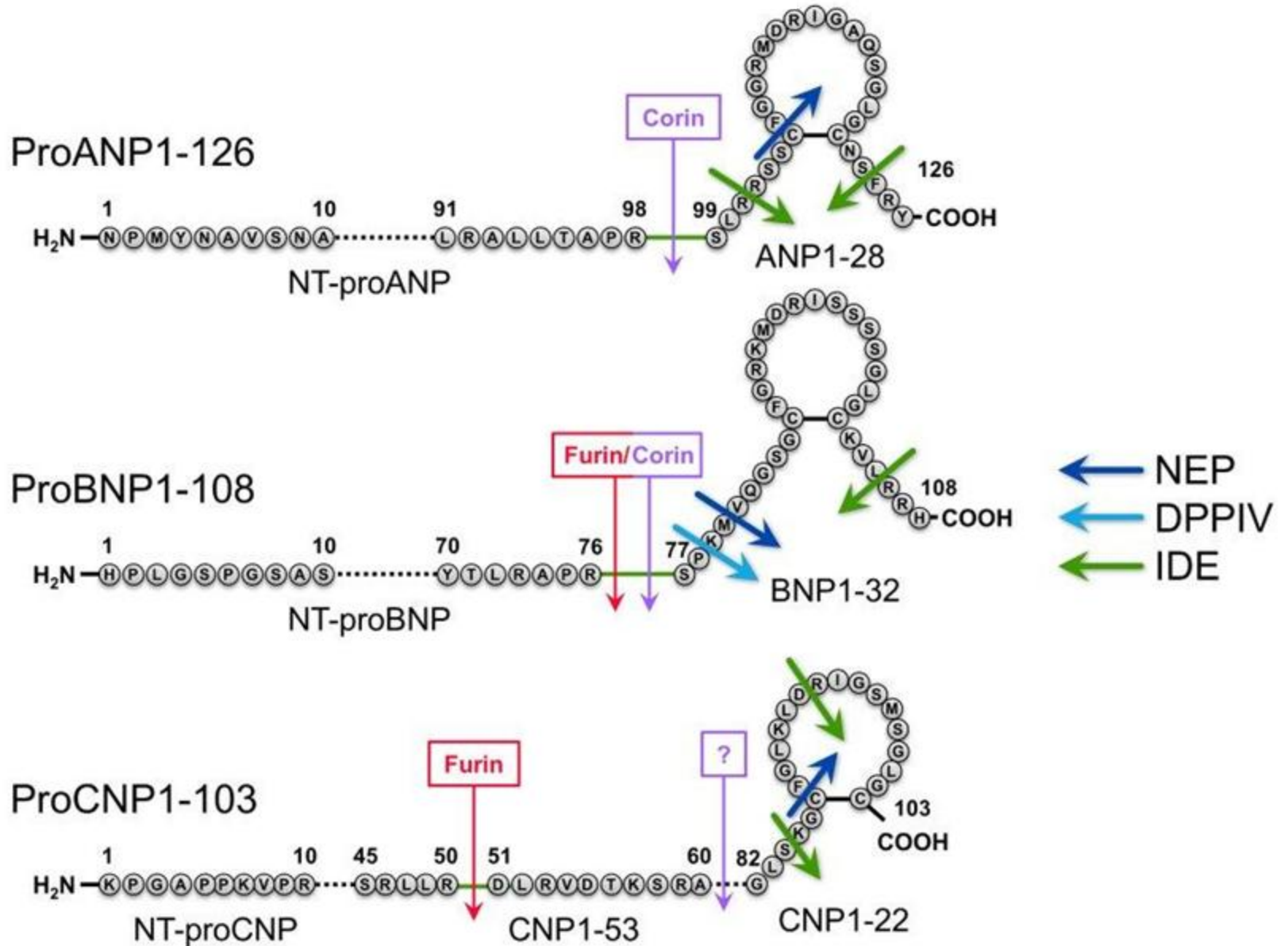


# **Natriuretic peptides and cardiovascular diseases: from old concepts to novel perspectives**

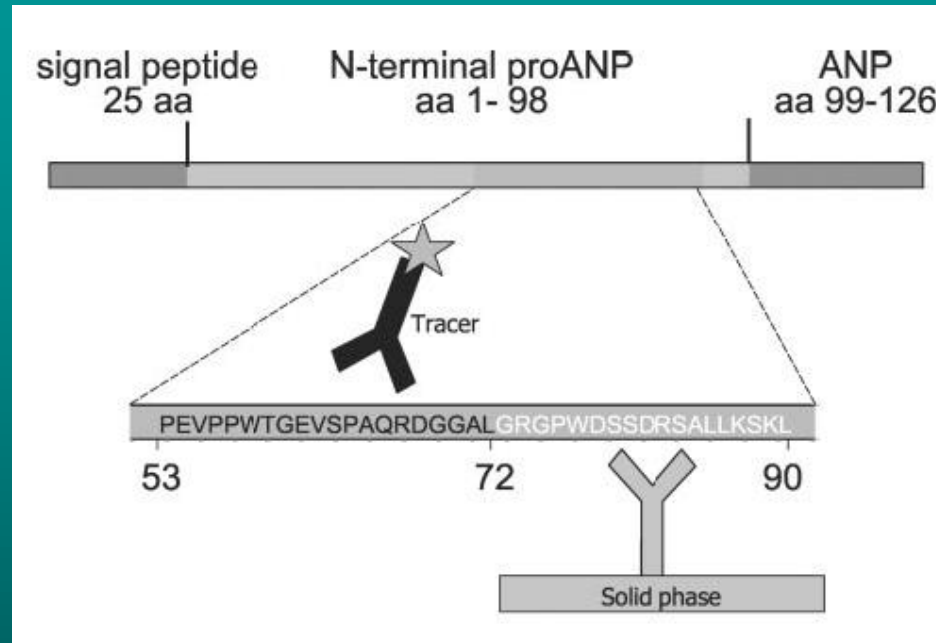
**Speranza Rubattu, M.D.**

**School of Medicine and Psychology,  
Sapienza University, Rome, Italy**

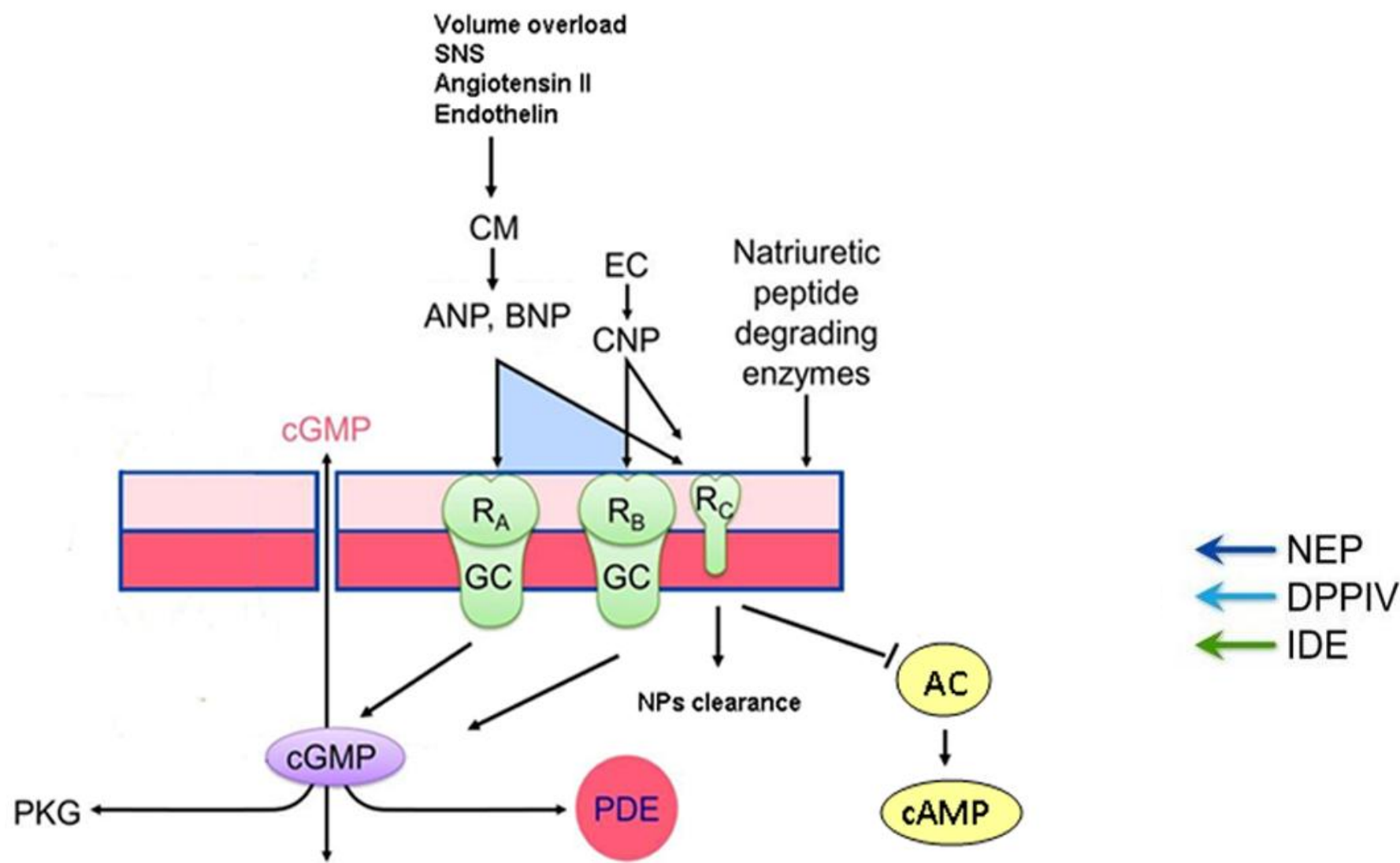
# Natriuretic peptides



# Mid regional NT-proANP



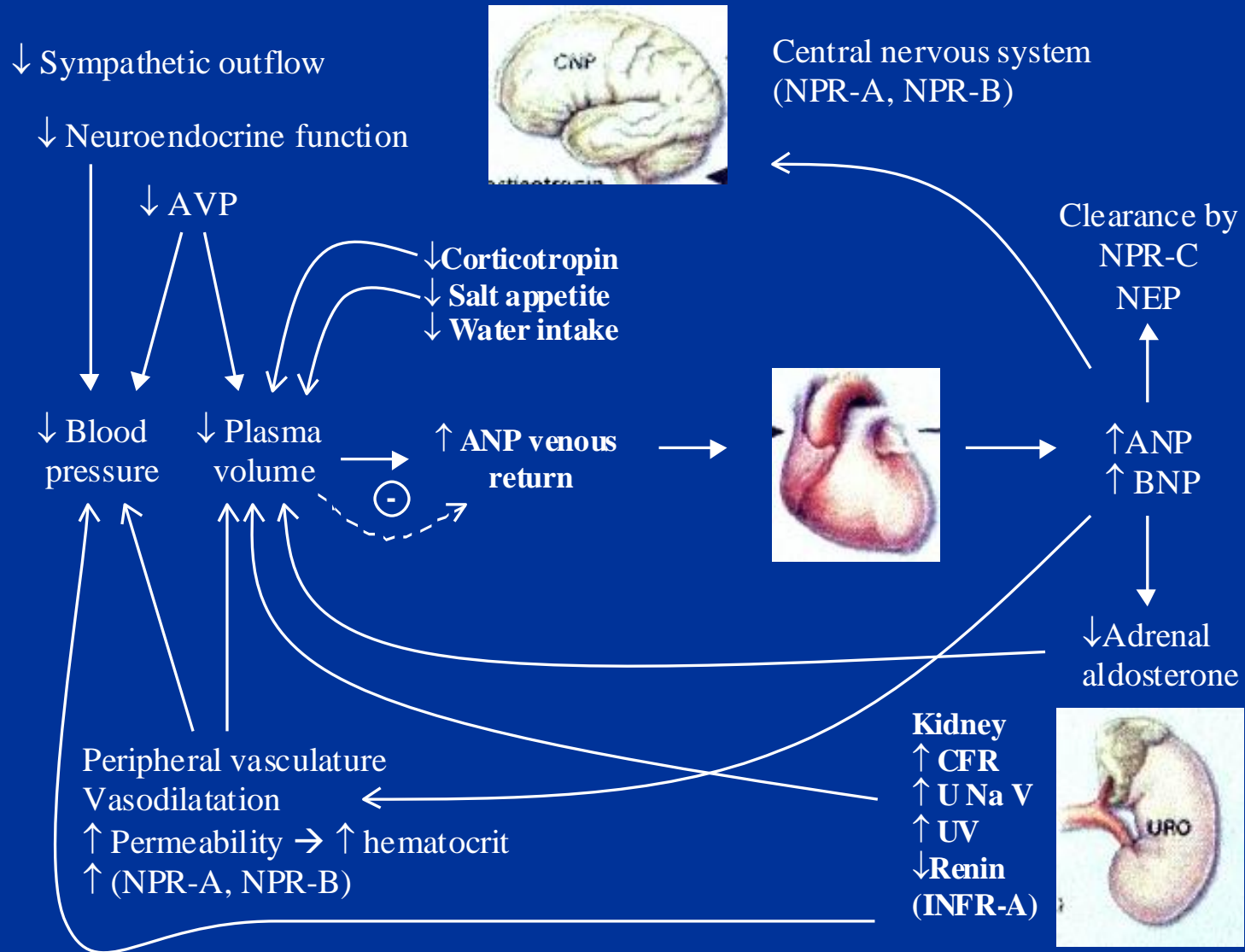
Relevant prognostic role in patients with HF, CAD, hypertension, stroke



Natriuretic (A), renin and aldosterone inhibiting (A), arterial vasodilating (A), Venodilating (B), antifibrotic (B>A), antihypertrophic (A/B), lusitropic (A), antiapoptotic (A), lipolytic (A) and vascular regenerating (A/B)

NO release  
Vasorelaxant effects  
Antiproliferative effects  
Antilipolytic effects

# Hemodynamic effects of NPs



# Protective cardiovascular effects of physiological levels of NPs

- ◆ regulation of volume/electrolytes homeostasis
- ◆ regulation of arterial blood pressure
- ◆ maintenance of normal endothelial function
- ◆ control of body weight (lypolitic effect)
- ◆ anti-inflammatory property

# Issues discussed in this presentation

- ◆ Role in Hypertension and in Heart Failure
- ◆ Prognostic role of NPs in CVDs
- ◆ NPs and CVD risk in the general population
- ◆ Emerging role of NPs gene variants on CVD risk and outcome

**Natriuretic peptides and  
hypertension:from  
etiopathogenesis to treatment**



# **ANP deficiency as a cause of hypertension the experimental evidence**

Genetic decreases in atrial natriuretic peptide  
and salt-sensitive hypertension

John SW, et al. Science 1995 Feb 3;267(5198):679-81

# Evidence in human hypertension

Journal of the American College of Cardiology  
© 2012 by the American College of Cardiology Foundation  
Published by Elsevier Inc.

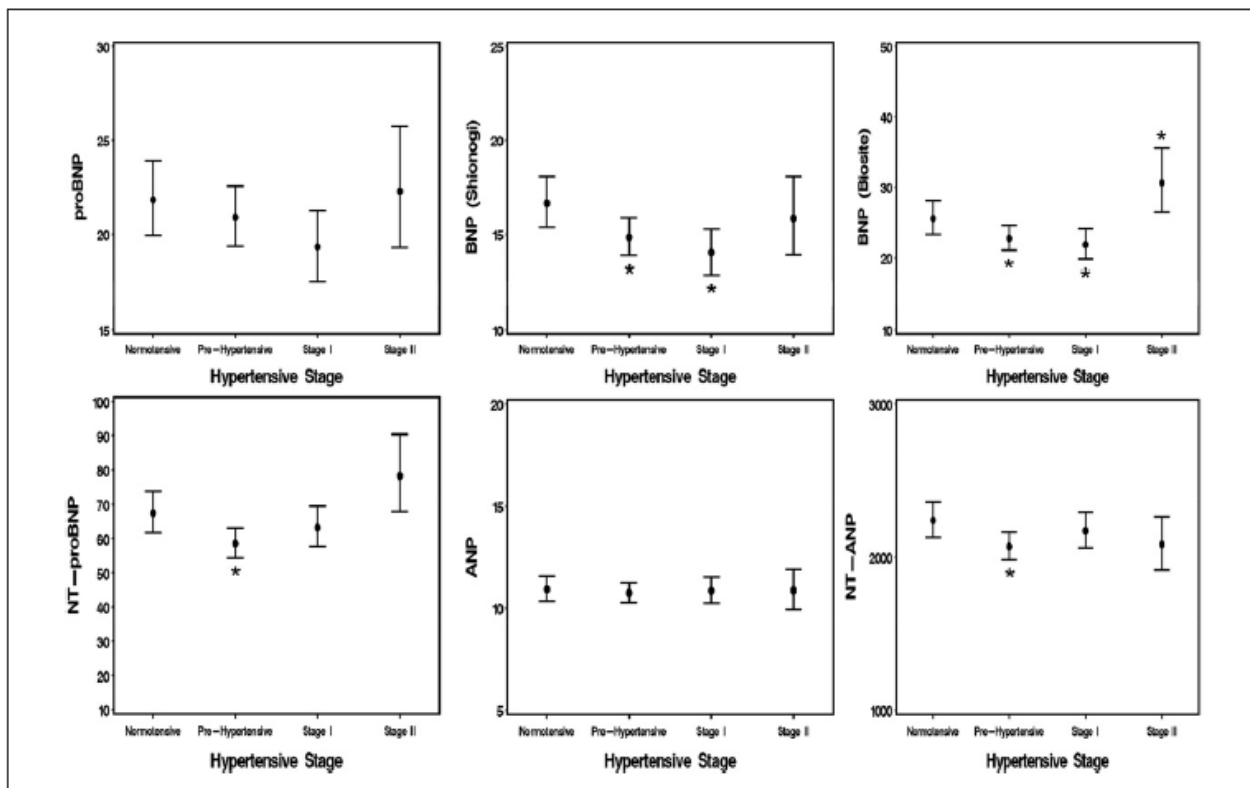
Vol. 60, No. 16, 2012  
ISSN 0735-1097/\$36.00  
<http://dx.doi.org/10.1016/j.jacc.2012.05.049>

**Hypertension**

## **Human Hypertension Is Characterized by a Lack of Activation of the Antihypertensive Cardiac Hormones ANP and BNP**

Fima Macheret, MD, MS,\*† Denise Heublein, CLT,† Lisa C. Costello-Boerrigter, MD, PHD,† Guido Boerrigter, MD,† Paul McKie, MD,† Diego Bellavia, MD,† Sarah Mangiafico, MD,†§ Yasuhiro Ikeda, MD, DVM,|| Kent Bailey, PHD,¶ Christopher G. Scott, MS,|| Sharon Sandberg, CLT,† Horng H. Chen, MD,† Lorenzo Malatino, MD,# Margaret M. Redfield, MD,¶ Richard Rodeheffer, MD, PHD,¶ John Burnett, JR, MD,† Alessandro Cataliotti, MD, PHD†  
*New York, New York; Rochester, Minnesota; and Catania, Italy*

# NPs levels over the course of hypertensive disease



**Figure 1** Results of Multivariable Analysis of All Subjects Adjusted for Age, Gender, BMI, LVH, Creatinine, and Number of Antihypertensive Medications

Figure displays least squares adjusted means for each stage of hypertension and each biomarker. ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; NT-ANP = N-terminal atrial natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; ProBNP = pro-B-type natriuretic peptide.

# The genetic evidence: role of NPs variants associated to altered peptide levels

## Association of Common Variants in *NPPA* and *NPPB* with Circulating Natriuretic Peptides and Blood Pressure

Christopher Newton-Cheh<sup>1,2,3,4</sup>, Martin G. Larson<sup>4,5</sup>, Ramachandran S. Vasan<sup>4,6,18</sup>, Daniel Levy<sup>4,7,18</sup>, Kenneth D. Bloch<sup>2,8</sup>, Aarti Surti<sup>3</sup>, Candace Guiducci<sup>3</sup>, Sekar Kathiresan<sup>1,2,3,4</sup>, Emelia J. Benjamin<sup>4,6</sup>, Joachim Struck<sup>9</sup>, Nils G. Morgenthaler<sup>9</sup>, Andreas Bergmann<sup>9</sup>, Stefan Blankenberg<sup>10</sup>, Frank Kee<sup>11</sup>, Peter Nilsson<sup>12</sup>, Xiaoyan Yin<sup>4</sup>, Leena Peltonen<sup>13,14,15</sup>, Erkki Vartiainen<sup>13</sup>, Veikko Salomaa<sup>13</sup>, Joel N. Hirschhorn<sup>3,16,17</sup>, Olle Melander<sup>12,19</sup>, and Thomas J. Wang<sup>2,4,19</sup>

*Nat Genet.* 2009 March ; 41(3): 348–353.

## LETTER

doi:10.1038/nature10405

## Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk

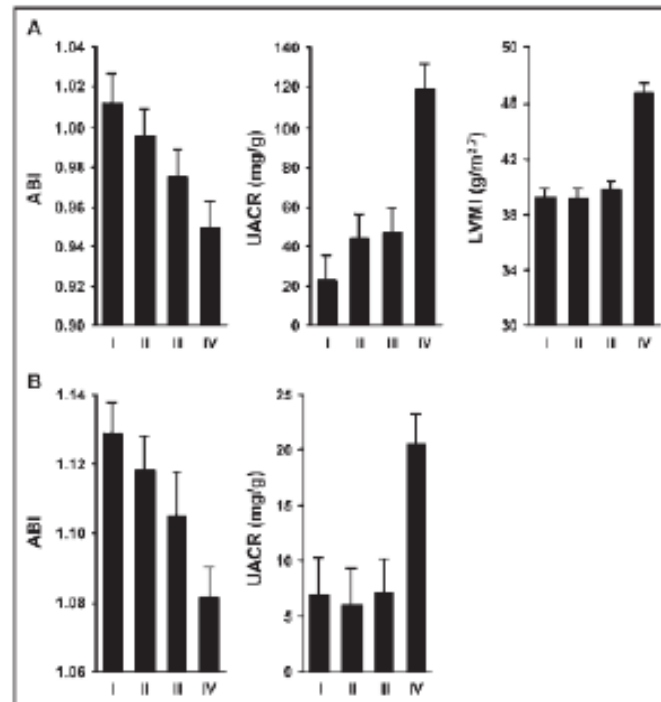
The International Consortium for Blood Pressure Genome-Wide Association Studies

the index SNP at this locus was associated with opposite effects on blood pressure and on ANP/BNP levels, consistent with a model in which the variants act through increased ANP/BNP production to lower blood pressure<sup>16</sup> (Supplementary Materials section 14).

# Prognostic role of NPs in hypertension

## Relation of Plasma Midregional Proatrial Natriuretic Peptide to Target Organ Damage in Adults With Systemic Hypertension

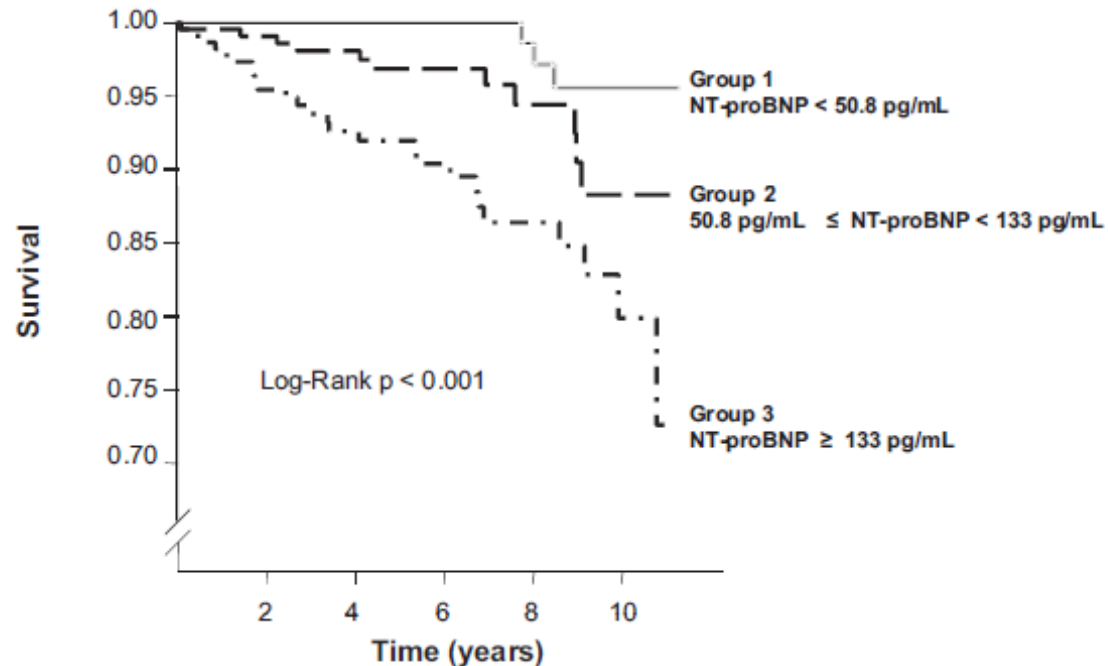
Mahyar Khaleghi, MD<sup>a</sup>, Malik A. Al-Omari, MD<sup>a</sup>, Venkateswarlu Kondragunta, PhD<sup>a</sup>, Nils G. Morgenthaler, MD<sup>b</sup>, Joachim Struck, PhD<sup>b</sup>, Andreas Bergmann, PhD<sup>b</sup>, Thomas H. Mosley, MD<sup>c</sup>, and Iftikhar J. Kullo, MD<sup>a,\*</sup>



After adjustment for age, gender, BMI, SBP, GFR, smoking, diabetes, cholesterol Levels, medication use, previous AMI or stroke, higher MR-proANP levels remained significantly associated with lower ABI, higher UACR, greater LV mass index, particularly in African-Americans

# N-Terminal Pro-Brain Natriuretic Peptide A Powerful Predictor of Mortality in Hypertension

Vinckane Paget, Lilliana Legedz, Nathalie Gaudebout, Nicolas Girerd, Giampiero Bricca, Hugues Milon, Madeleine Vincent, Pierre Lantelme

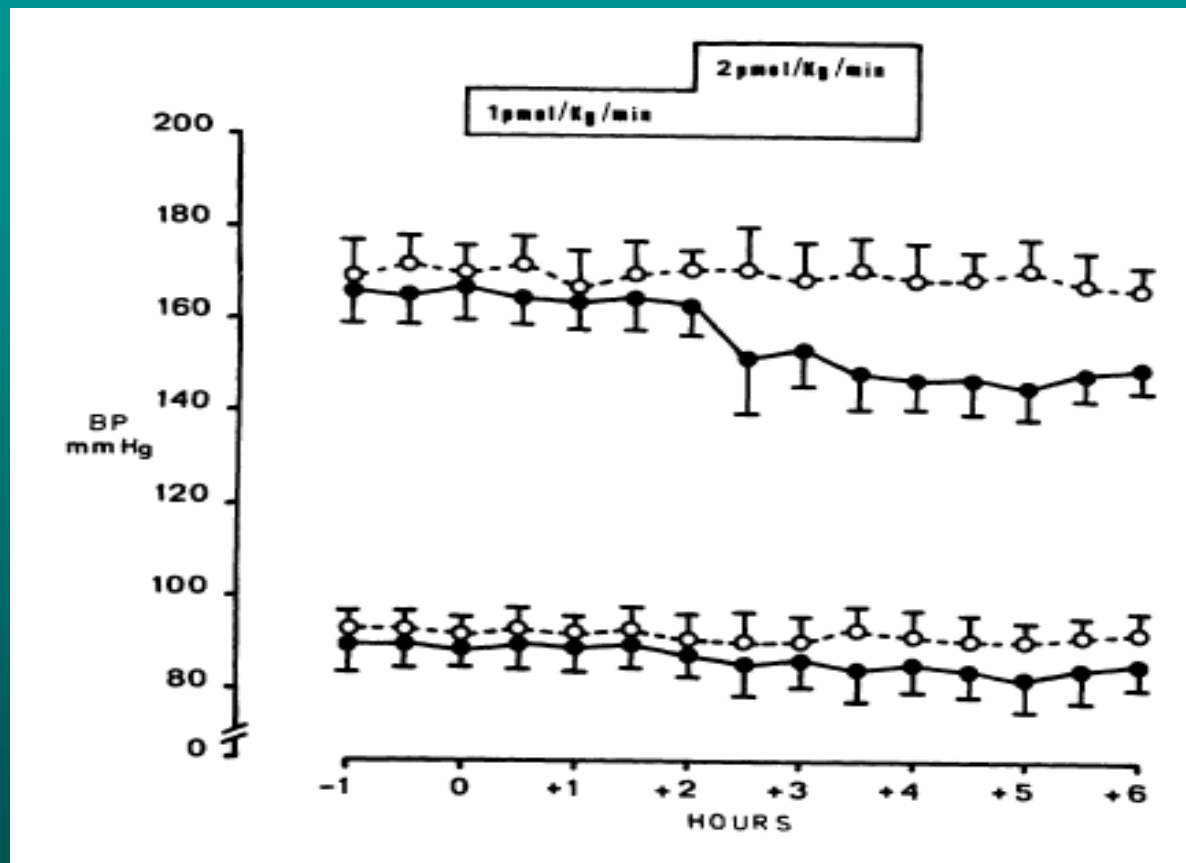


Number of patients at risk:

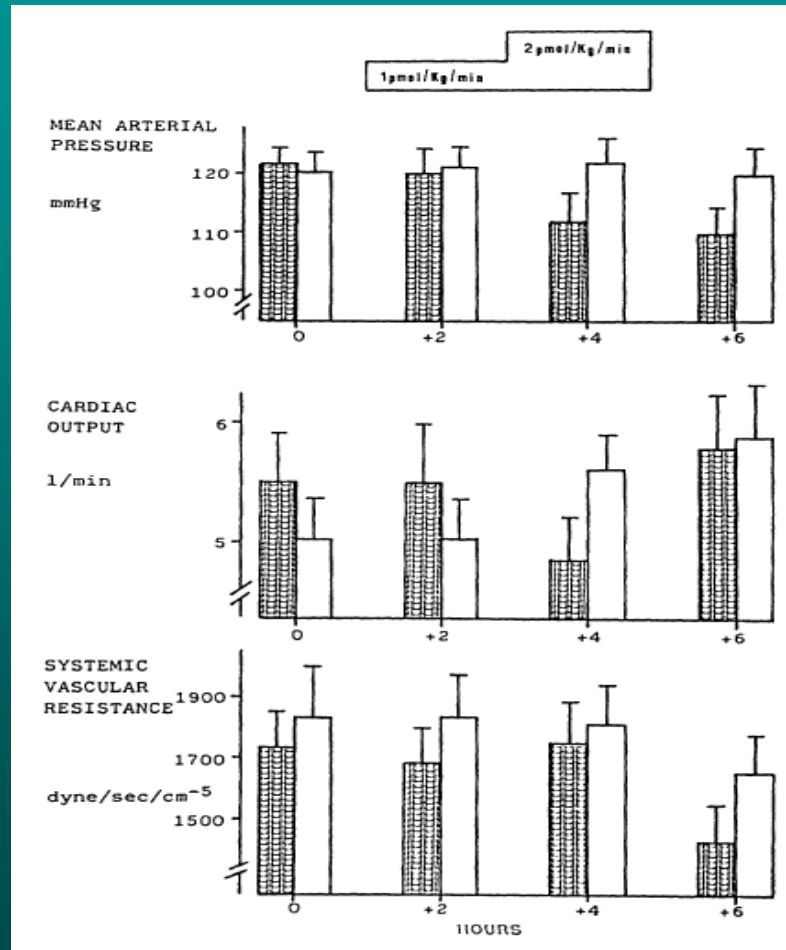
|         |     |     |     |     |    |    |
|---------|-----|-----|-----|-----|----|----|
| Group 1 | 228 | 182 | 141 | 104 | 68 | 26 |
| Group 2 | 228 | 203 | 164 | 112 | 67 | 24 |
| Group 3 | 228 | 193 | 144 | 106 | 68 | 24 |

Figure 1. Survival curves relative to the 3 groups defined by tertiles of plasma NT-proBNP levels (N=684).

## Infusion of low dose ANP in mild essential hypertension



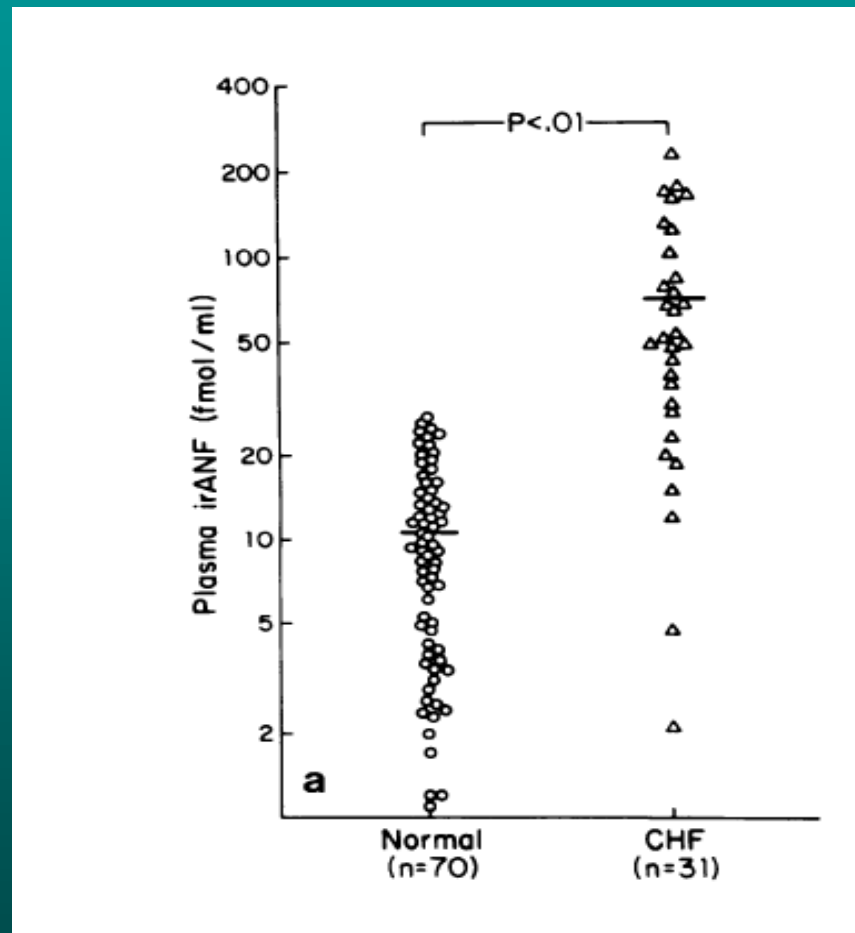
# Hemodynamic changes during ANP infusion in essential hypertension



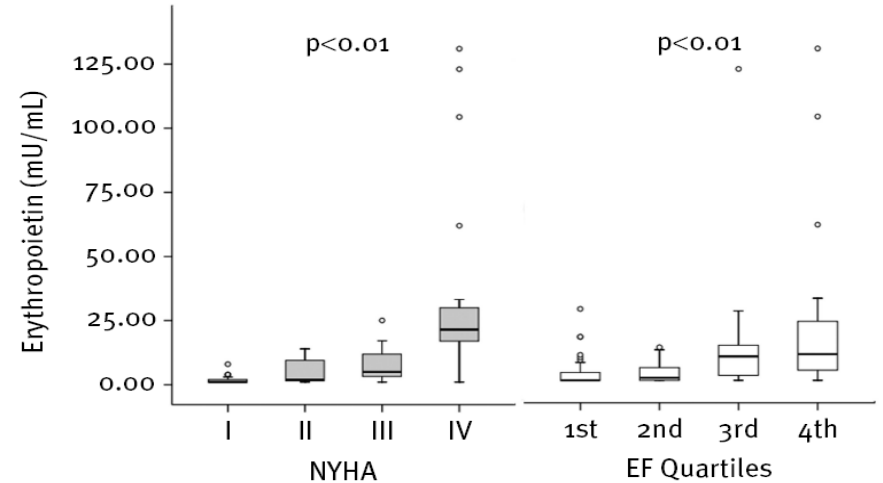
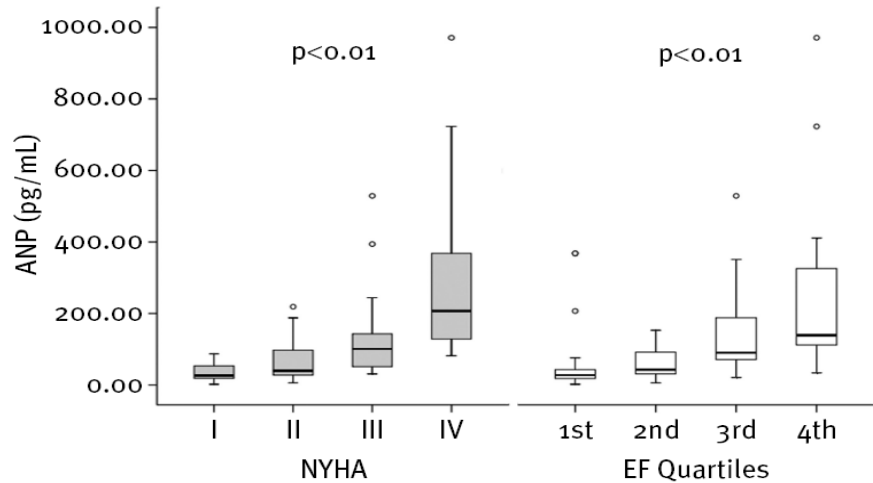
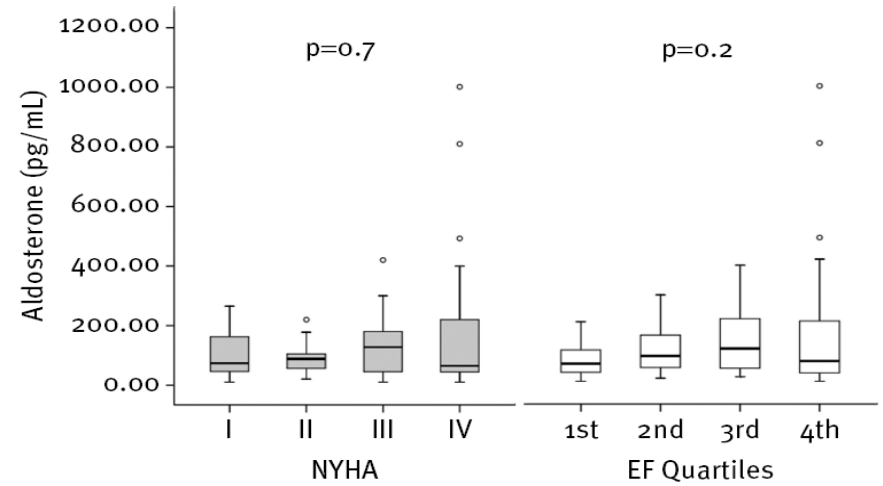
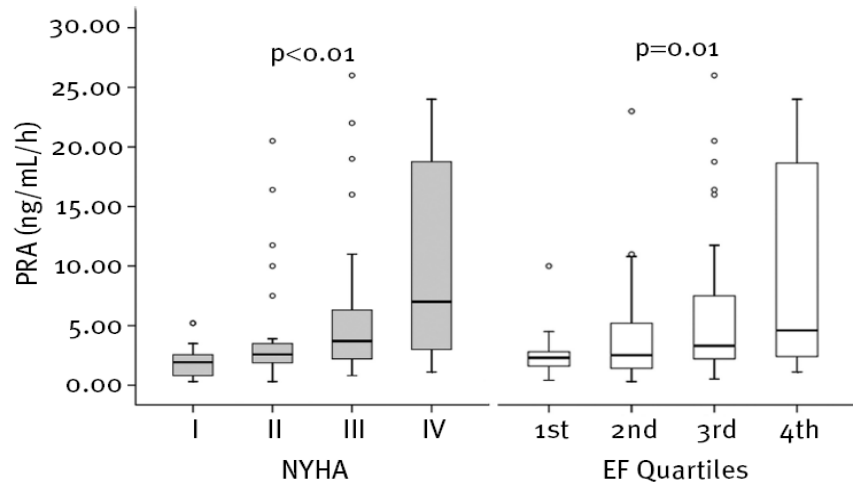


**Natriuretic peptides and heart failure: implications in diagnosis, prognosis and treatment**

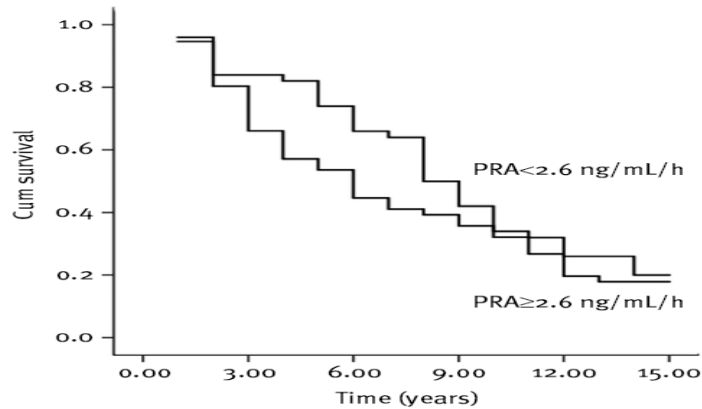
# Diagnostic role of circulating NPs levels in HF



# Prediction of Long-Term Survival in Chronic Heart Failure by Multiple Biomarker Assessment: A 15-Year Prospective Follow-Up Study



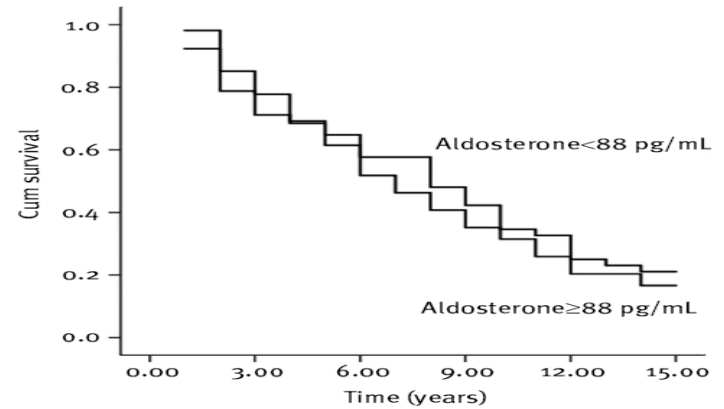
# Prediction of Long-Term Survival in Chronic Heart Failure by Multiple Biomarker Assessment: A 15-Year Prospective Follow-Up Study



N at risk

|                   |    |    |    |    |    |   |
|-------------------|----|----|----|----|----|---|
| PRA < 2.6 ng/mL/h | 50 | 41 | 36 | 24 | 15 | 9 |
| PRA ≥ 2.6 ng/mL/h | 56 | 44 | 29 | 21 | 14 | 9 |

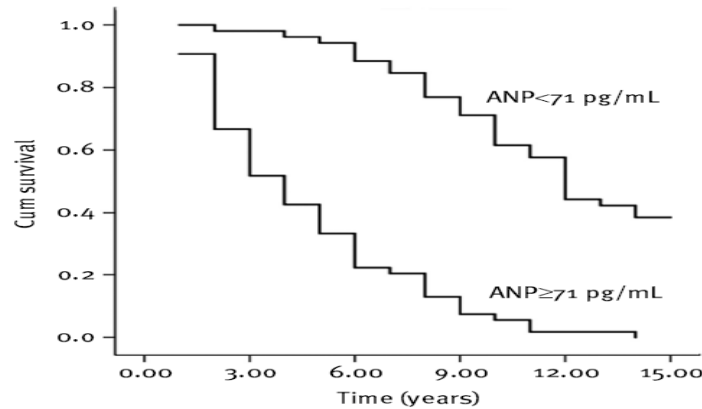
(A)



N at risk

|                    |    |    |    |    |    |    |
|--------------------|----|----|----|----|----|----|
| Aldost. < 88 pg/mL | 52 | 40 | 31 | 24 | 16 | 10 |
| Aldost. ≥ 88 pg/mL | 54 | 45 | 34 | 21 | 13 | 8  |

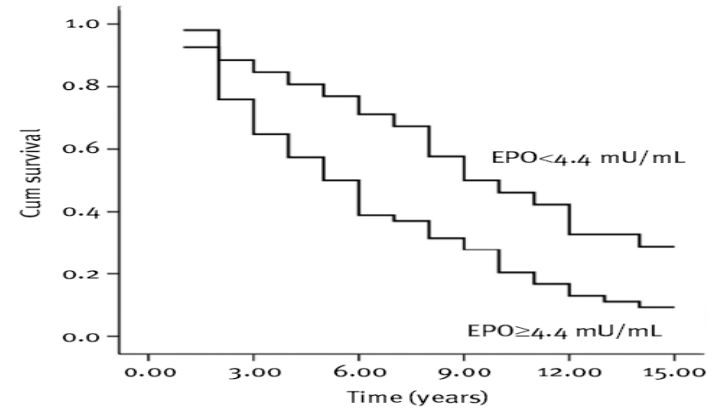
(B)



N at risk

|                |    |    |    |    |    |    |
|----------------|----|----|----|----|----|----|
| ANP < 71 pg/mL | 52 | 50 | 48 | 39 | 29 | 18 |
| ANP ≥ 71 pg/mL | 54 | 35 | 17 | 6  | 1  | 0  |

(C)



N at risk

|                 |    |    |    |    |    |    |
|-----------------|----|----|----|----|----|----|
| EPO < 4.4 mU/mL | 52 | 45 | 39 | 29 | 21 | 14 |
| EPO ≥ 4.4 mU/mL | 54 | 40 | 26 | 16 | 8  | 4  |

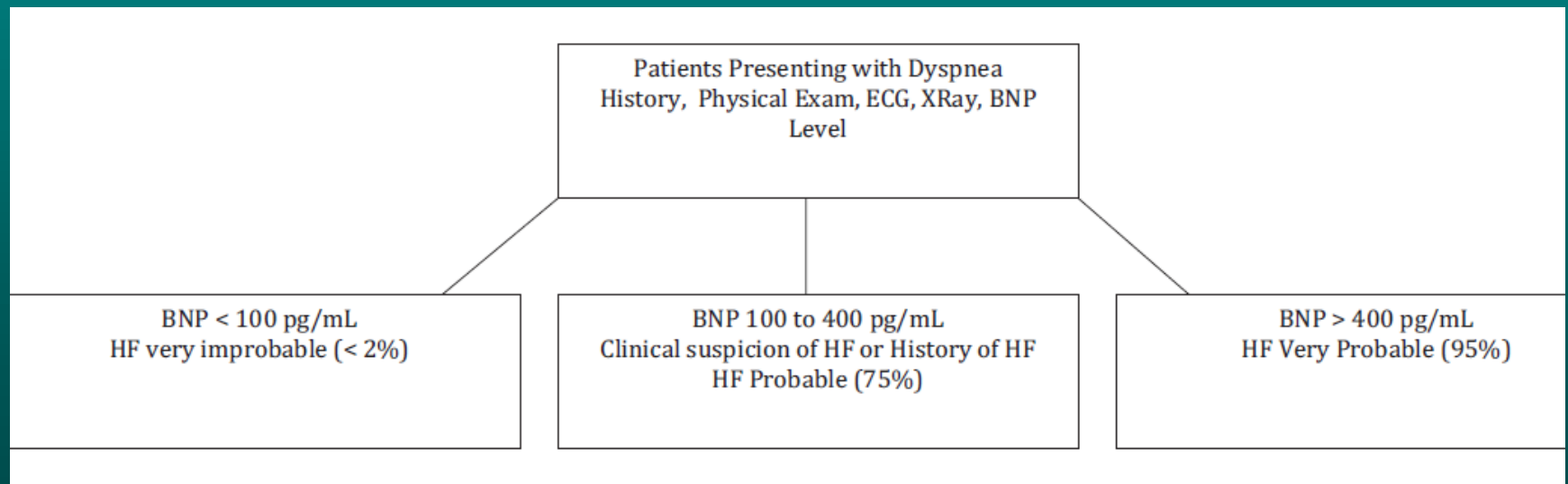
(D)

# Implications of plasma NPs levels for therapeutic management of HF: ADHF

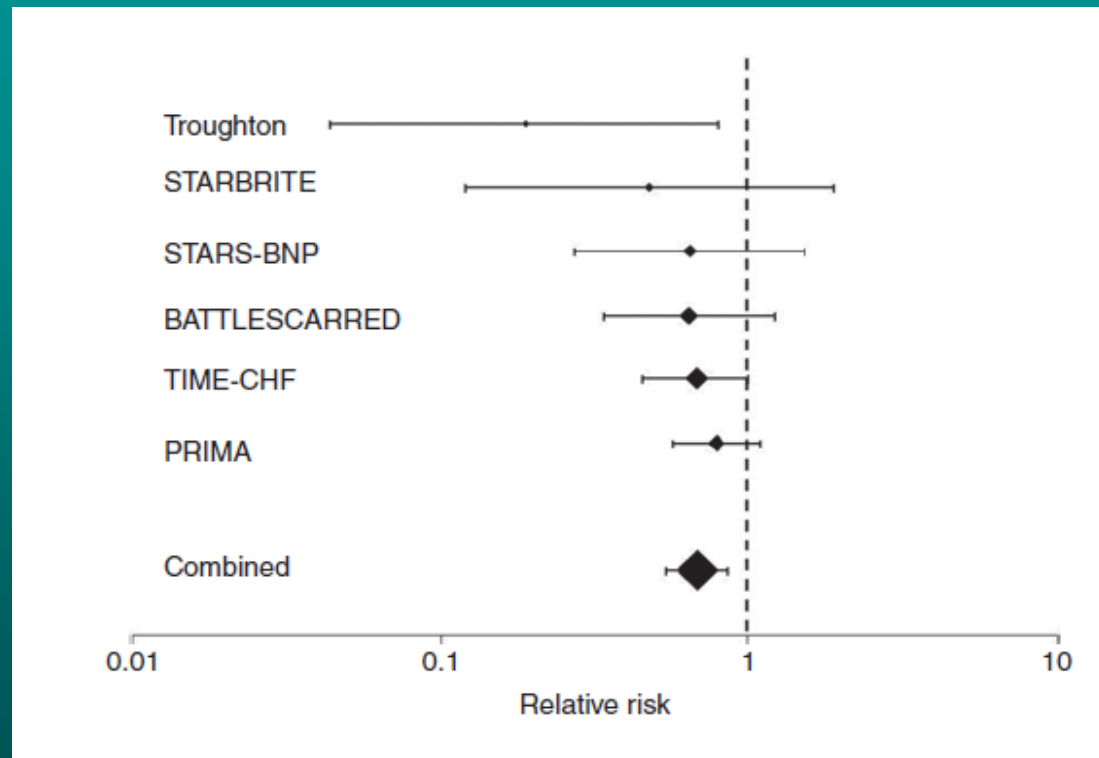
## The Role of Natriuretic Peptides: From the Emergency Department Throughout Hospitalization

Peter S. Pang, MD;<sup>1,2</sup> Yang Xue, MD;<sup>3</sup> Christopher DeFilippi, MD;<sup>4</sup> Marc Silver, MD;<sup>5</sup> James Januzzi, MD;<sup>6</sup> Alan Maisel, MD<sup>3</sup>

*Congest Heart Fail* Vol. 18 | No. 5 Suppl. 1 | September . October 2012



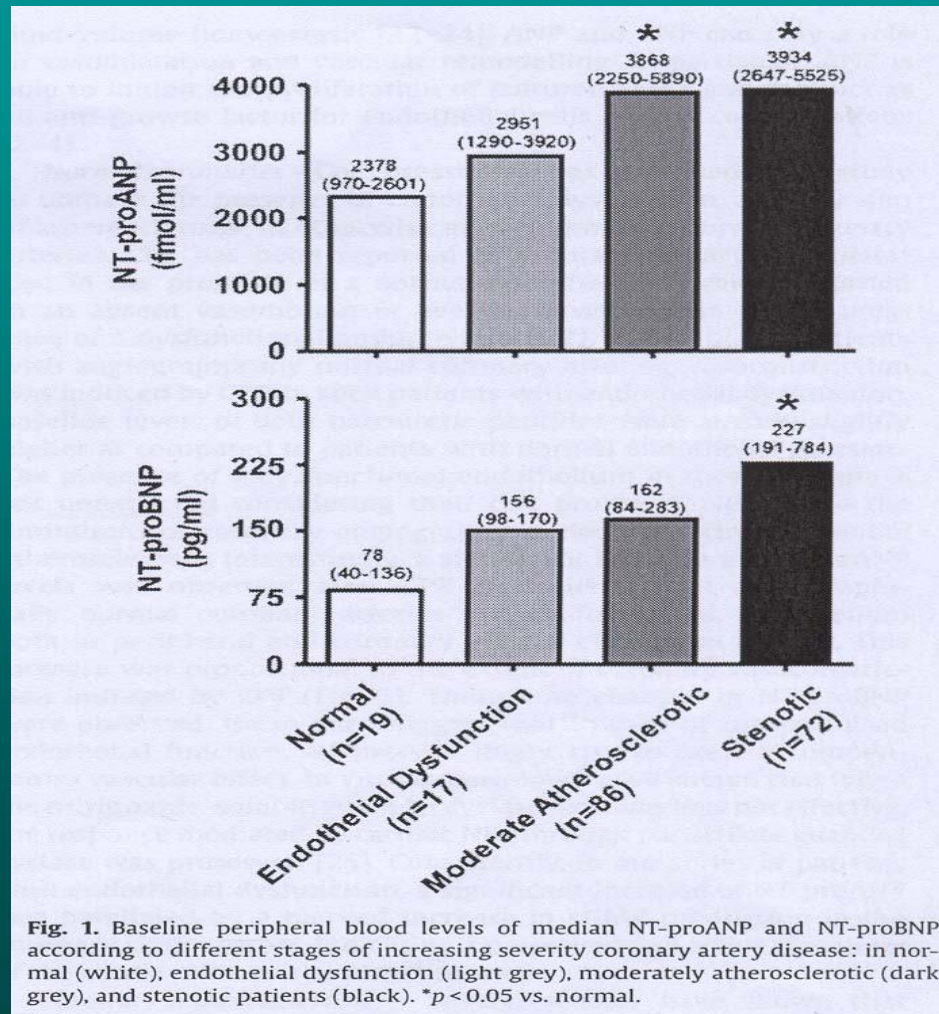
# The role of NPS as biomarkers for guiding the management of chronic heart failure



Meta-analysis results, pooling biomarker-guided therapy trial data, suggest a significant reduction in risk for mortality through use of B-type natriuretic peptide

**Natriuretic peptides and coronary  
artery disease: relevant  
prognostic role**

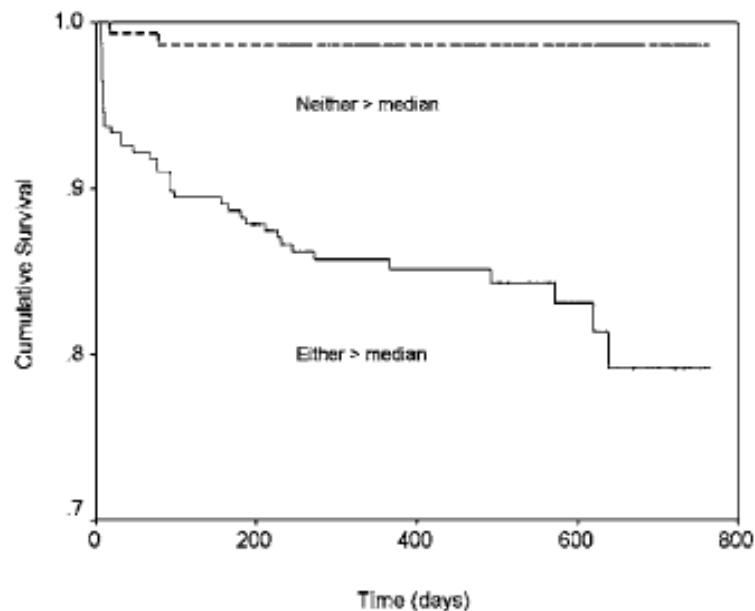
# NT-proANP and NT-proBNP levels in relation to coronary atherosclerosis





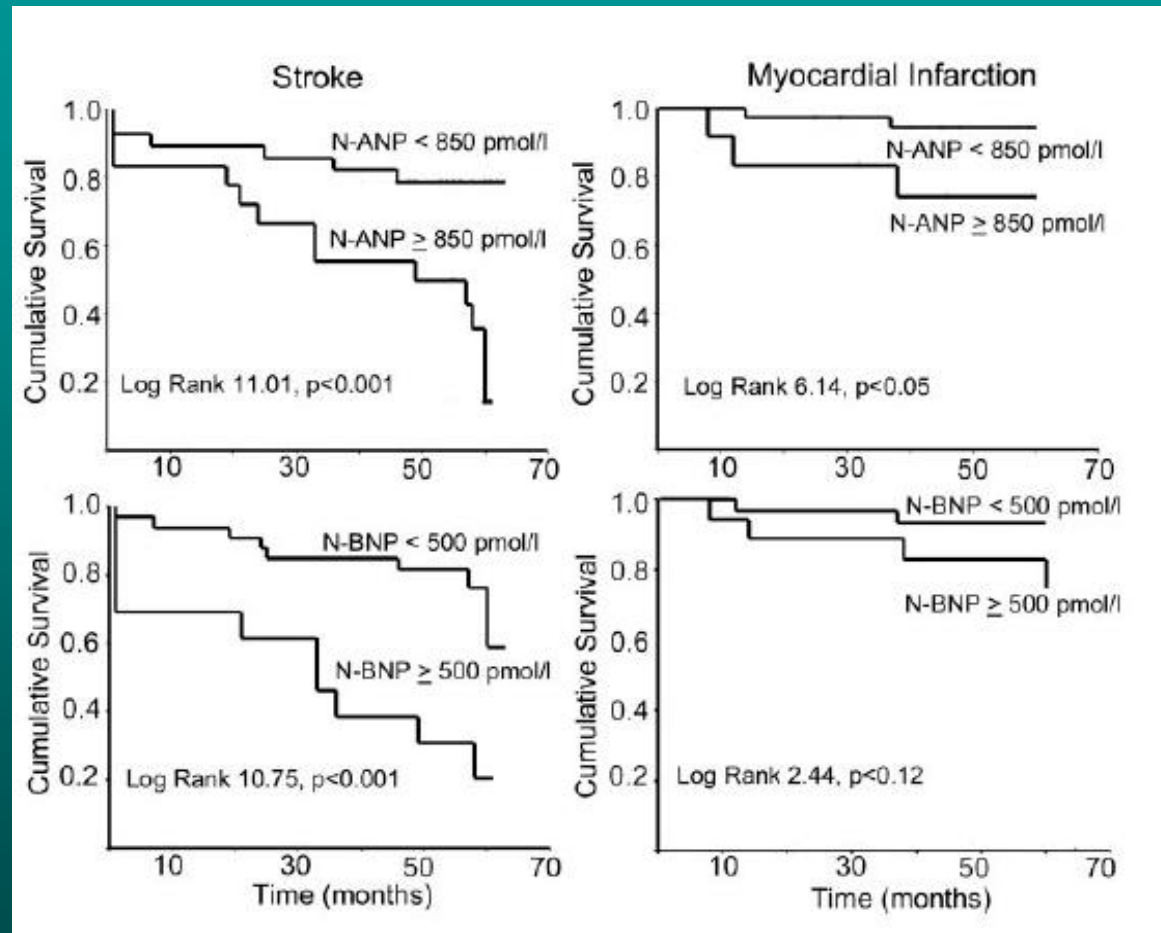
# Post-MI levels of NT-proANP and NT-proBNP identify subjects at higher risk for MACE

I. B. Squire and others

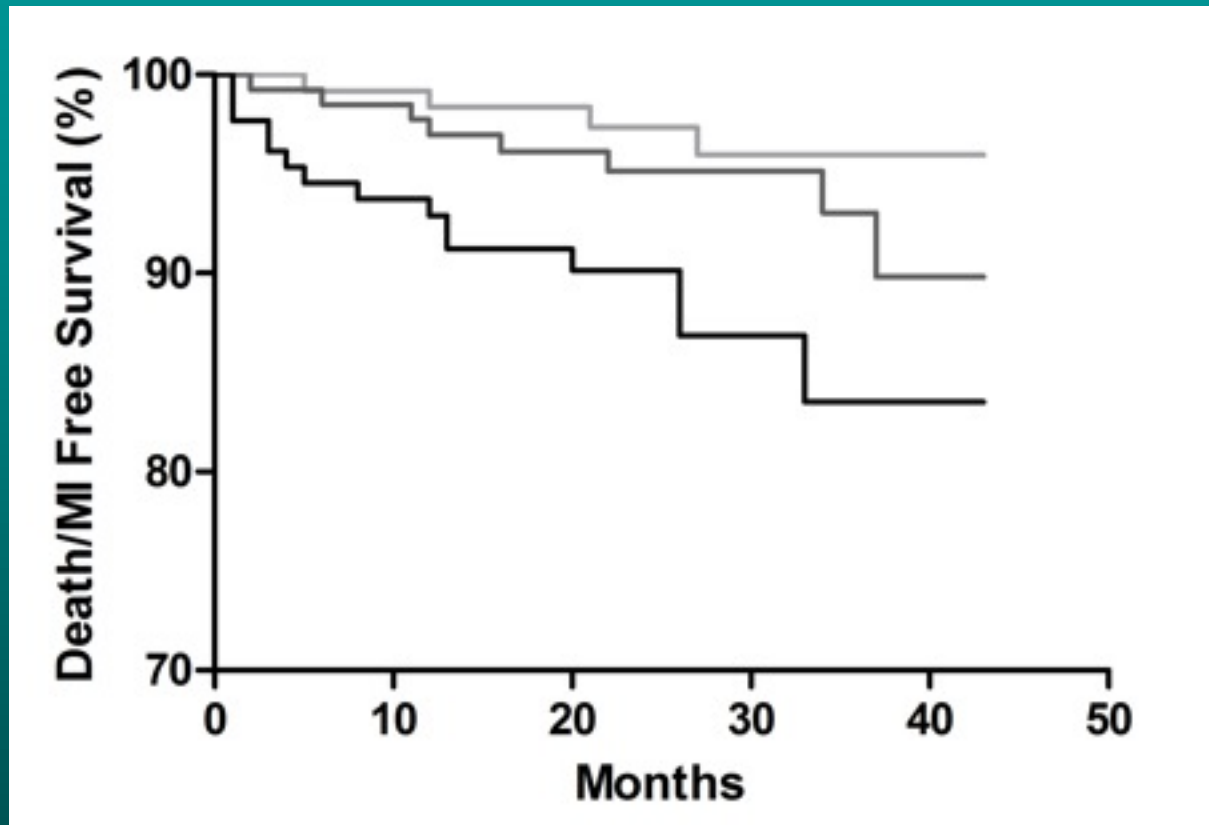


**Figure 4** Kaplan-Meier survival curves in 403 patients following AMI stratified on the basis of either N-ANP or N-BNP or both being above the respective median value

# NT-proANP and NT-proBNP plasma levels and mortality following acute cardiovascular events



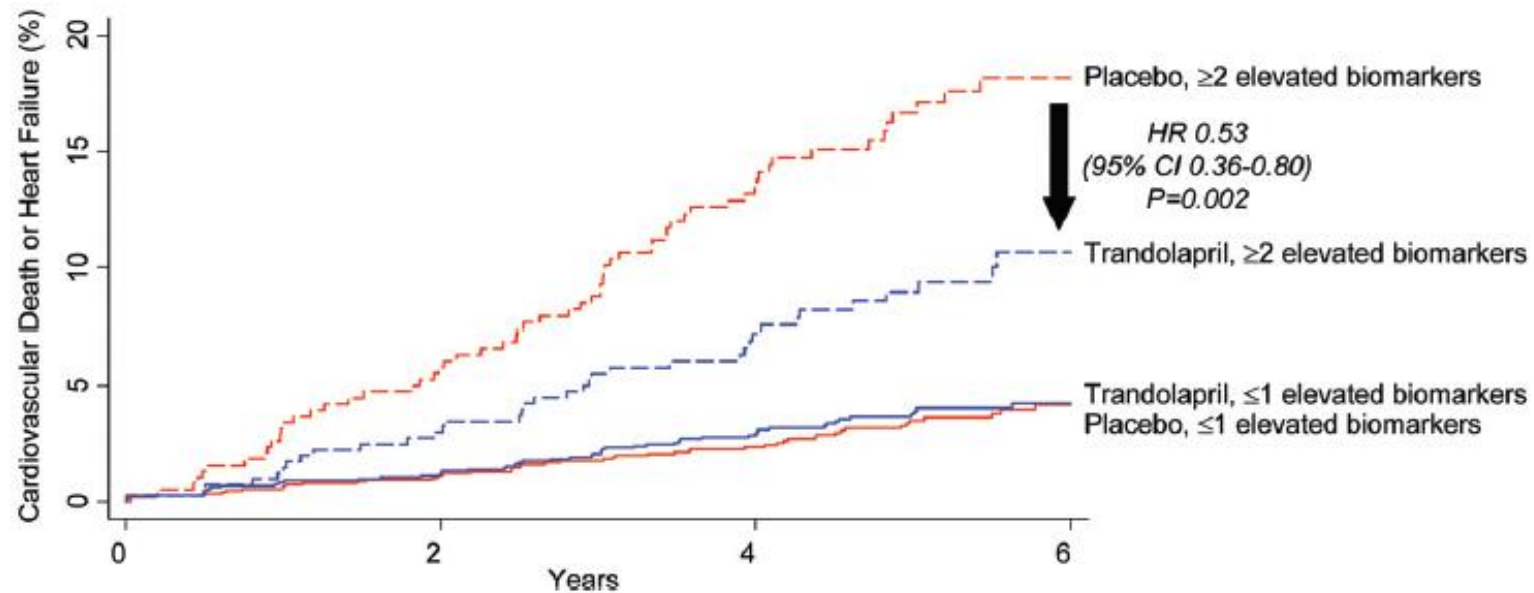
# Plasma levels of NT-proANP have a prognostic role in patients with stable ischaemic heart disease



(n=428) NT-proANP level >4749 identified as the cut off value to predict death/MI

# MR-proANP as biomarker for risk prediction and guiding medical therapy in patients with stable ischaemic heart disease

238 *Circulation* January 17, 2012



Elevated levels of MR-proANP and MR-proADM in subjects that appear to be at lower risk clinically may be useful to select patients who derive a significant benefit from ACEI therapy.

**Natriuretic peptides and  
cardiovascular risk prediction in  
the  
general population**

# NT-proBNP levels and prediction of acute cardiovascular events and mortality in apparently healthy subjects

## The Framingham Offspring Study

n=3346, 5.2 years FU

**Table 3.** Multivariate Analysis of the Association of Plasma B-Type Natriuretic Peptide (BNP) Levels and Outcomes.\*

| Outcome                               | Adjusted Hazard Ratio per 1 SD Increment in Log BNP Values (95% CI) | P Value | Adjusted Hazard Ratio for BNP Values above 80th Percentile (95% CI) | P Value |
|---------------------------------------|---|---------|---|---------|
| Death†                                | 1.27 (1.06–1.52)  | 0.009   | 1.62 (1.08–2.42)  | 0.02    |
| First major cardiovascular event‡     | 1.28 (1.03–1.59)  | 0.03    | 1.76 (1.06–2.92)  | 0.03    |
| Heart failure‡§                       | 1.77 (1.31–2.41)  | <0.001  | 3.07 (1.51–6.26)  | 0.002   |
| Atrial fibrillation§                  | 1.66 (1.30–2.11)  | <0.001  | 1.91 (1.13–3.25)  | 0.02    |
| Stroke or transient ischemic attack†‡ | 1.53 (1.16–2.02)  | 0.002   | 1.99 (1.09–3.62)  | 0.02    |
| Coronary heart disease events         | 1.10 (0.89–1.37)  | 0.37    | 1.30 (0.79–2.15)  | 0.30    |

# NT-proANP levels and prediction of acute cardiovascular events and mortality in apparently healthy subjects

## The Framingham Offspring Study

n=3346, 5.2 years FU

**Table 4.** Multivariate Analysis of the Association of Plasma N-Terminal Pro-Atrial Natriuretic Peptide (N-ANP) Levels and Outcomes.\*

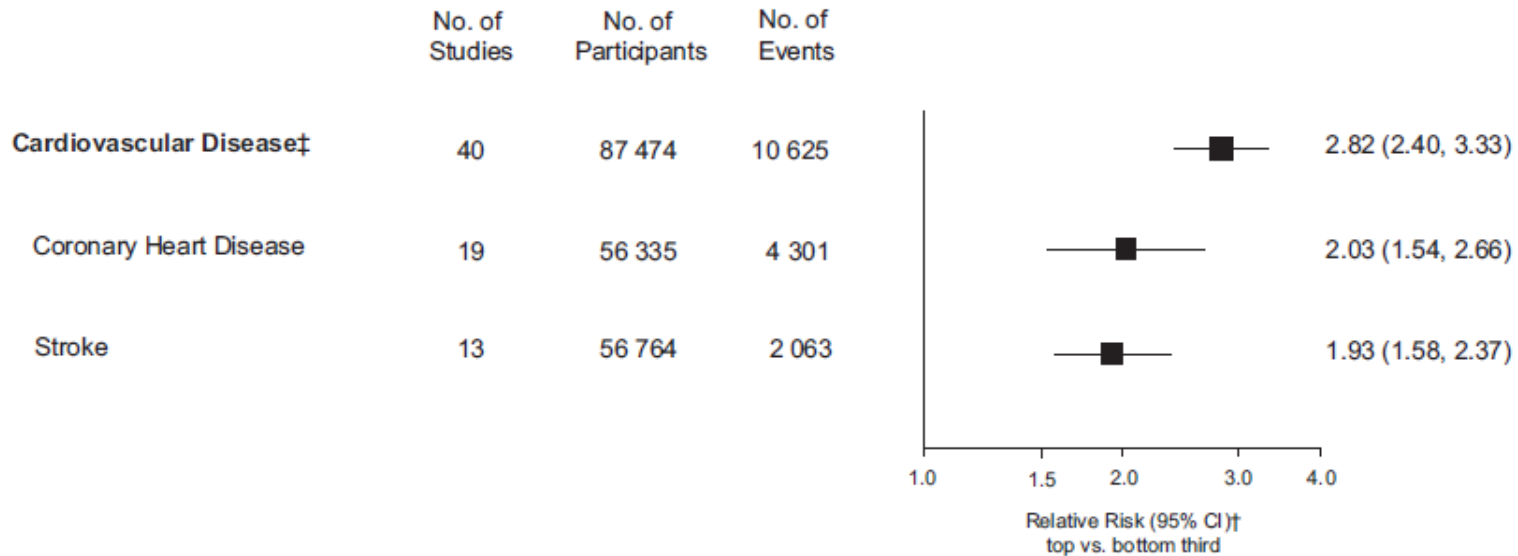
| Outcome                               | Adjusted Hazard Ratio per 1 SD Increment in Log N-ANP Values (95% CI) | P Value | Adjusted Hazard Ratio for N-ANP Values above 80th Percentile (95% CI) | P Value |
|---------------------------------------|---|---------|---|---------|
| Death†                                | 1.41 (1.14–1.74)  | 0.001   | 1.76 (1.15–2.68)  | 0.009   |
| First major cardiovascular event‡     | 1.30 (1.02–1.67)  | 0.04    | 1.52 (0.89–2.59)  | 0.12    |
| Heart failure‡§                       | 1.94 (1.37–2.75)  | <0.001  | 5.02 (2.32–10.85)   | <0.001  |
| Atrial fibrillation§                  | 1.72 (1.30–2.28)  | <0.001  | 2.09 (1.21–3.62)  | 0.008   |
| Stroke or transient ischemic attack†‡ | 1.37 (0.99–1.89)  | 0.06    | 2.08 (1.11–3.89)  | 0.02    |
| Coronary heart disease events         | 1.12 (0.88–1.42)  | 0.35    | 0.87 (0.50–1.51)  | 0.62    |

## B-Type Natriuretic Peptides and Cardiovascular Risk Systematic Review and Meta-Analysis of 40 Prospective Studies

Emanuele Di Angelantonio, MD, MSc\*; Rajiv Chowdhury, MD, MPhil\*;  
Nadeem Sarwar, MRPharmS, PhD; Kausik K. Ray, MD, MPhil; Reeta Gobin, MD, MPhil;  
Danish Saleheen, MD, MPhil; Alexander Thompson, PhD; Vilmundur Gudnason, MD, PhD;  
Naveed Sattar, FRCPath; John Danesh, FFFPH, FRCP

(*Circulation*. 2009;120:2177-2187.)

### Di Angelantonio et al Natriuretic Peptides and Cardiovascular Risk 2181



n= >80000

Assessment of BNP or NT-proBNP in addition to measurement of conventional CVD risk factors (and other characteristics) yielded apparently modest incremental improvement in risk discrimination for subsequent CVD.



## **N-Terminal Pro-Brain Natriuretic Peptide Is a More Useful Predictor of Cardiovascular Disease Risk Than C-Reactive Protein in Older Men With and Without Pre-Existing Cardiovascular Disease**

S. Goya Wannamethee, PHD,\* Paul Welsh, PHD,† Gordon D. Lowe, DSC,‡  
Vilmundur Gudnason, MD, PHD,§ Emanuele Di Angelantonio, MD,|| Lucy Lennon, MSc,\*  
Ann Rumley, PHD,‡ Peter H. Whincup, PHD,¶ Naveed Sattar, MD‡  
*London, Glasgow, Aberdeen, and Cambridge, United Kingdom; and Reykjavik, Iceland*

n=3649, 9 y FU

Inclusion of NT-proBNP in a Framingham-based model yielded significant improvement in C-statistics in both men with and without CVD and resulted in a net reclassification improvement of 8.8% ( $p = 0.0009$ ) and 8.2% ( $p = 0.05$ ), respectively, for major CVD events.



Contents lists available at ScienceDirect

## International Journal of Cardiology

journal homepage: [www.elsevier.com/locate/ijcard](http://www.elsevier.com/locate/ijcard)

### Aminoterminal natriuretic peptides and cardiovascular risk in an Italian male adult cohort ☆☆☆

Antonio Barbato<sup>a,1</sup>, Sebastiano Sciarretta<sup>c,1</sup>, Simona Marchitti<sup>b</sup>, Roberto Iacone<sup>a</sup>, Sara Di Castro<sup>b</sup>, Rosita Stanzone<sup>b</sup>, Maria Cotugno<sup>b</sup>, Renato Ippolito<sup>a</sup>, Luigi Palmieri<sup>d</sup>, Camilla Calvieri<sup>c</sup>, Allegra Battistoni<sup>c</sup>, Massimo Volpe<sup>b,c</sup>, Pasquale Strazzullo<sup>a</sup>, Speranza Rubattu<sup>b,c,\*</sup>  
and On behalf of the Olivetti Heart Study Research Group

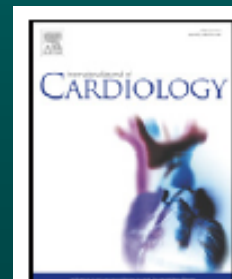
<sup>a</sup> Department of Clinical and Experimental Medicine, Federico II University of Naples Medical School, Naples, Italy

<sup>b</sup> IRCCS Neuromed, Pozzilli (Is) Italy

<sup>c</sup> Department of Cardiology, School of Medicine and Psychology, University Sapienza of Rome, Ospedale S. Andrea, Rome, Italy

<sup>d</sup> Department of Cerebro and Cardiovascular Diseases Epidemiology, Istituto Superiore di Sanità, Rome, Italy

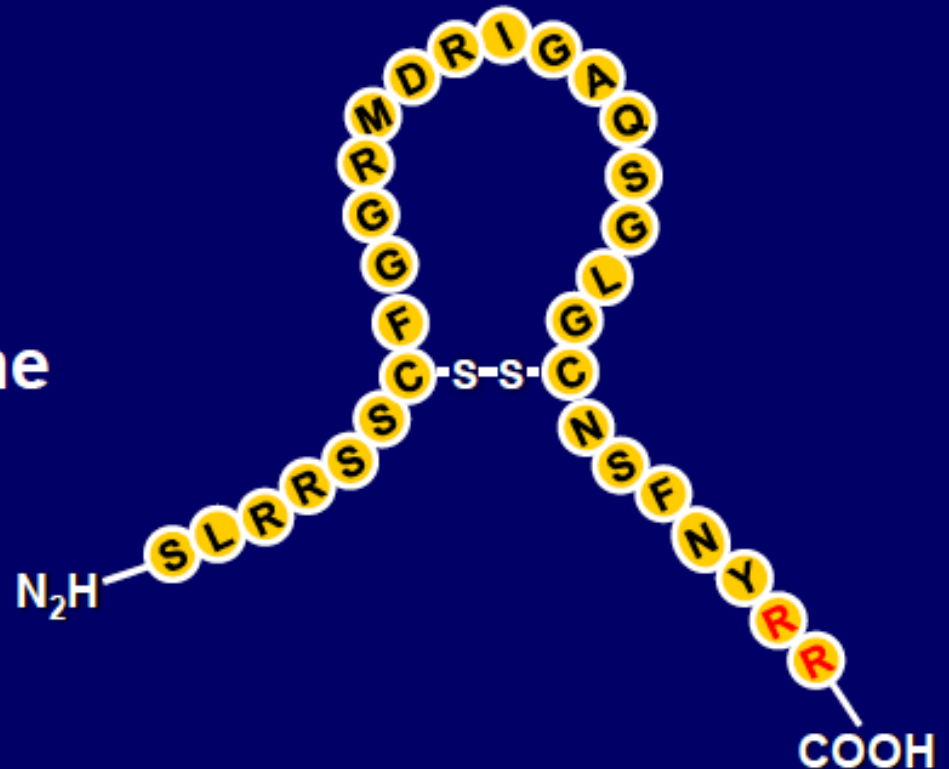
*Available online 8 September 2011*



# Genetic influence related to NPs for CV risk: the rs5065 (T2238C) molecular variant of hANP and its role in acute cardiovascular events occurrence

- Exon 3
- Stop codon region
- Thymine → Cytosine
- Two additional Arginines

↓  
ANP R-R



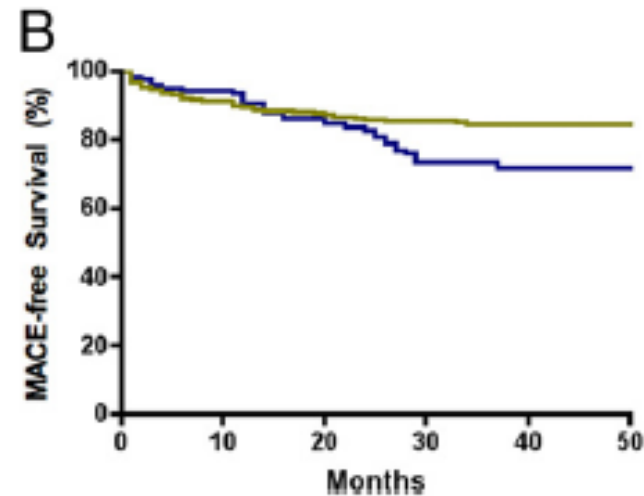
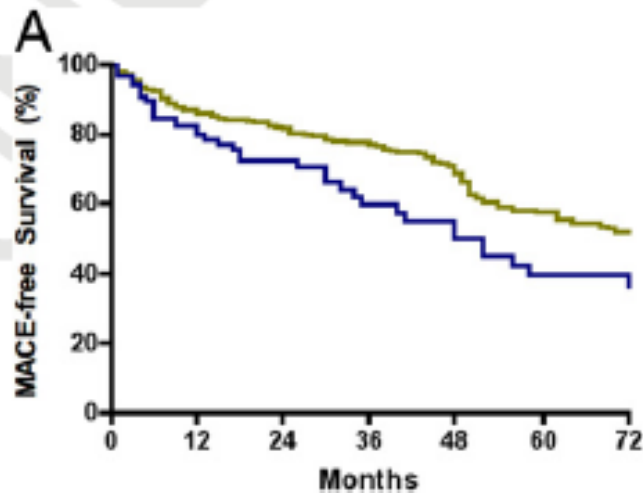
## Influence of rs5065 Atrial Natriuretic Peptide Gene Variant on Coronary Artery Disease

Emanuele Barbato, MD, PhD,\* Jozef Bartunek, MD, PhD,\* Fabio Mangiacapra, MD, PhD,\*  
Sebastiano Sciarretta, MD,†‡ Rosita Stanzione, PhD,‡ Leen Delrue, PhD,\* Maria Cotugno, PhD,‡  
Simona Marchitti, PhD,‡ Guido Iaccarino, MD,§ Giusy Sirico, MD,§ Sara Di Castro, PhD,‡  
Anna Evangelista, PhD,‡ Diether Lambrechts, MD, PhD,||¶ Peter Sinnaeve, MD, PhD,#  
Bernard De Bruyne, MD, PhD,\* Frans Van De Werf, MD, PhD,# Stefaan Janssens, MD, PhD,#  
Keith A.A. Fox, MD, PhD,\*\* William Wijns, MD, PhD,\* Massimo Volpe, MD,†‡  
Speranza Rubattu, MD†‡

*Aalst, and Leuven, Belgium; Rome, Pozzilli, and Salerno, Italy; and Edinburgh, United Kingdom*

# Role of T2238C/ANP in outcome prediction in stable ischemic heart disease

n=914

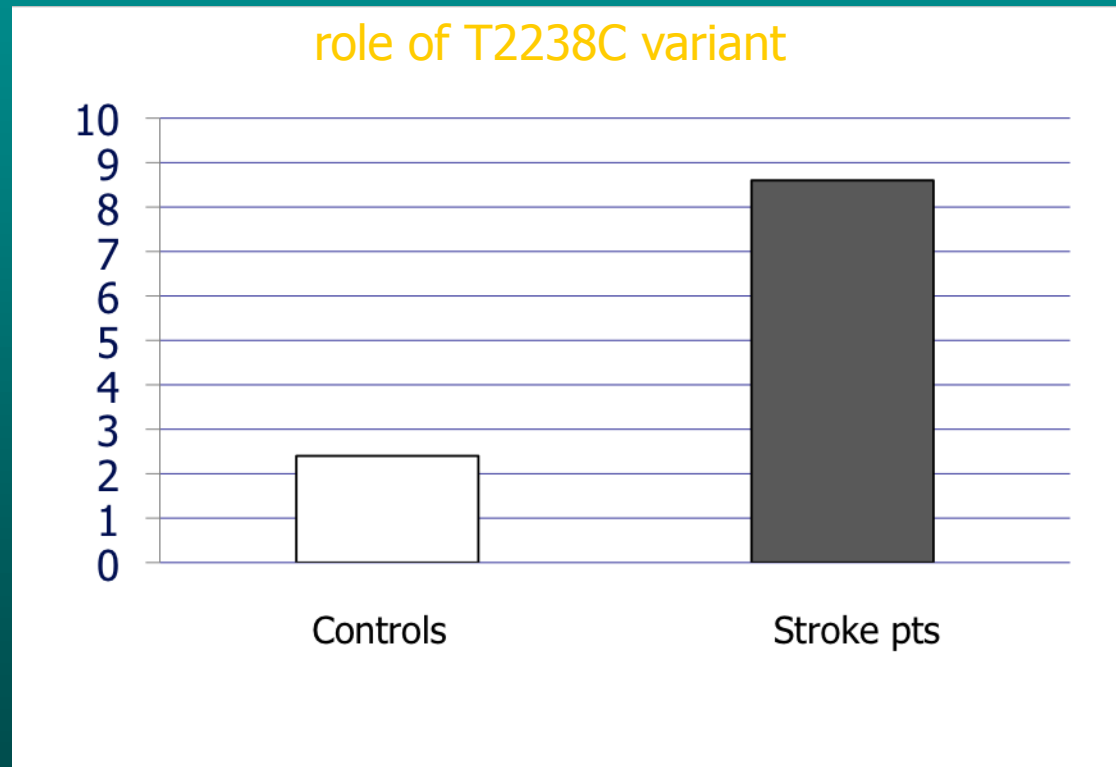


Survival Curves in Stable Angina and Independent Stable Angina Patient Populations

# Atrial Natriuretic Peptide Gene Polymorphisms and Risk of Ischemic Stroke in Humans

Speranza Rubattu, MD; Rosita Stanzione, PhD; Emanuele Di Angelantonio, MD; Bastianina Zanda, MD; Anna Evangelista, BS; David Tarasi, MD; Bruna Gigante, MD; Angelo Pirisi, MD; Ercole Brunetti, MD; Massimo Volpe, MD

Prevalence of CC2238 homozygosity (%)



# rs5065 and CV risk in the general population

## Original Article

### Atrial Natriuretic Peptide Genetic Variant rs5065 and Risk for Cardiovascular Disease in the General Community A 9-Year Follow-Up Study

Valentina Cannone, Brenda K. Huntley, Timothy M. Olson, Denise M. Heublein, Christopher G. Scott, Kent R. Bailey, Margaret M. Redfield, Richard J. Rodeheffer, John C. Burnett Jr

**Abstract**—We analyzed the phenotype associated with the atrial natriuretic peptide (ANP) genetic variant rs5065 in a random community-based sample. We also assessed and compared the biological action of 2 concentrations ( $10^{-10}$  mol/L,  $10^{-8}$  mol/L) of ANP and ANP-RR, the protein variant encoded by the minor allele of rs5065, on activation of the guanylyl cyclase (GC)-A and GC-B receptors, production of the second messenger 3',5'-cGMP in endothelial cells, and endothelial permeability. rs5065 genotypes were determined in a cross-sectional adult cohort from Olmsted County, MN ( $n=1623$ ). Genotype frequencies for rs5065 were 75%, 24%, and 1% for TT, TC, and CC, respectively. Multivariate analysis showed that the C allele was associated with increased risk of cerebrovascular accident (hazard ratio, 1.43; 95% confidence interval, 1.09–1.86;  $P=0.009$ ) and higher prevalence of myocardial infarction (odds ratio, 1.82; 95% confidence interval, 1.07–3.09;  $P=0.026$ ). ANP-RR  $10^{-8}$  mol/L activated the GC-A receptor ( $83.07\pm 8.31$  versus no treatment  $0.18\pm 0.04$  per 6 wells;  $P=0.006$ ), whereas ANP-RR  $10^{-10}$  mol/L did not. Neither  $10^{-8}$  mol/L nor  $10^{-10}$  mol/L ANP-RR activated GC-B receptor ( $P=0.10$ ,  $P=0.35$ ). ANP  $10^{-8}$  mol/L and ANP-RR  $10^{-8}$  mol/L stimulated 3',5'-cGMP production in endothelial cells similarly ( $P=0.58$ ). Both concentrations of ANP-RR significantly enhanced human aortic endothelial cell permeability (69 versus 29 relative fluorescence units [RFUs],  $P=0.012$ ; 58 versus 39 RFUs,  $P=0.015$ ) compared with ANP. The minor allele of rs5065 was associated with increased cardiovascular risk. ANP-RR activated the GC-A receptor, increased 3',5'-cGMP in endothelial cells, and when compared with ANP, augmented endothelial cell permeability. (*Hypertension*. 2013;62:00-00.) • [Online Data Supplement](#)



# Summary I

- Derangements of natriuretic peptides functions contribute to the development of hypertension, CAD, heart failure.
- Follow-up measurements of natriuretic peptides in HT, CAD, HF patients certainly provide long term prognostic information.
- The prognostic role of NPs reveal useful for better management of CVDs.
- Circulating natriuretic peptides have shown a significant predictive role for cardiovascular disease risk in the general population in several epidemiological studies.



## Summary II

- A genetic influence of NPs system contributes to the increased risk of major CVDs.
- An altered peptide structure of ANP, T2238C/rs5065, is emerging as a novel cardiovascular risk factor with significant prognostic implications in stable ischemic heart disease patients and in the general population.
- Assessment of both circulating natriuretic peptides level and T2238C/ANP allele status carrier promises to be a useful combination in order to provide important information in risk prediction and therapeutical decision making in patients affected by cardiovascular diseases.

# NPs-based therapies as promising tools for the treatment of CVDs

