Natriuretic peptides and cardiovascular diseases: an update on the underlying implications

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Volume overload
SNS
Angiotensin II
Endothelin

CM

ANP, BNP

EC

CNP

Natriuretic peptide degrading enzymes

NEP
DPPIV
IDE

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
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 (lypolytic effect)
- anti-inflammatory property
Functional derangements due to changes of ANP structure: the C2238/ANP story

Effects on endothelial cell viability

![Graphs showing cell number and cell death comparisons between Control, WT, and Mut conditions with statistical significance levels](Sciaretta S et al. Circ Res 2013)
C2238 ANP Variant and Endothelial Dysfunction

**Panel A**
- FMD (%)
- TT2238 (Controls)
- TC2238 (Heterozygous)
- CC2238 (Homozygous)

**Panel B**
- NTG (%)
- TT2238 (Controls)
- TC2238 (Heterozygous)
- CC2238 (Homozygous)

**Panel C**
- Diagram showing the regulatory pathways involving ANP (αANP), NPR-A/B, GC, cGMP/PKG, and the relationship with vasorelaxation and endothelial dysfunction.
Rubattu S et al. Plos One 2014
T2238C/ANP associates with increased risk of acute cardiovascular events

- Rubattu et al. Stroke 2004: Increased risk of ischemic stroke, first ever episode and recurrent strokes
- Zhang et al., 2005: Increased risk of AMI
- Arnett DK Lynch A JAMA 2008: Decreased CVD risk (including stroke) upon diuretic therapy in C allele hypertensive carriers
- Cannone V, Burnett J. Jr. Hypertension 2013: Increased risk of stroke and AMI in the general population
- Barbato E. et al. JACC 2012: Increased risk of AMI and worse CV outcome in patients with stable angina
- Rubattu S. et al. JCM 2015: Increased risk of re-AMI in patients with acute coronary syndrome
IMPLICATIONS OF NATRIURETIC PEPTIDES LEVELS IN HEART FAILURE
The role of NPs as biomarkers for guiding 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

Motiwala SR and Januzzi JL. Clin. Pharm Ther 2013; 57-67
Prediction of Long-Term Survival in Chronic Heart Failure by Multiple Biomarker Assessment: A 15-Year Prospective Follow-Up Study

Early post-discharge NT-proBNP levels trajectory associated with distinct clinical profile and carried independent prognostic value in patients hospitalized for chronic worsening HF

Greene SJ et al. EJHF 2015
Natriuretic Peptide-Based Screening and Collaborative Care for Heart Failure
The STOP-HF Randomized Trial

CONCLUSION AND RELEVANCE Among patients at risk of heart failure, BNP-based screening and collaborative care reduced the combined rates of LV systolic dysfunction, diastolic dysfunction, and heart failure.
IMPLICATIONS OF NATRIURETIC PEPTIDES LEVELS IN ISCHEMIC HEART DISEASE
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

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

Rubattu S., Niccoli G, et al. 2015 submitted
NATRIURETIC PEPTIDES LEVELS AND CVD PREDICTION IN THE GENERAL POPULATION
Ideal Cardiovascular Health

Associations With Biomarkers and Subclinical Disease and Impact on Incidence of Cardiovascular Disease in the Framingham Offspring Study

Vanessa Xanthakis, PhD; Danielle M. Enserro, MA; Joanne M. Murabito, MD; Joseph F. Polak, MD, MPH; Kai C. Wollert, MD; James L. Januzzi, MD; Thomas J. Wang, MD; Geoffrey Tofler, MD; Ramachandran S. Vasan, MD

**Background**—The American Heart Association Cardiovascular Health score (CVH score) is inversely associated with cardiovascular disease (CVD) incidence, but the mechanisms underlying this association warrant exploration.

**Methods and Results**—We related the CVH score to circulating biomarkers and prevalent subclinical CVD (defined as ≥1 of the following: increased carotid intima-media thickness or stenosis, left ventricular hypertrophy [by ECG or echocardiography], left ventricular systolic dysfunction, microalbuminuria, and a reduced ankle-brachial index) in 2680 Framingham Study participants (mean age, 58 years; 55% women). After adjustment for age and sex, an ideal CVH score (nonsmoking status, ideal body mass index, regular physical activity, healthy diet, and an optimal profile of serum cholesterol, blood pressure, and glucose; 1 point for each) was associated with higher circulating concentrations of natriuretic peptides (N-terminal pro-atrial natriuretic peptide and B-type natriuretic peptide) and lower blood concentrations of plasminogen activator inhibitor-1, aldosterone, C-reactive protein, D-dimer, fibrinogen, homocysteine, and growth differentiation factor-15 levels (P<0.001 for all), as well as lower odds of subclinical disease (odds ratio, 0.74 per 1-unit increase in CVH score; 95% confidence interval, 0.68–0.80). The incidence of CVD (267 events over 16 years) was inversely associated with the CVH score in age- and sex-adjusted models (hazard ratio, 0.77 per 1-unit increase in CVH score; 95% confidence interval, 0.70–0.86), which was slightly attenuated upon adjustment for biomarkers and subclinical disease (hazard ratio, 0.87; 95% confidence interval, 0.78–0.97).

**Conclusion**—In our prospective community-based study, the inverse association between an ideal cardiovascular health score and CVD incidence was partly attributable to its favorable impact on CVD biomarker levels and subclinical disease. (*Circulation. 2014;130:1676-1683.*)
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.
NPSC: associations of NT-proBNP and HDL cholesterol with cardiovascular outcome

- n= >90000

- In a comparison of people in the top third vs bottom third of NT-proBNP levels, the adjusted risk ratios were higher for fatal than non-fatal CHD. Corresponding risk ratios for HDL-cholesterol were similar or even lower (NPSC, 2015 unpublished).
Addition of NT-proBNP to a prognostic model for CVD including conventional risk factors increased the C-index and yielded a net reclassification improvement which was superior to that of HDL-cholesterol and of CRP (NPSC, unpublished 2015).
MR-proANP and NT-proBNP are equally efficient in predicting all-cause mortality, cardiovascular mortality and cardiovascular events in a prospective observational study (PREVEND)
ROC Analysis for NT-proANP and NT-pro-BNP levels towards high cardiovascular risk in a general population from Southern Italy (Olivetti Heart Study) (CUORE>20%)

Sensibilità vs 100-Specificità

NT-proANP
NT-proBNP

p per la differenza tra le aree=0.9738

Barbato A et al. Int J Cardiol 2011;152:245-246
NPs as therapeutic target

Rubattu S et al. J. Hypertens 2013
NPs as therapeutic target: mechanism of action of LCZ696

Angiotensin Receptor Neprilysin Inhibition (ARNI): LCZ696

- LCZ696
  - Sacubitril
  - Valsartan

Natriuretic peptides
- BK, ADM
- Subs-P, VIP, CGRP

Angiotensin II

- Neprilysin
  - Vasodilation
  - Natriuresis
  - Diuresis
  - Inhibition of pathologic growth/fibrosis
  - Degradation products

- AT1 Receptor
  - Vasoconstriction
  - Sodium/water retention
  - Fibrosis/hypertrophy
LCZ696 and BP control in essential hypertension

Ruílope JM et al. Lancet 2010;375:1255-1266
LCZ696 showed a statistically significant reduction in clinic blood pressure (BP) and pulse pressure (PP) at end point compared with placebo.
Effects of ARB vs ARNi on AngII-stimulated neonatal rat cardiomyocytes hypertrophy and fibroblasts collagen synthesis

**ARNi (Val+NEP)** provided dose-dependent superior anti-hypertrophic and anti-fibrotic effects compared to ARB alone

von Lueder et al. Circ Heart Fail. 2013
Effects of ARNi on cardiac remodeling after myocardial infarction in rats

von Lueder et al. Circ Heart Fail. 2013
Effects of ARB vs ARNi on high-salt induced cardiovascular injury in a model of SHR with metabolic syndrome (SHRcp)
Effects of ARB vs ARNi on endothelium and non-endothelium dependent vasorelaxation in high-salt fed SHRScp

Kusaka H, Am J Hypertens 2015
Next issues

- Resistant hypertension
- Protection from renal damage (in an animal model, SHRSP)
- Protection from stroke (in an animal model, SHRSP)
- HFpEF (PARAGON-HF)
- Arterial stiffness in the elderly (PARAMETER)
Conclusions

- NPs have predictive role for major CVDs in the general population, and both diagnostic and prognostic role in heart failure, arterial hypertension, ischemic heart disease.
- The beneficial effects of natriuretic peptides on cardiovascular structure and function have raised the need to develop novel therapeutic strategies aimed at increasing their favourable properties in CVDs.
- The recent development of a novel therapeutical approach combining Neprylisin and AT1R receptor inhibition promises to be a key strategy to combat CVDs and their complications.