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ACC Middle East Conference 2017

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The role of biomarkers in optimizing HF outcomes

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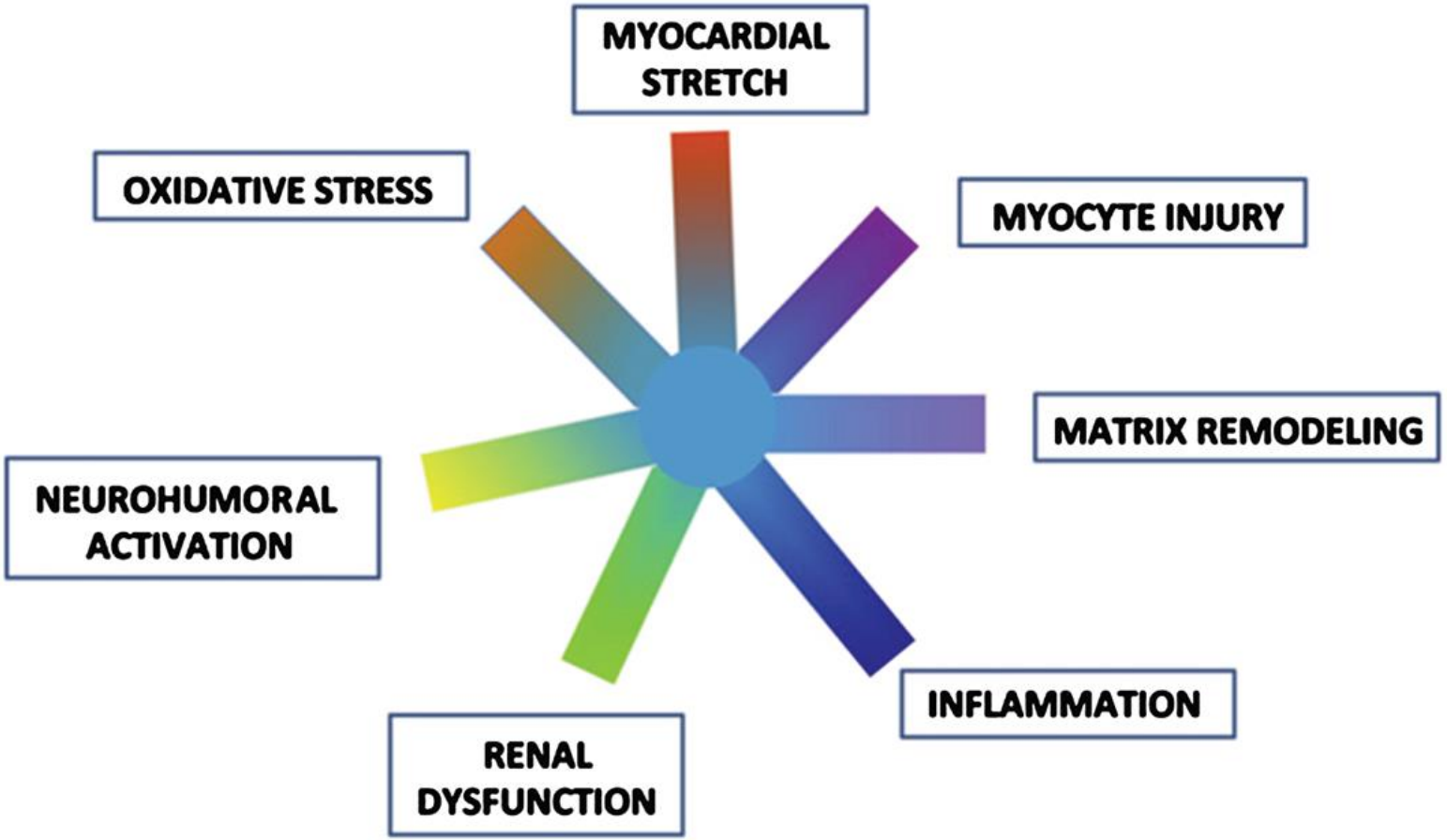
Another step toward personalized care of patients with heart failure



European Journal of Heart Failure
Volume 17, Issue 10, pages 988-990, 16 SEP 2015 DOI: 10.1002/ejhf.348
http://onlinelibrary.wiley.com/doi/10.1002/ejhf.348/full#ejhf348-fig-0001

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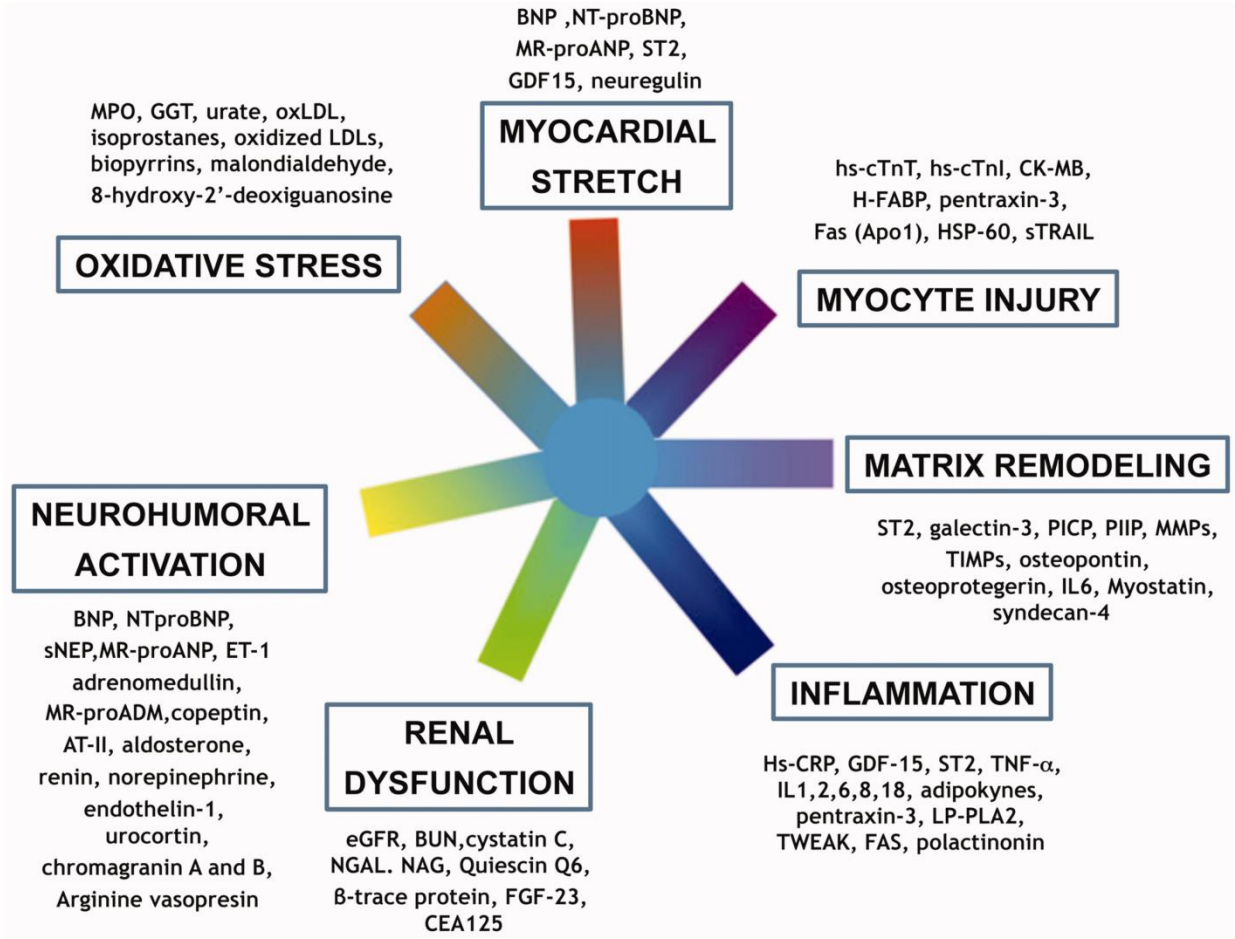

From: Transitioning from usual care to biomarker-based personalized and precision medicine in heart failure: call for action

Eur Heart J. Published online February 15, 2017. doi:10.1093/eurheartj/ehx027

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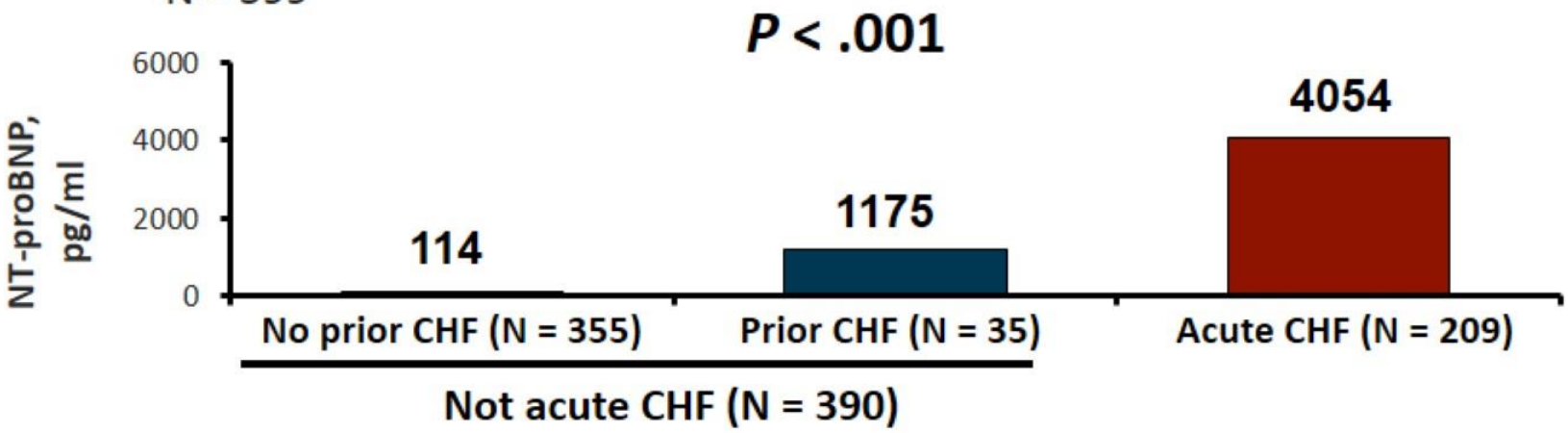
Natriuretic Peptides

- Biomarkers for Early Diagnosis of HF
  - BNP: secreted by cardiac ventricles during heart failure
  - NT-proBNP: amino terminal fragment of BNP precursor protein
- Provide diagnostic and prognostic information in patients w/ dyspnea,[a,b]
- May reduce clinical uncertainty in ED management of acute dyspnea[c]
- PRIDE study[d]
  - N = 599



a. Mueller C, et al. *Arch Intern Med.* 2006;166:1081-1087; b. Januzzi JL, et al. *Eur Heart J.* 2006;27:330-337; c. Green SM, et al. *Arch Intern Med.* 2008;168:741-748; d. Januzzi JL, et al. *Am J Cardiol*. 2005;95:948-954.

The Value of Serial NP Measurement in Prognostication for Chronic HF

- ValHeFT: valsartan vs placebo in patients with stable HF (N = 5010)
- NT-proBNP measured at baseline and 4 mos in patients on the placebo arm of ValHeFT (n = 1742)
- Results: serial NT-proBNP with classification by threshold concentration strongly predicts risk in patients with stable HF

Baseline → 4-month Category*	n	Hospitalization for HF, %	Mortality, %
High → high	1322	26.8	25.6
Low → high	180	21.1	17.2
High → low	368	10.1	13.6
Low → low	1618	8.6	6.7

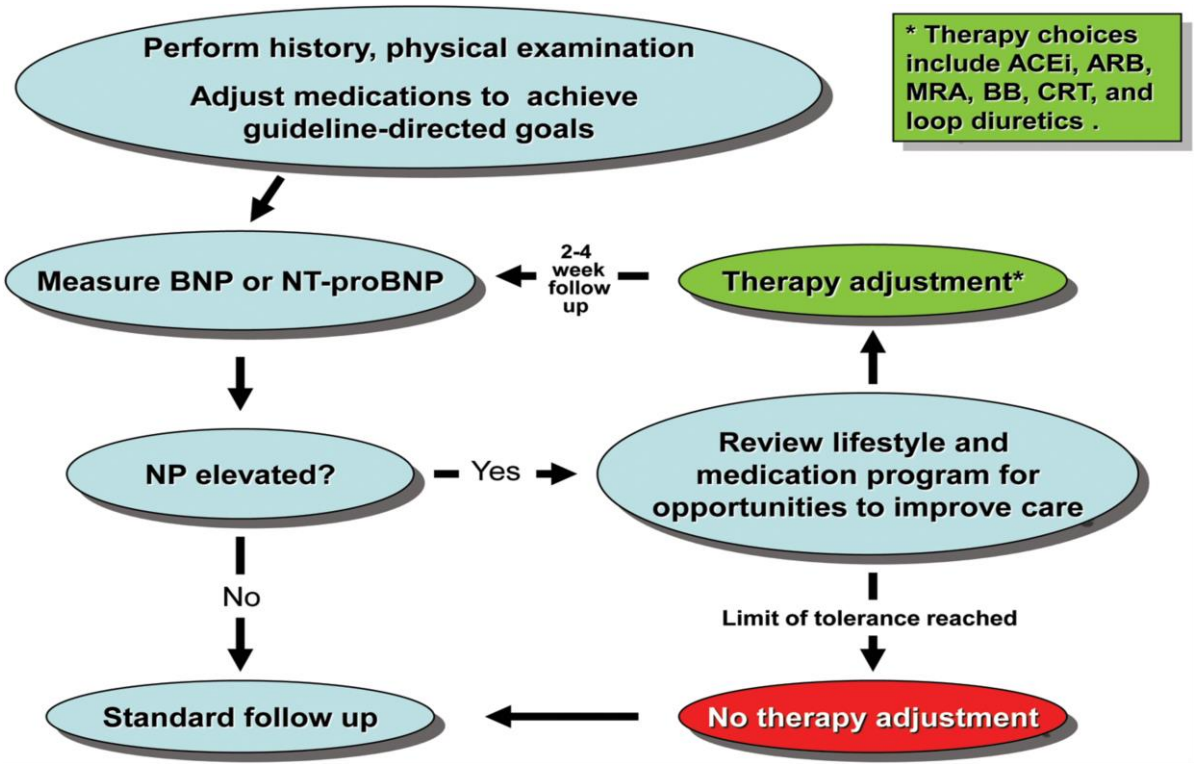
*High/low refer to NT-proBNP above or below a threshold concentration of 1078 pg/mL

Masson S, et al. *J Am Coll Cardiol*. 2008;52:997-1003.

Natriuretic Peptide Caveats
Understanding the Number

- NPs increased with female gender and age[a,b]
- Inverse relationship between NP and BMI[c]
- NPs increased with renal dysfunction[d,e]

a. Redfield MM, et al. *J Am Coll Cardiol*. 2002;40:976-82; b. Wang TJ, et al. *Am J Cardiol*. 2002;90:254-58; c. Krauser DG, et al. *Am J Heart*. 2005;149:744-50; d. McCullough PA, et al. *Am J Kidney Dis*. 2003;41:571-79; e. Anwaruddin S, et al. *J Am Coll Cardiol*. 2006;47:91-7.



From: Natriuretic peptide-guided heart failure management
Eur Heart J. 2013;35(1):16-24. doi:10.1093/eurheartj/eht463
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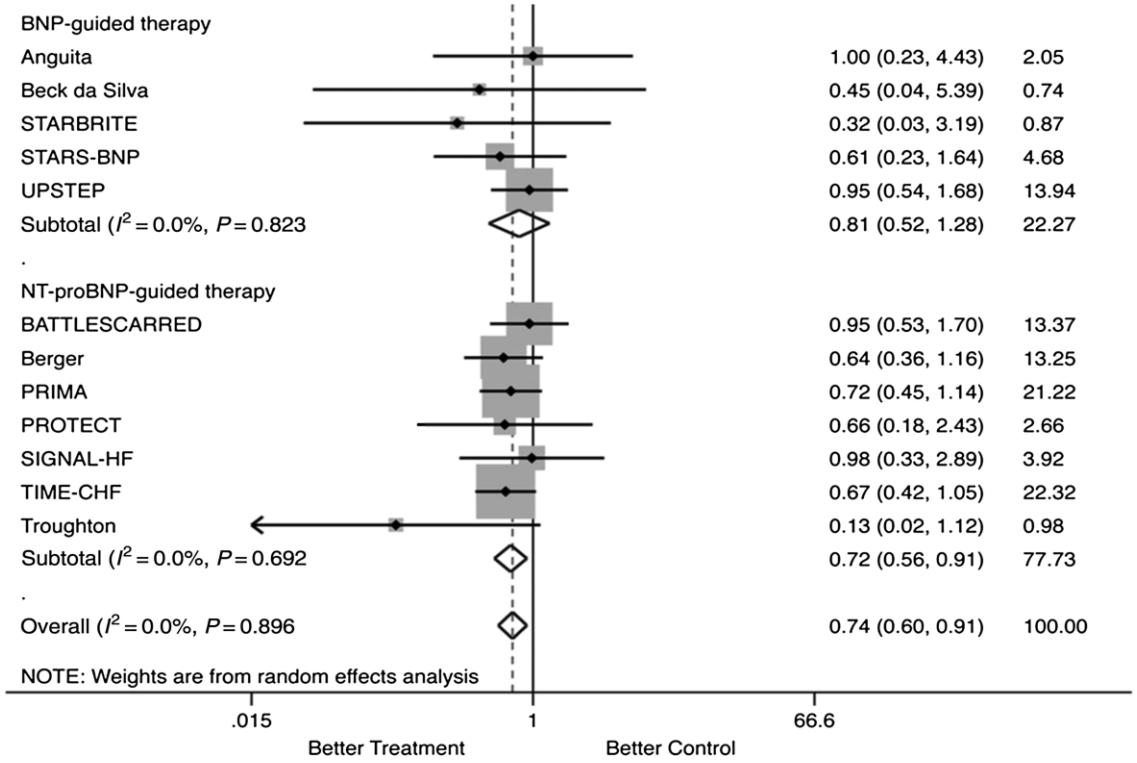

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Effect of Natriuretic Peptide–Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection Fraction

A Randomized Clinical Trial

G. Michael Felker, MD, MHS[1]; Kevin J. Anstrom, PhD[1]; Kirkwood F. Adams, MD[2]; et al

» Author Affiliations

JAMA. 2017;318(8):713-720. doi:10.1001/jama.2017.10565

- The data and safety monitoring board recommended stopping the study for futility.
- The primary end point occurred in 164 patients (37%) in the biomarker-guided group and 164 patients (37%) in the usual care group (adjusted hazard ratio [HR], 0.98; 95% CI, 0.79-1.22; *P* = .88).
- Cardiovascular mortality was 12% (n = 53) in the biomarker-guided group and 13% (n = 57) in the usual care group (HR, 0.94; 95% CI; 0.65-1.37; *P* = .75). None of the secondary end points nor the decreases in the NT-proBNP levels achieved differed significantly between groups.

JAMA. 2017;318(8):713-720

Role of Troponins in Acute HF

- Multiple causes of troponin release in heart failure[a]
  - Myocardial apoptosis
  - Coronary ischemia
  - Subendocardial ischemia
  - Direct toxicity
  - Proteolysis/turnover of myocardial contractile proteins
- Similar troponin I levels whether HF ischemic or non-ischemic[b]
- In patients with ADHF, positive cardiac troponin test associated with higher in-hospital mortality[c]

a. Januzzi JL Jr, et al. *Eur Heart J*. 2012;33:2265-2271; b. Felker GM, et al. *Eur J Heart Fail*. 2012;14:1257-1264; c. Peacock WF 4th, et al. *N Engl J Med*. 2008 May 15;358(20):2117-26.

CLINICAL PRACTICE GUIDELINE: FOCUSED UPDATE

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration with the American Academy of Family Physicians, American College of Chest Physicians, and International Society for Heart and Lung Transplantation

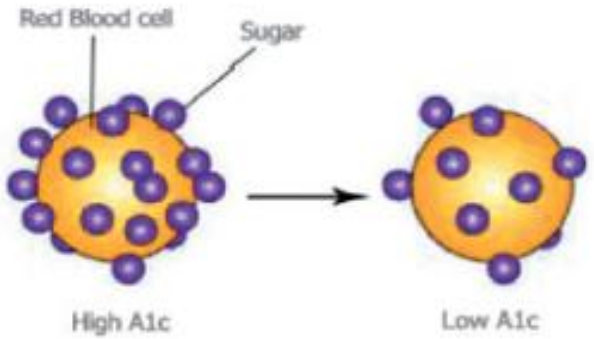
DOI: 10.1016/j.jacc.2017.04.025

Biomarkers: Recommendations for Prognosis

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	A	Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF (16,87-92).	2013 recommendation remains current.
I	A	Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF (27,93-100).	MODIFIED: Current recommendation emphasizes that it is admission levels of natriuretic peptide biomarkers that are useful.
IIa	B-NR	During a HF hospitalization, a predischarge natriuretic peptide level can be useful to establish a postdischarge prognosis (93,96,104-113).	NEW: Current recommendation reflects new observational studies.

See Online Data Supplements A and B

DOI: 10.1016/j.jacc.2017.04.025



sST2-The HbA1c of Heart Failure

sST2 as a decoy receptor → when elevated binds IL-33, effectively reducing the concentration of IL-33 that is available to ST2L, thus diminishing the cardioprotective effect of IL-33.

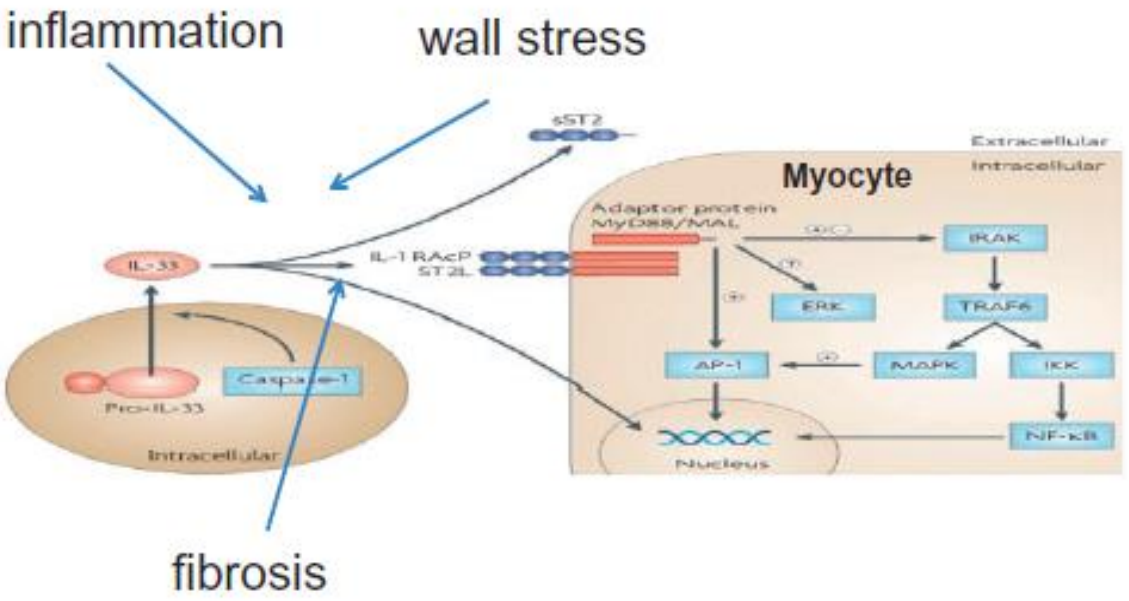


Figure 1 sST2 the HbA1c of heart failure.

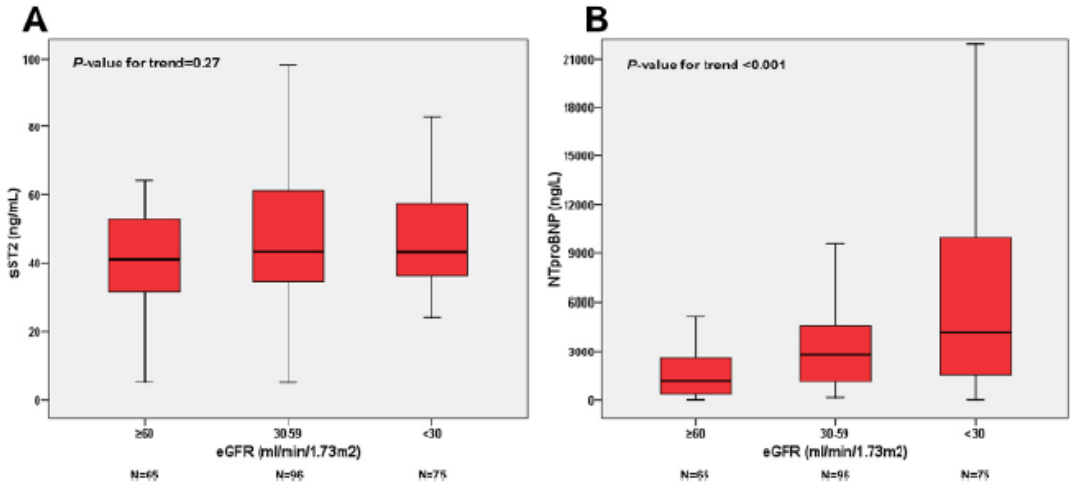
Maisel A and Di SommaS. E H J (2017) 38, 2325–2332

ST2 not effected by

- Age
- Sex
- BMI
- Etiology of HF
- Atrial Fibrillation
- Anemia

Maisel M and Di Somma.EHJ(2017) 38, 2325–2332

ST2 Not Correlated with Renal Function

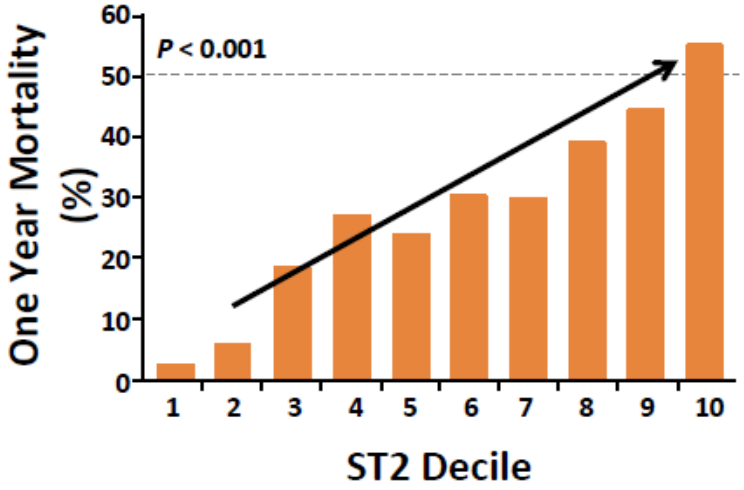


In a cohort of 879 heart failure patients ST2 did not show any correlation with renal function whereas NT-proBNP concentrations increased significantly with decreasing renal function.

Bayes-Genis et al. 2013 JCF

Mortality Risk Increases With ST2 Levels

One-year mortality exceeded 50% in the highest decile.



Rehman SU, Mueller T, Januzzi JL et al. *J Am Coll Cardiol*. 2008;52:1458-65.

IIb B-NR See Online Data Supplements A and B.	In patients with chronic HF, measurement of other clinically available tests, such as biomarkers of myocardial injury or fibrosis, may be considered for additive risk stratification (27,95,98,99,103,114-119).	MODIFIED: 2013 recommendations have been combined into prognosis section, resulting in LOE change from A to B-NR.

Biomarkers of myocardial fibrosis (e.g., soluble ST2 receptor, galectin-3, high-sensitivity cardiac troponin, and others) are predictive of hospitalization and death in patients with HF and also are additive to natriuretic peptide biomarker levels in their prognostic value (117,119-126). A combination of biomarkers may ultimately prove to be more informative than single biomarkers (127).

DOI: 10.1016/j.jacc.2017.04.025

European Heart Journal (2017) **0**, 1–7
doi:10.1093/eurheartj/ehx027

CURRENT OPINION

Transitioning from usual care to biomarker-based personalized and precision medicine in heart failure: call for action

Antoni Bayes-Genis[1,2,3]*, Adriaan A. Voors[4], Faiez Zannad[5], James L. Januzzi[6], A. Mark Richards[7,8], and Javier Díez[3,9,10]

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Personalized Medicine

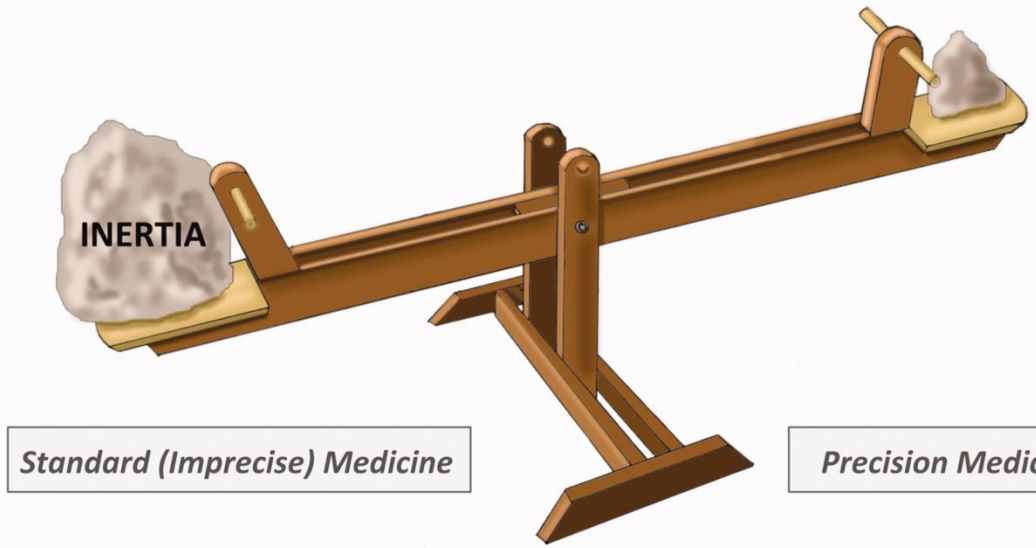
- This refers to collection and analysis of extensive information and data about a patient, including biomarkers, and beyond. The physician uses this information and data to make a more informed diagnosis and treatment plan.

Bayes-Genis A et al.EHJ (2017) 0, 1–7

Precision medicine

- This approach uses computational network knowledge that aggregates and analyses information from patient cohorts, healthy populations and experimental systems to define disease mechanisms and reach toward therapies that more precisely address the mechanism of HF, for better diagnosis, prevention and/or treatment for each individual.

Bayes-Genis A et al.EHJ (2017) 0, 1–7



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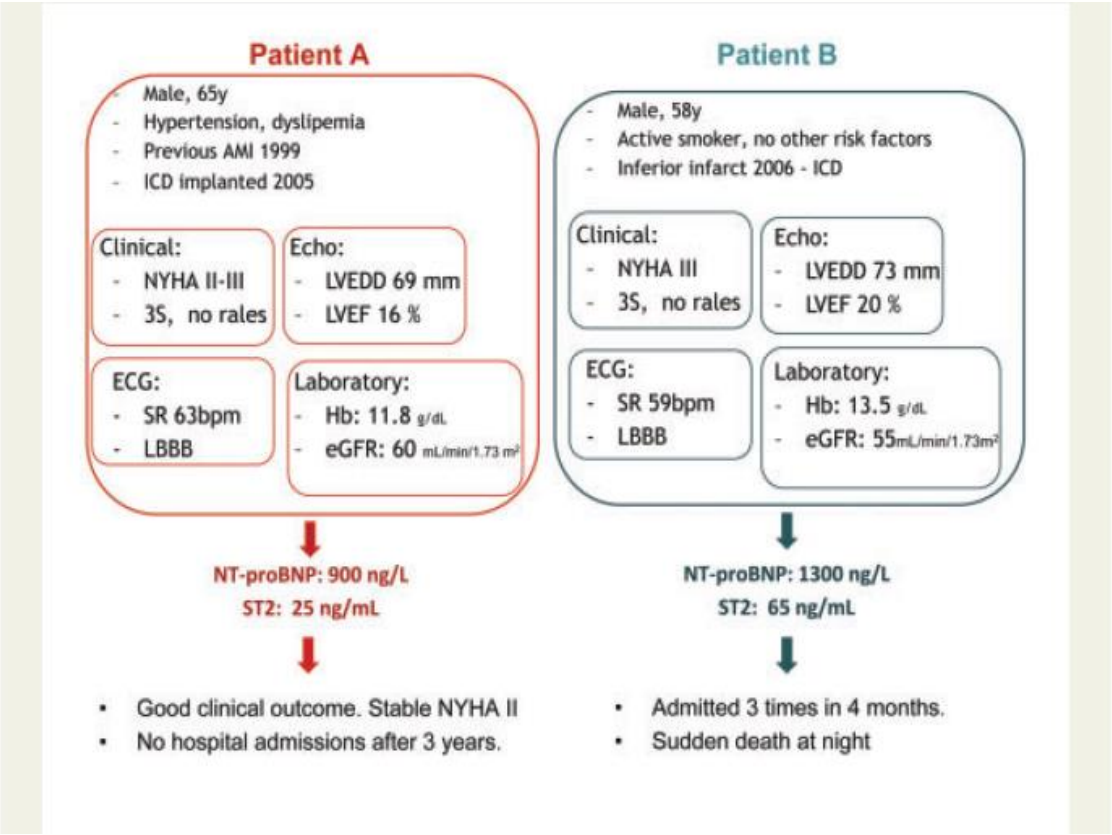

Bayes-Genis A et al.EHJ (2017) 0, 1–7

Conclusions

- Basically, the ‘one-fits-it-all’ and ‘average response therapy’ approaches may no longer be optimal in chronic diseases such as HF, and new approaches focused on individual variability are emerging. It must be recognized that HF is mechanistically diverse. Mechanistic phenotyping is soon to become a reality.
- There is, therefore, an increasing emphasis on tailoring of CVD to fit the unique characteristics of the individual patient, and even better, to match the target patient population to the mechanism of action of therapeutic candidates.

THANK YOU