Critical Review Form

Therapy

N-terminal pro–brain natriuretic peptide testing in the emergency department: Beneficial effects on hospitalization, costs, and outcome, *American Heart Journal* 2008; 156: 71-77

Objective: **"To investigate whether introduction of rapid NT-proBNP testing in the ED of our hospital associates with improved diagnostic decision making as reflected in cost savings without compromising clinical outcome". (p. 71)**

Methods: **Prospective, randomized, controlled trial from December 2004 to February 2006 in Erasmus Medical Center ED (Rotterdam, The Netherlands) of adult patients with chief complaint acute dyspnea. Exclusion criteria included trauma or cardiogenic shock, dialysis or failure to consent. Control group physicians were blinded to NT- proBNP levels. Treatment group physicians were provided the NT- proBNP levels with the following cut-points: CHF excluded if < 93 pg/mL in males or < 144 for females; CHF ruled-in if > 1017 pg/mL. Physicians rated the probability of AHF (from 1% to 100%) using a visual analogue scale before the sample was sent to the lab, but after history, physical exam, chest x-ray, and ECG. Pre-test probability was stratified as very unlikely (≤ 25%) intermediate (25% - 75%) or very likely (> 75%)**

If patients were referred to the ED by a primary care physician then they were evaluated by a resident in Cardiology, Pulmonology, or Internal Medicine who consulted a "senior specialist" before deciding upon definitive therapy and disposition. If patients presented to the ED without prior PCP evaluation, the resident assigned to the ED performed the assessment.

The primary and point was time-to-discharge for which the study had 80% power with α= 0.05 based upon hypothesized 3-day difference between groups (SD 10.3, (Mueller) if 376 patient were included. Secondary and points included costs, ED LOS, proportion admitted to the hospital and proportion admitted to ICU. Thirty-day outcomes were assessed by medical record review. If no records were found, telephone or mail contact used. Costs were calculated per patient based upon national averages (general ward = $612/day, ICU = $2165/day) for a university hospital. For diagnostic evaluations, the prices as charged to health insurance companies were used.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	Yes. "Patients were randomized 1:1 without stratification, according to a computer-generated scheme". (p. 72)
1.	Were patients randomized?	Yes. "The attending physician was unaware of the allocation of an included subject because the randomization was performed with sealed non–see-through envelopes. Upon arrival of the blood sample at the laboratory, the attending technician assigned the patients to either the NT-proBNP group or control group according to the instructions in the sealed envelope accompanying the blood sample". (p. 72) Of course, after the NT-proBNP physicians were informed of the test result, they knew which group the patient was in.
2.	Was randomization concealed (blinded)?	Yes. "The attending physician was unaware of the allocation of an included subject because the randomization was performed with sealed non–see-through envelopes. Upon arrival of the blood sample at the laboratory, the attending technician assigned the patients to either the NT-proBNP group or control group according to the instructions in the sealed envelope accompanying the blood sample". (p. 72) Of course, after the NT-proBNP physicians were informed of the test result, they knew which group the patents was in.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "All analyses were by the intention-to-treat principles". (p. 72)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. "The demographic and clinical characteristics of the 236 participants in the NT-proBNP group and 241 participants in the control group were well balanced. (Table I). (p. 73)

B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Unlikely since all had blood drawn and results not routinely presented to patients.
2.	Were clinicians aware of group allocation?	Yes. "Blinding of diagnostic strategy allocation is impossible in randomized studies assessing cost-effectiveness of diagnostic tests because the physicians are provided with the additional diagnostic information only in the study group. Because the discharge of a patient is determined by his or her clinical condition, we consider it very unlikely that unblinding of study group allocation per se was of any influence on the time to discharge in our trial". (p. 76)
3.	Were outcome assessors aware of group allocation?	Uncertain. Not clearly stated.
4.	Was follow-up complete?	"For nine patients in the NT-proBNP group and eight patients in the control group, follow-up data could not be obtained because of logistic reasons". (p. 74)
II.	**What are the results (answer the questions posed below)?**	

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<td>1.</td>
<td>How large was the treatment effect?</td>
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Over 14 months, there were 29,000 ED visits including 785 with dyspnea from which 477 were randomized with mean age 58.6 years.
Pre-existing co-morbidity included cardiac disease (20%) , pulmonary disease (35%) or both (24%).
Two-thirds of participants had been referred by their primary care provider and were evaluated in the ED by Pulmonary (32%), Internal Medicine (24%), Cardiology (18%), or Emergency Medicine (24%). 86% were evaluated by a senior staff member..
The NT- proBNP group had significantly shorter median length of hospitalization (1.9 days vs. 3.9 days, p = 0.04) with a trend towards decreased overall average costs (NT- proBNP $4984 vs. control $6352, mean difference $1364 with 95% CI - $246 to $3215).
There was no difference in hospitalization rates, ED length of stay, in-hospital or 30-day mortality rates.
Cost-effectiveness plane (Fig 2) demonstrated trend for reduced costs without increasing mortality.
The effect on costs was greatest among those with cardiac dyspnea (mean reduction $2627).
Pre-test probability included unlikely CHF (59%), indefinite (21%), or highly likely (15%).

Likelihood of CHF upon NT proBNP
<table>
<tr><th>Physician Pre-test gestalt</th><th>Low</th><th>Indefinite</th><th>High</th></tr>
<tr><td>Low risk</td><td>128 (45%)</td><td>93 (33%)</td><td>61 (22%)</td></tr>
<tr><td>Indeterminate</td><td>22 (20%)</td><td>24 (23%)</td><td>59 (56%)</td></tr>
<tr><td>High</td><td>2 (3%)</td><td>8 (11%)</td><td>60 (86%)</td></tr>
</table>

Agreement between clinician impression and NT- proBNP was poor. (K = 0.201)

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<td>2.</td>
<td>How precise was the estimate of the treatment effect?</td>
<td>See 95% CI reported above.</td>
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</table>

III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	No. Dutch patients with ready access to a primary care physician who is familiar with the patient's PMH, baseline status, and physical exam. This opens opportunity for spectrum bias since these pre-appraised patients may have different constellations of disease burden and clinical presentation than the undifferentiated dyspnea patient who walks into the typical urban U.S. ED without known PMH or baseline functional status/physician exam. Additionally, these patients were not routinely evaluated by an EP. Different specialists may have different aptitudes at physical diagnosis and assessing pre-test probability. Additionally, no accepted criterion standard for AHF was reported and the cut-points used lack sufficient diagnostic discriminatory power.
2.	Were all clinically important outcomes considered?	No assessment of clinician or patient satisfaction or false-positive related morbidity.
3.	Are the likely treatment benefits worth the potential harm and costs?	Possibly – although this study needs to be assessed carefully based upon the Dutch healthcare model and questionable NT-proBNP cut-points used (see III-1), these results are supported by two other studies (BASEL and IMPROVE-CHF) which also demonstrated significant cost savings in diagnostic RCT's assessing NT- pro-BNP.

Limitations

1) **No criterion standard used to diagnose AHF. How do we know who did or did not have AHF? Certainly not based upon NT- proBNP results above, particularly given the illogical cutoff points used. (see PGY-II articles).**

2) **Limited external validity to uninsured U.S. population without ready access to PCP or medical specialists.**

3) **No direct assessment of NT- proBNP result on clinician decision-making.**

Bottom Line

Single-center Dutch study adds to previous diagnostic RCT reports suggesting that NT- proBNP (or BNP) is cost-effective without increasing patient mortality. Future cost analyses will need to analyze truly undifferentiated dyspnea patients (not sent by PCP with suspected CHF) in conjunction with clinically useful BNP/NT—BNP cut points and accepted CHF criterion standards (Cardiology adjudication).