AN OVERVIEW OF BNP AND NT-PROBNP

WHITEPAPER REPORT

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BECKMAN COULTER

CONTENTS

1. WHAT ARE BNP AND NT-PROBNP?

B-type natriuretic peptide (BNP) - is a **member of a class of hormones,** constituting the cardiac endocrine function, that regulates blood pressure:

- **BNP induces the body's defense mechanism to reduce retention of fluids, stimulating excretion of sodium by the kidneys.**

BNP is produced primarily by cells in the left ventricle of the heart. The main stimulus for BNP synthesis and secretion from cardiac myocytes is myocyte stretch. Therefore, **BNP is a simple and objective measure of cardiac function and can be used to diagnose Heart Failure** (Figure 1).

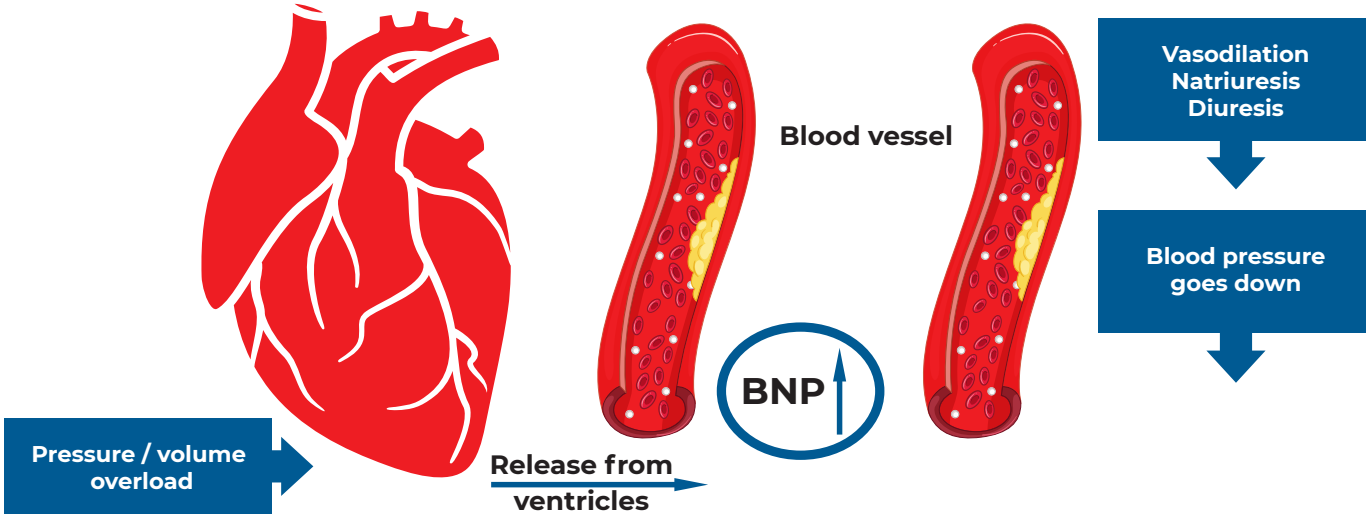
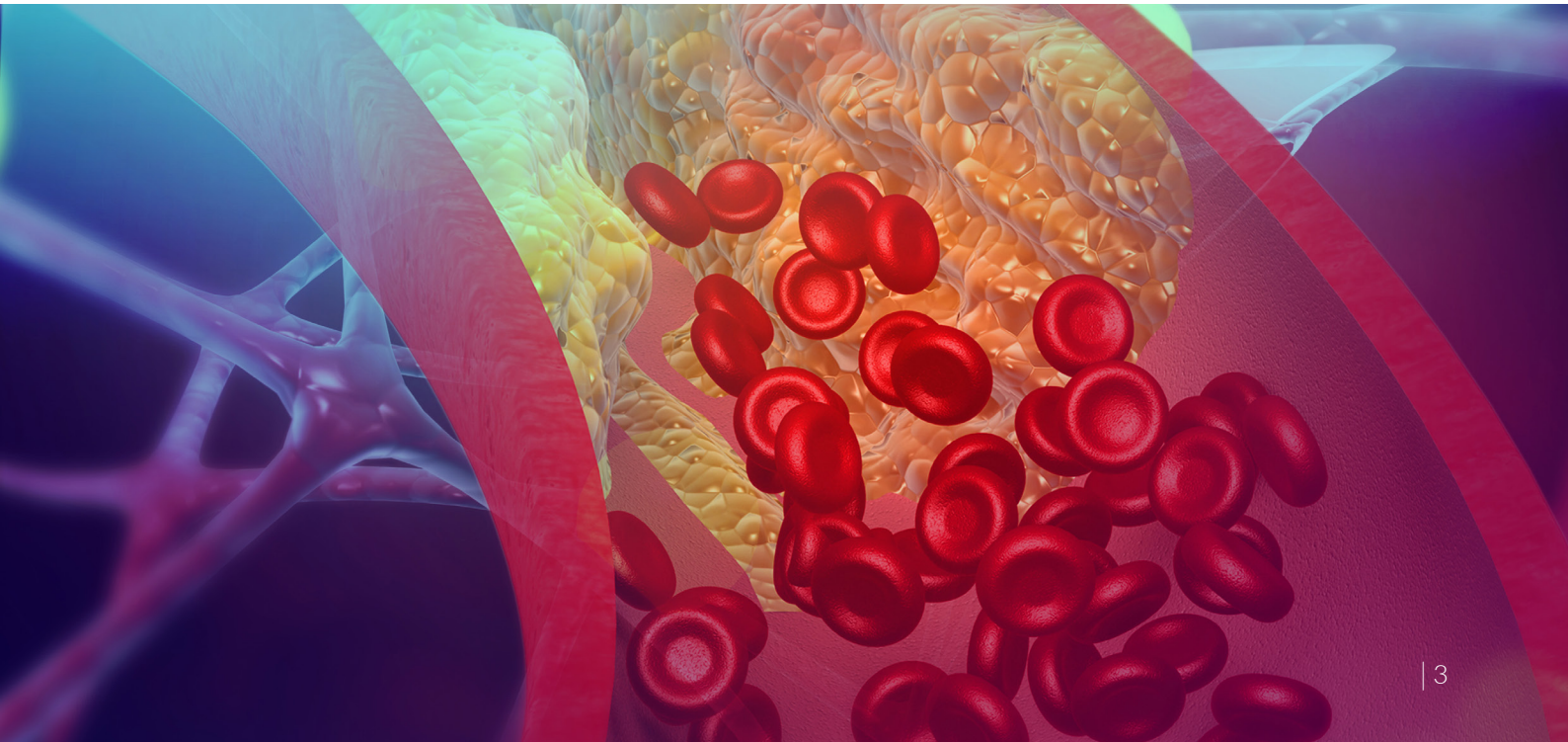


Figure 1. BNP secretion from the myocardium is stimulated by mechanical stress and/or neurohormonal stimulation.

The illustration is adopted from Semenov AG, Feygina EE. Standardization of BNP and NT-proBNP Immunoassays in Light of the Diverse and Complex Nature of Circulating BNP-Related Peptides. Adv Clin Chem. 2018[2] and https://www.gentian.com/products/nt-probnp-turbidimetric-assay



1.1. BNP AND NT-PROBNP CONVERSION

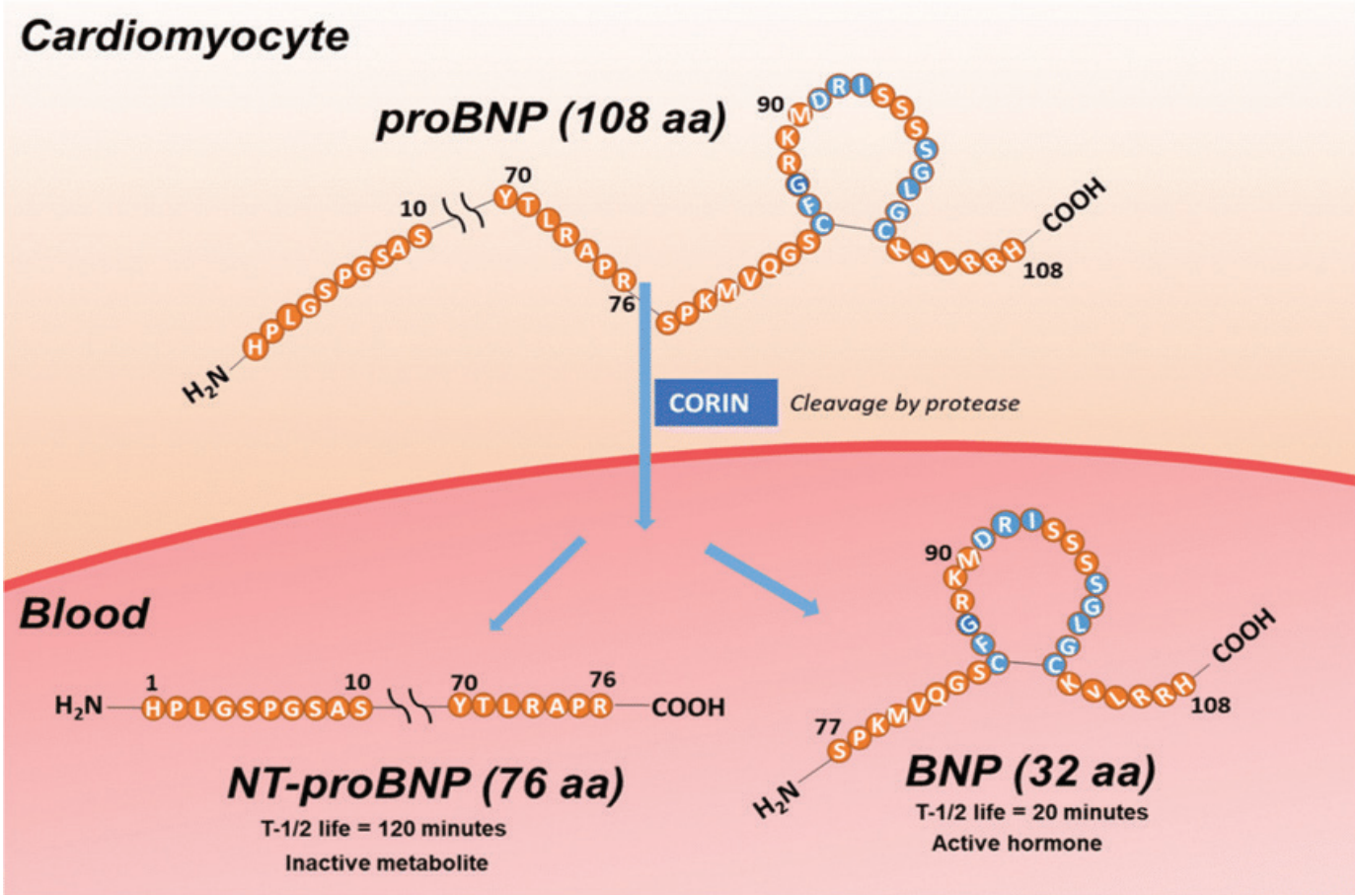
The ventricles of the heart synthesize pro-hormone of BNP (proBNP) that is cleaved and secreted in the blood in an equimolar ratio as:

- N-terminal proBNP (NT-proBNP), which is the **inactive form of the hormone** with half-life ~ 1-2 hours and
- BNP, which is the **active form of the hormone** with half-life ~ 20 minutes

by action of some cellular or circulating proteolytic enzymes (such as corin and furin) (Figure 2)[1].

NT-proBNP's 1-2 hour half-life means that it elevates sooner and higher due to its slower clearance and BNP more closely reflects the current condition of the patient with its 20 minute half-life.

Example: If a patient presents to the ED at 6:00am, BNP represents the patient's condition at around 4:00am to 5:00am and NT-proBNP represents their condition at around 8:00pm the night before.



Adopted from: *High-level production of N-terminal pro-brain natriuretic peptide, as a calibrant of heart failure diagnosis, in Escherichia coli June 2019 Applied Microbiology and Biotechnology 103(12); DOI:10.1007/s00253-019-09826-8*

Figure 2. Pathways of NT-proBNP and BNP synthesis from proBNP[3]

Plasma levels of the **active hormone BNP are directly related to peripheral hormonal response of the cardiac endocrine function** through the binding to **specific natriuretic peptides receptors** (NPR-A), which are present in all tissues of the body, including the central nervous system.

Active peptide BNP can stimulate the specific natriuretic receptor on renal tubular cells.

Natriuresis/diuresis and **blood pressure reduction are induced**.

1 AS A RESULT

- The specific measurement of the **active peptide BNP should be considered a direct index of cardiac endocrine system activity**[1]
- **NT-proBNP assay may not be a reliable index** of the biological (natriuretic) activity of cardiac endocrine system in severe heart failure because the concentration of less active peptides in patients with severe HF (such as NT-proBNP and proBNP) is greatly higher than that of the active peptide BNP[1]
- Due to a longer half-life, NT-proBNP represents an earlier condition of the patient in comparison to BNP

2. BNP AND NT-PROBNP RATIO IN DIFFERENT HEART CONDITIONS

Based on the PARADIGM- HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure):

The ratio of NT-proBNP to BNP ≈ 6.25:1

- The ratio of NT-proBNP to BNP varies considerably with age, renal function, and body mass index, although not with left ventricular ejection fraction
- The ratio of NT-proBNP to BNP in **heart failure** and **reduced ejection fraction differs between patients** with and without atrial fibrillation, and increases substantially with increasing age and decreasing renal function:
  - the NT-proBNP to BNP ratio was 8.03:1 in patients with Atrial Fibrillation (AF), compared with 5.75:1 in those not in AF
  - the NT-proBNP/BNP ratio in the oldest patients was ≈10:1 for those in AF compared with around 6.5:1 in participants in sinus rhythm[4]

2 AS A RESULT

- These findings regarding the change in ratio of BNP and NT-proBNP are important for comparison of natriuretic peptide concentrations in heart failure and reduced ejection fraction[4]
- NPs have very high diagnostic accuracy in discriminating HF from other causes of dyspnea: the higher the NP, the higher the likelihood that dyspnea is caused by HF[5]
- BNP, NT-proBNP (and MR-proANP) have comparable diagnostic and prognostic accuracy[5]
- Both tests (BNP and NT-pro BNP, especially when measured together), have practical clinical value and could be used as additional differentiators in diagnosis

3. BNP AND NT-PROBNP IN PATIENTS ON SACUBITRIL/VALSARTAN MEDICATION

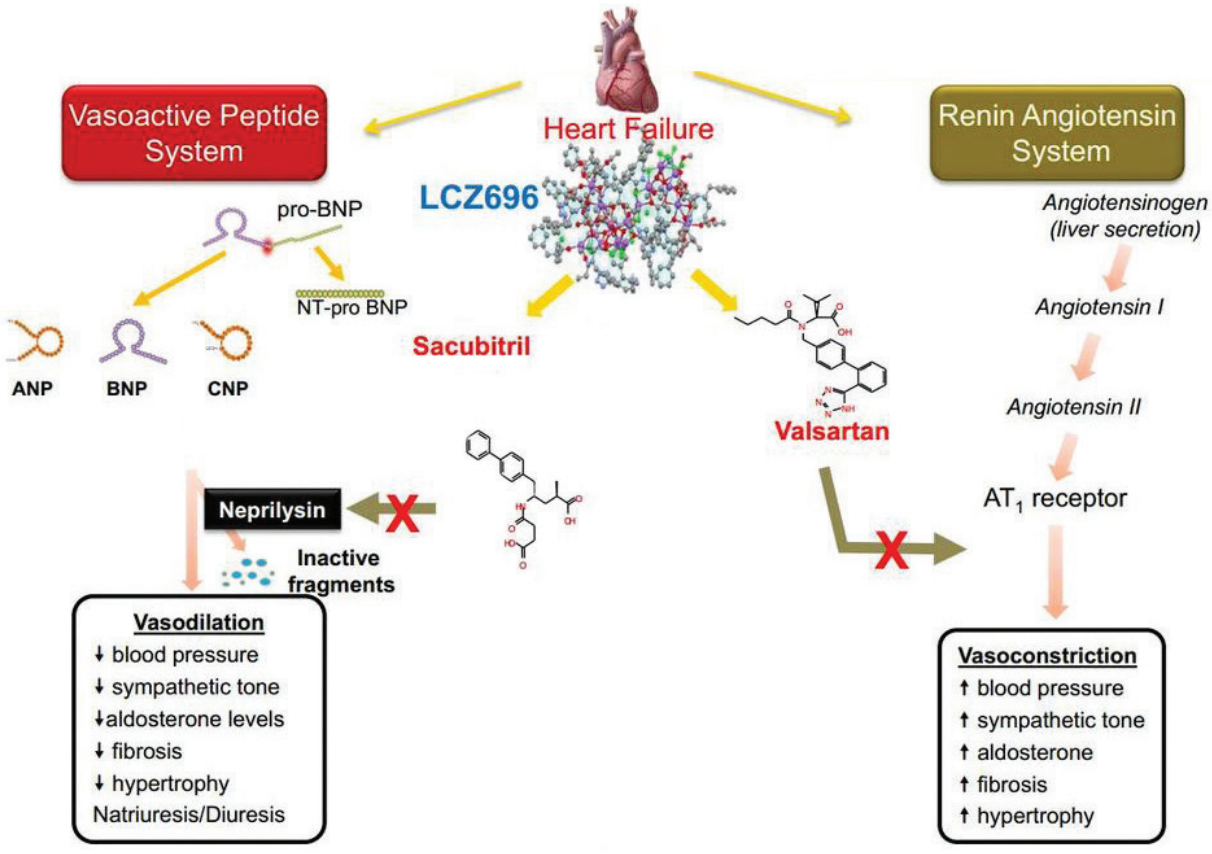
› **LCZ696 (Sacubitril/Valsartan; ENTRESTO)** - an angiotensin receptor blocker and **neprilysin inhibitor** (ARNi) – is used as a therapeutic agent developed by Novartis in patients exhibiting Heart Failure with a reduced ejection fraction.

- **Valsartan** reduces blood vessel tightening and the buildup of sodium and fluid
- **Sacubitril** helps to relax blood vessels and decrease sodium and fluid in the body

Neprilysin is a widely expressed membrane bound protease, particularly abundant in kidney, that cleaves BNP among other types of natriuretic hormones.

In normal conditions: Neprilysin cleaves BNP ▸ BNP concentration will decrease ▸ effect of vasodilatation will decrease ▸ **blood pressure will increase.**

In patients with Heart Failure who take Sacubitril/Valsartan: the drug will inhibit neprilysin ▸ BNP concentration will increase ▸ effect of vasodilatation will increase ▸ **blood pressure will decrease** (Figure 3).



Adopted from M.D. Scott Solomon

Figure 3. LCZ696 (Sacubitril/Valsartan) - a First-in-class Angiotensin Receptor Neprilysin Inhibitor

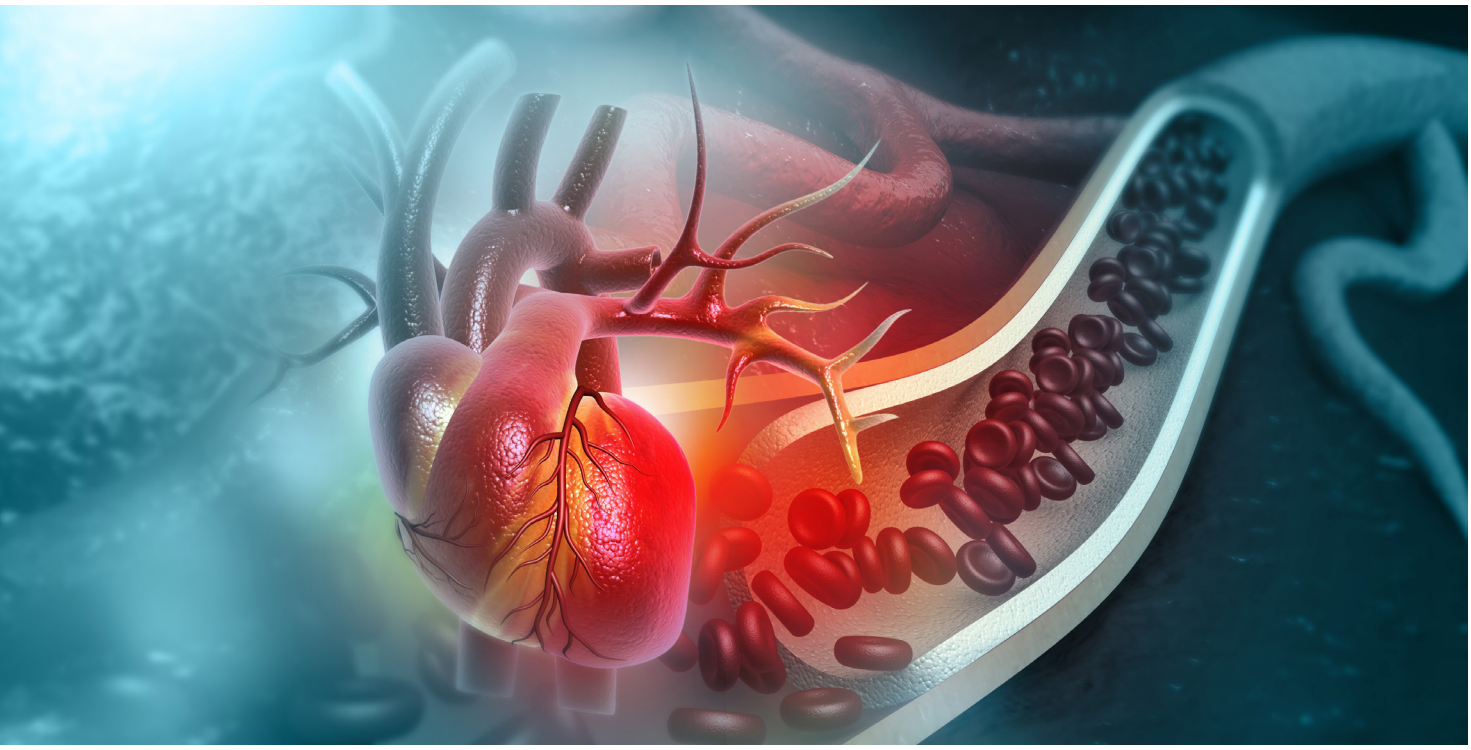
Since the drug inhibits degradation of BNP, it has been speculated that this might cause false results in assays designed to detect BNP.

But, based on literature overview, the following statements should be taken into consideration:

- The suggestion that inhibition of neprilysin should lead to a prompt and prominent increase in BNP level is rather debatable[6]
- Considering the complex biochemistry of proBNP-derived peptides, it is definitely not obvious **how the BNP and NT-proBNP levels are affected by treatment with Sacubitril/Valsartan in different disease states**[7]
  - if treatment with Sacubitril/Valsartan indeed affects the BNP levels measured by BNP immunoassays, then it seems that BNP measurements may be ambiguous in this case[7]
  - **but the increase in circulating BNP might decrease proBNP production and thus decrease the NT-proBNP level, which would then fail to reflect the improvement of cardiac function**[7]

Measurements of BNP:

- **may be very important to understand at what level of BNP increase the drug therapy works**
- **reflect the action of the drug, whereas NT-proBNP levels may reflect the effects of the drug on the heart**[7]



BNP AND NT-PROBNP IN PATIENTS ON SACUBITRIL/VALSARTAN MEDICATION

Clinical example in patients after Sacubitril/Valsartan treatment:

- BNP increased at 4 weeks, with a slight decrease after 8 months of treatment, whereas
- NT-proBNP levels, were significantly lower after 4 weeks compared to baseline and then they further decreased after 9 months of therapy[6,7]

3 AS A RESULT

In patients under Sacubitril/Valsartan treatment:

- the **rapid decrease in NT-proBNP** levels confirms the clinical evidences, suggesting that the majority of patients of shows a **clinical benefit from the drug,**
- whereas the **rapid increase followed by a trend to decrease of BNP levels indicates that this improvement in clinical conditions** is almost in part due to the **increase in natriuretic activity due to neprilysin inhibition on BNP and ANP degradation**

Therefore, BNP and NT-proBNP assay allows complementary (not contradictory) information on clinical conditions of patients treated with ARNi[1,6,7].

In reference to an article by Johannes Mair, MD, American College of Cardiology:

Do not measure BNP on patients that are within the first month of taking Entresto

Recommendation is to establish a new baseline following the first month of taking Entresto, then monitor as you would any other patient[8].

4 BNP AND NT-PROBNP IN GUIDELINES

Both U.S. & European Guidelines Recommend either BNP or NT-proBNP as an aid in the diagnosis of heart failure.

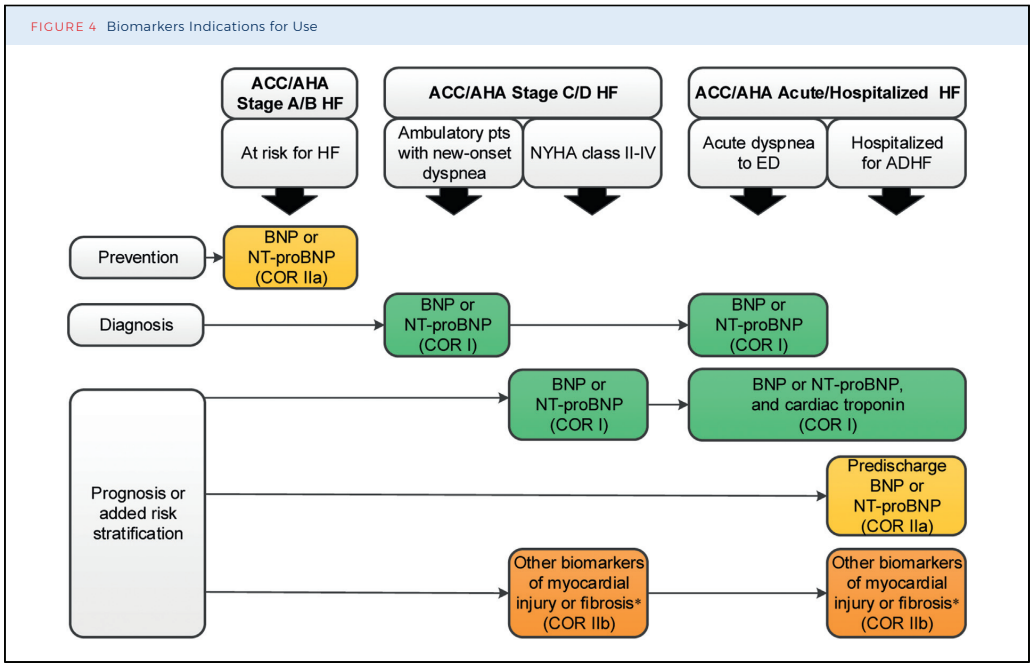
American College of Cardiology:

- Assays for **BNP and NT-proBNP have been used increasingly to establish the presence and severity of HF** (Figure 4)
- In general, **both natriuretic peptide biomarker values track similarly,** and **can be used in patient care settings** as long as their respective absolute values and cutpoints are not used interchangeably[8,9]

The diagnostic algorithm for heart failure:

a) American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) Guideline for the Management of Heart Failure[8]:

FIGURE 4 Biomarkers Indications for Use



**Other biomarkers of injury or fibrosis include soluble ST2 receptor, galectin-3, and high-sensitivity troponin. ADHF = acute decompensated heart failure; COR= Class of Recommendation; ED=emergency department; HF=heart failure; NYHA=New York Heart Association; and pts, patients. Colors correspond to class (strength) of recommendation: green – strong; yellow – moderate; orange - week*

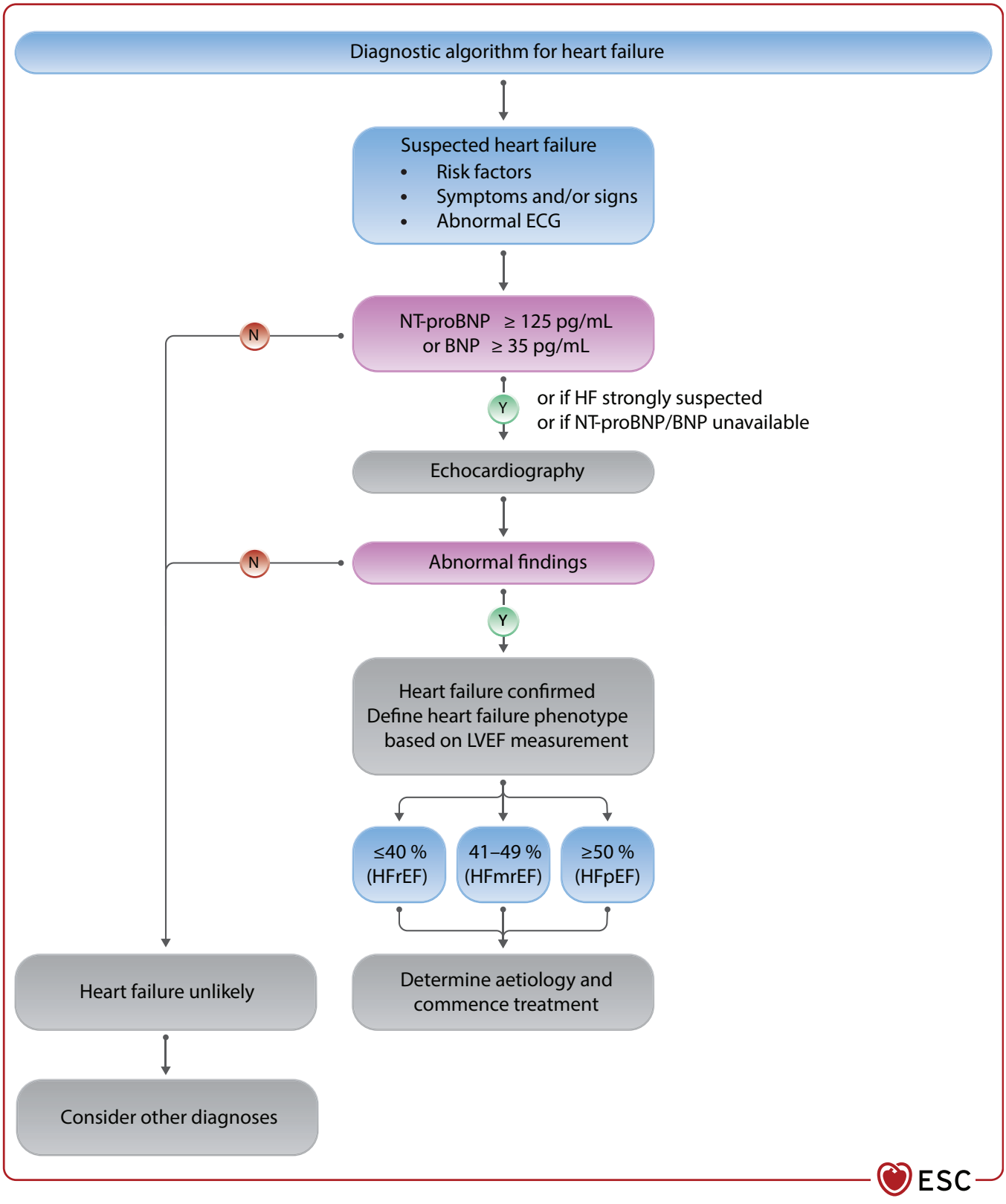
Thresholds for BNP and NT-proBNP for patients with mild-to-moderate HF:

1) Mildly elevated natriuretic peptide levels:
   - BNP [B-type natriuretic peptide] >150 pg/mL or
   - NT-proBNP [N-terminal pro-B-type natriuretic peptide] > 600 pg/mL

or

2) BNP > 100 pg/mL or NT-proBNP > 400 pg/mL with a prior hospitalization in the preceding 12 months[8].

b) 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[9]:



ECG=electrocardiogram; HFmrEF=heart failure with mildly reduced ejection fraction; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; LVEF= left ventricular ejection fraction

5. BNP AND NT-PROBNP IN PATIENTS WITH KIDNEY DISFUNCTION

› Heart failure (HF) is the leading cardiovascular complication in Chronic Kidney Disease (CKD) patients, and its prevalence increases with declining kidney function[10]

Current literature has shown that:

› Circulating levels of both BNP and NT-proBNP increased with deteriorating kidney function, the impact of kidney function on NT-proBNP was much more pronounced than that on BNP[11]

› Kidney function should be taken into account when interpreting data on BNP, NT-proBNP and their relationship

BNP AND NT-PROBNP IN PATIENTS WITH KIDNEY DISFUNCTION

In patients with End-Stage Kidney diseases (ESKD):

- ESKD-specific NT-proBNP and BNP level thresholds of elevation are associated with increased risk for cardiovascular and all-cause mortality and may help guide interpretation of NT-proBNP and BNP levels:
  - Hazard ratios (HR) for **cardiovascular mortality** were progressively greater for greater **thresholds of NT-proBNP**, from 1.45 for levels > 2,000 pg/mL to 5.95 for levels > 15,000 pg/mL
  - Risk for **all-cause mortality** was significantly higher at all NT-proBNP thresholds ranging from > 1,000 to > 20,000 pg/mL (HR: 1.53 – 4.00)
  - **BNP levels** > 550 pg/mL were associated with increased risk for **cardiovascular mortality** (HR 2.54), while the risks for **all-cause mortality** were 2.04 at BNP levels > 100 pg/mL and 2.97 at BNP levels > 550 pg/mL[12]
- Kidney dysfunction increases with age:
  - NT-pro-BNP plasma levels seem to have a stronger relation with glomerular filtration rate (GFR) and be more influenced by the normal age-related decline in renal function than circulating BNP levels. For that reason, some authors advocate that below a GFR of 60ml/min/1,73m2 and in the elderly, NT-proBNP plasma levels should be used carefully[13]

5 AS A RESULT

- Use of BNP and NTproBNP for cardiovascular risk assessment in patients with kidney disease remains unclear[12]
- BNP may be the more appropriate biomarker to screen for cardiac dysfunction in Chronic Kidney Disease[14]
- Kidney function should be taken into account when interpreting data on BNP, NT-proBNP and their relationship[13]

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