

B-type Natriuretic Peptide in the Prognosis and Management of Acute Coronary Syndromes

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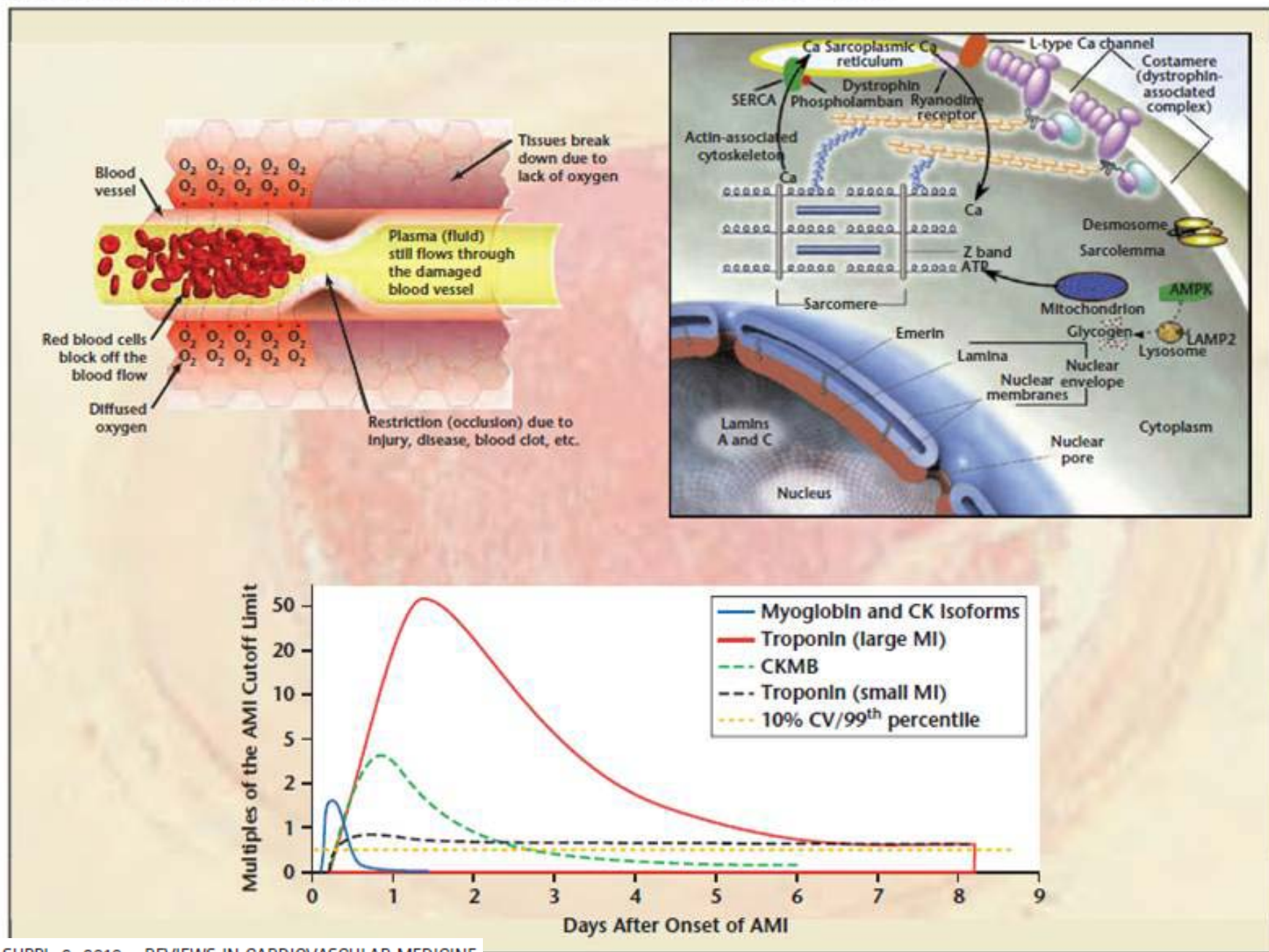
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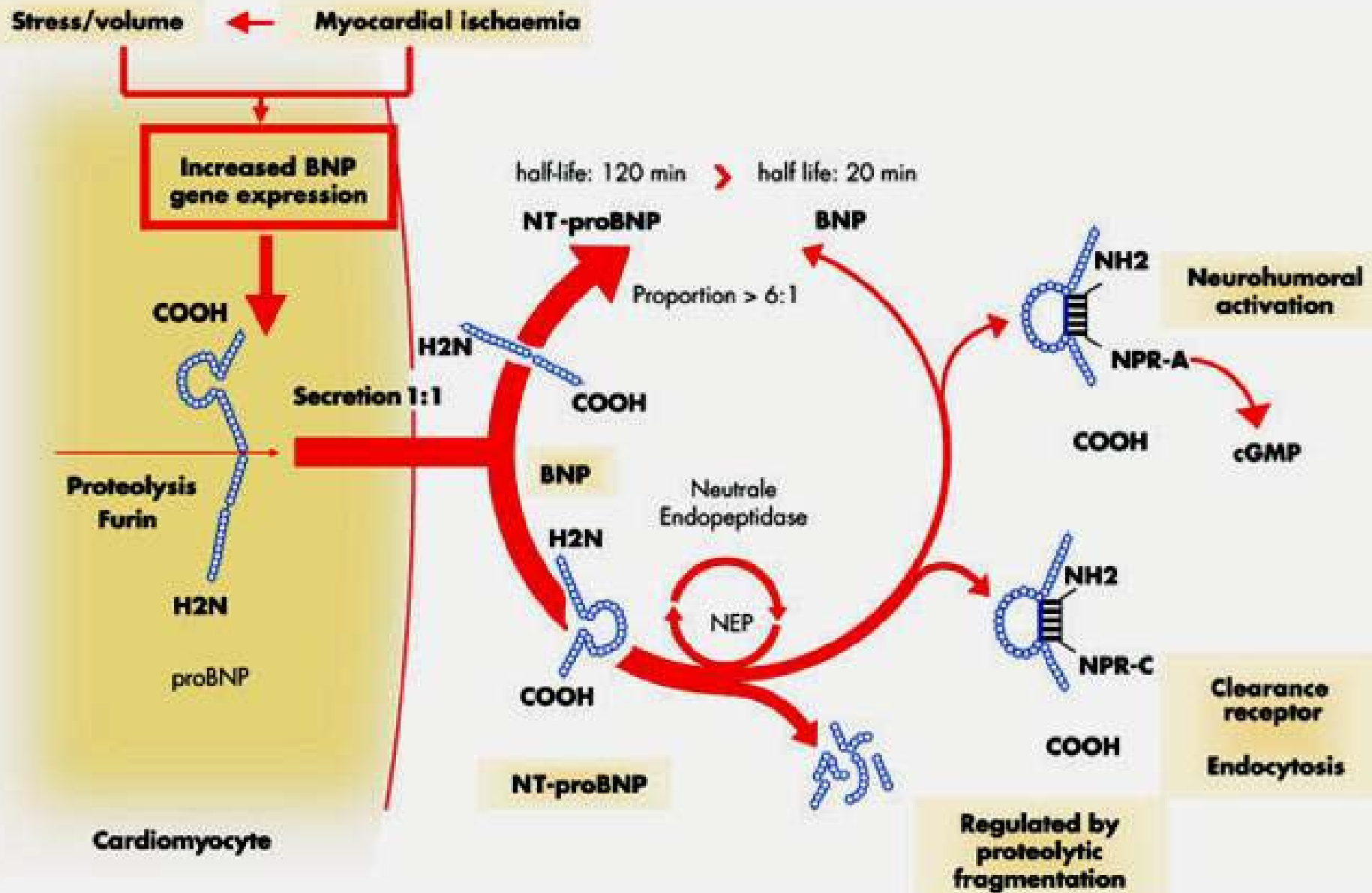
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Peter A. McCullough, MD, MPH, W. Frank Peacock, MD, Brian O'Neil, MD, James A. de Lemos, MD, Norman E. Lepor, MD, Robert Berkowitz, MD

Figure 2. Acute myocardial infarction (AMI) with disruption of cellular elements and the release of classic markers of myocardial necrosis used in the diagnosis of acute coronary syndromes. AMPK, adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; Ca, calcium; CK-MB, creatine kinase-myocardial band; LAMP2, lysosomal-associated membrane protein 2; MI, myocardial infarction; SERCA, Sarco/endoplasmic reticulum Ca^{2+} -ATPase.





Contemporary Prospective Studies Using Multiple Markers in Suspected ACS

ASPECT Study, N=3582, positive (↓major adverse cardiac events)

RATPAC Trial, N=2263, positive (↑successful discharge home, ↓LOS)



Than M, Cullen L, Reid CM, Lim SH, Aldous S, Ardagh MW, Peacock WF, Parsonage WA, Ho HF, Ko HF, Kasliwal RR, Bansal M, Soerianata S, Hu D, Ding R, Hua Q, Seok-Min K, Sritara P, Sae-Lee R, Chiu TF, Tsai KC, Chu FY, Chen WK, Chang WH, Flaws DF, George PM, Richards AM. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. *Lancet*. 2011 Mar 26;377(9771):1077-84.

Goodacre S, Bradburn M, Fitzgerald P, Cross E, Collinson P, Gray A, Hall AS. The RATPAC (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. *Health Technol Assess*. 2011 May;15(23):iii-xi, 1-102. PubMed PMID: 21616014.

Case 1



58 year
old male

Sudden onset
severe
substernal chest
pain walking out
of the house to
his car on the
way to work

No prior
history

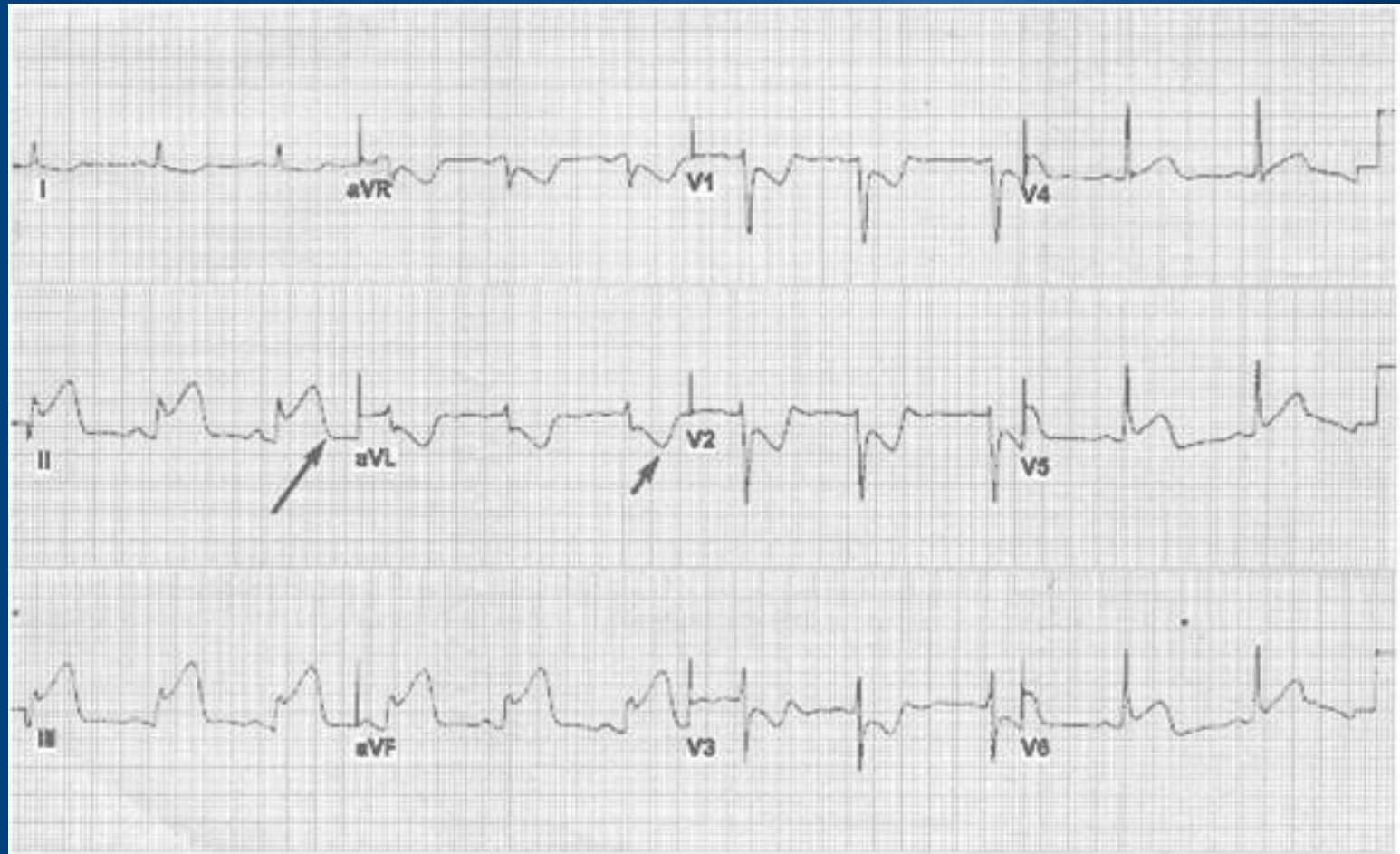
Wife calls 911

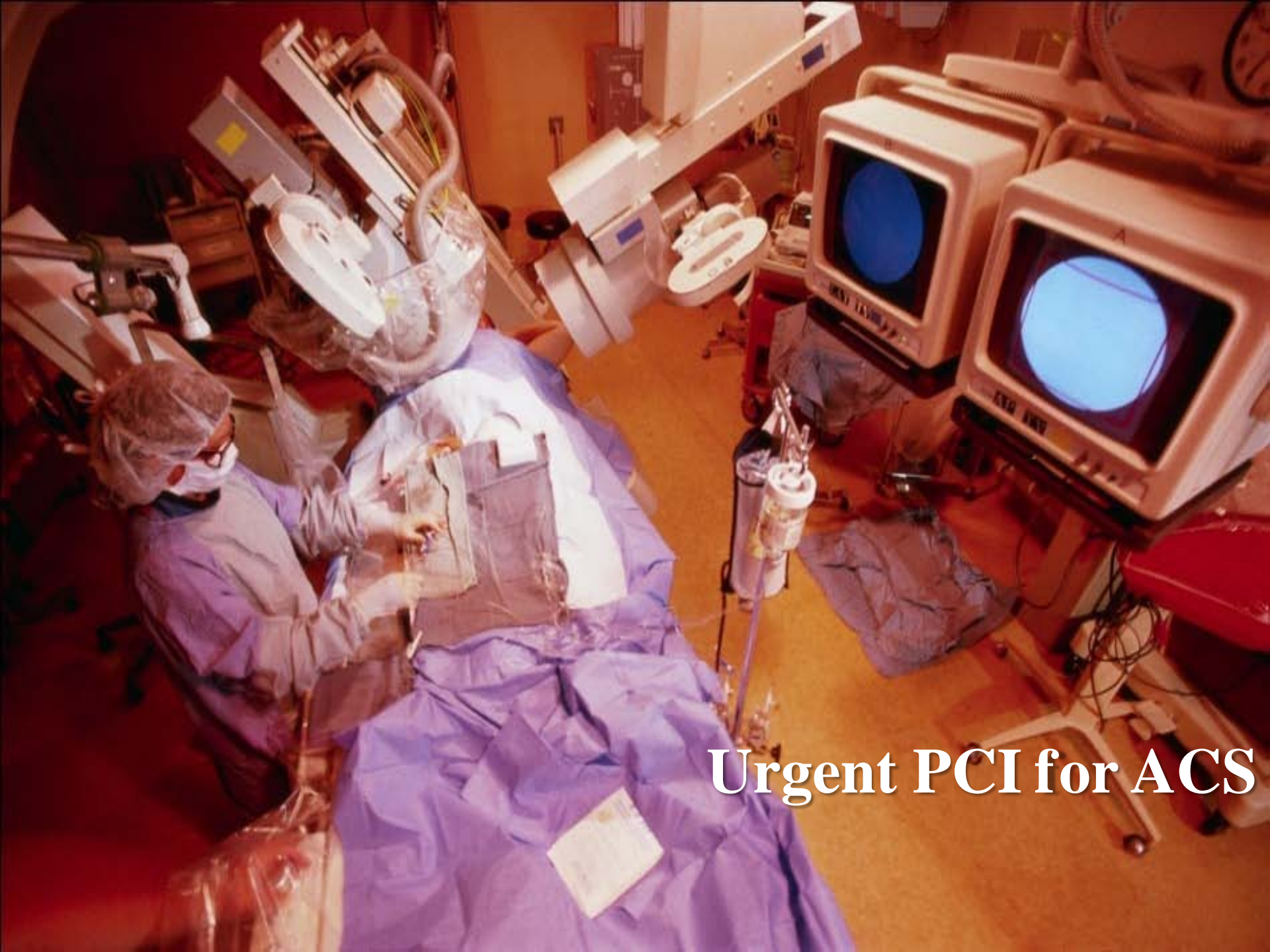
30 minutes
from onset of
pain to ECG
and blood
draw



Case 1 (cont)

- Acute inferior ST segment elevation myocardial infarction
- “Rainbow of tubes” drawn in field
- Taken directly to catheterization laboratory





Urgent PCI for ACS

Case 1 (cont)

- Troponin I 0.05 ng/ml
- CK-MB 4 ng/ml
- Myoglobin 80 ng/ml
- BNP 180 pg/ml

<u>Analyte</u>	<u>95th Percentile</u>	<u>97.5th Percentile</u>	<u>99th Percentile</u>
Troponin I	< 0.05 ng/mL	< 0.05 ng/mL	< 0.05 ng/mL

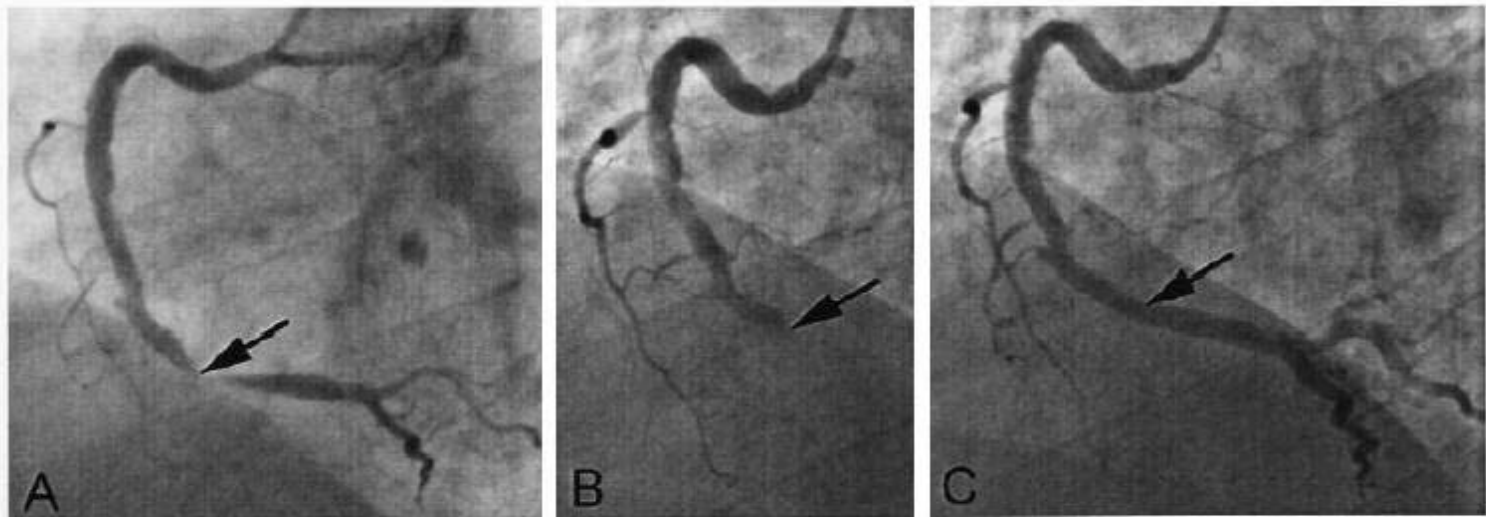


Figure 3 (A). Left anterior oblique projection showing distal right coronary artery (RCA) with atherosclerotic plaque (arrow). (B) Left anterior oblique projection showing total occlusion of distal RCA. (C) Left anterior oblique projection showing TIMI-3 flow in RCA post stent placement.

Case 1 (cont)

Admitted to CCU after PCI

Elevated BNP major signal of complicated early course

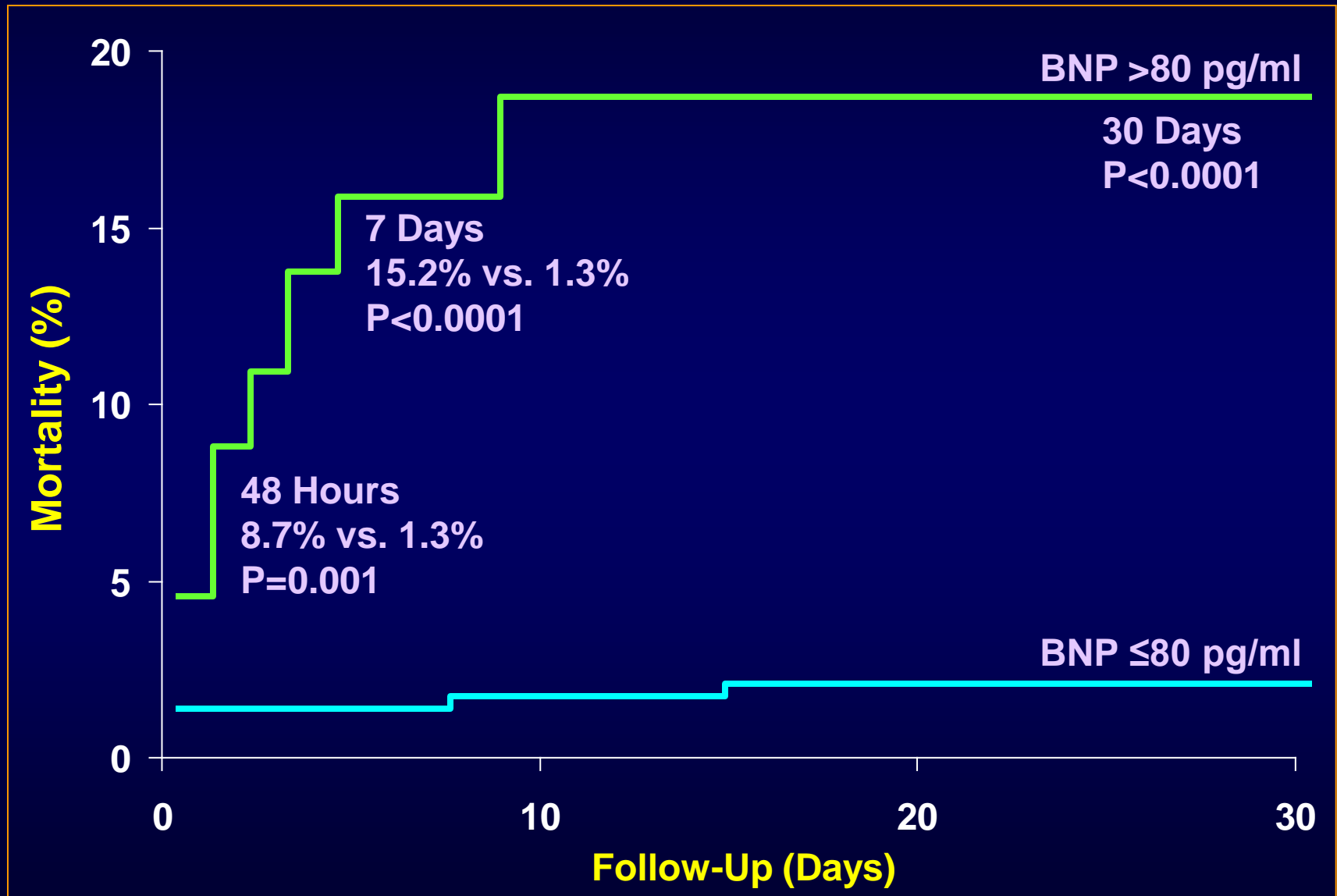
Held and not allowed early discharge

Day 3, has syncope and monitor reveals sustained ventricular tachycardia requiring cardioversion

Day 4, has ICD implanted



Probability of Death Through 30 Days Stratified by B-Type Natriuretic Peptide (BNP)



Serum BNP, hs-C-reactive protein, procollagen to assess the risk of ventricular tachycardia in ICD recipients after myocardial infarction

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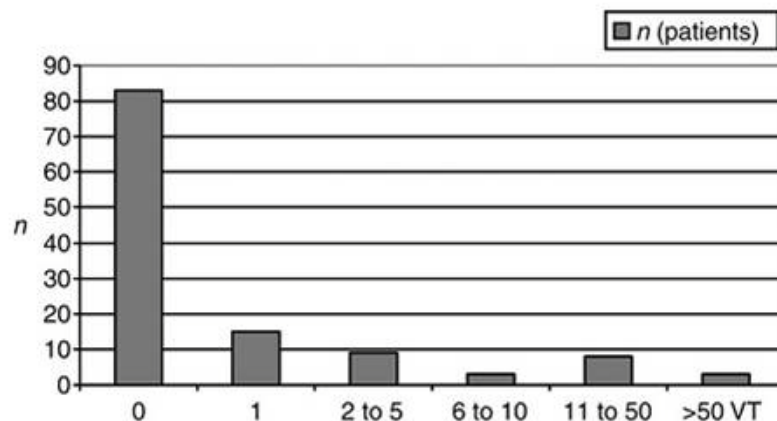


Figure 1 Ventricular tachycardia episodes in the 121 patients included in the study.

Table 2 Significant adjusted relative risks for ventricular tachycardia occurrence according to baseline clinical characteristics and to serum markers levels

	OR (95%CI)	P-value
BNP > median (64 ng/L)	3.75 (1.46–9.67)	0.014
hs-C-reactive protein > median (0.32 mg/dL)	3.20 (1.26–8.10)	0.006
PINP > median (36.5 µg/L)	3.71 (1.40–9.88)	0.009
PIIINP > median (4.3 µg/L)	0.21 (0.08–0.59)	0.003

BNP, brain natriuretic peptide; hs, high sensitivity; PINP, procollagen type I aminoterminal peptide; PIIINP, procollagen type III aminoterminal peptide.

Acute Myocardial Infarction

Multiple Biomarkers at Admission Significantly Improve the Prediction of Mortality in Patients Undergoing Primary Percutaneous Coronary Intervention for Acute ST-Segment Elevation Myocardial Infarction

Peter Damman, MD, Marcel A. M. Beijk, MD, Wichert J. Kuijt, MD, Niels J. W. Verouden, MD, Nan van Geloven, MSc, José P. S. Henriques, MD, PhD, Jan Baan, MD, PhD, Marije M. Vis, MD, Martijn Meuwissen, MD, PhD, Jan P. van Straalen, Johan Fischer, PhD, Karel T. Koch, MD, PhD, Jan J. Piek, MD, PhD, Jan G. P. Tijssen, PhD, Robbert J. de Winter, MD, PhD

Amsterdam, the Netherlands

Objectives

We investigated whether multiple biomarkers improve prognostication in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention.

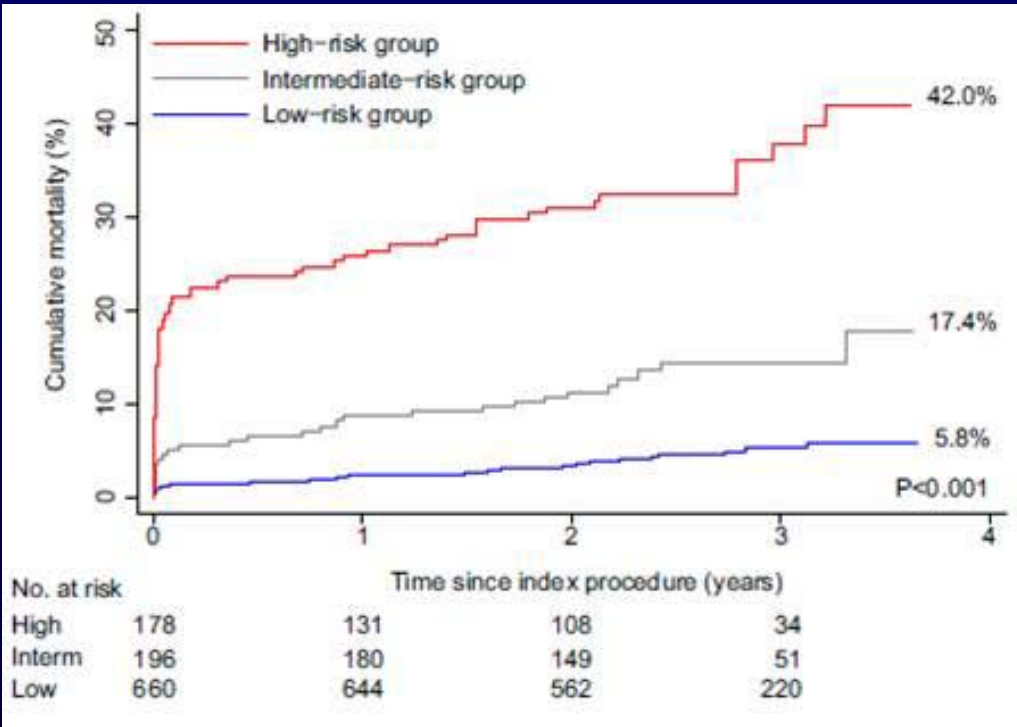
Background

Few data exist on the prognostic value of combined biomarkers.

Risk Factors and Biomarkers	Discrimination			
	Harrell's C Index	Net Reclassification Improvement	p Value	Integrated Discrimination Improvement
Established risk factors	0.77	Reference		Reference
Established risk factors plus troponin T	0.78	0.388	<0.01	0.0001
Established risk factors plus glucose	0.79	0.484	<0.001	0.0057
Established risk factors plus NT-proBNP	0.78	0.554	<0.001	0.0111
Established risk factors plus eGFR	0.78	0.345	<0.01	0.0193
Established risk factors plus CRP	0.77	0.375	<0.01	0.0047
Established risk factors plus glucose, NT-proBNP, eGFR	0.81	0.494	<0.001	0.0295

The NRI was defined as $(p_{\text{Improved_prediction_among_deceased}} + p_{\text{Improved_prediction_among_alive}}) - (p_{\text{Worsened_prediction_among_deceased}} + p_{\text{Worsened_prediction_among_alive}})$, where p = proportion of patients. The IDI was defined as $(\sum_{\text{death}} (p_{\text{new}(i)} - p_{\text{old}(i)})/n \text{ (deceased)}) - (\sum_{\text{alive}} (p_{\text{new}(j)} - p_{\text{old}(j)})/n \text{ (alive)})$, where p = predicted probability of mortality.

Biomarker	Add to Score
Glucose (mmol/l)	
<8	0
8-9	+2
≥10	+3
NT-proBNP (ng/l)	
<150	0
150-599	+2
≥600	+3
eGFR (ml/min)	
≥90	0
60-89	+2
<60	+4
Total score	
≤4	Low risk
5-6	Intermediate risk
>6	High risk



Case 2



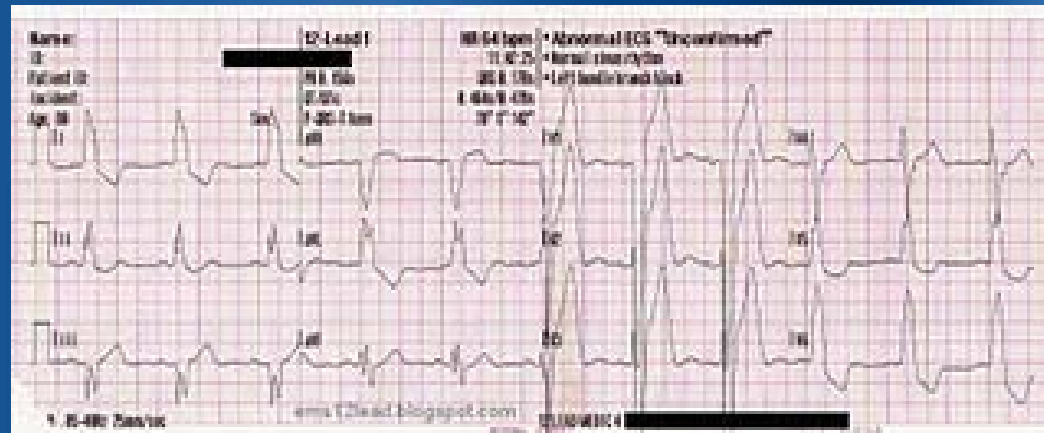
Police
do CPR
for 15
minutes

Daughter
calls 911

Collapse at
home in the
evening

Hx CAD
prior PCI

68 year
old male



Case 2 (cont)

Troponin I	0.05	1.2	3.4	2.2
CK-MB	3.8	3.0	7.3	5.0
Myoglobin	180	230	341	240
BNP	684	1527	3644	4589

MEASURABLE RANGES

Troponin I:	0.05 - 30 ng/mL
CK-MB:	1.0 - 80 ng/mL
Myoglobin:	5 - 500 ng/mL
BNP:	5 - 5,000 pg/mL

Case 2 (cont)

Admitted to the CCU

Remains intubated, initially stable

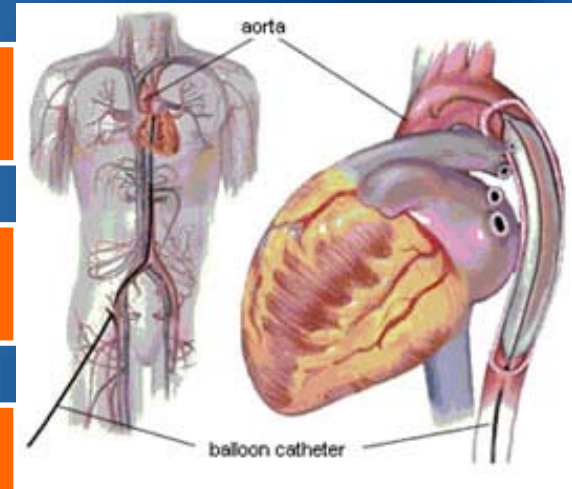
Systemically cooled for anoxic encephalopathy

BNP predicts very high risk of death, doctor counsels family appropriately

Day 2 develops cardiogenic shock

Balloon pump inserted at bedside

Expires on day 3



Brain natriuretic peptide for the prediction of sudden cardiac death and ventricular arrhythmias: a meta-analysis

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Received 9 April 2009

Aims

Methods and results

Sudden cardiac death was more frequent in patients with raised BNP (RR 3.68; 95% CI 1.90,7.14)

relative risk of 3.68 (95% CI 1.90, 7.14). Eight studies (1047 patients) evaluated BNP to predict the occurrence of VA in patients with ICDs. A raised BNP predicted the occurrence of VA with a relative risk of 2.54 (95% CI 1.87, 3.44).

BNP and Troponin

In the Prediction of In-hospital Mortality

Troponin and BNP Versus In-Hospital Mortality

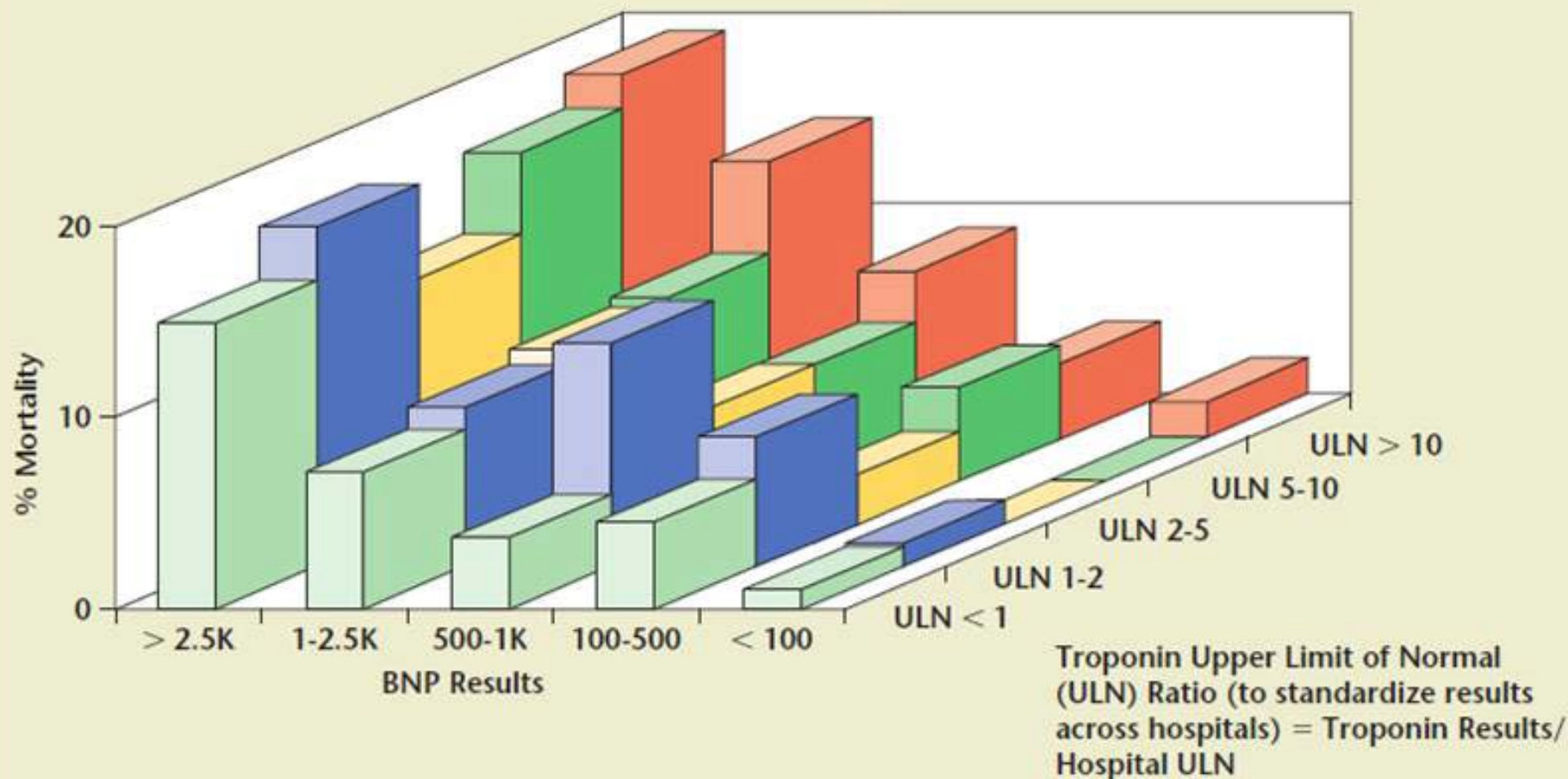
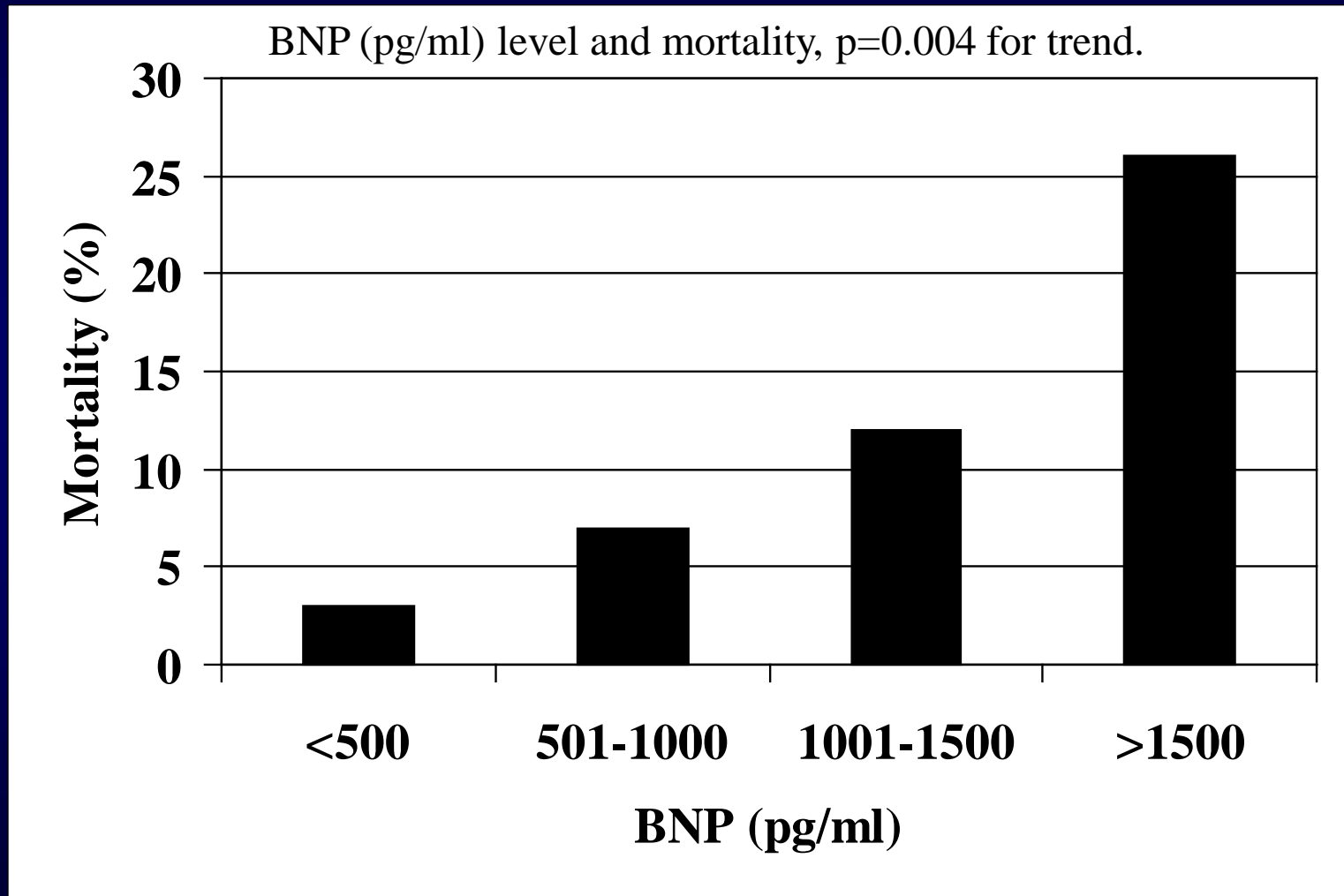


Figure 3. The interaction among troponin, BNP, and in-hospital mortality. BNP, B-type natriuretic peptide.

Markedly Elevated BNP in ACS and Mortality



Case 3



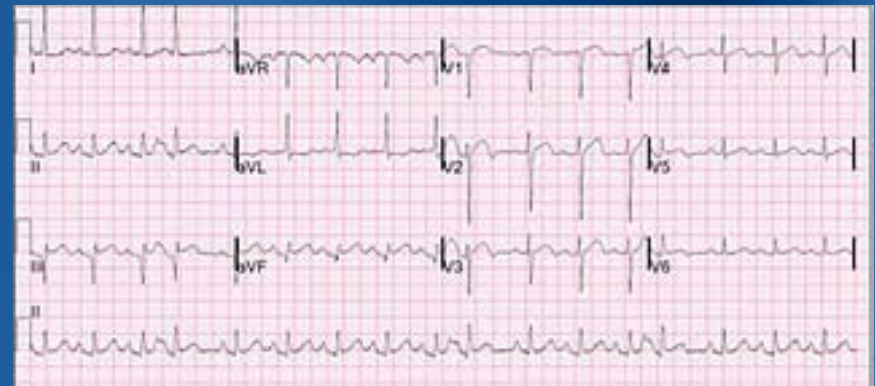
38 year
old male

No prior
history

4 hours of
burning
chest pain

Father
drives him
to ED

Admitted to
chest pain
unit



Case 3 (cont)

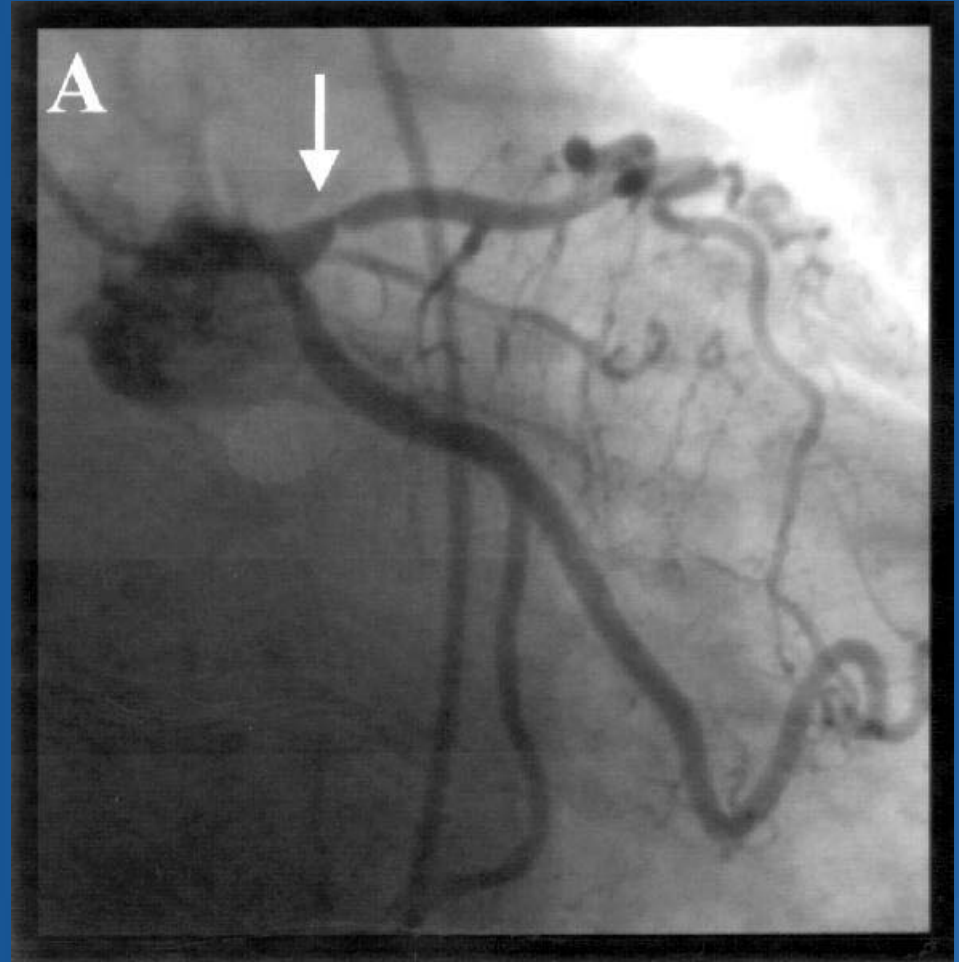
- Troponin I 0.05 ng/ml
- CK-MB 3 ng/ml
- Myoglobin 41 ng/ml
- BNP 132 pg/ml

Time					
# of samples	0-6 hrs. 40	6-12 hrs. 32	12-24 hrs. 43	> 24 hrs. 92	Overall 207
Cardiac Troponin I Sensitivity	65.0%	71.9%	93.0%	95.7%	85.5%



Case 3 (cont)

- Elevated BNP triggers prolonged observation and chest-x-ray
- While out of the ED and in radiology department
- Becomes unresponsive
- BP 70/30 and develops cardiogenic shock
- Rushed to the cath lab
- Plavix held until first diagnostic images
- Emergency angiography and PCI of a proximal LAD lesion



Association of B-Type Natriuretic Peptide, in Conjunction With Cardiac Troponin, and Mortality at 30 Days

Elevated BNP in ACS

- Large zones of ischemia
 - Left main lesions
 - Severe 3-vessel disease
- Large infarctions
- Pre-existing LV impairment
 - Systolic
 - Diastolic
- Renal dysfunction

McCullough PA, ACC, 2007; Neyou A, O'Neil B, Berman AD, Boura JA, McCullough PA. Determinants of markedly increased B-type natriuretic peptide in patients with ST-segment elevation myocardial infarction. Am J Emerg Med. 2010 Mar 24.

ACC/AHA GUIDELINE REVISION

ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction)

Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine

Class IIb: Measurement of B-type natriuretic peptide (BNP) or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS. (*Level of Evidence: B*)

NACB Guidelines

- **Class IIA recommendation for use of biomarkers in risk stratification for ACS**
 - Measurement of BNP or NT pro BNP may be useful in addition to a cardiac troponin for risk assessment in patients with a clinical syndrome consistent with ACS.
- **Class IIB recommendation for use of biomarkers in risk stratification for ACS**
 - A multimarker strategy that includes measurement of 2 or more pathobiologically diverse biomarkers in addition to a cardiac troponin may aid in enhancing risk stratification in patients with a clinical syndrome consistent with ACS.

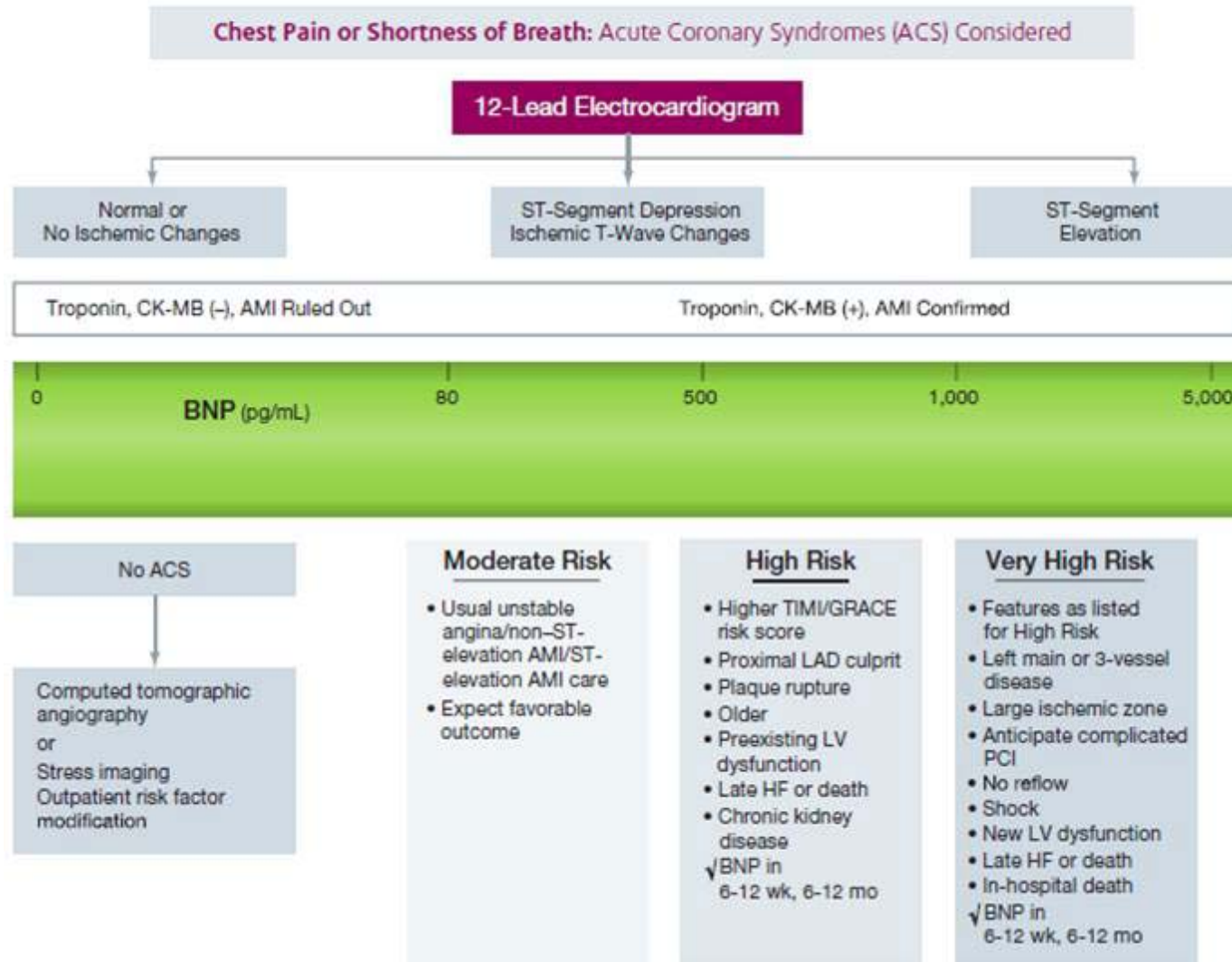
An Evidence-Based Algorithm for the Use of B-Type Natriuretic Testing in Acute Coronary Syndromes

Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA,¹ W. Frank Peacock, MD, FACEP,² Brian O'Neil, MD, FACEP,³ James A. de Lemos, MD, FACC,⁴ Norman E. Lepor, MD, FACC, FAHA, FSCAI,⁵ Robert Berkowitz, MD, PhD, FACC⁶

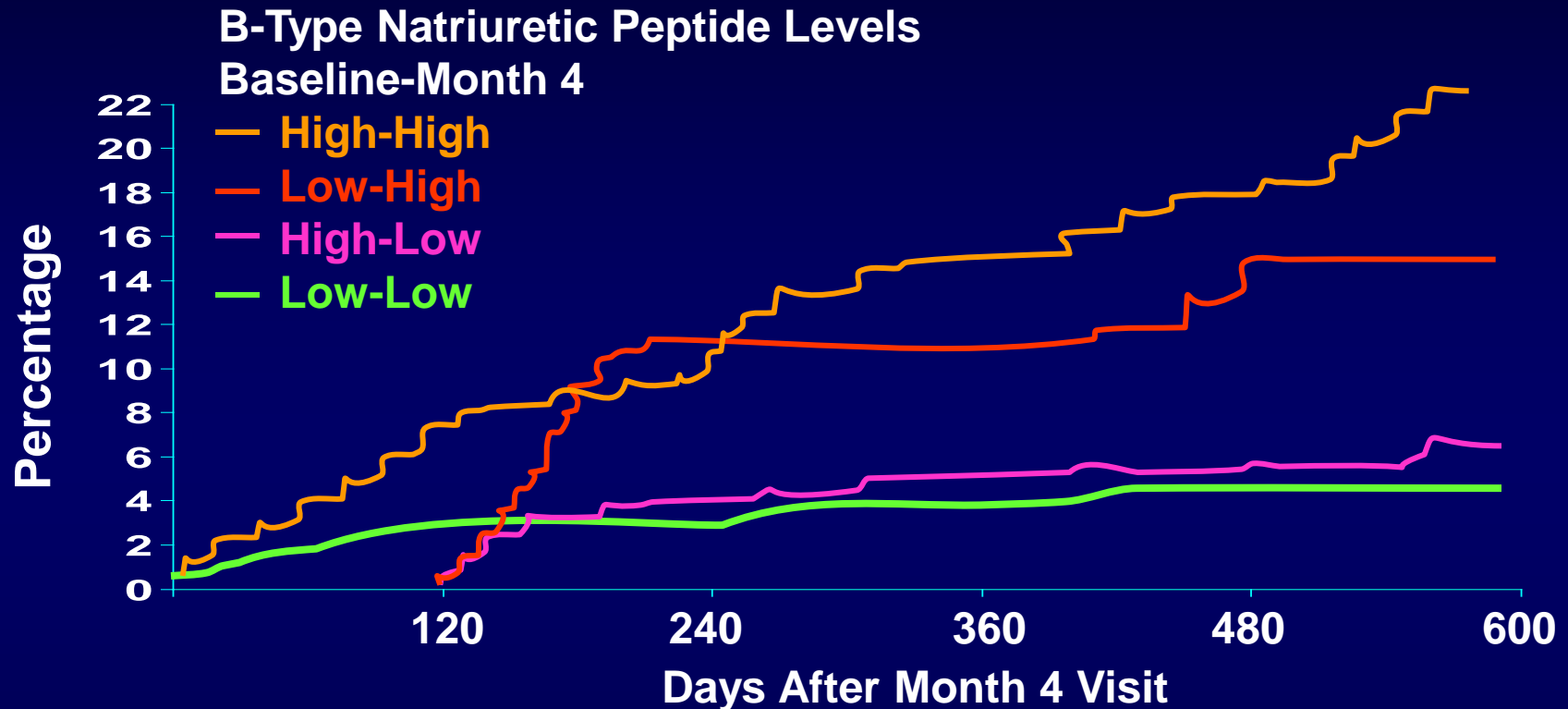
32 prospective studies with > 100 subjects with ACS measuring BNP or NT-proBNP... all showed that the baseline natriuretic peptide level was an independent predictor for the development of heart failure, rehospitalization, or death

for baseline predictors and clinical risk scores, elevated NP concentrations were independently predictive of the development of HF and all-cause mortality. In contrast, studies did not consistently demonstrate that NPs were predictive of myocardial infarction and rehospitalization for ACS. In addition to baseline measurement, there is consensus that repeat testing at 4 to 12 weeks and 6 to 12 months in follow-up is helpful in the anticipation of late cardiac sequelae and may assist in assessing prognosis and guiding management. [Rev Cardiovasc Med. 2010;11(suppl 2):S51-S65 doi: 10.3909/ricm11S2S0002]

Evidence-based algorithm for the measurement and clinical use of **Natriuretic Peptides** in NSTEMI-ACS¹



Cumulative Incidence of Subsequent Death or New or Worsening CHF



No. at Risk

High-High	137	128	121	91	59	35
Low-High	77	77	70	65	43	17
High-Low	330	322	292	225	161	97
Low-Low	2929	2877	2777	2539	2232	1649

BNP Used in Guiding Management after Hospitalization

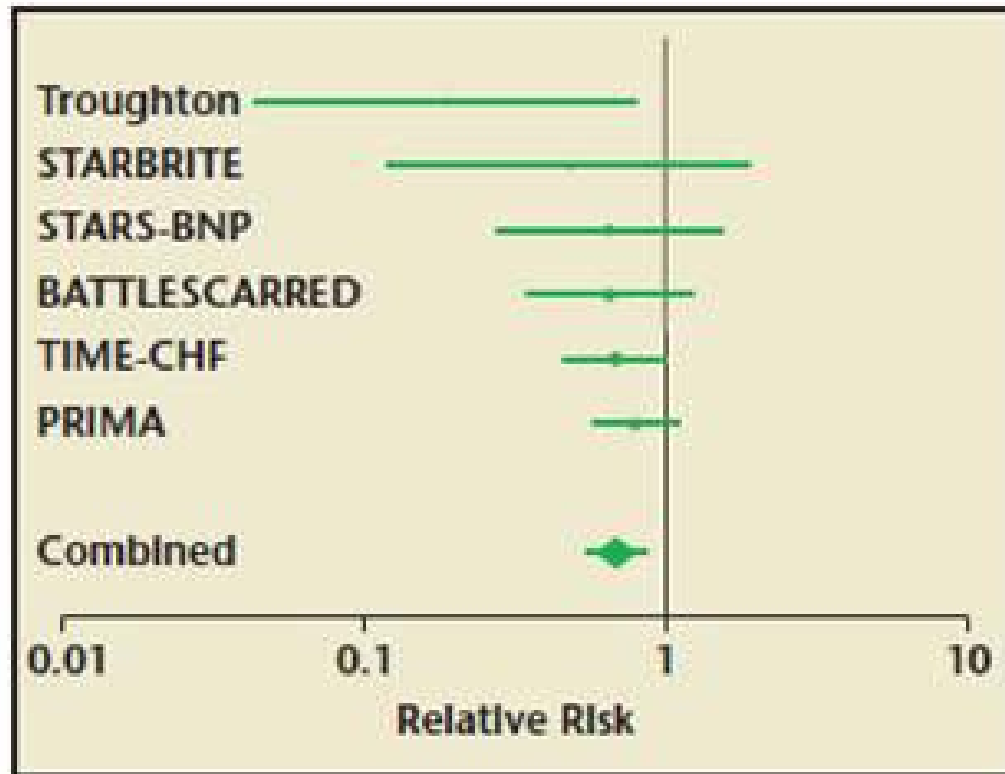


Figure 8. Meta-analysis of trials comparing BNP- or NT-proBNP-guided therapy versus usual care in patients with heart failure. Shown is a forest plot for all-cause mortality. BATTLESCARRED, NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PRIMA, Can Pro-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality?; STARBRITE, Pilot Trial of BNP-Guided Therapy in Patients With Advanced Heart Failure; STARS-BNP, Systolic Heart Failure Treatment Supported by BNP; TIME-CHF, Trial of Intensified (BNP-guided) versus standard (symptom-guided) Medical therapy in Elderly patients with Congestive Heart Failure. Adapted with permission from Felker GM et al.⁴³

Integration of the Clinical Laboratory in Cardiovascular Medicine

Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA

Figure 1. *Four major domains of activity in the use of the clinical laboratory.*

