Journal Reading

Natriuretic peptide testing in EDs for managing acute dyspnea: a meta-analysis

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Introduction

- Heart failure is a major public health concern that afftects more than 15 million people in North America and Europe
- Acute dyspnea is a key symptom of HF and one of the most common causes of admission to ED
  - pneumonia, asthma, exacerbation of COPD, and pulmonary embolism
  - CXR, EKG, ABG, and Doppler-echocardiography
- Higher in-hospital morbidity and mortality rates
  - delays in diagnosing and initial misdiagnosis of HF

Introduction

- The cardiac natriuretic hormones family released by cardiomyocytes has been shown to be useful in diagnosing HF in dyspneic p'ts
  - Pro-B-type natriuretic peptide, 108 amino acids
    - B-type natriuretic peptide (BNP), 32 amino acids, active
    - NT-proBNP, 76 amino acids, inactive
    - Released in response to increased ventricular wall stretch, volume expansion, and overload

Introduction

- No significant effect of early BNP testing was found neither on clinical outcomes nor on resource use
- The goal of this investigation was to perform a systematic review of all RCT that assessed the usefulness of BNP or NT-proBNP in the management of p't presenting with dyspnea into ED regarding short-term clinical outcomes and resource use

Materials and methods

- P'ts presenting with acite dyspnea as the main symptom to ED
- Results were communicated only to emergency physicians who managed the p'ts
- Cochrane (Issue 3,2009), MEDLINE, EMBASE, and LILACS (all up to Sep. 2009)
- RCT only with no language restrictions
- AHA congress 2007-2009; European Congress on Emergency Medicine 2008-2009; annual meeting of the Society for academic Emergency Medicine 2007-2009, and clinical trials registration websites

Materials and methods

- Primary outcome was the hospital admission rate
- Other outcomes included
  - ICU admission rate
  - time to discharge and length of hospital stay
  - in-hospital and 30-day mortality rates
  - 30-day rehospitalization rates
  - total direct medical costs

Materials and methods

- Inconsistency of findings across studies
  - Cochran's Q statistic and the I^2 statistic with associated 95% confidence interval (CI)

Results

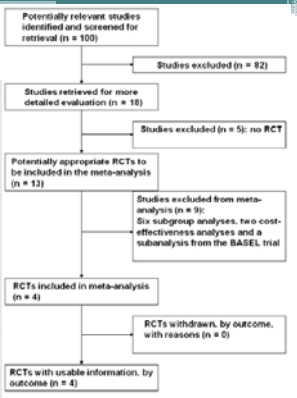

Table 1 Search strategies in Medline and Embase

Medline
("Atrial Natriuretic Factor"[Mesh] OR "Natriuretic Peptide, Brain"[Mesh] OR "BNP"[tiab] OR "NT-proBNP"[tiab]) AND ("Dyspnea"[Mesh] OR "dyspnea"[tiab] OR "dyspneic"[tiab] OR "dyspnoea"[tiab] OR "dyspnoeic"[tiab] OR "shortness of breath"[tiab]) AND (("Randomized Controlled Trial"[ptyp] OR "Controlled Clinical Trial"[ptyp] OR "randomised"[tiab] OR "placebo"[tiab] OR "Clinical Trials as Topic"[Mesh:noexp] OR "randomly"[tiab] OR "trial"[ti]) NOT ("Animals"[Mesh] NOT ("Humans"[Mesh] AND "Animals"[Mesh]))

Embase
('atrial natriuretic factor'/exp OR 'brain natriuretic peptide'/exp OR 'amino terminal pro brain natriuretic peptide'/exp OR 'BNP':ti,ab,de OR 'NT-proBNP':ti,ab,de) AND ('dyspnea'/exp OR 'dyspnea':ti,ab,de OR 'dyspneic':ti,ab,de OR 'dyspnoea':ti,ab,de OR 'dyspnoeic':ti,ab,de) AND (random$ OR factorial$ OR crossover$ OR cross over$ OR cross-over$ OR placebo OR doubl$ adj blind$ OR singl$ adj blind$ OR assign$ OR allocat$ OR volunteer$ OR 'crossover-procedure'/exp OR 'double-blind procedure'/exp OR 'randomised controlled trial'/exp OR 'single-blind procedure'/exp)

Fig. 1 Flow diagram of study selection.

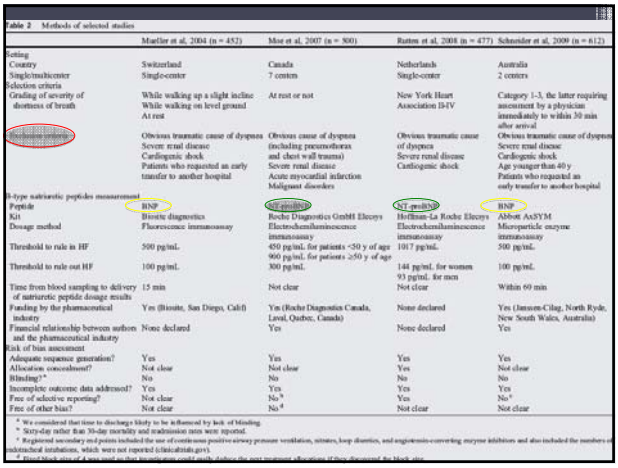

Table 2 Methods of selected studies

	Mueller et al, 2004 (n = 452)	Moe et al, 2007 (n = 500)	Rutten et al, 2008 (n = 477)	Schneider et al, 2009 (n = 612)
Setting				
Country	Switzerland	Canada	Netherlands	Australia
Single/multicenter	Single-center	7 centers	Single-center	2 centers
Selection criteria				
Grading of severity of shortness of breath	While walking up a slight incline While walking on level ground At rest	At rest or not	New York Heart Association II-IV	Category 1-3, the latter requiring assessment by a physician immediately to within 30 min after arrival
Exclusion criteria	Obvious traumatic cause of dyspnea Severe renal disease Cardiogenic shock Patients who requested an early transfer to another hospital	Obvious cause of dyspnea (including pneumothorax and chest wall trauma) Severe renal disease Acute myocardial infarction Malignant disorders	Obvious traumatic cause of dyspnea Severe renal disease Cardiogenic shock	Obvious traumatic cause of dyspnea Severe renal disease Cardiogenic shock Age younger than 40 y Patients who requested an early transfer to another hospital
B-type natriuretic peptides measurement				
Peptide	BNP	NT-proBNP	NT-proBNP	BNP
Kit	Biosite diagnostics	Roche Diagnostics GmbH Elecsys	Hoffman-La Roche Elecsys	Abbott AxSYM
Dosage method	Fluorescence immunoassay	Electrochemiluminescence immunoassay	Electrochemiluminescence immunoassay	Microparticle enzyme immunoassay
Threshold to rule in HF	500 pg/mL	450 pg/mL for patients <50 y of age 900 pg/mL for patients ≥50 y of age	1017 pg/mL	500 pg/mL
Threshold to rule out HF	100 pg/mL	300 pg/mL	144 pg/mL for women 93 pg/mL for men	100 pg/mL
Time from blood sampling to delivery of natriuretic peptide dosage results	15 min	Not clear	Not clear	Within 60 min
Funding by the pharmaceutical industry	Yes (Biosite, San Diego, Calif)	Yes (Roche Diagnostics Canada, Laval, Quebec, Canada)	None declared	Yes (Janssen-Cilag, North Ryde, New South Wales, Australia)
Financial relationship between authors and the pharmaceutical industry	None declared	Yes	None declared	Yes
Risk of bias assessment				
Adequate sequence generation?	Yes	Yes	Yes	Yes
Allocation concealment?	Not clear	Not clear	Yes	Not clear
Blinding?*	No	No	No	No
Incomplete outcome data addressed?	Yes	Yes	Yes	Yes
Free of selective reporting?	Not clear	No[b]	Yes	No[c]
Free of other bias?	Not clear	No[d]	Not clear	Not clear

* We considered that time to discharge likely to be influenced by lack of blinding.
† Sixty-day rather than 30-day mortality and readmission rates were reported.
‡ Registered secondary endpoints included the use of continuous positive airway pressure ventilation, nitrates, loop diuretics, and angiotensin-converting enzyme inhibitors and also included the numbers of endotracheal intubations, which were not reported (clinicaltrials.gov).
§ Fixed block size of 4 was used so that investigators could easily deduce the next treatment allocation. If they discovered the block size

Table 3 Participant characteristics in selected studies

	Mueller et al, 2004 (n = 452)	Moe et al, 2007 (n = 500)	Rutten et al, 2008 (n = 477)	Schneider et al, 2009 (n = 612)
Participants				
Age, y	71	70	59	73
Male	58%	51%	54%	53%
Current smoking	24%	Not clear	36%	13%
Medical history				
Heart failure	Not clear	34%	43%	36%
Coronary artery disease	50%	Not clear	21%	41%
Hypertension	50%	53%	25%	50%
Diabetes	23%	25%	16%	20%
Chronic kidney disease	25%	Not clear	8%	11%
Chronic obstructive pulmonary disease	31%	29%	26%	63%[a]
Asthma	6%	Not clear	13%	
Symptoms/signs at admission				
Shortness of breath at rest	27%	52%	32%	Not clear
Orthopnea	Not clear	45%	31%	20%
Coughing	49%	Not clear	57%	50%
Elevated jugular venous pressure	14%	26%	14%	28%
S3 gallop	2%	Not clear	2%	3%
Rales	46%	47%	37%	Not clear
Wheezing	22%	32%	24%	28%
Lower extremity edema	34%	45%	20%	15%
Heart rate, beat/min	97	86	97	96
SBP/DBP, mm Hg	145/85	135/78	Not clear	142/73
Final heart failure diagnosis	48%	46%	Not clear	45%

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.
[a] Chronic obstructive pulmonary disease or asthma.

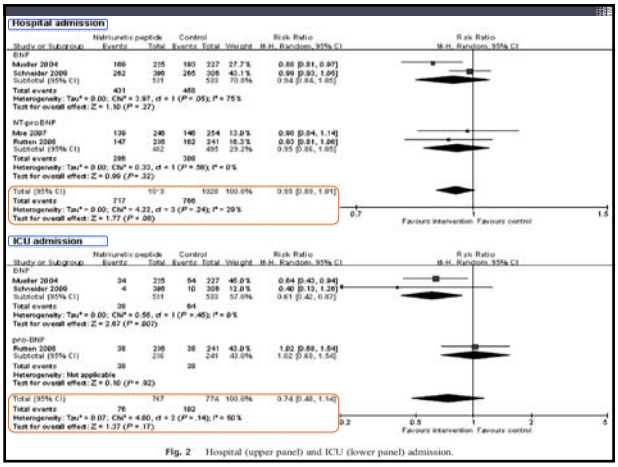

Fig. 2 Hospital (upper panel) and ICU (lower panel) admission.

Table 4 Time to discharge and length of stay outcomes in selected studies

	Intervention group		Control group		P[a]
	n	Median (25%-75% percentiles)	n	Median (25%-75% percentiles)	
Duration of ED visit, h					
NT-proBNP					
Moe et al, 2007	246	5.6 (4.0-8.0)	254	6.3 (4.3-8.6)	.031
Rutten et al, 2008	236	2.8 (2.0-3.7)	241	2.9 (2.2-3.9)	.12
Time to discharge, d					
BNP					
Mueller et al, 2004[b]	212	8.0 (1.0-16.0)	206	11.0 (5.0-18.0)	.001
NT-proBNP					
Rutten et al, 2008	236	1.9 (0.12-8.4)	241	3.9 (0.16-11.0)	.04
Length of stay, d					
BNP					
Schneider et al, 2009	262	4.4 (2.0-9.0)	265	5.0 (2.0-9.0)	.93
NT-proBNP					
Moe et al, 2007	139	6.0 (4.0-11.0)	146	7.0 (4.0-13.0)	.30
Rutten et al, 2008	147	7.8 (4.8-13.9)	162	8.1 (4.4-15.6)	.48

[a] Nonparametric 2-sample test.
[b] Patients who died in hospital were excluded.

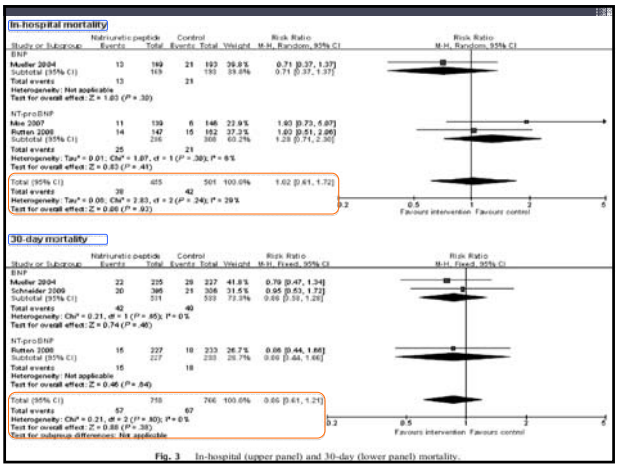

Fig. 3 In-hospital (upper panel) and 30-day (lower panel) mortality.

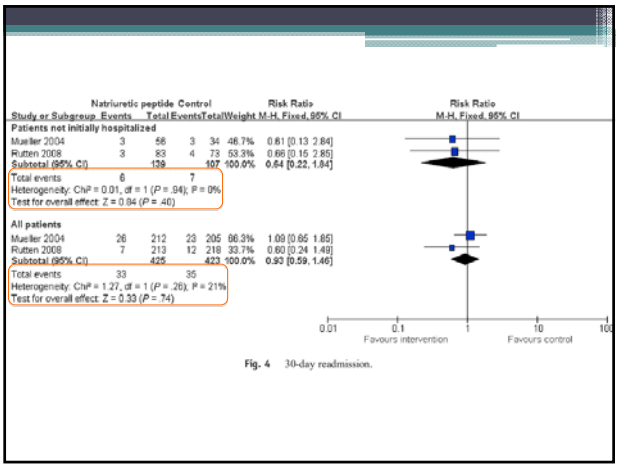

Fig. 4 30-day readmission.

- Final HF diagnosis
  - less frequently the by Mueller
  - more frequently by Schneider
  - not significantly, however
- Costs
  - 2 trials showed significantly reduced in the median total treatment cost

Discussion

- Arguments about the early use of natriuretic peptides in 65 y/o and older p'ts
  - HF is the leading cause of admission and is associated with an in-hospital death rate ≥ 15%
  - determination of the cause of dyspnea is highly challenging
- Those with a intermediate clinical suspicion for HF
  - pretest physician-estimated probability between 20% and 80%
  - higher mortality
- P'ts within the "gray zone" level
  - diagnostic accuracy is not satisfactory
  - no authors specify the rate

Limitations

- Sample size calculation
  - based on time to discharge in 2 trials, and on ED visit duration in another
- Contamination of the randomization
  - physicians being able to order testing on p'ts in the control arms
- Failed to distinguish true readmission
  - secondary admissions who had not been admitted initially

Limitations

- Limited number of available randomized trials that precluded formal investigation of sources of heterogeneity
  - expertise of physicians
  - the availability of facilities
  - other diagnostic tests
  - the presence of financial incentives to admit or discharge
- Diversity of study populations
- Variability in the method and intervention could be of importance

Conclusions

- This meta-analysis of 4 RCT showed that natriuretic peptide testing in all emergency p'ts with SOB had no apparent effects on p'ts outcomes, except a significant reduction in time to discharge
- Large multicenter randomized trials
  - more solid basis
  - useful in p'ts with an intermediate pretest probability of HF
  - recommendations

Thanks for your attention