Καρδιακή ανεπάρκεια: κατάταξη και αντιμετώπιση με βάση το κλάσμα εξώθησης;

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Είναι γεγονός ότι επί τουλάχιστον 30 έτη προόδου στην καρδιακή ανεπάρκεια...

- Ο ορισμός βασιζόταν στο κλάσμα εξώθησης
- Η θεραπεία βασιζόταν στο κλάσμα εξώθησης
- Η πρόγνωση βασιζόταν στο κλάσμα εξώθησης
30 years Progress in Heart failure history

Circulation. 2000;102:1126-1131
European Heart Journal 2015;36, 3467–3470
2016 ESC HF Guidelines and ACC/AHA/HFSA Focused Updates

- **Ponikowski P et al.,** ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 21 May 2016

- **Yancy CW et al.,** ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure, JACC. 21 May 2016
Ορισμός με βάση το κλάσμα εξώθησης

Table 3.1 Definition of heart failure with preserved (HFrEF), mid-range (HFrEF) and reduced ejection fraction (HFrEF)

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFrEF</th>
<th>HFrEF</th>
</tr>
</thead>
</table>
| 1          | Symptoms ± Signs
|            | Symptoms ± Signs
|            | Symptoms ± Signs |
| 2          | LVEF <40% | LVEF 40–49% | LVEF ≥50% |
| 3          | – | 1. Elevated levels of natriuretic peptides; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE); b. diastolic dysfunction (for details see Section 4.3.2). | 1. Elevated levels of natriuretic peptides; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE); b. diastolic dysfunction (for details see Section 4.3.2). |

BNP = B-type natriuretic peptide; HF = heart failure; HFrEF = heart failure with preserved ejection fraction; HFrEF = heart failure with mid-range ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

*Signs may not be present in the early stages of HF (especially in HFrEF) and in patients treated with diuretics.

1BNP > 35 pg/ml and/or NT-proBNP > 125 pg/mL.

...αλλα με βασικό κριτήριο τα συμπτώματα... ενώ ο ορισμός επεκτείνεται και σε υψηλά KE....
Καρδιακή ανεπάρκεια με διατηρημένο κλάσμα εξώθησης

- Αυτοδύναμη οντότητα ή άθροισμα συνοσηροτήτων;
- …The proportion of patients with HFpEF ranges from 22 to 73%, depending on the definition applied, the clinical setting (primary care, hospital clinic, hospital admission), age and sex of the studied population, previous myocardial infarction and the year of publication… ESC 2016
Διάγνωση Καρδιακής Ανεπάρκειας

• Κλινικό ιστορικό-εξέταση

• NPs /echo
NP levels seem to reflect LV wall stress more closely than other ventricular parameters in HF.
Διάγνωση οξείας Καρδιακής Ανεπάρκειας

- Το κλάσμα εξώθησης απουσιάζει από την κλινική ταξινόμηση
- Σε αυτή την ταξινόμηση βασίζεται η αντιμετώπιση
- Esc 2016
Ενδείξεις μεταμόσχευσης-ρόλος ΚΕ

Table 13.3 Patients potentially eligible for implantation of a left ventricular assist device

| Patients with >2 months of severe symptoms despite optimal medical and device therapy and more than one of the following: |
| LVEF <25% and, if measured, peak VO₂ <12 mL/kg/min. |
| ≥3 HF hospitalizations in previous 12 months without an obvious precipitating cause. |
| Dependence on i.v. inotropic therapy. |
| Progressive end-organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥20 mmHg and SBP ≤80–90 mmHg or CI ≤2 L/min/m²). |
| Absence of severe right ventricular dysfunction together with severe tricuspid regurgitation. |

CI = cardiac index; HF = heart failure; i.v. = intravenous; LVEF = left ventricular ejection fraction; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure; VO₂ = oxygen consumption.

Table 13.4 Heart transplantation: indications and contra-indications

| Patients to consider | End-stage HF with severe symptoms, a poor prognosis, and no remaining alternative treatment options. Motivated, well informed, and emotionally stable. Capable of complying with the intensive treatment required postoperatively. |
| Contra-indications | Active infection. |
| | Severe peripheral arterial or cerebrovascular disease. |
| | Pharmacologically irreversible pulmonary hypertension (LVAD should be considered with a subsequent re-evaluation to establish candidacy). |
| | Cancer (a collaboration with oncology specialists should occur to stratify each patient as to their risk of tumour recurrence). |
| | Irreversible renal dysfunction (e.g. creatinine clearance <30 mL/min). |
| | Systemic disease with multi-organ involvement. |
| | Other serious co-morbidity with poor prognosis. |
| | Pre-transplant BMI >35 kg/m² (weight loss is recommended to achieve a BMI <35 kg/m²). |
| | Current alcohol or drug abuse. |
| | Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting. |

BMI = body mass index; HF = heart failure; LVAD = left ventricular assist device.
Table 1. Indications and Contraindications for Heart Transplantation

Absolute indications in appropriate patients:
- For hemodynamic compromise caused by HF
  - Refractory cardiogenic shock
  - Documented dependence on intravenous inotropic support to maintain adequate organ perfusion
  - Peak $\dot{V}O_2 < 10$ mL kg$^{-1}$ min$^{-1}$ with achievement of anaerobic metabolism
  - Severe symptoms of ischemia that consistently limit routine activity and are not amenable to coronary artery bypass surgery or percutaneous coronary intervention
  - Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities

Relative indications:
- Peak $\dot{V}O_2$ 11 to 14 mL kg$^{-1}$ min$^{-1}$ (or 55% predicted) and major limitation of the patient’s daily activities
- Recurrent unstable ischemia not amenable to other intervention
- Recurrent instability of fluid balance/renal

Insufficient indications:
- Low left ventricular ejection fraction
- History of functional class III or IV symptoms of HF
- Peak $\dot{V}O_2 > 15$ mL kg$^{-1}$ min$^{-1}$ (and >55% predicted) without other indications

Absolute contraindications:
- Systemic illness that will limit survival despite heart transplantation
  - HIV/AIDS (definition: CD4 count <200 cells/mm$^3$)
  - Neoplasm other than skin or low-grade prostate cancer that has not been cured or is not in remission
  - Systemic lupus erythematosus or sarcoid with multisystem involvement
- Fixed pulmonary hypertension
  - Pulmonary vascular resistance >6 Wood units
  - Transpulmonary gradient >15 mm Hg

Relative contraindications:
- Age >72 y
- Severe peripheral vascular or cerebrovascular disease
- Diabetes mellitus with end-organ damage
- Severe lung, liver, or renal disease
- Uncorrected abdominal aortic aneurysm (≥4–6 cm)
- Systemic infection (HIV, hepatitis B, Hepatitis C)
- Psychosocial impairment

HF indicates heart failure. Adapted from Mancini and Lietz.²⁶
Μοντέλα κινδύνου Seattle HF model

- Ηλικία
- Φύλο
- KE
- %λεμφοκυττάρων
- Δόσεις διουρητικών
- Λήψη αγωγής άξονα
- Λήψη β αποκλειστή
- NYHA
- Ουρικό οξύ
- Χοληστερίνη
- Νατριο
- Λήψη αλλοπουρινόλης
### Μοντέλα κινδύνου Seattle HF model

<table>
<thead>
<tr>
<th>Μέτρα</th>
<th>Θηλυ</th>
<th>Θηλυ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ηλικία</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Φύλο</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>ΚΕ</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>%λεμφοκυττάρων</td>
<td>240</td>
<td>40</td>
</tr>
<tr>
<td>Δόσεις διουρητικών</td>
<td>Ναι</td>
<td>Ναι</td>
</tr>
<tr>
<td>Λήψη αγωγής άξονα</td>
<td>Ναι</td>
<td>Ναι</td>
</tr>
<tr>
<td>Λήψη β αποκλειστή</td>
<td>IV</td>
<td>II</td>
</tr>
<tr>
<td>NYHA</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Ουρικό οξύ</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>Χοληστερίνη</td>
<td>132</td>
<td>134</td>
</tr>
<tr>
<td>Νατριο</td>
<td>Ναι</td>
<td>Ναι</td>
</tr>
<tr>
<td>Λήψη αλλοπουρινόλης</td>
<td>59,6%</td>
<td>91,2%</td>
</tr>
<tr>
<td>Πιθανότητα επιβίωσης έτους</td>
<td>7,5%</td>
<td>63,2%</td>
</tr>
</tbody>
</table>
Τι αλλάζει σε αυτές τις περιπτώσεις?

- Τη σημαντικότερη θέση έχει το κλινικό στάδιο και η ανάγκη χορήγησης υψηλών δόσεων διουρητικών, ανεξαρτήτως κλάσματος εξώθησης
- Τελοδιαστολικές πιέσεις πλήρωσης αριστερής κοιλίας;
- Λειτουργικότητα δεξιάς κοιλίας;
- Σημαντικότητα ανεπάρκειας μιτροειδούς βαλβίδας;
Είναι ζήτημα αιμοδυναμικής;

Table 1: Haemodynamic Parameters at Rest in Healthy Adults and HFrEF Patients

<table>
<thead>
<tr>
<th></th>
<th>Healthy adults</th>
<th>Early HFrEF</th>
<th>Advanced HFrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mmHg)</td>
<td>0–6</td>
<td>0–8</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&gt;25</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>6–15</td>
<td>6–18</td>
<td>&gt;20</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>&lt;16</td>
<td>&lt;16</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>

HFrEF haemodynamics result from the tight interplay of both cardiac and non-cardiac factors. HF = heart failure, HFrEF = heart failure with preserved ejection fraction, LVEDP = left ventricular end-diastolic pressure.
Η καρδιά στο κέντρο..
Παράδειγμα ασθενούς Α

Ασθενής 55 ετών με ισχαιμική καρδιακή ανεπάρκεια σε NYHA I-II, σε αγωγή valsartan 160mg, Furosemide 40mg, eplerenone 50mg, carvedilol 25mg, aspirine, statin.
Παράδειγμα: ασθενής B
Παράδειγμα ασθενής Β

Ο καρδιακός καθετηριασμός RA=10, V=15 (32), RV=61/11. PA=62/22/37, PW=18, SAT=95% Lvdiasstole=19, Pa SAT=64%, PVR=4woods και επηρεασμένη απόδοση δεξιάς κοιλίας (Κλάσμα εξώθησης αυτής 30%).

Η καρδιοαναπνευστική δοκιμασία κόπωσης είναι σταδίου C κατά Weber με Vo2mas=12,6 ml/k/min, VE/VCO2=39,
Στην κλινική πράξη

- Τα μοντέλα αδυνατούν να αποτυπώσουν την πραγματικότητα
- BUN και Na έχουν δείξει υψηλή διαγνωστική αξία σε μοντέλα (αντανάκλαση νευροορμονικού άξονα)
- Στο Seattle Heart Failure model σε 7000 ασθενείς η δόση διουρητικού είχε υψηλότερη διαγνωστική αξία (ROC) από BUN και Na.

- Data from patients with HFrEF (Val-HeFT [Valsartan Heart Failure Trial]) and HFpEF (I-PRESERVE [Irbesartan in Heart Failure With Preserved Ejection Fraction Study]) trials show that despite significantly higher baseline levels of NP in HFrEF, the hazard for mortality associated with 1 log unit increase in N-terminal pro-B-type natriuretic peptide (NT-proBNP) is similar in both HFrEF and HFpEF populations (hazard ratio: ∼1.70)

- Στην κλινική πράξη την πορεία του ασθενούς με καρδιακή ανεπάρκεια καθορίζει η λειτουργικότητα της δεξιάς κοιλίας και η εμφάνιση λειτουργικής ανεπάρκειας μιτροειδούς μιτροειδούς βαλβίδας.
Καρδιοαναπνευστική δοκιμασία κόπωσης

**CENTRAL ILLUSTRATION** Integrated Assessment of CPET Variables for Risk Stratification in HF

- **HIGH RISK:**
  - >20% 1 year mortality
  - \( \frac{V_{E}}{V_{CO2}} \text{ slope } > 36 \)
  - \( \text{Peak } SBP < 120 \text{mmHg} \)
  - \( \downarrow \text{HR recovery} (<60 \text{bpm}) \)
  - \( \Delta \text{to} < 12 \text{ml/kg/min} \)
  - \( \Delta \text{to} < 50\% \text{pred} \)

  - Ventilatory efficiency and stability
  - Hemodynamic response
  - \( OUES \times 1.4 \)
  - \( \text{VO}_2 @ VT < 9 \text{ml/kg/min} \)

  - **Submaximal test (RER < 1.0)**
    - Focus on submax/effort independent variables
    - \( \text{VO}_2 @ VT > 11 \text{ml/kg/min} \)

  - **Symptomatic Ambulatory HF Patients (NYHA II-IV)**
    - Peak \( \text{VO}_2 < 14 \text{ml/kg/min} \)
    - \( \downarrow \text{Age, } \uparrow \text{BMI} \)

  - \( \text{Maximal test (RER } > 1.0, \text{ preferably } > 1.1) \)
    - Peak \( \text{VO}_2 \)
    - \( 14-20 \text{ ml/kg/min, } 50-80\% \text{ pred} \)
    - Focus on hemodynamic/ventilatory variables

- **LOW RISK:**
  - >95% Event-free Survival at 1 year
  - \( \frac{V_{E}}{V_{CO2}} \text{ slope } < 30 \)
  - No Exercise Oscillatory Ventilation

Risk estimation with CPET in patients with heart failure (2nd step)

- **HFrEF**
  - peak VO$_2$ mL/kg/min
    - **≤10**
      - pRER $\geq 1.15$?
        - Yes
          - High risk
        - No
          - Moderate to high risk
    - **10-18**
      - VE/VO$_2$ slope $\geq 35$
        - Yes
          - Mild to moderate risk
        - No
          - Very low risk
    - **≥18**
      - peak VO$_2$ mL/kg/min
        - ≤8
          - Moderate to high risk
        - >8-12
          - Mild to moderate risk
        - >12
          - Very low risk

- **HFpEF**
  - Peak percentage of predicted VO$_2$ (%)
    - <50
      - Mild to moderate risk
    - ≥50
      - Very low risk

If exercise oscillatory ventilation is identified...

- Very high risk
- High risk
- Moderate risk
- Low risk
Arrhythmic Risk Stratification in Post Myocardial Infarction Patients with Preserved Ejection Fraction. The PRESERVE EF Study

K Gatzoulis EHJ 2019
The median duration of follow-up was 39 months in the trial. The Kaplan-Meier 2-year total mortality rate was 22% for the entire study population. The Kaplan-Meier 2-year rate of arrhythmic death or cardiac arrest was 14%.
### Table 3: Multivariable Relationships With Arrhythmic Death or Cardiac Arrest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chi-Square</th>
<th>p Value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducible VT</td>
<td>12.55</td>
<td>0.0004</td>
<td>1.89 (1.33–2.69)</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>6.84</td>
<td>0.0089</td>
<td>1.99 (1.19–3.33)</td>
</tr>
<tr>
<td>Patient enrolled as inpatient</td>
<td>6.80</td>
<td>0.0091</td>
<td>1.88 (1.17–3.02)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>6.35</td>
<td>0.0118</td>
<td>1.19 (1.07–1.37)*</td>
</tr>
<tr>
<td>NSVT not discovered within 10 days after CABG</td>
<td>4.04</td>
<td>0.0443</td>
<td>1.86 (1.02–3.40)</td>
</tr>
<tr>
<td>LVCD or LBBB</td>
<td>3.94</td>
<td>0.0473</td>
<td>1.46 (1.01–2.11)</td>
</tr>
</tbody>
</table>

*Hazard ratio for a 5% decrease in ejection fraction.

### Table 4: Calculation of Total Mortality Score

- **EF ≤20**
- **For values of EF between 20 and 40, add 1 point for each EF point <40**
- **EF = 40**
- **LVCD or LBBB**
- **NYHA functional class**
  - Class III
  - Class II
- **Inducible VT**
- **Age ≥80 yrs**
- **For each year between 50 and 80, add 0.5 point**
- **Age ≤50 yrs**
- **No prior CABG**
- **History of atrial fibrillation**
- **History of congestive heart failure**

### Table 5: Calculation of Arrhythmic Death/Cardiac Arrest Score

| Inducible VT                    | 17 |
| History of CHF                  | 19 |
| Patient enrolled as inpatient   | 17 |
| EF ≥20                          | 20 |
| For values of EF between 20 and 40, add one point for each EF point <40 |     |
| EF = 40                         | 0  |
| NSVT not discovered within 10 days after CABG | 17 |
| LVCD or LBBB                    | 10 |

---

Διαβάθμιση κινδύνου 2-ετίας

**Buxton et al JACC 2007; 50Q:1153**
The present study demonstrates the potential danger of focusing efforts to reduce risk of sudden death only on patients with EF 30%.

...consideration of multiple risk factors has the potential to provide more accurate prediction for risk of sudden death as well as total mortality. As a result, the model identifies a population of patients that meets current guidelines for prophylactic ICD implantation in patients with coronary disease but is unlikely to derive a significant improvement in 2-year survival with the ICD.
CMR LGE in NICM patients strongly predicts adverse cardiac outcomes (hospitalization for heart failure, appropriate ICD firing, and cardiac death). Its identification may significantly improve risk stratification strategies in this high risk population.

- Scar >5% & EF <30% increases risk
- Combination biomarkers with MRI
  - Klem JACC 2012;408
  - JACC 2008;51:2414
Left Ventricular Midwall Fibrosis as a Predictor of Mortality and Morbidity After Cardiac Resynchronization Therapy in Patients With Nonischemic Cardiomyopathy

J Am Coll Cardiol 2012;60:1659–67
Electrophysiologic testing guided risk stratification approach for sudden cardiac death beyond the left ventricular ejection fraction.

- Current risk stratification strategies focus on combinations of non invasive methods like T wave alternans, late potentials, heart rate turbulence, deceleration capacity and others, with invasive methods like the electrophysiologic study.
- Programmed ventricular stimulation provides important prognostic information for the selection of the patients expected to benefit from an ICD implantation, while due to its high negative predictive value, patients at low risk level may also be detected.

DANISH evaluated cardiac resynchronization therapy (CRT), with or without ICD, in 1116 patients with DCM along with heart failure class II or III; although SCD decreased in the younger cohort, no overall survival benefit was evident, even in patients receiving CRT-ICD. Corroborating the absence of survival benefit in three small-scale randomized clinical trials DANISH reinforces earlier considerations on the value of LV ejection fraction and functional class as the sole criterion for risk-stratifying patients with DCM. Moreover, such benefit was of borderline statistical significance in the Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT) DCM subpopulation.

Gatzoulis KA et al WJC 2016
Gatzoulis KA, HJC 2018
Should we merely consider ejection fraction for the evaluation of left ventricular function in patients with aortic valve stenosis?

- Deformation imaging (strain and strain rate) using speckle-tracking echocardiography has been shown to be more sensitive than EF in detecting myocardial contractility.
- Symptomatic status merely depends on diastolic function and modestly on systolic function.
- Dichotomising function using LV ejection fraction is a major oversimplification, as those with small cavity size (due to hypertrophy), or significantly impaired long axis function may also develop low flow.

Chrysohoou C, HJC 2019
In fact, patients with preserved or mid-range LVEF may present with a low cardiac output due to several mechanisms, such as modifications in loading conditions and the presence of arrhythmias like atrial fibrillation.

Therefore, it is important to decipher pathophysiological mechanisms that underlie the functional status, beyond the simplistic definition of preserved, mid-range, and reduced LVEF.

In the management of patients with HF, we believe that the assessment of ventricular function, which depends on chamber volumes and pressures, as well as on Doppler flows and TDI images, could be more accurate and useful than the mere identification of LVEF that is suggested by the latest ESC guidelines.

ESC 2018