Novel Biomarkers and Acute Medicine

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Disclosure of Commercial Relationships

• Richard M Nowak MD
  Principle Investigator: Henry Ford Hospital System

Funding for the BACH Trial provided by BRAHMAktiengesellschaft, Biotechnology Center, Hennigsdorf/Berlin, Germany
RAPID MEASUREMENT OF B-TYPE NATRIURETIC PEPTIDE IN THE EMERGENCY DIAGNOSIS OF HEART FAILURE

ALAN S. MAISEL, M.D., PADMA KRISHNASWAMY, M.D., RICHARD M. NOWAK, M.D., M.B.A., JAMES MCCORD, M.D., JUDD E. HOLLANDER, M.D., PHILIPPE DUC, M.D., TORBJÖRN OMLAND, M.D., PH.D., ALAN B. STORROW, M.D., WILLIAM T. ABRAHAM, M.D., ALAN H.B. WU, PH.D., PAUL CLOPTON, M.S., PHILIPPE G. STEG, M.D., ARNE WESTHEIM, M.D., PH.D., M.P.H., CATHERINE WOLD KNUDSEN, M.D., ALBERTO PEREZ, M.D., RADMILA KAZANEGRA, M.D., HOWARD C. HERRMANN, M.D., AND PETER A. MCCULLOUGH, M.D., M.P.H., FOR THE BREATHING NOT PROPERLY MULTINATIONAL STUDY INVESTIGATORS*
Biomarkers in the Assessment of Congestive Heart Failure

A Multi National Trial Examining Acute Shortness of Breath, Heart Failure and a Novel Panel of Biomarkers

A Maisel MD PI
S Anker MD co-PI
Adrenomedullin (ADM), Endothelin-1 (ET-1), Atrial Natriuretic Peptide (ANP), and Vasopressin (AVP)

Important regulators of microcirculation and heart function. Unstable in vivo and ex vivo and thus not suitable for clinical assessments.
Background/Methods

Mid-Region Pro-Hormone Markers for Diagnosis and Prognosis in Acute Dyspnea: Results From the BACH (Biomarkers in Acute Heart Failure) Trial


15 enrolling centers

831 (8)

84 (1)

UCSF, California

Cleveland Clinic, OH

VAMC, Minn.

Henry Ford, MI

Virg. Coll. Med, VA

Univ. MD, MD

VASD, California

UCSD, California

1641 SOB patients

726 (6)

Basel, SUI

Leicester, UK

Athens, GR

Wroclaw, POL

Rome, IT

Berlin, GER

Otago Univ. Christchurch, NZ
Methods

Patients enrolled presented to the ED with a primary complaint of SOB not from trauma, or obvious MI, and not on hemodialysis

Two independent cardiologists agreed on the final diagnosis of CHF or non CHF at 30 days post discharge

Pulmonologist reviewed all primary and secondary diagnoses of pneumonia
Two BACH Primary Endpoints

- The primary **diagnostic** end point was the diagnosis of AHF, where the noninferiority of MR-proANP compared with BNP was evaluated.

- The primary **prognostic** end point was 90-day survival, where the superiority of the utility of MR-proADM versus BNP for predicting survival over a period of 90 days was evaluated in patients with a diagnosis of AHF.
Adrenomedullin Literature

Adrenomedullin: ~160 publications

MR-proADM: ~50 paper +
~30 abstracts/posters
~80 publications
(70 published, 10 accept./submit)

Diabetes, Alzheimer 7%
Assay, basic research 7%
Kidney 2%
Stomach 1%
Liver 1%
LRTI (CAP, COPD, bronchitis) 17%
Sickle cell anaemia 2%
Heart failure 33%
Cardiovascular disease 21%
Sepsis, organ dysfunction 9%
Background/Methods

- Plasma adrenomedullin (ADM) is ubiquitous in all tissues/organs examined
- High expression in the adrenal medulla and vascular system
- Plasma ADM is derived mainly from endothelial cells

ADM measurement is not suitable for clinical routine diagnosis assessment due to its ex vivo instability (immediate binding to receptors, 22min half-life time)

Mid regional pro-ADM (MR-proADM) is a stable and reliable surrogate marker for ADM release

Tissue Specific Functions

Lung
- \( \downarrow \) Pulmonary hypertension
- \( \uparrow \) Synthesis of ET-1 and NO
  - vasoprotective

Kidney
- \( \uparrow \) Sodium excretion
- \( \uparrow \) Urine volume
- \( \uparrow \) Renal blood flow
- \( \downarrow \) Aldosterone

CNS and Endocrine Glands
- \( \downarrow \) Thirst
- \( \downarrow \) Salt Appetite
- \( \downarrow \) Vasopressin secretion
- \( \downarrow \) ACTH secretion
- \( \downarrow \) Insulin secretion

Reproductive System
- \( \uparrow \) Stimulatory Effect on FSH

Vascular System
- \( \uparrow \) Vasodilation
- \( \downarrow \) Blood pressure

Heart
- \( \uparrow \) Contractility
- \( \downarrow \) ANP

Mid-Region Pro-Hormone Markers for Diagnosis and Prognosis in Acute Dyspnea

Results From the BACH (Biomarkers in Acute Heart Failure) Trial

Alan Maisel, MD,*** Christian Mueller, MD,† Richard Nowak, MD,‡ W. Frank Peacock, MD,§
Judd W. Landsberg, MD,¶ Piotr Ponikowski, MD, PhD,∥ Martin Mockel, MD,#
Christopher Hogan, MD,** Alan H. B. Wu, PhD,†† Mark Richards, MD, PhD,‡‡ Paul Clopton, MS,*
Gerasimos S. Filippatos, MD, §§ Salvatore Di Somma, MD,|| Inder Anand, MD, DPHIL (OXON),¶¶
Leong Ng, MD,## Lori B. Daniels, MD, MAS,*** Sean-Xavier Neath, MD, PhD,***
Robert Christenson, PhD,††† Mihael Potocki, MD, James McCord, MD,‡ Garret Terracciano, BS,‡‡‡
Dimitrios Kremastinos, MD, §§ Oliver Hartmann, MSc, §§§ Stephan von Haehling, MD,††
Andreas Bergmann, PhD, §§§ Nils G. Morgenthaler, MD, PhD, §§§ Stefan D. Anker, MD, PhD#||||
San Diego, La Jolla, and San Francisco, California; Basel, Switzerland; Detroit, Michigan; Cleveland, Ohio;
Wroclaw, Poland; Berlin, Germany; Richmond, Virginia; Christchurch, New Zealand; Athens, Greece;
Rome, Italy; Minneapolis, Minnesota; Leicester, United Kingdom; and Baltimore, Maryland
Survival in AHF: Area Under the Time Dependent ROC Plot

MR-proADM predicts short term (30 day) survival exceptionally well
Survival in AHF - MR-proADM Quartiles

Risk is great in the highest quartile of MR-proADM

<table>
<thead>
<tr>
<th>Quartile</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>1</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>0.8</td>
<td>0.3-2.0</td>
<td>0.640</td>
</tr>
<tr>
<td>3rd</td>
<td>1.1</td>
<td>0.5-2.5</td>
<td>0.822</td>
</tr>
<tr>
<td>4th</td>
<td>3.2</td>
<td>1.6-6.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Quartile | HR  | 95% CI   |   p   |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1st-3rd</td>
<td>1</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>3.3</td>
<td>2.0-5.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Prognostic Summary

High levels of MR-proADM may help risk stratify patients who present to the ED with an acute exacerbation of CHF

The MR-proADM level measured in the ED may help determine which of these CHF patients can be safely discharged home, those who require very close follow up and those who should be admitted for more intensive therapy
Midregion Prohormone Adrenomedullin and Prognosis in Patients Presenting With Acute Dyspnea

Results From the BACH (Biomarkers in Acute Heart Failure) Trial

Alan Maisel, MD,*# || Christian Mueller, MD,† Richard M. Nowak, MD,‡ W. Frank Peacock, MD,§ Piotr Ponikowski, MD, PhD,|| Martin Mockel, MD,¶ Christopher Hogan, MD,# Alan H. B. Wu, PhD,** Mark Richards, MD, PhD,†† Paul Clopton, MS,* Gerasimos S. Filippatos, MD,‡‡ Salvatore Di Somma, MD,§§ Inder Anand, MD, DPHIL (OxON),||| Leong L. Ng, MD,¶¶ Lori B. Daniels, MD, MAS,## Sean-Xavier Neath, MD, PhD,## Robert Christenson, PhD,*** Mihael Potocki, MD,† James McCord, MD,‡ Oliver Hartmann, MSc,††† Nils G. Morgenthaler, MD, PhD,### Stefan D. Anker, MD, PhD¶¶¶§§

San Diego and San Francisco, California; Basel, Switzerland; Detroit, Michigan; Cleveland, Ohio; Wroclaw, Poland; Berlin, Germany; Richmond, Virginia; Christchurch, New Zealand; Athens, Greece; Rome, Italy; Minneapolis, Minnesota; Leicester, United Kingdom; and Baltimore, Maryland
Mid-region Prohormone Adrenomedullin (MR-proADM) Identifies Acutely Dyspneic ED Patients with High 90 Day Mortality: Results from The Biomarkers in Acute Heart Failure (BACH) Trial

Richard M Nowak MD, MBA, FACEP, FAAEM, for the BACH Investigators
ESC Scientific Congress
Paris, France, 27-31 August, 2011

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Adrenomedullin in Sepsis

MR-proADM and severity of disease

Setting: Medical ICU

- 101 consecutive patients
- 213 healthy controls

Adrenomedullin in Sepsis
MR-proADM and outcome

Setting: Medical ICU

Patients with sepsis, severe sepsis and septic shock

MR-ProADM measured on the day of admission

Acute Myocardial Infarction

Prognostic Value of Midregional Pro-Adrenomedullin in Patients With Acute Myocardial Infarction

The LAMP (Leicester Acute Myocardial Infarction Peptide) Study

Sohail Q. Khan, BSc (Hons), MBChB, MRCP,* Russell J. O’Brien, MBChB, MRCP,* Joachim Struck, PhD,† Paulene Quinn, MPhil,* Nils Morgenthaler, PhD,† Iain Squire, MD, FRCP,* Joan Davies, PhD, FRCP,* Andreas Bergmann, PhD,† Leong L. Ng, MD, FRCP*

Leicester, United Kingdom; and Hennigsdorf, Germany

Khan SQ, et al. JACC 2007
Acute Heart Failure

Comparative Evaluation of B-Type Natriuretic Peptide, Mid-Regional Pro-A-type Natriuretic Peptide, Mid-Regional Pro-Adrenomedullin, and Copeptin to Predict 1-Year Mortality in Patients With Acute Destabilized Heart Failure

ALFONS GEGENHUBER, MD,1 JOACHIM STRUCK, PhD,2 BENJAMIN DIEPLINGER, MD,3 WERNER POELZ, PhD,4 RICHARD PACHER, MD,5 NILS G. MORGENTHALER, PhD,2 ANDREAS BERGMANN, PhD,2 MEINHARD HALTMAYER, MD,3,6 AND THOMAS MUELLER, MD3

Linz, Austria; Berlin, Germany; Vienna, Austria; Salzburg, Austria

Fig. 4. Kaplan-Meier plots showing survival in 137 patients with acute destabilized heart failure who were stratified into 3 groups according to plasma mid-regional pro-adrenomedullin tertiles at baseline (1st tertile <0.75 nmol/L, n = 46, solid line; 2nd tertile 0.75–1.23 nmol/L, n = 45, dashed line; and 3rd tertile >1.23 nmol/L, n = 46, dotted line; log-rank test for trend, P < .001).
MR-proADM predicts best 30- and 90-day mortality in ED patients (n=287) with SOB (regardless of etiology)

The addition of MR-proADM to NT-proBNP has an incremental value on risk stratification

Potocki M et al. Crit Care 2009
Background/Methods

PRIMARY BACH RESULTS

568 (34.6%) with acute CHF, using cutoffs from ROC analysis:

- MR-proADM was more accurate (73%) than BNP (62%) or NT-proBNP (64%) in predicting all cause 90 day mortality [65 deaths (11.4%)]

NON CHF Diagnosis [65 deaths (6.1 %)]
The goals of this secondary BACH analysis were:

1. to evaluate the prognostic accuracy of MR-proADM to other biomarkers in predicting all cause 90 day mortality in all 1641 enrolled cases [130 (7.9%) deaths]

2. to determine the added value of MR-proADM in addition to clinically used variables
Results

MR-proADM was superior to natriuretic peptides, troponin, copeptin and procalcitonin (p<0.0001 for all comparisons) for predicting death within 90 days for all patients that presented to the ED with a primary complaint of SOB.

Predicting all cause mortality

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>LR $c^2$</th>
<th>C-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR-proADM</td>
<td>129.7*</td>
<td>0.755</td>
</tr>
<tr>
<td>Copeptin</td>
<td>96.6</td>
<td>0.727</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>83.8</td>
<td>0.721</td>
</tr>
<tr>
<td>MR-proANP</td>
<td>77.7</td>
<td>0.705</td>
</tr>
<tr>
<td>BNP</td>
<td>60.1</td>
<td>0.691</td>
</tr>
<tr>
<td>PCT</td>
<td>55.5</td>
<td>0.704</td>
</tr>
<tr>
<td>Troponin</td>
<td>28.7</td>
<td>0.655</td>
</tr>
</tbody>
</table>

Kaplan-Meier: MR-proADM by diagnosis

*all p<0.0001  ** Cut off 1.985 nmol/L, optimal cut point in AHF patients as previously published
Results

ACS (n=39)  |  AHF (n=564)  |  Arrhythmia (n=55)  |  COPD (n=201)  |  Pneumonia (n=111)  |  Pulm. Emb. (n=38)  |  Other (n=304)
---|---|---|---|---|---|---
% dead if MR-proADM < 1.985 nmol/L
n=3/36  |  n=1/3  |  n=1/53  |  n=11/191  |  n=5/92  |  n=4/35  |  n=8/27
% dead if MR-proADM > 1.985 nmol/L
n=31/412  |  n=33/152  |  n=1/2  |  n=3/10  |  n=7/19  |  n=1/3  |  n=20/277
Results

- MR-proADM adds to the best clinical model (top 9 variables plus AHF diagnosis), p < 0.0001 and the c index increases from 0.775 to 0.807* with a Net Reclassification Improvement of 8.9%
- Within the model MR-proADM is the strongest contributor, followed by BMI and sodium: (c² = 38.2, p < 0.0001)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Best clinical model</th>
<th>... including MR-proADM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wald c²</td>
<td>p-value</td>
</tr>
<tr>
<td>MR-proADM [log10, pmol/L]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>14.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>Sodium [mmol/l]</td>
<td>22.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic Blood Pressure [mmHg]</td>
<td>10.4</td>
<td>0.0012</td>
</tr>
<tr>
<td>Pulse Oxymetry [%]</td>
<td>8.5</td>
<td>0.0035</td>
</tr>
<tr>
<td>JVP on Examination [yes]</td>
<td>2.4</td>
<td>0.1196</td>
</tr>
<tr>
<td>Age [years]</td>
<td>5.0</td>
<td>0.0259</td>
</tr>
<tr>
<td>History of Asthma [yes]</td>
<td>1.6</td>
<td>0.2073</td>
</tr>
<tr>
<td>Diagnosis AHF [yes]</td>
<td>0.0</td>
<td>0.8658</td>
</tr>
<tr>
<td>History of CRI [yes]</td>
<td>4.9</td>
<td>0.0265</td>
</tr>
<tr>
<td>Rales on Examination [yes]</td>
<td>0.3</td>
<td>0.5751</td>
</tr>
</tbody>
</table>

Multivariable Cox regression, best model and best model plus MR-proADM

* bootstrap corrected
Conclusions

• MR-proADM provides unique prognostic information (90 day all cause mortality) in patients presenting to the ED with a primary complaint of SOB, independent of etiology

• Further studies should center around its use as a guide to therapeutic interventions, admission decisions and follow-up requirements
Adrenomedullin Changes Predict Survival in Dyspneic Emergency Department Patients

The Sixth Mediterranean Emergency Medicine Congress
Kos, Greece, September 10-14, 2011

WF. Peacock, R. Nowak, AS. Maisel, C. Mueller, P. Ponikowski, M. Mockel, C. Hogan, AHB. Wu, S. Disomma, S. Anker
Objectives

• To determine if ADM changes are prognostic of 90 day mortality in a cohort of patients presenting to the ED with a primary complaint of SOB, irrespective of the etiology
Methods

- ADM was measured at ED admission and re-measured 14 to 48 hrs later.

- A high or low ADM was defined by a 2.0 nmol/L cut point.

- Patients were divided into 4 groups defined by initial and repeat ADM:
  - high-high, high-low
  - low-low, and low-high
Results

• Of 1641 patients;

• At 90 days there were 130 deaths;
  – 65 had AHF
  – 65 were non-AHF
Results

• Median time to discharge: 7 days (IQR 3-12)
  – Overall, 532 (32.4%) were discharged on the day of admission
  – Of the remaining 1109, 981 had $>1$ blood draw

• Initial ADM levels
  – Range: 0.03 to 12.6 nmol/l
  – Median 0.88 nmol/l (IQR 0.57, 1.44 nmol/l)
Results

• At admission, 191 (19.5%) had high ADM, suggesting increased risk for death

  – 70 (36.6%) had ADM levels that declined with therapy

• declining ADM cohort had a survival rate similar to patients who were never at risk based on the initial ADM

– Including serial measurements into a time-dependent Cox model gave added value vs patients with just an admission ADM (p=0.0005)
Delta ADM and 90 day Mortality

MR-proADM, admission plus follow up

- A: high/high: n=121 (45)
- B: high/low: n=70 (7)
- C: low/low: n=766 (61)
- D: low/high: n=24 (7)
Conclusions

• An initial and repeat low ADM level or an initial high but repeat low ADM level can identify patients at lower risk for 90 day mortality

• An initial and repeat high ADM level or an initial low and repeat high ADM level can identify patients at higher risk for 90 day mortality

• Sequential ADM measurements may help in the initial risk stratification of patients presenting to the ED with a primary complaint of SOB and also guide the efficacy of their clinical therapy
Short-term Mortality Risk in Emergency Department Acute Heart Failure

W. Frank Peacock, MD, Richard Nowak, MD, Robert Christenson, PhD, Salvatore DiSomma, MD, Sean Xavier Neath, MD, Oliver Hartmann, Christian Mueller, MD, Piotr Ponikowski, MD, PhD, Martin Möckel, MD, Christopher Hogan, MD, Alan H. B. Wu, PhD, Mark Richards, MD, PhD, FRACP, Gerasimos S. Filippatos, MD, Inder Anand, MD, FRCP, D Phil (Oxon.), Leong L. Ng, MD, FRCP, Lori B. Daniels, MD, MAS, Nils Morgenthaler, MD, PhD, Stefan D. Anker, MD, PhD, and Alan S. Maisel, MD

Abstract

Objectives: Few tools exist that provide objective accurate prediction of short-term mortality risk in patients presenting with acute heart failure (AHF). The purpose was to describe the accuracy of several biomarkers for predicting short-term death rates in patients diagnosed with AHF in the emergency department (ED).

Methods: The Biomarkers in ACute Heart failure (BACH) trial was a prospective, 15-center, international study of patients presenting to the ED with nontraumatic dyspnea. Clinicians were blinded to all investigational markers, except troponin and natriuretic peptides, which used the local hospital reference range. For this secondary analysis, a core lab was used for all markers except troponin. This study evaluated patients diagnosed with AHF by the on-site emergency physician (EP).
Objectives

• Emergency physicians have few tools providing objective accurate prediction of short term mortality risk in patients presenting to the ED with acute heart failure (AHF)

• Our purpose was to describe the accuracy of BACH trial markers for predicting short term (14 day) death rates in ED patients presenting with AHF
Vasopressin/Copeptin in stress situation

Myocardial Infarction
Background/Methods

Copeptin: surrogate marker for Vasopressin

- Synthesis as a precursor hormone (pre-pro-vasopressin) in the Hypothalamus
- Cleavage and transport in granules down the axons
- Storage in granules in the posterior pituitary
- Release into nearby capillaries upon appropriate stimulation

Figures adapted from: Golenhofen, Basilehrbuch Physiologie, Urban & Fischer; and Morgenthaler NC et al.: Clin Chem 2006
Figure 1. Time-dependent AUC plot comparing MR-proADM, copeptin, BNP, and troponin and the combination of MR-proADM and copeptin. Thin lines represent linear interpolated curves based on determination of time-dependent AUC by follow-up day, while thick lines represent curves smoothed by a locally weighted polynomial regression. Vertical red lines
Limitations

• Observational analysis
  
  – We have no idea what the consequence of intervention would be in those patients identified as high risk for short term mortality
Conclusions

• Both arginine vasopressin (copeptin) and adrenomedullin, alone and in combination, have superior short term mortality prognostic ability vs. natriuretic peptides and other markers

• Objective determination of mortality risk may provide opportunities to improve Emergency Department AHF decision making and consequent clinical outcomes
Both MR-proADM and Copetin, individually and in combination (AUC = 0.818), are the best short term (14 day) mortality predictors in patients presenting to the ED with acute CHF.

Each biomarker is significantly better and independent of the natriuretic peptides or troponin and available clinical variables.
Novel Biomarker Prediction of 14-Day Mortality in Emergency Department Patients Presenting with the Symptom of Acute Shortness of Breath

Richard M Nowak MD, MBA, FACEP, FAAEM, for the BACH Investigators
ACEP Research Forum, October 15-16, 2011
San Francisco, California

Past Chairperson
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Clinical Professor, Emergency Medicine
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University of Michigan Medical School
Ann Arbor, Michigan
Objectives

• Emergency physicians have few tools providing objective accurate prediction of short term mortality (14 day) risk in patients presenting to the ED with a primary complaint of acute SOB

• The purpose of this secondary BACH analysis was to describe the accuracy of novel BACH trial biomarkers (Copeptin and MR-proADM) for predicting short term death rates in this ED population
# Results

<table>
<thead>
<tr>
<th>Patient Variables</th>
<th>All Patients (n=1641)</th>
<th>14-Day Survivor (n=1598)</th>
<th>14-Day Mortality (n=43)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.8 (16.9)</td>
<td>63.4 (16.89)</td>
<td>76.0 (11.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male Gender</td>
<td>859 (52.3)</td>
<td>836 (52.3)</td>
<td>23 (53.5)</td>
<td>0.9978</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>140.8 (28.64)</td>
<td>141.2 (28.47)</td>
<td>127.3 (31.95)</td>
<td>0.0034</td>
</tr>
<tr>
<td>Pulse Oximetry (%)</td>
<td>96 [94-98]</td>
<td>96 [94-98]</td>
<td>93 [88.25-96]</td>
<td>0.0002</td>
</tr>
<tr>
<td>Rales</td>
<td>524 (32.3)</td>
<td>498 (31.5)</td>
<td>26 (61.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Wheezing</td>
<td>452 (27.9)</td>
<td>441 (27.9)</td>
<td>11 (26.8)</td>
<td>0.985</td>
</tr>
<tr>
<td>Elevated JVP</td>
<td>271 (17.6)</td>
<td>258 (17.2)</td>
<td>13 (36.1)</td>
<td>0.0064</td>
</tr>
<tr>
<td>Edema</td>
<td>588 (36.4)</td>
<td>570 (36.2)</td>
<td>18 (42.9)</td>
<td>0.473</td>
</tr>
<tr>
<td>Creatinine [mg/dl]</td>
<td>1 [0.8-1.3]</td>
<td>1 [0.8-1.32]</td>
<td>1.2 [0.9-1.91]</td>
<td>0.0139</td>
</tr>
<tr>
<td>Admitted to hospital</td>
<td>1107 (67.5)</td>
<td>1068 (66.8)</td>
<td>41 (95.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
## Results

### Cox Regression: Overview of Predictive Performance

<table>
<thead>
<tr>
<th>Model</th>
<th>14 day follow up, HF patients (n=19 events)</th>
<th>14 day follow up, all patients (n=43 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chi²</td>
<td>p-value</td>
</tr>
<tr>
<td>BNP [log$_{10}$ pg/mL]</td>
<td>0.1</td>
<td>0.768</td>
</tr>
<tr>
<td>NT-proBNP [log$_{10}$ pg/mL]</td>
<td>1.8</td>
<td>0.179</td>
</tr>
<tr>
<td>MR-proANP [log$_{10}$ pmol/L]</td>
<td>3.5</td>
<td>0.061</td>
</tr>
<tr>
<td>Systolic blood pr. [mmHg]</td>
<td>3.7</td>
<td>0.056</td>
</tr>
<tr>
<td>Pulse Oximetry [%]</td>
<td>4.5</td>
<td>0.033</td>
</tr>
<tr>
<td>Age [years]</td>
<td>8.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Troponin (T or I, quantile transf.)</td>
<td>12.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MR-proADM [log$_{10}$ nmol/L]</td>
<td>18.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Copeptin [log$_{10}$ pmol/L]</td>
<td>29.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Copeptin and MR-proADM</td>
<td>33.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Results
Both Copeptin and MR-proADM add significant predictive value to other biomarkers and clinical variables.

<table>
<thead>
<tr>
<th>Model including ... and ...</th>
<th>... adding Copeptin</th>
<th>... adding MR-proADM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Added Chi²</td>
<td>p-value</td>
</tr>
<tr>
<td>BNP [log₁₀ pg/mL]</td>
<td>46.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP [log₁₀ pg/mL]</td>
<td>34.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MR-proANP [log₁₀ pmol/L]</td>
<td>40.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pr. [mmHg]</td>
<td>61.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse Oximetry [%]</td>
<td>52.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age [years]</td>
<td>43.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Troponin (T or I, quantile transf.)</td>
<td>29.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MR-proADM [log₁₀ nmol/L]</td>
<td>15.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Copeptin [log₁₀ pmol/L]</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Results

Short Term Survival Prediction: Kaplan-Meier

Copeptin by quartile

MR-proADM by quartile
Results

Area Under time dependent ROC-Curve (AUC(t))
Conclusions

Both copeptin and adrenomedullin, alone and in combination, have superior short term mortality (14 day) prognostic ability vs. the natriuretic peptides, other biomarkers and clinical variables in ED patients with a primary complaint of acute SOB.

Objective determination of mortality risk may provide opportunities to improve Emergency Department decision making and consequent clinical outcomes in this patient population.
For the Brilliant SAM members

• Both adrenomedullin (vasodilator) and vasopressin (anti-diuretic, vasoconstrictor) are both elevated in acute SOB, the levels seem to be related to severity of disease causing the problem irrespective of the etiology and thus seem to predict outcome (especially short term)

• HOW CAN THIS BE!!!!!!!!!!!!! SAM members could solve this riddle!!!!!!!!!!!
Mid-regional pro-adrenomedullin improves disposition strategies for patients with acute dyspnoea: results from the BACH trial

Martin Möckel,1 Julia Searle,1 Oliver Hartmann,2 Stefan D Anker,3,4 W Frank Peacock,5 Alan H B Wu,6,7 Alan Maisel,8,9 on behalf of the BACH Writing group
Biomarkers and SAM

Novel biomarkers can help accurately diagnose and risk stratify patients coming to the ED with a primary complaint of SOB and thus aid in management decisions.

The trending of these novel biomarkers over the ensuing few days may help in determining the adequacy of therapy and discharge decisions.

SAM physicians could play a major role in clarifying point number 2.
Questions