

# IL RUOLO CHIAVE DELLA CARDIOLOGIA DEL TERRITORIO NELLA GESTIONE FARMACOLOGICA INNOVATIVA DEL PAZIENTE CON SCOMPENSO CARDIACO

Roma, 22-23 Novembre 2019

GESTIONE NEL TERRITORIO DEL PAZIENTE AFFETTO DA SCOMPENSO  
CARDIACO DOPO LA DIMISSIONE DALL'OSPEDALE

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## OTTIMIZZAZIONE DELLA CAPACITA' DI ESERCIZIO DOPO INIZIO DI SACUBITRIL/VALSARTAN

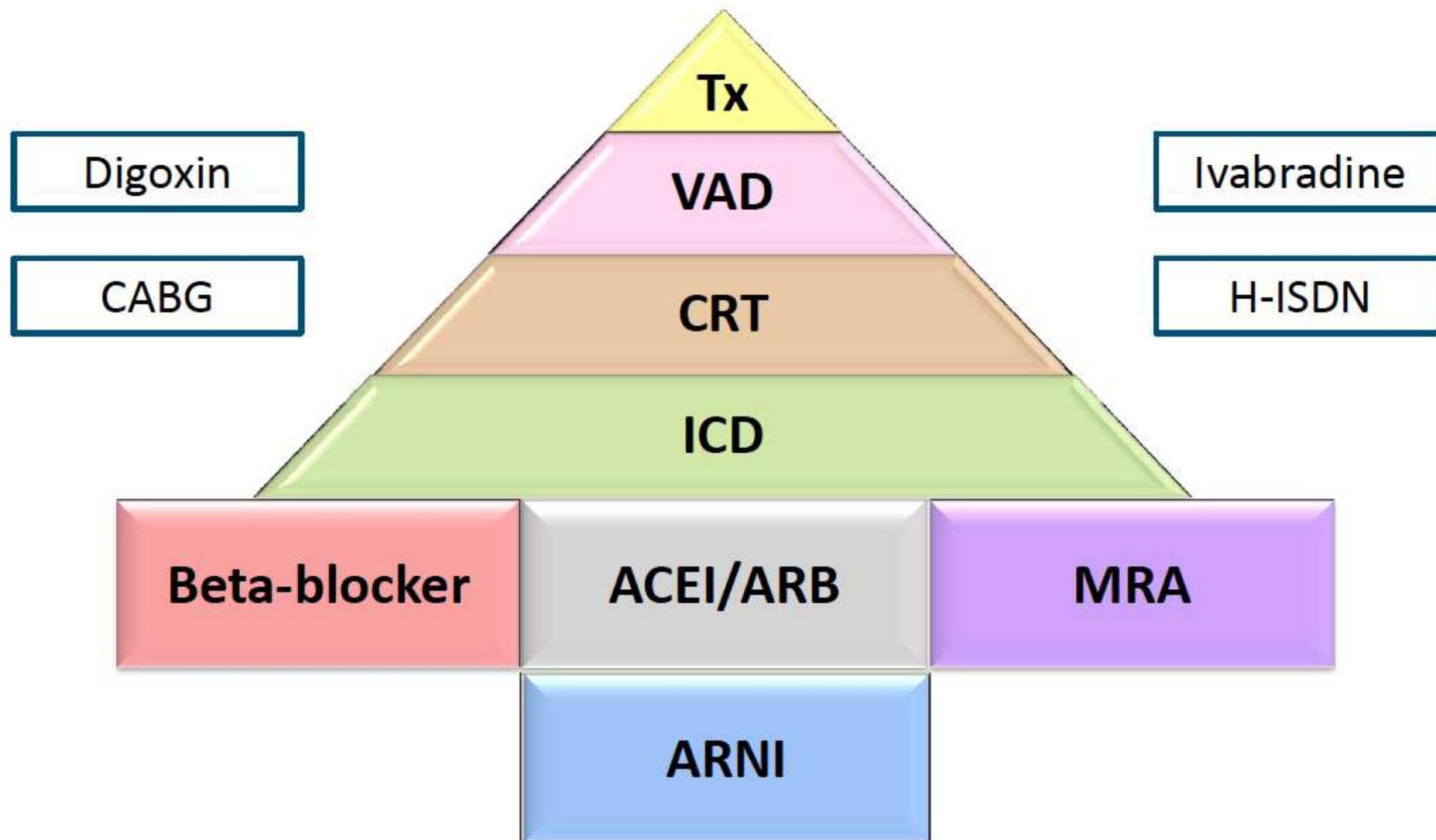
**Stefania Paolillo**

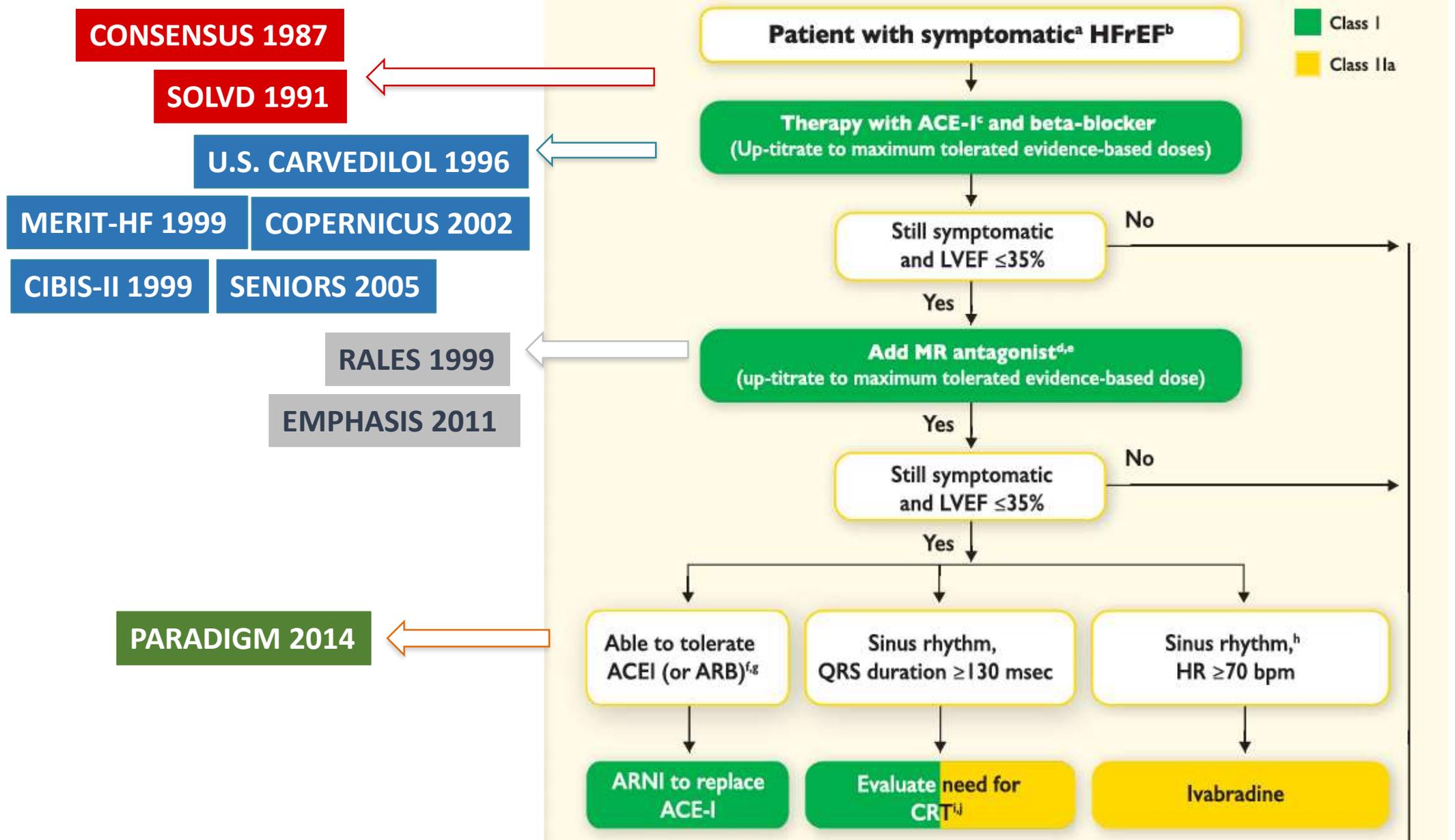
Dipartimento di Scienze Biomediche Avanzate

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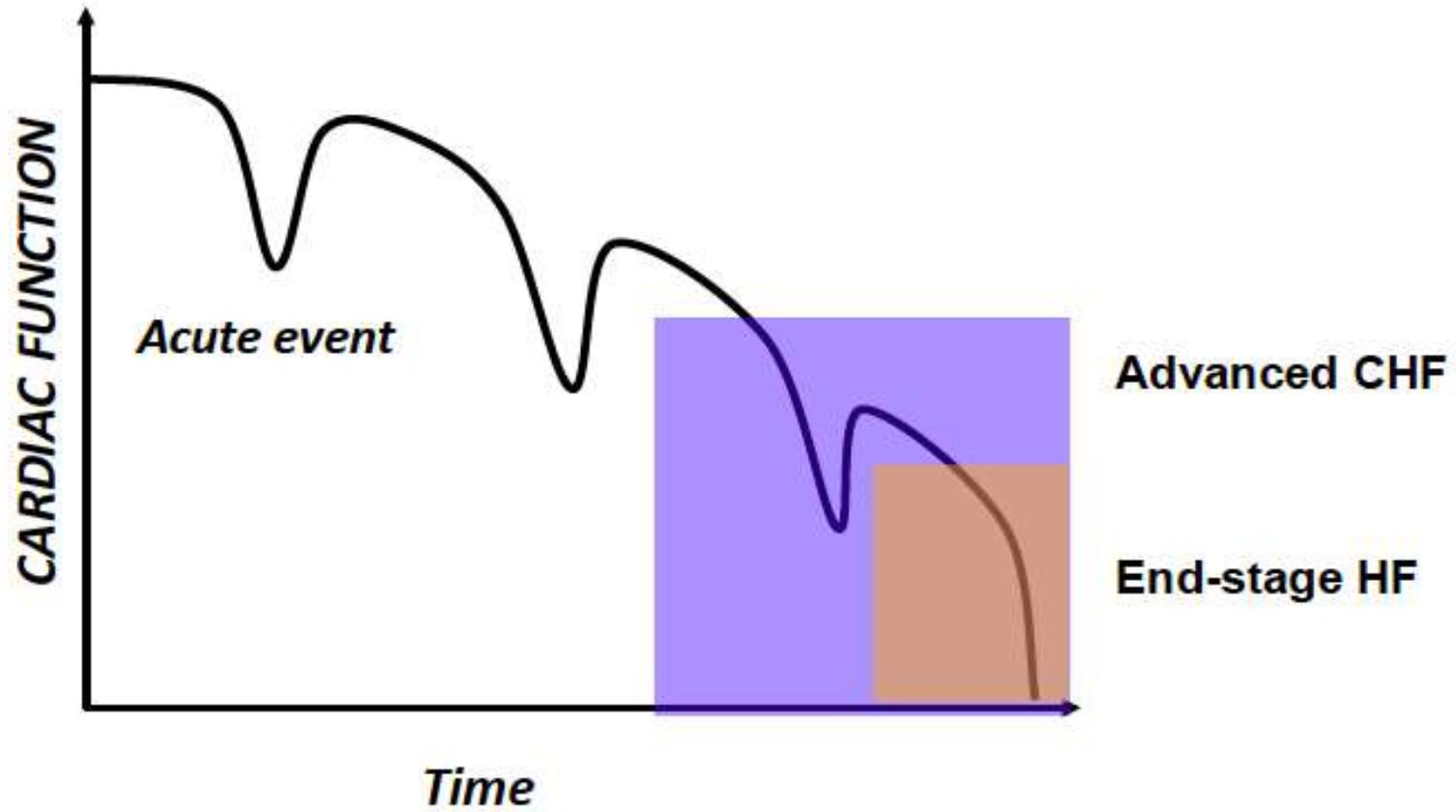


# HF: the building box of therapy





## HF: storia naturale

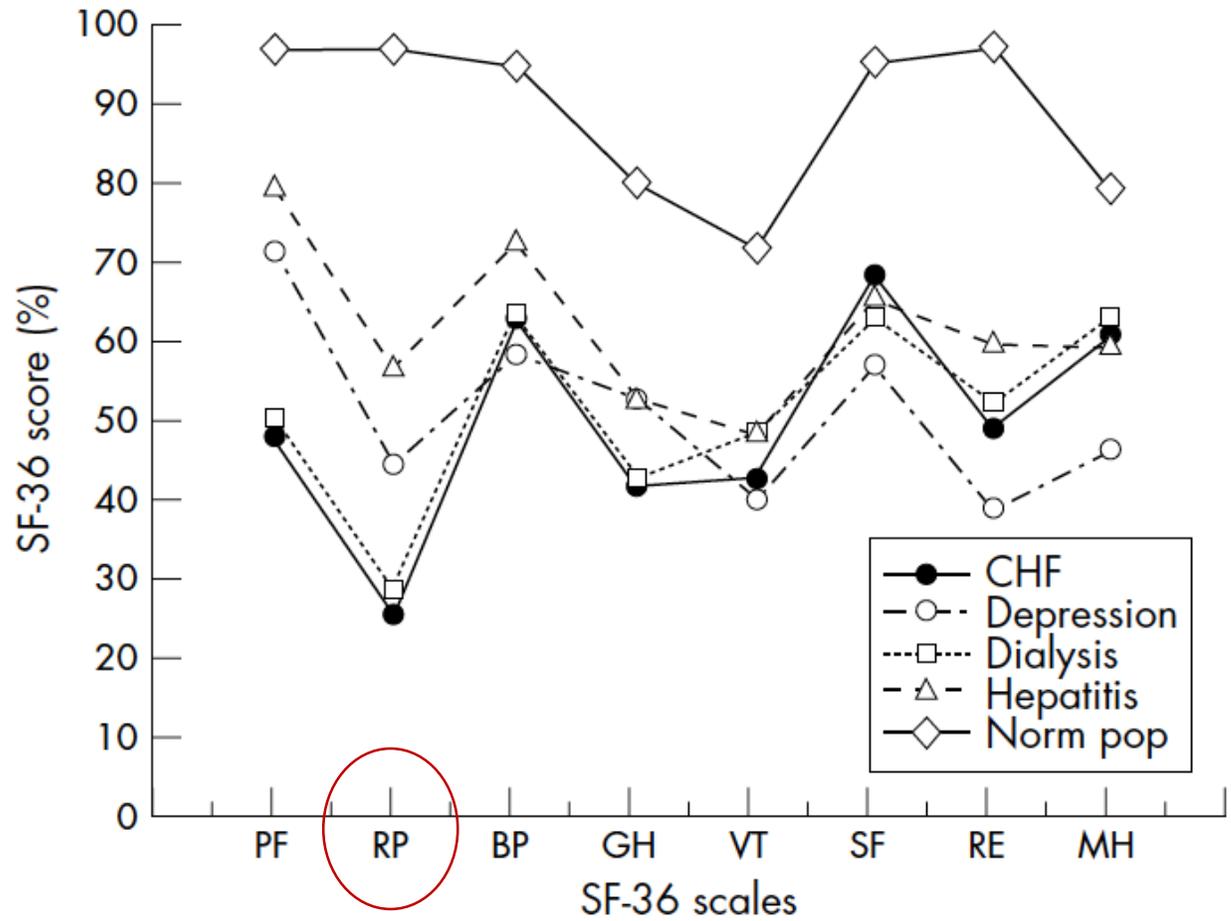


## Capacità di esercizio: cosa dicono le linee guida?

**Table 4.1** Symptoms and signs typical of heart failure

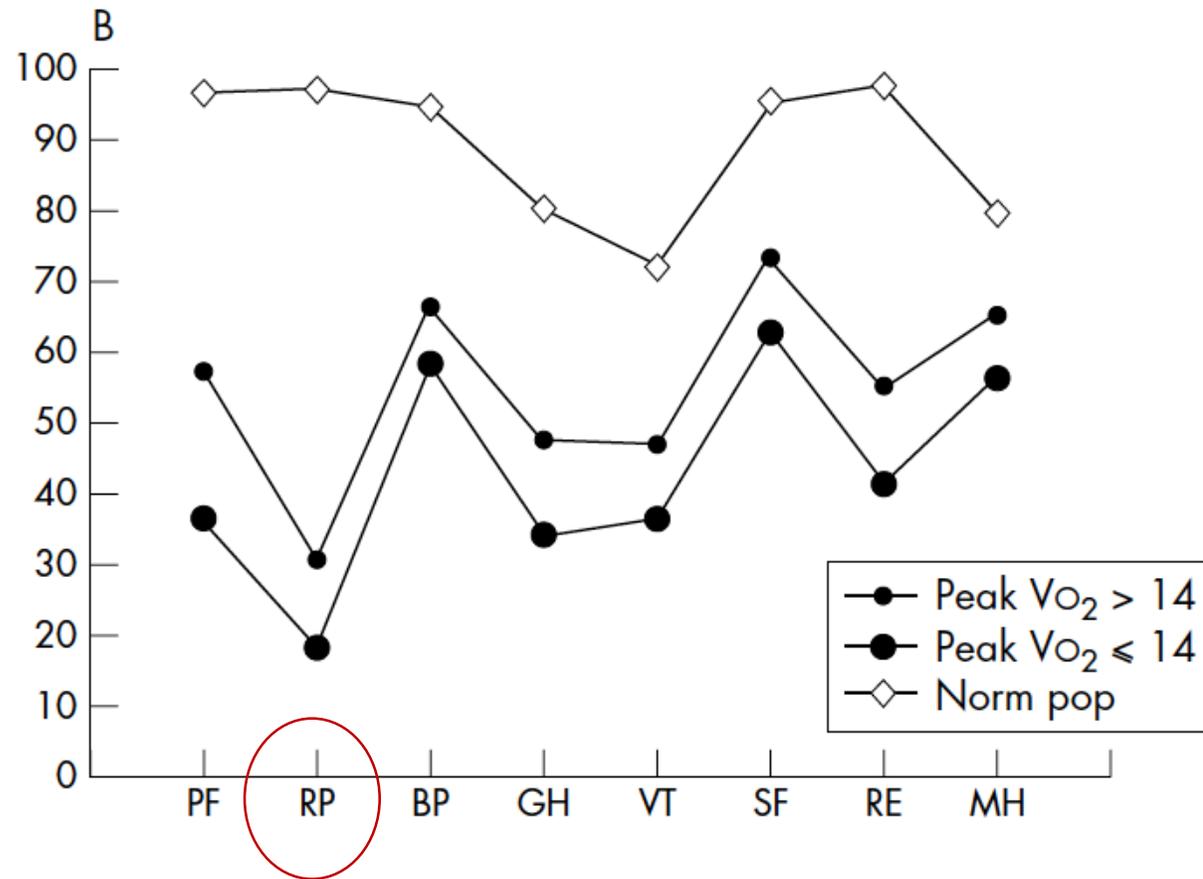
Symptoms	Signs
Typical	More specific
Breathlessness Orthopnoea Paroxysmal nocturnal dyspnoea <u>Reduced exercise tolerance</u> Fatigue, tiredness, increased time to recover after exercise Ankle swelling	Elevated jugular venous pressure Hepatojugular reflux Third heart sound (gallop rhythm) Laterally displaced apical impulse

# HF: quality of life



Physical limitation

## HF: quality of life



Physical limitation

## Capacità di esercizio: cosa dicono le linee guida?

### Exercise testing in patients with HF:

- is recommended as a part of the evaluation for heart transplantation and/or mechanical circulatory support (cardiopulmonary exercise testing);
- should be considered to optimize prescription of exercise training (preferably cardiopulmonary exercise testing);
- should be considered to identify the cause of unexplained dyspnoea (cardiopulmonary exercise testing).
- may be considered to detect reversible myocardial ischaemia.

I

IIa

IIa

IIb

## Studio della capacità di esercizio: quali altre valutazioni in HF?

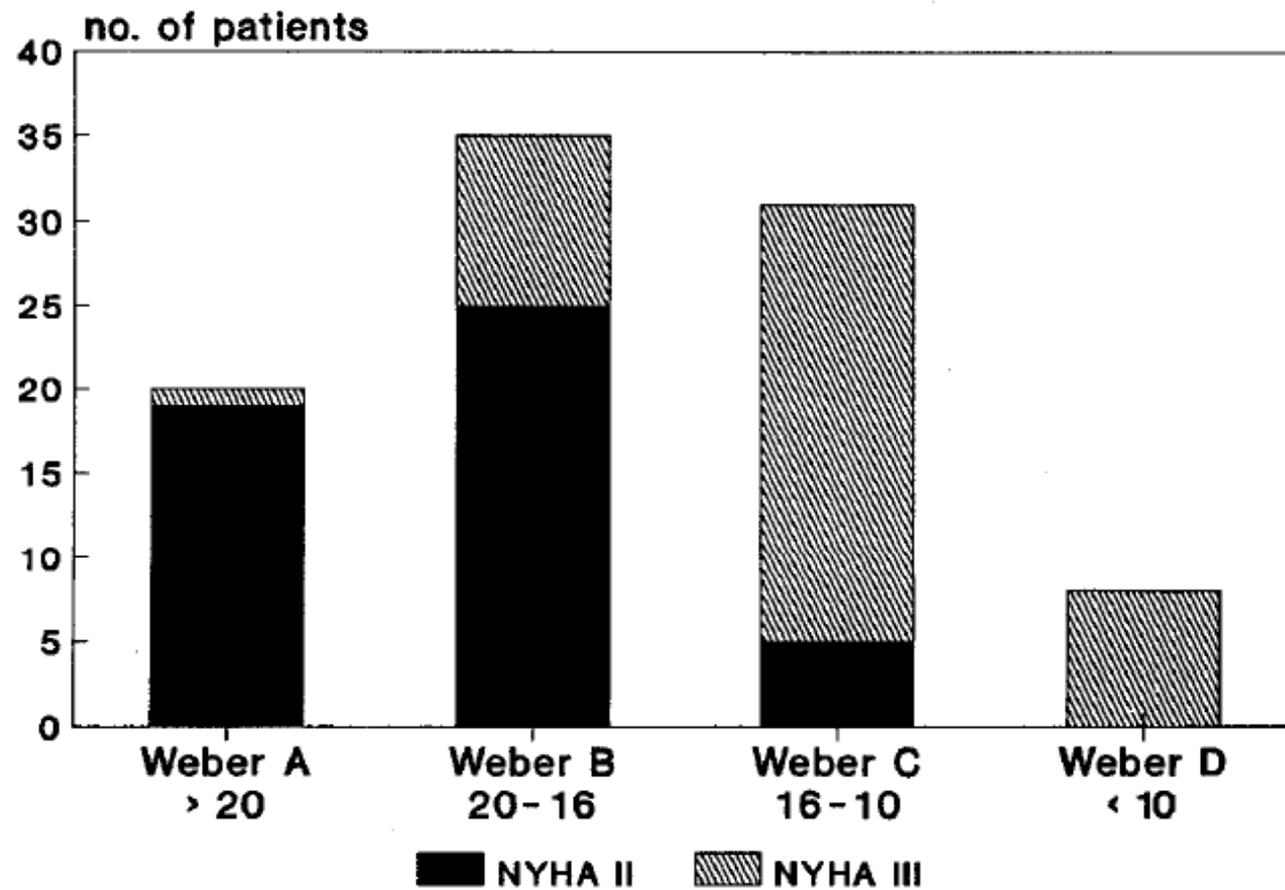
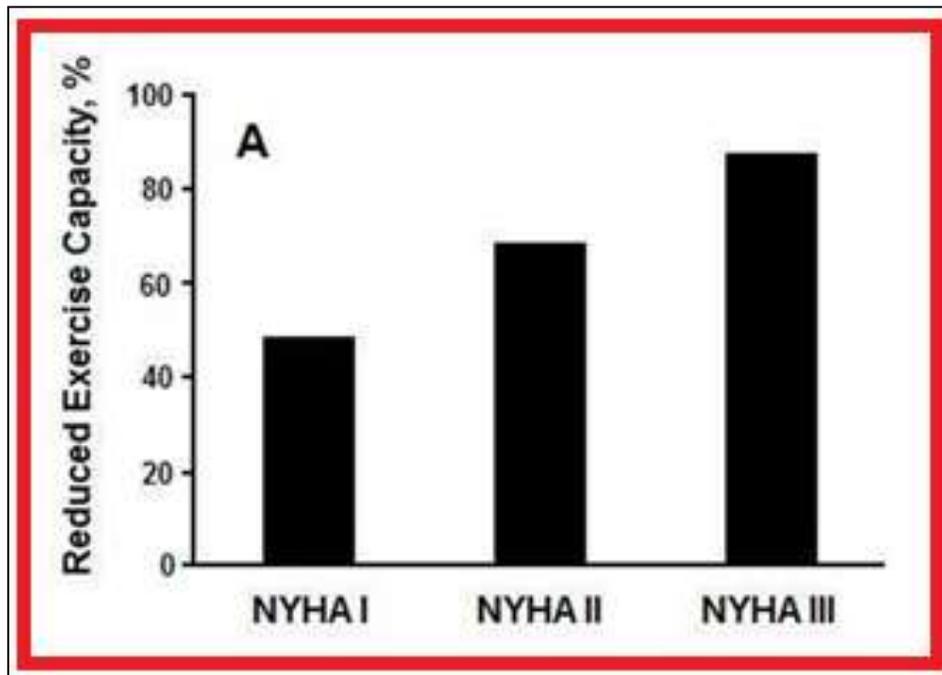
Limitazione funzionale

Stratificazione prognostica

Guida alla terapia non farmacologica

Guida alla terapia farmacologica

# Limitazione funzionale



## Limitazione funzionale in HF

### Limitazione da causa mista

**Limitazione cardiogenica**  
legata alla disfunzione  
sistolica e diastolica del VS

**Limitazione vascolare polmonare**  
( $VE/VCO_2$  slope)

**Limitazione ventilatoria**

## Studio della capacità di esercizio: quali altre valutazioni in HF?

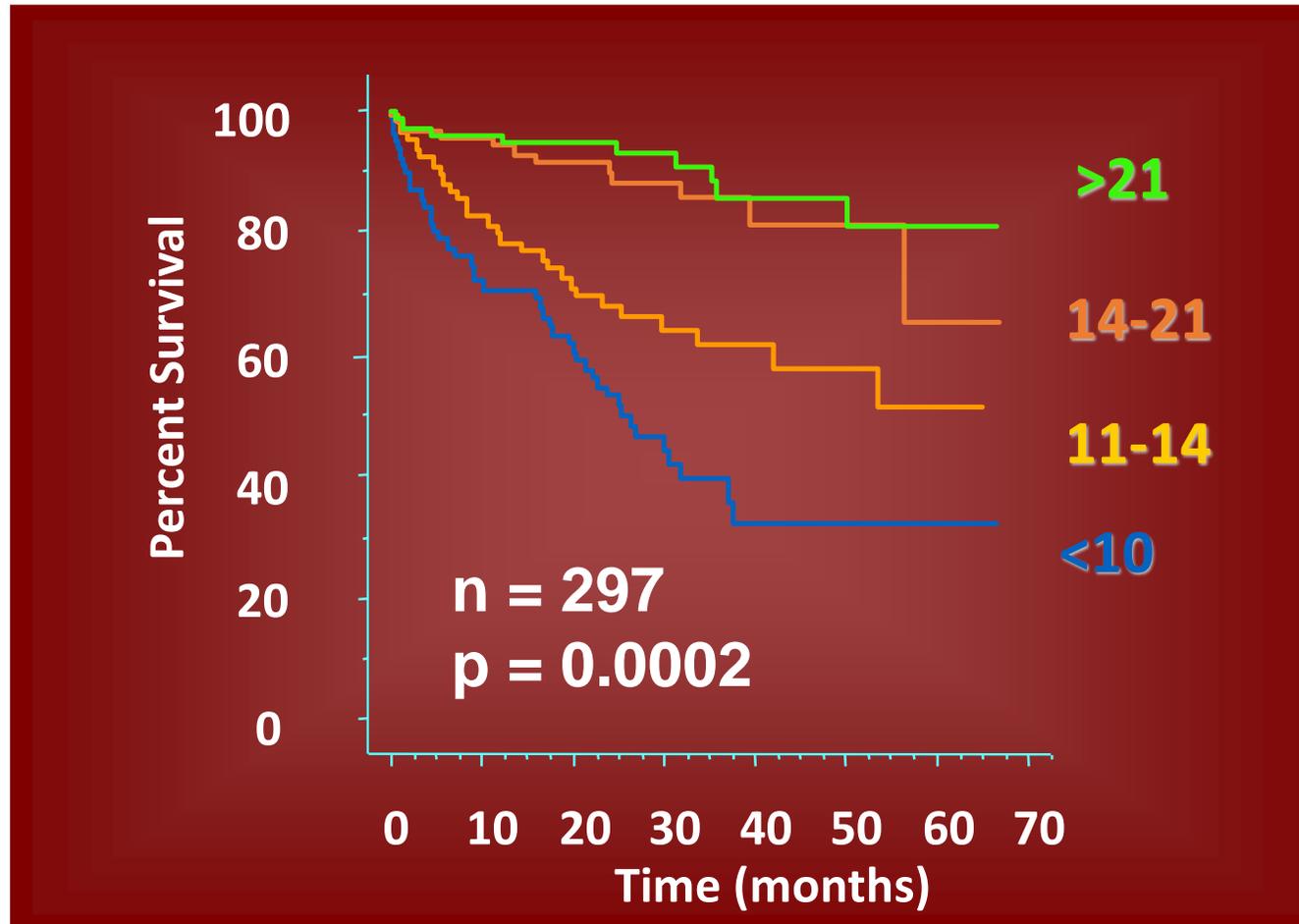
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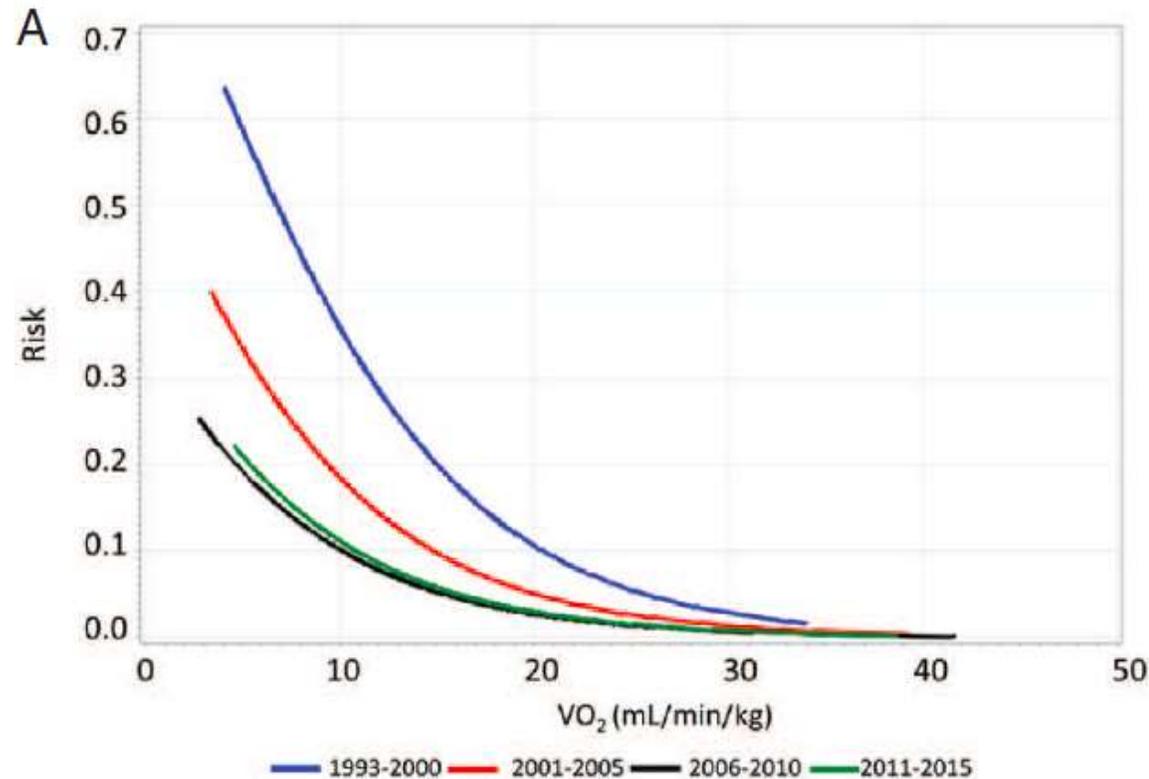
Guida alla terapia farmacologica

# Survival by peak $\text{VO}_2$



# Heart failure prognosis over time: how the prognostic role of oxygen consumption and ventilatory efficiency during exercise has changed in the last 20 years

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# Mecki Score: Metabolic Exercise Cardiac Kidney Index

<b>PEAK VO<sub>2</sub> (%PRED)</b>	<b>VE/VCO<sub>2</sub> (SLOPE)</b>
50	39
<b>HEMOGLOBIN (G/DL)</b>	<b>NA<sub>s</sub> (MMOL/L)</b>
12.2	140
<b>LVEF (%)</b>	<b>MDRD (ML/MIN)</b>
25	35
<b>CALCULATE</b>	

21.73% risk of cardiovascular death or urgent heart transplant within 2 years

<https://www.cardiologicomonzino.it/it/mecki-score/>



## CPET: quali altre valutazioni in DCM?

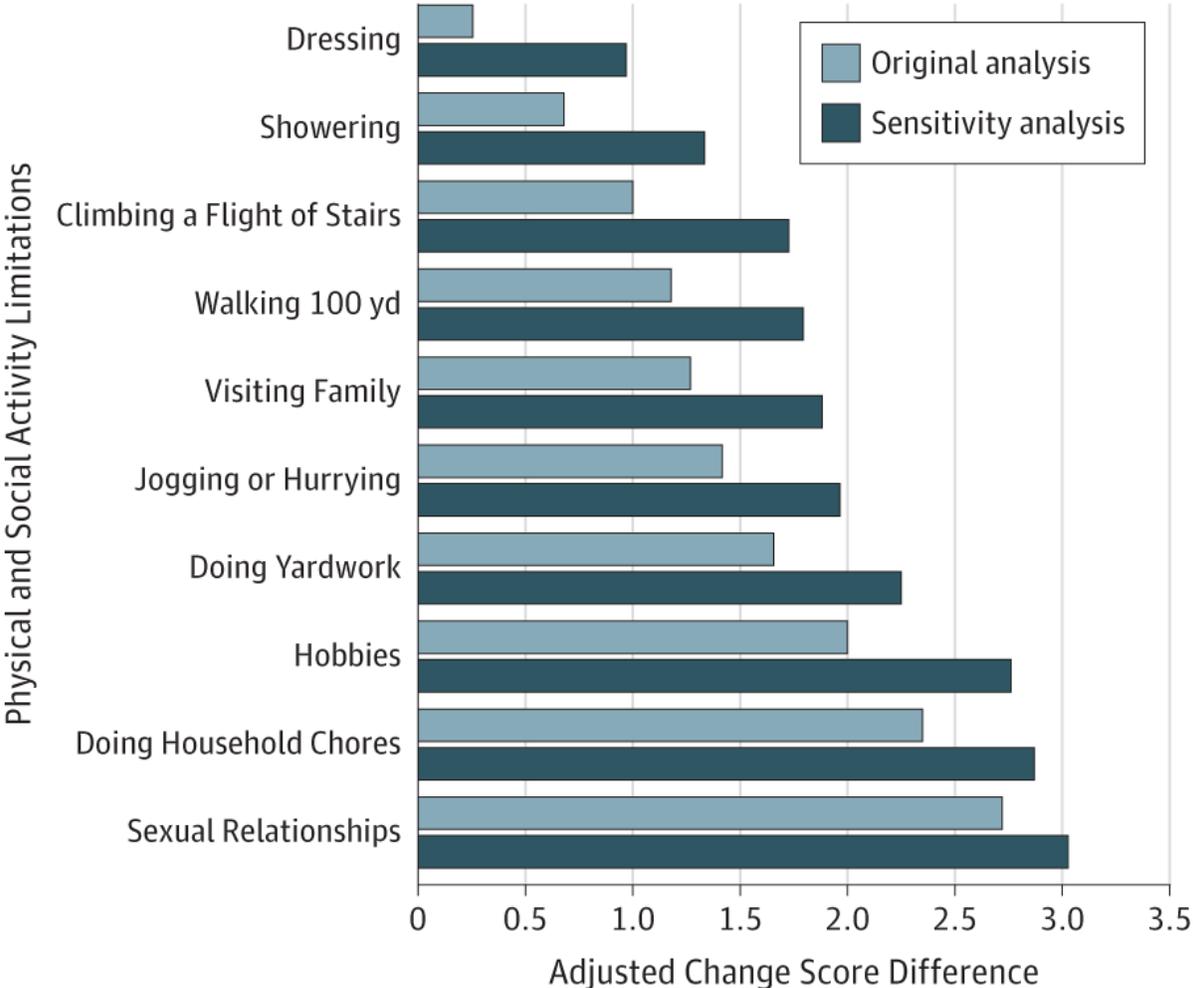
Limitazione funzionale

Stratificazione prognostica

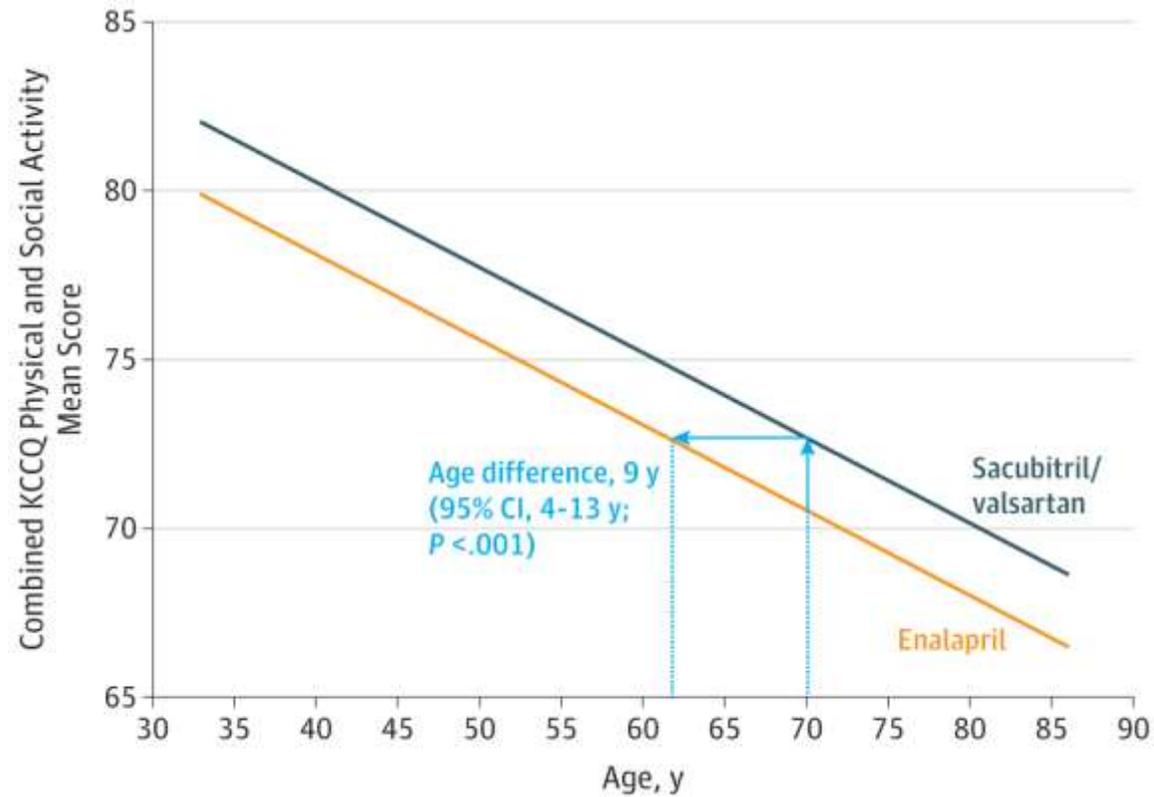
Guida alla terapia non farmacologica

Guida alla terapia farmacologica

# Effects of Sacubitril/Valsartan on Physical and Social Activity Limitations in Patients With Heart Failure: A Secondary Analysis of the PARADIGM-HF Trial



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# Effects of Sacubitril/Valsartan on Physical and Social Activity Limitations in Patients With Heart Failure: A Secondary Analysis of the PARADIGM-HF Trial

**Table 3. Multivariable Linear Regression Model Demonstrating Baseline Clinical Factors That Were Independently Associated With 8-Month Change Scores of Combined Scores of All Physical and Social Activities**

Baseline Clinical Factor	$\beta$ (95% CI)	z Score
Baseline mean scores of combined physical and social activities	-0.36 (-0.38 to -0.34)	35.5
Baseline body mass index	-0.23 (-0.31 to -0.15)	5.8
Baseline NYHA functional class	-2.42 (-3.24 to -1.61)	5.8
White race	-2.68 (-3.64 to -1.72)	5.5
History of myocardial infarction	-1.90 (-2.71 to -1.08)	4.6
History of atrial fibrillation	-1.59 (-2.46 to -0.72)	3.6
Female sex	-1.73 (-2.69 to -0.76)	3.5
History of diabetes mellitus	-1.39 (-2.22 to -0.55)	3.3
Baseline log NT-proBNP	-0.70 (-1.12 to -0.27)	3.2
Baseline age	-0.06 (-0.10 to -0.02)	3.0
Randomization to sacubitril/valsartan	1.08 (0.31 to 1.85)	2.7
Prior heart failure hospitalization	-1.04 (-1.85 to -0.23)	2.5
History of stroke	-1.73 (-3.11 to -0.35)	2.5

Abbreviations: NT-proBNP, N-terminal pro-brain-type natriuretic peptide; NYHA, New York Heart Association.

  
**American Journal of Cardiovascular Disease**  
Home | Editorial Board | Contents | Submission

Am J Cardiovasc Dis. 2017; 7(6): 108–113. PMID: 29348971  
Published online 2017 Dec 20.

**Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure with reduced ejection fraction patients**

Awa Almulleh,<sup>1,2</sup> Jeffrey Marbach,<sup>1</sup> Sharon Chih,<sup>1</sup> Ellamae Stadnick,<sup>1</sup> Ross Davies,<sup>1</sup> Peter Liu,<sup>1</sup> and Lisa Miodniczuk<sup>1</sup>

  
**Revista Española de Cardiología (English Edition)**  
Volume 72, Issue 2, February 2019, Pages 167-169

Scientific letter  
**Early Sacubitril/Valsartan-driven Benefit on Exercise Capacity in Heart Failure With Reduced Ejection Fraction: A Pilot Study**

  
**International Journal of Cardiology**  
Volume 252, 1 February 2018, Pages 136-139

Short communication  
**Sacubitril/valsartan and short-term changes in the 6-minute walk test: A pilot study**

Paola Beltrán<sup>1,2</sup>, Patricia Palau<sup>1,3</sup>, Eloy Domínguez<sup>1</sup>, Mercedes Farfaldó<sup>4</sup>, Eduardo Núñez<sup>5</sup>, Olga Guri<sup>6</sup>, Anna Mollar<sup>7</sup>, Juan Sanchis<sup>8</sup>, Antoni Bayés-Genís<sup>1,9</sup>, Julio Núñez<sup>1,9</sup>

**Cardiovascular Therapeutics**

ORIGINAL RESEARCH ARTICLE | Free Access

**The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction**

Pieter Martens, Hanne Belien, Matthias Dupont, Pieter Vandervoort, Wilfried Mullens

ACTA CARDIOLOGICA  
<https://doi.org/10.1080/00015385.2018.1521054>

ORIGINAL SCIENTIFIC PAPER

**Effects of sacubitril/valsartan on functional status and exercise capacity in real-world patients**

Chirik Wah Lau<sup>1,2</sup>, Pieter Martens<sup>1,3,4</sup>, Seppe Lambaerts<sup>5</sup>, Matthias Dupont<sup>6</sup> and Wilfried Mullens<sup>1,4</sup>

**cardiology**

**Sacubitril/Valsartan: Effect on Walking Test and Physical Capability**

Sgorbini L · Rossetti A · Galati A.

  
**Journal of Clinical Medicine**  
MDPI

Article  
**Early Effects of Sacubitril/Valsartan on Exercise Tolerance in Patients with Heart Failure with Reduced Ejection Fraction**

Giuseppe Vitale<sup>1</sup>, Giuseppe Romano<sup>2</sup>, Antonino Di Franco<sup>3</sup>, Giuseppa Caccamo<sup>1</sup>, Cinzia Nugara<sup>1,4</sup>, Laura Ajello<sup>2</sup>, Salvo Storniole<sup>5</sup>, Silvia Sarullo<sup>5</sup>, Valentina Agnese<sup>2</sup>, Francesco Giallauria<sup>6</sup>, Giuseppina Novo<sup>5</sup>, Francesco Clemenza<sup>2</sup> and Filippo M. Sarullo<sup>1,4</sup>

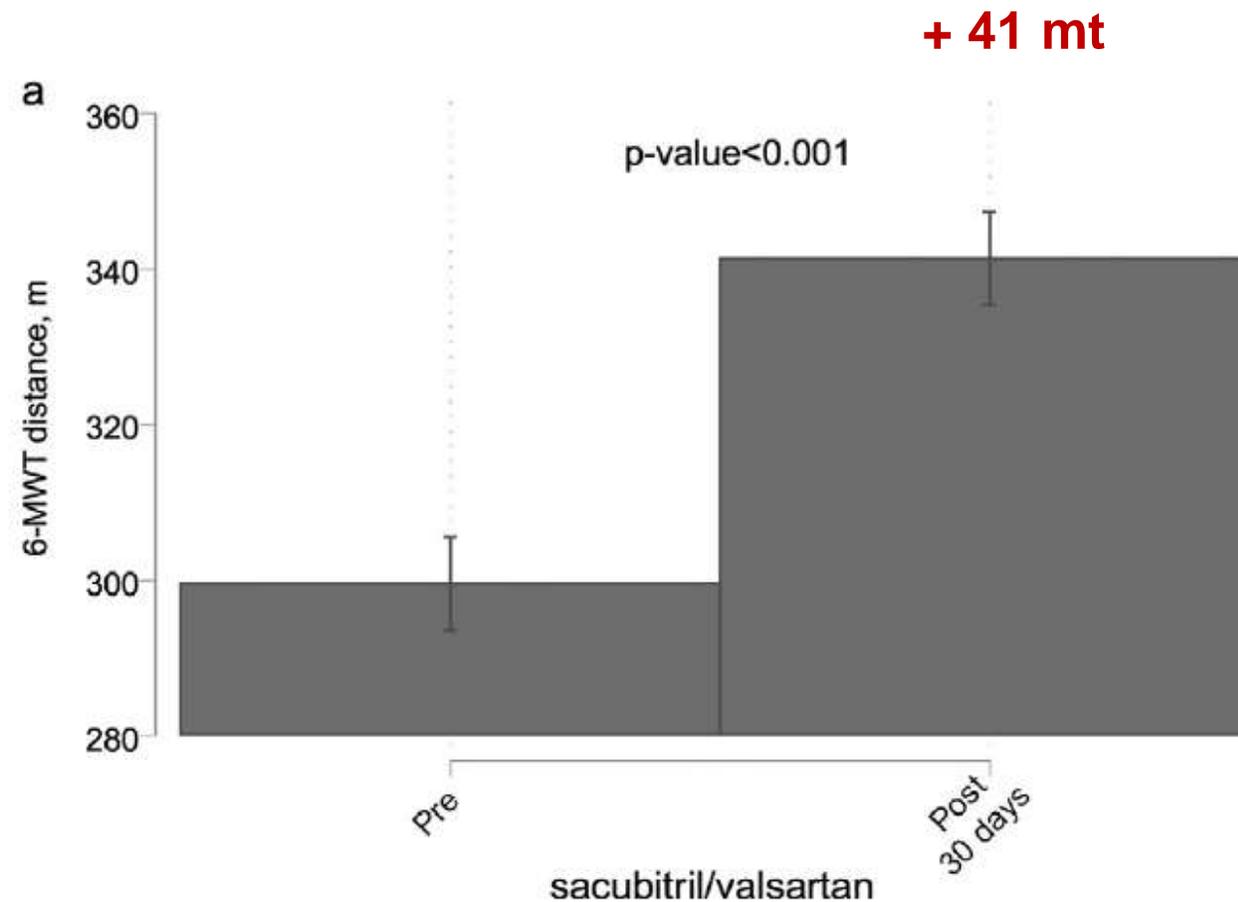
# Sacubitril/valsartan and short-term changes in the 6-minute walk test: A pilot study

Baseline characteristics of study population.

Variables	Included patients (n = 58)		
<i>Demographic, medical history and vital signs</i>			
Age, years <sup>a</sup>	70 ± 11		
Female, n (%)	42 (72.4)		
Hypertension, n (%)	43 (74.1)		
Diabetes mellitus, n (%)	26 (44.8)		
Ischemic heart disease, n (%)	27 (46.6)		
Baseline NYHA class III/IV, n (%)	30 (51.7)		
Prior admission for AHF <6 months, n (%)	17 (29.3)		
ICD and CRT, n (%)	5 (8.6)		
Atrial fibrillation, n (%)	22 (37.9)		
Systolic blood pressure, mm Hg <sup>a</sup>	123 ± 16		
Diastolic blood pressure, mm Hg <sup>a</sup>	67 ± 10		
		<i>Laboratory</i>	
		Serum potassium, mEq/L <sup>a</sup>	4.4 ± 0.4
		eGFR, ml/min/m <sup>2a</sup>	60 ± 17
		NT-proBNP, pg/ml <sup>b</sup>	2701 (1087–4200)
		<i>Treatment</i>	
		Furosemide doses, mg/day <sup>a</sup>	61 ± 44
		β-Blockers, n (%)	53 (91.4)
		Antialdosterone, n (%)	43 (74.1)
		Starting dose of sacubitril/valsartan 24/26 mg, n (%)	41 (70.7)
		Starting dose of sacubitril/valsartan 49/51 mg, n (%)	17 (29.3)
		<i>Exercise performance</i>	
		6-MWT, m <sup>b</sup>	262 (198–350)

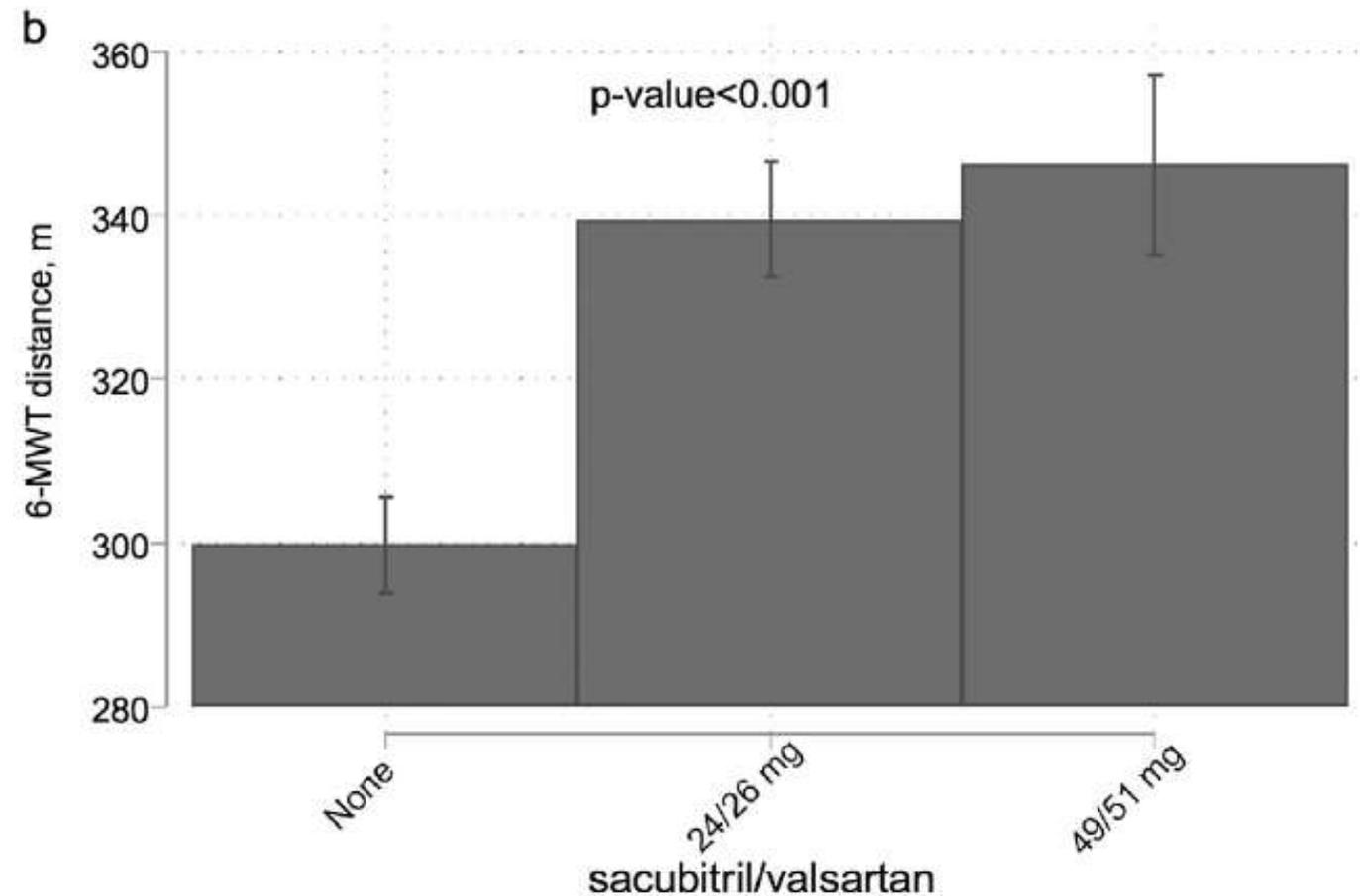
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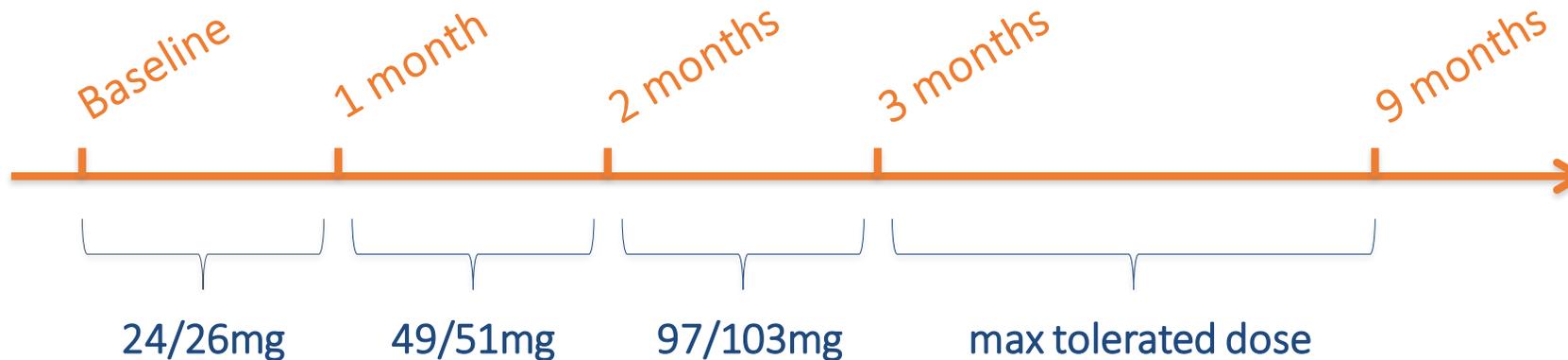
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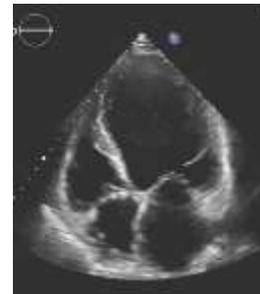


# Sacubitril/valsartan e capacità di esercizio

PROSPECTIVE, MULTICENTRIC, NON-randomized (ethical reasons)



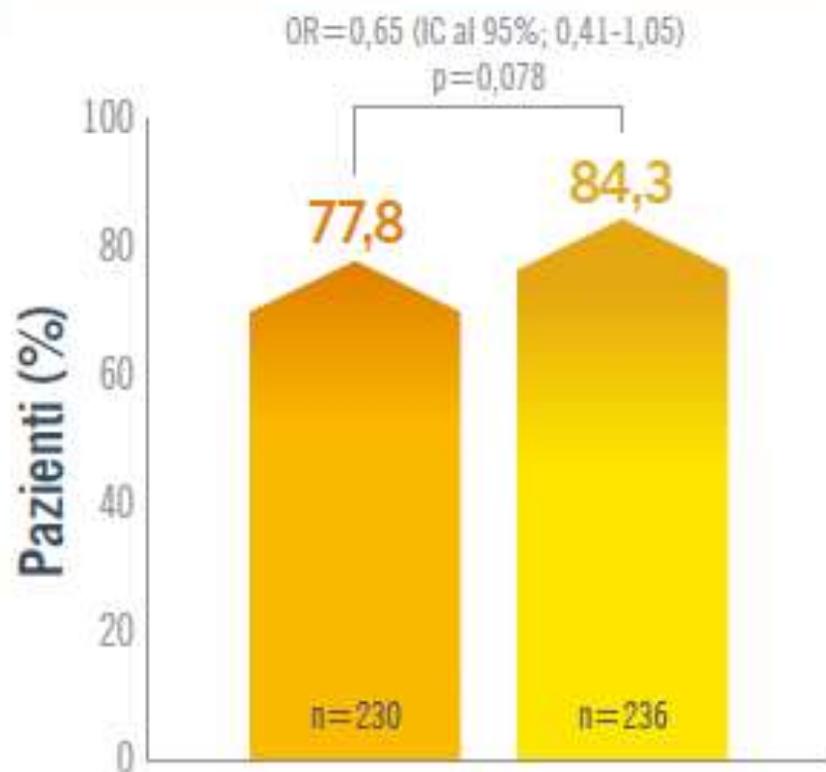
- Blood venous sample collection
- QoL questionnaire
- Cardiopulmonary exercise test (CPET)
- Echocardiography
- Spirometry and DLCO



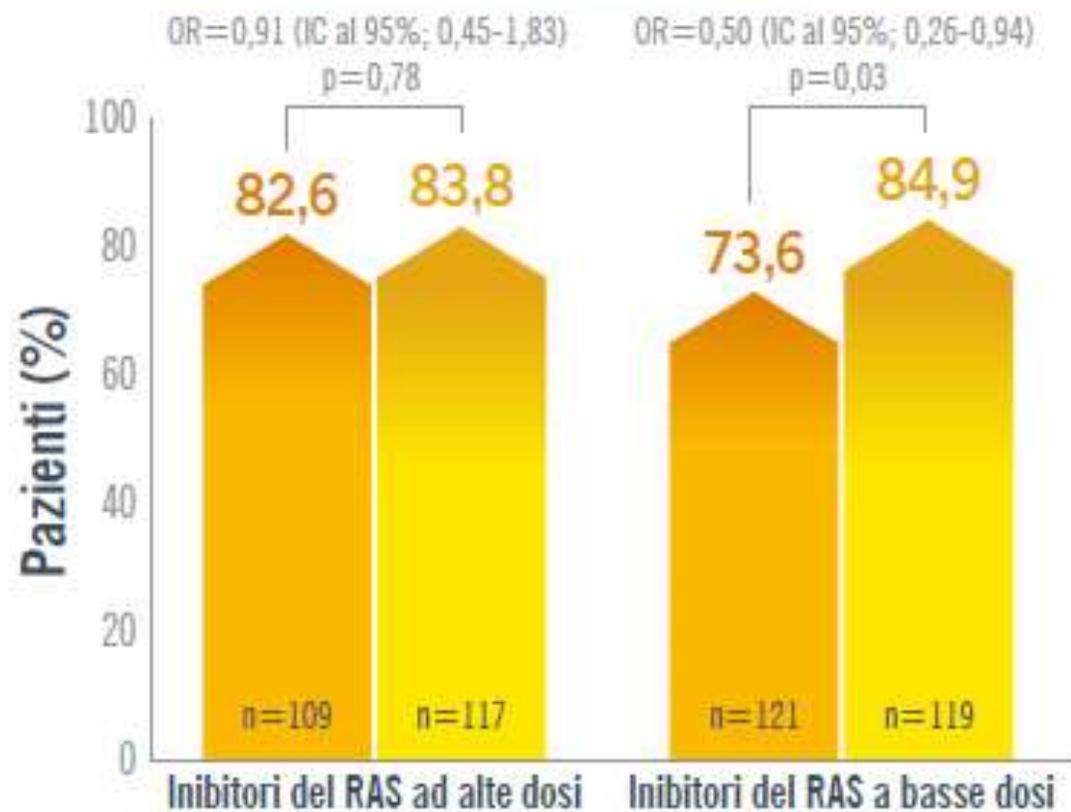
# TITRATION: la dose target è stata raggiunta in entrambi i regimi<sup>1</sup>

Il regime conservativo ha massimizzato il successo del trattamento anche nei pazienti trattati con basse dosi di ACE/ARB<sup>1</sup>

## SUCCESSO COMPLESSIVO



## SUCCESSO PER LIVELLO DI RAS INIBIZIONE



# Sacubitril/valsartan e capacità di esercizio

Inclusion criteria:

- Over 18 years of age;
- **Symptomatic** heart failure defined as NYHA functional class II or III, **despite optimized treatment**;
- Stable clinical conditions;
- LVEF  $\leq$  35%, as measured using echocardiography or MRI;
- Eligible for treatment with sacubitril/valsartan;
- **Ability to perform CPET.**

## Primary end-points

- 1) **Increase in oxygen consumption at peak exercise**
- 2) **Improvement in pulmonary function and in cardiac performance**

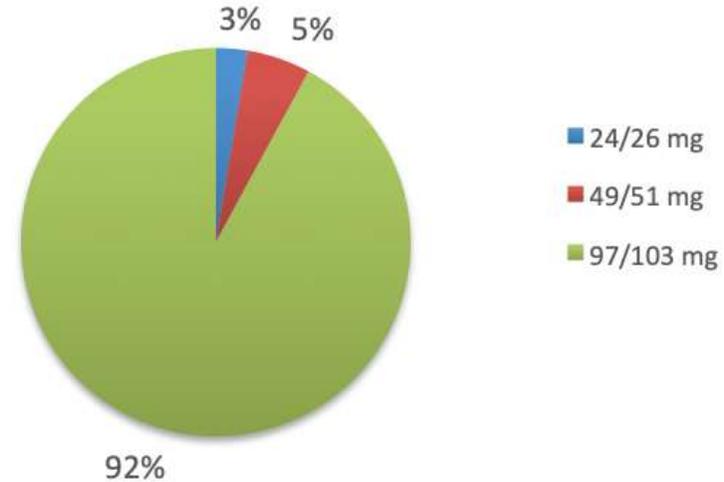
## Secondary end-points

- 1) **Decrease in NTproBNP values**
  - 2) **Improvement in cardiac remodeling assessed with cardiac echo**
-

### Sacubitril/valsartan dose

**38 patients**

**Follow-up 145 ± 68 days**



Variable	Baseline mean ± SD	Follow-up mean ± SD	p-value
SBP (mmHg)	115 ± 17	107 ± 15	0,007
DBP (mmHg)	73 ± 9	70 ± 10	0,085
eGFR (ml/min/1.73m <sup>2</sup> )	68,8 ± 18,2	65,3 ± 17,9	0,108
K <sup>+</sup> (mmol/l)	4,4 ± 0,4	4,5 ± 0,4	0,033

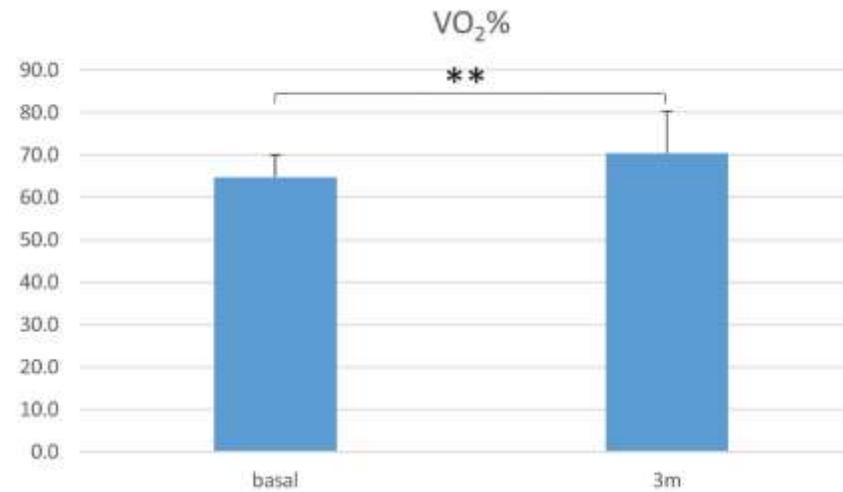
No serious adverse events or need for discontinuation

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## RESULTS ON EXERCISE CAPACITY

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Variable	Baseline mean $\pm$ SD	Follow-up mean $\pm$ SD	p-value
PeakVO <sub>2</sub> (ml/kg/min)	15,9 $\pm$ 3,8	16,9 $\pm$ 3,7	0,007
PeakVO <sub>2</sub> (% pred)	64,7 $\pm$ 14,6	70,4 $\pm$ 13,1	0,001
Peak workload (watt)	95,3 $\pm$ 38,6	101,5 $\pm$ 39,6	0,0005
VE/VCO <sub>2</sub> slope	32,8 $\pm$ 7,1	34,1 $\pm$ 7,3	0,150



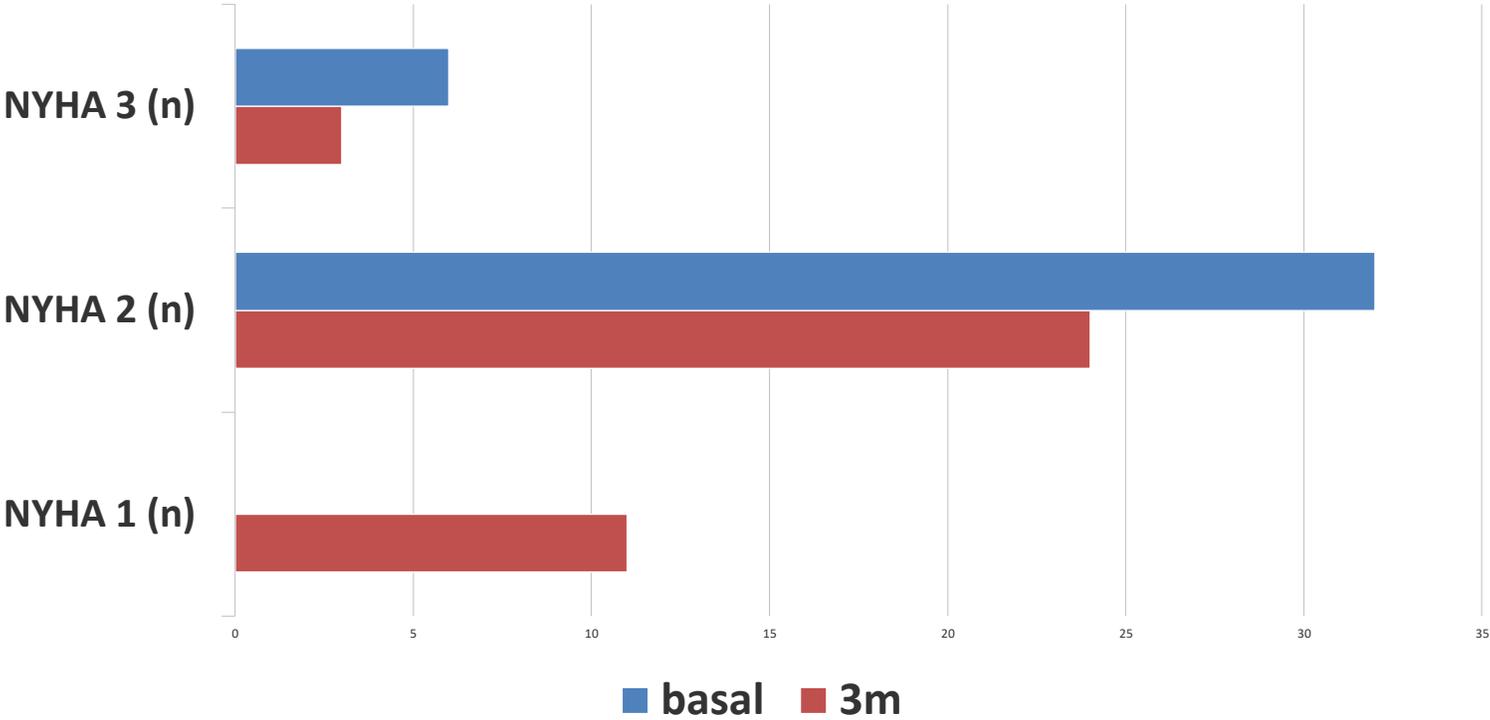
\*\* p<0,01

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**RESULTS ON FUNCTIONAL STATUS**

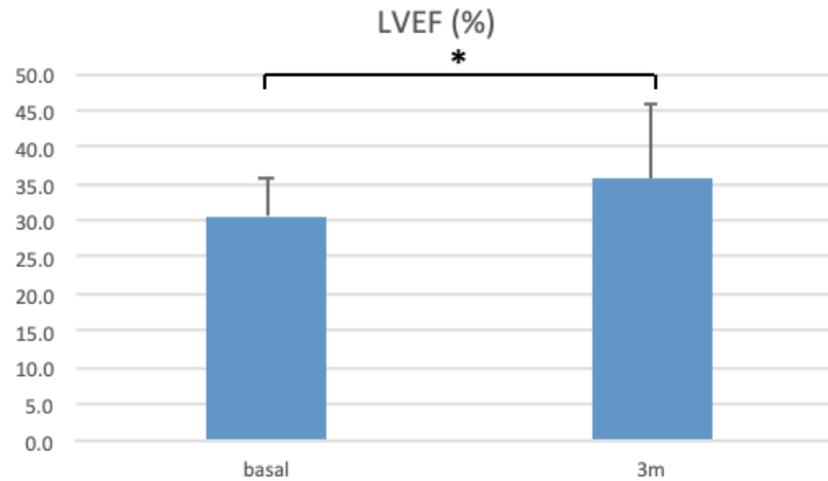
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NYHA functional class



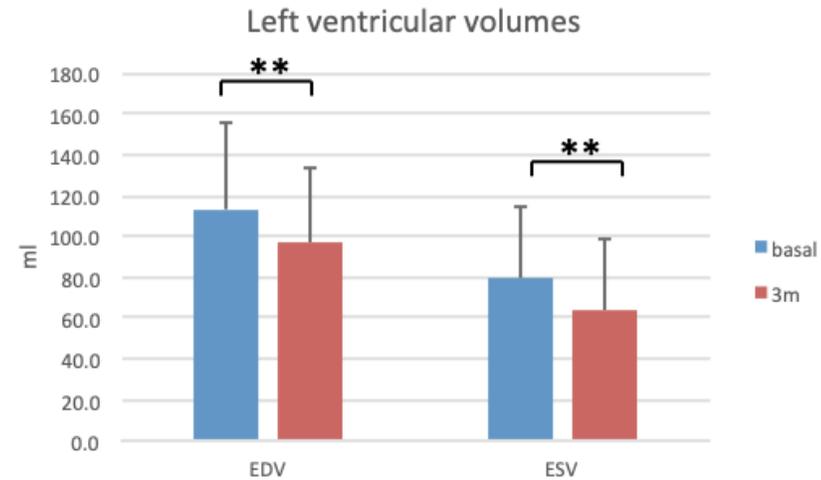
# RESULTS ON VENTRICULAR REMODELING

\*  $p < 0,05$   
\*\*  $p < 0,01$



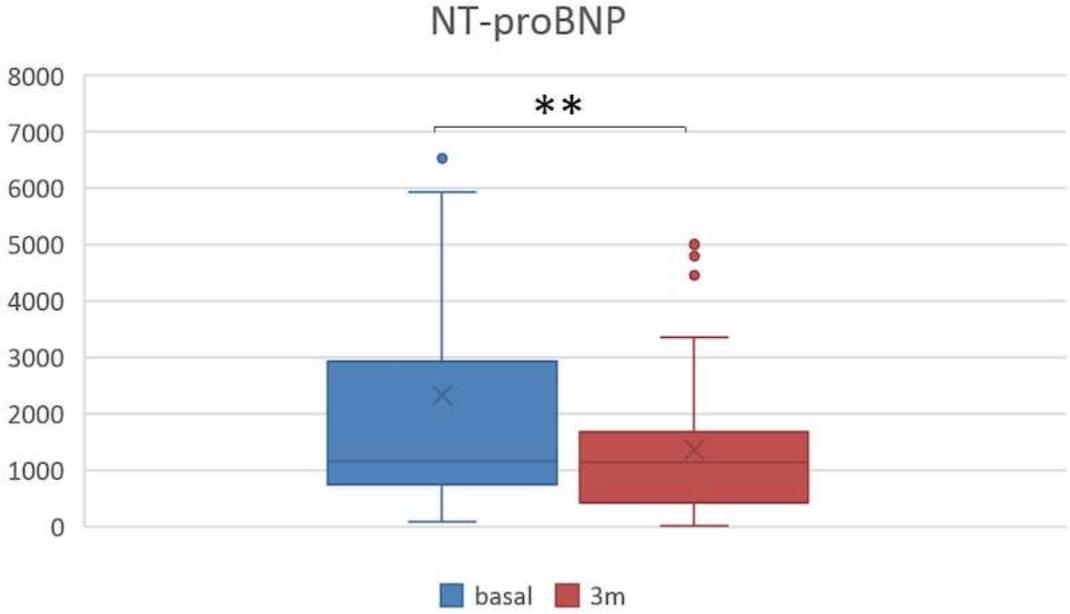
Left ventricular  
ejection fraction

Left ventricular  
end-diastolic (LVEDV) and  
end-systolic (LVESV) volumes



# EFFECTS ON HEART FAILURE BIOMARKERS

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\*\* p<0,01

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## Take home message

- ✓ **Importanza della valutazione della capacità funzionale in HF**
- ✓ **La capacità funzionale correla con la qualità della vita e con la prognosi**
- ✓ **Sacubitril/valsartan migliora la qualità della vita in differenti aspetti e sembra migliorare la capacità funzionale**
- ✓ **Capacità funzionale e dose?**

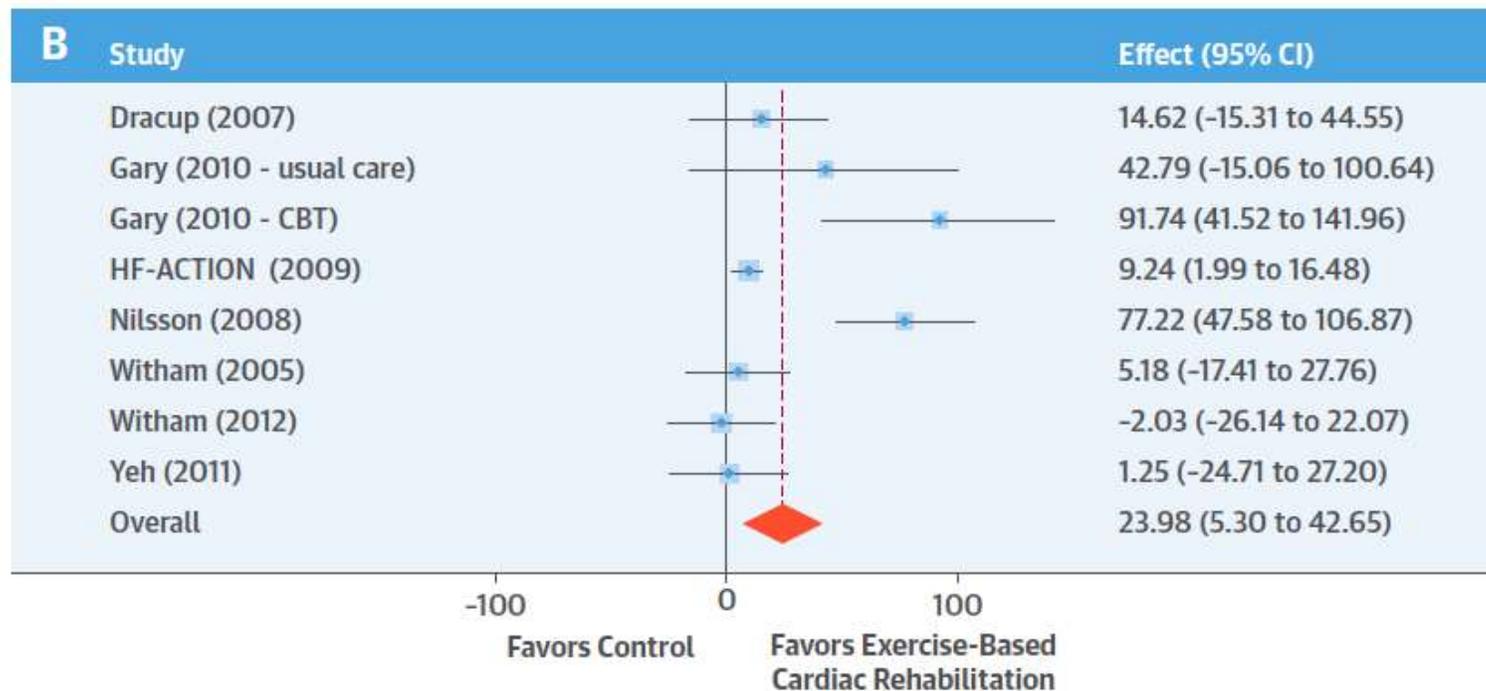
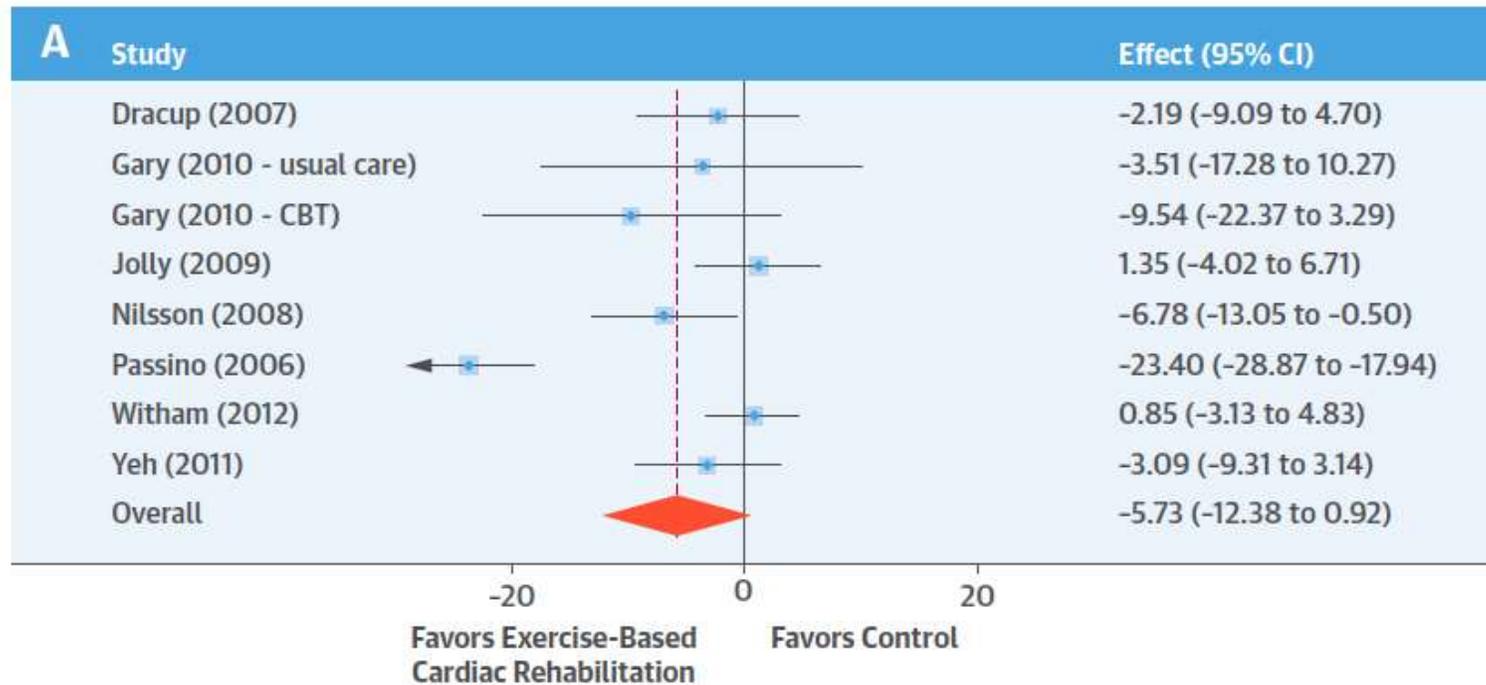
Limitazione funzionale

Stratificazione prognostica

Guida alla terapia farmacologica

Guida





$$VO_2 = VE (FiO_2 - FeO_2)$$

$$VO_2 = Q (CaO_2 - CvO_2)$$

## Guida alla terapia non farmacologica

**Table 1** Comparison Between Maximal CPET at LVAD Speed 3 Versus Incremental Speed ( $n = 15$ )

Variable	Speed 3	Speed 3-4-5	Delta	<i>p</i> -value
Workload, watt	57 ± 17	59 ± 17	1.3 ± 5.3	0.349
Heart rate, beats/min				
Rest	73 ± 14	72 ± 10	-0.4 ± 6.7	0.820
Peak	100 ± 22	99 ± 19	-1.4 ± 7.9	0.501
VO <sub>2</sub> peak, ml/min	948 ± 238	1,014 ± 219	65.3 ± 85.3	0.001
VO <sub>2</sub> peak, ml/min/kg	11.7 ± 2.8	12.5 ± 2.5	0.8 ± 1.1	0.001
VO <sub>2</sub> peak, % of predicted	45.1 ± 12.0	48.4 ± 11.4	3.3 ± 4.1	0.008
VO <sub>2</sub> /work slope	9.3 ± 1.7	10.4 ± 1.8	1.1 ± 1.3	0.006
V <sub>E</sub> /V <sub>CO<sub>2</sub></sub> slope	34 ± 6	32 ± 6	-1.9 ± 3.1	0.031
O <sub>2</sub> pulse, liters/beat	9.7 ± 2.7	10.3 ± 2.1	0.6 ± 1.0	0.030
VO <sub>2</sub> AT, ml/min	643 ± 171	693 ± 161	50.6 ± 97.3	0.064
VO <sub>2</sub> AT, ml/min/kg	7.9 ± 1.9	8.5 ± 1.6	0.6 ± 1.1	0.061
V <sub>E</sub> peak, liters/min	49.3 ± 13.4	48.1 ± 11.5	-1.2 ± 7.7	0.564
Respiratory rate peak, breath/min	33.2 ± 5.4	32.1 ± 5.6	-1.1 ± 3.7	0.253

**Listing patients solely on the criteria of heart failure survival prognostic scores should not be performed (Class III, Level of Evidence: C).**

1.1. Care  
listing  
A maxim

respiratory exchange ratio (RER)  $> 1.05$  and achievement of an anaerobic threshold on optimal pharmacologic therapy (Class I, Level of Evidence: B).

In patients intolerant of a  $\beta$ -blocker, a cutoff for peak oxygen consumption ( $V_{O_2}$ ) of  $\leq 14$  ml/kg/min should be used to guide listing (Class I, Level of Evidence: B).

In the presence of a  $\beta$ -blocker, a cutoff for peak  $V_{O_2}$  of  $\leq 12$  ml/kg/min should be used to guide listing (Class I, Level of Evidence: B).

In young patients ( $< 50$  years) and women, it is reasonable to consider using alternate standards in conjunction with peak  $V_{O_2}$  to guide listing, including percent of predicted ( $\leq 50\%$ ) peak  $V_{O_2}$  (Class IIa, Level of Evidence: B).

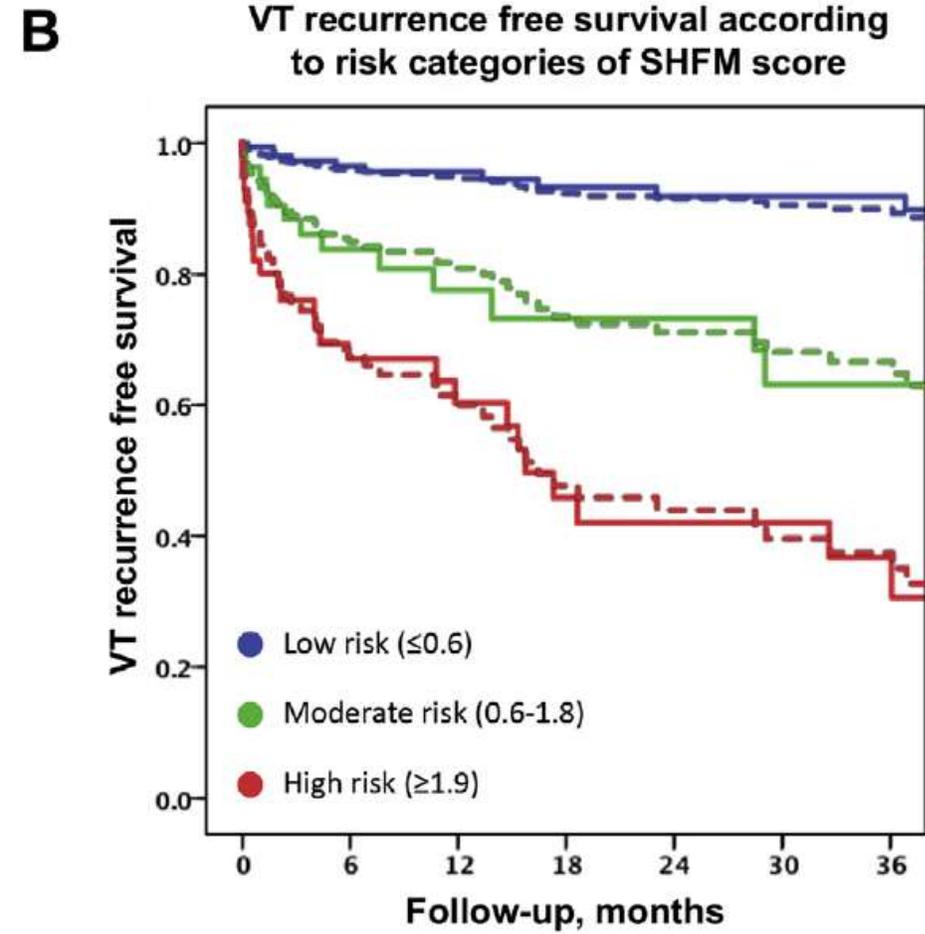
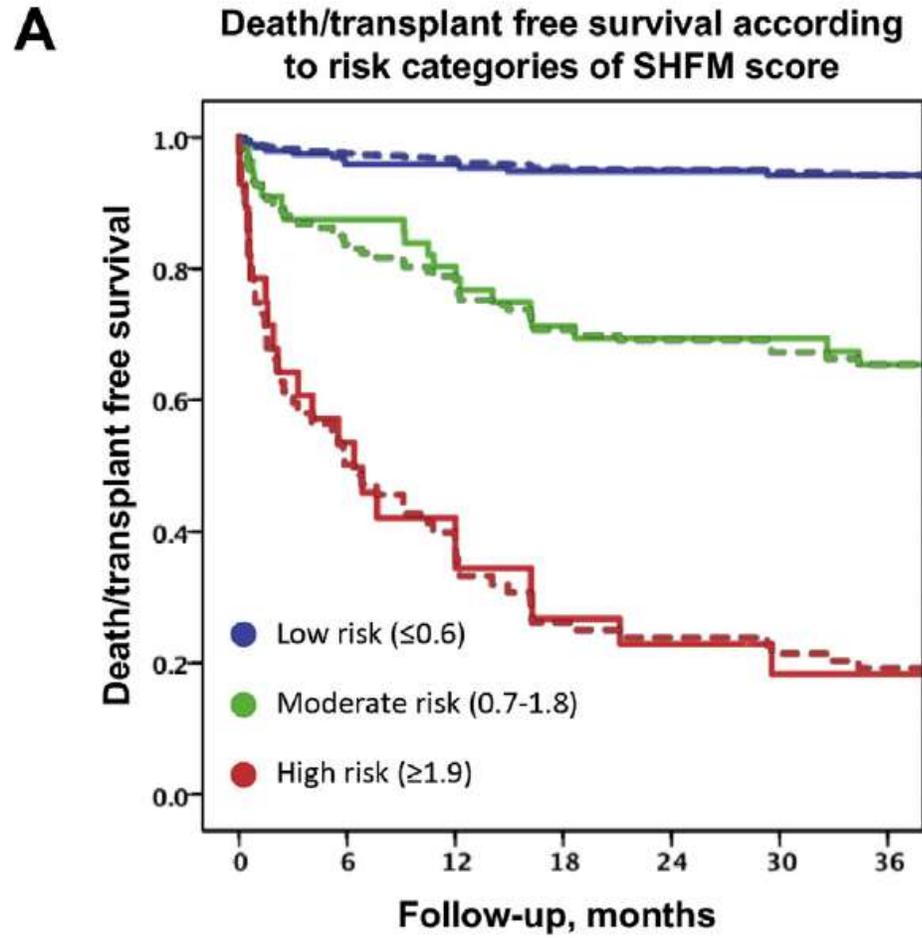
The presence of a CRT device does not alter the current peak  $V_{O_2}$  cutoff recommendations (Class I, Level of Evidence: B).  
Continuing approval without change.

Continuing approval without change.

Continuing approval without change.

## Stratificazione prognostica

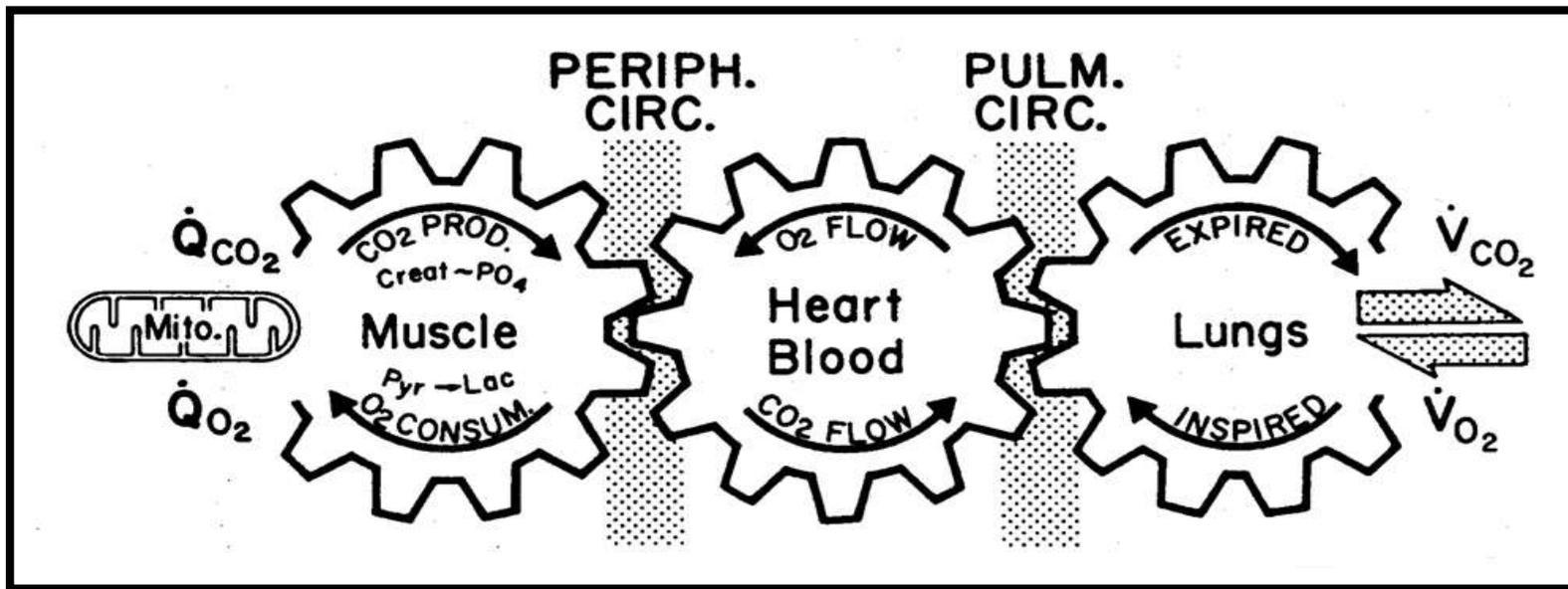
## Seattle Heart Failure Model



Limitazione funzionale

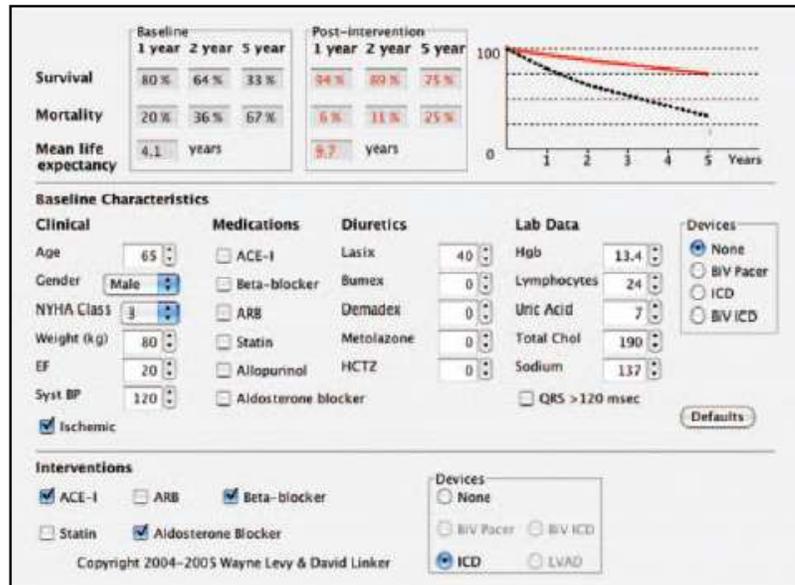
**CAUSA**

## Basi fisiologiche dell'esercizio fisico



## Stratificazione prognostica

14 continuous variables and  
10 categorical variables



## Seattle Heart Failure Model

