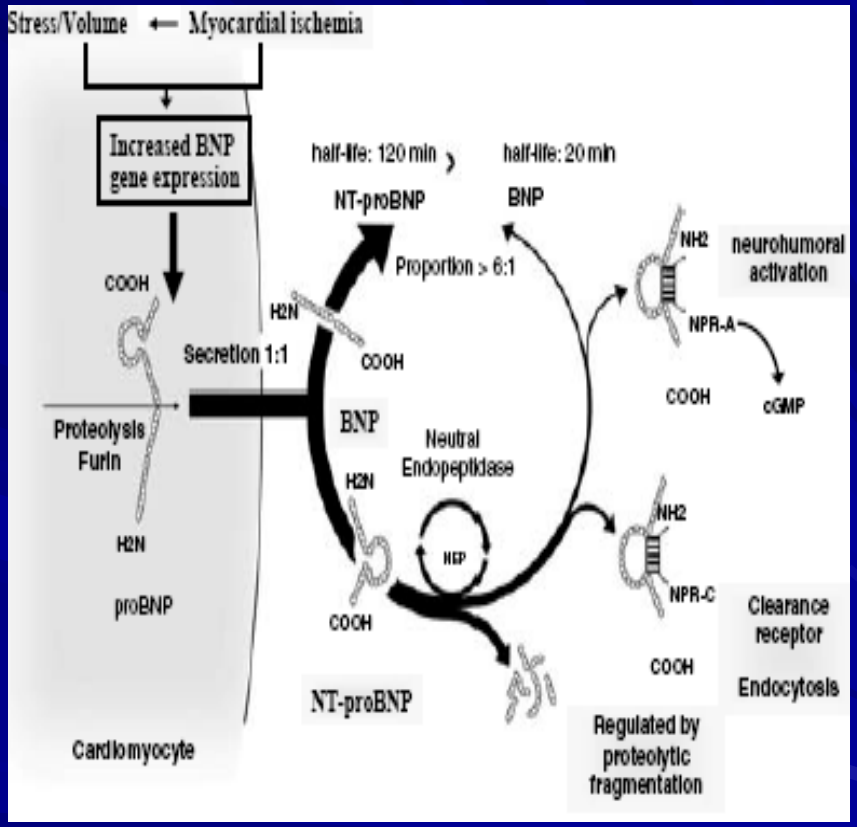
- A separate natriuretic peptide created from ANP pro-hormone and called Urodilatin is released from distal tubular cells



BNP – Physiology (2)

- BNP is synthesized as a 108 amino acid prohormone (proBNP)
- Upon release into circulation, proBNP is cleaved into equal proportions, that is, into the biologically active 32 amino acid BNP, which is the C-terminal fragment, and into the biologically inactive 76 amino acid N-terminal fragment (NT-proBNP)

- **The main stimulus** for increased BNP and NT-proBNP synthesis and secretion is myocardial wall stress



BNP – Physiology (3)

- In systemic circulation, BNP mediates a variety of biological effects by interacting with natriuretic peptide receptor type A, which leads to intracellular cyclic GMP production

- The physiological effects of BNP are manifold and comprise (1) natriuresis/diuresis, (2) peripheral vasodilation and (3) inhibition of the reninangiotensin-aldosterone system and sympathetic nervous system

BNP – Physiology (4)

- The half-life of BNP is 20 min, whereas NT-proBNP has a half life of 120 min
- BNP is cleared from the plasma by binding to natriuretic peptide receptor type C and through proteolysis by neutral endopeptidases
- In contrast, NT-proBNP is mainly cleared by renal excretion

BNP in Practice

- NP testing improves diagnostic accuracy and thus has become a standard part of the evaluation in patients presenting to the ED with dyspnea
- The higher the NP value the greater the likelihood that the dyspnea is due to HF

- When BNP is low (<100 pg/ml), it is unlikely that HF is contributing to the clinical presentation
- On the other hand, a high BNP (>400 pg/ml) suggests that HF is a contributor to the patient's symptoms with specificity exceeding 90%

NT-proBNP

- When using NT-proBNP, a cut point of 300 pg/ml is proposed to “rule out” a diagnosis of HF, while higher age-dependent cut points are suggested to “rule in” HF

- Patients with NT-proBNP levels >450 pg/ml (<50 years), >900 pg/ml (50–75 years), and >1800 pg/ml (>75 years) all have a high likelihood of heart failure as the diagnosis

NT-proBNP (2)

	BNP	NT-proBNP
Half-life	20 min.	120 min.
Major clearance mechanism	Natriuretic peptide receptors	Renal clearance
Cut points for HF diagnosis	pg/ml 100	pg/ml 300
-in patients with GFR<60 ml/min./1.73m2	pg/ml 200	pg/ml 1200

BNP – The "grey zone"

- While a 2 cut-point approach provides high diagnostic accuracy, this does leave a "grey zone" of BNP values between 100 and 400pg/ml
- If a large proportion of patients with acute breathlessness had values in the grey zone this could reduce the clinical utility of NP but, in practice, **75%** of patients have values above or below these cut-off values

The grey zone is defined as follows:

- **BNP** - 100–400 pg/ml
- **NT-proBNP** – 300-450 pg/ml (age<50y), 300–900 pg/ml (50-75y), 300–1800 pg/ml (>75y)

BNP – Other Conditions

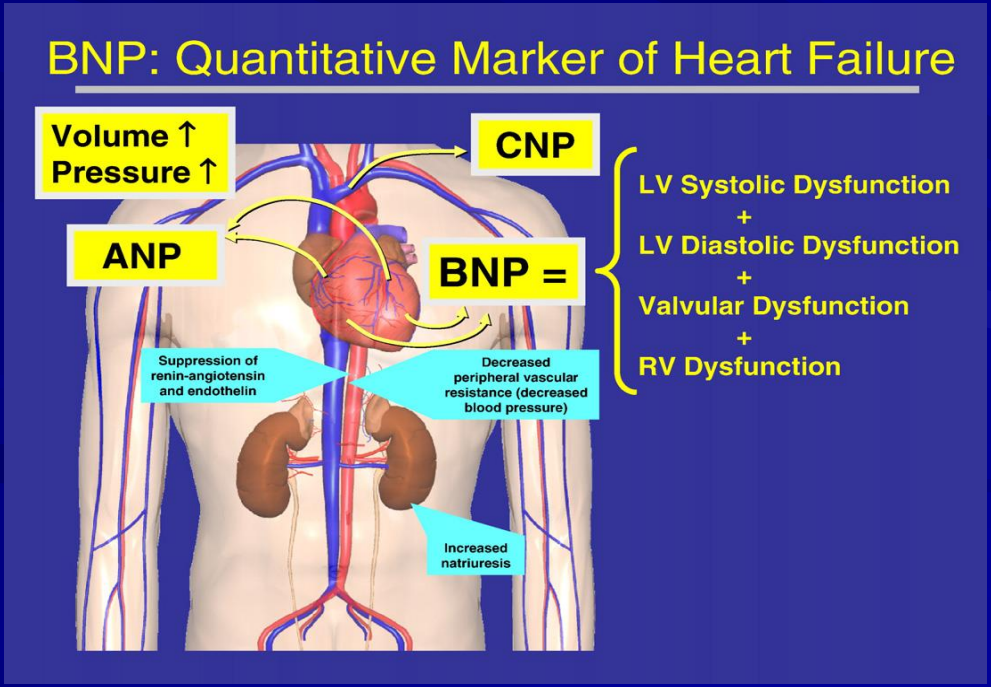
Other conditions that result in an increased BNP should also be considered:

- Acute Pulmonary Embolus
- Acute Coronary Syndrome
- Primary Pulmonary Hypertension
- Renal Failure
- Age and Gender
- Systemic Hypertension
- Atrial Fibrilation

BNP – Other Conditions (2)

- COPD patients with core pulmonale
- Pneumonia

Obesity lowers BNP levels



BNP - Practical Points and Recommendations

- Patients presenting with dyspnea, especially of uncertain origin, to emergency services should undergo a history, physical examination, chest X-ray, ECG and blood should be sampled for a NP and renal function measurement

- When using cut-off values for BNP in patients with acute dyspnea, apply two values: one to “rule out” (<100 pg/ ml) and one to “rule in” HF (>400 pg/ml)

- The grey zone between 100 and 400 pg/ml needs additional physician interpretation

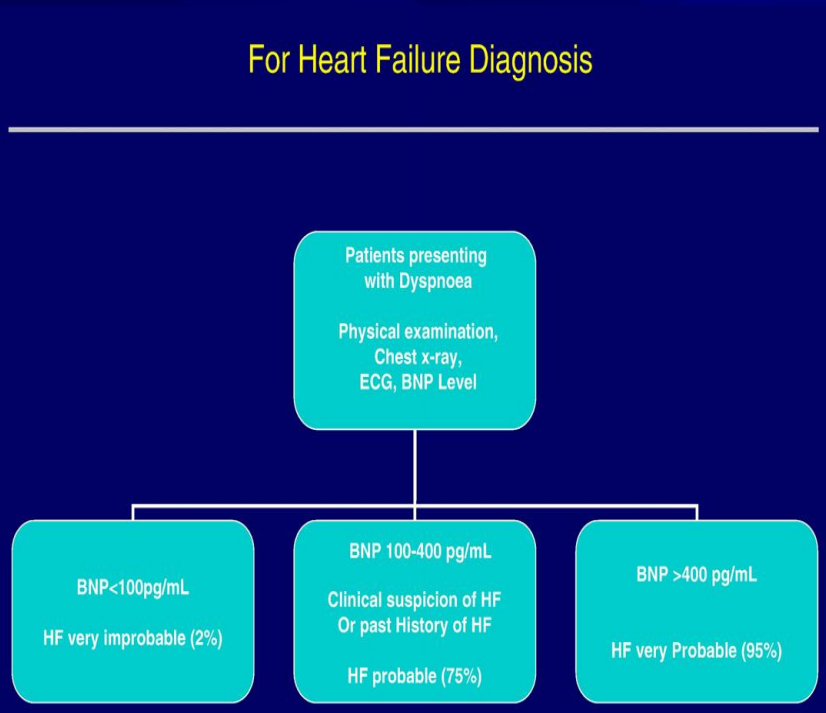
BNP - Practical Points and Recommendations (2)

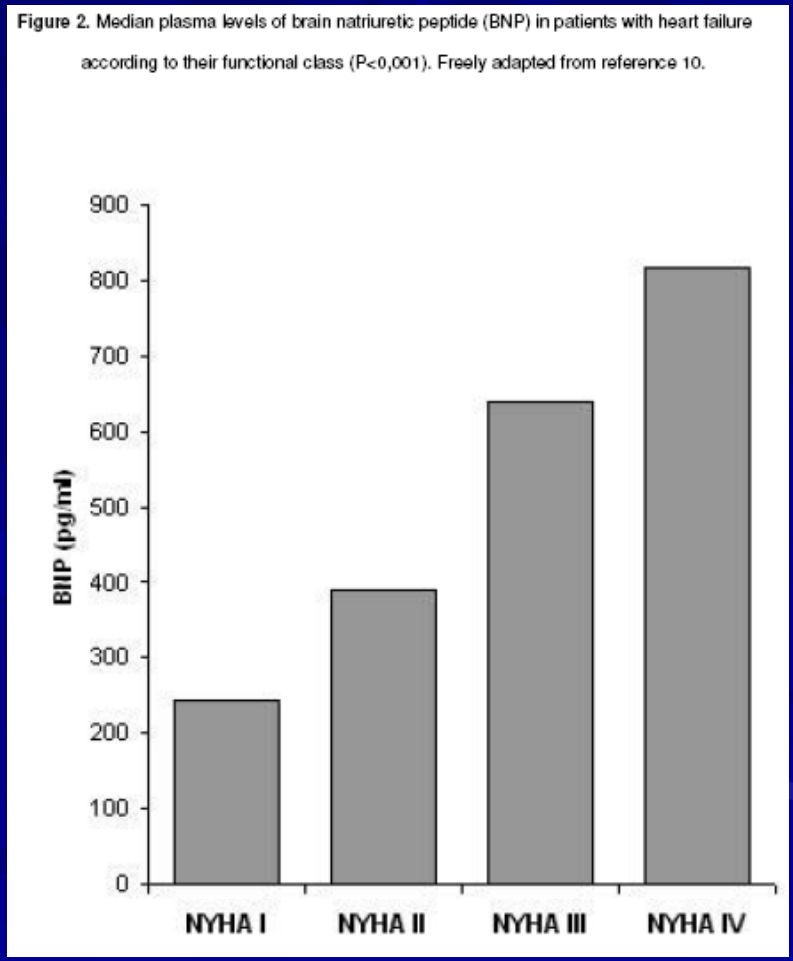
- When using NT-proBNP, apply one rule-out value (<300 pg/ml) and one of three rule-in values based on age
- The rule-out values for both BNP and NT-proBNP in the acutely dyspneic patient do not need to be adjusted for age or sex. To optimize diagnostic accuracy with either NP, adjustments should be made for renal dysfunction and obesity
- If NP levels fail to decrease with appropriate and intensive therapy or remain elevated at the time of discharge, anticipate a poor prognosis. Consider more aggressive in-hospital treatment and careful post-discharge monitoring

BNP-Guided Therapy

- NP levels are commonly reduced by treatment with diuretics, ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists and cardiac resynchronization therapy (CRT)
- Beta-blockers may increase NP levels in the first weeks and months after administration but after 6–12 months may cause NP levels to fall
- Regular assessment of renal function is required to avoid deterioration in renal function when using this approach

BNP-Guided Therapy (2)



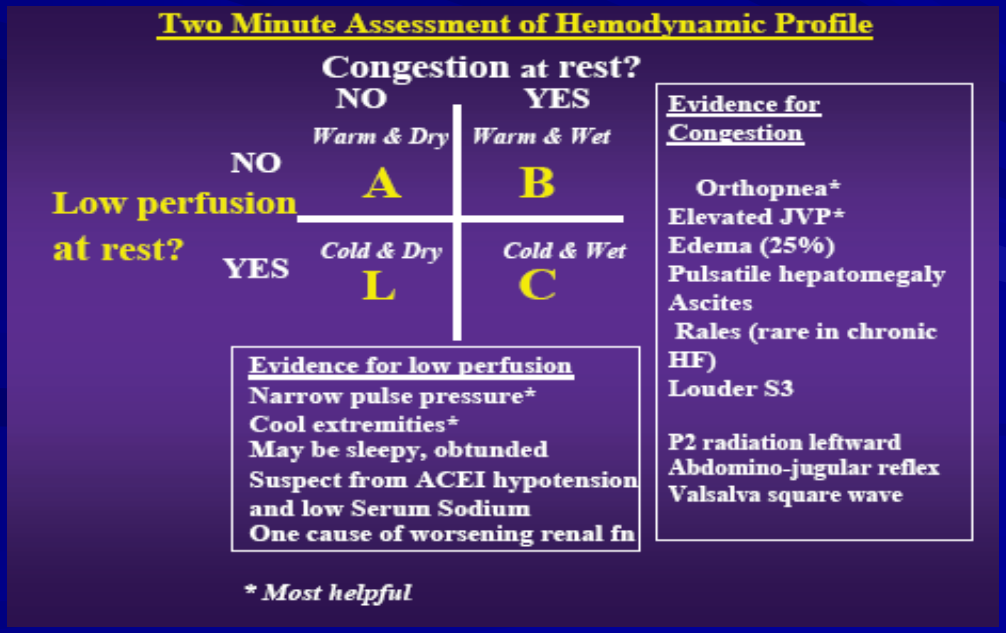


Symptom-Guided Therapy

- Widespread use of ACE-I and beta adrenergic blocking agents have improved the prognosis of heart failure in mild-moderate stages
- For many, however, heart failure remains a progressive disease, eventually leading to decompensation
- For the most part, management of advanced heart failure is guided by reported and personal experience

Symptom-Guided Therapy (2)

- Before symptoms of heart failure ever appear, progression of disease is already influenced by the contribution of subtle increases in wall stress and filling pressures
- When symptoms later dominate the picture, they are primarily symptoms of congestion, related to excess circulating volume



Treating Symptoms

- The goals are to eliminate or minimize all the evidence of congestion beyond the level of initial symptomatic relief
- For the “wet and warm” patients (profile B), this generally can be achieved with high doses of intravenous diuretics administered two to three times daily, and may be more effective with continuous intravenous infusion
- Addition of a thiazide or metolazone potentiates diuresis by inhibiting reabsorption in the distal tubule

Treating Symptoms (2)

- For patients who are “wet and cold” (profile C), the general concept is that they need to “warm up” before they can “dry out”
- Addition of intravenous vasodilators such as nitroprusside, nitroglycerin, more recently nesiritide may be useful
- Intravenous inotropic agents at low doses such as 1–3 Ag of dobutamine are also helpful for facilitating diuresis, but are associated with higher risk of arrhythmias, ischemia, and troponin leak than vasodilators

Treating Symptoms (3)

- Once optimal fluid status has been restored, maintenance of fluid balance is the challenge
- Patients should be instructed in daily weights and given a specific routine for temporary enhancement of diuretics
- Once furosemide dose is over 200 mg daily, it may be helpful to change to the loop diuretic torsemide, with more consistent gastrointestinal absorption and bioavailability, particularly in patients with some right heart failure

Treating Symptoms (4)

- Sodium restriction is generally to 2 grams, although a lower level can be feasible and beneficial for occasional highly-motivated patients
- Once patients have had repeated episodes of fluid retention despite high-dose maintenance diuretics, it may be helpful to restrict fluid intake, but there is no basis of evidence other than collective experience to support this

The Outpatient Regimen

- The major purposes of therapies for mild–moderate heart failure are to decrease disease progression (often measured as hospitalization) and prolong survival
- As the disease becomes more advanced, the goal of symptom relief begins to dominate
- ACE-I and beta-blockers remain cornerstones of therapy even when heart failure becomes advanced
- Inhibition of the sympathetic nervous system helps to decrease progression of heart failure but is associated with initial worsening of hemodynamic status

The Cardio–Renal Syndrome

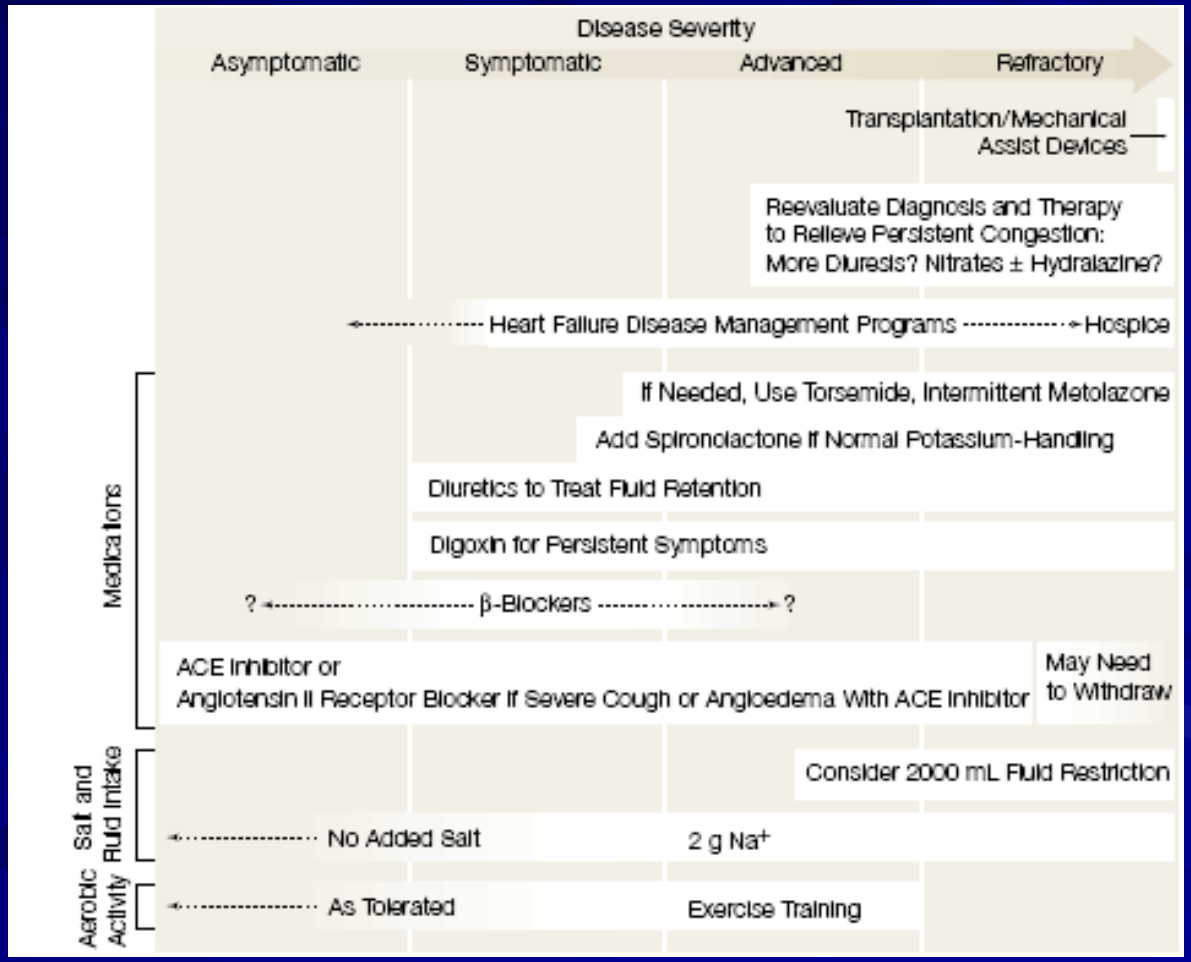
- The most common reason for truly refractory congestive symptoms among the advanced heart failure population is the recently recognized cardio–renal syndrome
- The cardio–renal syndrome may be defined as worsening of renal function during diuresis despite persistently elevated circulating volume and symptoms of congestion
- This occurs most commonly in patients with underlying renal dysfunction, older patients, and long duration of fluid retention

The Cardio-Renal Syndrome (2)

- The cardio–renal syndrome occurs in over 25% of patients hospitalized with heart failure
- Even small elevations in creatinine and BUN predict lower likelihood of maintaining freedom from congestion and higher risk of death

- Decrease or discontinuation of diuretics will usually improve renal function but at the price of exacerbating congestive symptoms
- Inhibitors of the renin–angiotensin–aldosterone system may need to be discontinued

Summary


Disease Severity
Asymptomatic
Symptomatic
Advanced
Refractory
Transplantation/Mechanical Assist Devices
Reevaluate Diagnosis and Therapy to Relieve Persistent Congestion: More Diuresis? Nitrates ± Hydralazine?
Heart Failure Disease Management Programs
Hospice
If Needed, Use Torsemide, Intermittent Metolazone
Add Spironolactone if Normal Potassium-Handling
Diuretics to Treat Fluid Retention
Digoxin for Persistent Symptoms
β-Blockers
ACE Inhibitor or Angiotensin II Receptor Blocker if Severe Cough or Angioedema With ACE Inhibitor
May Need to Withdraw
Medications
Consider 2000 mL Fluid Restriction
No Added Salt
2 g Na+
Salt and Fluid Intake
As Tolerated
Exercise Training
Aerobic Activity

The Study

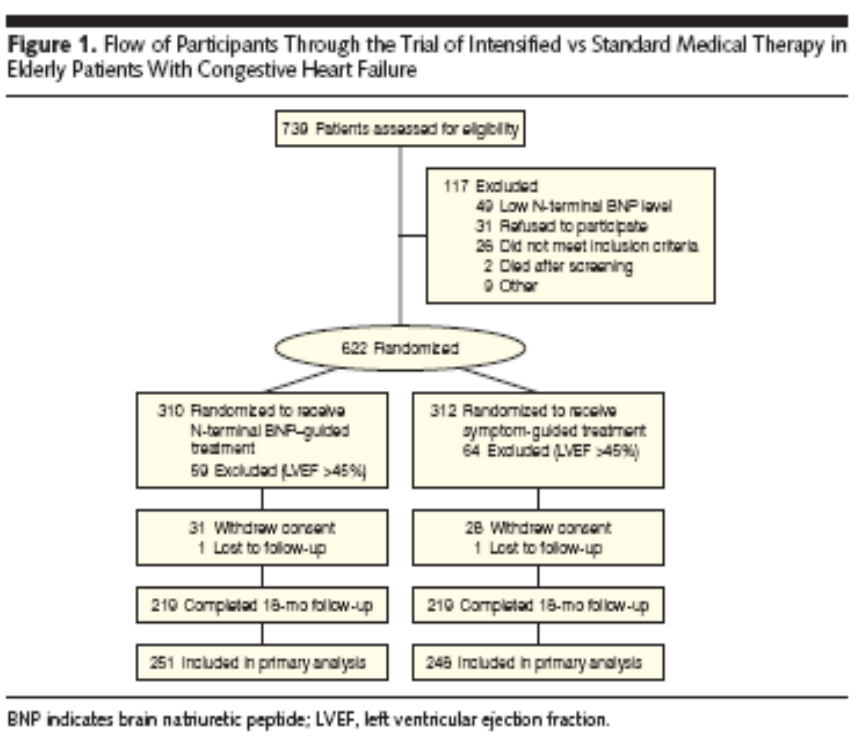
The study compared 18-month outcomes of N-terminal BNP-Guided vs Symptom-Guided heart failure therapy among elderly patients with:

- Systolic HF
- NYHA class >/2
- Prior hospitalization for HF within 1 year
- N-terminal BNP level of 2 or more times than the upper limit of normal

- It was conducted at 15 outpatient centers in Switzerland and Germany between January 2003 and June 2008

Methods - Patients

- 739 patients assessed for eligibility
- 117 were excluded
- Of the 622 patients, 499 had systolic dysfunction defined as LVEF<45% by echocardiography



Included Patients

Inclusion criteria were:

- Age > 60y
- Dyspnea (NYHA>/2)
- History of hospitalization within the last year
- N-terminal BNP>/400 pg/mL (age<75) or >/ 800 (age>75y)

Excluded Patients

Exclusion criteria were:

- Dyspnea not mainly due to HF
- Valvular disease requiring surgery
- ACS within the previous 10 days
- Angina Pectoris classified as CCSC>/2
- Revascularization within the previous month
- BMI>35
- Creatinine>2.49 mg/dL
- Life expectancy of less than 3 years for non-CVS diseases
- Unable to give informed consent
- No follow-up possible
- Participating in another study

Baseline Characteristics

Table 1. Baseline Characteristics in Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure[a]

Characteristic	Treatment Group: Symptom-Guided (n = 248)	Treatment Group: N-Terminal BNP–Guided (n = 251)	P Value	Age Group, y: 60-74 (n = 210)	Age Group, y: ≥75 (n = 289)	P Value
Demographics						
Age, mean (SD), y	77 (6)	76 (7)	.16	69 (4)	82 (4)	<.001
Female	92 (37.1)	80 (31.9)	.22	53 (25.2)	119 (41.2)	<.001
Body mass index, mean (SD)[b]	25.3 (4.3)	25.4 (4.0)	.75	26.4 (4.5)	24.6 (3.7)	<.001
NYHA class ≥III	185 (74.6)	186 (74.1)	.53	138 (65.7)	233 (80.6)	.001
Atrial fibrillation	78 (31.5)	82 (32.7)	.94	56 (26.7)	104 (36.0)	.03
Primary cause of congestive heart failure[c]						
Coronary artery disease	149 (60.1)	138 (55.0)	.46	102 (48.6)	185 (64.0)	<.001
Hypertensive heart disease	47 (19.0)	60 (23.9)		40 (19.0)	67 (23.2)	
Dilated cardiomyopathy	42 (16.9)	46 (18.3)		59 (28.1)	29 (10.0)	
Other	10 (4.0)	7 (2.7)		9 (4.3)	8 (2.8)	
LVEF, mean (SD), %	29.7 (7.9)	29.8 (7.7)	.87	27.8 (7.2)	31.2 (7.9)	<.001
N-terminal BNP, median (IQR), pg/mL	4657 (2455-7520)	3998 (2075-7220)	.12	2998 (1691-5901)	5053 (2953-8589)	<.001
Creatinine, mean (SD), mg/dL	1.33 (0.42)	1.32 (0.45)	.69	1.26 (0.41)	1.37 (0.44)	.004
Heart rate, mean (SD), beats/min	77 (15)	75 (14)	.23	74 (14)	77 (15)	.03
Systolic blood pressure, mean (SD), mm Hg	119 (19)	119 (18)	.97	117 (18)	120 (18)	.04
Medical History						
Hypertension	179 (72.2)	175 (69.7)	.56	130 (61.9)	224 (77.5)	<.001
Diabetes mellitus	95 (38.3)	77 (30.7)	.08	79 (37.6)	93 (32.2)	.22
Insulin-dependent diabetes	22 (8.9)	33 (13.1)	.15	24 (11.4)	31 (10.7)	.89
Stroke/transient ischemic attack	40 (16.1)	36 (14.3)	.62	20 (9.5)	56 (19.4)	.002
COPD	44 (17.7)	60 (23.9)	.10	45 (21.4)	59 (20.4)	.82
Cancer	35 (14.1)	33 (13.1)	.80	18 (8.6)	50 (17.3)	.005
Kidney disease	135 (54.4)	140 (55.8)	.79	94 (44.8)	181 (62.6)	<.001
Arthritis	62 (25.0)	63 (25.1)	>.99	34 (16.2)	91 (31.5)	<.001
Quality of Life						
Minnesota Living With Heart Failure questionnaire, mean (SD) (n = 491) (range, 0-105; lower values = better quality of life)	40 (21)	40 (20)	.78	40 (21)	40 (20)	.94
Duke Activity Status Index, median (IQR) (n = 483) (range, 0-58.2; higher values = better quality of life)	7.2 (1.8-15.5)	7.2 (2.7-15.5)	.71	9.0 (2.7-19.0)	7.2 (1.8-12.9)	.007
Short Form 12, mean (SD) (n = 417) (range, 0-100; higher values = better quality of life)						
Mental component	46 (11)	46 (11)	.94	48 (11)	45 (11)	.02
Physical component	34 (9)	34 (10)	.92	35 (10)	33 (9)	.12
Medication/Devices						
Implantable cardioverter-defibrillator	12 (4.8)	13 (5.2)	.86	17 (8.1)	8 (2.8)	.01
ACE inhibitor or ARB	235 (94.8)	238 (94.8)	.95	199 (94.8)	274 (94.8)	.98
Target dose, mean (SD) (n = 499)[d]	50 (36)	53 (41)	.72	52 (38)	51 (39)	.56
β-Blocker	201 (81.0)	191 (76.1)	.19	176 (83.8)	216 (74.7)	.02
Target dose, median (IQR) (n = 499)[d]	25 (12.5-50)	25 (6-50)	.18	25 (12.5-50)	25 (0-50)	.06
Mineralocorticoid receptor antagonist	100 (40.3)	102 (40.6)	.92	98 (46.7)	104 (36.0)	.02
Loop diuretic	234 (94.4)	232 (92.4)	.47	191 (91.0)	275 (95.2)	.07
Dose, median (IQR) (n = 499)[e]	80 (40-115)	60 (40-80)	.06	40 (40-80)	80 (40-120)	.04
Nitrate	72 (29.0)	71 (28.3)	.92	44 (21.0)	99 (34.3)	.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
SI conversion factors: To convert BNP to ng/L, multiply by 1.0; creatinine to μmol/L, multiply by 88.4.
[a] Values are expressed as number (percentage) unless otherwise indicated.
[b] Calculated as weight in kilograms divided by height in meters squared.
[c] Investigator's clinical diagnosis.
[d] Indicates percentage of target dose patients were receiving.
[e] A dose of 10 mg of torasemide is equivalent to 40 mg of furosemide.

Study Design

- Patients, but not treating physicians, were blinded to group allocation
- Prespecified visits after 1, 3, 6, 12 and 18 months
- Treatments were adjusted at all but the last visit with the attempt to achieve treatment goals by the 6-month visit followed by 12 months of outcome observation

End Points

- The primary end points were 18-months survival free of any hospitalization and quality of life measured at 18 months

- Secondary end points included components of primary end points, specific causes of death or hospitalization (HF, arrhythmia, etc), effects of baseline characteristics on outcome and tolerability and effect of medication

Treatment and Achievement of Treatment Goals

- **Uptitration of therapy** to reduce symptoms was recommended in 192 patients in the symptom-guided group at baseline (77%), in 140 of 229 patients at visit month 1 (61%), in 111 of 210 patients at visit month 3 (53%) and in 101 patients of 194 at visit month 6 (52%)

- **An increase in therapy** was recommended in 213 patients at baseline in the N-terminal BNP group (86%), in 221 of 232 patients at visit month 1 (95%), in 198 of 218 patients at visit month 3 (91%) and in 190 of 211 patients at visit month 6 (90%)

Treatment and Achievement of Treatment Goals (2)

- Doses of drugs with proven prognastic efficacy were uptitrated to a significantly greater extent in the N-terminal BNP group
- The **dose increase** in ACE-I or ARB's did not differ between the age groups
- Spironolactone and eplerenone were given more frequently in the N-terminal BNP group
- Changes in use of diuretics, nitrates, digoxin and other treatment did not differ between the groups

Treatment and Achievement of Treatment Goals (3)

- Dyspnea improved and BNP levels decreased significantly in both groups with no significant differences during the uptitration phase of the study

- The **treatment effects** were similar for both age groups, although there was a significant interaction between treatment and age groups

- N-terminal BNP-guided therapy was a reason for increases in drug therapy in patients with little or no dyspnea

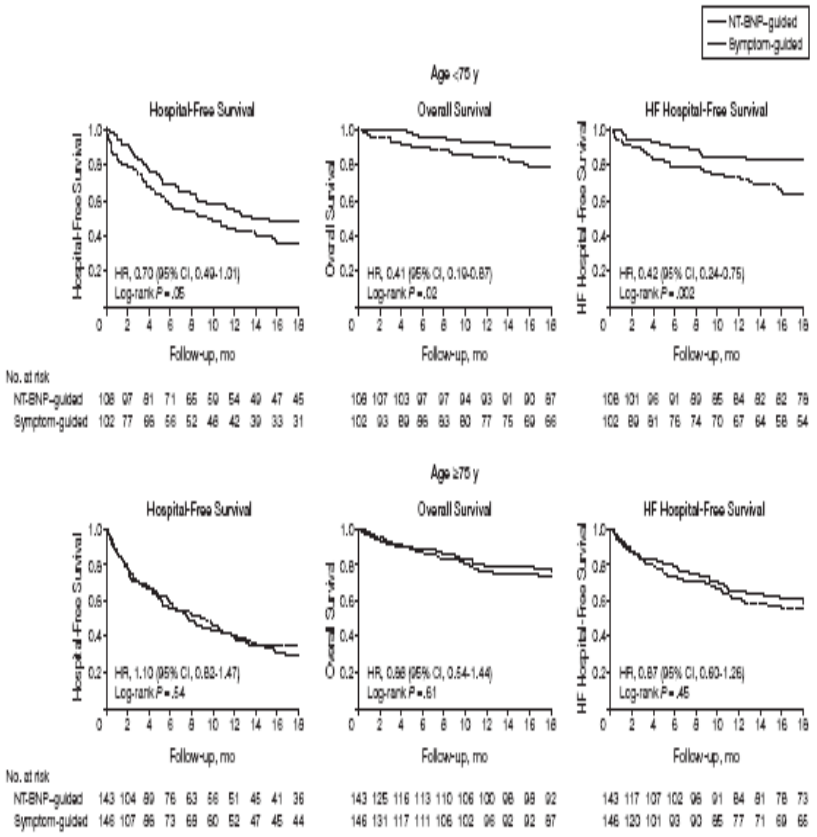
Outcomes

- N-terminal BNP-guided therapy did not improve 18-month survival free of any hospitalization compared with symptom-guided therapy
- **Overall survival rates** did not differ significantly (84% vs 78%)

- **Survival free of hospitalization** for HF was significantly improved with the N-terminal BNP-guided therapy
- The effects of the N-terminal BNP-guided treatment differed significantly between younger and older patients

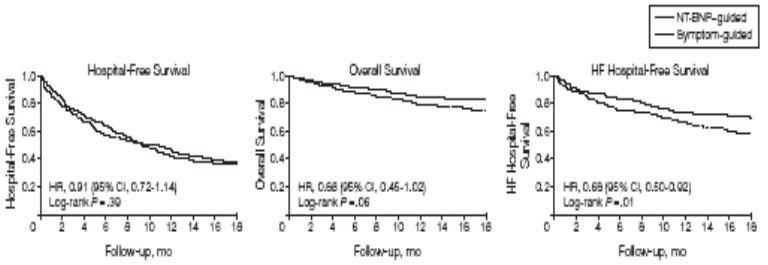
Outcomes (2)

Figure 6. Treatment Effects on Main Outcomes in Younger Compared With Older Patients



The differences between treatment groups were observed only in younger but not older patients. NT-BNP indicates N-terminal brain natriuretic peptide; CI, confidence interval; HF, heart failure; HR, hazard ratio.

Figure 5. Primary and Secondary Outcomes in the 2 Treatment Groups



NT-BNP indicates N-terminal brain natriuretic peptide; CI, confidence interval; HF, heart failure; HR, hazard ratio.

Table 2. Quality of Life in Patients With All 3 Treatment Month

Outcomes by Group	Baseline	Month 12	Month 18	*P* Value
Minnesota Living With Heart Failure questionnaire, mean (SD)[a]				
Symptom-guided	42.0 (20.3)	27.0 (18.6)	27.3 (21.5)	<.001
N-terminal BNP–guided	38.3 (20.2)	27.7 (17.9)	28.2 (17.6)	<.001
Duke Activity Status Index, median (IQR)[b]				
Symptom-guided	7.3 (2.7-15.4)	15.2 (7.2-27.5)	12.7 (4.9-27.0)	<.001
N-terminal BNP–guided	7.2 (2.7-18.6)	12.8 (7.2-27.0)	12.8 (4.5-25.7)	<.001
Short Form 12, mean (SD)[c]				
Physical component				
Symptom-guided	34.4 (9.1)	40.6 (10.3)	40.7 (10.2)	<.001
N-terminal BNP–guided	33.4 (9.8)	37.9 (10.1)	37.4 (10.2)	<.001
Mental component				
Symptom-guided	45.8 (10.5)	51.1 (9.5)	51.5 (9.9)	<.001
N-terminal BNP–guided	46.1 (11.0)	50.8 (10.4)	50.1 (10.3)	.001

Abbreviations: BNP, brain natriuretic peptide; IQR, interquartile range.
[a] Range of possible values is 0 to 105; lower values indicate better quality of life.
[b] Range of possible values is 0 to 58.2; higher values indicate better quality of life.
[c] Range of possible values is 0 to 100; higher values indicate better quality of life (a value of 50 is the average in the population).

Serious Adverse Events

- Overall, 236 patients had at least 1 serious adverse event – 49% in the N-terminal BNP-guided group and 45.6% in the symptom-guided group

- Incomplete adherence to the investigator's recommendations by general practitioners and/or patients due to hypotension or renal failure were more common in the BNP-guided group, both in younger patients and in patients aged 75 years or older

Limitations

- It is not possible to determine from this study which single drug treatment component added to the specific findings
- The strategies used many not completely reflect current standard of care according to the recommended guidelines, the use of evidence-based treatment was high and exceeded even that in large randomized controlled trials
- It is uncertain how much the knowledge of BNP levels contributed to the observed effect of the intensified treatment strategy

Limitations (2)

- The patients may be representative of a large part but not of all patients with HF seen in private practice
- Findings of the 2 age groups are subgroup findings only

Conclusions

- Intensified N-terminal BNP-guided therapy did not improve overall 18-month survival free of hospitalization or improve quality of life more than those receiving standrad symptom-guided therapy
- Survival free of hospitalization for HF was higher among the N-terminal BNP-guided group
- N-terminal BNP-guided therapy was not more beneficial in patients aged 75 years or older vs patients aged 60 to 74 years

Conclusion (2)

- Both treatment strategies improved symptoms and quality of life and reduced BNP levels similarly over time, although these effects tended to be lower in patients aged 75 years or older
- There was no significantly difference in the reduction of N-terminal BNP levels between the 2 treatment groups
- High BNP levels were observed with little or no symptoms and lead to intensification of therapy in the N-terminal BNP-guided strategy

Conclusion (3)

- Patients aged 75 years or older had no benefit from N-terminal BNP-guided therapy but had greater adverse effects
- Drugs with proven prophylactic effects could be increased more in patients receiving N-terminal BNP-guided therapy

Thank You!

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