

## Acute Heart Failure: New Evidence, New Guidelines

### Abstract

Acute heart failure (AHF) is a clinical syndrome that represents a heterogeneous group of disorders that typically present as dyspnea. Despite the high prevalence of AHF and its associated major morbidity and mortality, diagnosis of AHF can be difficult and treatment remains empiric and poorly defined. As stated in recent practice guidelines on AHF,<sup>1,2</sup> timely and accurate diagnosis as well as bedside characterization of cardiac filling pressures and output is the key to management of patients with AHF. Recent evidence suggests that a biomarker approach, particularly with the use of B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP), optimizes the overall management of patients with AHF.<sup>3</sup> The recently reported multicenter randomized controlled IMPROVE-CHF study has demonstrated that a management strategy that incorporates knowledge of NT-proBNP results improves the management of patients with suspected AHF by facilitating the diagnosis while improving health economic and selected clinical outcomes in the Canadian health care setting.<sup>4</sup>

Diuretics, vasodilators, continuous positive airway pressure and inotropes can be used to alleviate symptoms. However, none of the agents currently available for the treatment of AHF have been definitively shown in large prospective randomized trials to provide meaningful improvements in intermediate-term clinical outcomes. Numerous novel therapies are being developed for clinical use and a large-scale international outcome trial of the use of the human recombinant BNP nesiritide is underway.

### References:

1. Arnold JM, Liu P, Demers C, Dorian P, Giannetti N, Haddad H, Heckman GA, Howlett JG, Ignaszewski A, Johnstone DE, Jong P, McKelvie RS, Moe GW, Parker JD, Rao V, Ross HJ, Sequeira EJ, Svendsen AM, Teo K, Tsuyuki RT, White M. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management. *Can J Cardiol* 2006;22:23-45.
2. Arnold JM, Howlett JG, Dorian P, Ducharme A, Giannetti N, Haddad H, Heckman GA, Ignaszewski A, Isaac D, Jong P, Liu P, Mann E, McKelvie RS, Moe GW, Parker JD, Svendsen AM, Tsuyuki RT, O'Halloran K, Ross HJ, Rao V, Sequeira EJ, White M. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure update 2007: Prevention, management during intercurrent illness or acute decompensation, and use of biomarkers. *Can J Cardiol* 2007;23:21-45.
3. Moe GW. BNP in the Diagnosis and Risk Stratification of Heart Failure. *Heart Fail Monit* 2005;4:116-122.
4. Moe GW, Howlett J, Januzzi JL, Zowall H. N-Terminal proB-type natriuretic peptide improves the management of patients with acute decompensated heart failure: primary results of the Canadian multicenter IMPROVE-CHF study. *Circulation* 2007 (in press).

## Acute heart failure: an emerging public health problem

- Commonest cause of hospital admission in patients aged >65
- High mortality and rehospitalization rate
- Compared to acute coronary syndrome, AHF has much less RCTs and management guidelines

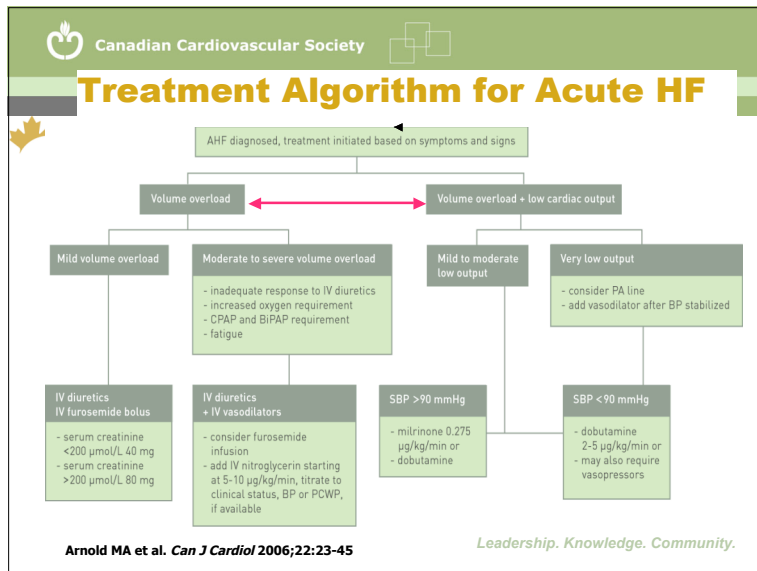
## AHF: a syndrome of heterogeneous orders

### Clinical syndromes

- Transient acute HF
  - *De novo*, adequate myocardial function on recovery
- Acute decompensated HF
  - Decompensation of chronic HF, structural damages with each episodes

### Clinical presentation

- HF with SBP > 140 mm Hg (50%)
- HF with SBP 90 – 140 mm Hg (48%)
- HF with SBP < 90mm Hg (2%)
- Cardiogenic shock (<1%)
- Pulmonary edema (<3%)
- Radiographic pulmonary congestion (74%)
- Isolated right-sided HF (?)
- ACS with HF (?)



## International Guidelines of Management of Acute HF: Diagnosis

	HFSA	ESC	CCS
<b>Timing of diagnosis and treatment</b>		As soon as possible after arrival at ED	Within 2 hrs of presentation to ED Response determined within 2 hrs Disposition within 8 hrs
<b>Primary diagnostic tools</b>	Clinical history, physical examination, Chest X ray, ECG, routine biochemical studies	Clinical history, physical examination, Chest X ray, ECG, routine biochemical studies	Clinical history, physical examination, chest X ray, ECG, routine biochemical studies
<b>Secondary diagnostic tools</b>	Echocardiography, BNP or NT-proBNP when there is clinical uncertainty about the diagnosis	ECG, chest x-ray, plasma BNP/NT-proBNP and other laboratory tests, and echocardiography	BNP if clinical uncertainty about diagnosis, echocardiography if available



Adams KS et al. *J Card Fail* 2006;12:10-38.  
 Neiminen MS et al. *Eur J Cardiol* 2005;26:384-416  
 Arnold MA et al. *Can J Cardiol* 2006;22:23-45

## Biomarker Approach in the Management of AHF: "Landmark Trials" of BNP/NT-proBNP

Trial	Natriuretic peptide	Design	Location
<b>BNP</b>	BNP	Diagnosis	US, multicenter
<b>BASEL</b>	BNP	RCT	Switzerland, single center
<b>PRIDE</b>	NT-proBNP	Diagnosis	US, single center

How applicable are these data to physicians in the Canadian health care system?

Maisei AS et al. E Engl J Med 2002;347:161-7  
 Januzzi JL et al. Am J Cardiol 2005;95:948-54  
 Mueller C et al. N Engl J Med 2004;354:647-54

## N-Terminal proB-Type Natriuretic Peptide Improves the Management of Patients with Suspected Acute Decompensated Heart Failure: Primary Results of the Canadian Multicenter IMPROVE-CHF Study

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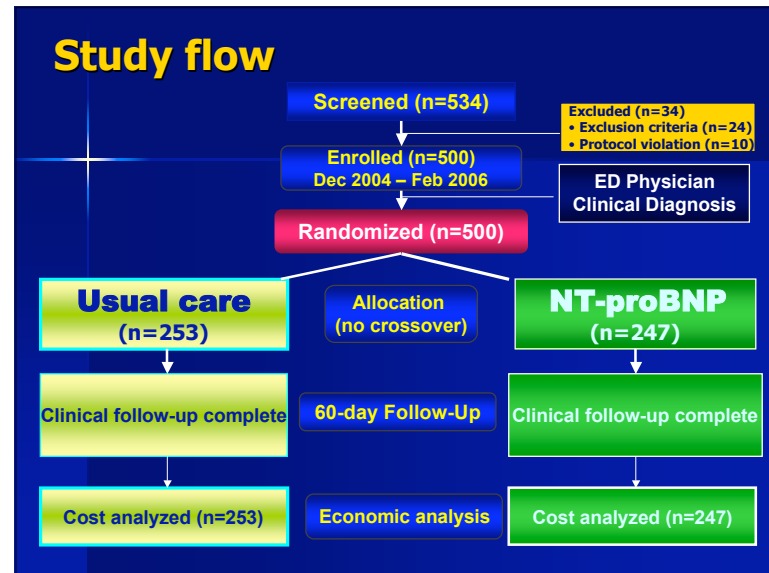
Presented in Late breaking clinical trial AHA 2006  
 Circulation 2007 (in press)

## Study Objectives

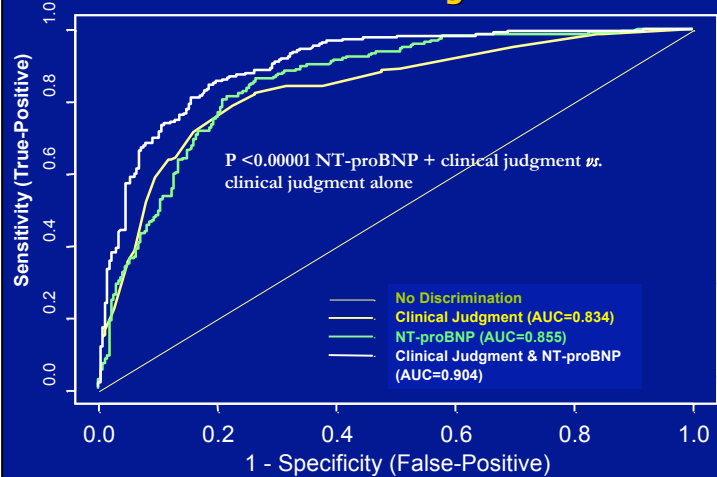
*General:* To test the hypothesis that a knowledge of NT-proBNP values improves the management of patients with dyspnea and suspected AHF in Canadian health care setting, a model for publicly funded universal access system.

*Primary:* To conduct a prospective multicenter double-blind randomized-controlled evaluation comparing Usual Care vs. NT-proBNP-guided care on clinical and health economic outcomes

*Secondary:* To document the diagnostic and prognostic utility of NT-proBNP in the Canadian setting



### Addition of NT-proBNP results to clinical evaluation in the ED diagnosis of AHF



### Primary Analysis - Usual Care vs NT-proBNP-Guided Care: Clinical Parameters

	NT-proBNP (n=247)	Usual Care (n=253)	P-value
Duration of ED visit, median (Q1-Q3), hrs	5.6 (3.9-8.0)	6.3 (4.2-8.6)	0.038
ICU admission, no. (%)	11 (8.5%)	14 (9.9%)	0.71
Duration of ICU stay, median (Q1-Q3), days	6.1 (1-11)	5.5 (3-11)	0.62
Initial hospitalization from ED, no. (%)	138 (57%)	146 (58%)	0.72

### Usual Care vs NT-proBNP-Guided Care: Mortality and Hospitalization

	NT-proBNP (n=247)	Usual Care (n=253)	P-value
Hospital LOS, median (IQR), days	6 (4-11)	7 (4-13)	0.28
In-hospital mortality, patient no. (%)	11 (4.5%)	6 (2.4%)	0.20
60-day mortality, no. (%)	13 (5.6%)	11 (4.4%)	0.59
Patients hospitalized in 60 days, no. (%)	33 (14%)	51 (20%)	0.040

### Usual Care versus NT-proBNP-Guided Care - Health Economics Analysis

Cost Outcomes	NT-proBNP (n=244)	Usual Care (n=251)	P-value
Initial ED visits (includes costs of NT proBNP test)	\$2196 (\$1602-\$3644)	\$2387 (\$1654-\$3190)	0.11
Initial and subsequent ED Visits	\$2841 (\$1791-\$4232)	\$3040 (\$1878-\$5103)	0.16
Initial and subsequent hospitalizations	\$4921 (\$2769-\$8365)	\$5924 (\$3388-\$10230)	0.04
Initial ED visits and initial hospitalization	\$4464 (\$2574-\$7438)	\$4857 (\$2953-\$9227)	0.05
<b>All ED visits and all hospitalizations</b>	<b>\$6007 (\$3246-\$10040)</b>	<b>\$7087 (\$3595-\$10807)</b>	<b>0.011</b>
<b>All ED visits, all hospitalizations and all outpatient visits</b>	<b>\$6310 (\$3640-\$10197)</b>	<b>\$7405 (\$4101-\$11828)</b>	<b>0.017</b>

Medians (Q1-Q3), 2005 Canadian dollars, US exchange rate in 2005 = 1.21163240



### **BNP/NT-proBNP in HF: Recommendations**

- BNP/NT-proBNP levels should be measured to help confirm or rule out a diagnosis of heart failure in the acute or ambulatory care setting in patients in whom the clinical diagnosis is in doubt (class I, level A).
- Measurement of BNP/NT-proBNP levels may be considered in patients with an established diagnosis of heart failure for prognostic stratification (class IIa, level A).
- Sequential measurements of BNP/NT-proBNP levels may be considered to guide the therapy of patients with heart failure (class IIb, level B).

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### **BNP/NT-proBNP in Heart Failure: Practical Tips**

- The use of such biomarkers as BNP and NT-proBNP levels should be complementary to, but not replace, good clinical evaluation.
- There are no compelling factors that favor the use of the BNP versus the NT-proBNP assay. The choice is dictated by availability as well as the clinician's familiarity, particularly with respect to interpretation.

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### **BNP and NT-proBNP Assay Cut Points for the Diagnosis of AHF**

	Age (years)	HF is unlikely	HF is possible but other diagnoses need to be considered	HF is highly likely
<b>BNP (point-of-care assay)</b>	All	< 100 pg/ml	100-500 pg/ml	> 500 pg/ml
<b>NT-proBNP</b>	< 50	< 300 pg/ml	300-450 pg/ml	> 450 pg/ml
	50 - 75	< 300 pg/ml	450-900 pg/ml	> 900 pg/ml
	> 75	< 300 pg/ml	900-1800 pg/ml	> 1800 pg/ml

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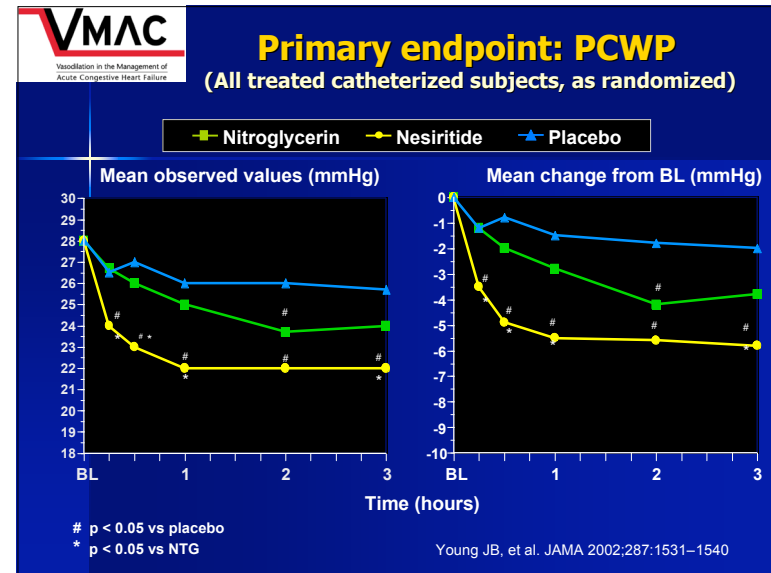
### **Available IV Therapies for AHF**

- Decrease congestion
  - Diuretics
- Decrease impedance/neurohormonal improvement
  - Nitroglycerin
  - Nitroprusside
  - Nesiritide (mostly US, Canada very soon)
- Improve cardiac function
  - Digoxin
  - Dobutamine
  - Dopamine
  - Milrinone
  - Enoximone (Europe)
  - Levosimendan (Europe, Japan)

## International Guidelines on the management of AHF: Therapy

	HFSA	ESC	CCS
<b>Initial Treatment</b>	Loop diuretics (furosemide, bumetanide, torsemide) at adequate dose to achieve optimal volume status,	Loop diuretics when symptoms are secondary to fluid retention.	IV diuretic (furosemide) bolus (for those with predominant volume overload)
<b>Vasodilators</b>	In patients with acute pulmonary edema or hypertension, IV vasodilators (nitroglycerin or nitroprusside or nesiritide) in combination with diuretics	In most if acceptable BP and with congestion Improve hemodynamics with nesiritide with fewer adverse effects	If inadequate response to diuretics, administration of combined IV diuretics and vasodilator therapy (IV nitroglycerin infusion)
<b>Inotropes</b>	For relief of symptoms, to improve end organ function in patients with evidence of fluid overload unresponsive to IV diuretics or vasodilators or poor perfusion	When peripheral hypoperfusion as evidenced by hypotension and decreased renal function, is present.	In patients with low cardiac output and systolic BP < 90 mmHg.

Adams KS et al. J Card Fail 2006;12:10-38.  
 Neiminen MS et al. Eur J Cardiol 2005;26:384-416  
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## ASCEND-HF Trial

- Study Design:** A simple phase III randomized, double blind, placebo controlled, multi-center study evaluating the efficacy and safety of nesiritide administered in addition to standard care compared with placebo in subjects with acute decompensated heart failure
- Endpoints:** Heart failure rehospitalization, mortality, symptom relief, and quality of life
- Study size:** 7000 patients at approximately 700 sites worldwide