AMERICAN COLLEGE of CARDIOLOGY

Biomarkers in Heart Failure

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Disclosures

- Grant support from Novartis Pharmaceuticals, Applied Therapeutics, and Innolife
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- Clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Amgen, CVRx, Janssen, MyoKardia, and Takeda
- Trustee, American College of Cardiology

HF Clinical Practice Guidelines

Indication	Class	LOE
NPs for diagnosis[1-3]	I	A
NPs for prognosis[1-3]	I	A
NPs for predischarge risk assessment[1-3]	IIa	B-NR
NPs to prevent HF onset[1-3]	IIa	B-R
NPs to guide HF therapy[4]	IIa	B

JACC Journal of the American College of Cardiology

Circulation Journal of the American Heart Association

Journal of Cardiac Failure

LOE, level of evidence.

1. Yancy CW et al. *J Am Coll Cardiol.* 2017. doi: 10.1016/j.jaac.2017.04.025. 2. Yancy CW et al. *Circulation.* 2017. doi: 10.1161/CIR.0000000000000509. 3. Yancy CW et al. *J Card Fail.* 2017. doi: 10.1016/j.cardfail.2017.04.014. 4. Yancy CW, et al. *Circulation.* 2013;e240-327.

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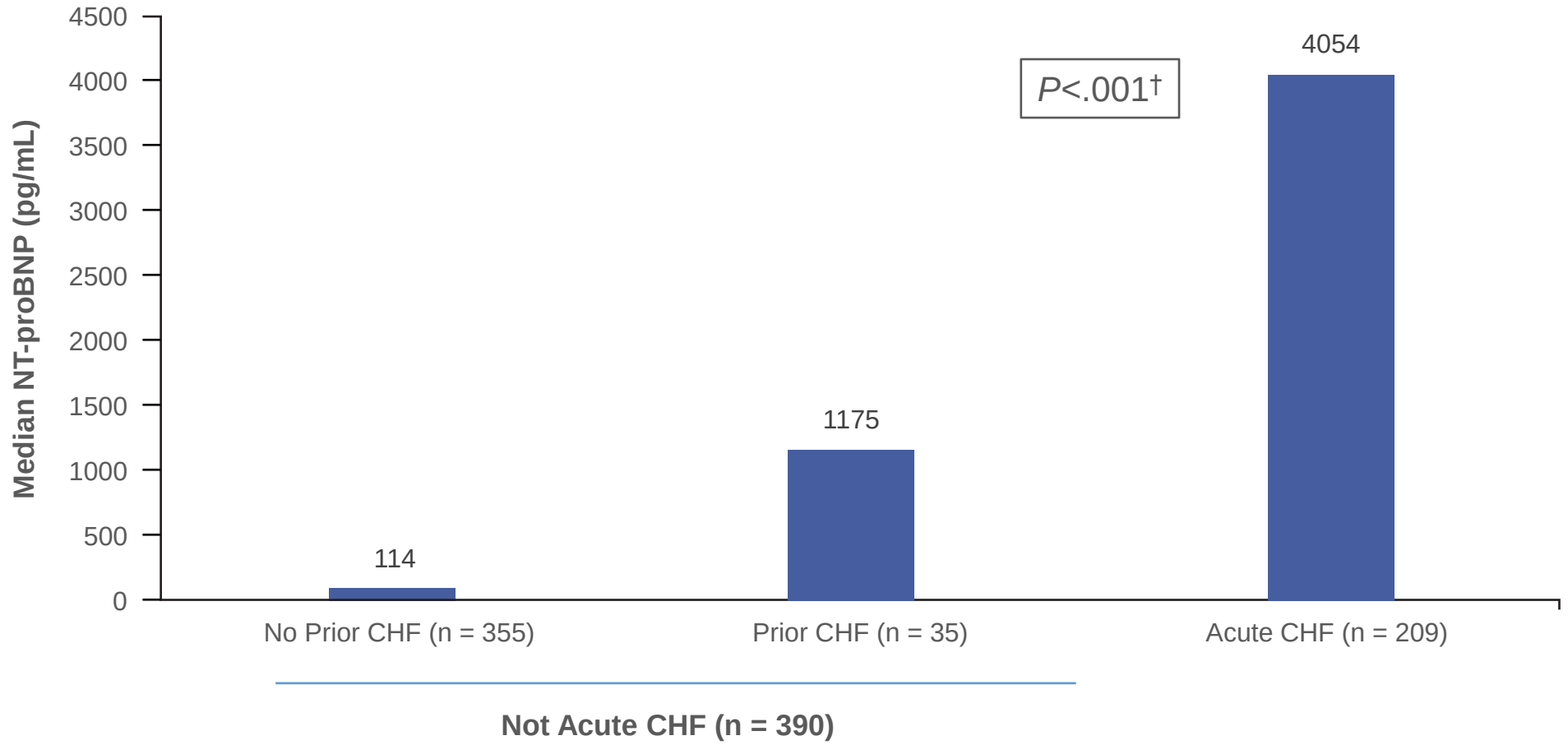
NT-proBNP Levels Were Elevated in Patients With Acute HF in the PRIDE Study*



CHF, congestive heart failure; PRIDE, N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department.
*Patients (N = 599) were consenting adults ≥21 years of age presenting to the emergency department of the Massachusetts General Hospital with complaint of dyspnea. †*P* value represents the comparison of acute CHF with patients with not-acute CHF.
Januzzi JL Jr et al. *Am J Cardiol.* 2005;95:948-954.

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Was another trial necessary?

- In the decade since ICON, the NT-proBNP age-stratified approach has been adopted world wide for use.
- The age-stratified approach is in (most) clinical practice guidelines for HF.
- However, much has changed since the original ICON study, which made re-consideration of NT-proBNP cut-offs worthwhile.

Changes in HF demographics since early 2000's

Changes	Possible effects on NT-proBNP cut offs
Patients are older	Higher optimal threshold?
More AF	Higher optimal threshold?
More CKD	Higher optimal threshold?
More HFpEF	Lower optimal threshold?
Patients are heavier	Lower optimal threshold?
Clinicians are treating to lower NT-proBNP	Lower optimal threshold?
Changes in HF therapies (neprilysin inhibition)	Lower optimal threshold?

A new trial was needed to validate NT-proBNP cut-offs in the ED setting

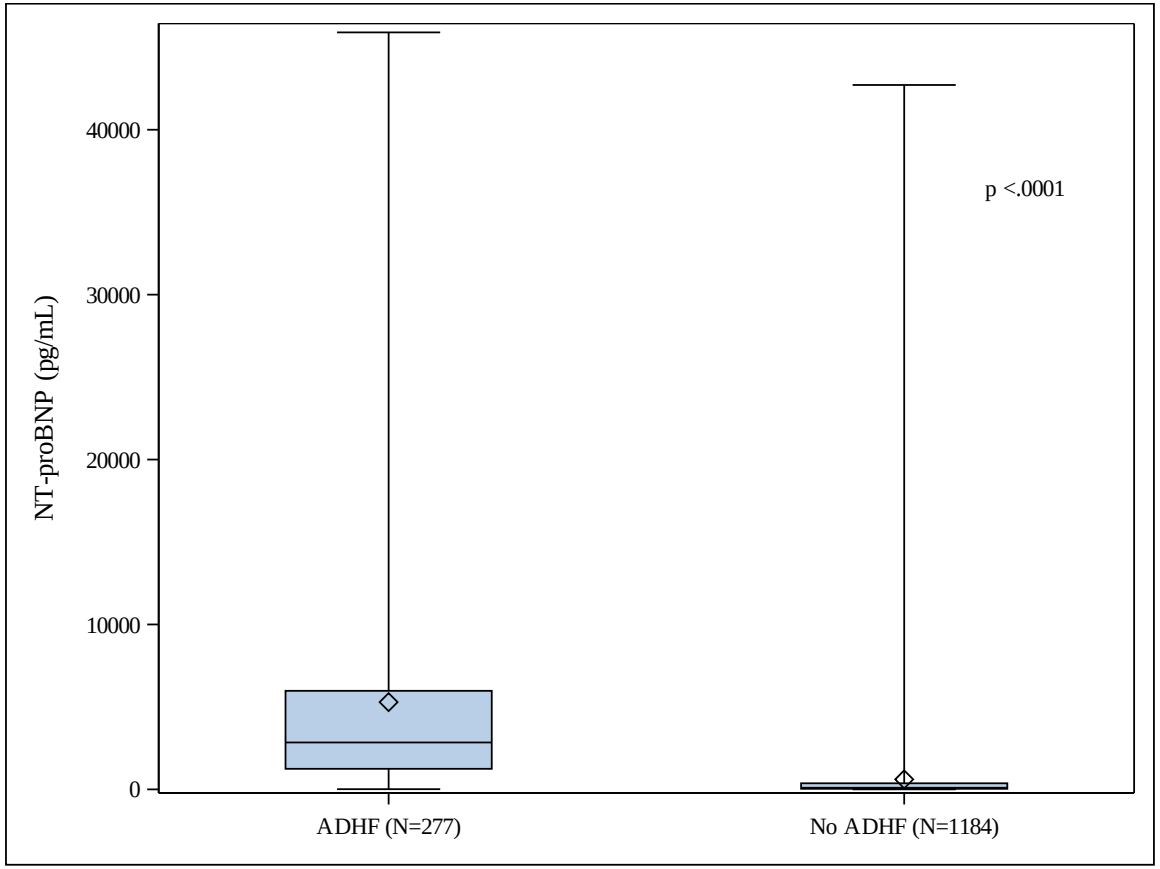
International Collaborative of NT-proBNP:

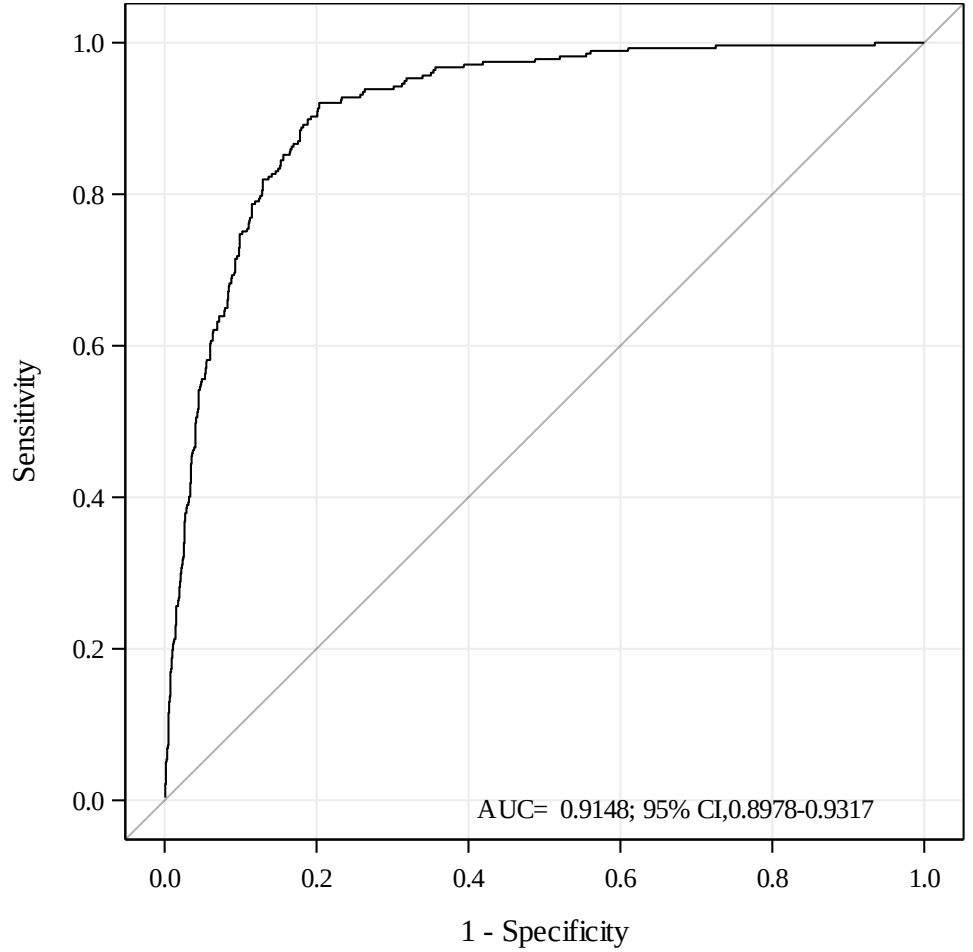
Re-evaluation of Acute Diagnostic Cut-Offs in the Emergency Department

- A multi-center, international trial, sponsored by Roche Diagnostics and performed by the Baim Institute for Clinical Research (Boston, MA)

Gaggin,et al, Am Heart J, 2017; 192:26-37; Januzzi, et al, J Am Coll Cardiol, 2018;71(11):1191-1200

ICON-RELOADED Results: NT-proBNP





Januzzi, et al, J Am Coll Cardiol, 2018;71(11):1191-1200

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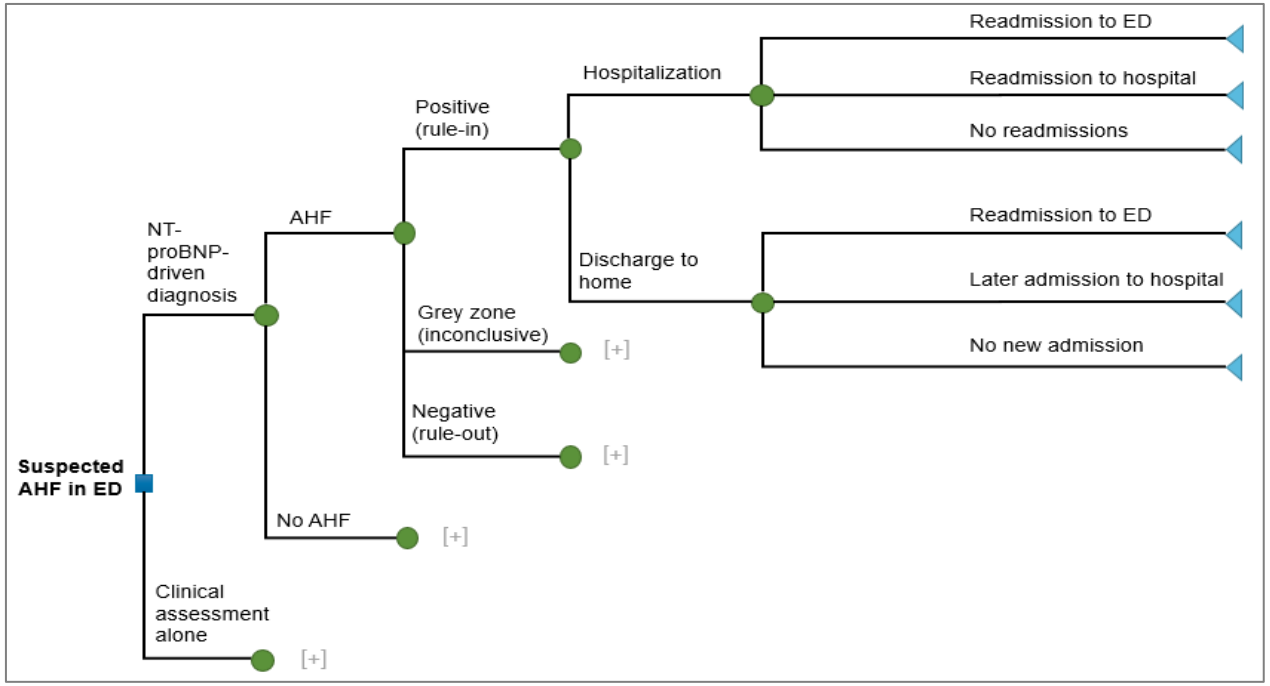
ICON-RELOADED Results: Cost-effectiveness



- 14% fewer initial hospitalizations
- 15% fewer admissions to cardiology or ICU
- 30% reduction in echocardiograms
- 26% fewer ED or hospital readmissions

Siebert, et al, Submitted, 2020

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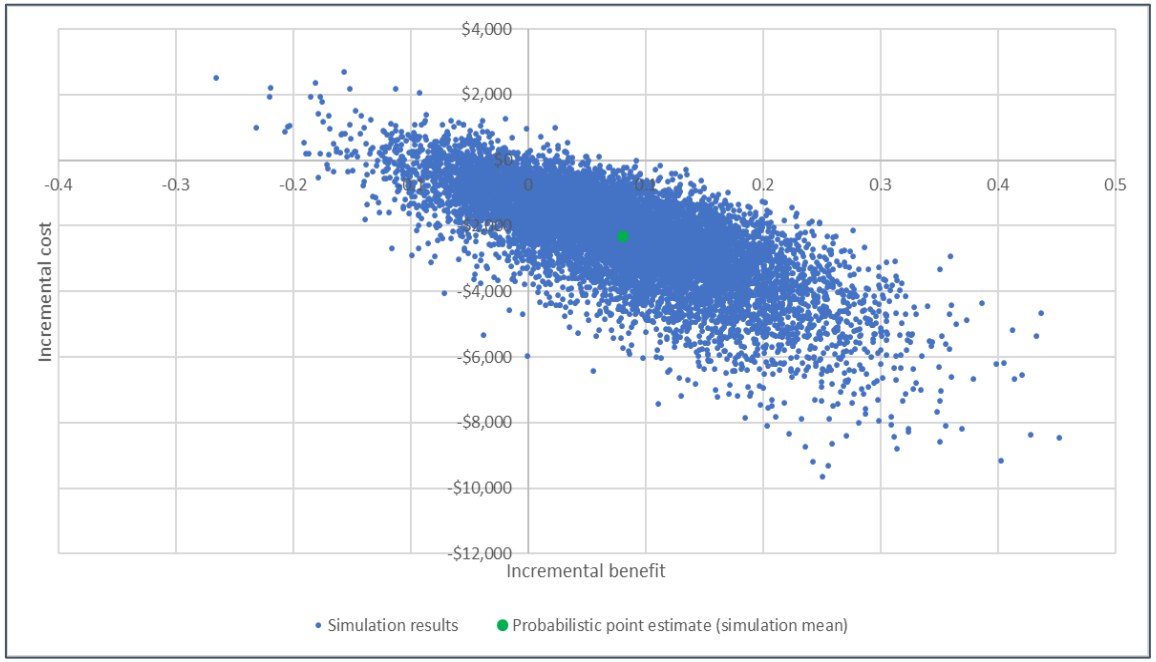
ICON-RELOADED Results: Cost-effectivess

- Use of NT-proBNP decreased the average inpatient management costs by a relative 10.4% ($20,247 vs. $22,584) and reduced the total length of stay in ED and hospital, yielding cost savings of $2,337/pt
- NT-proBNP reduced SAEs by 5.9% compared to clinical assessment alone



Siebert, et al, Submitted, 2020

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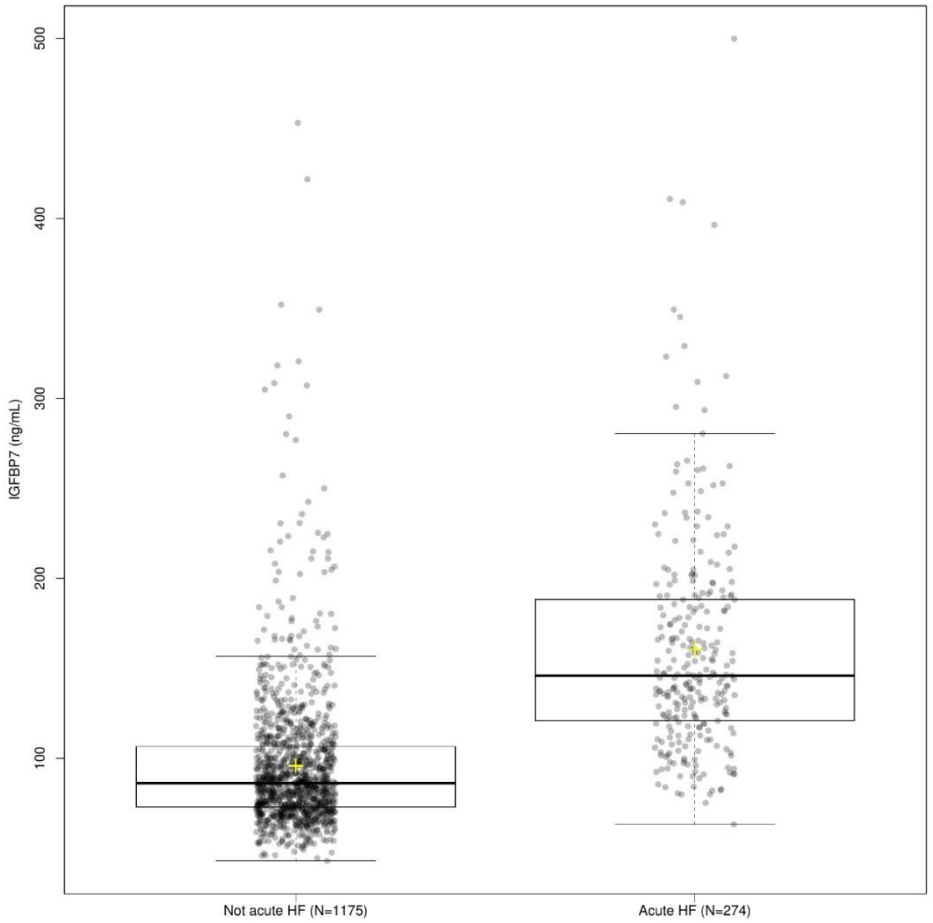
Are any other biomarkers useful for HF dx?



Concentrations of IGFBP7—a biomarker of tissue aging and senescence were highly associated with adjudicated diagnosis of acute HF…

Ibrahim, et al; JACC HF, 2020

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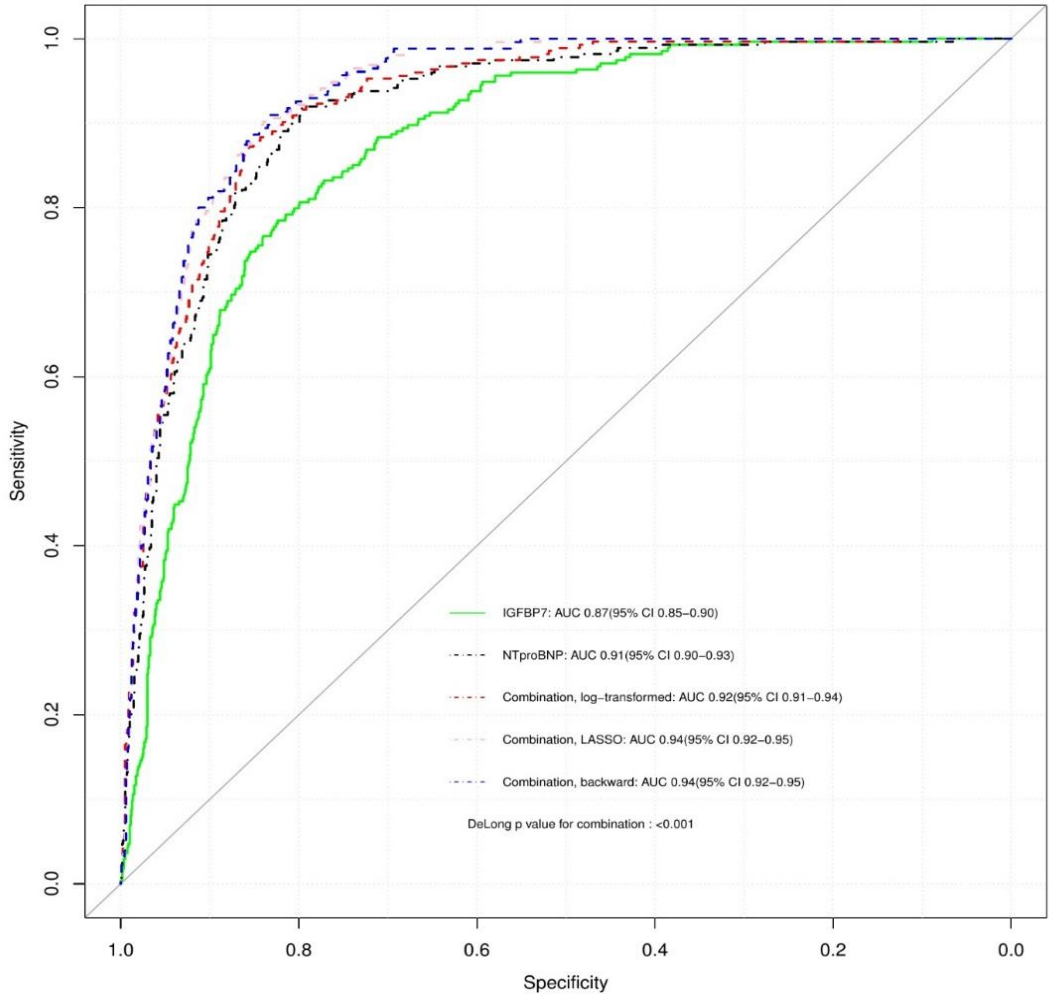
ROC Analysis and NRI for acute HF



The AUC_{HF} for IGFBP7 was 0.87
The AUC_{HF} for NT-proBNP was 0.91

The two were additive with a combined AUC_{HF} of 0.94…due entirely to IGFBP7 up-classifying false – NT-proBNP results

	NRI
NRI	0.25
NRI events	0.28
NRI non-events	-0.04

Ibrahim, et al; JACC HF, 2020

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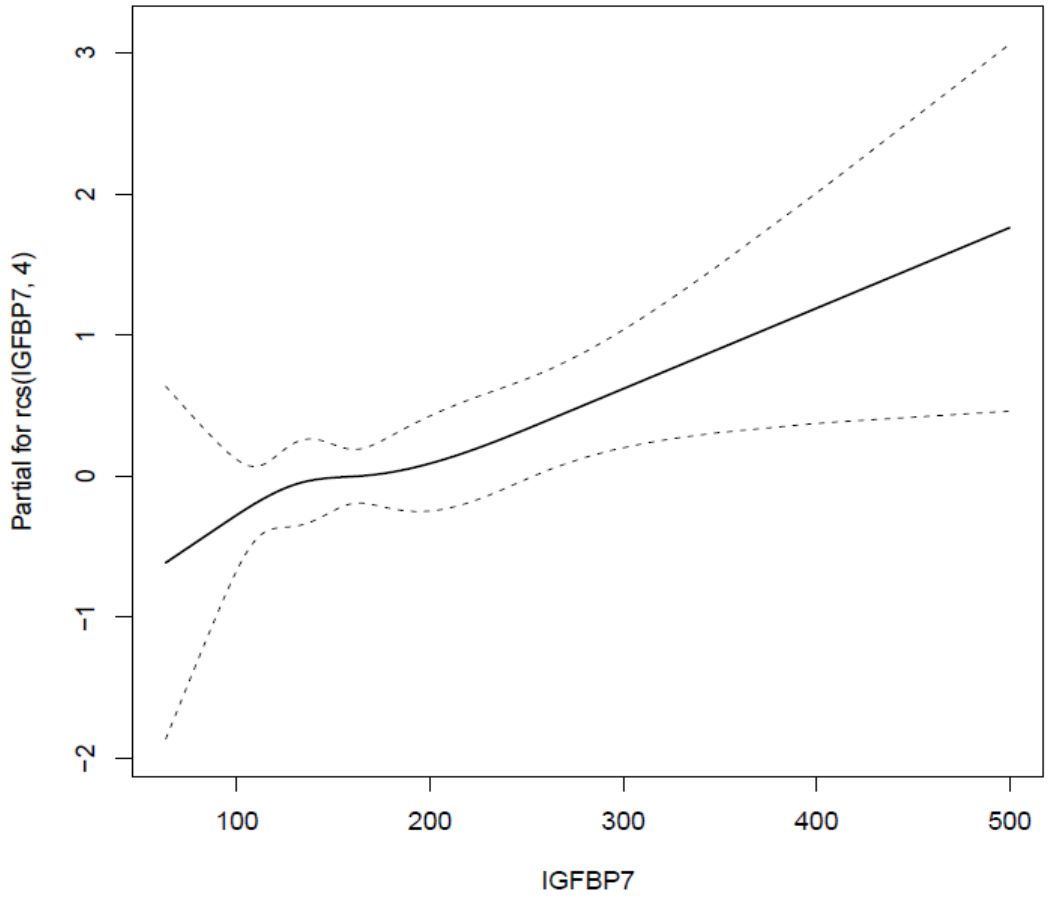
Outcomes in acute dyspnea: Death/repeat hospitalization



Predictors	Hazard ratio	P-value
log_2-IGFBP7	1.86	0.001
log_2-NT-proBNP	1.34	<0.001
log_2-hs-cTnT	1.12	0.19
log_2-creatinine	0.82	0.21
Male sex	1.13 (0.82-1.57)	0.49
Age	0.99 (0.98-1.01)	0.24

Ibrahim, et al; JACC HF, 2020

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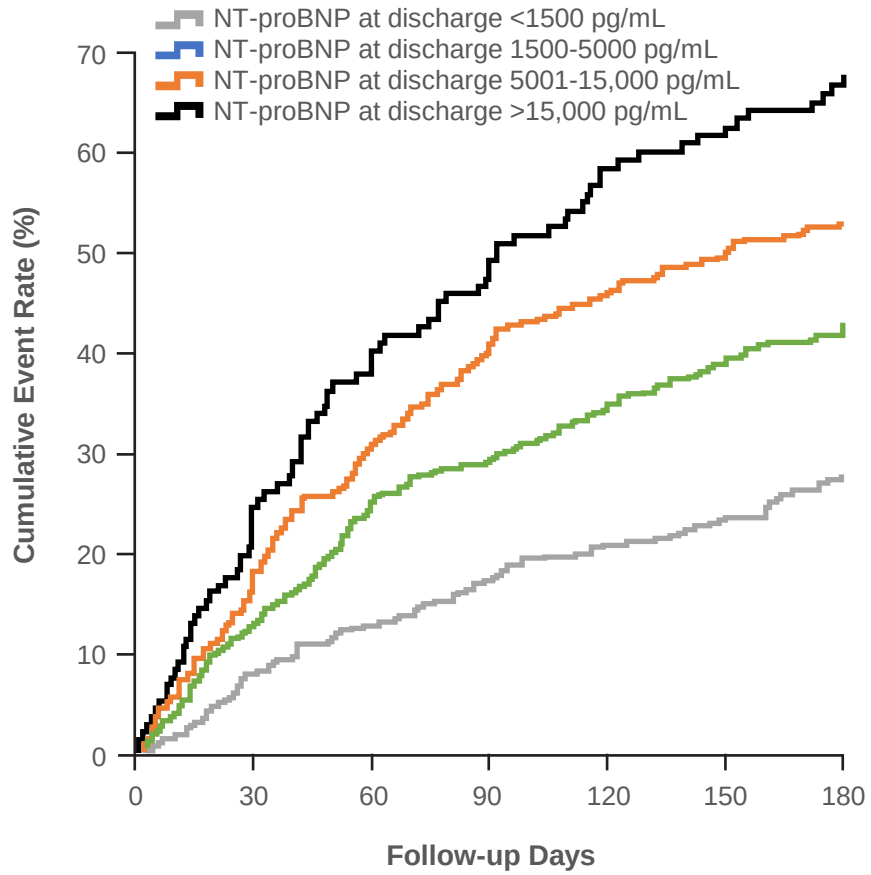
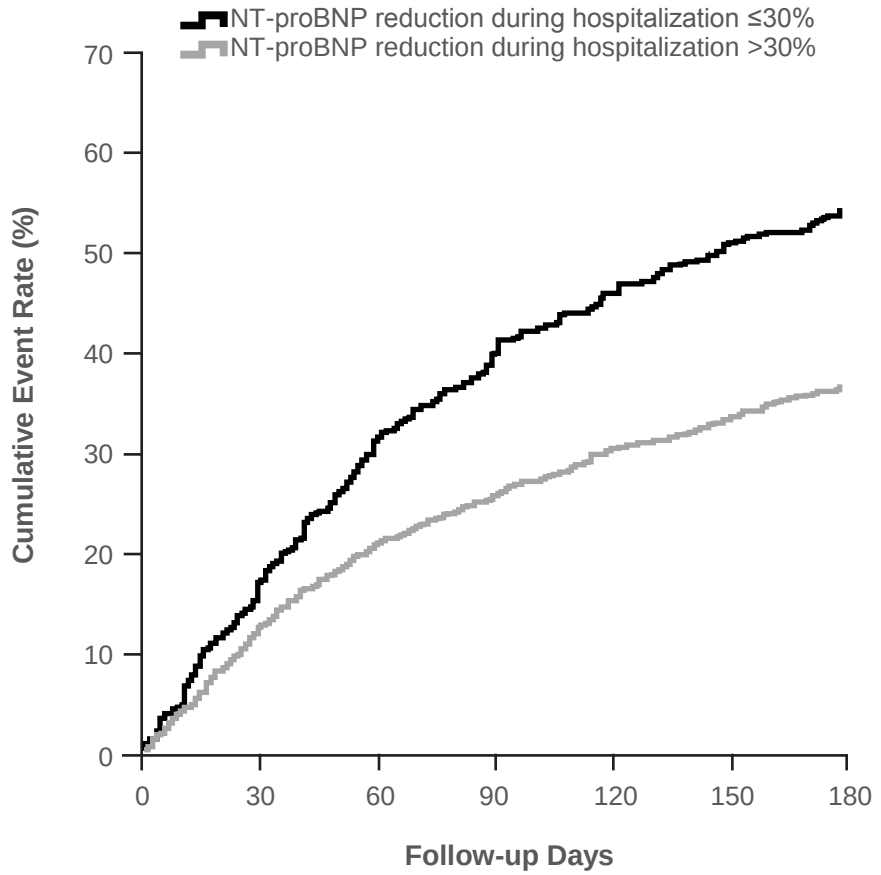
Discharge NT-proBNP Values and Change in NT-proBNP Levels During Hospitalization Predict CV Event Rates





Meta-ananlysis of patients (N = 1301) hospitalized for acute decompensated heart failure from 7 prospective cohort studies.
Permission requested from Heart for figure use.
Salah K et al. *Heart.* 2014;100:115-125.

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Operationalizing NT-proBNP Monitoring to Enhance Clinical Decision Making in ADHF

- Two measurements:
  - At presentation for diagnosis, triage, and prognostication
  - At the end of hospitalization to evaluate for treatment response and provide hospital to home link
    - ✓30% drop is desirable, and lower is always better
    - ✓If baseline levels are not available, discharge NT-proBNP <4000 pg/mL is desirable
    - ✓Non-falling or rising values identify a patient at imminent risk for rehospitalization and/or death

ADHF, acute decompensated heart failure.

Bhardwaj A, Januzzi JL Jr. *Crit Pathw Cardiol.* 2009;8:146-150.

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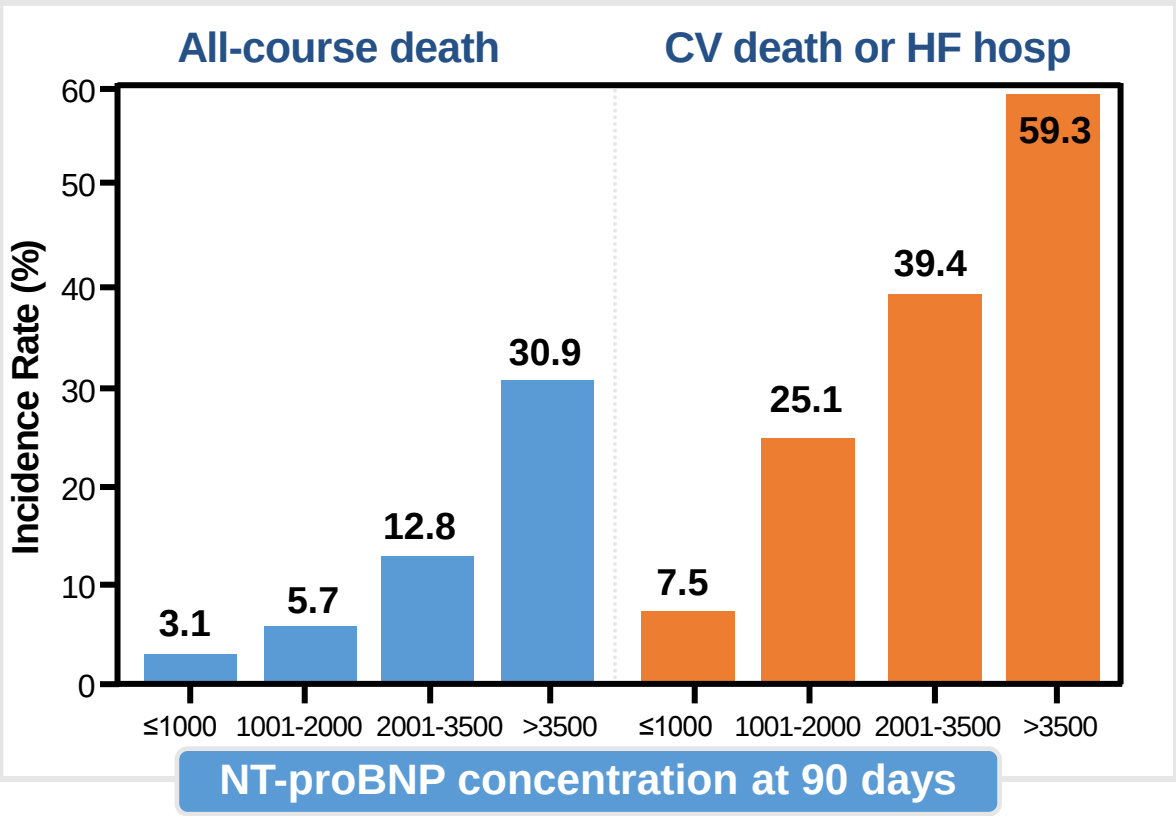
Judging longitudinal risk in chronic HF

- Physical findings
- Signs/symptoms
- Quality of life scores (e.g. KCCQ)
- Filling pressures (e.g. CardioMems)
- Biometric data (e.g. activity, HR patterns)
- Imaging
- Biomarkers

Outcomes and achieved NT-proBNP

Number of events per 100 patient-years of follow-up



Log2 of NT-proBNP at 90 days and clinical outcomes

	Adjusted	
Outcome	**HR (95% CI)**	**P-value**
All Cause Death[A]	0.58 (0.50–0.68)	<.001
HF Hosp/CV Death[B]	0.65 (0.57–0.73)	<.001

HR is with respect to halving of NT-proBNP

[A]Adjusted for history of ischemic heart disease, depression treated with medication, third heart sound, age, diastolic BP, congestion score, HF duration, heart rate, SpO2, sodium, and 6-minute walk distance.

[B]Adjusted for sleep apnea, depression treated with medication, Hispanic ethnicity, ICD or pacemaker, atrial fibrillation at baseline, Black race, history of ischemic heart disease, NYHA class, diastolic BP, creatinine, heart rate, potassium, and sodium.

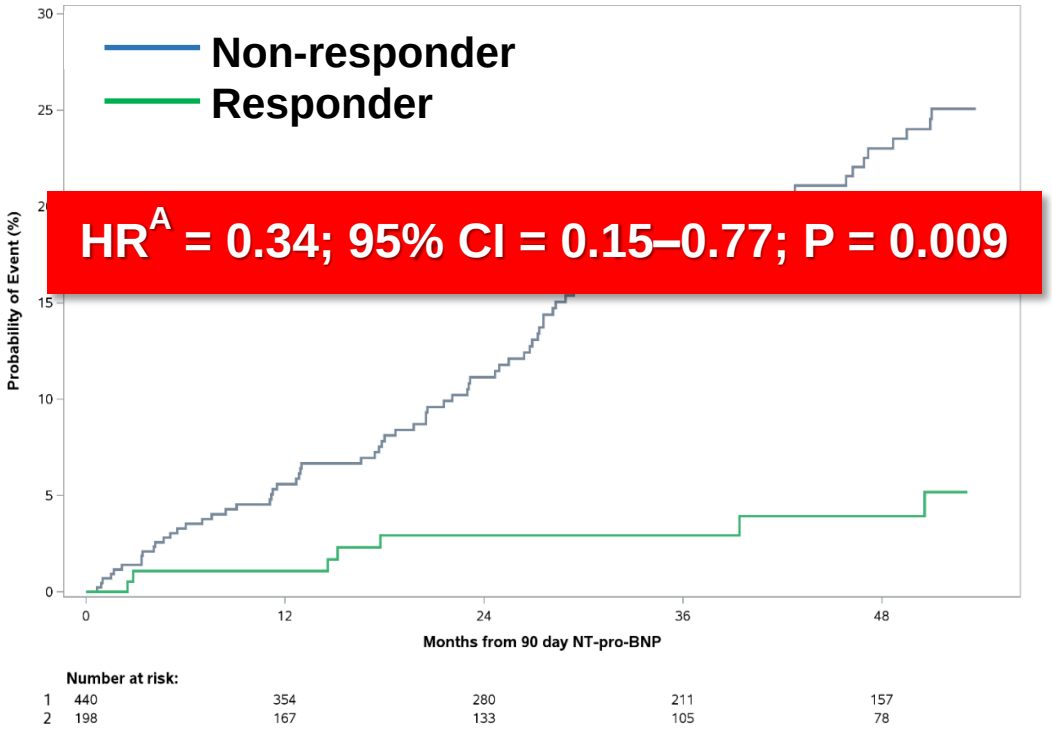
BNP, B type natriuretic peptide; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NT-proBNP, N-terminal-pro-B type natriuretic peptide.

Januzzi J, et al. *J Am Coll Cardiol.*2019;74:1205-17.

Time to first event after 90 days

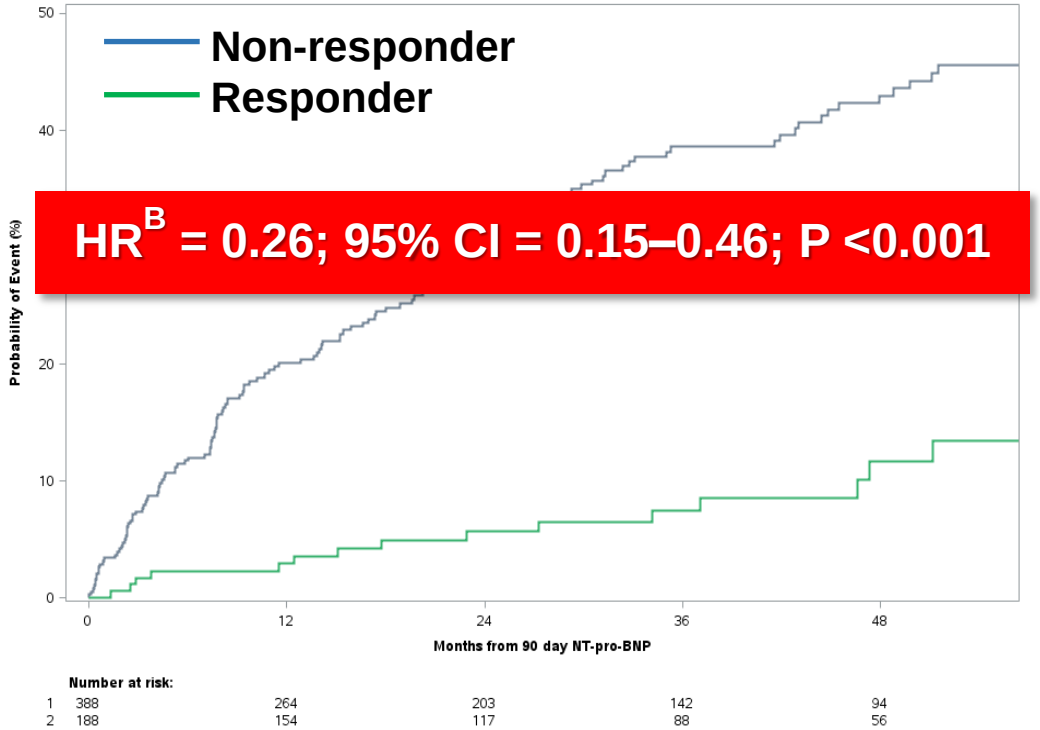
GUIDE-IT
GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment

All-cause mortality



[A]Adjusted for history of ischemic heart disease, depression treated with medication, third heart sound, age, diastolic BP, congestion score, HF duration, heart rate, SpO2, sodium, and 6-minute walk distance.

CV death/HF hospitalization



[B]Adjusted for sleep apnea, depression treated with medication, Hispanic ethnicity, ICD or pacemaker, atrial fibrillation at baseline, Black race, history of ischemic heart disease, NYHA class, diastolic BP, creatinine, heart rate, potassium, and sodium.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NTproBNP, N-terminal pro-B type natriuretic peptide.

Januzzi J, et al. *J Am Coll Cardiol.*2019;74:1205-17.

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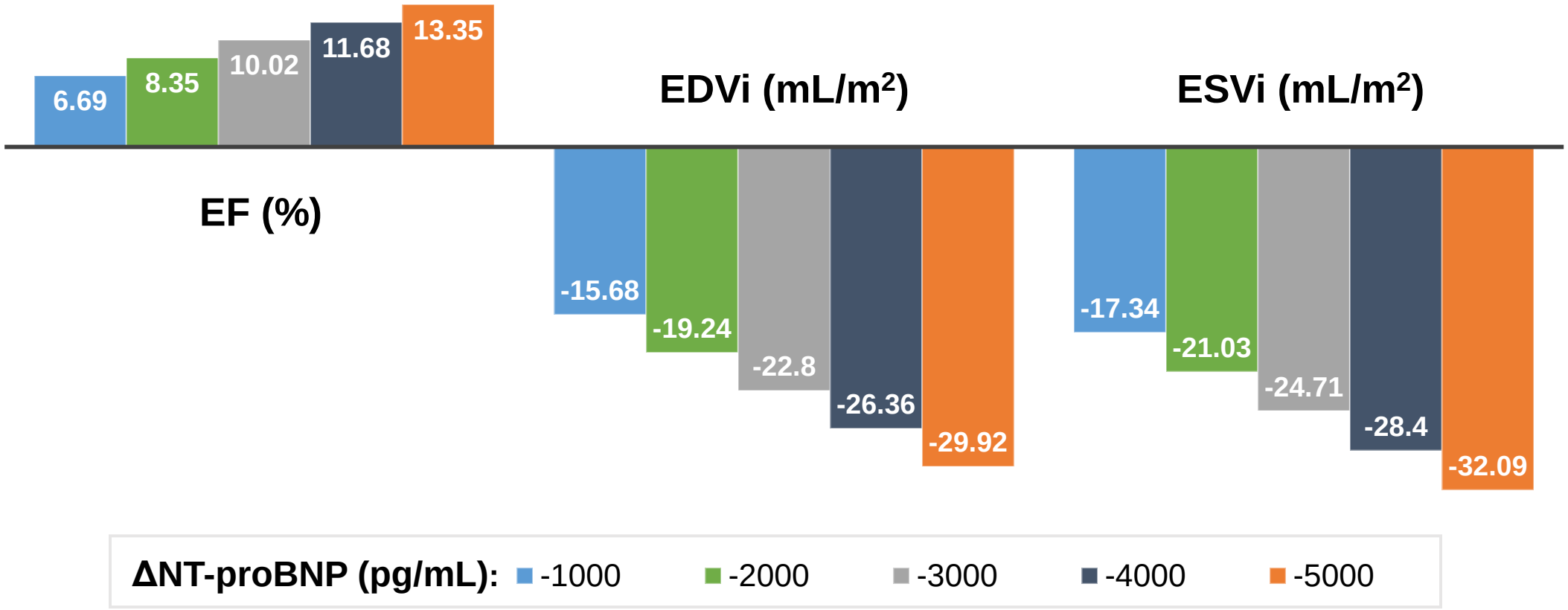
Change in LV structure and function at 1 year by NT-proBNP reduction

GUIDE-IT
GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment



EF, ejection fraction; EDVi, end-diastolic volume index; ESVi, end-systolic volume index; LV, left ventricular; NTproBNP, N-terminal-pro-B type natriuretic peptide.

Daubert MA, et al. *JACC Heart Fail.* 2019;7:158–168.

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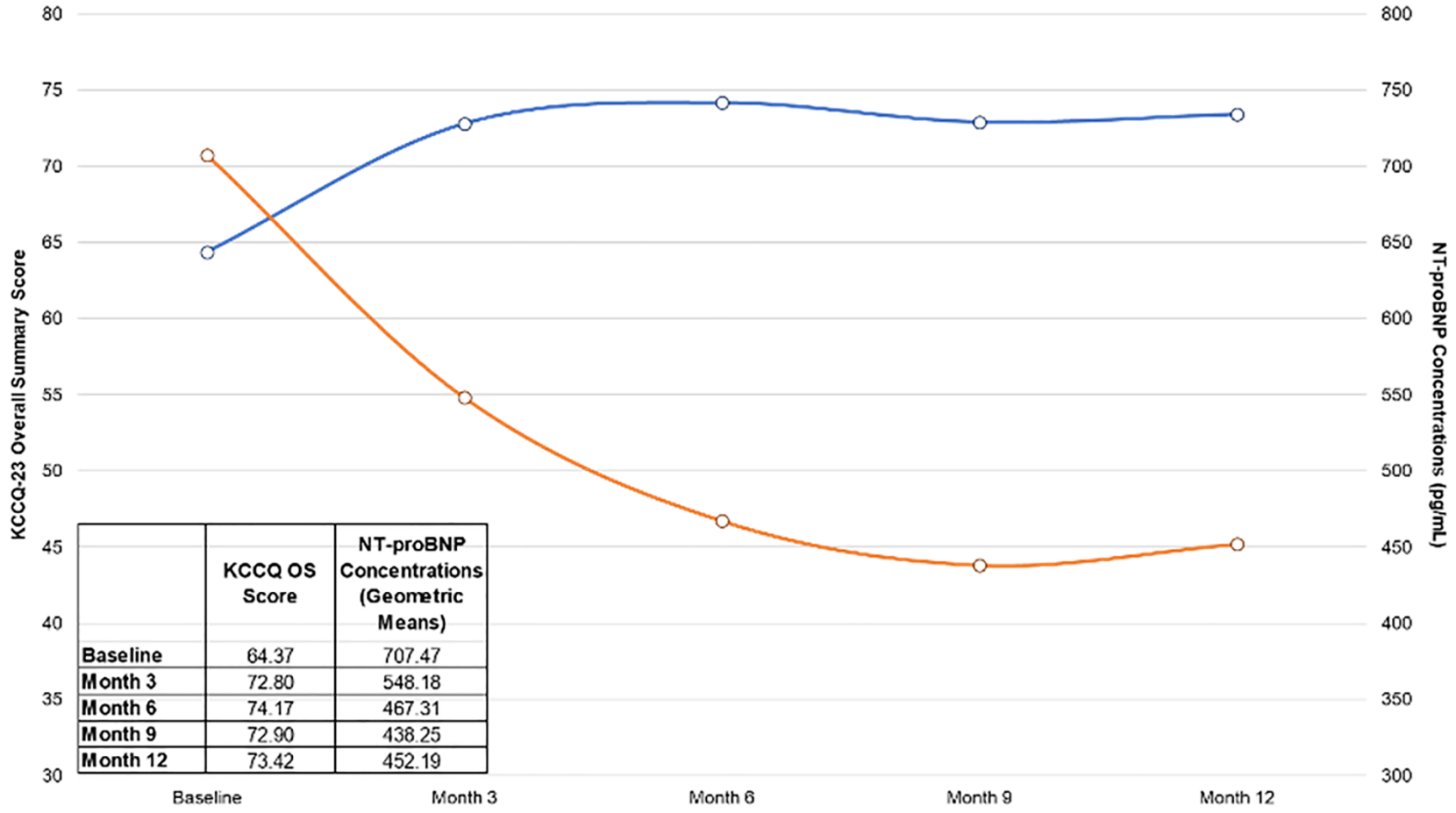
Lower NT-proBNP is associated with better KCCQ scores

PROVE-HF



	KCCQ OS Score	NT-proBNP Concentrations (Geometric Means)
Baseline	64.37	707.47
Month 3	72.80	548.18
Month 6	74.17	467.31
Month 9	72.90	438.25
Month 12	73.42	452.19

Pina, et al, AHA 2019

Importance of biomarker testing for HF monitoring

Intensification 2–4 months (1–4 week cycles) → **Stabilisation** ~3 months

Studies to Consider Initially: (see full guidelines for details)

- BNP/NT-proBNP
- CBC, basic metabolic panel, liver function, iron studies, thyroid studies, HbA1c
- EKG
- Chest X-ray
- Echocardiogram
- Coronary angiogram, cardiac MRI, biopsy, other imaging as appropriate

Serial Evaluation and Titration of Medications

- Clinic visit with history symptoms, vitals, exam, labs
- If volume status requires treatment, adjust diuretics, follow up 1–2 weeks
- If euvolemic and stable, start/increase/switch GDMT, follow-up 1–2 weeks via phone or repeat clinic visit with basic metabolic panel as may be indicated
- Repeat cycle until no further changes are possible or tolerated

End-intensification/ maintenance

- Ongoing assessment
- Additional adjustments as indicated
- Repeat objective data as needed to reestablish prognosis

Assess response to therapy and cardiac remodeling

- Repeat laboratory tests, for example, BNP/NT-proBNP and basic metabolic panel
- Repeat echocardiogram (or similar imaging modality for cardiac structure and function
- Repeat EKG
- Consider EP referral for those eligible for CRT or ICD

Lack of response/instability

Remember acronym to assist in decision making for referral to advanced heart failure specialist: I-NEED-HELP

I	N	E	E	D	H	E	L	P
IV inotropes	**N**YHA IIIB/IV or persistently elevated natriuretic peptides	**E**nd-organ dysfunction	**E**jection fraction ≤ 35%	**D**efibrillator shocks	**H**ospitalisations >1	**E**dema despite escalating diuretics	**L**ow blood pressure, high heart rate	**P**rognostic medication – progressive intolerance or down titration of GDMT

BNP, B type natriuretic peptide; HF, heart failure; NT-proBNP, N-terminal-pro-B type natriuretic peptide.
Yancy CW, et al. *J Am Coll Cardiol*. 2018;71:201–230.

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Operationalizing NT-proBNP monitoring to enhance clinical decision-making in chronic HF

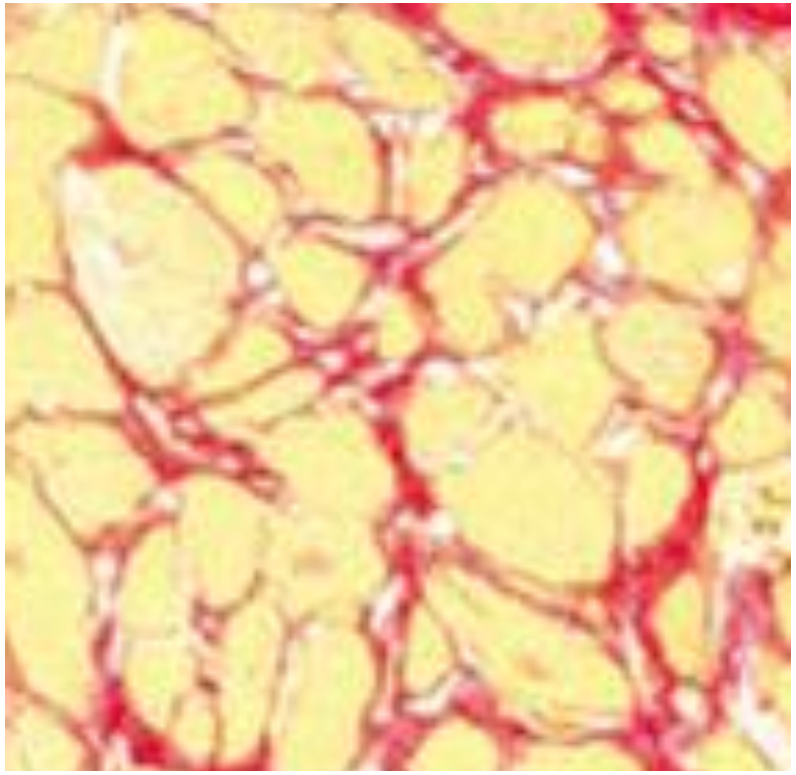
- In recently decompensated patients, measure 1–2 weeks after discharge (office or home).
- In stable ambulatory patients, measure every 3 months
  - Stable concentrations <1000 pg/mL: imaging and other testing may be deferred
  - Elevated/rising concentrations: repeat imaging, further evaluations, review medication/lifestyle program and adjust as appropriate
- Markedly elevated concentrations: Consider transplant referral, consider diagnoses associated with “unexpectedly elevated” NT-proBNP (amyloidosis).

HF, heart failure; NT-pro-BNP, N-terminal pro-B type natriuretic peptide.
Yancy CW, et al. *J Am Coll Cardiol*. 2018;71:201–230.

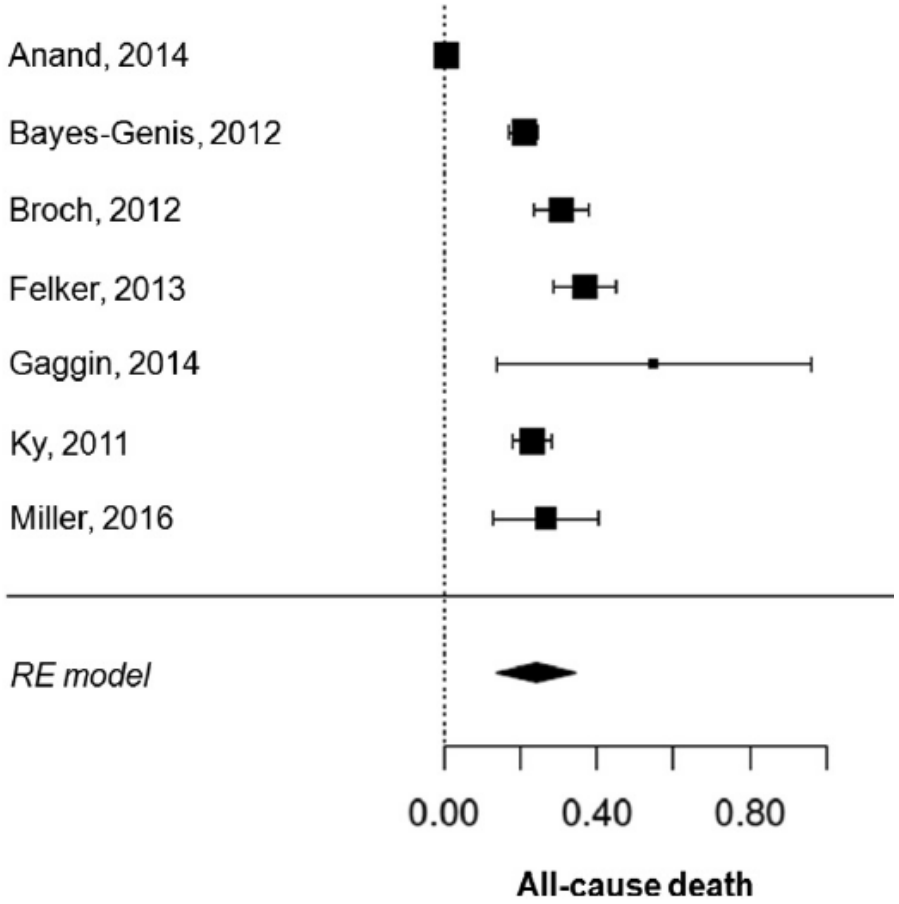
Other risk biomarkers predictive of remodeling

- Soluble ST2: a biomarker of myocardial fibrosis and remodeling
- High sensitivity cardiac troponin
- Collagen markers, mimecan, IGFBP7

ST2 and risk: Meta analysis

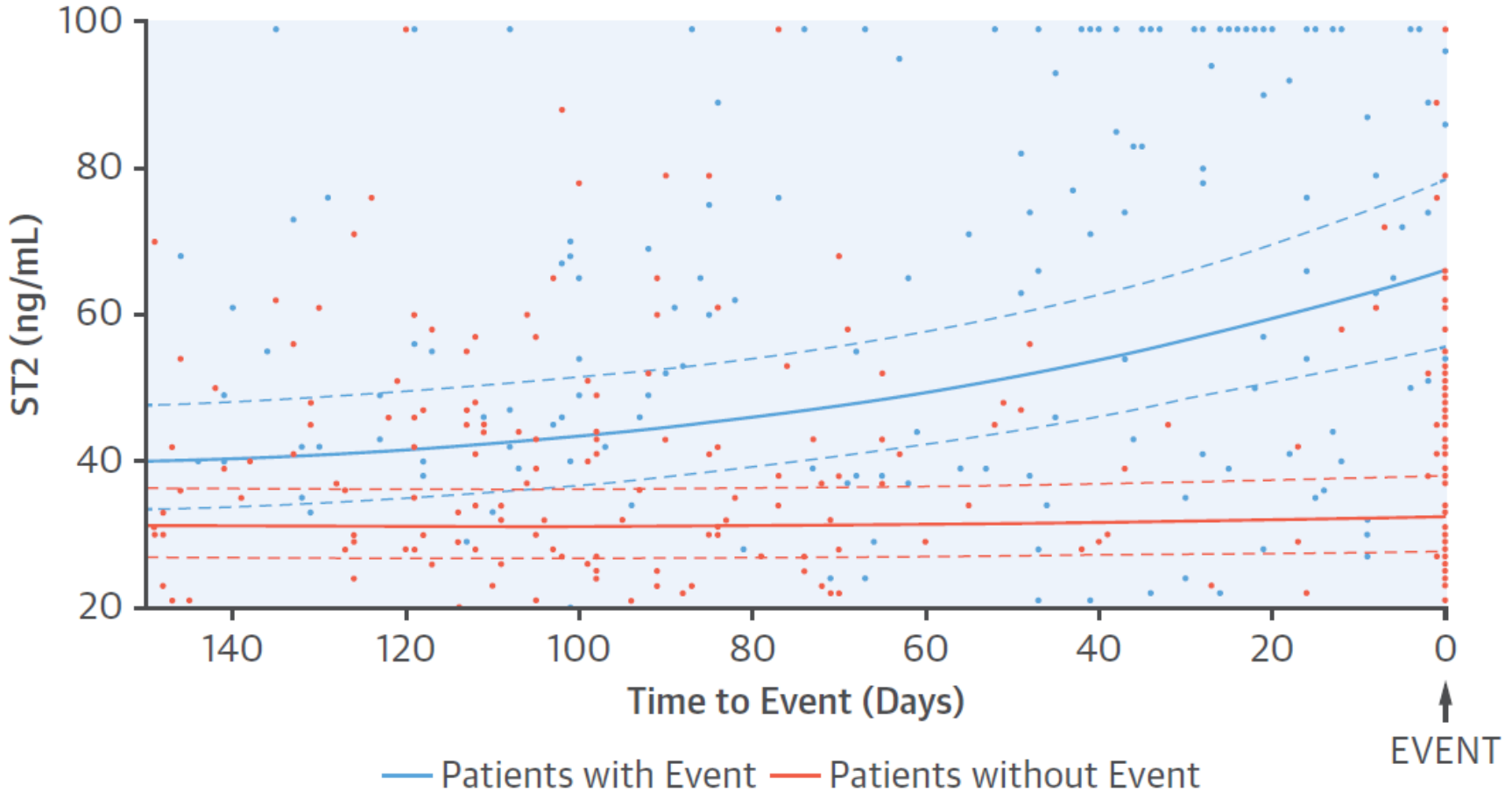


Excessive fibrosis in dysregulated ST2 signaling



Aimo, et al, JACC Heart Failure 2017

Serial measurement of sST2



van Vark, L.C. et al. J Am Coll Cardiol. 2017;70(19):2378-88.

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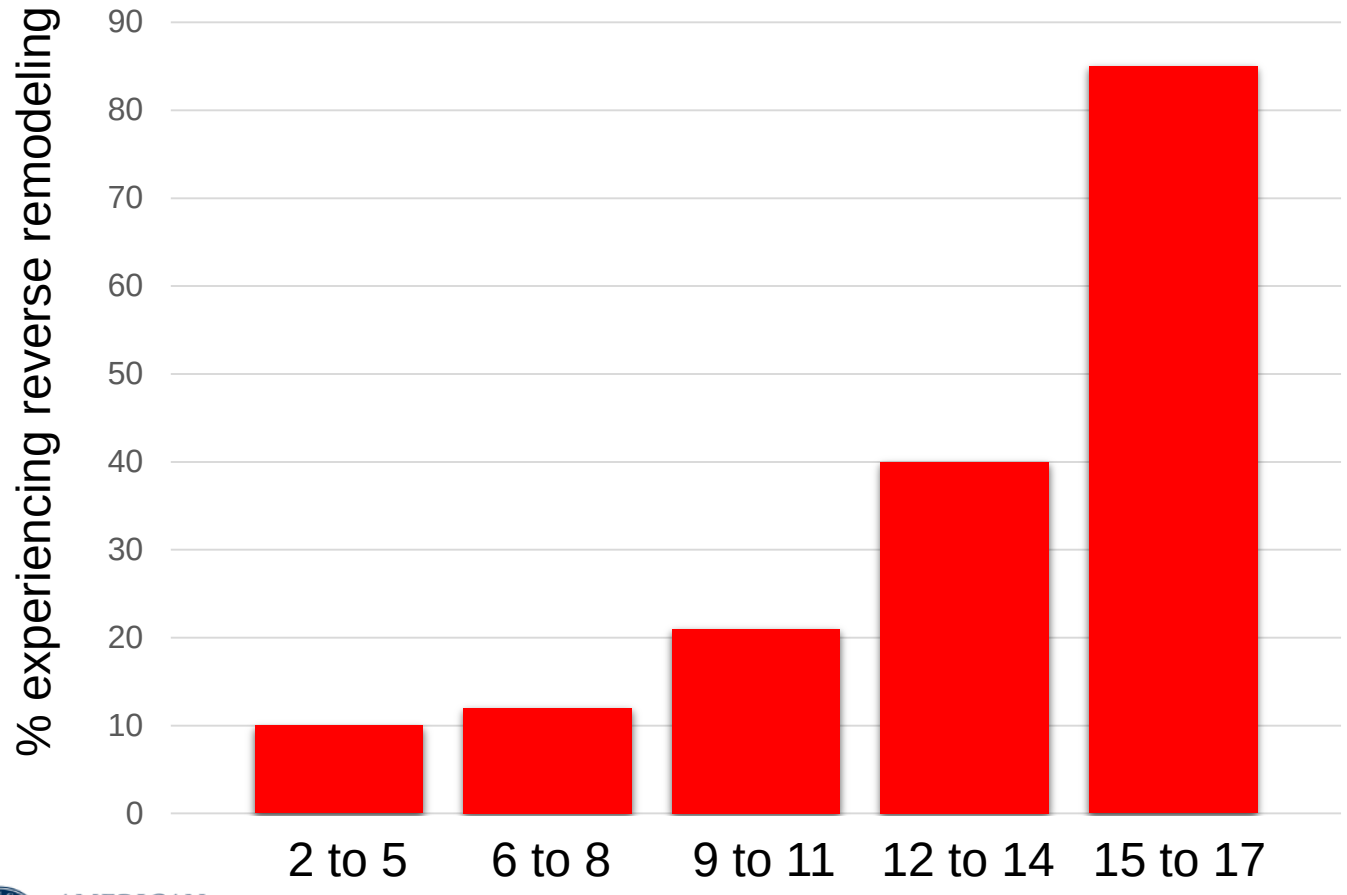
ST2 and cardiac remodeling

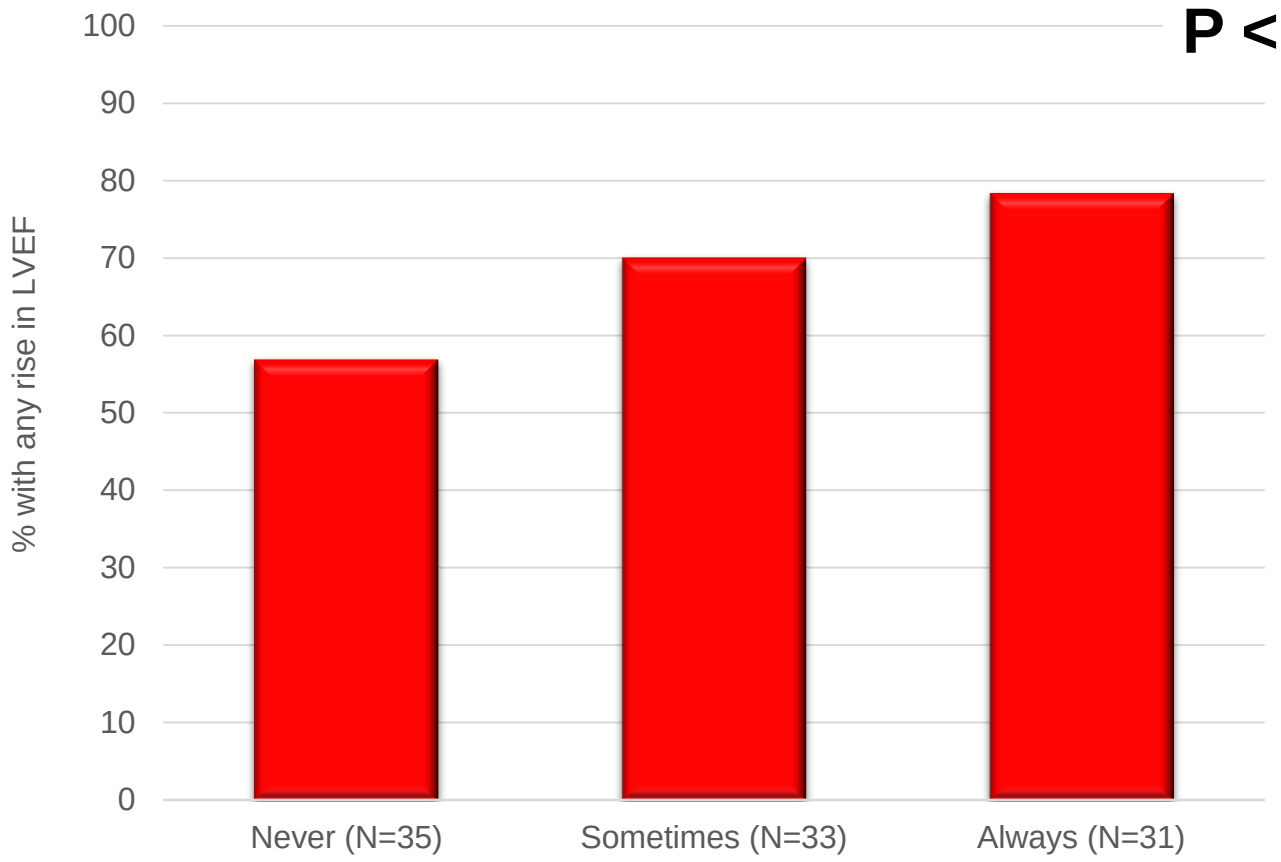


Lupon, et al, Int Journal Cardiol, 2017

The ST2-R2 score consists of:

- sST2 < 48 ng/mL = 3 pts
- Non-ischemic etiology = 5 pts
- No LBBB = 4 pts
- HF < 1 year = 2 points
- LVEF <24% = 1 point
- Beta blocker therapy = 2 points

Elevated hs-cTnI predicts worse remodeling



P <0.001

Serial measurement of hsTnI over a year's time revealed patterns that predict change in LV function:

Sustained reduction in hsTnI <10.9 ng/L predict reverse remodeling

Is the hs-cTnI low?

Motiwala et al, J Cardiovas Transl Research, 2015

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STOP-HF Trial to Investigate the Efficacy of a Screening Program Using BNP and Collaborative Care

Routine PCP Care

- Annual BNP not available to clinicians
- At least annual review by PCP
- Cardiology review only if requested by PCP

BNP-Directed Care

- In addition to routine care, annual BNP in all patients
- If BNP >50 pg/mL at any time
  - Shared care
    - Cardiology review
    - Echo-Doppler
    - Other CV investigations
    - CV nurse coaching
    - Cardiology follow-up

A parallel-group randomized trial involving 1374 participants with cardiovascular risk factors recruited from 39 primary care practices in Ireland between January 2005 and December 2009 and followed up until December 2011.
PCP, primary care physician; STOP-HF, St. Vincent's Screening to Prevent Heart Failure.
Ledwidge M et al. *JAMA.* 2013;310:66-74.

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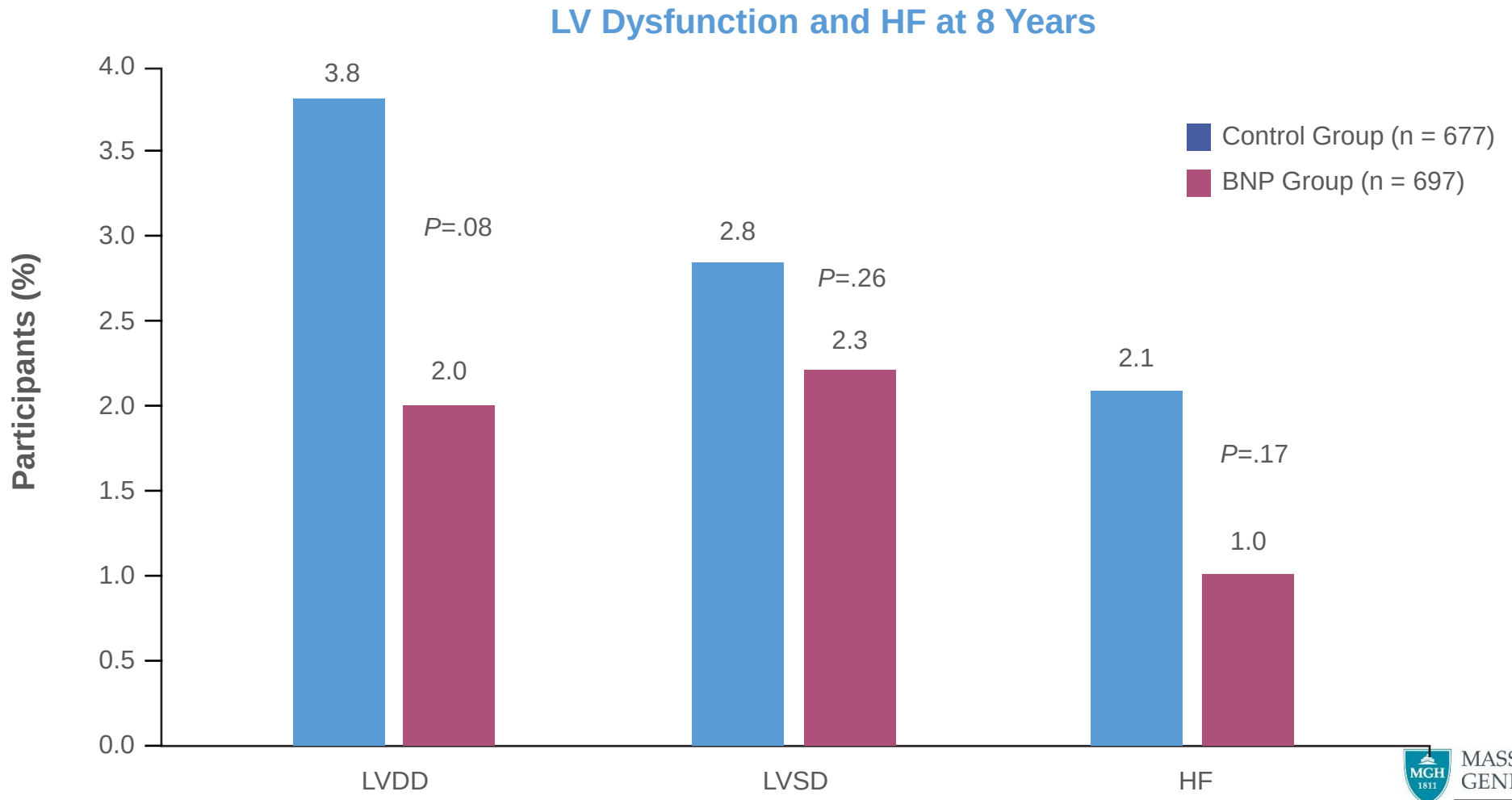
Prevalence of Asymptomatic LVSD Was Lower Following BNP-Directed Care



LVDD, left ventricular diastolic dysfunction.

Ledwidge M et al. *JAMA.* 2013;310:66-74.

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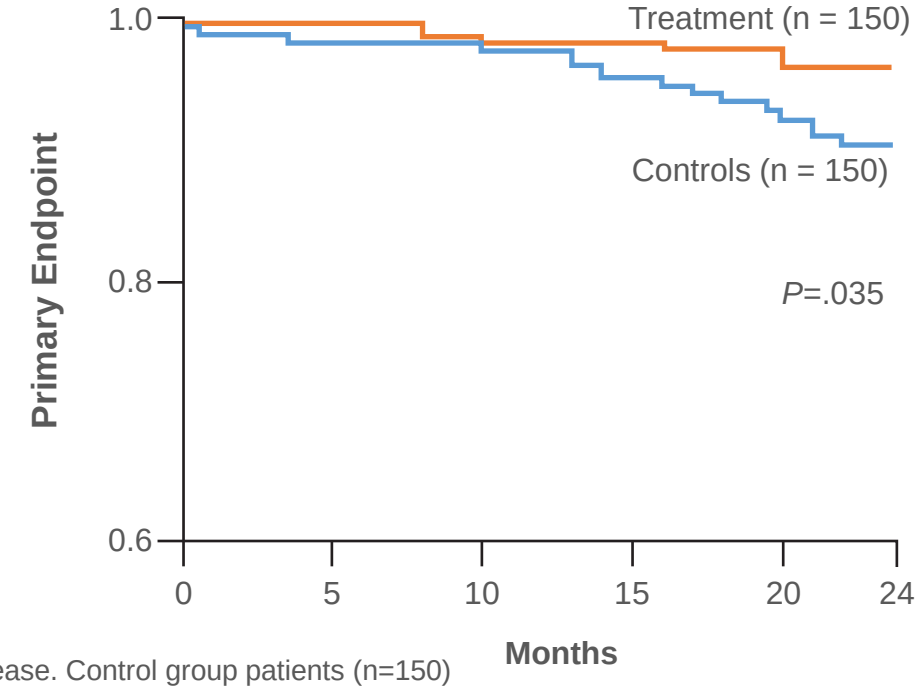
Neurohormonal Therapy for Primary Prevention of CV Events in Patients With Diabetes With Elevated NT-proBNP

The PONTIAC Trial investigated the preventive effect of neurohormonal therapy in high-risk patients with diabetes with elevated NT-proBNP

Cox Regression Models

Endpoint	HR	95% CI	*P* value
Hospitalization or death due to cardiac disease	0.351	0.127-0.975	.04
All-cause hospitalizations	0.657	0.465-0.927	.02
Unplanned CV hospitalization or death	0.376	0.157-0.899	.03
HF hospitalizations	0.140	0.017-1.137	.07

Hospitalization or Death Due to Cardiac Disease



Patients (N = 300) with type 2 diabetes and elevated NT-proBNP (>125 pg/mL), but free of cardiac disease. Control group patients (n=150) were treated at 4 diabetes care units. Treatment group patients (n=150) were additionally treated at a cardiac outpatient clinic for the up-titration of RAAS antagonists and beta-blockers.

PONTIAC, NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease. Huelsmann M et al. *J Am Coll Cardiol.* 2013;62:1365-1372.

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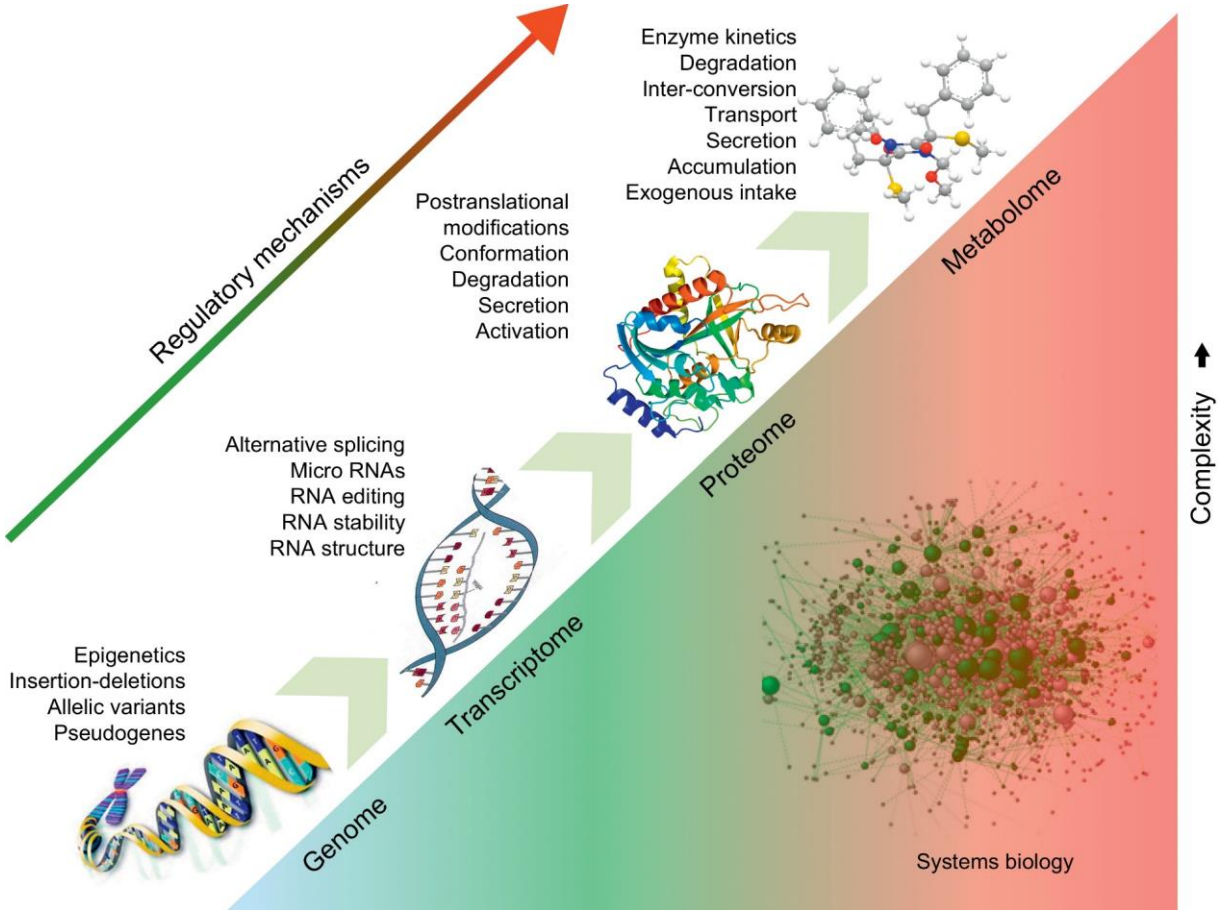
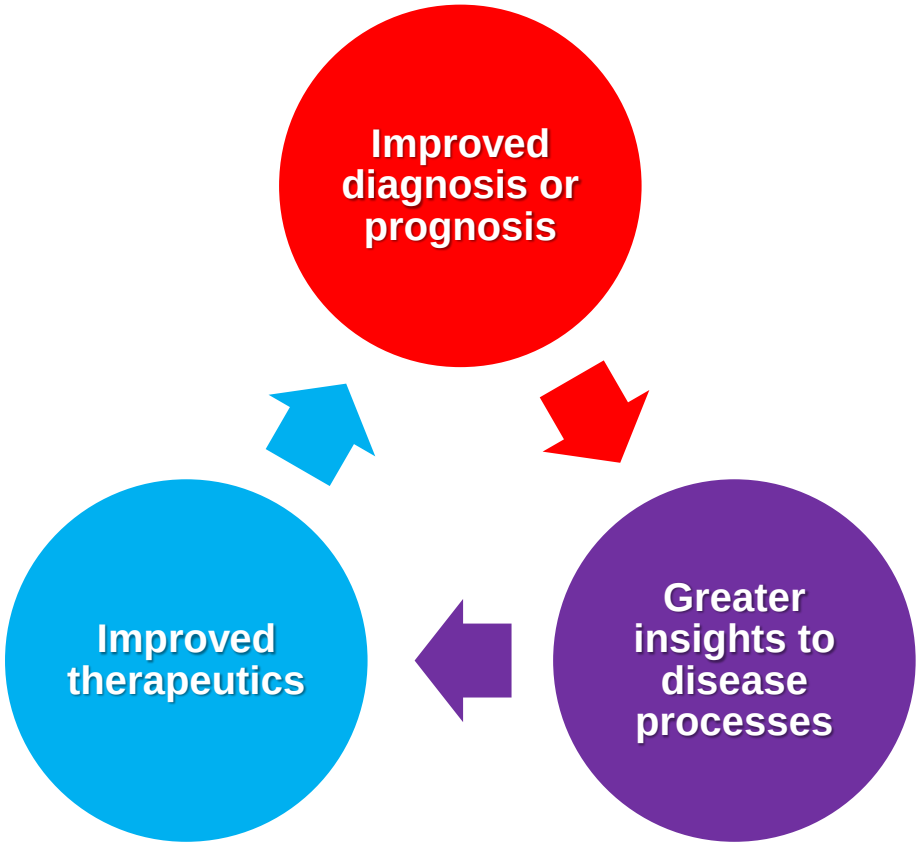
Biomarkers in HF: What is in the future?

OMICs and discovery in HF





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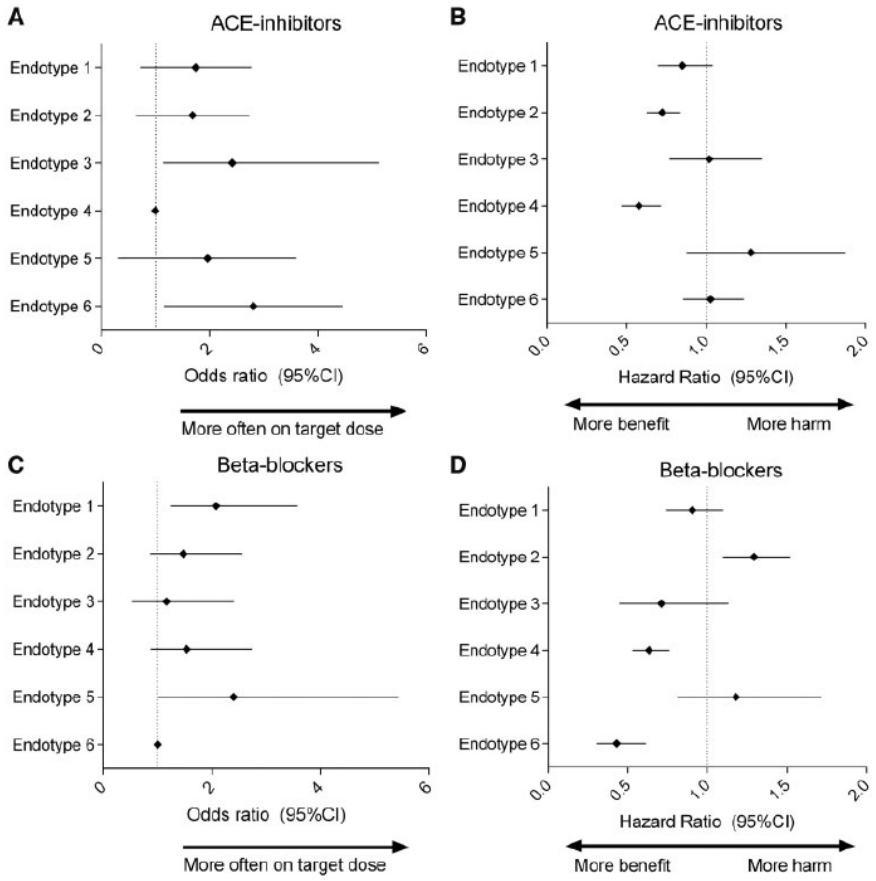
Proteomics to define HF endotypes

Endotype 1		Endotype 2		Endotype 3	
Marker	C-index	Marker	C-index	Marker	C-index
IGFBP1	0.83	PAI	0.77	SELP	0.93
IGFBP2	0.70	PDGFsA	0.74	PECAM1	0.93
NT-proBNP	0.65	SELP	0.7	JAMA	0.97
Combined	0.83	Combined	0.78	Combined	0.97
Endotype 4		**Endotype 5**		**Endotype 6**	
Marker	C-index	Marker	C-index	Marker	C-index
ST2	0.81	CHIT1	0.99	TPA	0.70
NT-proBNP	0.80			NT-proBNP	0.70
IGFBP1	0.80			VWF	0.70
Combined	0.86	Combined	NA	Combined	0.78



Tromp et al, EHJ, 2018;39:4269-4276

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Conclusions

- Biomarkers play a clinical role for diagnosis, prognosis, management and possibly prevention of HF
- The natriuretic peptides play the largest role
- Other biomarkers with links to remodeling may add information for diagnosis and prognostication
- Omics will provide information regarding HF biology, allow for biomarker discovery, treatment targets and possibly individualize treatment