Incorporating Biomarkers in Daily Practice

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No Disclosures

Outline

- Definition of biomarkers
- Interest in biomarkers in heart failure
- Major biomarkers utilized in clinical practice
- BNP and NT pro BNP
- Role in Diagnosis in acute setting
- Chronic setting
- Prognosis
- Prevention
- Caveats
- HsTNI
- Future outlook for biomarkers in clinical practice

What are biomarkers

- WHO definition
- "Any substance, structure, or process that can be measured in the body or its product and influence or predict the incidence of outcome or disease"
- "Effect into treatment and intervention"

- Thoroughly studies and validated
- Robust
- Reflect the pathophysiology of that disease
- Provide additive information
- Additive value in diagnosis, treatment and screening.

WHO, 2010; Ibrahim et al, Circ Res, 2018

How big is the problem and how serious is it?

"HF affects 26 million worldwide"

"HF is the leading cause of hospitalization in US and Europe (1-2% of all hospitalizations)"

"More than 670,000 newly diagnosed cases of heart failure annually in the US alone"

							EFICA (21)
N	105,388	48,612	110,621	3,580	1,892	1,855	581
Timeframe	2001–2004	2003–2004	2005 to present	2004–2005	2009–2010	2007–2009	2001
Age, yrs							73 ± 13
Male							59
Ischemic etiology							61
Hyperten etiology							15
LVSD							73
LVEF, %	34 ± 16	39 ± 18	40 (25–55)	38 ± 15	—	38 ± 14	38 ± 15
HTN	73	71	76	63	62	58	60
HL	37	32	44	—	—	—	30
CAD							—
Prior MI							22
Afib							25
DM							27
CKD							53
COPD							—

Ambrosy et al, JACC 2014; Savarese et al, Card Fail Rev 2017

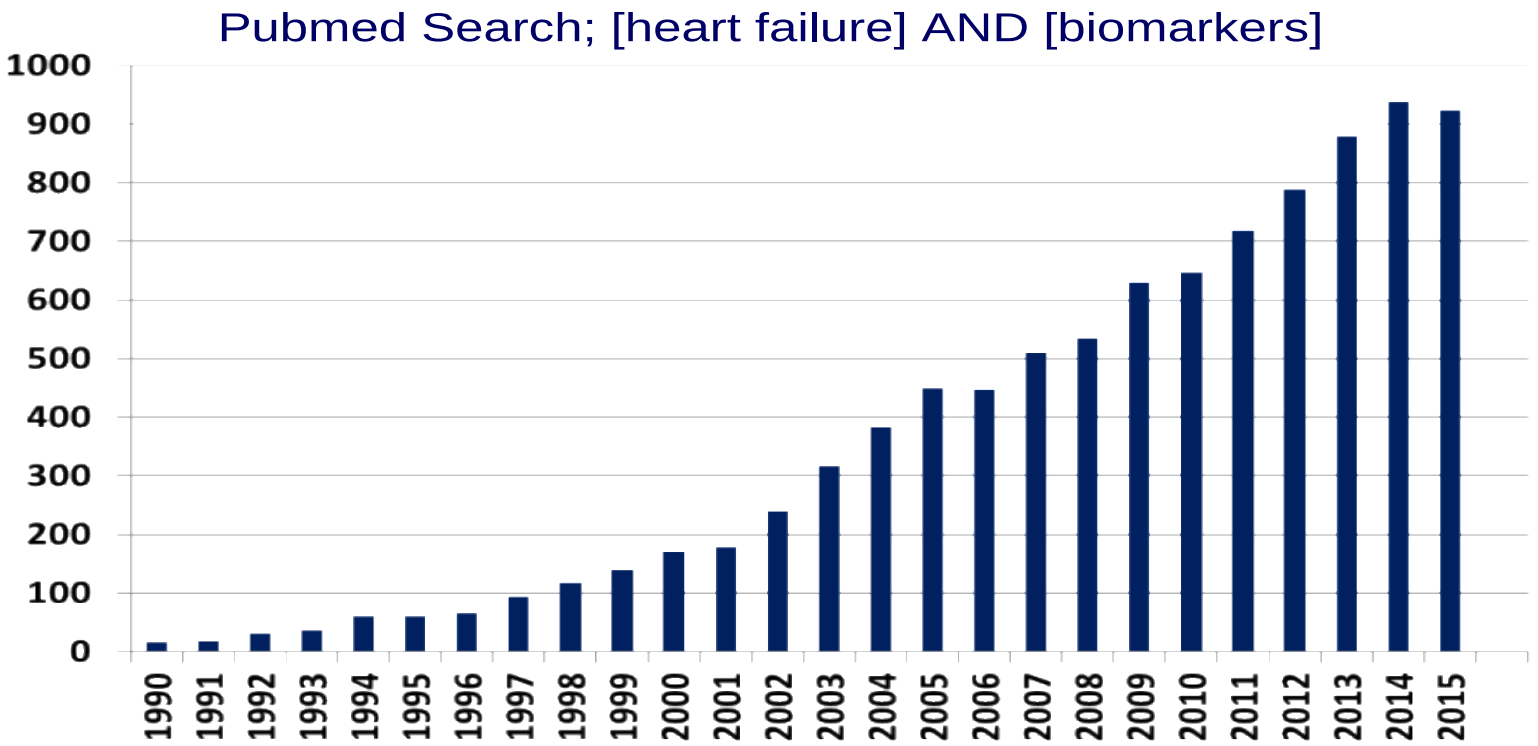
Outcome statistics..

- ~50% of patients die within one year of diagnosis..

NEED TO ID THOSE PATIENTS THAT ARE AT RISK , DIAGNOSE, AND BETTER MANAGE THEM

Zarrinkoub et al. Eur J of Heart Failure 2013

Research on Biomarkers..



de Boer, Eur Heart Fail,2017

List of biomarkers studied in HF

Myocardial Insult	
[illegible]	NT-proBNP, BNP, MR-proANP
Myocardial Injury	Troponin T, troponin I, myosin light-chain I, heart-type fatty-acid protein, CKMB
Oxidative stress	Myeloperoxidase, uric acid, oxidized low-density lipoproteins, urinary biopyrrins, urinary and plasma isoprostanes, plasma malodialdehyde
Neurohormonal Activation	
[illegible]	Renin, angiotensin II, aldosterone
Sympathetic nervous system	Norepinephrine, Chromogranin A, MR-proADM
Arginine vasopressin system	Arginine vasopressin, copeptin
[illegible]	ET-1, big proET-1
Remodeling	
[illegible]	C-reactive protein, TNF-α, soluble TNF receptors, Fas, interleukins (I, 6 and 18), osteoprotegerin, adiponectin
Hypertrophy/Fibrosis	Matrix metalloproteinases, collagen propeptides, galectin-3, soluble ST2
[illegible]	GDF-15
Comorbidities	
[illegible]	Creatinine, BUN, eGFR, cystatin C, β-trace protein
Renal Injury markers	NGAL, KIM-1, NAG, liver-type fatty acid binding protein, IL-18
Hematologic biomarkers	Hemoglobin, RDW, iron deficiency (ferritin, transferrin sat)
LFTs	

Gaggin et al, 2015

Biomarkers and HF..

ACC/AHA/HFSA 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

6. INITIAL AND SERIAL EVALUATION OF THE HF PATIENT

6.3. Biomarkers

Table 1. 2017 ACC/AHA/HFSA Clinical Practice Guideline Recommendations for the Use of Biomarkers in the Management of HF[7]

Biomarkers	Indication for Use	Recommendation	Evidence
BNP or NT-proBNP	Diagnosis	I	A
	Hospital admission prognosis	I	A
	Prevention	IIa	B
	Hospital discharge	IIa	B
	Guided therapy (chronic HF)	IIb	B
Troponin T or I	Hospital admission prognosis	I	A
sST2, galectin-3	Prognosis (chronic HF)	IIb	B

ACC indicates American College of Cardiology; AHA, American Heart Association; BNP, B-type natriuretic peptide; HF, heart failure; HFSA, Heart Failure Society of America; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and sST2, soluble ST2.

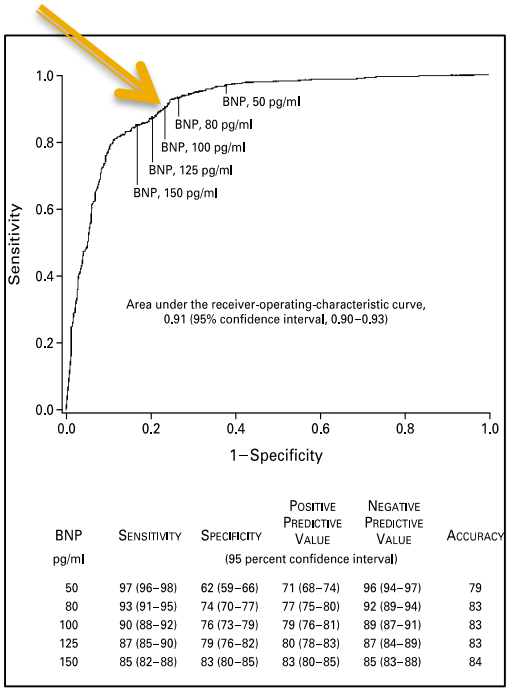
ACC, 2017; Ibrahim et al, Circ Res, 2018

NP.. When to use in HF..

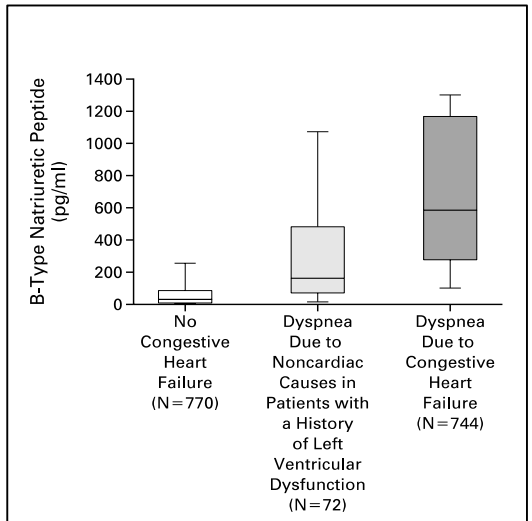
- BNP and NT pro BNP
- Mainly for assessment of patients with shortness of breath
- Its utility in the ED
- Its applicability in the OPD setting

Biomarkers in the ED..

RAPID MEASUREMENT OF B-TYPE NATRIURETIC PEPTIDE IN THE EMERGENCY DIAGNOSIS OF HEART FAILURE



BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
		(95 percent confidence interval)			
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)	84



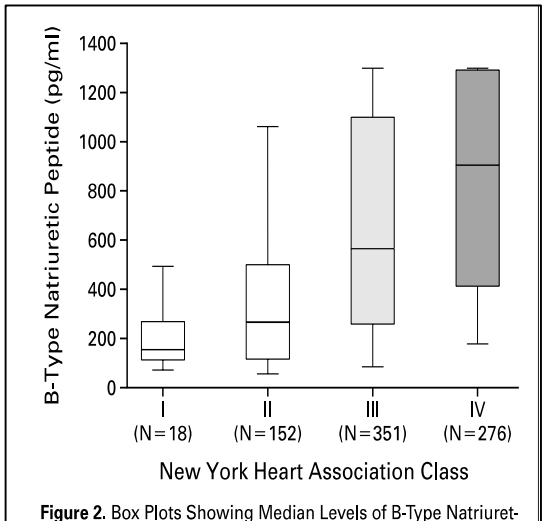


Figure 2. Box Plots Showing Median Levels of B-Type Natriuret-

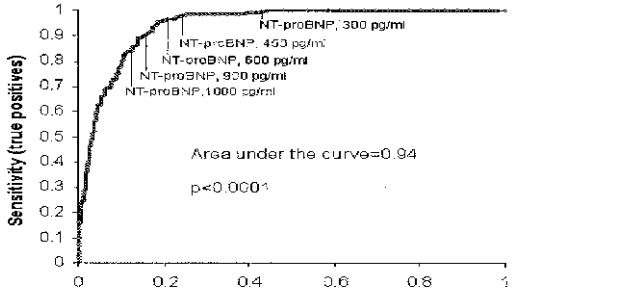
<200→ no HF
>400→ HF

Higher BNP→sicker patients

Maisel et al, NEJM, 2002

More evidence

The N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study



Cut Point	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
300 pg/ml	99%	68%	62%	99%	78%
450 pg/ml	98%	76%	68%	99%	83%
600 pg/ml	96%	81%	73%	97%	86%
900 pg/ml	90%	85%	76%	94%	87%
1000 pg/ml	87%	88%	78%	91%	87%

FIGURE 4. NT-proBNP was highly sensitive and specific for the diagnosis of acute CHF, with a highly significant area under the curve. A strategy of partitioning patients in age categories of < 50 and > 50 years (with cutpoints of 450 and 900 pg/ml, respectively) was optimal, with areas under the curve of 0.98 and 0.93, respectively ($p < 0.0001$ for the 2 categories).

TABLE 2 Optimal NT-proBNP Cutpoints for Ruling In and Ruling Out Acute Congestive Heart Failure (CHF)*

	Optimal Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
Rule-in cutpoints						
All patients (n = 599)	900	90	85	76	94	87
<50 yrs old (n = 144)	450	93	95	67	99	95
≥50 yrs old (n = 455)	900	91	80	77	92	85
Rule-out cutpoints						
All patients (n = 599)	300	99	68	62	99	83

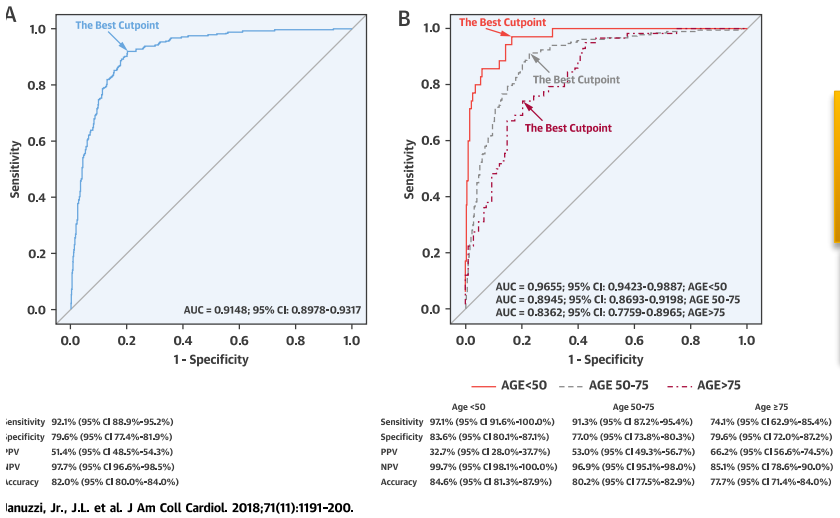
NT-proBNP testing was of value to identify and exclude acute CHF with high accuracy. In the PRIDE study, the optimal rule-in strategy using NT-proBNP was an age-stratified approach with 2 cutpoints, whereas a single cutpoint of 300 pg/ml was of value for excluding the diagnosis.

Januzzi et al, The Am J of Card, 2005

Further evidence..

N-Terminal Pro–B-Type Natriuretic Peptide in the Emergency Department

The ICON-RELOADED Study



	Age <50	Age 50-75	Age ≥75
Sensitivity	97.1% (95% CI 91.6%-100.0%)	91.3% (95% CI 87.2%-95.4%)	74.1% (95% CI 62.9%-85.4%)
Specificity	83.6% (95% CI 80.1%-87.1%)	77.0% (95% CI 73.8%-80.3%)	79.6% (95% CI 72.0%-87.2%)
PPV	32.7% (95% CI 28.0%-37.7%)	53.0% (95% CI 49.3%-56.7%)	66.2% (95% CI 56.6%-74.5%)
NPV	99.7% (95% CI 98.1%-100.0%)	96.9% (95% CI 95.1%-98.0%)	85.1% (95% CI 78.6%-90.0%)
Accuracy	84.6% (95% CI 81.3%-87.9%)	80.2% (95% CI 77.5%-82.9%)	77.7% (95% CI 71.4%-84.0%)

Category	Cutpoint, pg/ml	Sensitivity	Specificity	PPV	NPV	LR+	LR−
Confirmatory ("rule-in") cutpoints							
<50 yrs (n = 462)	450	85.7 (74.1-97.3)	93.9 (91.6-96.2)	53.6 (43.7-63.2)	98.8 (97.3-99.4)	14.08 (8.48-19.67)	0.15 (0.03-0.28)
50-75 yrs (n = 833)	900	79.3 (73.5-85.2)	84.0 (81.2-86.8)	58.4 (53.7-63.0)	93.5 (91.5-95.0)	4.95 (4.00-5.90)	0.25 (0.18-0.32)
>75 yrs (n = 166)	1,800	75.9 (64.8-86.9)	75.0 (66.8-83.2)	62.0 (53.3-70.0)	85.3 (78.4-90.2)	3.03 (1.94-4.13)	0.32 (0.17-0.47)
Exclusionary ("rule-out") cutpoint							
All patients (n = 1,461)	300	93.9 (91.0-96.7)	71.7 (69.1-74.3)	43.7 (41.4-46.1)	98.0 (96.9-98.8)	3.32 (3.00-3.63)	0.09 (0.05-0.13)

The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios are presented as % (95% confidence interval) for the age-dependent rule-in cutoffs of 450, 900, and 1,800 pg/ml for ages <50, 50-75, >75 years, and for the rule-out cutoff of 300 pg/ml, in all enrolled subjects.

HF = heart failure; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; NPV = negative predictive value; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PPV = positive predictive value.

Januzzi, Jr., J.L. et al. J Am Coll Cardiol. 2018;71(11):1191-200.

Januzzi et al, JACC, 2018

What did we learn??

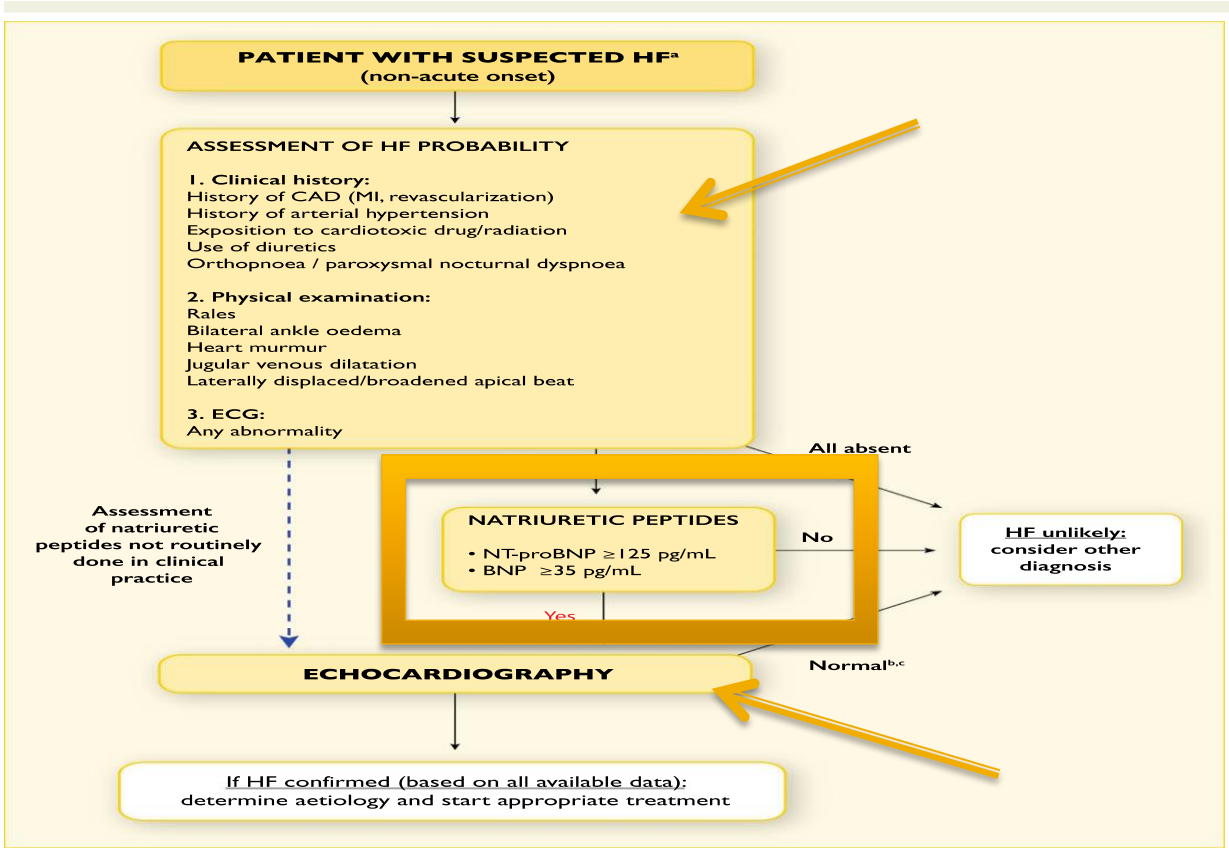
- Patients with acute HF have a much higher BNP/NT pro BNP levels than those whose dyspnea is not related to HF
- In those with HF, there is a linear correlation between higher BNP levels and severity of HF and disease process
- BNP > 100pg/mL was the most accurate predictor of diagnosis of AHF than clinical exam, CXR, or other labs.
- In the case of NT pro BNP the use of age stratification for delineation of cut offs had even a better correlation with diagnosis
- Biomarkers, however, do NOT replace the clinical assessment and should be used as an adjunctive tool.

Moving from the acute to the non acute setting..

- These biomarkers were examined to RULE OUT diagnosis of HF in the non acute setting..
- NPPV
- Not very ill
- Thresholds were lower

How to use it in the ambulatory setting..

- Further testing warranted or not..



ESC, 2016

How did all this data get incorporated in the guidelines??

6.3.2 Biomarkers for Diagnosis: Recommendation

Biomarkers: Recommendation for Diagnosis

COR	LOE	Recommendation	Comment/Rationale
I	A	In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF.[15–24,28–30]	**MODIFIED:** 2013 acute and chronic recommendations have been combined into a diagnosis section.
See Online Data Supplements A and B.			

ACC, 2017

Pre-discharge BNP..

Linked patients ≥65 years from hospitals in OPTIMIZE-HF to Medicare claims.

Higher pre-discharge BNP correlate to worse outcomes

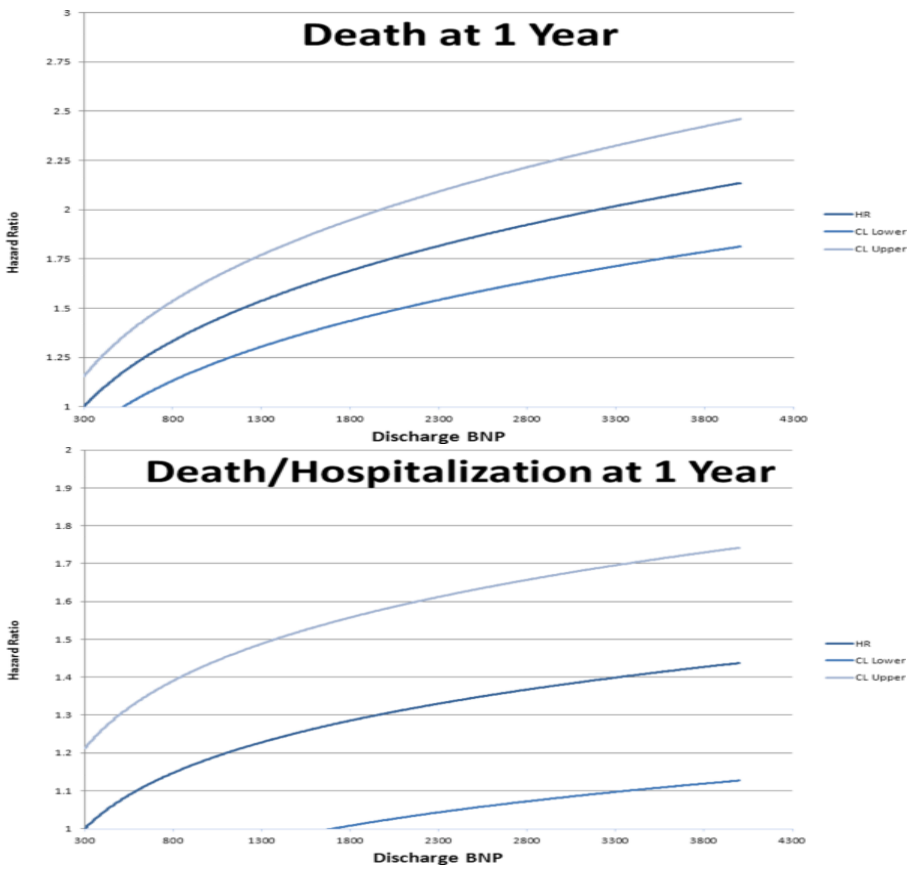
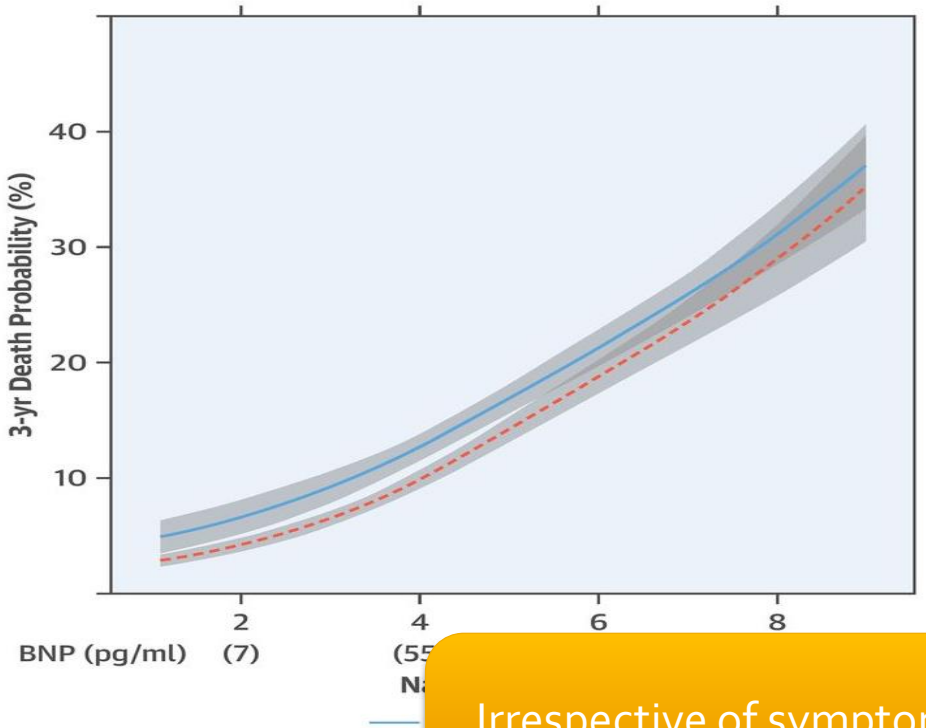


Figure 1.
Adjusted hazard ratio and 95% confidence interval for (A) 1-year mortality and (B) 1-year mortality or rehospitalization by discharge BNP (versus discharge BNP=300).

Kociol et al, Circ HF, 2011

Moving along.. NP's role in prognostication..

CENTRAL ILLUSTRATION: Estimated 3-Year Death Probability Across the Spectrum of Plasma B-Type Natriuretic Peptide Levels Stratified by the Presence or Absence of Heart Failure

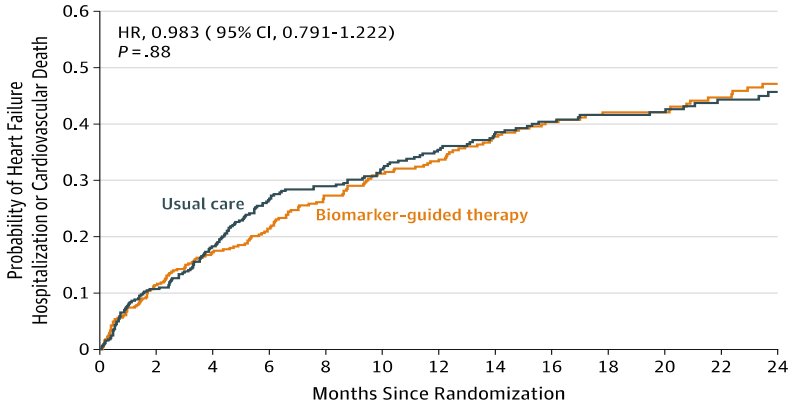


York, M.K. et al. J Am Coll Cardiol. 2018;71(1

Irrespective of symptoms, high NPs incur worse prognosis

GUIDE-IT

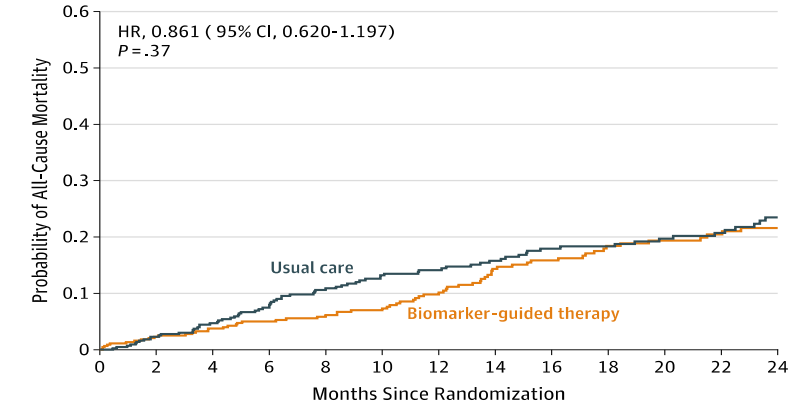
A First heart failure hospitalization or cardiovascular death



No. at risk

Biomarker-guided therapy	446	376	331	293	254	225	202	175	152	128	128	93	78
Usual care	448	381	330	278	257	227	199	175	153	138	115	90	77

B All-cause mortality



No. at risk

Biomarker-guided therapy	446	418	391	371	327	304	275	239	221	186	167	145	137
Usual care	448	423	391	358	323	297	273	248	217	205	171	150	134

The median duration of biomarker-guided therapy was 15 months (interquartile range [IQR], 7-24) and 15 months (IQR, 7-7) for usual care. HR indicates hazard ratio.

No added value of biomarker guided therapy.

Felker et al, JAMA, 2017

How did these findings translate into the guidelines..

6.3.3 Biomarkers for Prognosis or Added Risk Stratification: Recommendations

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.

Biomarkers: Recommendations for Prognosis (Continued)

COR	LOE	Recommendations	Comment/Rationale
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.
See Online Data Supplements A and B.			
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.			

ACC, 2017

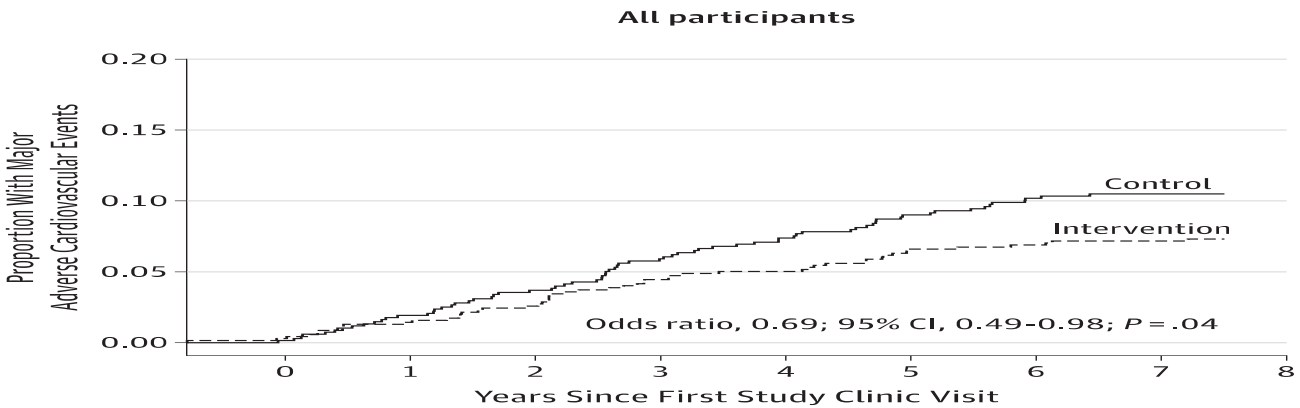
A word on prevention..

Original Investigation

Natriuretic Peptide–Based Screening and Collaborative Care for Heart Failure

The STOP-HF Randomized Trial

Figure 2. Kaplan-Meier Analysis of Major Adverse Cardiovascular Events in the



No. at risk								
Intervention	697	605	582	533	441	305	141	41
Control	677	587	558	501	418	296	118	27

BNP indicates brain-type natriuretic peptide. Major adverse cardiovascular events included arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or heart failure. In the full sample, 51 (7.3%) of 697 patients were admitted for major adverse

Ledwidge et al, JAMA, 2013

Recommendations..

6.3.1 Biomarkers for Prevention: Recommendation

Biomarkers: Recommendation for Prevention of HF			
COR	**LOE**	**Recommendation**	**Comment/Rationale**
IIa	**B-R**	**For patients at risk of developing HF, natriuretic peptide biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF.[85,86]**	**NEW:** New data suggest that natriuretic peptide biomarker screening and early intervention may prevent HF.
See Online Data Supplements A and B.			

ACC, 2017

Clinical caveats..

- Other conditions can cause relative elevations or suppression of those biomarkers

List of factors that may affect NP levels..

Table 2. Factors Influencing the Clinical Interpretation of BNP or NT-proBNP Concentrations

Factors that decrease BNP or NT-proBNP concentrations
Obesity
Flash pulmonary edema
Cardiac tamponade
Pericardial constriction
Factors that increase BNP or NT-proBNP concentrations
Left ventricular dysfunction
Hypertrophic heart muscle diseases
Infiltrative myocardiopathies
Acute cardiomyopathies
Inflammatory
Valvular heart disease
Arrhythmias
Acute coronary syndromes
Cardiotoxic drugs
Anthracyclines and related compounds
Significant pulmonary disease
Acute respiratory distress syndrome, lung disease with right-sided heart failure, obstructive sleep apnea, pulmonary hypertension
Pulmonary embolism
Advanced age
Renal dysfunction
Anemia
Critical illness
Burns
Stroke
High output states
Sepsis
Cirrhosis
Hyperthyroidism

BNP indicates B-type natriuretic peptide; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Ibrahim et al, Circ Res, 2018

However, they can still help in these situations..

- CKD..
- Patients with chronic kidney disease typically have higher BNP and NT-proBNP concentrations.
- Increased wall stretch secondary to hypertension and chronic volume overload.
- The age-stratified NT-proBNP cutoffs may be used with good accuracy and without adjustment.
- Of note, both BNP and NT-proBNP are considerably prognostic in patients with chronic kidney disease, even in the absence of obvious cardiovascular disease.

Ibrahim NE, J *Clin Chem*. 2017

Another caveat.. Obesity..

- BNP and NT-proBNP levels are generally lower
- Possibly due to suppression of synthesis or release of natriuretic peptides in obese subjects.
- However, regardless of body mass index, BNP or NT-proBNP concentrations are typically higher in patients with HF compared with patients without
- NT-proBNP value <300 pg/mL maintained excellent diagnostic performance in ruling out acute HF across all weight categories.
- ? Lowering decision limits for BNP by 50% in those with higher body mass index to prevent missed HF diagnoses

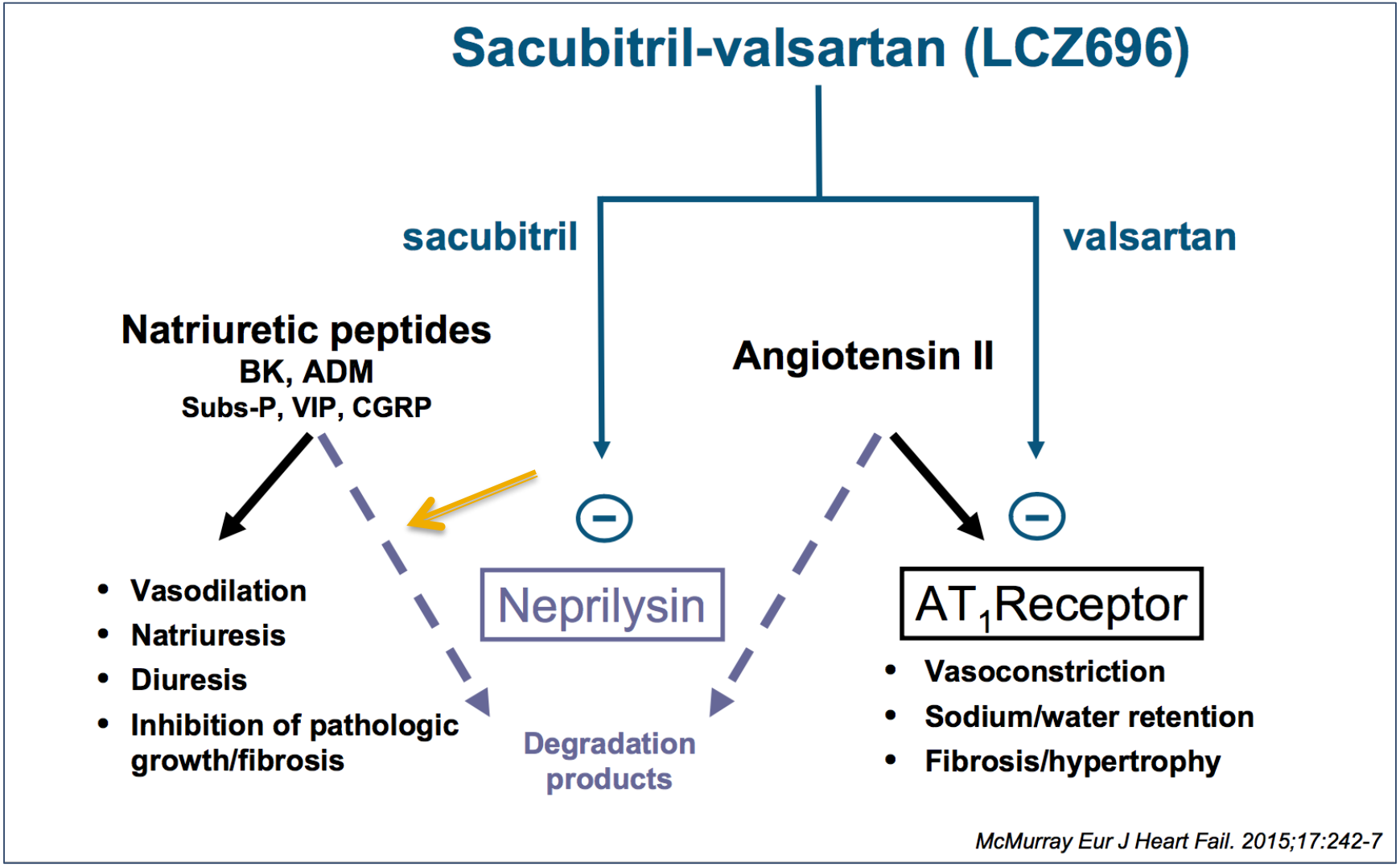
Januzzi et al, The Am J of Card, 2005; Ibrahim NE, J *Clin Chem*. 2017

HFpEF vs. HFrEF.. Does it make a difference..

- HFpEF usually have lower NP levels than HFrEF patients.
- ? smaller LV size and lower wall stress in HFpEF.
- Although the sensitivity is reduced in HFpEF, The same cutoff values for BNP and NT-proBNP are recommended for the diagnosis of HF in both categories.

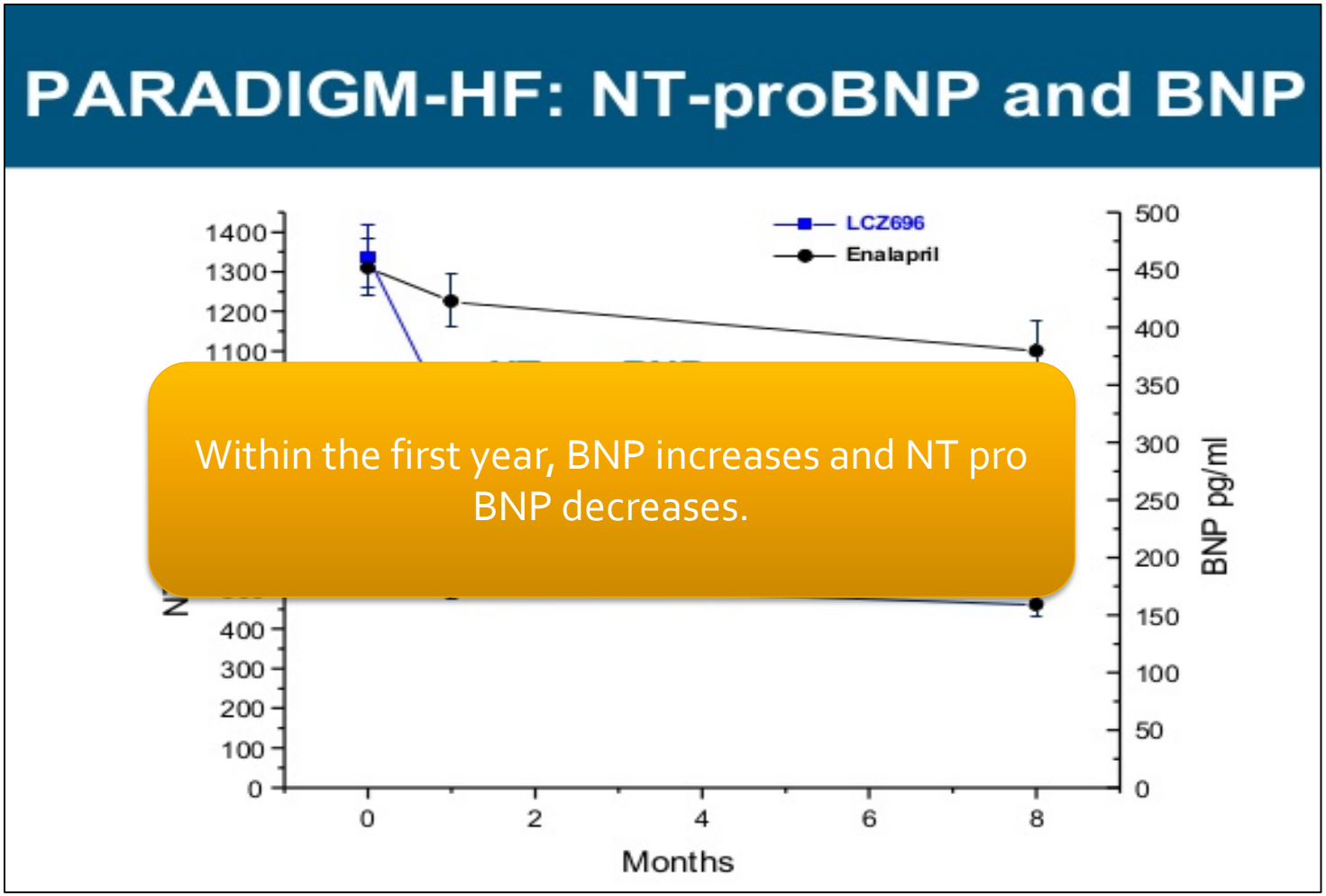
Ibrahim NE, J *Clin Chem*. 2017

What about ARNIs?



McMurray Eur J Heart Fail. 2015;17:242-7

Biomarkers with ARNI..

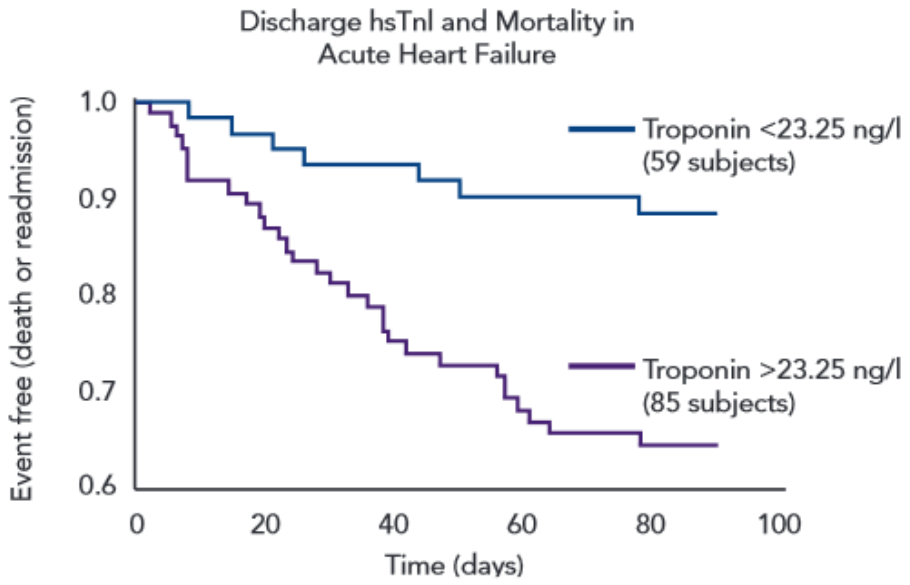


McMurray et al, NEJM, 2016

A word on Troponin..

- Marker of myocyte injury

Figure 3: 90-day Event-free (Death or Readmission) Curves for Patients Based on Discharge hsTnI



hsTnI = high-sense troponin I. Source: reproduced with permission from Xue et al, 2011.

Cardiac Failure Review , 2015; 1 (2): 102–6

Recommendations..

IIb	B-NR	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.
See Online Data Supplements A and B.			

ACC, 2017

Summarize indications of Biomarker use..

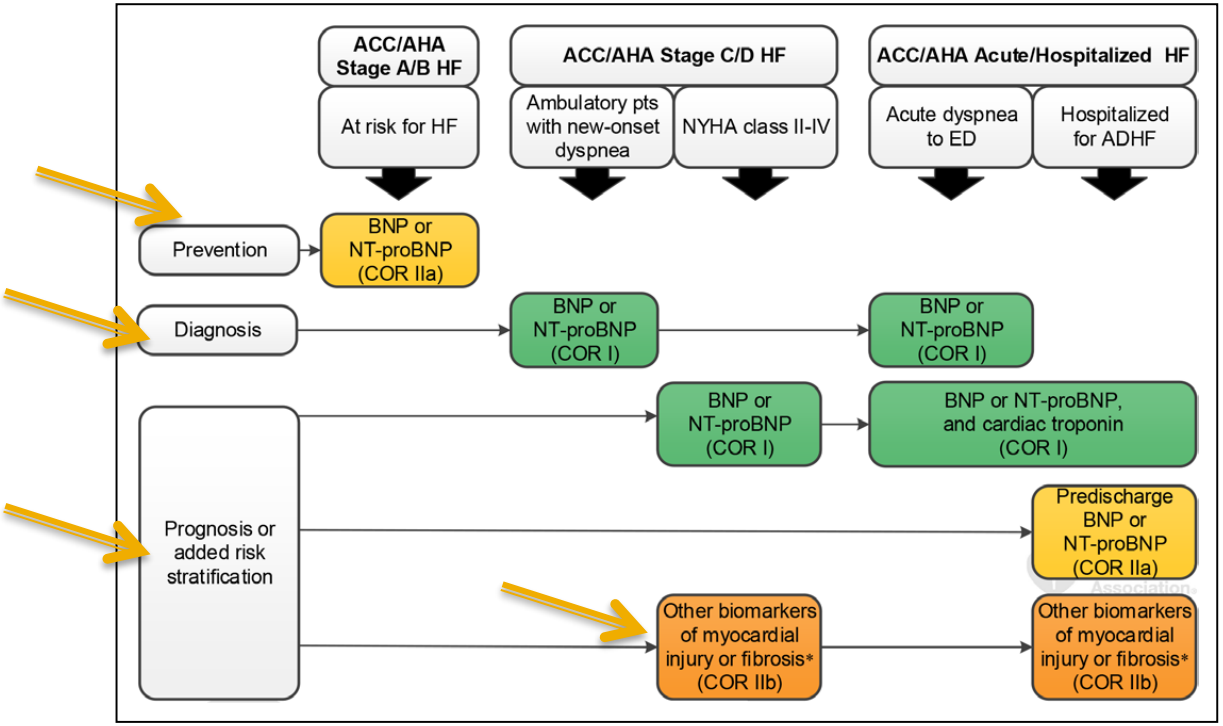


Figure 1. Biomarkers Indications for Use.
Colors correspond to COR in Table 1. *Other biomarkers of injury or fibrosis include soluble ST2 receptor, galectin-3, and high-sensitivity troponin. ACC indicates American College of Cardiology; AHA, American Heart Association; ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; COR, Class of Recommendation; ED, emergency department; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and pts, patients.

What does the future hold??

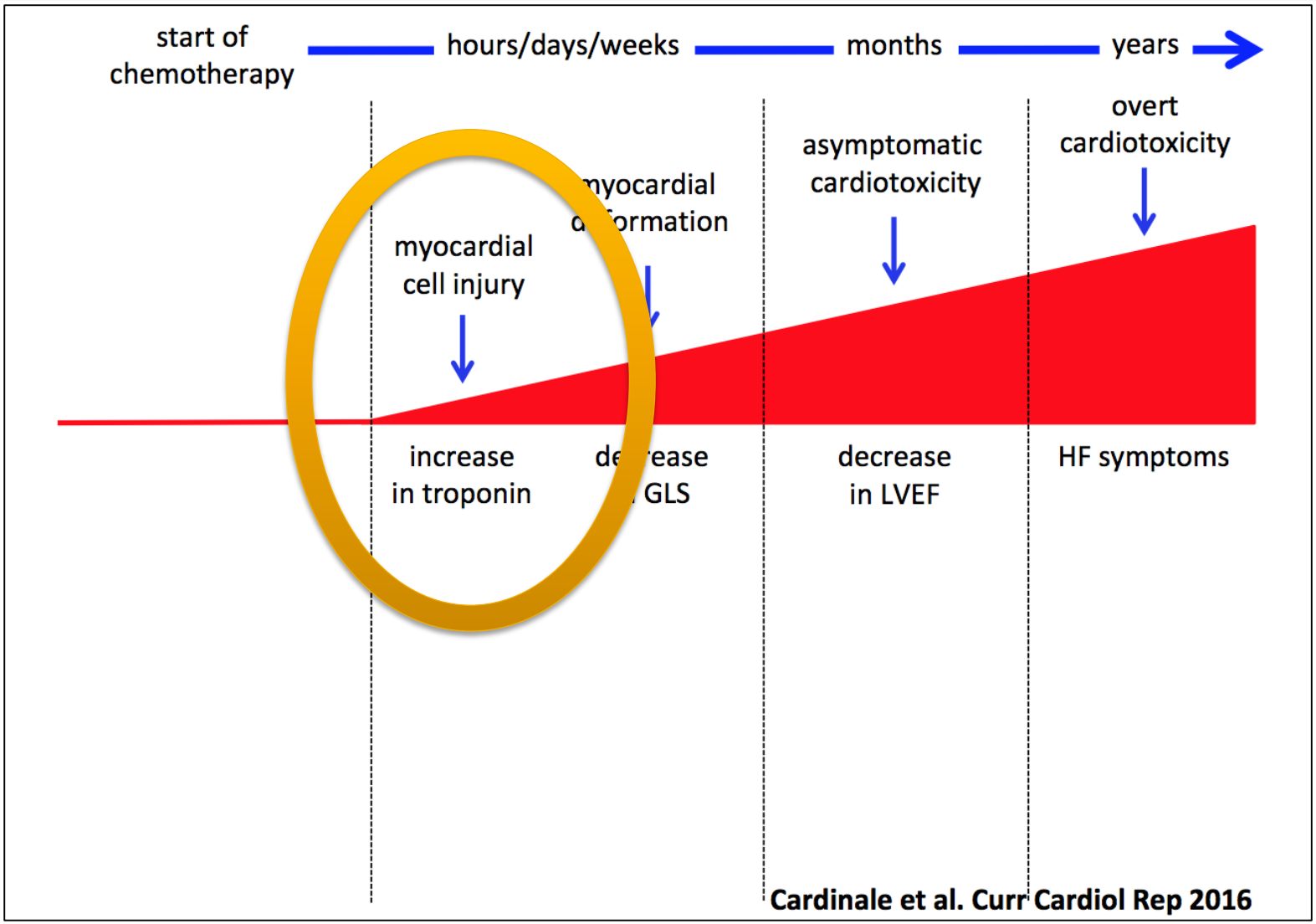
- Metabolomic profiling aims to comprehensively measure byproducts of metabolism with a goal to identify metabolic signature profiles in particular cohorts.
- Transcriptomics is the study of complete sets of RNA transcripts produced by the genome, allows the identification of genes that are differentially expressed in distinct cell populations or in response to different treatments.
- Genetic testing may play a role in the diagnosis and prognostication of patients presenting with HF, providing information on genetic cause of disease, as well as to monitor clinical status.

Vaarhorst et al. *Am Heart J*. 2014; Transcriptomics. Nature. 2018; Bondar et al, *PLoS One*. 2017.

Questions??

Thanks..

A quick word on cancer therapies..



What other algorithms are available out there?

Patients at standard risk (normal LVEF)

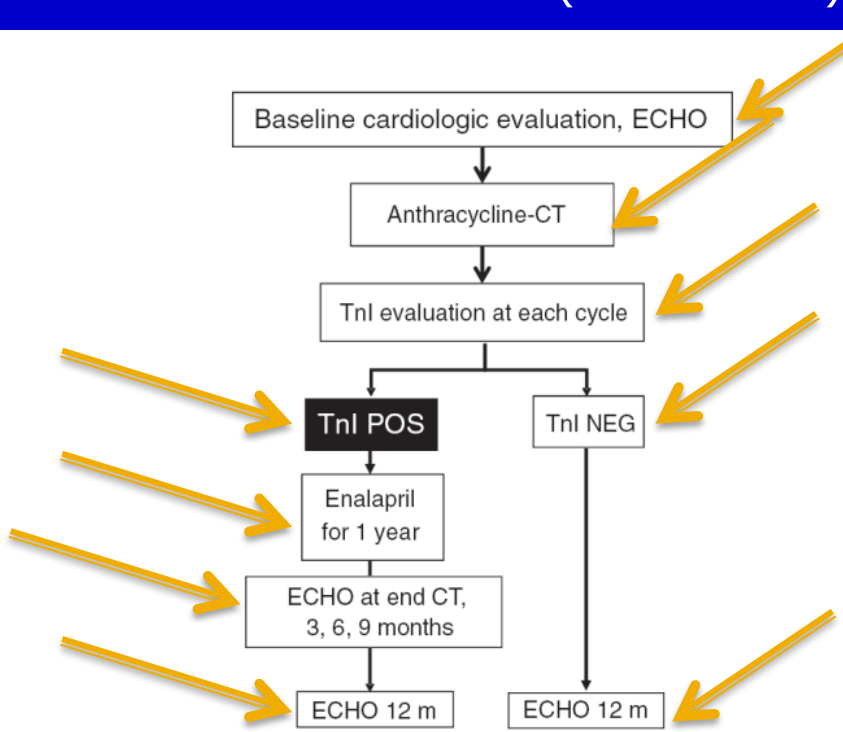


Fig. 1. Algorithm for the management of cardiotoxicity in patients receiving anthracyclines. CT = chemotherapy; ECHO = echocardiogram; TnI = Troponin I.

Cardinale, D., ESC, 2017

High risk patients.. Different algorithm?

Patients are admitted to hospital to receive CT

Troponin + BNP approach

cycle n.	day	phase	TnI	BNP	EKG + visit	ECHO
1°	1°	baseline preCT	X	X	X	X
	2°	soon after CT	X	X	X	
	3°	before discharge	X	X	X	
2°	1°	baseline preCT	X	X	X	
	2°	soon after CT	X	X	X	
	3°	before discharge	X	X	X	
3°	1°	baseline preCT	X	X	X	X
	2°	soon after CT	X	X	X	
	3°	before discharge	X	X	X	
4°	1°	baseline preCT	X	X	X	
	2°	soon after CT	X	X	X	
	3°	before discharge	X	X	X	
After end CT		FU	X	X	X	X

Cardinale, D., ESC, 2017