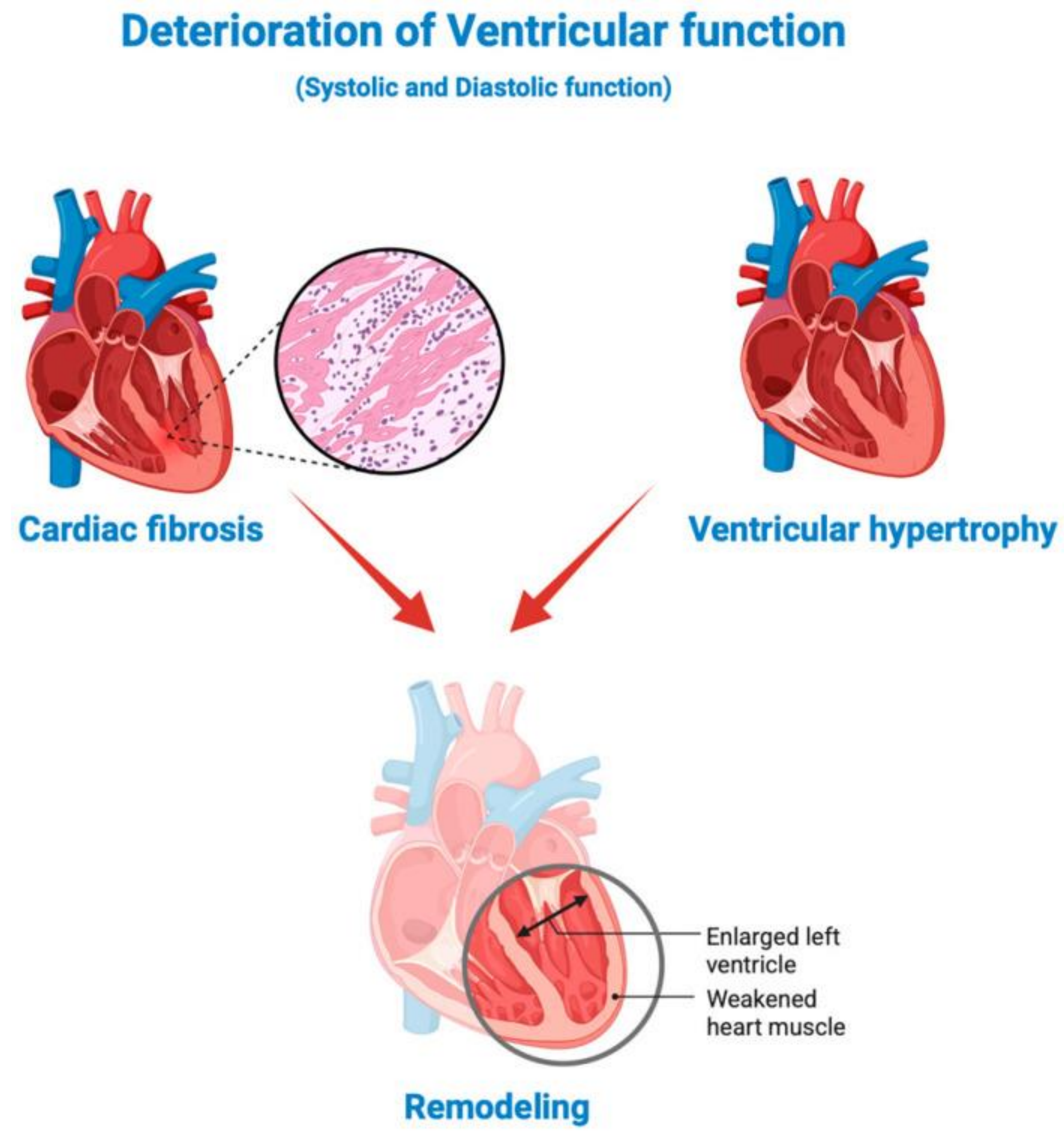
Biomarcatori, point of care, genetica: personalizzare lo scompenso

Prof. Nadia Aspromonte

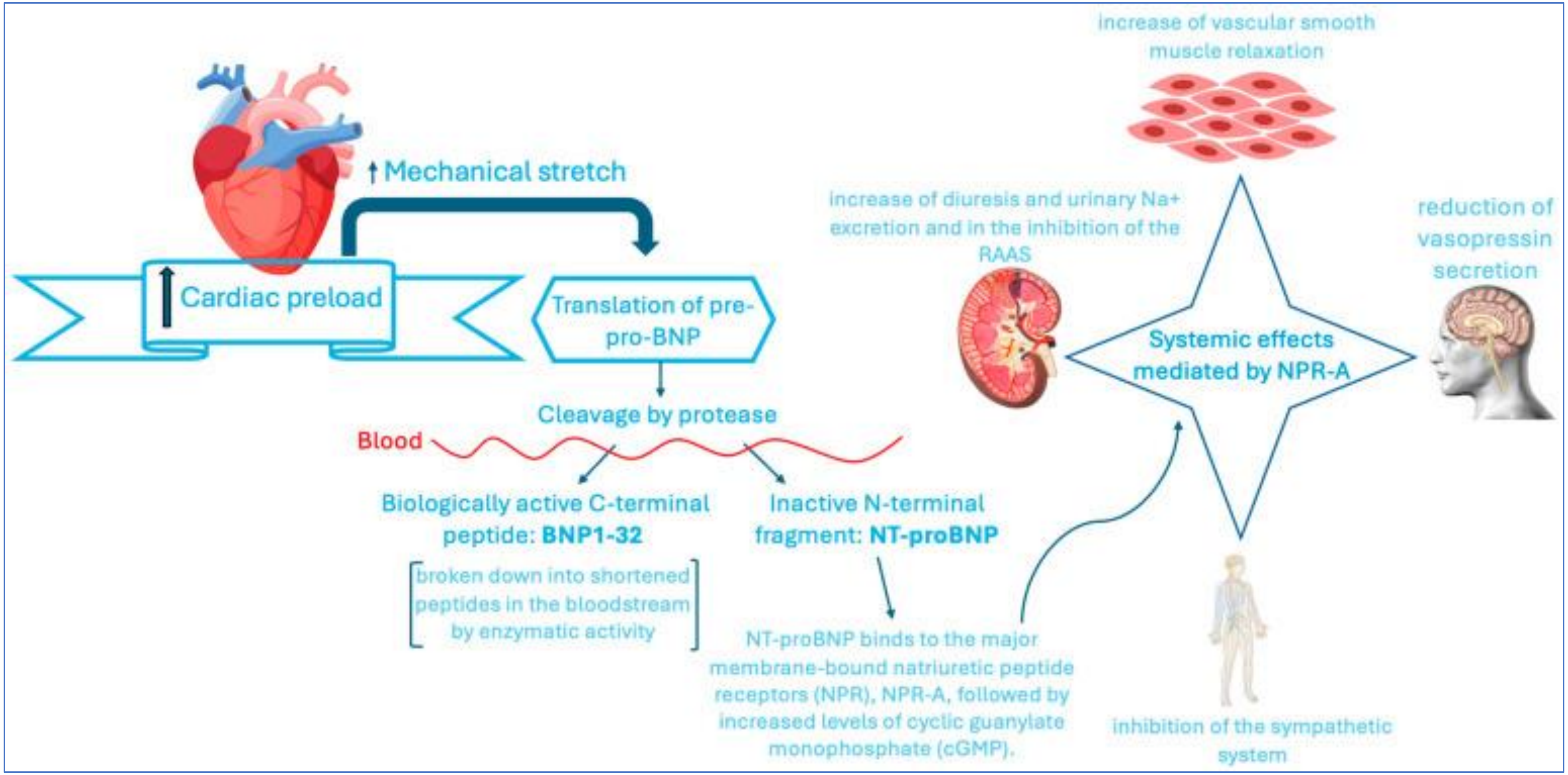
Direttore UOSD Scompenso Cardiaco e Riabilitazione
Dipartimento Scienze Cardiovascolari
Fondazione Policlinico Gemelli IRCCS Roma

Traditional and Emerging Biomarkers in Heart Failure

Cardiac Troponins and Natriuretic Peptides


Deterioration of Ventricular function
(Systolic and Diastolic function)
Cardiac fibrosis
Ventricular hypertrophy
Enlarged left ventricle
Weakened heart muscle
Remodeling

NT-pro-BNP synthesis.

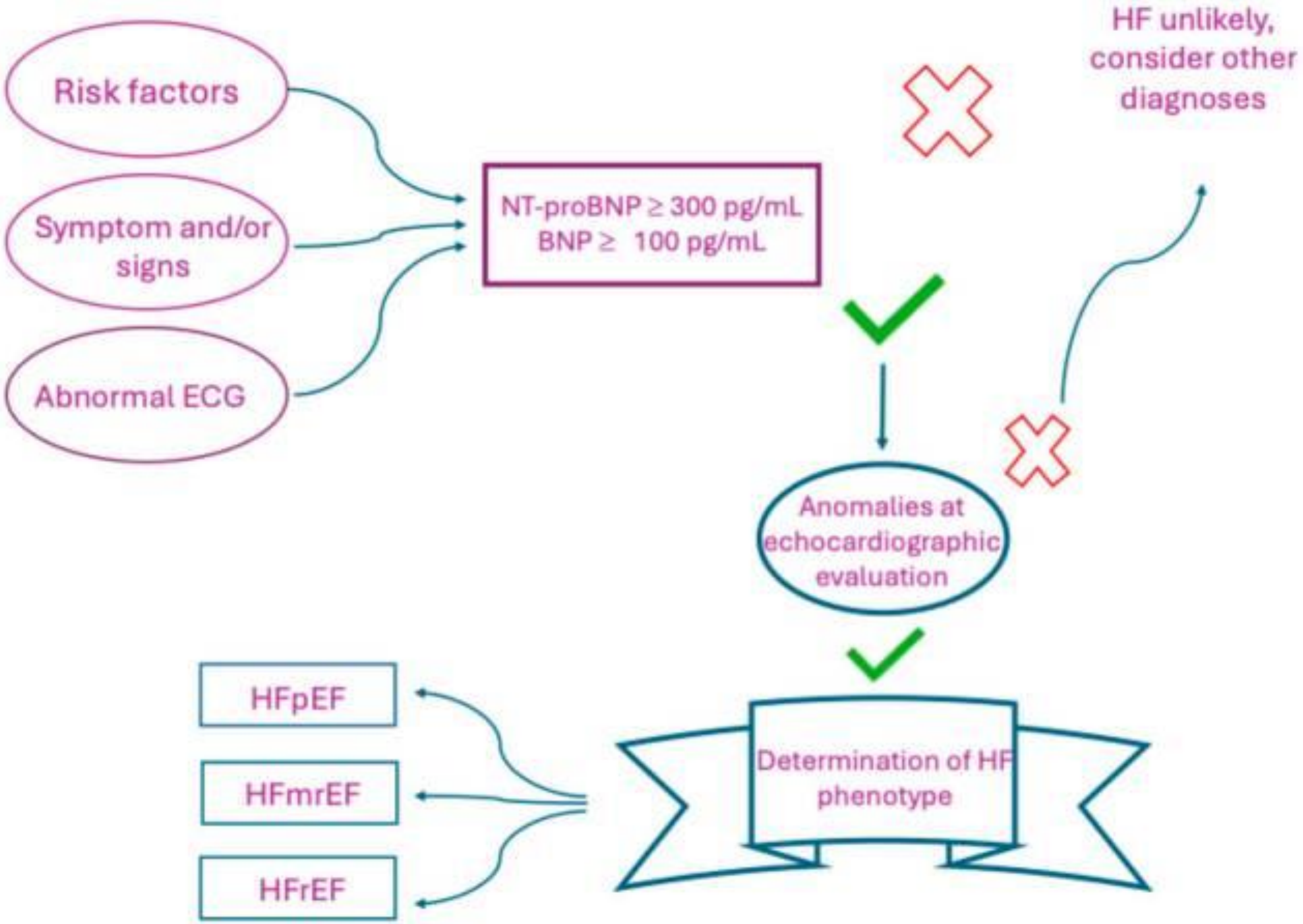


Comparison of BNP and NT-proBNP are vital cardiac biomarkers used to diagnose, assess the prognosis of, and manage various cardiovascular diseases

Feature	BNP	NT-proBNP
Source	Secreted by cardiac ventricles in response to stretch	Cleaved from proBNP during BNP synthesis
Molecular structure	Active hormone	Inactive fragment
Half-life	~20 min	~60–120 min
Stability	Less stable in blood samples	More stable in blood samples
Diagnostic role	Heart failure (HF) diagnosis, prognosis, and treatment monitoring	Heart failure diagnosis, prognosis, and treatment monitoring
Age impact	Less affected by age	Levels increase significantly with age
Renal impact	Moderately influenced by renal dysfunction	More significantly influenced by renal dysfunction
Reference ranges	<100 pg/mL typically indicates no HF	Age-specific cutoffs; <300 pg/mL often indicates no HF
Clinical use	Acute and chronic HF management	Acute and chronic HF management
Advantages	Directly reflects cardiac activity	Higher stability; useful for longer sample transport
Disadvantages	Short half-life, less stable	Age- and renal-dependent levels

The main advantages and limitations of clinical use of NP.

Advantages	Limitations
Early diagnosis marker in patients with diabetes in the absence of a clear clinical expression of heart failure.	The increase in BNPs and NT-proBNPs may also depend on other comorbidities such as chronic renal failure or atrial fibrillation.
In the absence of a defined cardiovascular pathology, the dosage of NT-proBNP values could predict the onset of heart failure, coronary artery disease and stroke.	The value of NT-proBNPs should also be correlated with age, sex, and BMI.
NT-proBNP values are significantly associated with increased odds of advanced HF.	There is a significant "gray area" in which the diagnosis is rather indeterminate.
Correlation between NT-proBNP values and the risk of adverse events in patients with heart failure with preserved ejection fraction.	

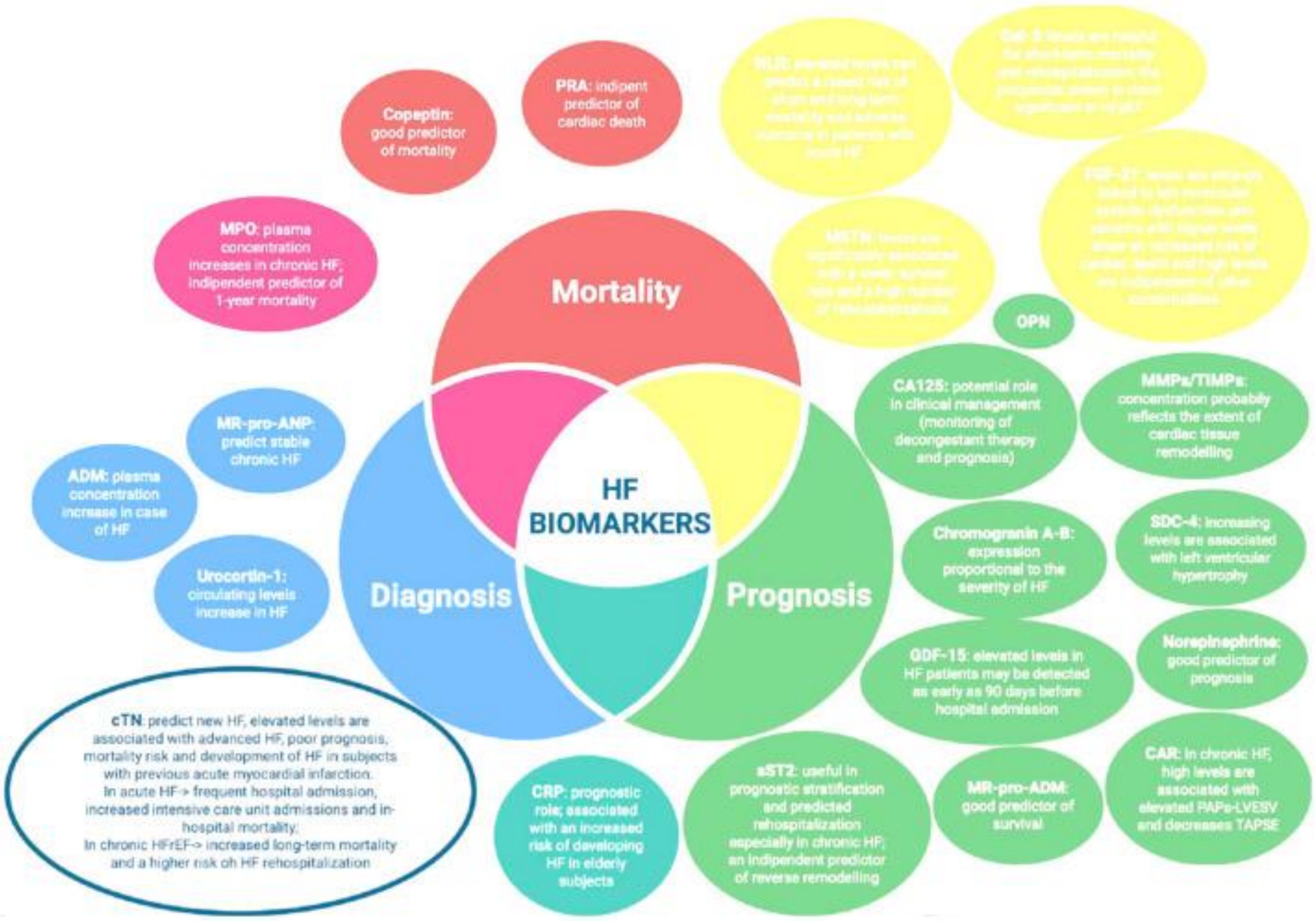

Risk factors
Symptom and/or signs
Abnormal ECG
NT-proBNP ≥ 300 pg/mL
BNP ≥ 100 pg/mL
HF unlikely, consider other diagnoses
Anomalies at echocardiographic evaluation
Determination of HF phenotype
HFpEF
HFmrEF
HFrEF

HF phenotype and typical and atypical diagnostic biomarkers

HF Phenotype	Typical Diagnostic Biomarker	Atypical Diagnostic Biomarker
HFpEF	NT-proBNP, MR-pro-ANP	MR-proADM, Gal-3, sST2, GDF-15, MMPs/TIMPs, FGF21, CRP
HFmrEF	NT-proBNP, MR-pro-ANP	chromogranin A, copeptin, sST2, CA125, CAR
HFrEF	NT-proBNP, MR-pro-ANP, cTn	chromogranin A, copeptin, sST2, CA125, CAR

Mid-Regional Pro-Atrial Natriuretic Peptide (MR-proANP) and Mid-Regional Pro-Adrenomedullin (MR-proADM)

Feature	MR-proANP	MR-proADM
Biochemical source	Derived from the stable N-terminal portion of pro-atrial natriuretic peptide (proANP).	A stable fragment of adrenomedullin, a peptide involved in vasodilation, natriuresis, and diuresis.
Primary role	Reflects atrial stretch and fluid overload, primarily linked to heart failure (HF).	Reflects vascular stress, endothelial dysfunction, and cardiovascular stress.
Stability	Highly stable in circulation due to its longer half-life compared to atrial natriuretic peptide (ANP).	Highly stable, offering reliable measurement and prognostic insights.
Diagnostic utility	Effective for diagnosing heart failure (HF), although slightly less sensitive than BNP and NT-proBNP.	Useful in acute and chronic HF, acute coronary syndrome (ACS), and acute myocardial infarction (AMI). Adds diagnostic value beyond natriuretic peptides.
Prognostic utility	Excels in long-term prognostic value, particularly in predicting mortality over five years in chronic HF.	Superior prognostic value in predicting mortality and cardiovascular events in HF, ACS, and AMI. Outperforms natriuretic peptides
Heart failure (HF)	Strongly associated with disease severity and mortality in chronic HF; valuable for monitoring disease progression and treatment efficacy.	Levels correlate with HF severity and NYHA class; provides predictive value for long-term outcomes and mortality.
Acute coronary syndrome (ACS) and AMI	Limited data on utility in ACS and AMI.	Independently associated with fatal and nonfatal cardiovascular events in ACS and AMI. Enhances risk stratification beyond traditional models and natriuretic peptides.
Screening potential	Effective for screening atrial fibrillation (AF), particularly in community populations, and identifying individuals at risk of developing AF.	Primarily used for prognostic and risk stratification purposes; limited use in AF screening.
Influencing factors	Levels influenced by age, BMI, race, and sex; despite variability, it remains reliable due to its stability.	Levels independent of renal function, age, and systolic blood pressure; remains highly predictive despite other clinical variations.
Advantages	Long half-life, stable, and highly prognostic for HF and atrial fibrillation risk.	Adds significant prognostic value to traditional risk models, particularly in ACS and AMI; strong correlation with cardiovascular stress and mortality.
Limitations	Diagnostic sensitivity slightly lower than BNP and NT-proBNP; levels vary with demographic and physiological factors.	Limited availability in routine clinical practice; specific role in AF screening not established.


Copeptin: good predictor of mortality
PRA: indipent predictor of cardiac death
MPO: plasma concentration increases in chronic HF; indipendent predictor of 1-year mortality
Mortality
OPN
MR-pro-ANP: predict stable chronic HF
ADM: plasma concentration increase in case of HF
Urocortin-1: circulating levels increase in HF
HF BIOMARKERS
Diagnosis
Prognosis
CA125: potential role in clinical management (monitoring of decongestant therapy and prognosis)
MMPs/TIMPs: concentration probably reflects the extent of cardiac tissue remodelling
Chromogranin A-B: expression proportional to the severity of HF
SDC-4: increasing levels are associated with left ventricular hypertrophy
GDF-15: elevated levels in HF patients may be detected as early as 90 days before hospital admission
Norepinephrine: good predictor of prognosis
cTN: predict new HF, elevated levels are associated with advanced HF, poor prognosis, mortality risk and development of HF in subjects with previous acute myocardial infarction. In acute HF-> frequent hospital admission, increased intensive care unit admissions and in-hospital mortality; In chronic HFrEF-> increased long-term mortality and a higher risk oh HF rehospitalization
CRP: prognostic role; associated with an increased risk of developing HF in elderly subjects
sST2: useful in prognostic stratification and predicted rehospitalization especially in chronic HF; an indipendent predictor of reverse remodelling
MR-pro-ADM: good predictor of survival
CAR: In chronic HF, high levels are associated with elevated PAPs-LVESV and decreases TAPSE

Stages, Phenotypes and Treatment of HF

2013 ACCF/AHA Heart Failure Guideline

At Risk for Heart Failure

STAGE A
At high risk for HF but without structural heart disease or symptoms of HF

e.g., Patients with:
- HTN
- Atherosclerotic disease
- DM
- Obesity
- Metabolic syndrome

or

Patients
- Using cardiotoxins
- With family history of cardiomyopathy

→ Structural heart disease →

THERAPY

Goals
- Heart healthy lifestyle
- Prevent vascular, coronary disease
- Prevent LV structural abnormalities

Drugs
- ACEI or ARB in appropriate patients for vascular disease or DM
- Statins as appropriate

STAGE B
Structural heart disease but without signs or symptoms of HF

e.g., Patients with:
- Previous MI
- LV remodeling including LVH and low EF
- Asymptomatic valvular disease

→ Development of symptoms of HF →

THERAPY

Goals
- Prevent HF symptoms
- Prevent further cardiac remodeling

Drugs
- ACEI or ARB as appropriate
- Beta blockers as appropriate

In selected patients
- ICD
- Revascularization or valvular surgery as appropriate

Heart Failure

STAGE C
Structural heart disease with prior or current symptoms of HF

e.g., Patients with:
- Known structural heart disease and
- HF signs and symptoms

→ Refractory symptoms of HF at rest, despite GDMT →

HF*p*EF

THERAPY

Goals
- Control symptoms
- Improve HRQOL
- Prevent hospitalization
- Prevent mortality

Strategies
- Identification of comorbidities

Treatment
- Diuresis to relieve symptoms of congestion
- Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
- Revascularization or valvular surgery as appropriate

HF*r*EF

THERAPY

Goals
- Control symptoms
- Patient education
- Prevent hospitalization
- Prevent mortality

Drugs for routine use
- Diuretics for fluid retention
- ACEI or ARB
- Beta blockers
- Aldosterone antagonists

Drugs for use in selected patients
- Hydralazine/isosorbide dinitrate
- ACEI and ARB
- Digoxin

In selected patients
- CRT
- ICD
- Revascularization or valvular surgery as appropriate

STAGE D
Refractory HF

e.g., Patients with:
- Marked HF symptoms at rest
- Recurrent hospitalizations despite GDMT

THERAPY

Goals
- Control symptoms
- Improve HRQOL
- Reduce hospital readmissions
- Establish patient's end-of-life goals

Options
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

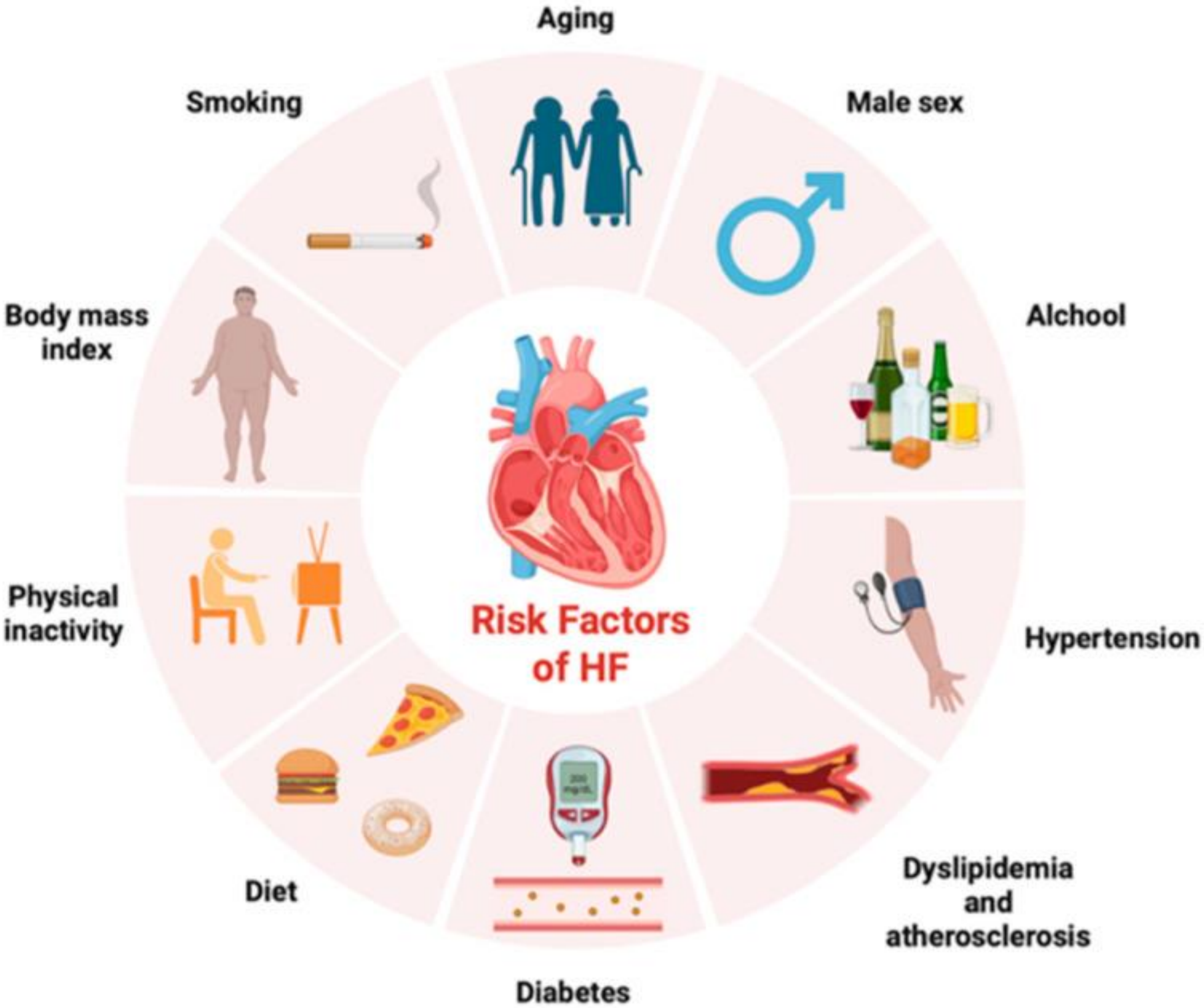
Risk factors and comorbidities involved in the development of HFpEF, HFmrEF and/or HFrEF[1,2]

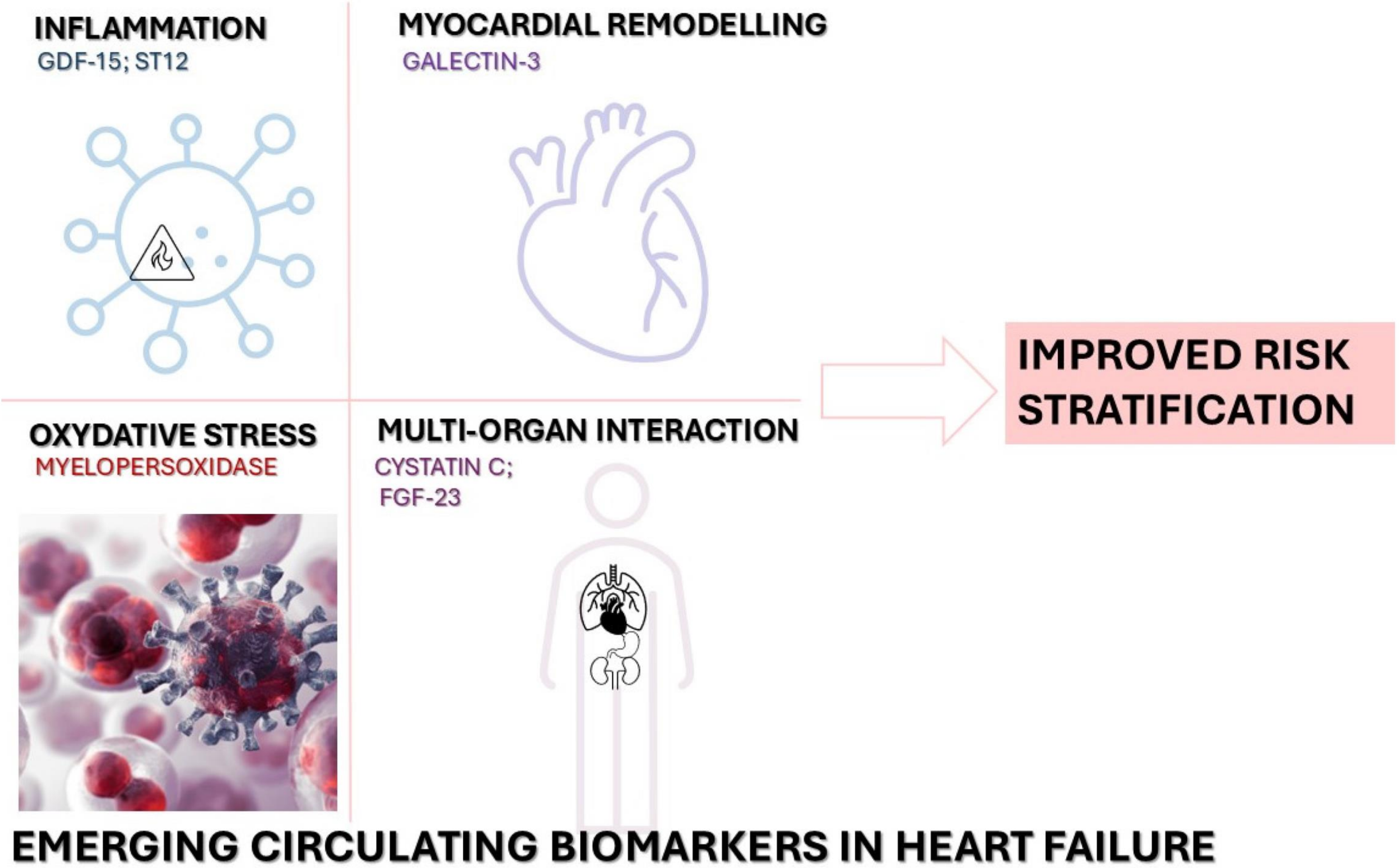
	HFrEF	HFmrEF	HFpEF
Age[1,2]	↑	↑↑	↑↑↑
Female[1]	↓↓	↓	↑
Hypertension[1,2]	↑	↑↑	↑↑↑
Obesity[2]	↑	↑	↑↑
Diabetes mellitus[2]	↑	↑↑	↑↑
Ischaemic heart disease[1,2]	↑↑↑	↑↑↑	↑
Atrial fibrillation[1,2]	↑	↑↑	↑↑↑
Chronic kidney disease[1]	↑↑	↑↑	↑↑↑
COPD[2]	↑	↑↑	↑↑↑

- HFpEF and HFrEF share many risk factors, but some comorbidities differ
- Compared with HFrEF, **patients with HFpEF are more likely to**:[3]
  - Be female
  - Be older
  - Have non-cardiac comorbidities
  - Be hospitalised for comorbidity-related illness

COPD, chronic obstructive pulmonary disease; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failue with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction
Figured modified from

1. Savarese G et al. Nat Rev Cardiol 2022;19:100–116; 2. Cvjjic M et al. Heart Fail Rev 2022 (Epub ahead of print); 3. Simmonds SJ et al. Cells 2020;9:242


Aging
Male sex
Alchool
Hypertension
Dyslipidemia
and
atherosclerosis
Diabetes
Diet
Physical
inactivity
Body mass
index
Smoking
Risk Factors
of HF


INFLAMMATION
GDF-15; ST12
MYOCARDIAL REMODELLING
GALECTIN-3
OXYDATIVE STRESS
MYELOPERSOXIDASE
MULTI-ORGAN INTERACTION
CYSTATIN C;
FGF-23
IMPROVED RISK STRATIFICATION
EMERGING CIRCULATING BIOMARKERS IN HEART FAILURE

Summary of Biomarkers in Heart Failure: Roles, Utility, and Limitations

NT-proBNP/BNP Ventricular stretch, volume overload Diagnosis, risk stratification, prognosis, therapy guidance Influenced by age, renal function, and obesity

Galectin-3 (Gal-3) Fibrosis, inflammation Prognosis, risk stratification in HF Non-cardiac specificity (renal, cancer); variability across studies

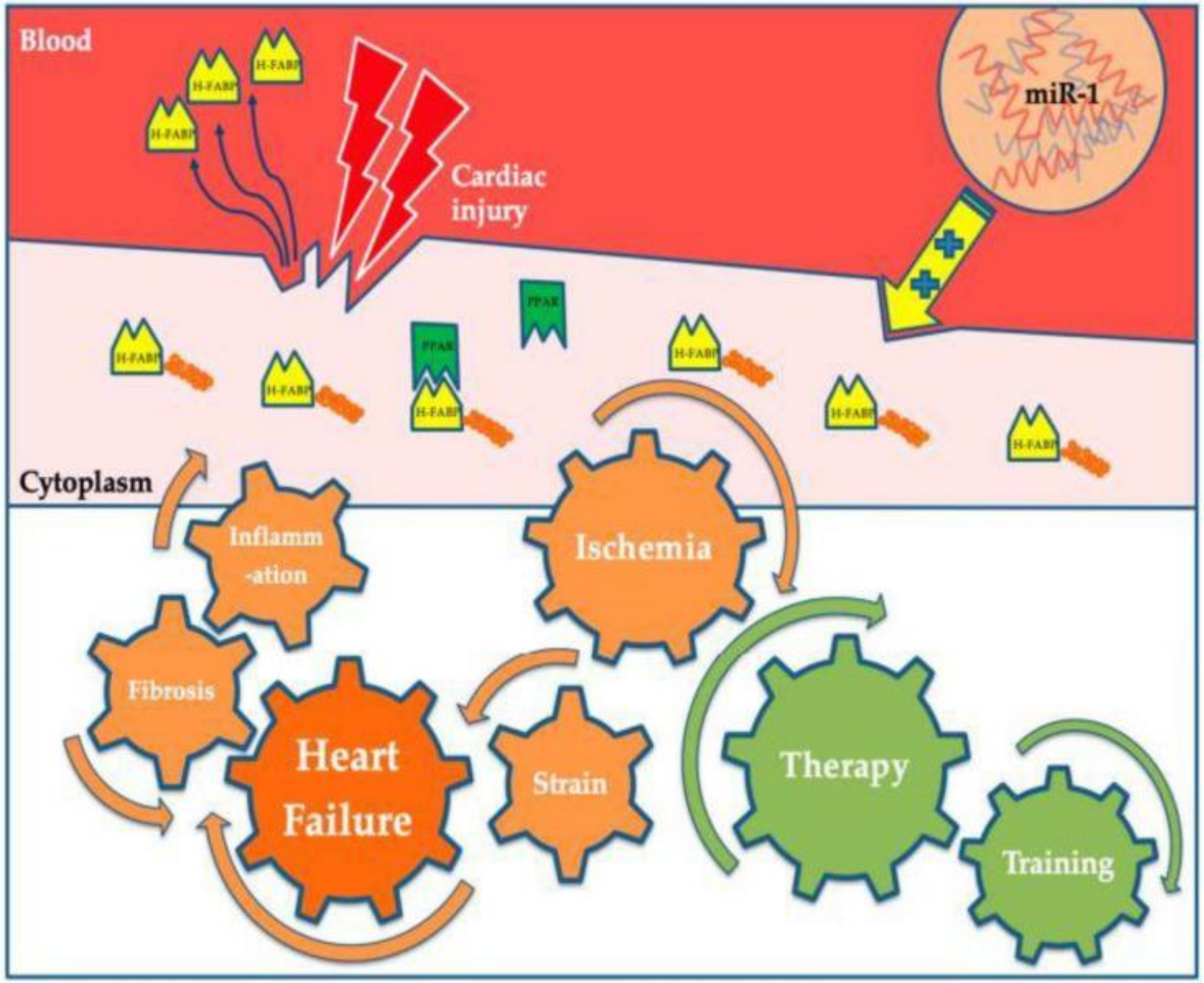
sST2 (soluble ST2) Myocardial stress, fibrosis Prognosis, risk stratification, and potential therapy guidance No reduction in mortality as a standalone marker

microRNAs (miRNAs) Gene regulation, myocardial remodeling, fibrosis Early diagnosis, HF phenotyping, risk stratification Lack of standardization, small sample sizes

Role of H-FABP (Heart-Type Fatty Acid-Binding Protein)

Increased H-FABP levels are associated with ischemia, inflammation, fibrosis, and strain, ultimately leading to heart failure.

Physical training and pharmacological interventions, such as anti-tachycardic therapy, have been shown to reduce plasma H-FABP levels, supporting their role in therapy



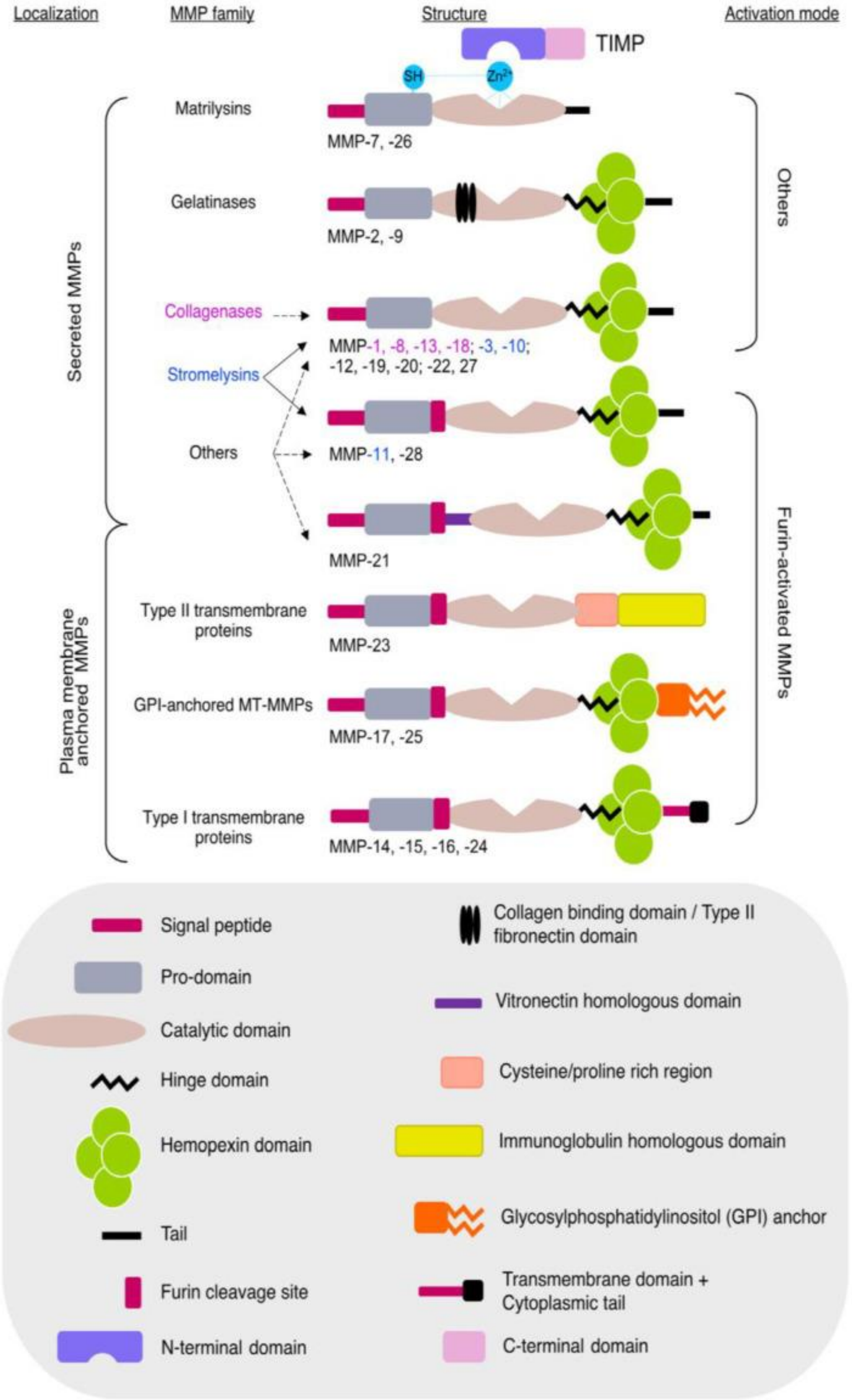
J. Clin. Med. 2020;9:164

Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of Metalloproteinases (TIMPs)

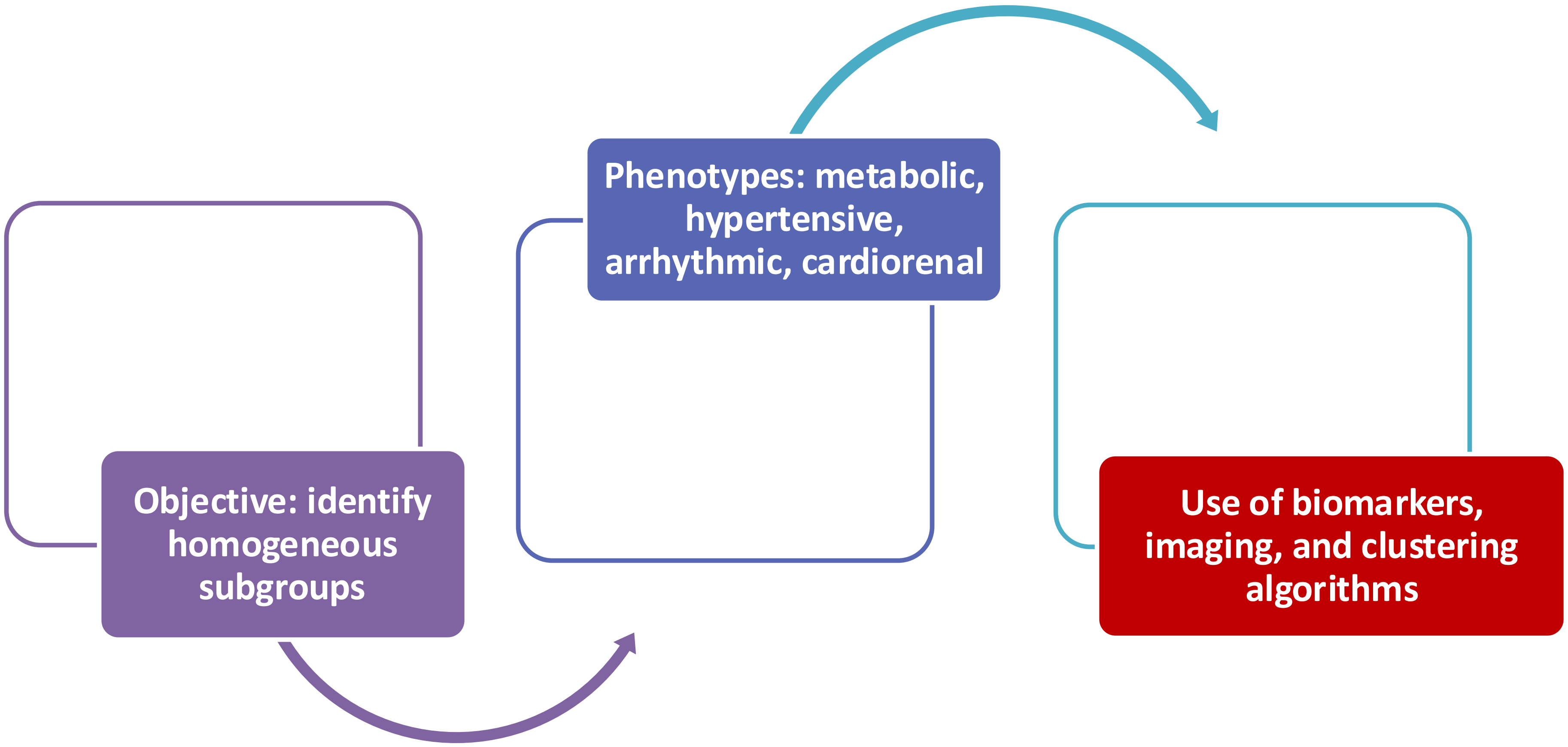
MMPs and TIMPs are implicated in cardiac extracellular matrix remodeling, play a pivotal role in ventricular remodeling and fibrosis, impacting heart failure prognosis.

MMP-2 is involved in cardiac injury and repair, can impair ventricular function in the absence of superimposed injury, and may play roles in the maintenance of sarcomere proteostasis within striated muscle

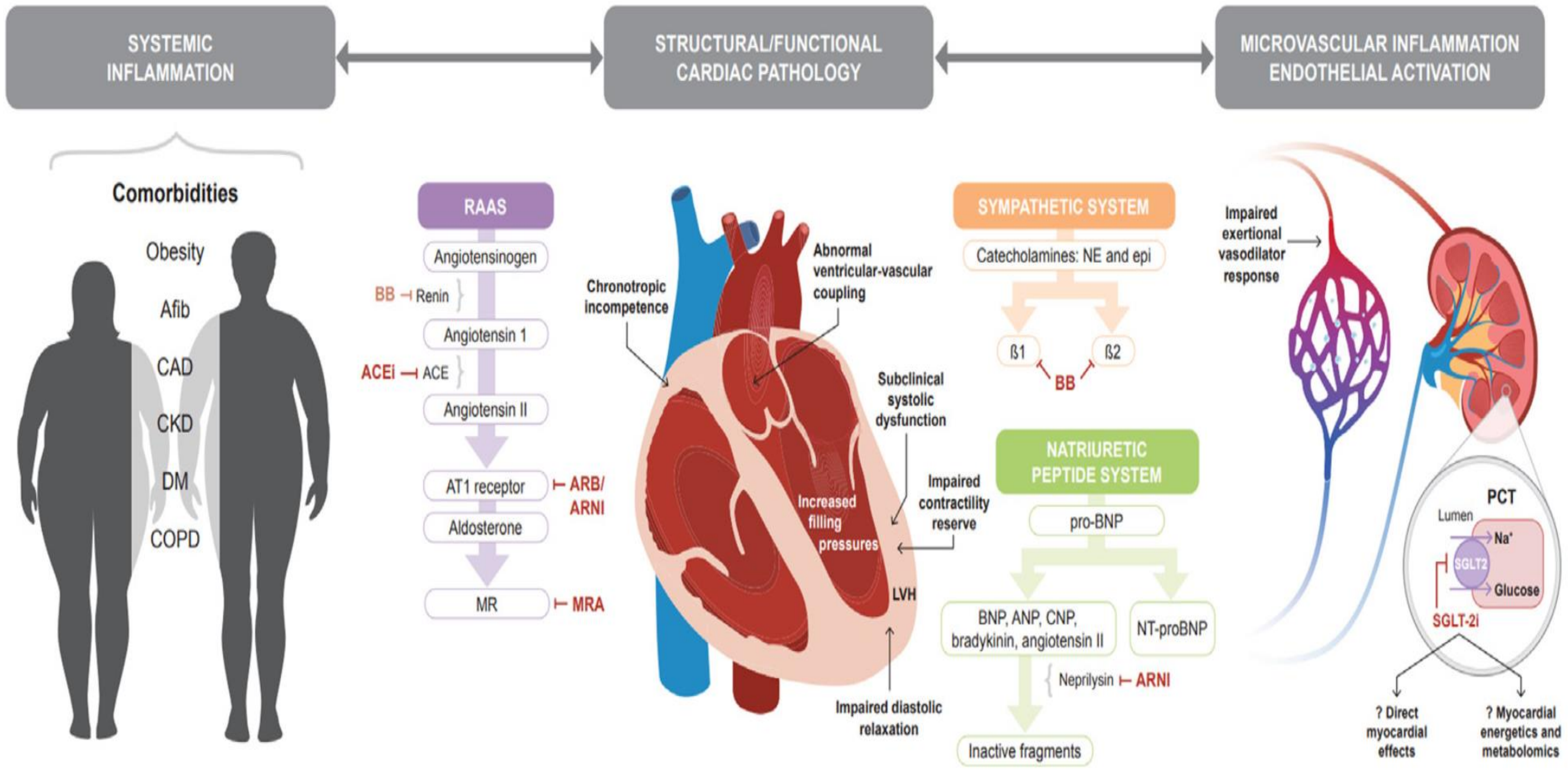
Int. J. Mol. Sci. 2023;24:10649.

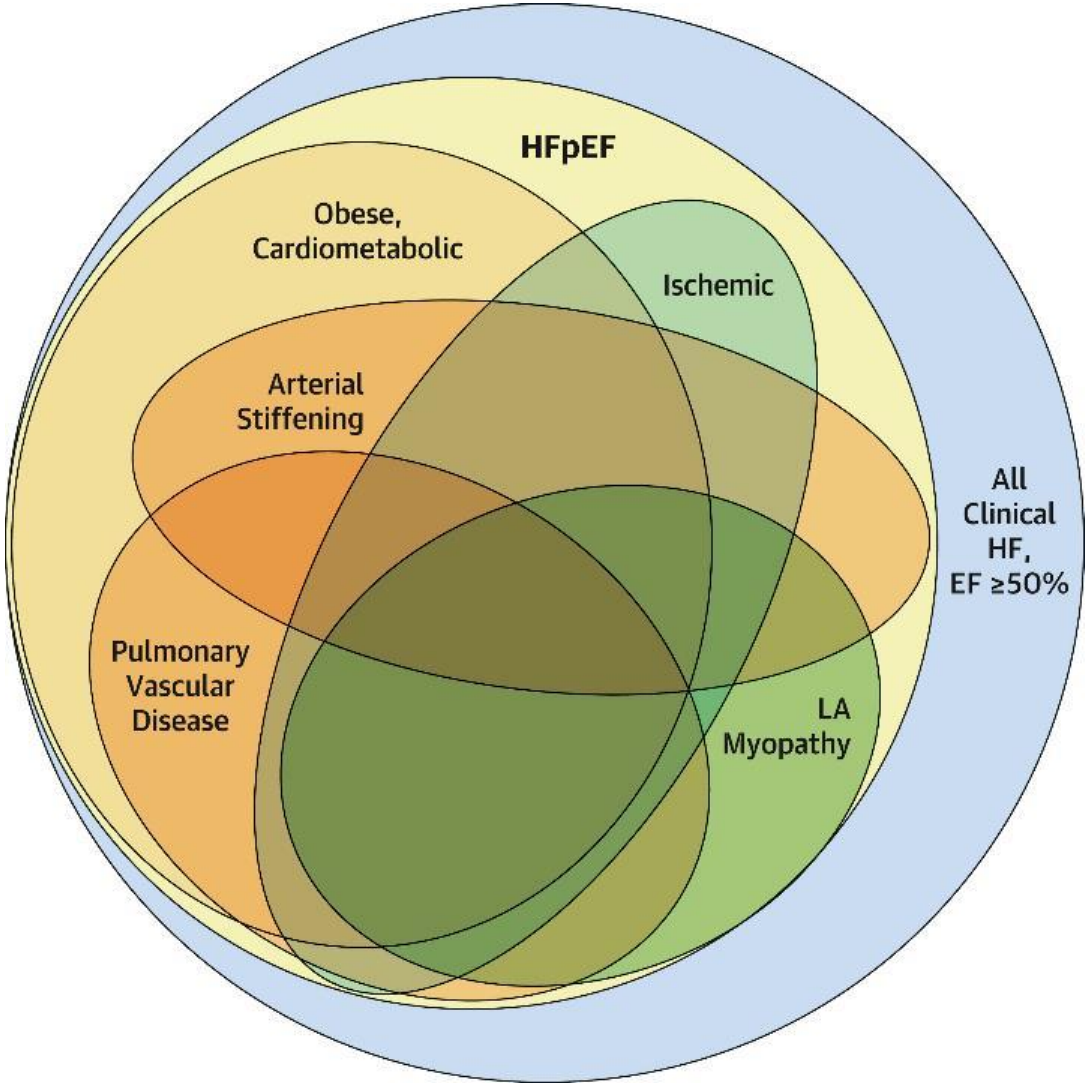


Phenotypes profiling



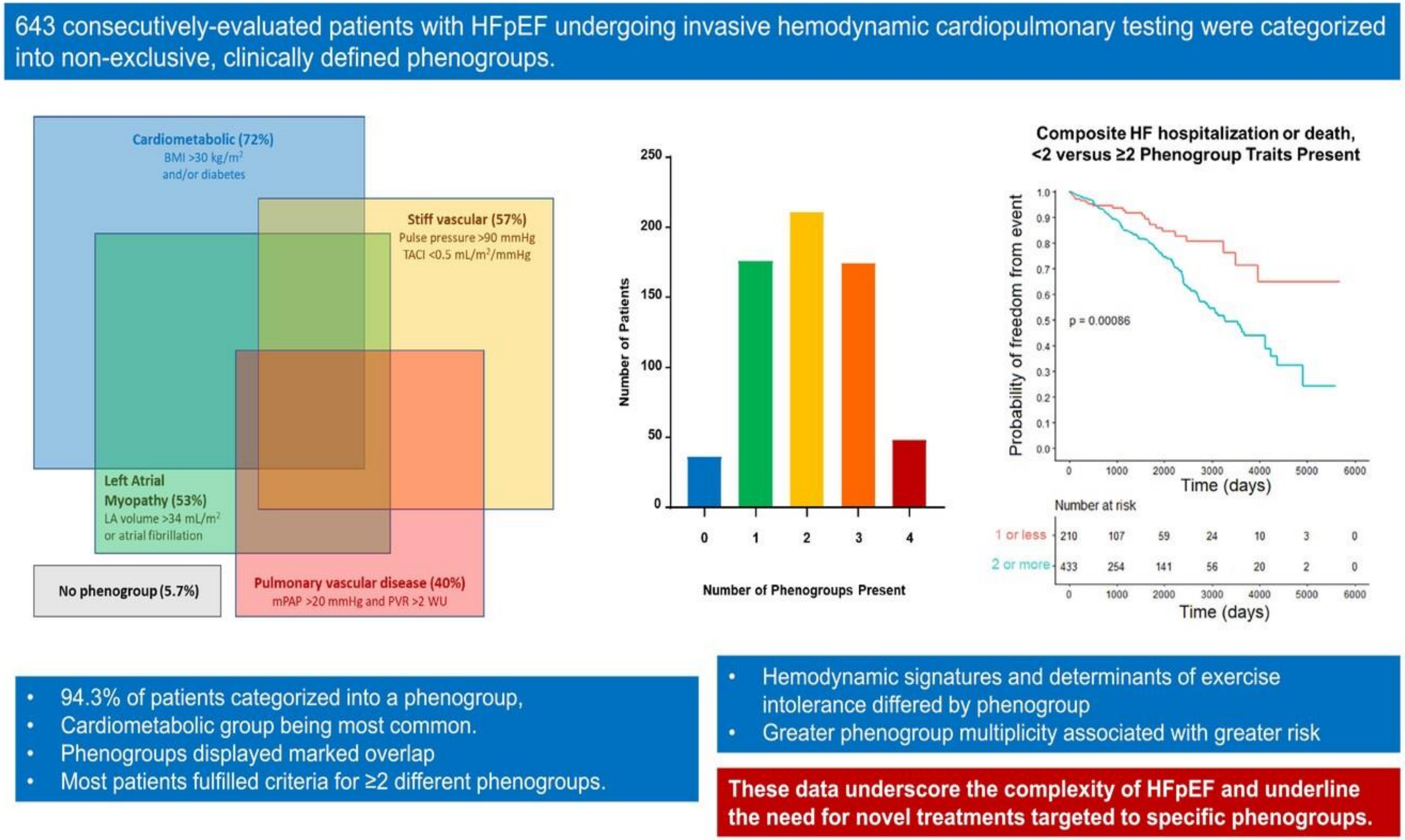
Phenomapping: HFpEF model




HFpEF
Obese, Cardiometabolic
Ischemic
Arterial Stiffening
All Clinical HF, EF ≥50%
Pulmonary Vascular Disease
LA Myopathy

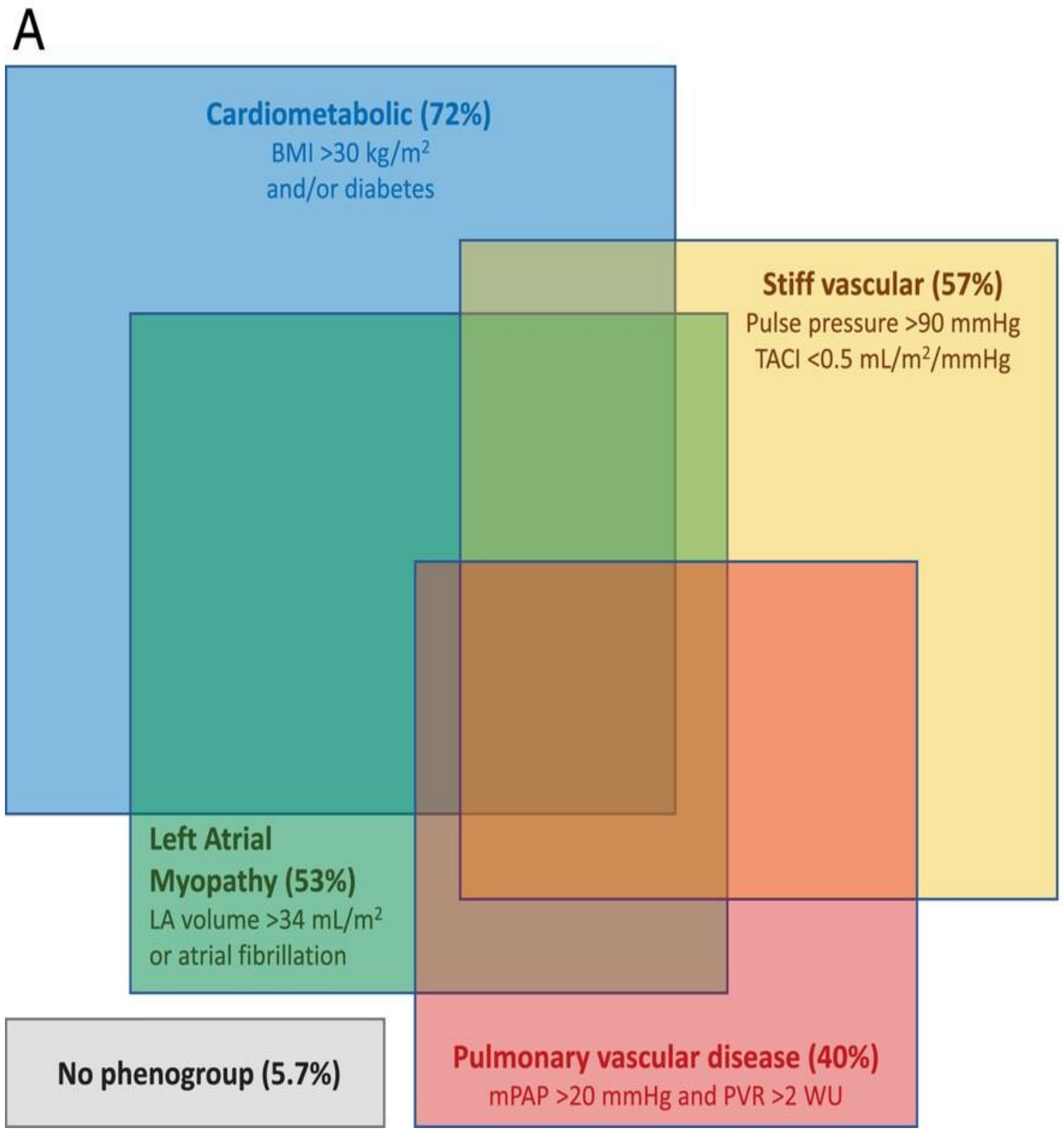
Clinical phenogroup diversity and multiplicity: Impact on mechanisms of exercise intolerance in heart failure with preserved ejection fraction

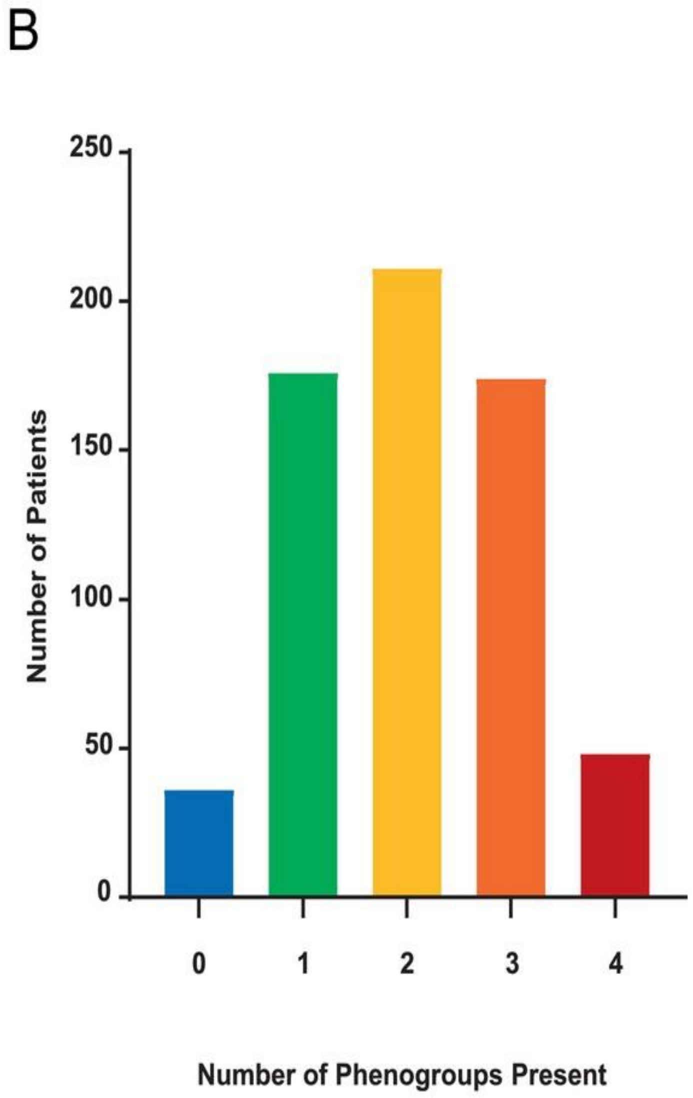
Eur J Heart Fail 2024;26:564–577



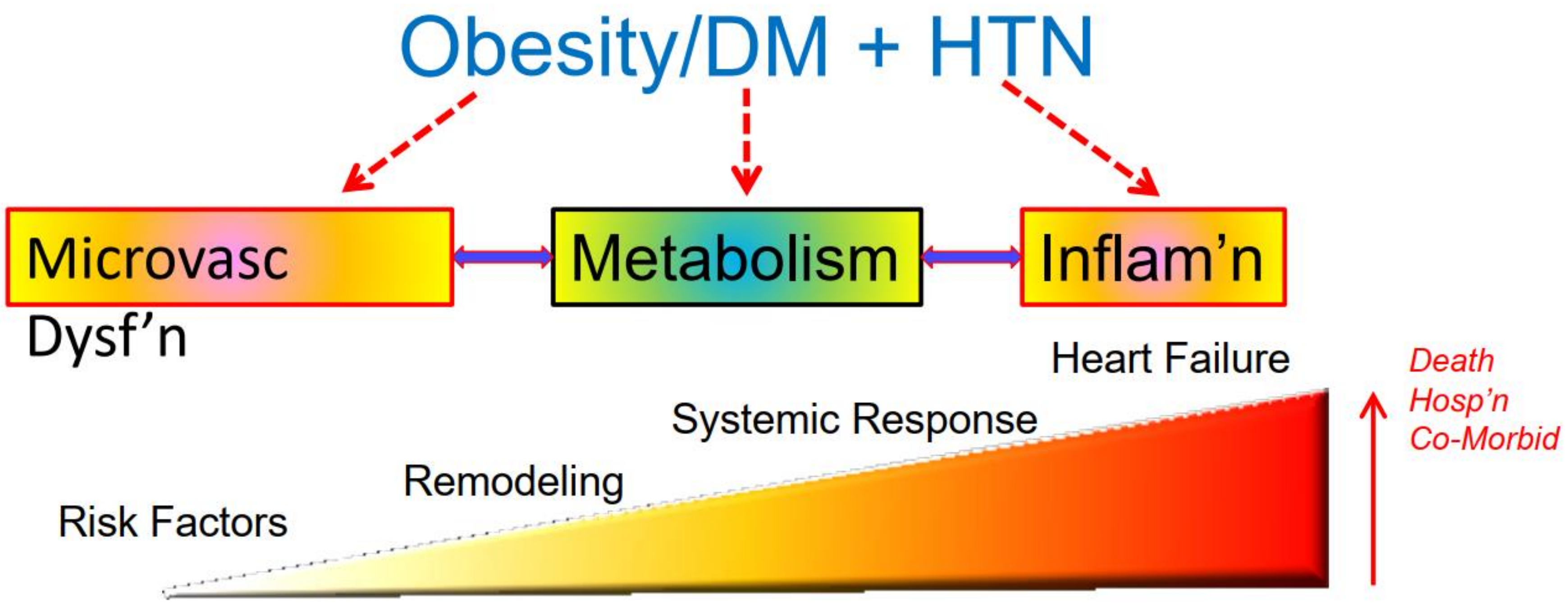
Clinical phenogroup diversity and multiplicity: Impact on mechanisms of exercise intolerance in heart failure with preserved ejection fraction

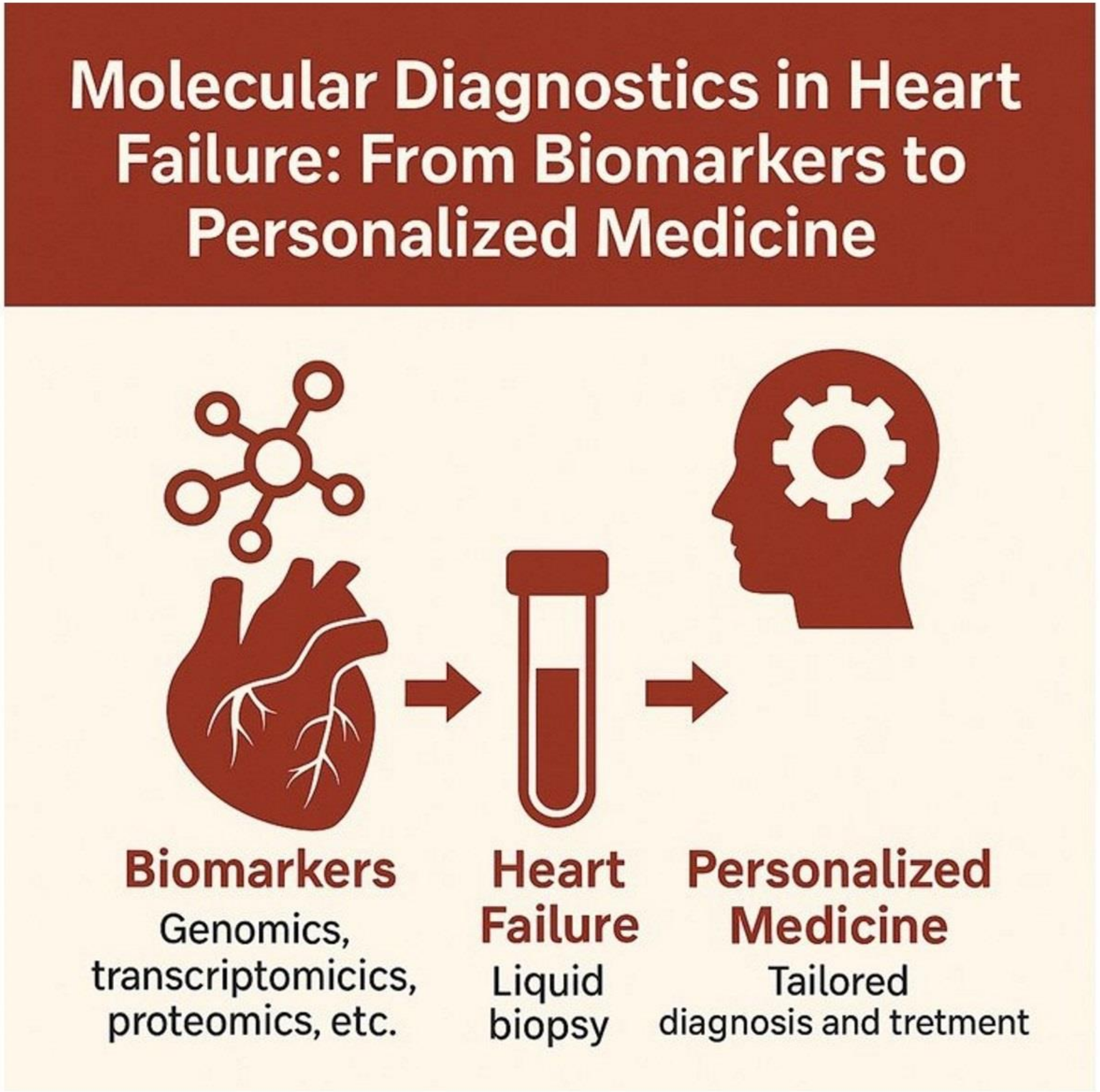
Eur J Heart Fail 2024;26:564–577

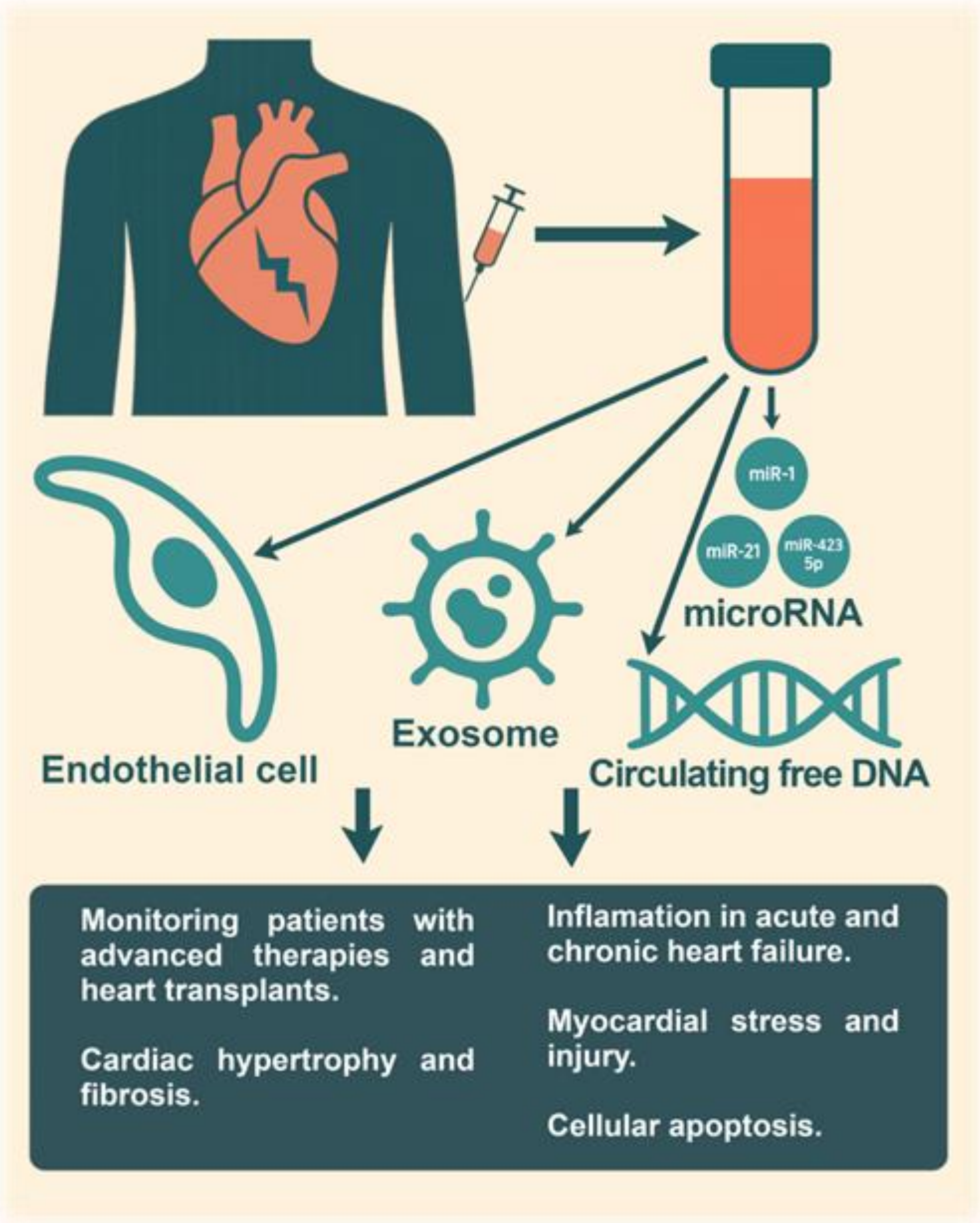




Stress and HFpEF:
Inflam'n / Microvasc / Metabolic Link

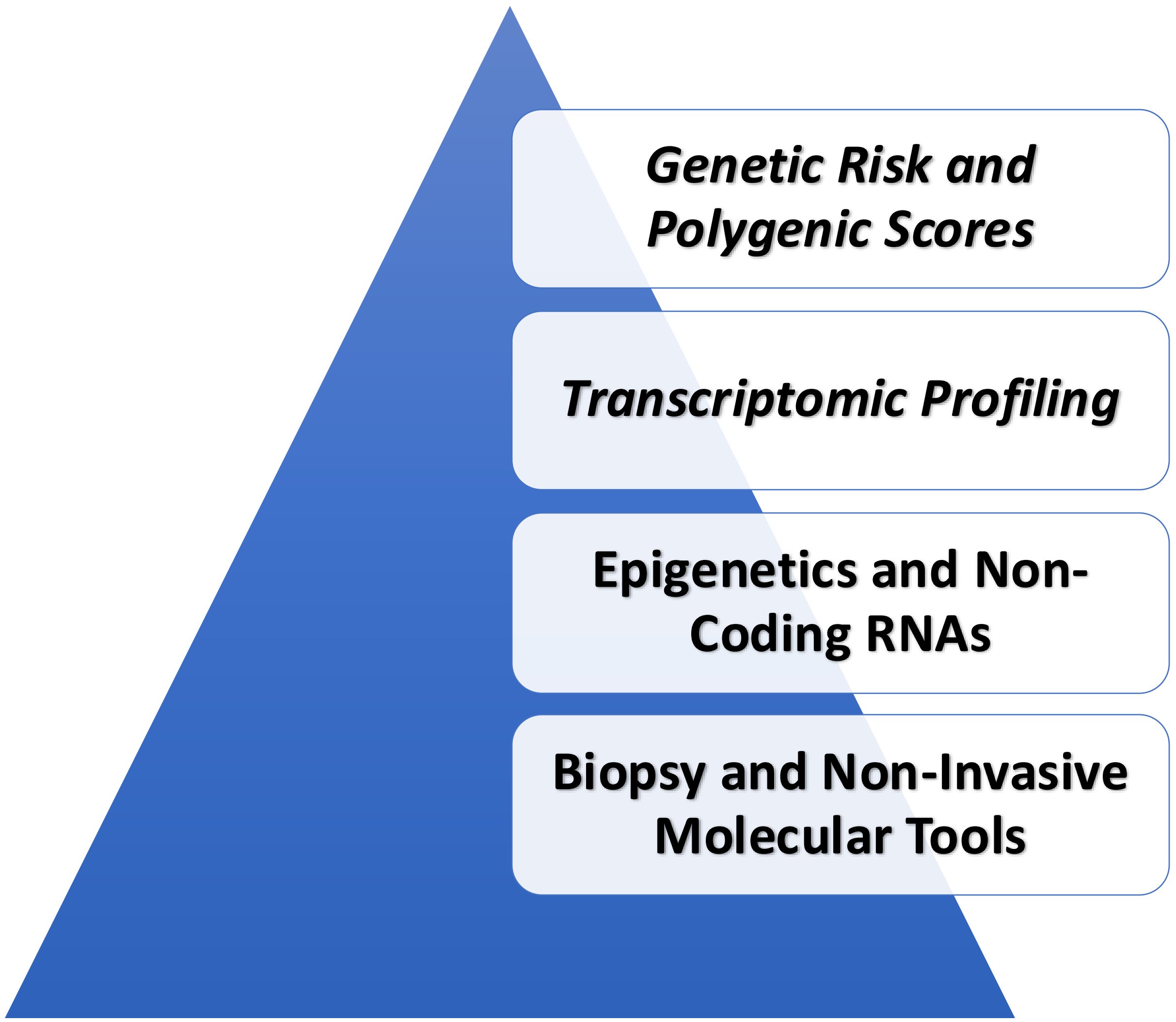


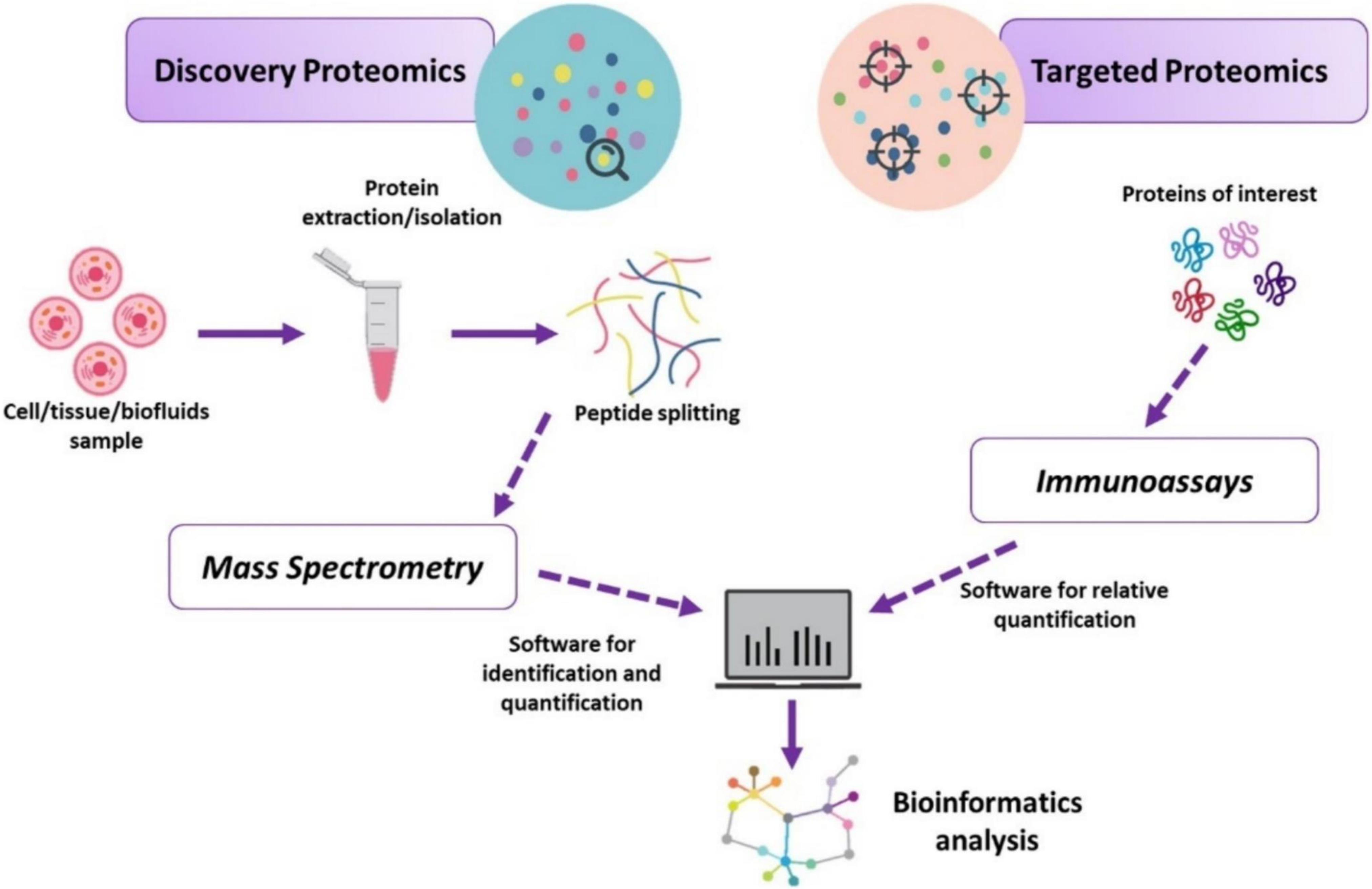

Molecular Diagnostics in Heart Failure: From Biomarkers to Personalized Medicine
Biomarkers
Genomics, transcriptomicics, proteomics, etc.
Heart Failure
Liquid biopsy
Personalized Medicine
Tailored diagnosis and tretment



miR-1
miR-21
miR-423 5p
microRNA
Endothelial cell
Exosome
Circulating free DNA
Monitoring patients with advanced therapies and heart transplants.
Cardiac hypertrophy and fibrosis.
Inflamation in acute and chronic heart failure.
Myocardial stress and injury.
Cellular apoptosis.

Genomics and Transcriptomics in HF Diagnostics




Discovery Proteomics
Targeted Proteomics
Protein extraction/isolation
Proteins of interest
Cell/tissue/biofluids sample
Peptide splitting
Immunoassays
Mass Spectrometry
Software for relative quantification
Software for identification and quantification
Bioinformatics analysis

miRNA in HF.

miRNA	Role
mir-22	• Regulates calcium reuptake by sarcoplasmic reticulum • Associated with hypertrophy and myocardial fibrosis
miR-133/miR-223-3p	• Their silencing reduces GLUT4 expression and thus increases myocardial glucose uptake in HF patients
miR-21	• Involved in HF-related fibrosis through the stimulation of the ERK-MAP pathway
miR-1	• Involved in regulating myocardial hypertrophy
miR-212/132	• Associated with cardiac hypertrophy and HF

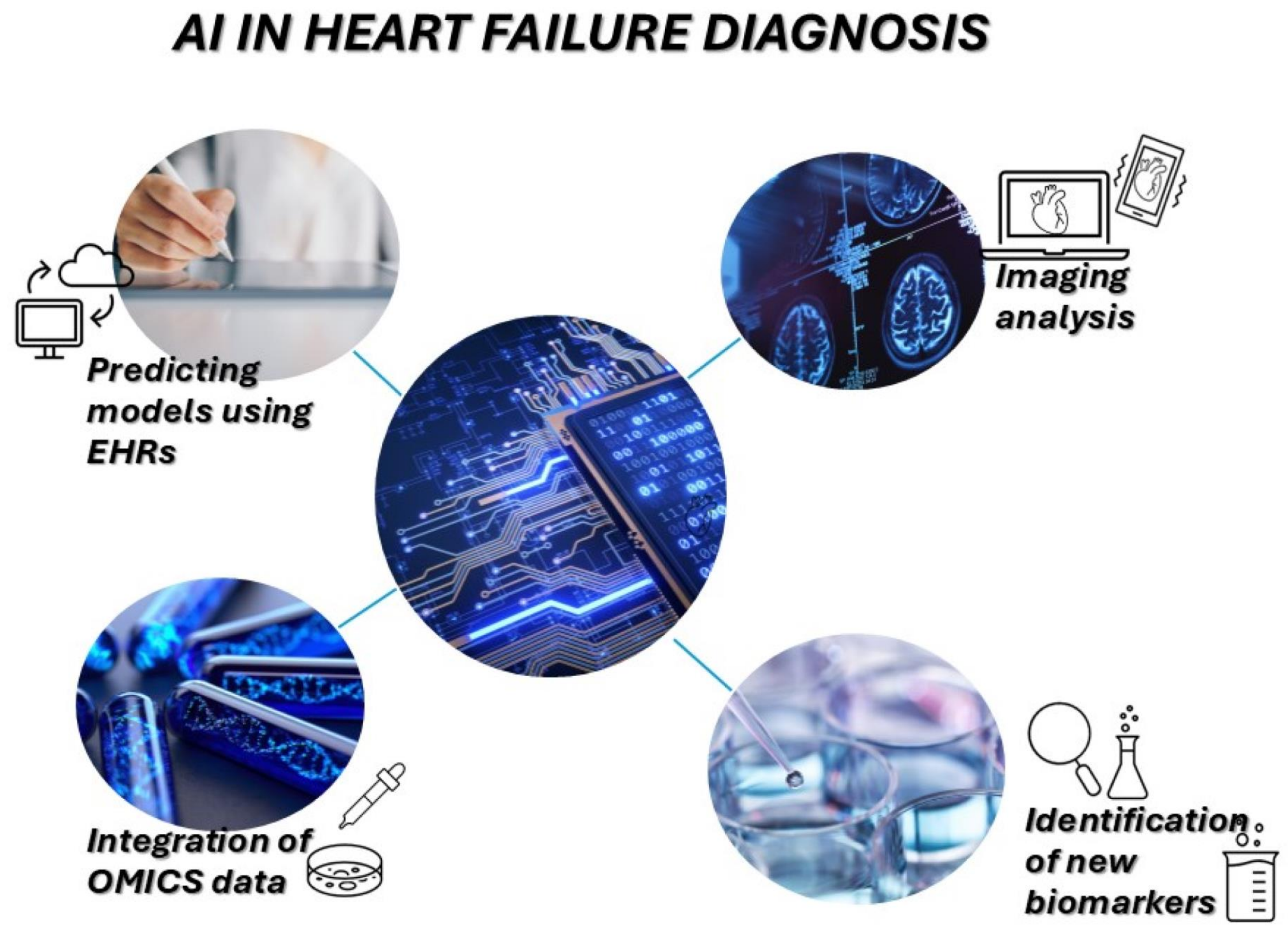
Nuove frontiere:
intelligenza artificiale e medicina di precisione

La crescente disponibilità di **big data clinici e omici** consente l'applicazione di modelli di machine learning per:

Clustering di fenotipi nascosti

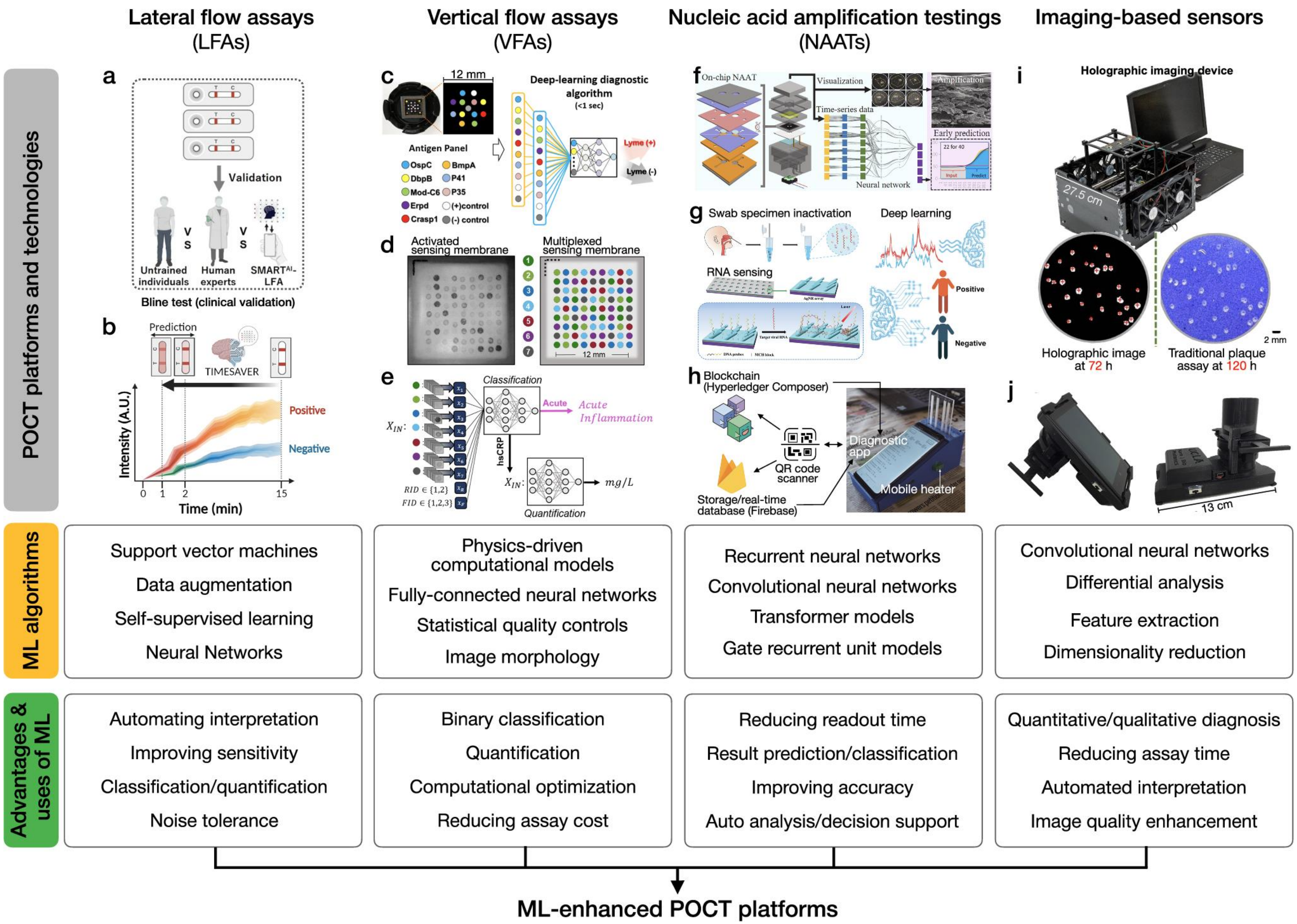
Predizione di risposta terapeutica

L'integrazione tra **AI e biotecnologia** apre la strada alla personalizzazione terapeutica per ogni paziente HFpEF.

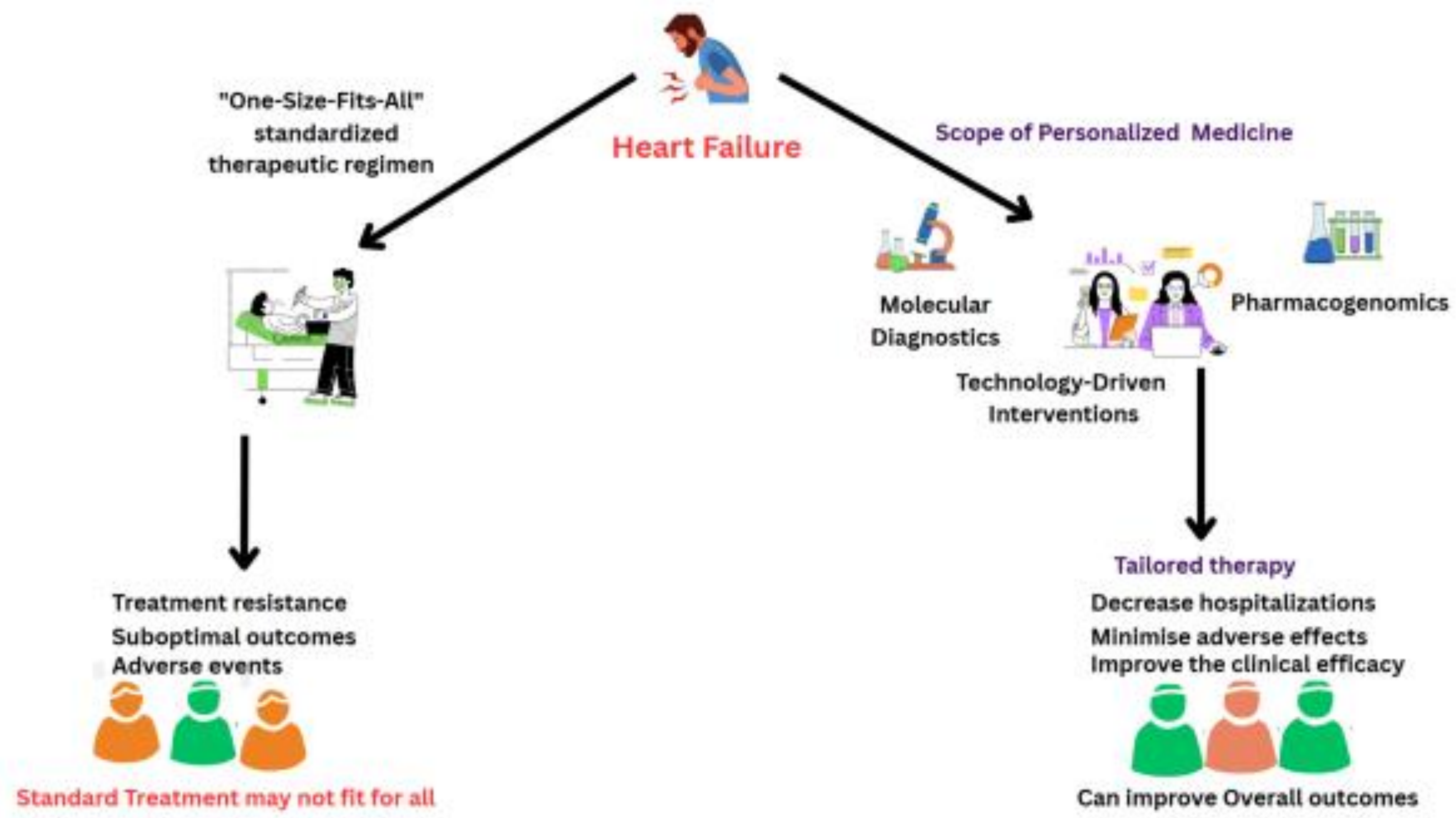

AI IN HEART FAILURE DIAGNOSIS
Predicting models using EHRs
Imaging analysis
Integration of OMICS data
Identification of new biomarkers

Summary of Technology-Driven Interventions in Heart Failure Management

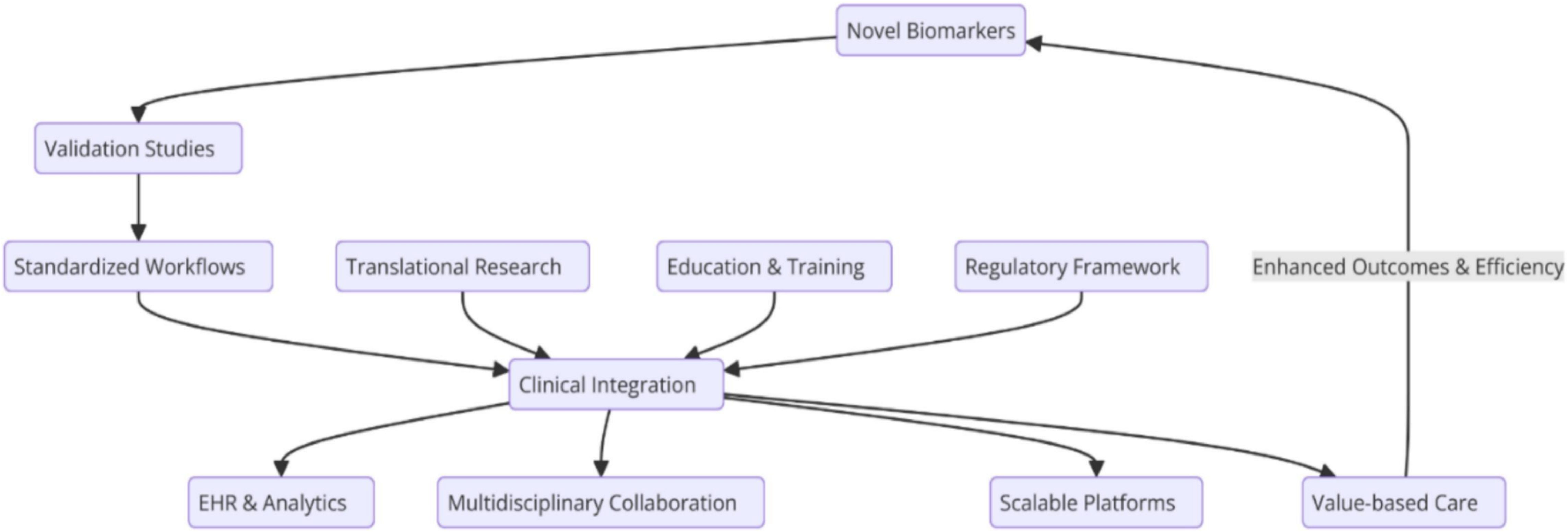
Technology/Intervention	Device/Platform	Functionality Monitored	Clinical Outcomes Observed
Pulmonary artery pressure monitoring [28]	CardioMEMS	Pulmonary artery pressure	48% reduction in hospitalizations; improved QoL
Wearable devices [33]	Apple Watch, Fitbit, ActiGraph	ECG, HR, oxygen saturation, physical activity	Improved self-care behaviors; mixed evidence for hospitalization reduction
AI-driven predictive algorithms [31,32]	Heart-Logic, SELENE-HF, Triage HF	Multi-parametric (HR, impedance, arrhythmias, activity)	Early warnings for decompensation, reduced hospitalizations
Telemedicine & mobile health [27]	Telehealth platforms, Health apps	Symptom reporting, vitals, medication adherence, and patient education	Improved self-care, no major impact on clinical outcomes


Lateral flow assays (LFAs)
Vertical flow assays (VFAs)
Nucleic acid amplification testings (NAATs)
Imaging-based sensors
POCT platforms and technologies
a
Validation
Untrained individuals
vs
Human experts
vs
SMART^AI-LFA
Bline test (clinical validation)
b
Prediction
TIMESAVER
Intensity (A.U.)
Positive
Negative
Time (min)
c
12 mm
Antigen Panel
OspC
BmpA
DbpB
P41
Mod-C6
P35
Erpd
(+)control
Crasp1
(-) control
Deep-learning diagnostic algorithm
(<1 sec)
Lyme (+)
Lyme (-)
d
Activated sensing membrane
Multiplexed sensing membrane
12 mm
e
Classification
Acute Inflammation
hsCRP
mg/L
Quantification
f
On-chip NAAT
Visualization
Amplification
Time-series data
Early prediction
Neural network
g
Swab specimen inactivation
Deep learning
RNA sensing
Positive
Negative
h
Blockchain (Hyperledger Composer)
QR code scanner
Diagnostic app
Mobile heater
Storage/real-time database (Firebase)
i
Holographic imaging device
27.5 cm
Holographic image at 72 h
Traditional plaque assay at 120 h
2 mm
j
13 cm
ML algorithms
Support vector machines
Data augmentation
Self-supervised learning
Neural Networks
Physics-driven computational models
Fully-connected neural networks
Statistical quality controls
Image morphology
Recurrent neural networks
Convolutional neural networks
Transformer models
Gate recurrent unit models
Convolutional neural networks
Differential analysis
Feature extraction
Dimensionality reduction
Advantages & uses of ML
Automating interpretation
Improving sensitivity
Classification/quantification
Noise tolerance
Binary classification
Quantification
Computational optimization
Reducing assay cost
Reducing readout time
Result prediction/classification
Improving accuracy
Auto analysis/decision support
Quantitative/qualitative diagnosis
Reducing assay time
Automated interpretation
Image quality enhancement
ML-enhanced POCT platforms

Clinical Translation:
Challenges and Opportunities



Clinical Translation: Challenges and Opportunities



Clinical Translation: Challenges and Opportunities