Diagnosing Heart Failure: How, where and who?

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Berlin, Germany
Diagnosing Heart Failure – how, where, and who?

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Heart Failure

• Heart Failure is a silently progressive condition

• Heart Failure (as is fever) is not a disease, it is a manifestation of distinct cardiovascular disorders

• We begin to look at the disorder at the end of its natural history – this is too late.

• Many patients at earlier/less severe stages fly “under the radar”

• Different clinical projectories: Same EF, different speeds of progression – role of metabolomics, genomics etc.? 
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

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www.escardio.org
Diagnosing Heart Failure

• Scope of the problem & general approach
• Assessing asymptomatic LV dysfunction
• Workup Heart failure with reduced EF
• Workup Heart Failure with preserved EF
The cardiovascular continuum

- Physical activity ↓
- Environmental determinants
- CVD risk factors & biomarkers
- Genetic determinants

Vascular Remodeling
- LVH
- Disturbed Microcirculation
- CAD / Infarktion

Myocardial Remodeling
- Diastolic Dysfunction
- Systolic Dysfunction
- Diastolic Heart Failure
- Systolic Heart Failure

Stage A → B → C/D
# Classification of Heart Failure

## By structural abnormalities

<table>
<thead>
<tr>
<th>ACC/AHA stages of heart failure</th>
<th>NYHA functional classification</th>
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</thead>
<tbody>
<tr>
<td>Stage A</td>
<td>Class I</td>
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<tr>
<td>At high risk for developing heart failure. No identified structural or functional abnormality; no signs or symptoms.</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.</td>
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<tr>
<td>Stage B</td>
<td>Class II</td>
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<tr>
<td>Developed structural heart disease that is strongly associated with the development of heart failure, but without signs or symptoms.</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.</td>
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<tr>
<td>Stage C</td>
<td>Class III</td>
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<tr>
<td>Symptomatic heart failure associated with underlying structural heart disease.</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnoea.</td>
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<tr>
<td>Stage D</td>
<td>Class IV</td>
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<tr>
<td>Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy.</td>
<td>Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.</td>
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</table>

## ACC/AHA Guideline: Classification of HF

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Description</th>
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<tr>
<td>A</td>
<td>Risk for developing HF (60mil.)</td>
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<td>• HTN</td>
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<td>• CAD</td>
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<td></td>
<td>• Diabetes mellitus</td>
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<td>• Family history of cardiomyopathy</td>
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<tr>
<td>B</td>
<td>Asymptomatic HF (10 mil.)</td>
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<td></td>
<td>• Previous MI</td>
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<td></td>
<td>• LV systolic dysfunction</td>
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<tr>
<td></td>
<td>• Asymptomatic valvular disease</td>
</tr>
<tr>
<td>C</td>
<td>Symptomatic HF (5 mil.)</td>
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<tr>
<td></td>
<td>• Known structural heart disease</td>
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<td></td>
<td>• Shortness of breath and fatigue</td>
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<td></td>
<td>• Reduced exercise tolerance</td>
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<tr>
<td>D</td>
<td>Refractory end-stage HF (200.000)</td>
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<tr>
<td></td>
<td>• Marked symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)</td>
</tr>
</tbody>
</table>

*Hunt SA et al. J Am Coll Cardiol. 2009*
What is heart failure?

Why are we here?
Is there life after death?

Definition and outcomes of in-hospital WHF?

What should be the discharge criteria for HHF patients?
Defining heart failure

R. Coronel\textsuperscript{a,*}, J.R. de Groot\textsuperscript{a}, J.J. van Lieshout\textsuperscript{b}
On behalf of the editorial team of Cardiovascular Research

Braunwald definition

A clinical \textit{syndrome} caused by the inability of the heart to supply blood to the tissues commensurate to the metabolic needs of that tissue, or is achieved so only at \textit{the expense of} \textit{elevated filling pressures}.
“Heart failure is the label for a cardiovascular syndrome that is lacking uniform criteria for definition”
Principles of Diagnosis

1. Consider! (Medical history, signs, symptoms)

1. Confirm (e.g., Natriuretic peptides, Echocardiography)

1. Assess clinical phenotype (e.g., HFrEF vs. HFpEF)

1. Assess etiology (Angiography, cMRI, Biopsy)

1. Risk stratification

1. Workup for targeted therapies
Definitions of HF

• **HFrEF** (reduced EF)  
  EF <40%

• **HFmEF** (mildly impaired EF)  
  EF 40-49%

• **HFpEF** (preserved EF)  
  EF ≥50%

• New onset, transient, chronic

• Acute, worsening

• Left heart, right heart, combined
Increased circumferential strain in HFpEF

Definitions of HF

- HFrEF (reduced EF)  \( EF < 40\% \)
- HFmEF (mildly impaired EF)  \( EF 40-49\% \)
- HFpEF (preserved EF)  \( EF \geq 50\% \)
- New onset, transient, chronic
- Acute, worsening
- Left heart, right heart, combined
Diagnosing Heart Failure

The diagnosis of HF-REF requires three conditions to be satisfied:

1. Symptoms typical of HF
2. Signs typical of HF
3. Reduced LVEF

The diagnosis of HF-PEF requires four conditions to be satisfied:

1. Symptoms typical of HF
2. Signs typical of HF
3. Normal or only mildly reduced LVEF and LV not dilated
4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction (see Section 4.1.2)
Assessment of cardiac remodeling: Targets for Therapy

1. **Structural remodeling**
   - Left ventricular hypertrophy, left atrial volume (HFpEF)
   - Left ventricular end-diastolic volume; end-systolic volume
   - Regional wall motion abnormalities
   - Fibrosis (late enhancement, T1 mapping)
   - Vascular remodeling (CAD)

2. **Functional remodeling**
   - Diastolic function (E’, E/E’, LVEDP)
   - Systolic function (e.g. ejection fraction, strain)

3. **Electrical remodeling**
   - LBBB
   - Atrial fibrillation
   - Ventricular arrhythmia

4. **Metabolic remodeling/ energetic function**
   - Mitochondrial dysfunction
   - Myocardial substrate utilization
Coronary microvascular dysfunction

Herrmann J et al., Eur Heart J, 2012, 33, 2771-2781
The need for phenotyping: Hibernation?

**Central Illustration**
Enhanced Phenotyping of Myocardial Substrate Leading to Targeted Therapies With the Goal of Achieving Myocardial Recovery

- Heart Failure with Reduced EF
- Recovery: "Normal" Structure and Function
- Vulnerable Myocardium
- Dysfunctional Myocyte
- Dysfunctional Myocardium
- Non-Viable Tissue

**Components of DVM**
1. Myocyte
2. Interstitium
3. Microcirculation
4. Abnormal mitochondria
5. Metabolic abnormalities

DVM = dysfunctional but viable myocardium; EF = ejection fraction.

Diagnosing Heart Failure

Diagnosis of Heart Failure – A staged process

A

Risk assessment at preclinical stage

B

Initial diagnostic workup in symptomatic patients

C

Detailed workup in case of uncertainty

- Clinical assessment/Comorbidities
- Biomarkers (Cardiac +EOD)
- Echocardiography
- Stress test

- Stress echocardiography
- Invasive tests & hemodynamics
- Cardiac MRI
- Comorbidities

- Cardiac MRI +++
- Biopsy
- Scintigraphy
- SPECT, Molecular imaging (?)
Diagnosing Heart Failure

- Scope of the problem & general approach
- Assessing asymptomatic LV dysfunction
- Workup Heart failure with reduced EF
- Workup Heart Failure with preserved EF
Asymptomatic systolic dysfunction

VALIANT Registry:

5,578 patients after myocardial infarction:

Incidence LV systolic dysfunktion (asymptomatic or symptomatic): 42%

Mortality 13%

(vs 2% in patients without asymptomatic or symptomatic LVSD)

Metoprolol Reverses Left Ventricular Remodeling in Patients With Asymptomatic Systolic Dysfunction
The REversal of VEntricular Remodeling with Toprol-XL (REVERT) Trial

Wilson S. Colucci, MD; Theodore J. Krias, MD; Kirkwood F. Adams, MD; William F. Armstrong, MD; Jalal K. Ghali, MD; Stephen S. Gottlieb, MD; Barry Greenberg, MD; Michael I. Klibaner, MD, PhD; Marrick L. Kukin, MD; Jennifer E. Sugg, MS; on behalf of the REVERT Study Group*

Figure 2. Effect of metoprolol succinate on LV volumes. Shown are the least square mean changes (SE) in LVESVI (A), LVEDVI (B), LVEF (C), and LVM (D) compared with baseline for patients receiving metoprolol succinate 200 mg (triangles), 50 mg (squares), or placebo (diamonds). *P<0.05 vs baseline; †P<0.05 vs placebo.
Asymptomatic diastolic dysfunction in the general population:

USA (Olmsted County, 67 years): 28%

Europe (Belgium, 58 years): 27%
Asymptomatic diastolic dysfunction & outcomes

**DIAST-CHF prospective cohort**

- n=1937
- 6 years-Follow-Up
- Prediction of death & Hospitalisation

![Graph showing the relationship between time from baseline and death or cardiovascular hospitalization.](image)

- Log rank tests
  - P<0.001 (four groups overall)
  - P<0.001 (Paulus positive vs. negative, stratified for HF signs/symptoms)
  - P=0.002 (HF signs/symptoms yes vs. no, stratified for Paulus)
Diagnosing Heart Failure

- Scope of the problem & general approach
- Assessing asymptomatic LV dysfunction
- Workup Heart failure with reduced EF
- Workup Heart Failure with preserved EF
HFrEF: Functional mitral regurgitation

Asgar AW et al., J Am Coll Cardiol. 2015 Mar 31
Inflammatory cardiomyopathy: Role of CMR and Myocardial Biopsy

Clinically suspected myocarditis
- cardiac signs and/or symptoms
- biomarkers, ECG changes, arrhythmias
- or LV dysfunction
- or exclusion of other cardiac causes

ACS-like presentation
- CMR
  - CMR evidence of myocarditis + chronic or recurrent symptoms
    - no
      - Consider EMB
    - yes

New-onset HF or arrhythmias
- CMR
  - CMR evidence of myocarditis or high clinical suspicion + HF despite treatment, worsening of HF or new ventricular arrhythmias
    - no
      - EMB
    - yes

Hemodynamic compromise or rapid worsening of HF
- EMB

Follow-up CMR

PS Biesbroek, Int J Cardiol. 2015 Jul 15;191:211-9
Left ventricular non-compaction CMP

Abnormal trabecularisations of the LV, associated with LV dilatation or hypertrophy, systolic and/or diastolic dysfunction. Genetic inheritance in 30-50%.

ECG abnormalities in 87%: Hypertrophy...

Trabeculations & intratrabecular recesses

Towbin JA et al., Lancet 2015; 386:813-825
Left ventricular non-compaction CMP

Prevalence: uncertain, presumably rare. 0.05-0.26% (all comers echo) vs. 3.7% in EF<45% ; up to 8 subtypes.

MRI: Thickness ratio of non-compacted to compacted layer (>2.3 : 1 at end-diastole)

Coarseley trabeculated LV (short axis view)

Towbin JA et al., Lancet 2015; 386:813-825
ESC HF GL 2012: Specific workup of HFrEF

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</table>

**Main advantages**
- Wide availability
- Parallelisty
- No radiation
- Relatively low cost
- Good quality images: low radiation
- Good availability
- Good availability
- Reasonable availability
- High quality images
- Limited availability
- Good quality images

**Main disadvantages**
- Echo window needed
- Limited availability
- Functional analysis
- Image quality limited if arrhythmia
- Radiation invasive
- Radiation
- Radiation: quality limited if arrhythmia
- Radiation: limited availability

McMurray et al Eur J Heart Fail. 2012
Diagnosing Heart Failure

- Scope of the problem & general approach
- Assessing asymptomatic LV dysfunction
- Workup Heart failure with reduced EF
- Workup Heart Failure with preserved EF
Do these patients really have heart failure?

“Hypertensive, overweight elderly Women with swollen ankles”

Outcomes in HF-PEF compared to other populations.
What Have We Learned About Patients With Heart Failure and Preserved Ejection Fraction From DIG-PEF, CHARM-Preserved, and I-PRESERVE?

Ross T. Campbell, MB ChB, BSc,* Pardeep S. Jhund, MB ChB, PhD,* Davide Castagno, MD,† Nathaniel M. Hawkins, MB ChB, MD,‡ Mark C. Petrie, MB ChB, BSc,§ John J. V. McMurray, MD* Glasgow, United Kingdom; Turin, Italy; and Liverpool, United Kingdom
Current HFA/ESC Diagnostic Recommendations

Paulus W et al. Eur Heart J 2007
NTproBNP in HFpEF: I-Preserve

Baseline plasma NT-proBNP and clinical characteristics

Majority in NYHA III

Median NTproBNP: 341 (135-974) pg/ml

No Atrial fibrillation: around 250 pg/ml

With atrial fibrillation: >900 pg/ml

McKelvie et al.; J Card Fail 2010; 16(2):128-134
### Soluble Guanylate Cyclase stimulator Heart Failure Studies: The SOCRATES Program

#### Key inclusion criteria

<table>
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<th>SOCRATES-REDUCED</th>
<th>SOCRATES-PRESERVED</th>
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<tr>
<td>WCHF requiring hospitalization or IV diuretic treatment for HF without hospitalization</td>
<td>LVEF ≥45%</td>
</tr>
<tr>
<td>LVEF &lt;45%</td>
<td>LA enlargement</td>
</tr>
<tr>
<td>NYHA class II–IV and treatment with standard HF therapy ≥30 days</td>
<td>NYHA class II–IV ≥30 days</td>
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<tr>
<td>Symptoms and signs of congestion</td>
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<td>Clinical stabilization defined by no IV vasodilator for &gt;24 h and no IV diuretic for &gt;12 h before randomization and</td>
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<tr>
<td>- SBP ≥110 but &lt;160 mmHg and</td>
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<td>- Resting HR ≥50 but &lt;100 bpm at randomization</td>
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<td>or</td>
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<td>or</td>
<td>≥200</td>
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AF, atrial fibrillation; DBP, diastolic blood pressure; HF, heart failure; IV, intravenous; LA, left atrial; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; WCHF, worsening chronic heart failure.
TOPCAT: Prediction of outcomes

HFpEF: Hemodynamics during exercise

Controls vs. HFPEF patients, invasive hemodynamics & exercise

Borlaug et al.; Eur Heart J 2011; 32: 670-679
The MEDIA diastolic stress test protocol

Whenever patient develops symptoms, or HR = 100-110/min, hold workload constant

After completing acquisition of images (~3 minutes), resume ramped protocol

Ramp + 5 W m⁻¹
"Accelerators"

Risk Factors
- Age
- Hypertension
- Diabetes mellitus
- Obesity
- Sedentary lifestyle

"Red flag" indicators
- LV hypertrophy
- Reduced LV long-axis function
- Impaired relaxation
- Enlarged left atrium
- Atrial fibrillation

Diagnostic criteria
- Reduced suction reserve
- Reduced stroke volume / cardiac output reserve
- High LV filling pressures
- Pulmonary hypertension

"Brakes"

Rule out other causes
- Anaemia
- Heart valve disease
- Coronary artery disease
- Chronic obstructive pulmonary disease

Other findings during stress
- LV outflow tract obstruction
- Dynamic mitral regurgitation
- New regional wall motion abnormalities / ischaemia
- Chronotropic incompetence

Normal LVEF

Diastolic stress echo

HFPEF
Diagnosis of Heart Failure – A staged process

A

Risk assessment at preclinical stage

Initial diagnostic workup in symptomatic patients

B

Detailed workup in case of uncertainty

C

Underlying pathophysiology & etiology

- Clinical assessment/Comorbidities
- Biomarkers (Cardiac +EOD)
- Echocardiography
- Stress test
- Stress echocardiography
- Invasive tests & hemodynamics
- Cardiac MRI
- Comorbidities
- Cardiac MRI +++
- Biopsy
- Scintigraphy
- SPECT, Molecular imaging (?)
Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction

Esther González-López¹, Maria Gallego-Delgado¹, Gonzalo Guzzo-Merello¹, F. Javier de Haro-del Moral², Marta Cobo-Marcos¹, Carolina Robles¹, Belén Bornstein³,⁴,⁵, Clara Salas⁶, Enrique Lara-Pezzi⁷, Luis Alonso-Pulpon¹, and Pablo Garcia-Pavia¹,⁷*

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Prospective cross-sectional study, symptomatic HFpEF including LVH (LVEDWT ≥12mm)

¹⁹⁹m⁹⁹Tc-3,3-diphosphono-1,2-propanodi-carboxylic acid scintigraphy (¹⁹⁹m⁹⁹Tc-DPD)

Genetic analysis for mutations in the TTR gene
Wild-type transthyretrin amyloidosis: Scintigraphy

$^{99m}$Tc-3,3-diphosphono-1,2-propanodi-carboxylic acid scintigraphy (severe $^{99m}$Tc-DPD cardiac uptake)
Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction

Esther González-López¹, Maria Gallego-Delgado¹, Gonzalo Guzzo-Merello¹, F. Javier de Haro-del Moral², Marta Cobo-Marcos¹, Carolina Robles¹, Belén Bornstein³,⁴,⁵, Clara Salas⁶, Enrique Lara-Pezzi⁷, Luis Alonso-Pulpon¹, and Pablo García-Pavia¹,⁷*

• 120 HFpEF patients included
• 16 patients (13.3%) with moderate-severe $^{99m}$Tc-DPD cardiac uptake
• No mutations found on genetic testing
• EMB in 4 patients demonstrated ATTR WT in all cases
Targeting therapies to the HF phenotype!!

HF symptoms
Preserved LVEF

Plus Primary Comorbidity(ies)

HTN
- ARB/ACEI
- MRA
- ARNI
- Autonomic modulation

Fluid retention
Elevated filling pressure
- ARNI

Diabetes, obesity, metabolic syndrome, conditions associated with oxidative stress
- Glycemic control
- Metformin (pleiotropic effects)
- Weight loss, bariatric surgery, diet
- PKG stimulation
- AGE crosslink breakers?

Pulmonary hypertension or right heart involvement
- PDE5 inhibitor
- Orally active soluble guanylate cyclase stimulator

Cardiac fibrosis
- MRA

Ischemia
- Na channel blockers
- Nitrates
- Beta-blockers

Renal
- Sodium restriction
- ACEI or ARB

Senni & Pieske, Eur Heart J 2014; in press
Summary

• Heart failure is a syndromal disorder with multiple phenotypic expressions

• HF Diagnosis should be considered at all levels of care: Lay education, Nurse, GP, Internist, Cardiologists

• Screening for cardiac dysfunction in patients at risk

• Confirmation of HF diagnosis by objective diagnostic measures essential (ECG, echo, BNP)

• Minute further workup for the underlying phenotype (HFrEF vs HFpEF!) and etiology is crucial

• New diagnostic technologies allow better and targeted therapies