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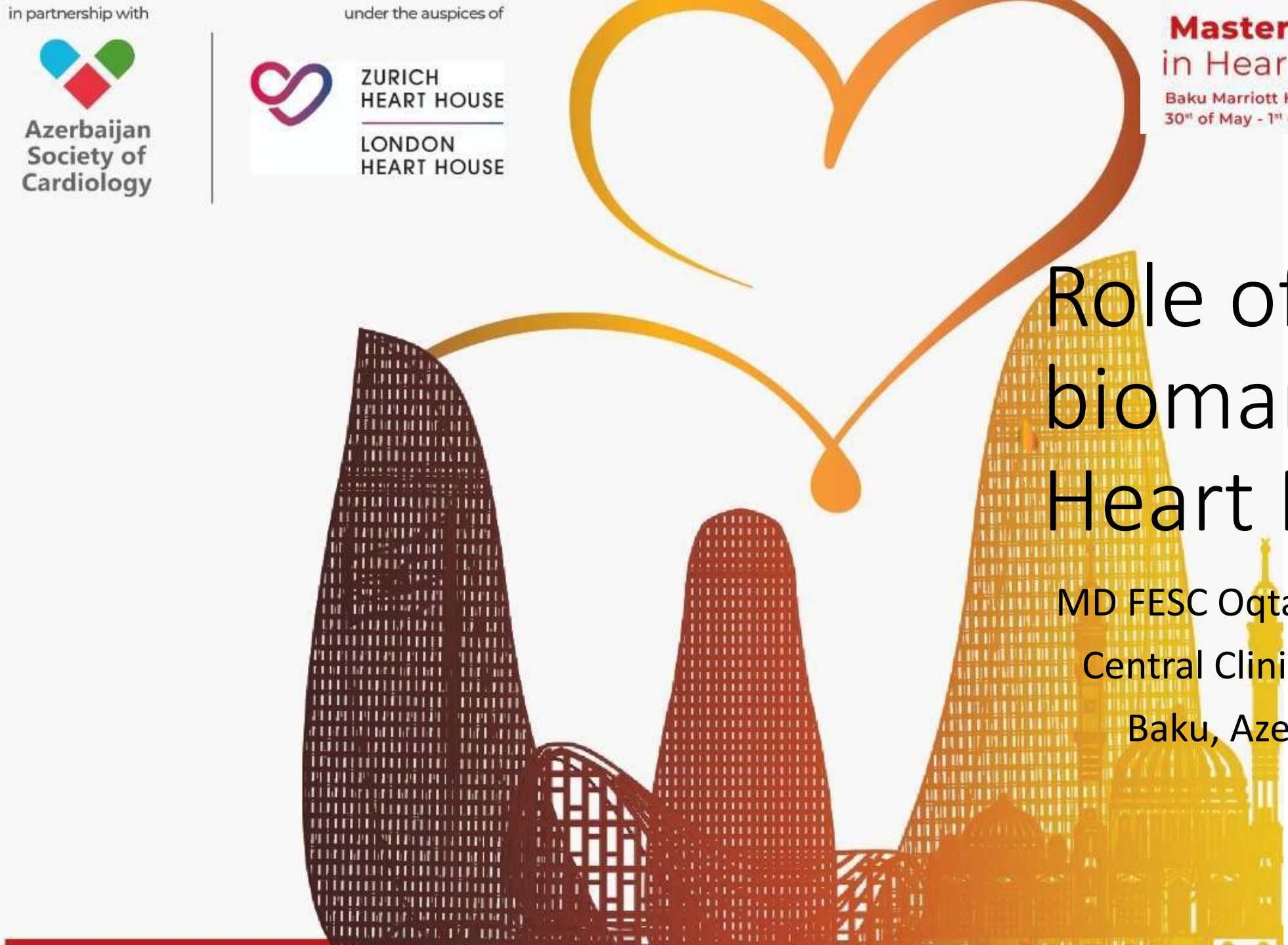
Master Course in Heart failure 25 BAKU

Baku Marriott Hotel Boulevard

30st of May - 1st of June



Role of biomarkers in Heart Failure

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Declaration of interest

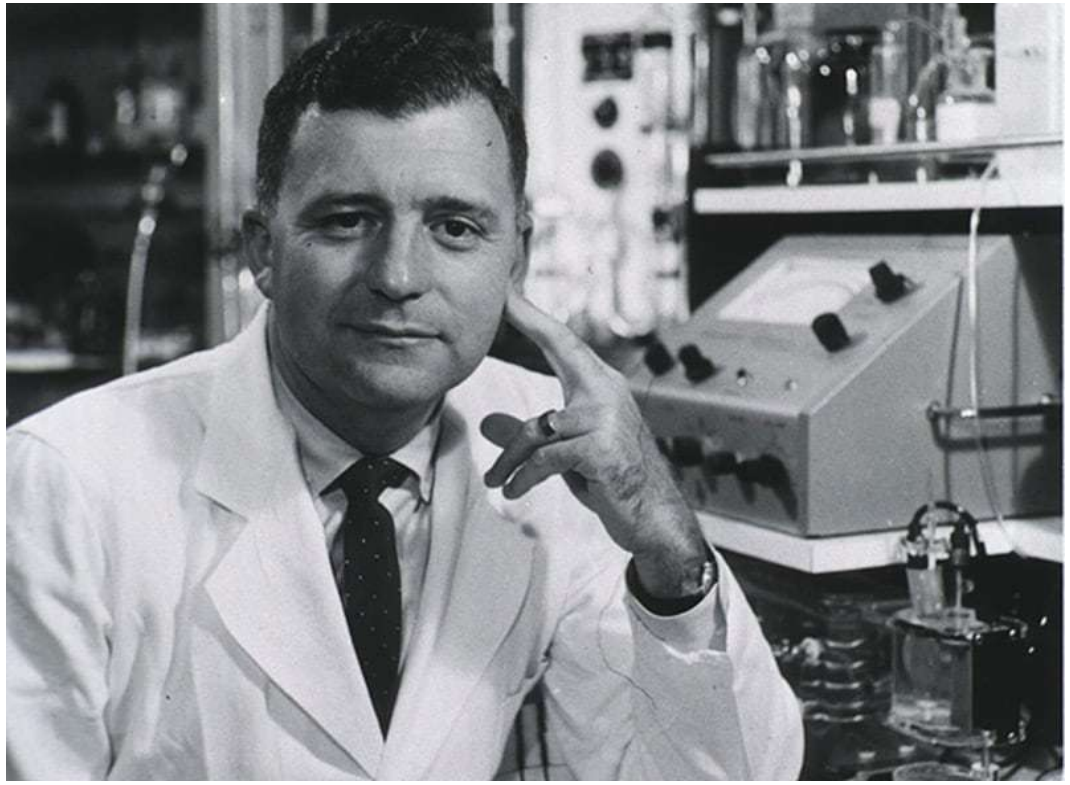
- There are no conflicts of interest to declare.

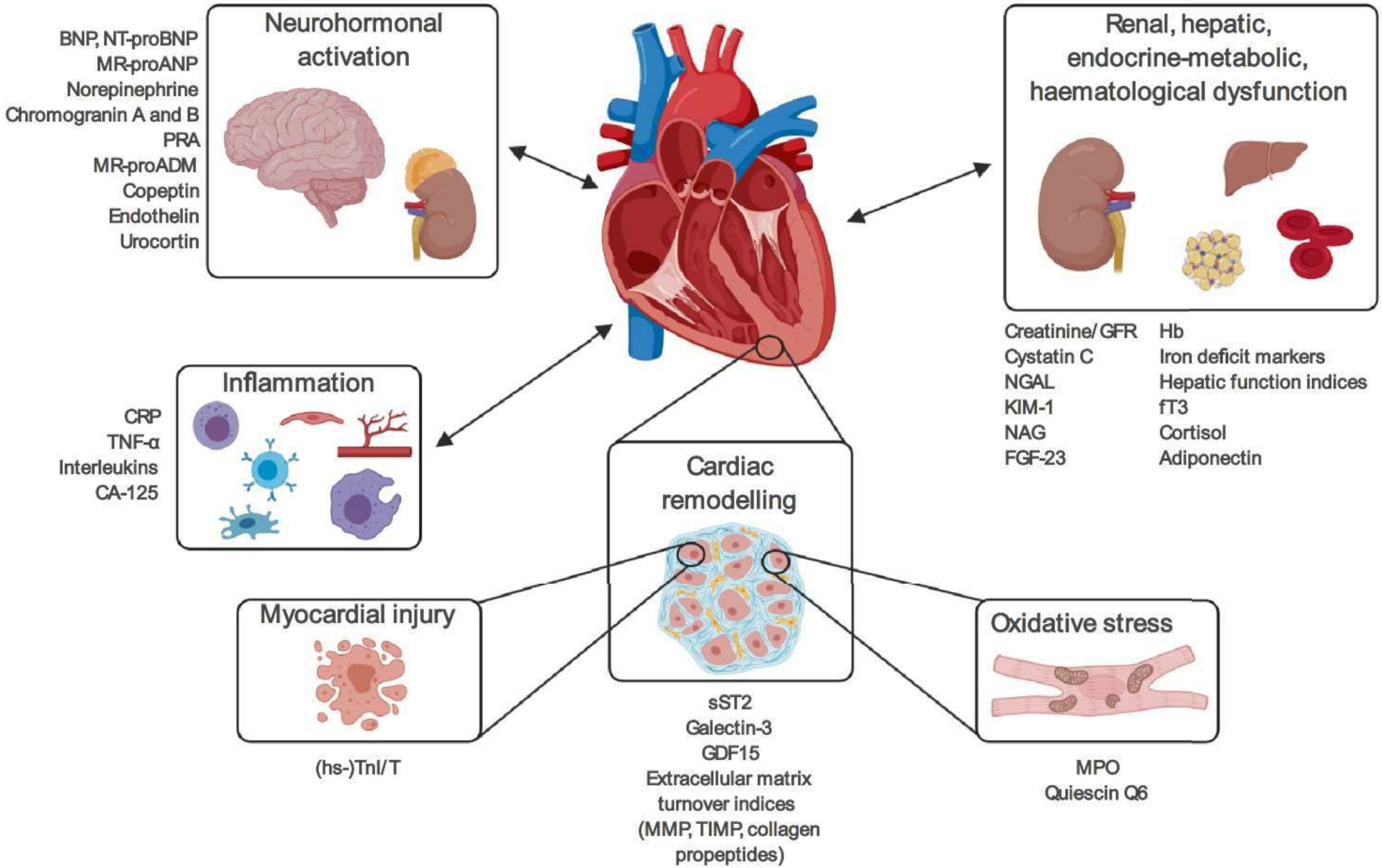
What is a biomarker?

Definition:
In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a **biomarker** is a measurable indicator of a **biological state**, **pathological process**, or **response to a therapeutic intervention**.

Historical Perspective: The first biomarker in HF

- **Biomarker testing in heart failure dates back to the 1950s**, when **Braunwald et al.** used an early **C-reactive protein (CRP)** assay to analyze serum samples from patients with acute heart failure (Elster et al., 1956).
- Although CRP was the **first biomarker associated with HF**, it is a **non-specific marker of inflammation** and not widely used for diagnosis today.




BNP, NT-proBNP
MR-proANP
Norepinephrine
Chromogranin A and B
PRA
MR-proADM
Copeptin
Endothelin
Urocortin
Neurohormonal activation
Renal, hepatic, endocrine-metabolic, haematological dysfunction
Creatinine/ GFR
Cystatin C
NGAL
KIM-1
NAG
FGF-23
Hb
Iron deficit markers
Hepatic function indices
fT3
Cortisol
Adiponectin
Inflammation
CRP
TNF-α
Interleukins
CA-125
Cardiac remodelling
sST2
Galectin-3
GDF15
Extracellular matrix turnover indices (MMP, TIMP, collagen propeptides)
Myocardial injury
(hs-)TnI/T
Oxidative stress
MPO
Quiescin Q6

Why Do We Need Biomarkers in HF?

- Biomarkers are **non-invasive**, **cost-effective**, and **easily accessible** tools.
- They reflect different aspects of HF **pathophysiology** and are essential in complementing clinical assessment.

Main Roles of Biomarkers in HF

- **Diagnosis**
- **Risk stratification**
- **Prognosis assessment**
- **Monitoring response to therapy**

- ESC 2023 quote:

“Biomarkers are essential for the diagnosis and management of HF.”

Soluble suppression of tumourigenicity-2 (ST-2)

- Shown to be associated with adverse outcomes in HF and predict mortality risk
- It is also known as interleukin-1 receptor-like 1, and is a member of the interleukin-1 receptor family.
- In the **PRIDE study** ST2 values >0.20 ng/ml had an increased risk of death at 1 year.

[1]Baggish AL, Cameron R, Anwaruddin S, Chen AA, Krauser DG, Tung R, Januzzi JL Jr. Crit Pathw Cardiol. 2004 Dec;3(4):171-6. doi.10.1097/01.hpc.0000145817.68289.a2. PMID: 18340169.

Galectin - 3

- Secreted by macrophages, causes cardiac fibrosis by proliferation of fibroblasts.
- Also regulates inflammation, immunity & cancer, & can act as a surrogate marker of cardiac remodeling and the fibrosis.
- Not useful in diagnosis, but strong prognostic value.
- In PROVE-ITTIMI 22 study[1], higher galectin-3 levels correlated with the development of heart failure.
- Similarly, in the Coordinating Study Evaluating Outcomes Of Advising And Counselling In Heart Failure (COACH) trial[2] ,higher levels increased the risk of death or rehospitalisation over 18 months.
- Its value also correlated with inflammatory markers such as CRP, VEGF and IL-6.

1Giraldez RR, Braunwald E. J Am Coll Cardiol. 2008 Sep 9;52(11):914-20. doi: 10.1016/j.jacc.2008.05.046. PMID: 18772061.
2Jaarsma T, van der Wal MH, Arch Intern Med. 2008 Feb 11;168(3):316-24. doi: 10.1001/archinternmed.2007.83. PMID: 18268174.

Troponins

- Often elevated in patients with HF
- Not specific for making a diagnosis
- Only represent myocardial injury and
- Increased in any condition that puts increased stress on the heart muscle
- High baseline troponin corresponded to a worse prognosis with an OR of 2.5 for death within a year.
- Serial measurements during hospitalisation for acute HF can risk stratify patients for 90-day mortality and readmission.
- Another study showed that an elevated hsTn as well as a >20% increase in the value was associated with increased mortality.
- The prognostic value is enhanced when combined with natriuretic peptides

Natriuretic peptides: MR-proANP

- MR-proANP was studied in the **Biomarkers In Acute Heart Failure (BACH) study**
  - In those presenting to the emergency department with dyspnoea, a MR-proANP level > 120 pmol/l found to be noninferior to BNP at the 100 pg/ml cut point in the diagnosis of acute heart failure.

- More useful in
  - obesity,
  - old age,
  - renal dysfunction or
  - 'grey zone' values,

- MR-proANP added value when used in combination with each biomarker.

- Thus it has been suggested that the addition of MR-proANP with other natriuretic peptides adds to diagnostic accuracy

Maisel A, Mueller C, Nowak RM, Peacock WF, Ponikowski P, J Am Coll Cardiol. 2011 Aug 30;58(10):1057-67. doi: 10.1016/j.jacc.2011.06.006. PMID: 21867843.

Natriuretic peptides

Breathing Not Properly **(BNP)** Study – Key highlights

- first major trials studying the role of natriuretic peptides in the emergency for diagnosis of HF
- 1,586 patients presenting to the emergency with acute breathlessness
- clinically diagnosed HF had higher BNP levels compared to without heart failure (mean 675 ± 450 pg/ml versus 110 ± 225 pg/ml; p=0.001)
- A cut-off BNP value of 100 pg/ml had sn= 90% and sp= 76%.
- In addition, BNP was more accurate (83%) than either the National Health and Nutrition Examination Survey criteria (67%) or the Framingham criteria (73%)

Maisel AS, Krishnaswamy P, Nowak RM, et al., **N Engl J Med.** 2002;347(3):161-167.

Natriuretic peptides

- **ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study[1]**
  - NT-proBNP in the diagnosis of acutely decompensated heart
  - had a high sensitivity for the diagnosis of heart failure

- **International Collaborative Of NT-proBNP (ICON) study[2]**
  - examined NT-proBNP in 1256 acutely dyspnoeic patients.
  - ADHF patients had higher NT-proBNP concentrations than those without heart failure (4,639 pg/ml versus 108 pg/ml; $p<0.001$)
  - symptom severity correlated with NT-proBNP concentrations
  - investigators found the best approach for use of NT-proBNP was through use of age-stratified cut-off points

[1]Baggish AL, Cameron R, Anwaruddin S, Chen AA, Krauser DG, Tung R, Januzzi JL Jr. Crit Pathw Cardiol. 2004 Dec;3(4):171-6. doi.10.1097/01.hpc.0000145817.68289.a2. PMID: 18340169.

2 Gaggin HK, Chen-Tournoux AA, Christenson RH, Januzzi JL. Am Heart J. 2017 Oct;192:26-37. doi: 10.1016/j.ahj.2017.07.002. Epub 2017 Jul 8. PMID: 28938961.

What Do the Guidelines Say?

ESC Guidelines: "Natriuretic peptides (BNP or NT- pro BNP) should be measured in all patients with suspected HF to help in the diagnosis.“
ACC/AHA “Measure BNP or NT-pro BNP to support clinical diagnosis of HF, assess prognosis, and guide therapy.”

Biomarker Group	Primary Clinical Use(s)	Recommendation Strength
Natriuretic Peptides	***Diagnosis / Prognosis/ Monitoring***	Guideline-recommended (Class I)
Cardiac Troponins	Prognosis / Risk stratification	Widely recommended
ST2	Prognosis/ Fibrosis indication	Optional (Class IIb)
Galectin-3	Prognosis (limited) / Fibrosis	Optional / Limited
Cystatin C, NGAL	Cardiorenal assessment / Prognosis	Limited clinical use
CRP, IL-6	Inflammation (non-specific) / Research use	Not routinely recommended

Stages of heart failure: Stage B (pre-HF)

Stages in the development and progression of heart failure

Stage A: At-risk for heart failure

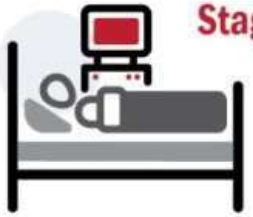
Patients at risk for HF but without current or prior symptoms or signs of HF and without structural or biomarkers evidence of heart disease.

Stage B: Pre–heart failure

Patients without current or prior symptoms or signs of HF, but evidence of structural heart disease or abnormal cardiac function, or elevated natriuretic peptide levels.

Stage C: Heart failure

Patients with current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality.



Stage D: Advanced heart failure

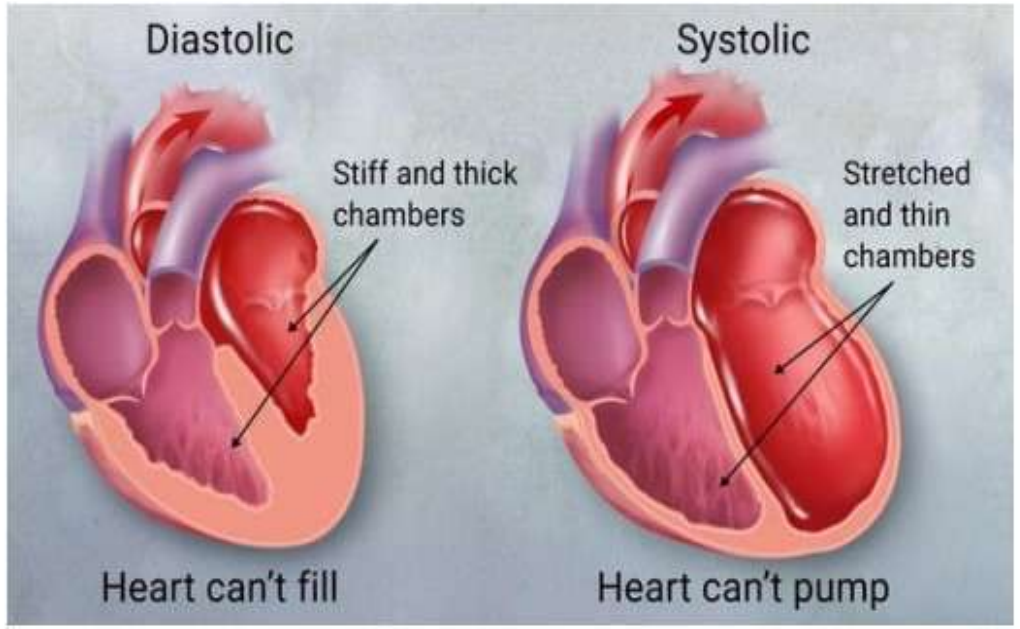
Patients with severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite guideline-directed management and therapy (GDMT), refractory or intolerant to GDMT, requiring advanced therapies such as consideration for transplant, mechanical circulatory support, or palliative care.

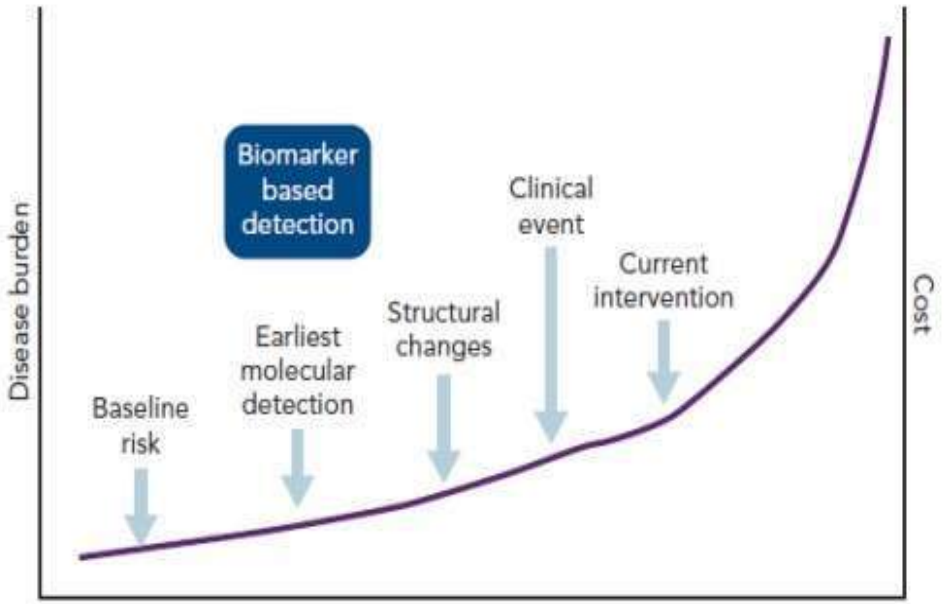
SOURCE: J Card Fail. 2021 Mar 1; doi:10.1016/j.cardfail.2021.01.022

"The presence of structural heart disease and/or congestion, as evidenced by elevated filling pressures or abnormal natriuretic peptide or high sensitivity cardiac troponin, is a key indicator of heart failure (HF)"

Several medications can help reduce the risk of heart failure progression from Stage B to Stage C, including RAAS inhibitors, beta-blockers, SGLT2 inhibitors, and GLP-1 receptor agonists (GLP-1RAs).

Stage B heart failure and biomarkers for early detection



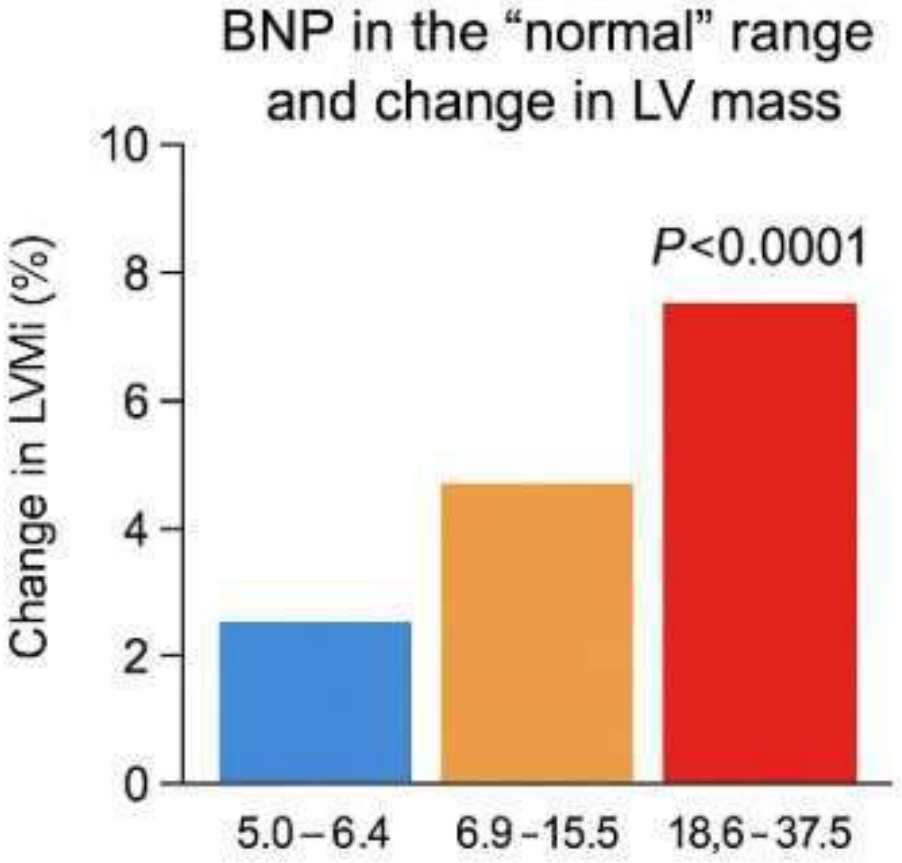


NP in the “normal range” can predict change in LV mass

An Increased B-Type Natriuretic Peptide in the Absence of a Cardiac Abnormality Identifies Those Whose Left Ventricular Mass Will Increase Over Time

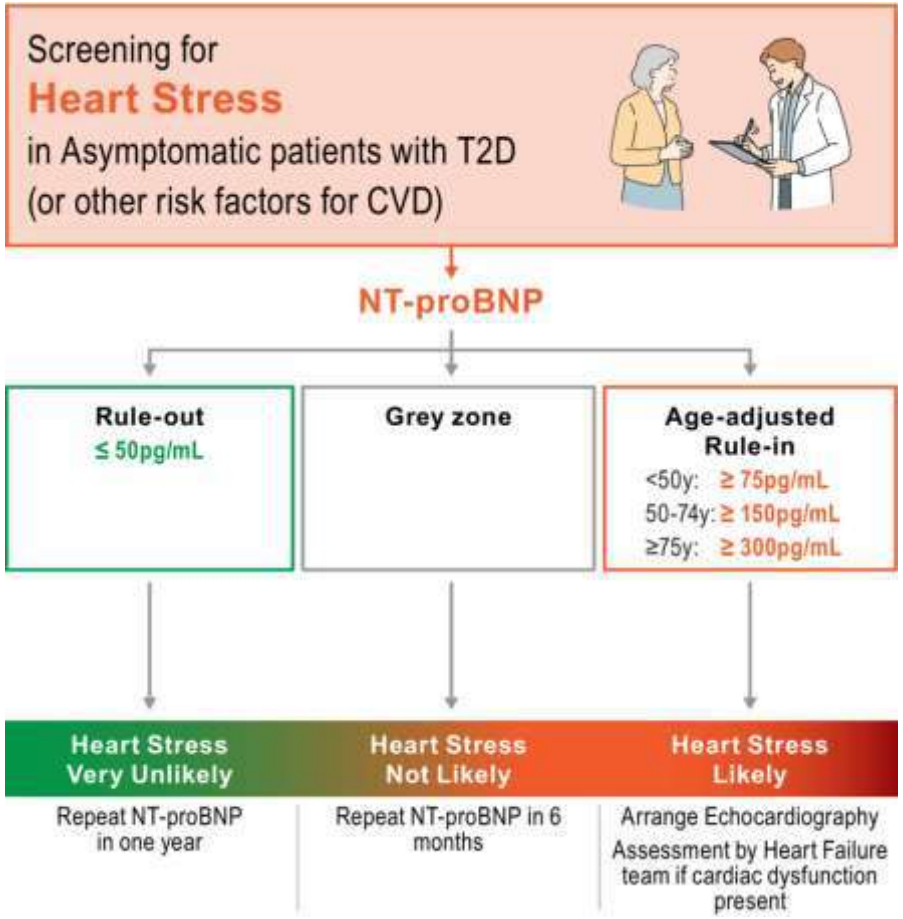
M. Adnan Nadir, MD, Stephen Gandy, PhD, Sheila Ireland, SRN, Tom MacDonald, MD, Ellie Dow, PhD, Graeme Houston, MD, Chim Lang, MD, Allan Struthers, MD

- Patients were ≥50 years of age, without incident or prevalent CV disease, stable on therapy and with control of risk factors
- BNP was checked at baseline and a cardiac MRI was performed at baseline and 3 years
- Higher BNP values in the “normal” range at baseline predicted increase in LVMi at 3 years



Nadir MA, Gandy S, Ireland S, MacDonald T, Dow E, Houston G, Lang C, Struthers A. JACC Heart Fail. 2015 Jan;3(1):87-93

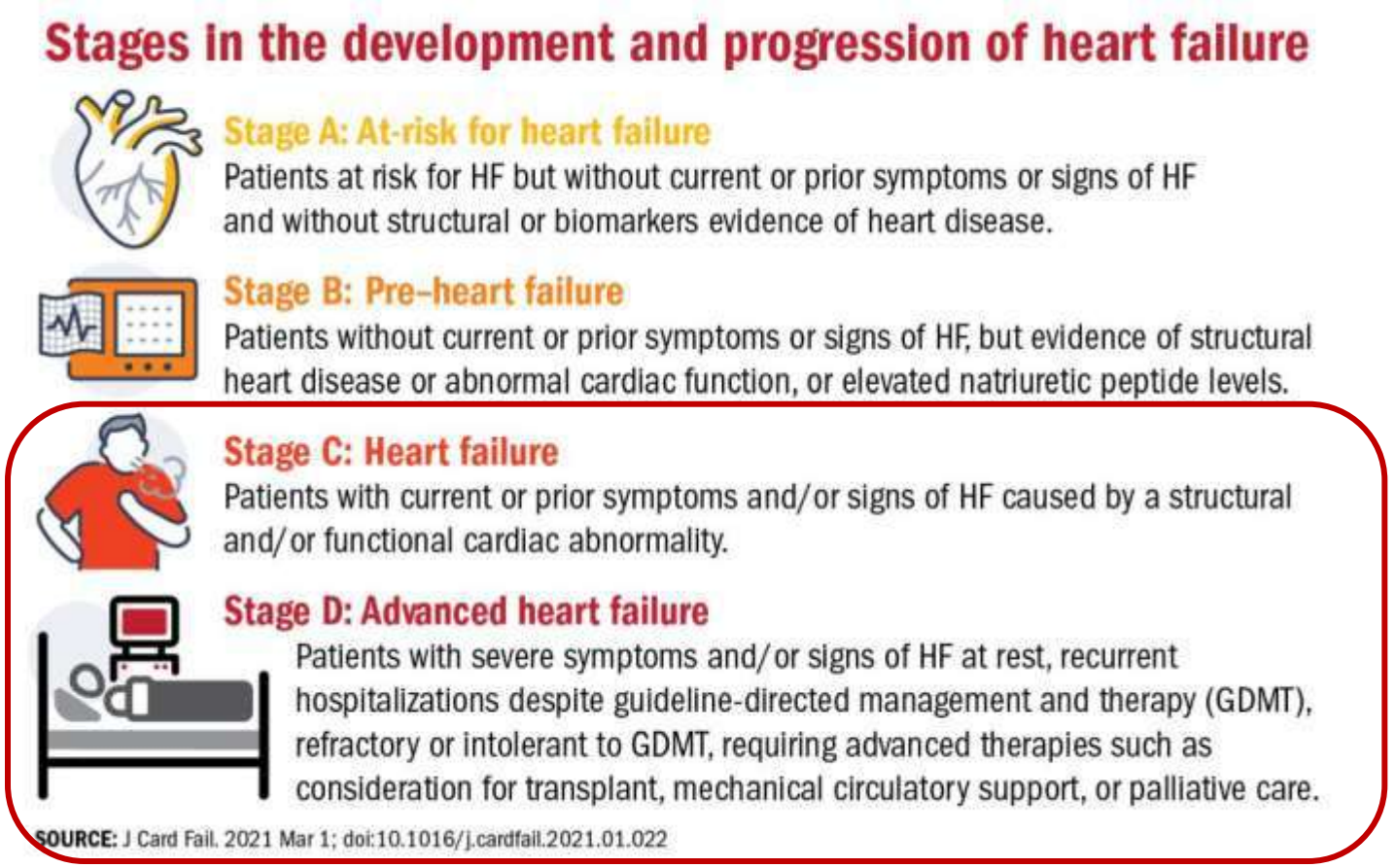
The inidividualized approach to detecting SBHF



- A single NT-proBNP cut-point of 125 pg/mL can be useful in assessing heart failure
- Age-stratified cut-offs also endorsed by the European Society of Cardiology (ESC)
- Very low values may exclude future heart failure events
- The magnitude of elevation is directly proportional to the risk of imminent events
- The American Diabetes Association (ADA) recommends yearly NT-proBNP measurement in chronic diabetes mellitus

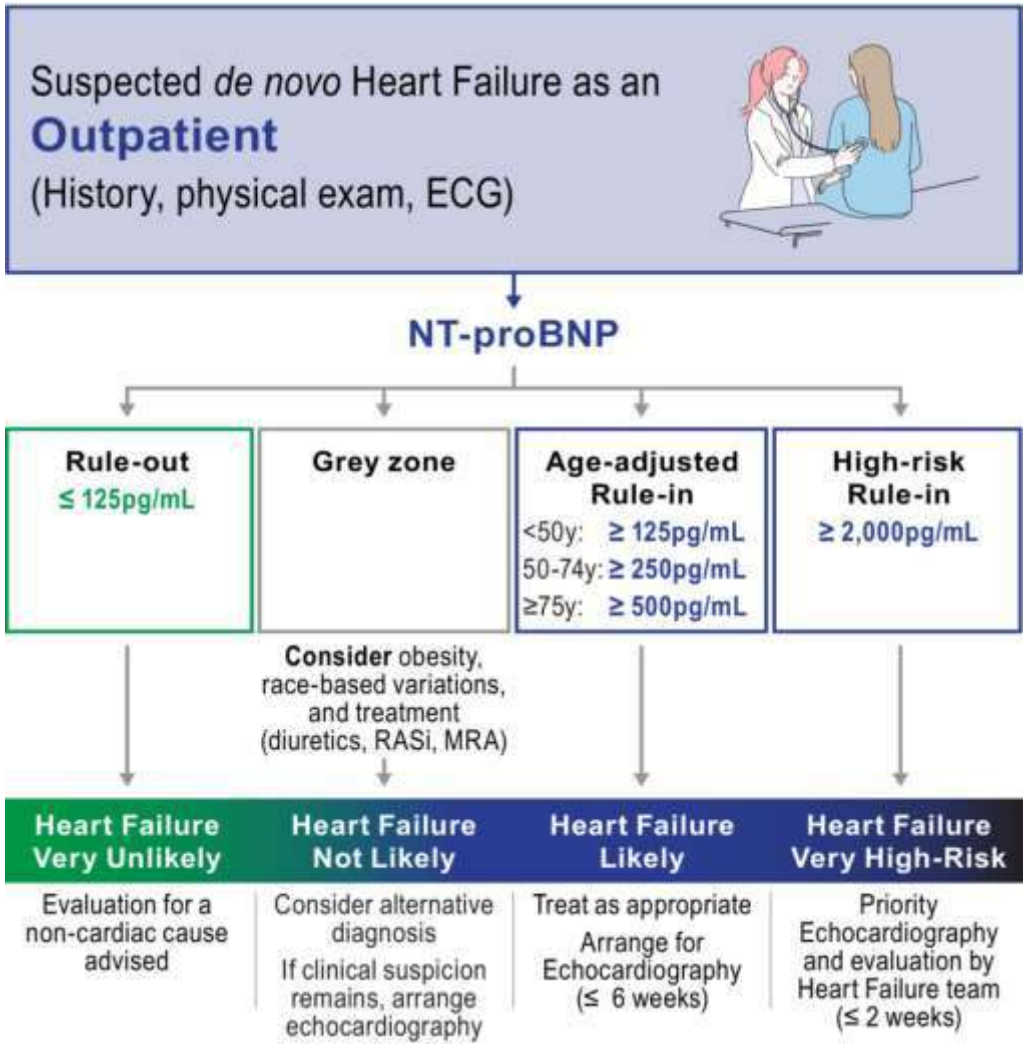
Bayes-Genis A, Docherty KF, Petrie MC, Januzzi JL, Mueller C, Anderson L, Bozkurt B, Butler J, Chioncel O, Cleland JGF, Christodorescu R, Del Prato S, Gustafsson F, Lam CSP, Moura B, Pop-Busui R, Seferovic P, Volterrani M, Vaduganathan M, Metra M, Rosano G. Eur J Heart Fail. 2023 Nov;25(11):1891-1898.

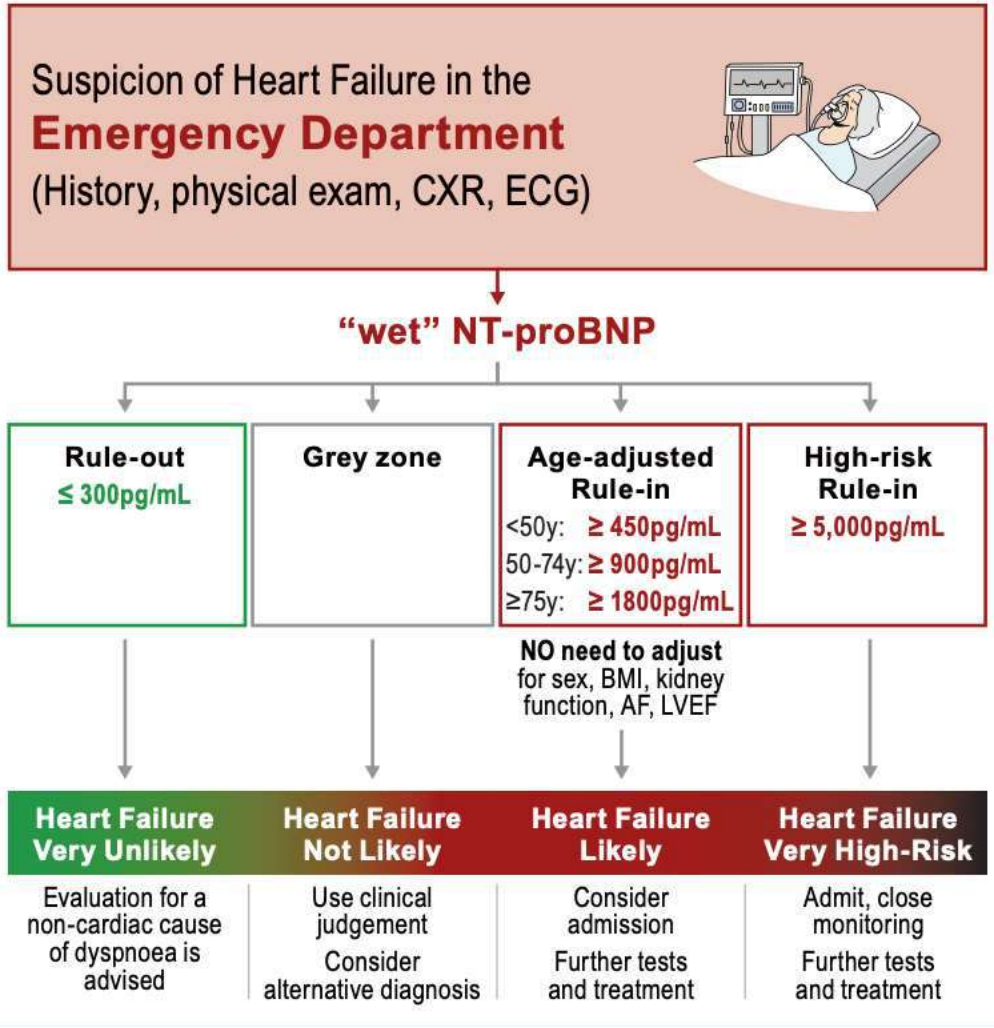
Stages of heart failure: Stages C/D (symptomatic)



Use of natriuretic peptides has completely changed the diagnostic and prognostic landscape in symptomatic heart failure

ESC Consensus on NT-proBNP use





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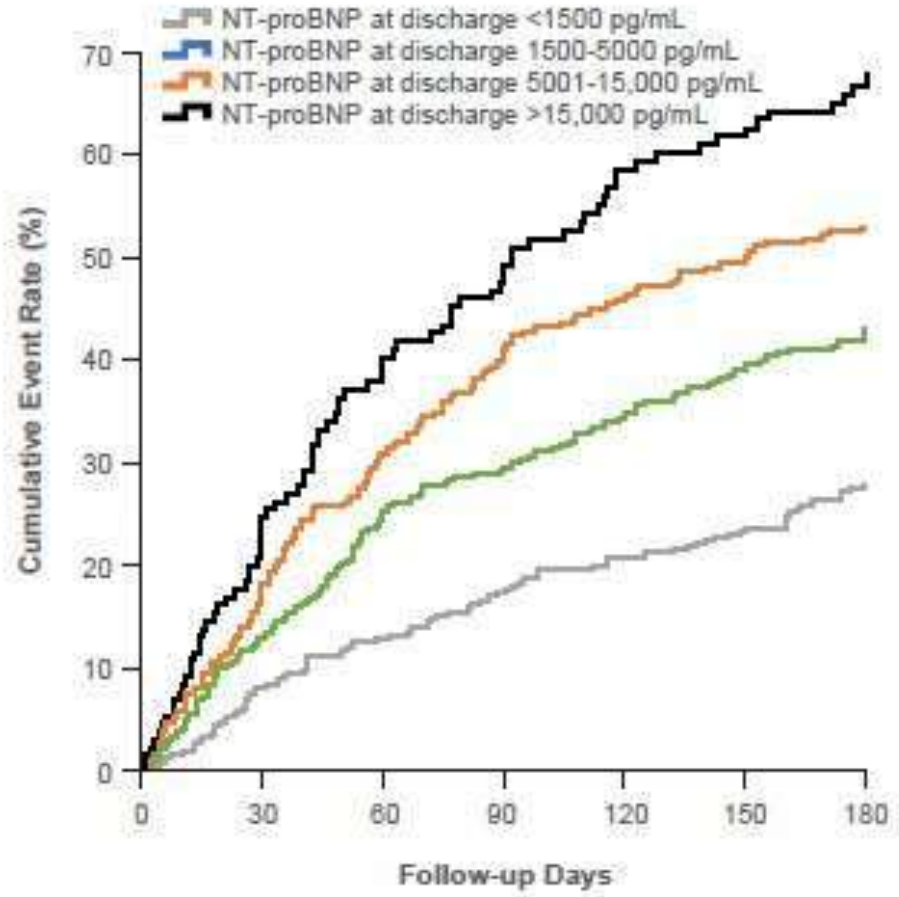
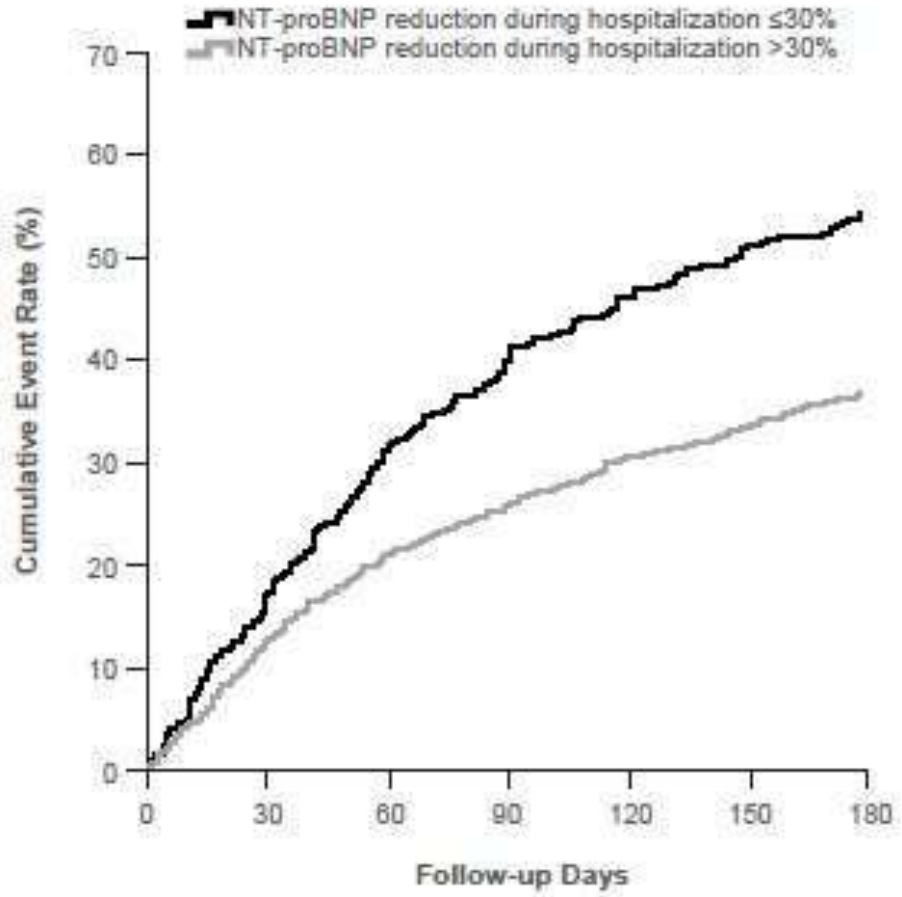
NPs to guide pre-discharge risk decision making





Meta-ananlysis of patients (N = 1301) hospitalized for acute decompensated heart failure from 7 prospective cohort studies. Salah K, Kok WE, Eurlings LW, Bettencourt P, Pimenta JM, Metra M, Bayes-Genis A, Verdiani V, Bettari L, Lazzarini V, Damman P, Tijssen JG, Pinto YM. Heart. 2014 Jan;100(2):115-25.

NPs to guide pre-discharge risk decision making

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 not available discharge NT-proBNP <4000/BNP <350 pg/mL is desirable
  - ✓Non-falling or rising values identify a patient at imminent risk for hospitalization

Roles of NP testing in the outpatient Stage C setting

- Medication titration
- Longitudinal monitoring

Biomarkers are bridge from hospital to home

What do the guidelines say?

- Both ACC & ESC give measuring natriuretic peptides for the diagnosis of heart failure a class 1A recommendation.

- The European guidelines recommended
  - In non-acute setting cut-off values are 35 pg/ml for BNP and 125 pg/ml for NT-proBNP.
  - In the acute setting, the cut-off values are 100 pg/ml for BNP and 300 pg/ml for NT-proBNP

- The NPV are similar and high at 0.94–0.98 in both the acute and non-acute settings but the PPV are low.

- It is suggested that use of natriuretic peptides are mainly for ruling out a diagnosis of HF rather than establishing it

Heart Failure with Preserved Ejection Fraction (HFpEF)

- All the biomarkers as in HF with reduced EF are also increased in HFpEF.

- **COACH study**, higher levels of galectin-3 were associated with higher rates of rehospitalisation & death in HFpEF but not HFrEF patients

- Insulin growth factor–binding protein-7

- MMP-2, MMP-8, tissue inhibitor of MMP-4, & procollagen-III N-terminal peptide

Jaarsma T, van der Wal MH, Arch Intern Med. 2008 Feb 11;168(3):316-24. doi: 10.1001/archinternmed.2007.83. PMID: 18268174.

PARADIGM-HF Trial

Population: 8,442 HFrEF patients
Intervention: Sacubitril/valsartan vs Enalapril
Key Findings:

- ↓ 20% in CV death or HF hospitalization *(p<0.001)*
- ↓ All-cause mortality: 17.0% vs 19.8%
- More hypotension, less renal dysfunction with sacubitril/valsartan

Biomarker Note:

- NT-proBNP levels **were used to confirm eligibility** (BNP ≤400 or NT-proBNP ≤1600 pg/mL at screening)
- NT-proBNP **significantly decreased** with sacubitril/valsartan → **associated with reverse remodeling & outcome improvement**

McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11;371(11):993-1004. doi: 10.1056/NEJMoa1409077. Epub 2014 Aug 30. PMID: 25176015.

PARAGON-HF Trial

Population: 4,822 HFpEF patients
Intervention: Sacubitril/valsartan vs Valsartan
Key Findings:

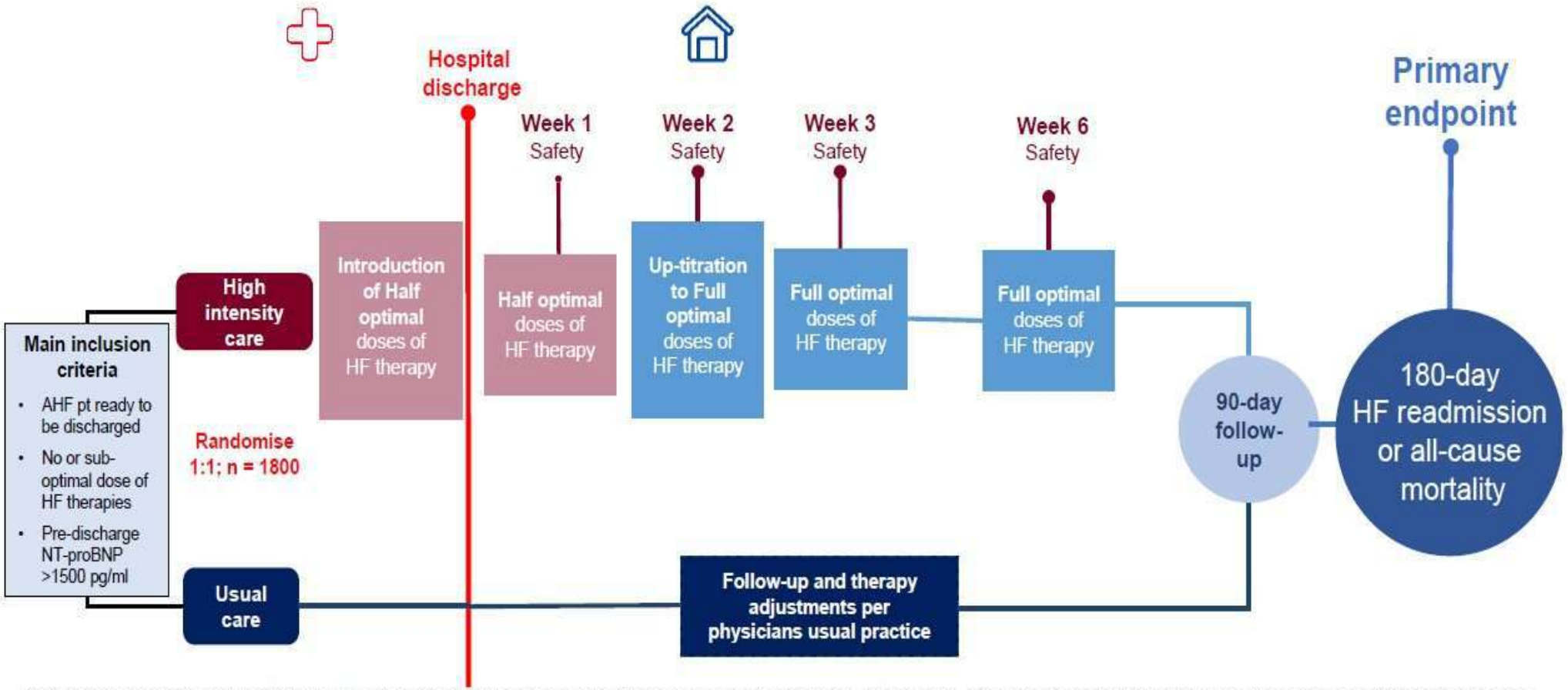
- ↓ 13% in total HF hospitalizations & CV death *(not statistically significant, p=0.059)*
- Greater benefit in women and EF <57% subgroup
- Similar safety profile as PARADIGM-HF

Biomarker Note:

- NT-proBNP levels **used to confirm HFpEF diagnosis**
- NT-proBNP tracked over time, but **no significant difference** between groups in change patterns

Gronda E, Vanoli E, Iacoviello M. The PARAGON-HF trial: the sacubitril/valsartan in heart failure with preserved ejection fraction. Eur Heart J Suppl. 2020 Nov 18;22(Suppl L):L77-L81. doi: 10.1093/eurheartj/suaa140. PMID: 33727901; PMCID: PMC7944492.

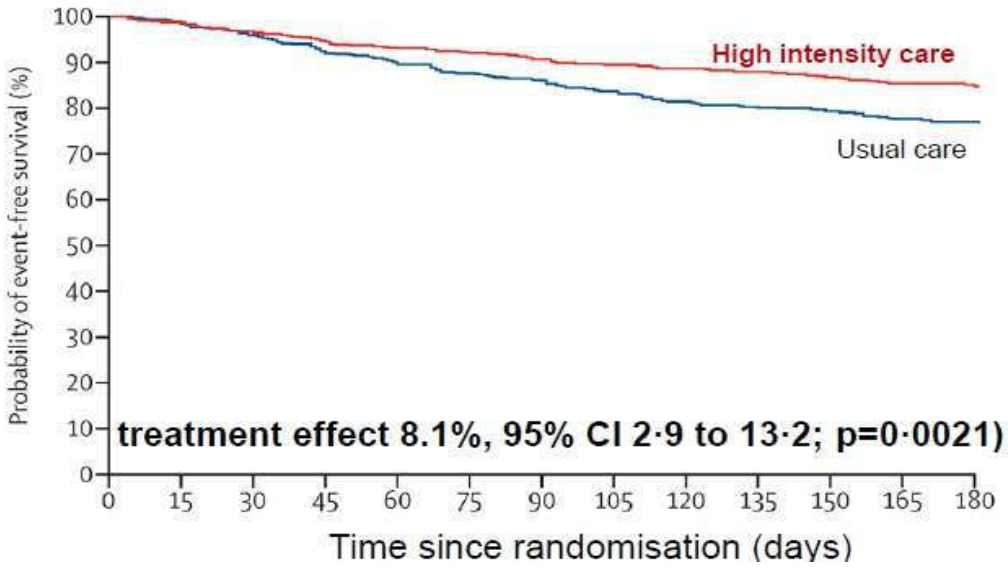
STRONG-HF Study design



Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, Metra M, Ponikowski P, Sliwa K, Voors AA, Edwards C, Novosadova M, Takagi K, Damasceno A, Saidu H, Gayat E, Pang PS, Celutkiene J, Cotter G. Lancet. 2022 Dec 3;400(10367):1938-1952.

STRONG-HF: efficacy outcomes

Primary endpoint:
180-Day readmission for heart failure or all-cause death



Main secondary endpoint: Patient's QoL

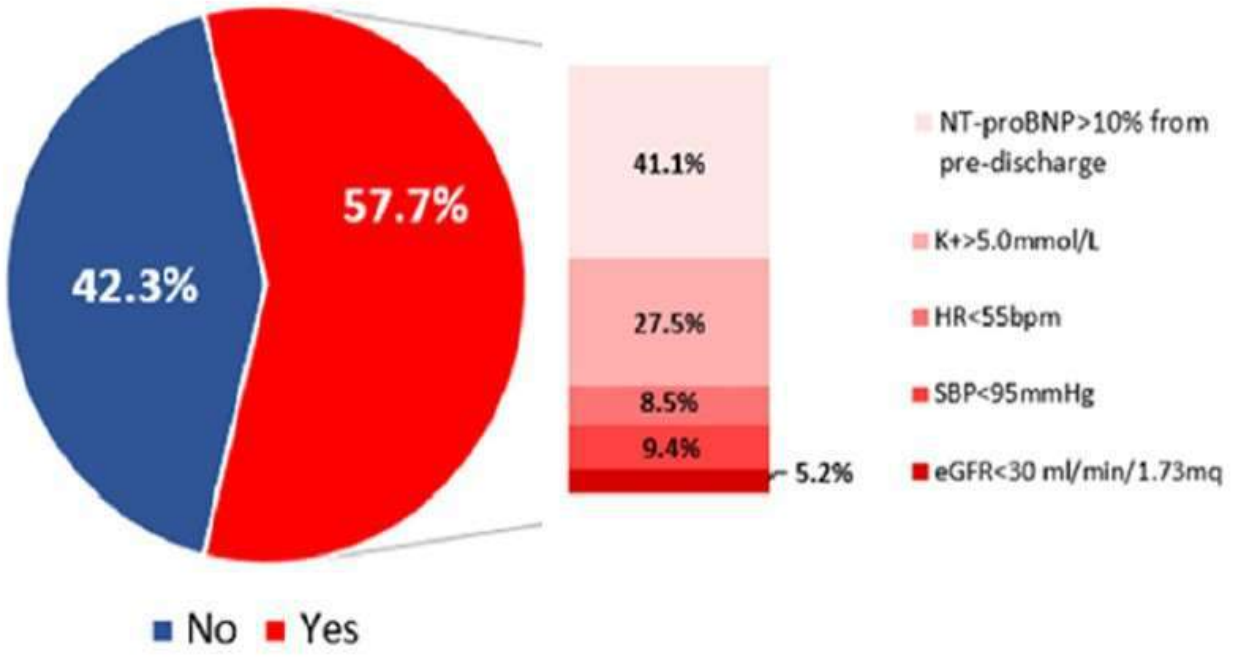
High intensity	Usual	Treatment effect	P value
10.7 (0.9)	7.2 (0.9)	3.5 (1.7 to 5.2)	< 0.0001

Improvement in all parameters of congestion at Day 90

Parameter	Adjusted Treatment Effect (95% CI)	P-value
Weight, kg	-1.36 (-1.91, 0.80)	<0.0001
Respiratory Rate	-0.4 (-0.7, -0.1)	0.0028
Peripheral edema	1.30 (1.17, 1.44)	0.0002
JVP, cm	1.13 (1.05, 1.21)	0.015
NYHA, class	1.36 (1.22, 1.53)	<0.0001
NT-proBNP, pg/mL*	0.77 (0.67, 0.89)	0.0003

Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, Metra M, Ponikowski P, Sliwa K, Voors AA, Edwards C, Novosadova M, Takagi K, Damasceno A, Saidu H, Gayat E, Pang PS, Celutkiene J, Cotter G. Lancet. 2022 Dec 3;400(10367):1938-1952.

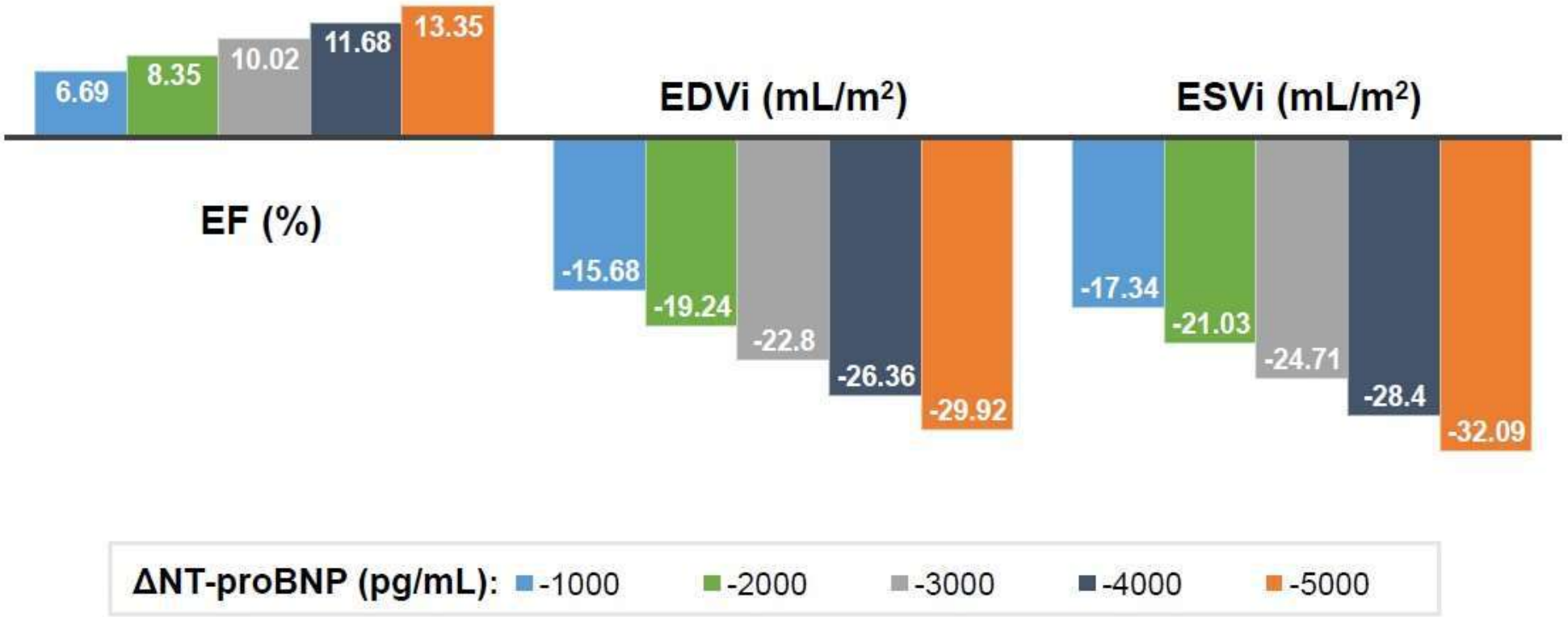
Safety indicators during medication titration: STRONG - HF



- **>50% of study participants had abnormal safety indicators during treatment**
- **NT-proBNP, potassium, or eGFR accounted for nearly 75% of the indicators**

Tomasoni D, et al. J Card Fail. 2024 Apr;30(4):525-537.

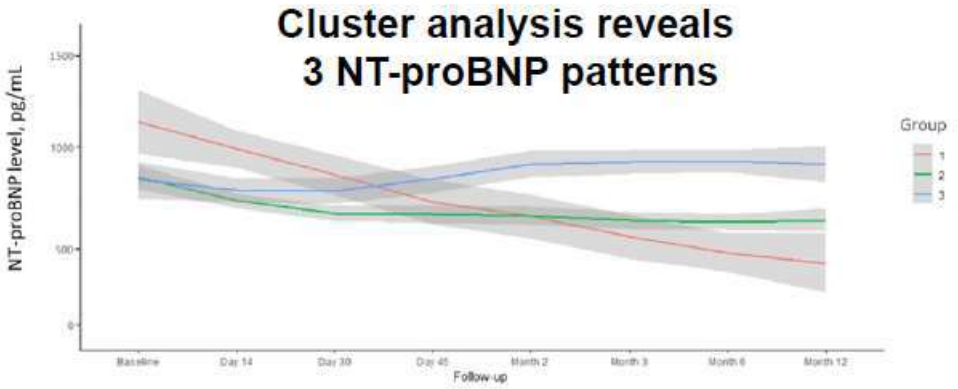
Change in LV structure and function at 1 year by NT – proBNP reduction



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.

Understanding NT – pro BNP trends

- One can calculate the “area under the curve” for serial measurements of NT proBNP[1]
  - **Low starting values:** reverse remodeling is the same regardless of subsequent AUC
  - **Moderate or high starting values:** lowering the AUC is associated with greater reverse cardiac remodeling and better health status[2]
    - Rapid and sustained: better
    - Rapid, non-sustained: less good
    - Non-response: worst



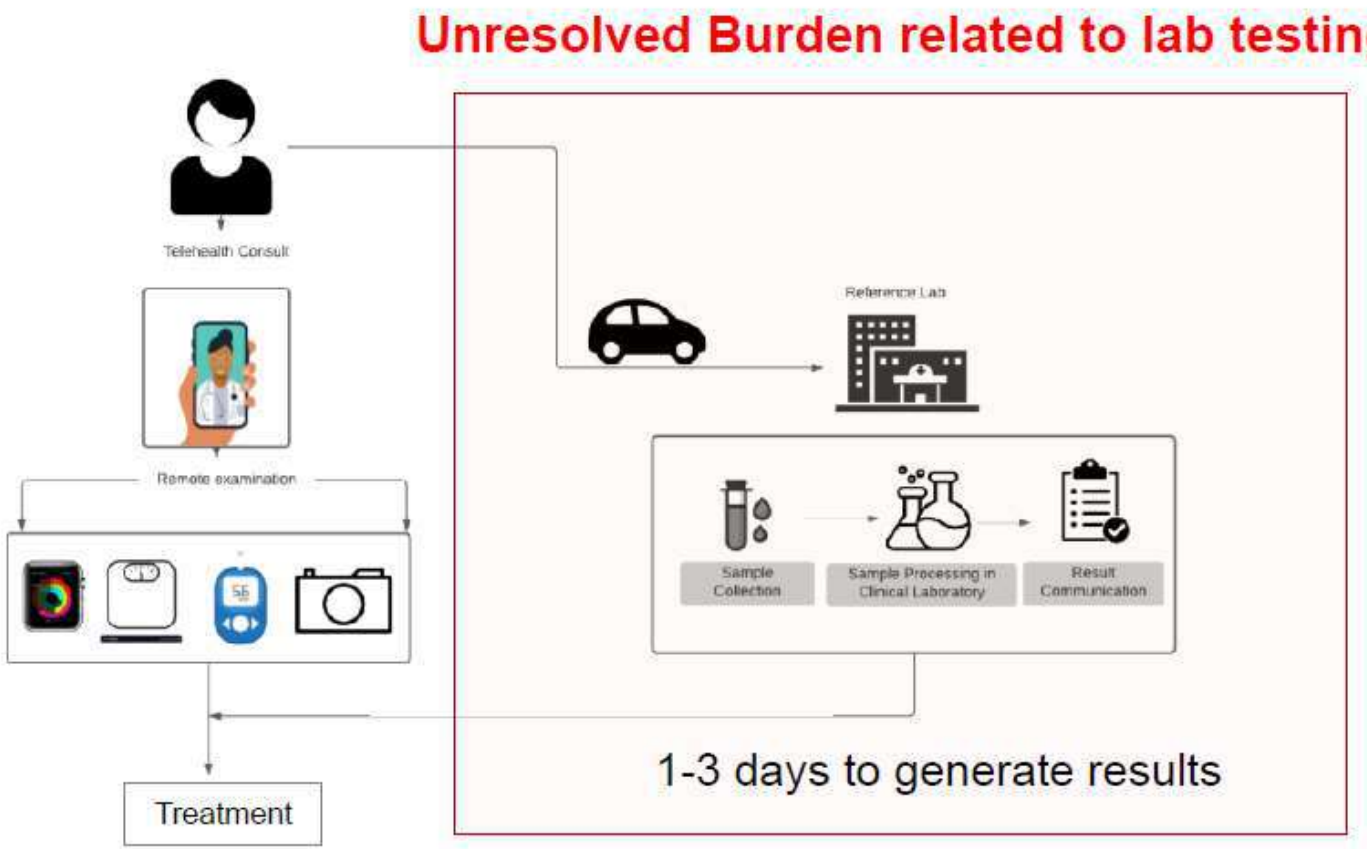
- Group 1 (rapid response, lowest AUC): Largest rise in LVEF, Greatest KCCQ increase
- Group 2 (transient response, intermed AUC): Moderate LVEF and KCCQ improvement
- Group 3: (non-responders, highest AUC): least LVEF improvement, least KCCQ rise

1Mohebi R, Liu Y, Myhre PL, Butler J, Felker GM, Ward JH, Prescott MF, Piña IL, Solomon SD, Januzzi JL Jr. ESC Heart Failure, 2023;10(5): 3133-40.
2MohebiRLiuYMyhrePLFelkerGMPrescottMFPiñaILButlerJWardJHSolomonSDJanuzziJLJrJACCHeartFail2023

Operationalizing NP monitoring to enhance clinical decision-making in chronic HF

- Hospital to home: In recently decompensated patients, measure 1– 2 weeks after discharge (office or home).
- Outpatients: measure every 3 months
  - Facilitates GDMT decision making (removal of diuretic after GDMT)
  - **Stable concentrations** <1000 pg/mL (NT-proBNP) or <100 pg/mL (BNP): imaging and other testing may be reasonably 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” NP (amyloidosis).

Challenges with lab access

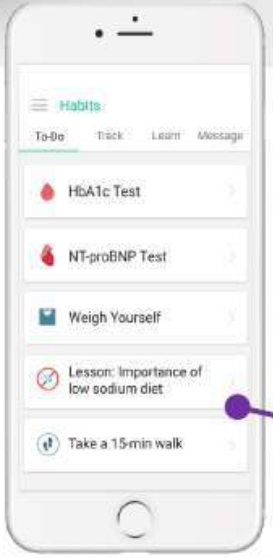


Access issues

Physical Limitation & Compliance: Patients with chronic illnesses have higher prevalence of frailty and mobility disability. These patients require more logistical help to coordinate a trip to the lab. Test compliance= ~10-20%

Social Inequality: Strong association between low socioeconomic status, unequal access to care, and higher incidence and prevalence and more complications related to chronic illness

Home NT-proBNP, K+ , creatinine fingerstick testing: the Jana Care Aina*



RX, Home Based Blood Testing: NT-proBNP, K, Creat

Digital Management for Care Coordination

Management of Comorbidities

Reduces Health Disparity

AINA: Lay-use. Smartphone-based analytical platform.
- Bluetooth/NFC Enabled
- Multiplex capability (optical: Visible and fluorescence)
- Digitally Connected & Designed for lay-user

Capillary Blood: Rx, physician supervised, lab quality home testing
- ~30uL of whole, unprocessed blood
- No sample processing by patient or shipping logistics
- Quantitative test results

Cost Competitive: Ensures flexibility and accessibility
- <$100/device
- Inexpensive test strips

Telemedicine: Results digitally sent to clinician dashboard
- Application can be customizable for third-party platform or database

Home biomarker testing

Biomarkers Measured

- **NT-proBNP** – for monitoring heart failure status
- **Potassium (K^+)** – important for patients on RAAS inhibitors
- **Creatinine** – for assessing renal function

Clinical Purpose

- Detect early signs of decompensation in ambulatory HF patients
- Support remote patient monitoring and telemedicine programs
- Enhance safety during **transition from hospital to home**

Technology Highlights

•Connects to a smartphone for **real-time data sharing with healthcare providers**
•**AI-assisted data interpretation**
•Enables personalized care decisions outside the clinical setting

Clinical Context

•Studies like **GUIDE-HF** and **PARADIGM-HF** have shown that biomarker-guided therapy, particularly with **NT-proBNP**, improves outcomes in heart failure.
•Jana Care Aina operationalizes this strategy at the **point of care**, making frequent monitoring **practical, accessible, and scalable**.

What else is in the future for biomarkers in HF?

- Multi-biomarker panels: Combine markers of stress, injury, inflammation, and fibrosis for better risk stratification.
- AI & Big Data: Integrate biomarkers with clinical/imaging data to guide personalized treatment.
- Genomics & Proteomics: Discover novel biomarkers through high-throughput technologies.
- Home-based monitoring: Point-of-care tools (e.g., Jana Care Aina) enable early detection and remote therapy titration.
- Biomarker-guided therapy: Use serial NT-proBNP or hs-TnT to monitor response and adjust medications.

What to remember

- The natriuretic peptides have completely changed the landscape of HF diagnosis and prognosis for cost-effective care
- Future roles for the natriuretic peptides include earlier diagnosis and support of HF management
  - Ambulatory patients: diagnosis of Stage B HF allowing for early intervention
  - Acute HF: natriuretic peptide supported hospital discharge decision-making
  - Chronic HF: natriuretic peptide supported GDMT administration and longitudinal monitoring
- The next big change will come from introduction of home testing very soon
- AI-supported multimarker testing will shape the future

Protect your **HEART** — let **LOVE** be your strongest biomarker.

Thanks for attention!