



**Primo Congresso
Interregionale
AME Sud - Italia**

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Interregionale
ANIED Sud - Italia**

Responsabile Scientifico Vincenzo Triggiani



Matera, 9-10 Maggio 2014 - HILTON GARDEN INN

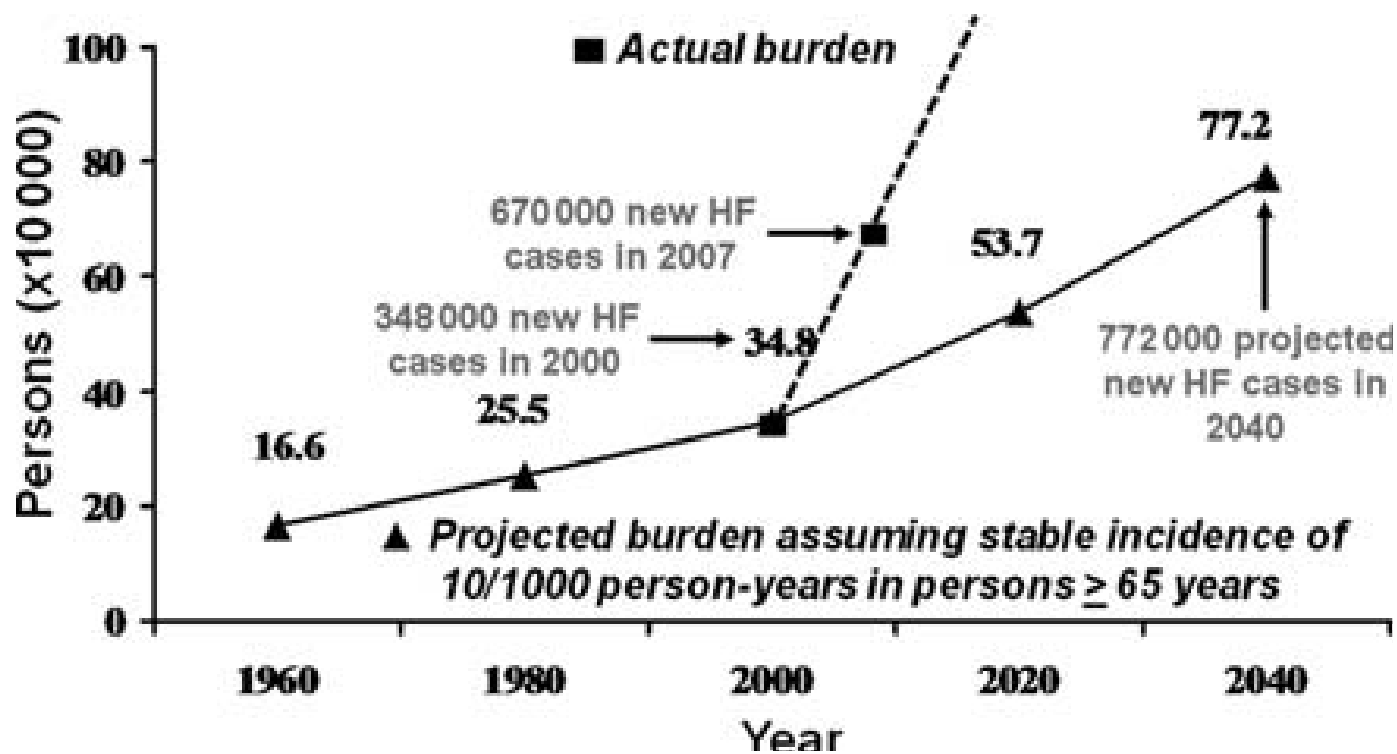
1° Sessione: Deficit di GH nello scompenso cardiaco

Il punto di vista del cardiologo

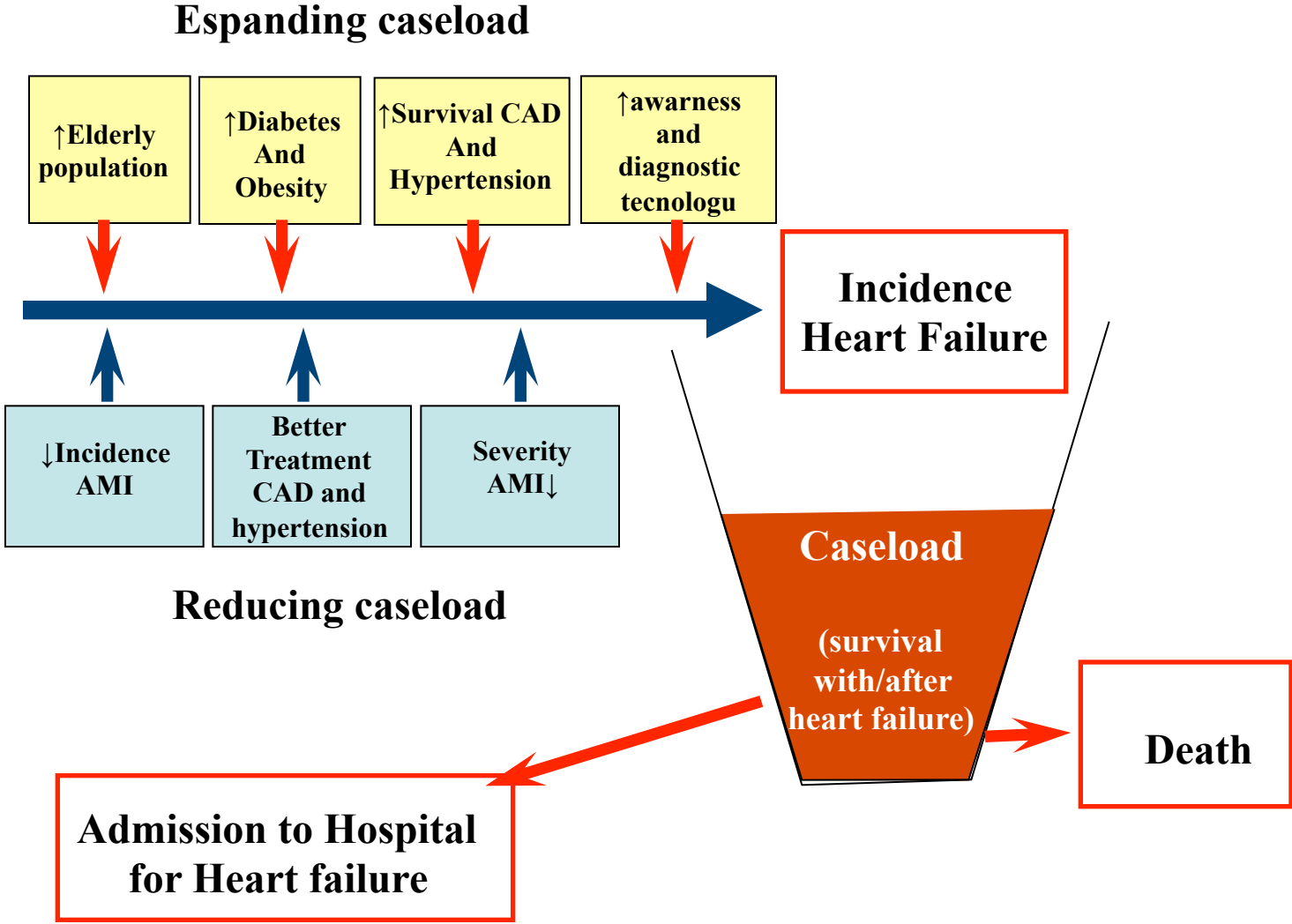
M. Iacoviello

Epidemiologia dell' insufficienza cardiaca

Proiezione relativa agli U S A

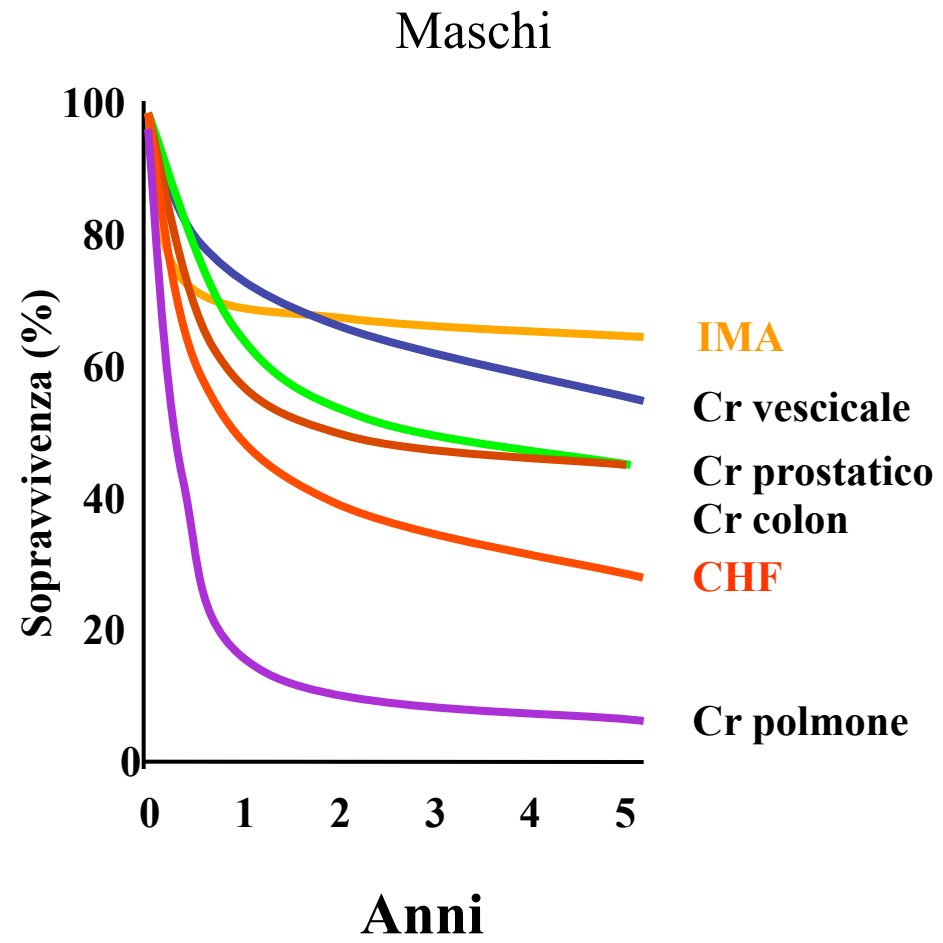
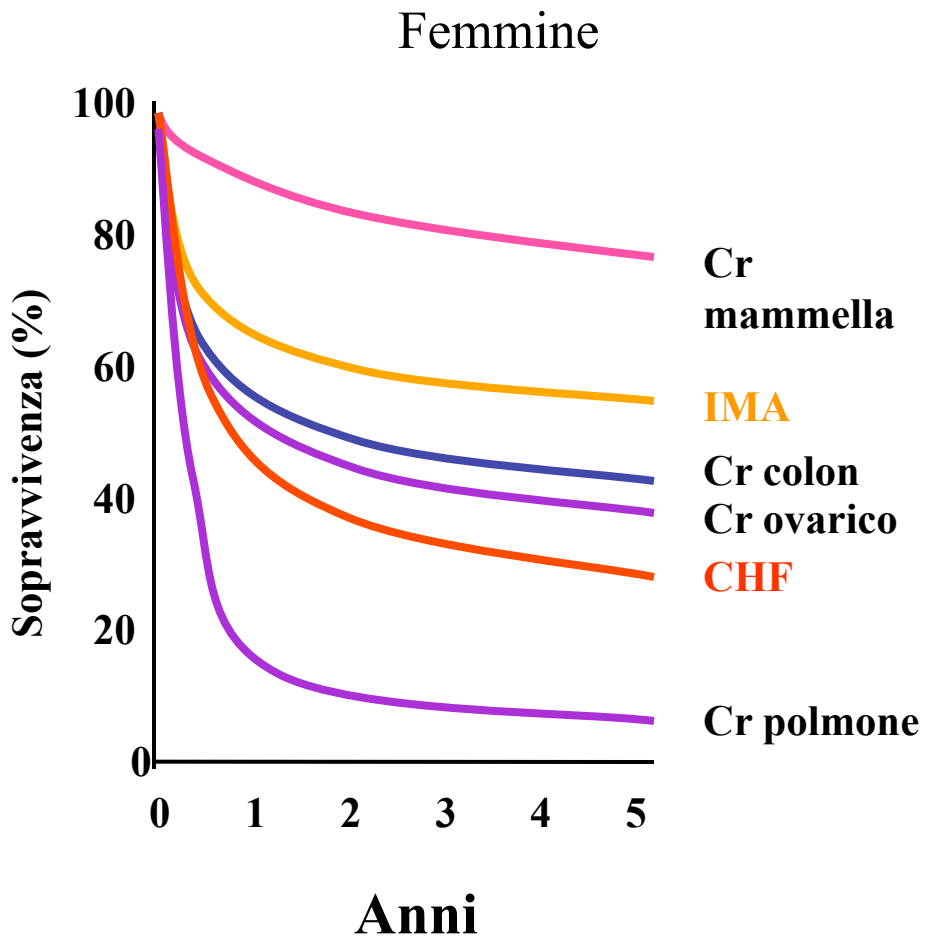


Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

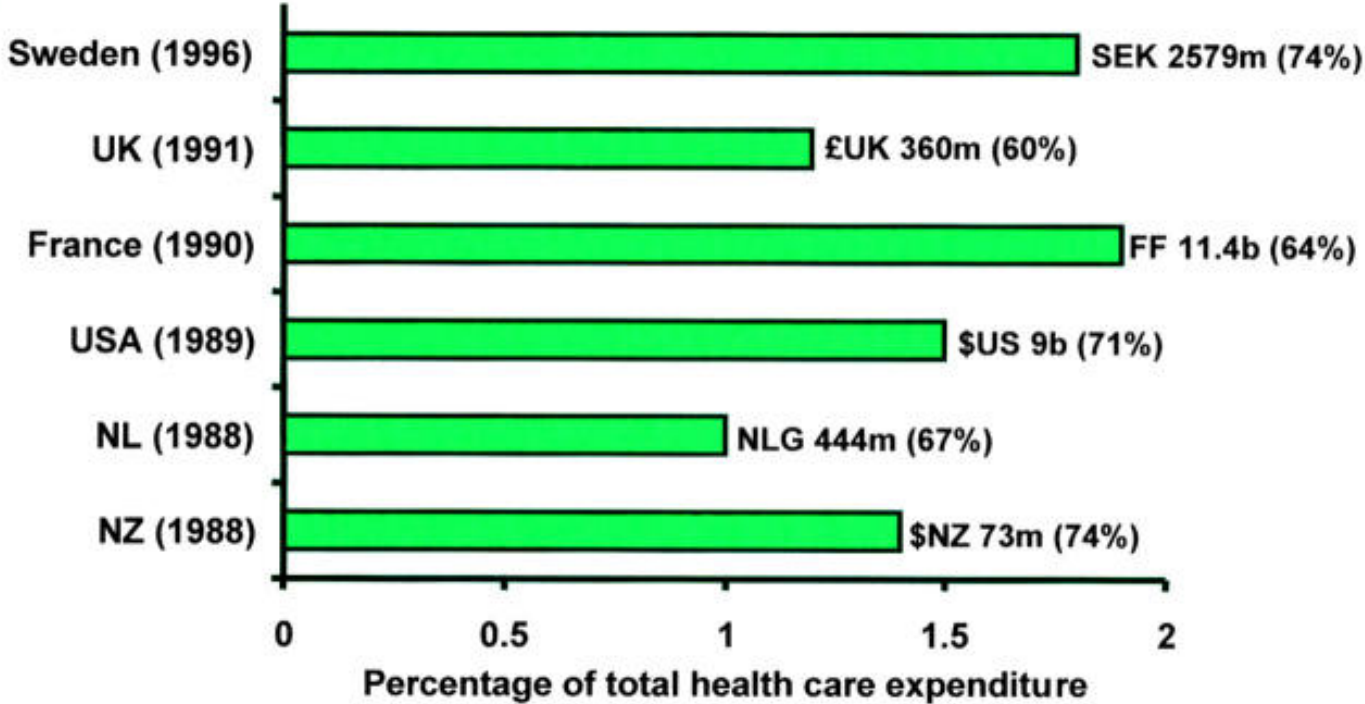


Modif. Da Najafi F et Al. Eur J Heart Fail; 2009;11:472-479

Sopravvivenza dei pazienti con scompenso cardiaco

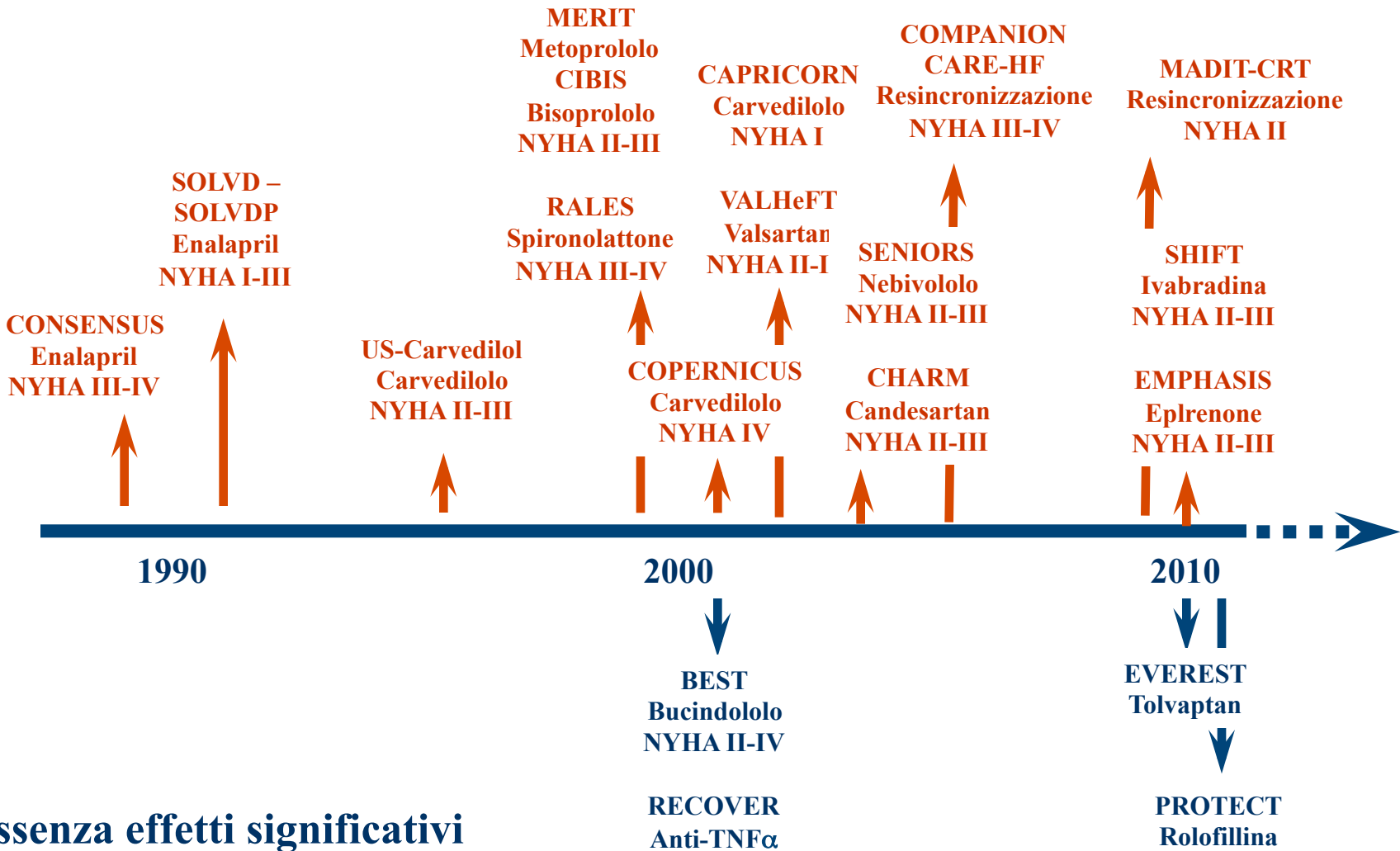


Costi di gestione ed ospedalizzazioni



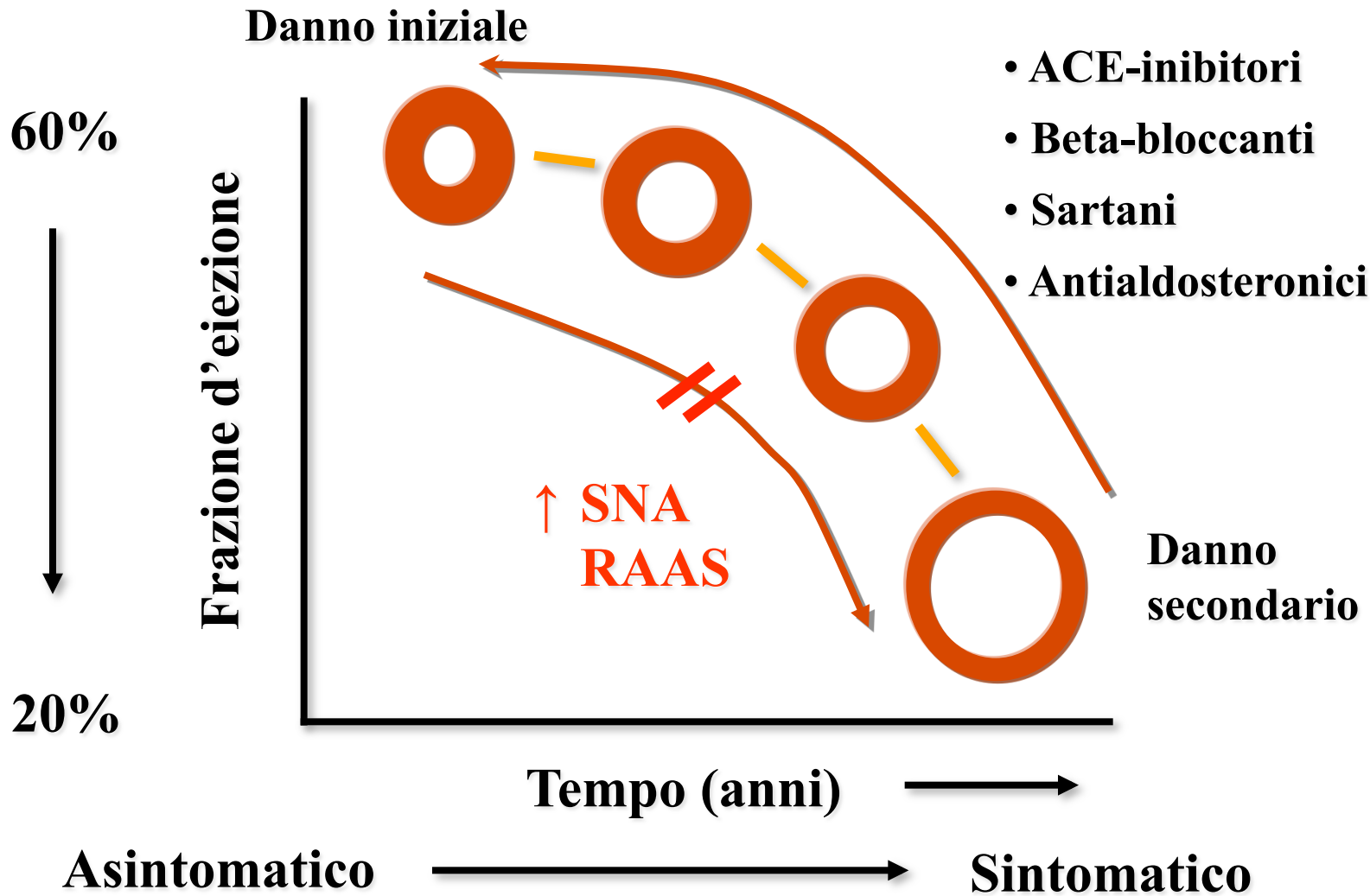
Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

Riduzione Mortalità - Ospedalizzazione

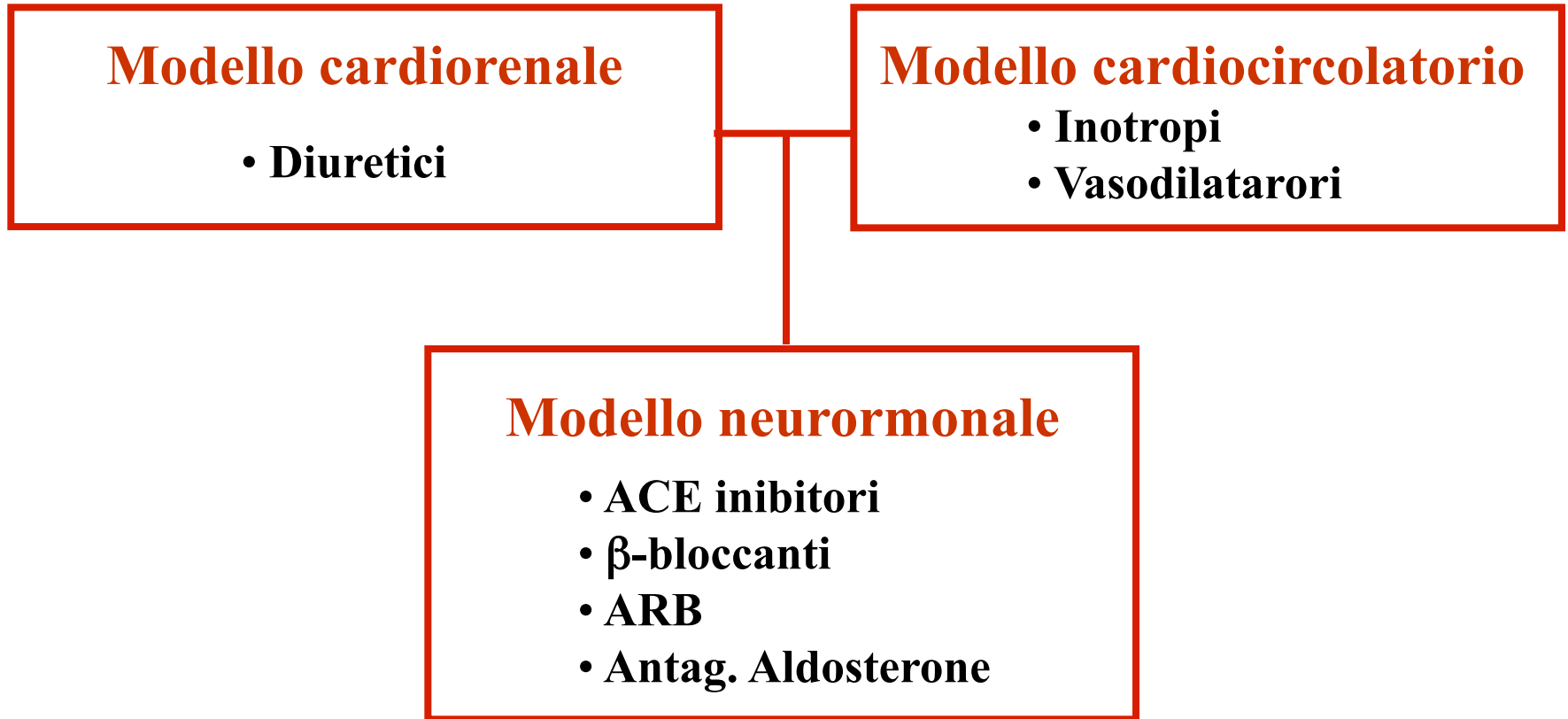


Assenza effetti significativi

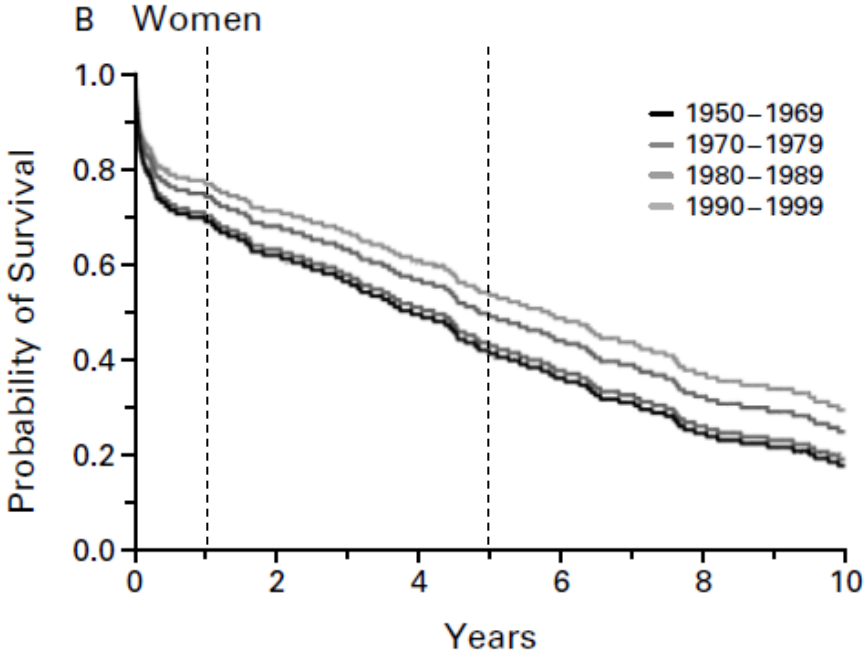
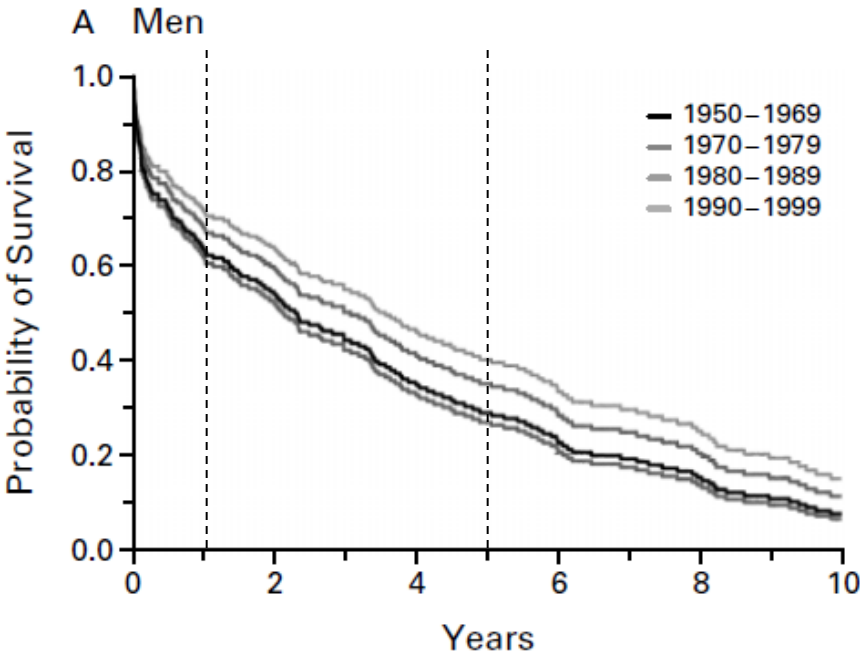
Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo



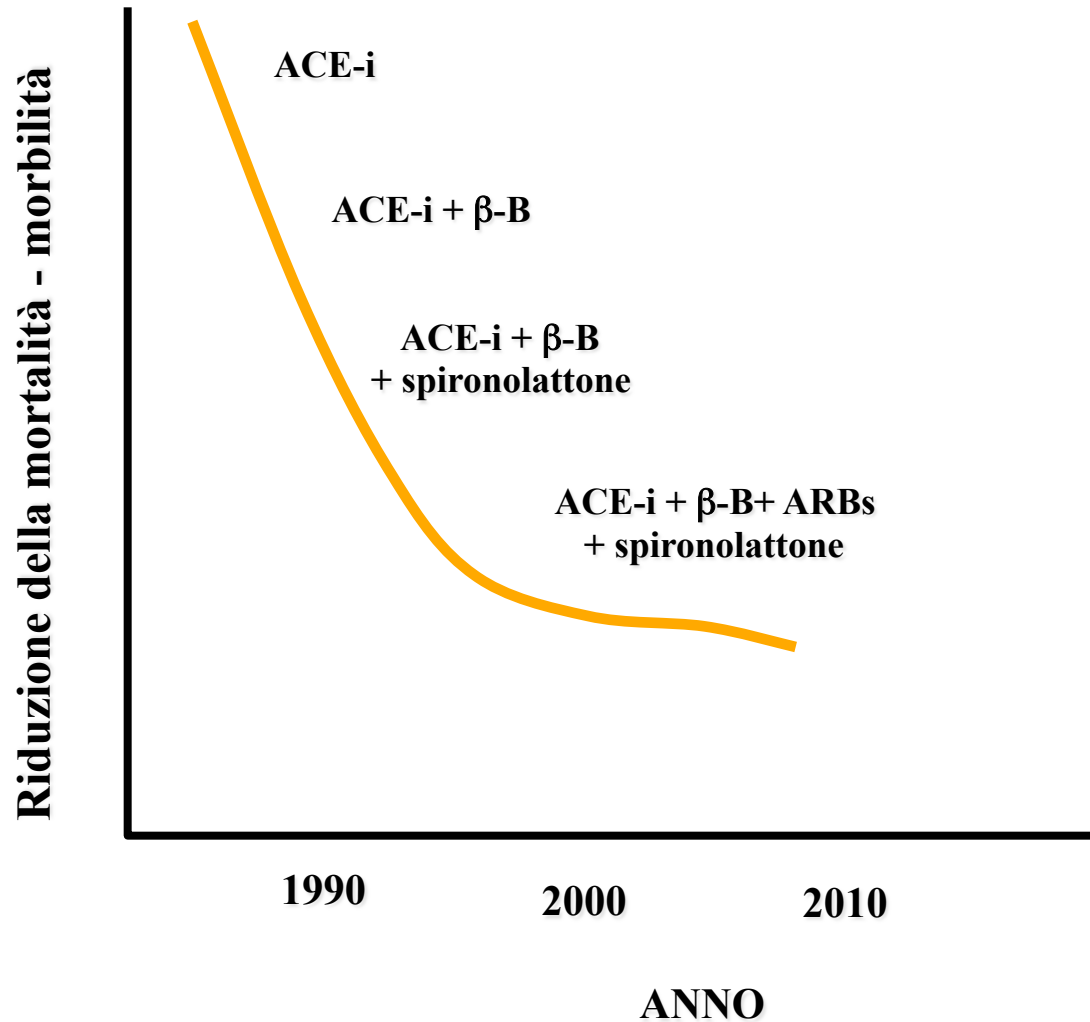
Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo



Riduzione Mortalità - Ospedalizzazione



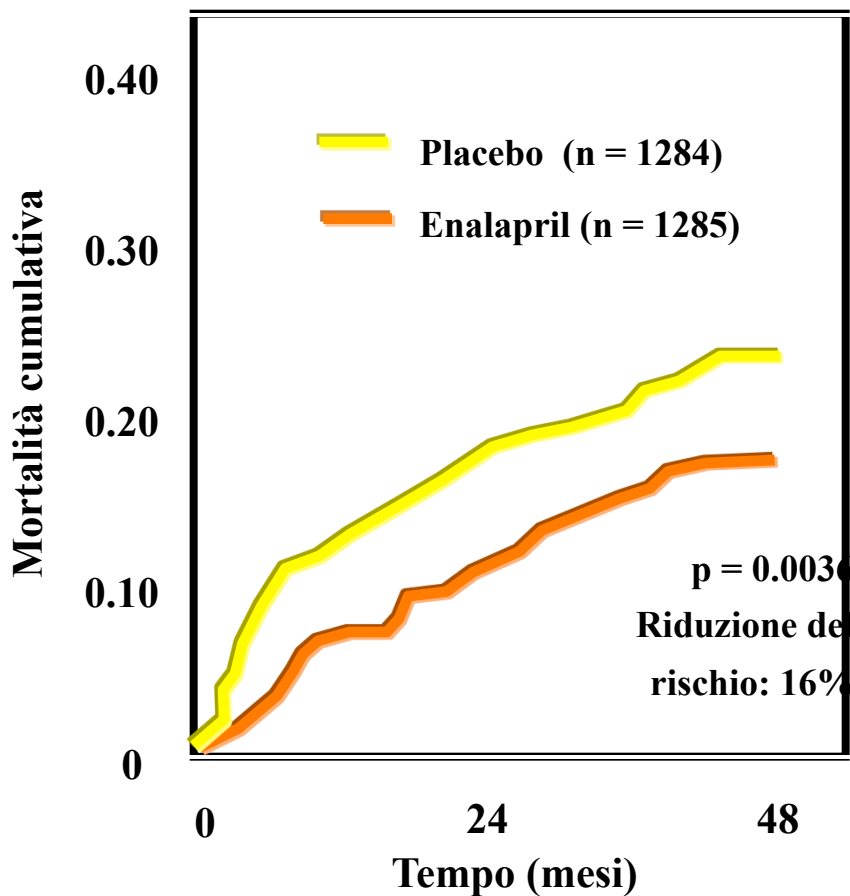
Antagonisti dei sistemi neuroormonali



Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

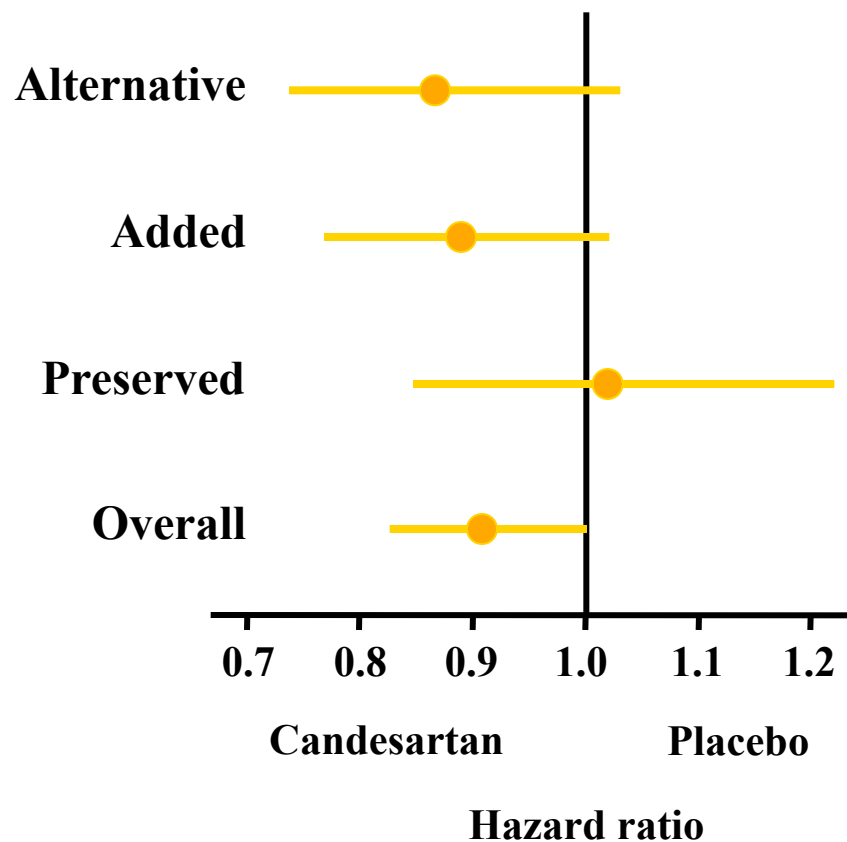
SOLVD – treatment (Enalapril)

FE<35%; Classe NYHA II-III



CHARM programme (ACE-i + β B + ARB)

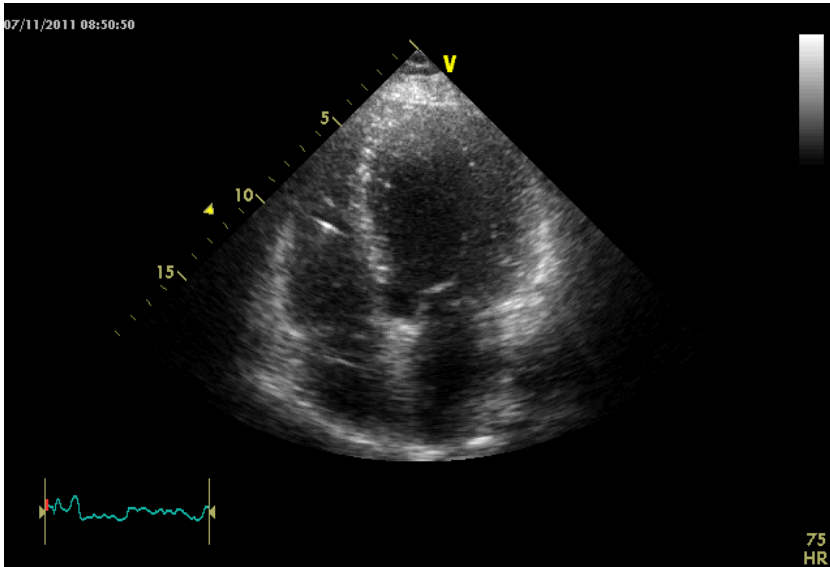
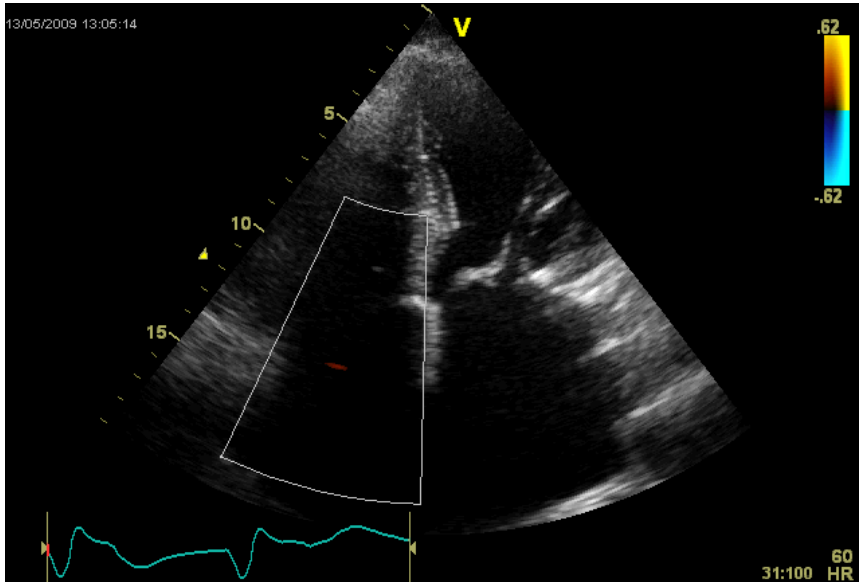
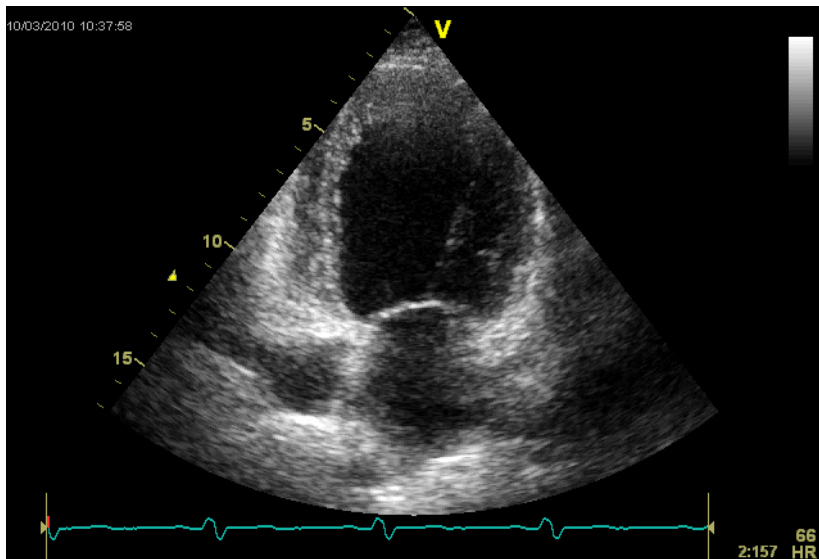
All-cause death



Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

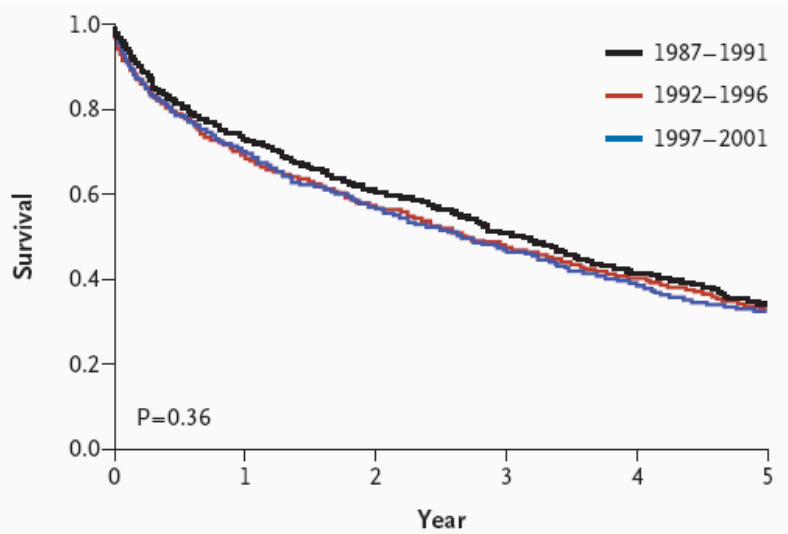
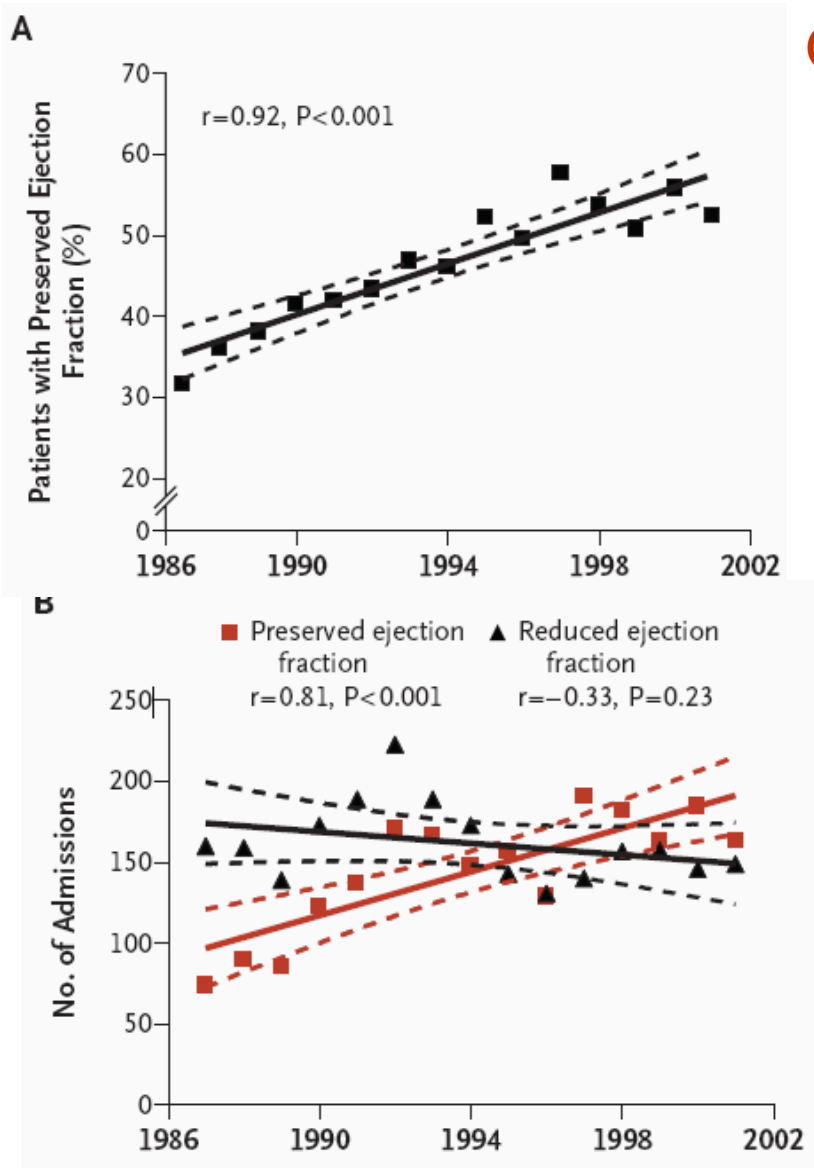
	PAZIENTI NELLA PRATICA CLINICA	PAZIENTI ARRUOLATI NEI TRIALS CLINICI
ETA'	> 75 ANNI	50-70 ANNI
SESSO M:F	1:1	4:1
FE (%)	> 40 % (SCOMPENSO DIASTOLICO)	< 35 % (SCOMPENSO SISTOLICO)
CO-MORBIDITA'	IRC, DIABETE MELLITO, ANEMIE, BPCO, FA, ECC.	-
COMPLIANCE ALLA TERAPIA	+/-	++
OTTIMIZZAZIONE DELLA TERAPIA	+/-	++

Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo



Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

Funzione sistolica preservata (HFPEF)



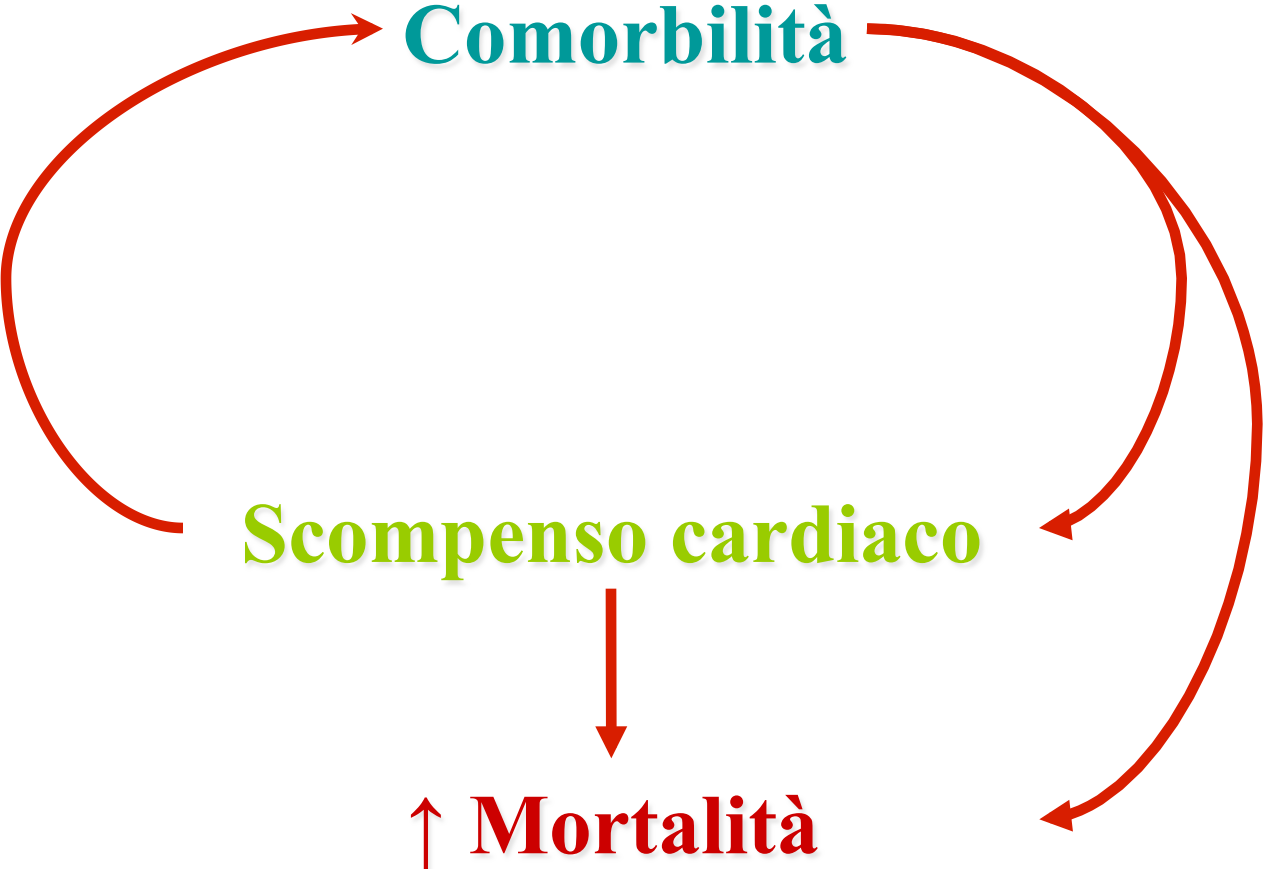
No. at Risk

1987–1991	510	377	313	263	216	117
1992–1996	771	537	447	375	314	262
1997–2001	885	629	513	365	230	138

Scompenso cardiaco con funzione sistolica preservata (HFPEF)

Table 1. Characteristics of Patients with Heart Failure and Preserved or Reduced Ejection Fraction.*

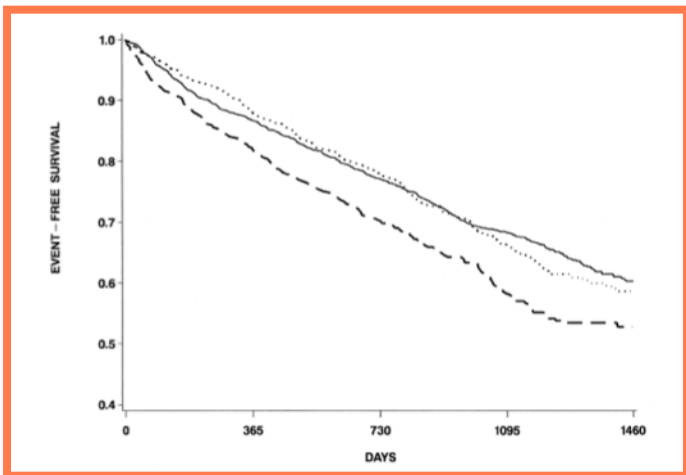
Characteristic	Reduced Ejection Fraction (N=2429)	Preserved Ejection Fraction (N=2167)	P Value	Adjusted P Value†
Age (yr)	71.7±12.1	74.4±14.4	<0.001	NA
Male sex (% of patients)	65.4	44.3	<0.001	<0.001
Body-mass index‡	28.6±7.0	29.7±7.8	0.002	0.17
Obesity (% of patients)‡§	35.5	41.4	0.007	0.002
Serum creatinine on admission (mg/dl)	1.6±1.0	1.6±1.1	0.31	0.30
Hemoglobin on admission (g/dl)	12.5±2.0	11.8±2.1	<0.001	<0.001
Hypertension (% of patients)	48.0	62.7	<0.001	<0.001
Coronary artery disease (% of patients)	63.7	52.9	<0.001	<0.001
Atrial fibrillation (% of patients)	28.5	41.3	<0.001	<0.001
Diabetes (% of patients)	34.3	33.1	0.42	0.61
Substantial valve disease (% of patients)	6.5	2.6	<0.001	0.05
Ejection fraction (%)	29±10	61±7	<0.001	NA



Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

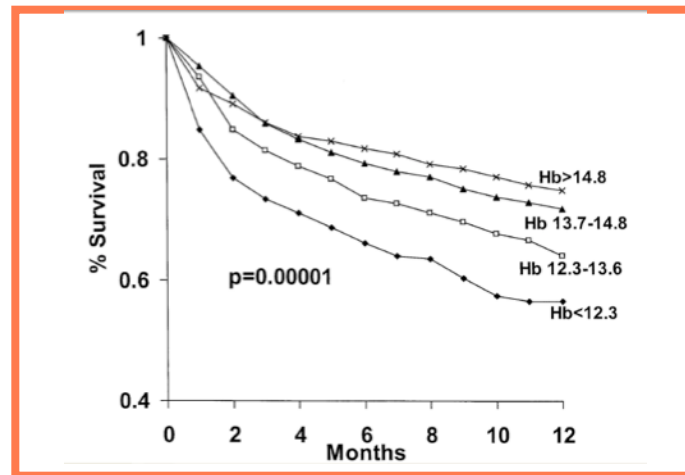
Diabete

(Dries DL et al, J Am Coll Cardiol 2001;38:421)



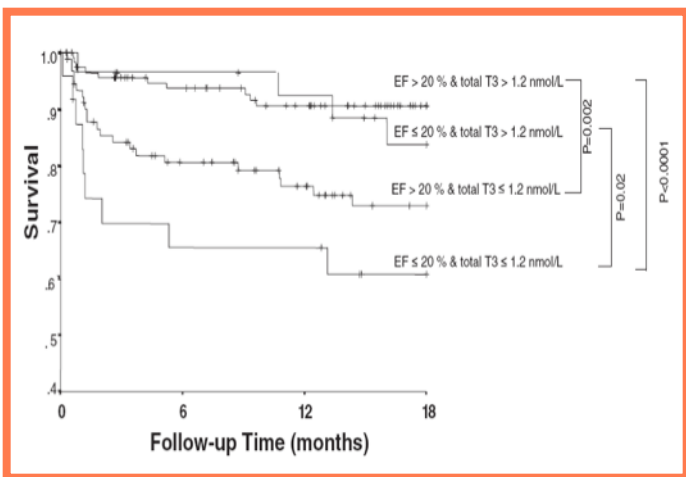
Anemia

(Horwich TP et al, J Am Coll Cardiol 2002;39:1780)



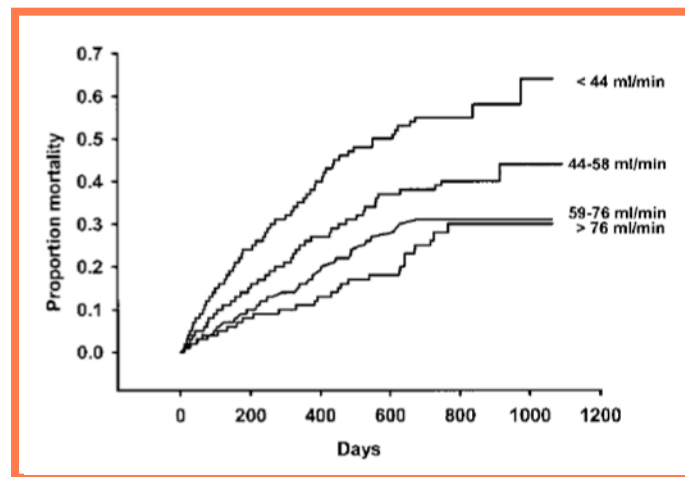
LT3

(Pingitore A et al., Am J Med 2005;118:132)



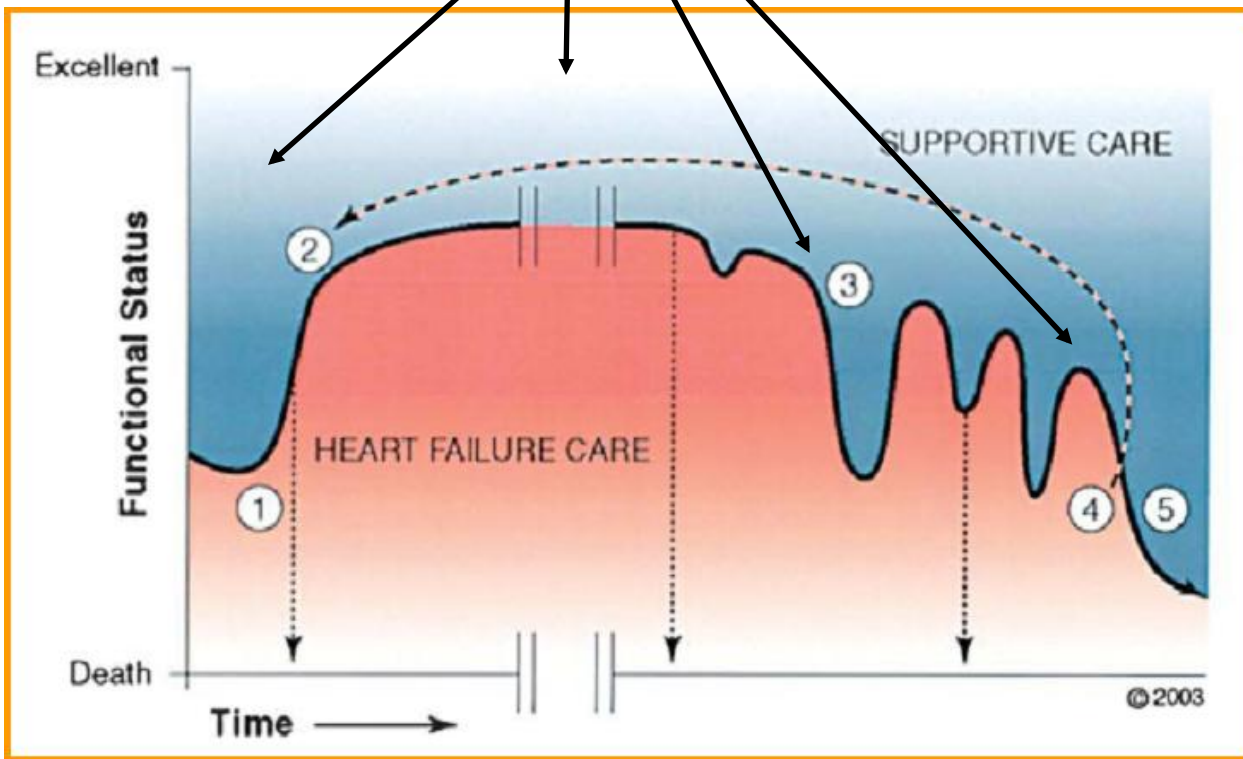
GFR

(Hillege HL et al., Circulation 2000;103:203)

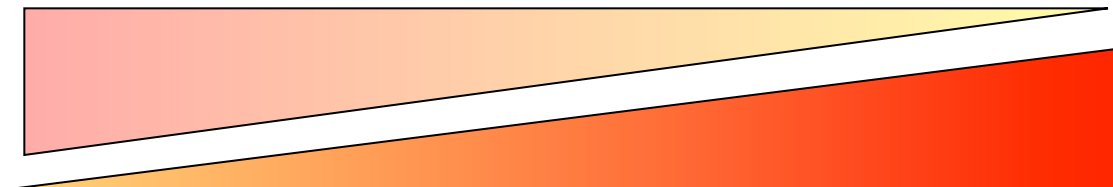


Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

Comorbidità



Ipotiroidismo

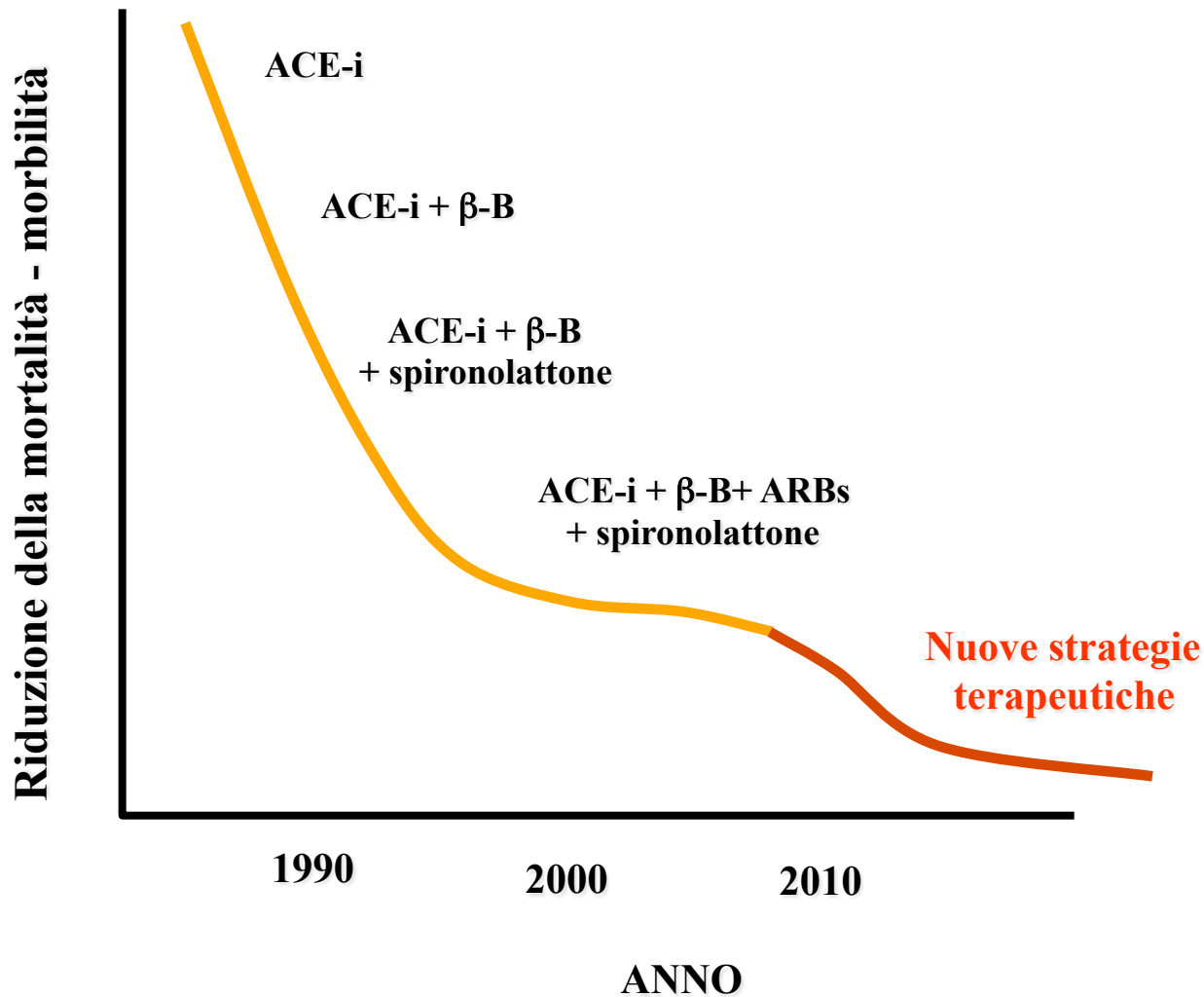


LT3

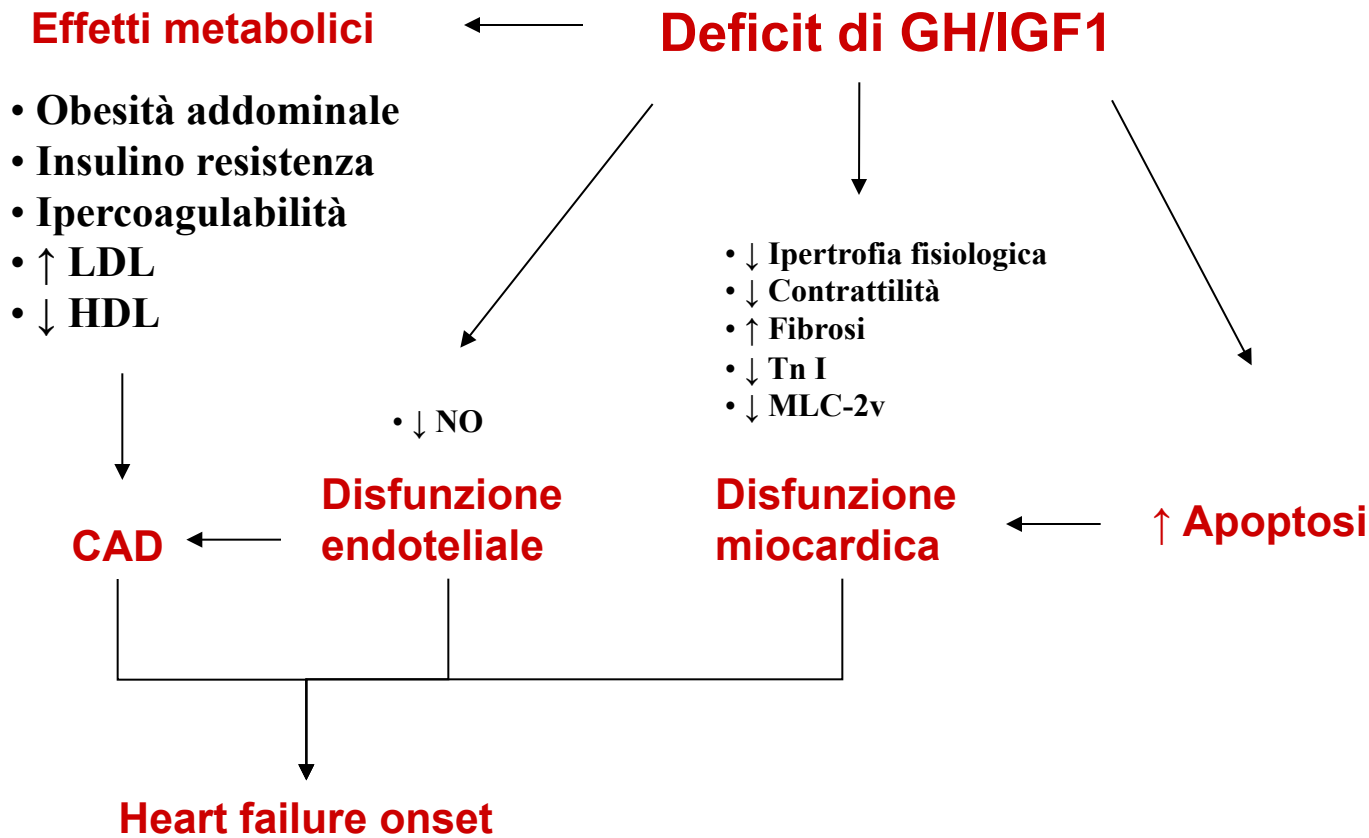
Impatto clinico delle comorbidità

- **Ruolo fisiopatologico e significato prognostico**
- **Influenza delle comorbidità sulla terapia dello scompenso**
(es. b-bloccanti BPCO o ACE/ARBs in MRC)
- **Comorbidità come target terapeutico per migliorare la sopravvivenza dei pazienti con scompenso**

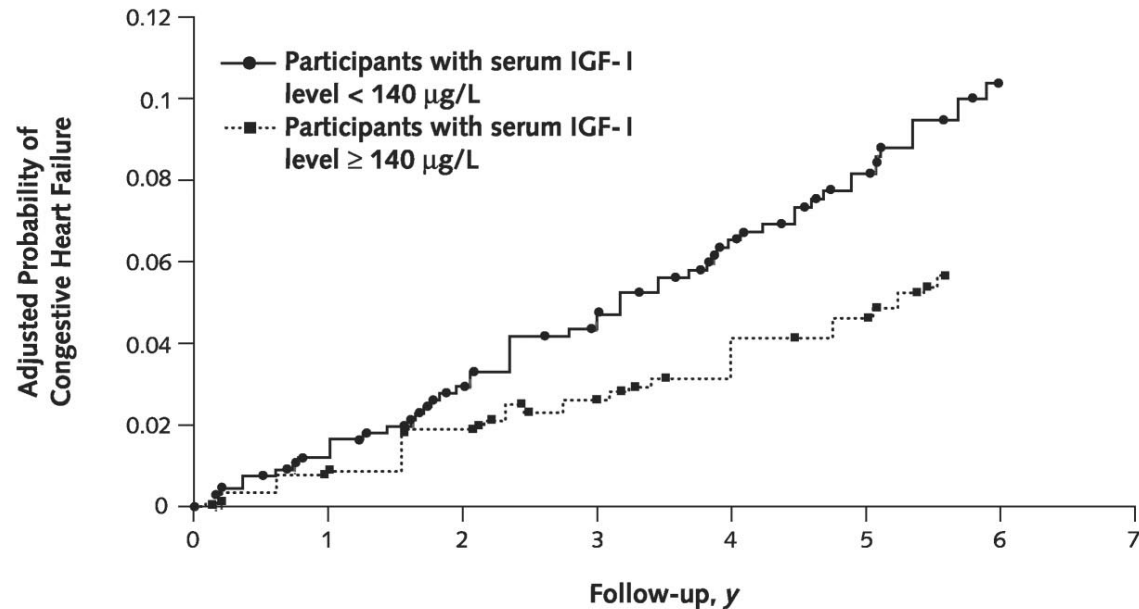
Antagonisti dei sistemi neuroormonali



Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo



Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo



Participants with Congestive Heart Failure/Participants at Risk, *n/n*

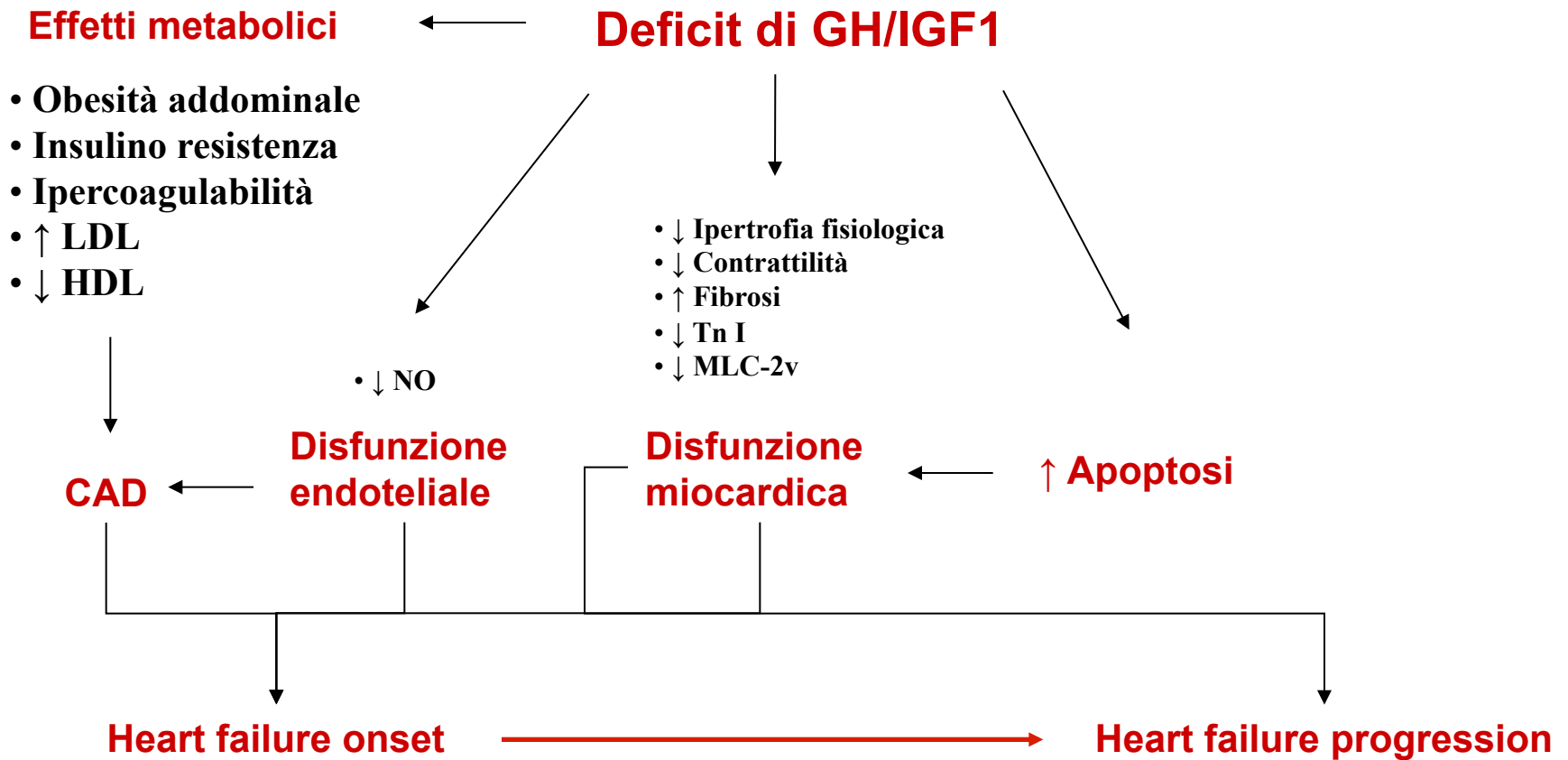
Serum IGF-I Level

< 140 µg/L 0/361 6/323 14/290 18/277 25/256 31/228 37/143

Serum IGF-I Level

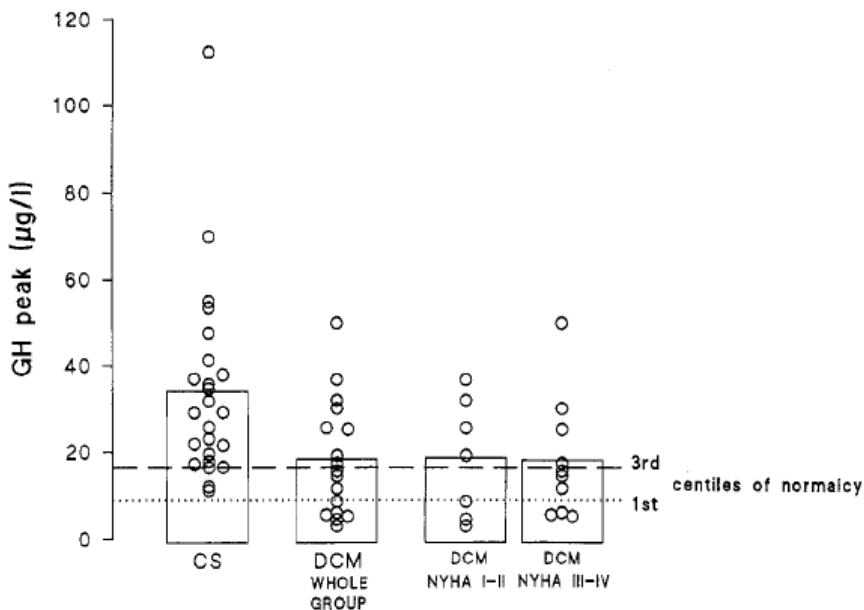
≥ 140 µg/L 0/356 3/336 4/303 9/290 13/272 14/261 19/158

Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

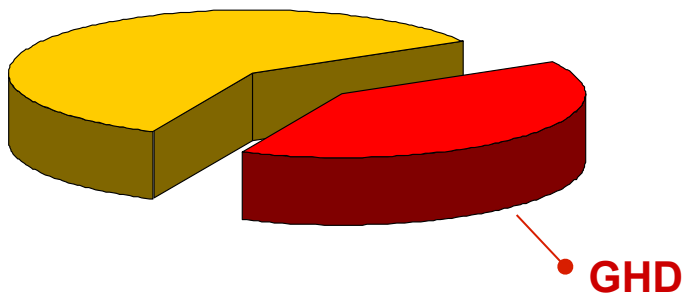


Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

GH stimulation test



Broglia F et al. Eur J Endocrinol 2000;142:157-63.



Cittadini A et al. J Clin Endocrinol Metab 2009;94:3329

Comorbilità	Prevalenza
Anemia	15-60%
Insufficienza renale cronica	25-39%
Diabete	12-30%
BPCO	20-30%
Tireopatie	10-15%
GHD	30-40%

Deficit GH e prognosi

TABLE 3. Single-Predictor Models of Cox Proportional Hazard Analyses in Men With CHF

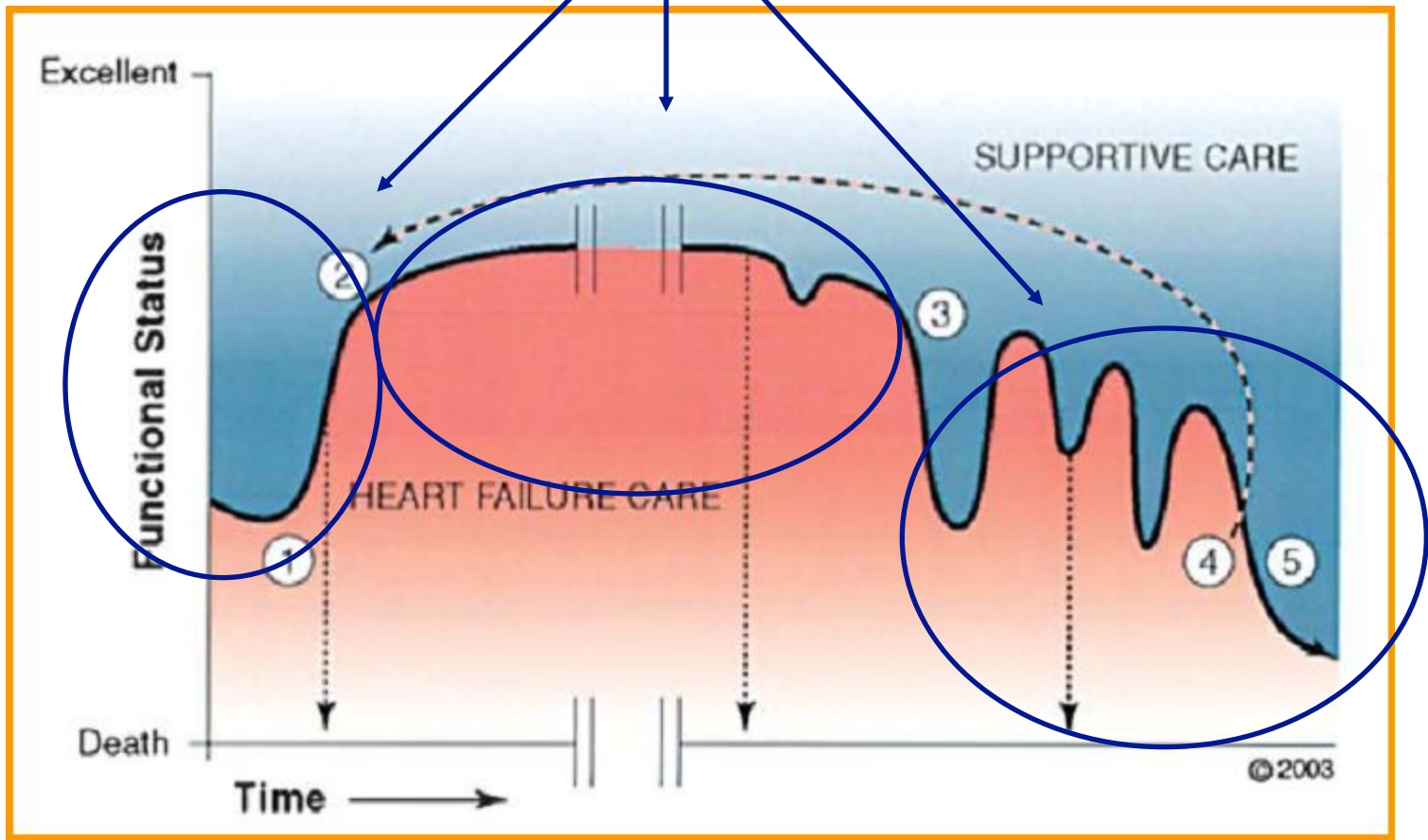
Variables	Units	HR	95% CI	<i>P</i>
Age	1 y	1.04	1.01–1.06	0.002
NYHA class	I/II/III/IV	2.83	2.08–3.85	<0.0001
CHF origin	CAD/non-CAD	1.40	0.73–2.65	0.31
LVEF	1%	0.92	0.89–0.95	<0.0001
Plasma NT-proBNP	500 pg/mL	1.05	1.03–1.06	<0.0001
GFR	5 mL · min ⁻¹ · 1.73 m ⁻²	0.83	0.77–0.90	<0.0001
Hemoglobin	1 g/dL	0.81	0.71–0.92	0.001
Presence of diabetes mellitus	Yes/no	1.03	0.62–1.70	0.91
Serum TT	1 ng/mL	0.72	0.62–0.84	<0.0001
Serum eFT	10 pg/mL	0.89	0.84–0.95	0.0002
Serum DHEAS	100 ng/mL	0.87	0.81–0.93	<0.0001
Serum IGF-1	10 ng/mL	0.94	0.90–0.98	0.002
No. of anabolic deficiencies	0/1/2/3	1.73	1.31–2.27	0.0001

CAD indicates coronary artery disease.

Model With Serum Levels of 3 Anabolic Hormones				
Variables	Units	HR	95% CI	<i>P</i>
Serum TT	1 ng/mL	0.84	0.72–0.97	0.02
Serum DHEAS	100 ng/mL	0.92	0.87–0.99	0.02
Serum IGF-1	10 ng/mL	0.95	0.91–0.99	0.03
-				
NYHA class	III/IV	1.60	1.11–2.33	0.01
LVEF	1%	0.95	0.92–0.99	0.007
Plasma NT-proBNP	500 pg/mL	1.03	1.01–1.04	0.008
GFR	5 mL · min ⁻¹ · 1.73 m ⁻²	0.91	0.84–0.98	0.02
-				

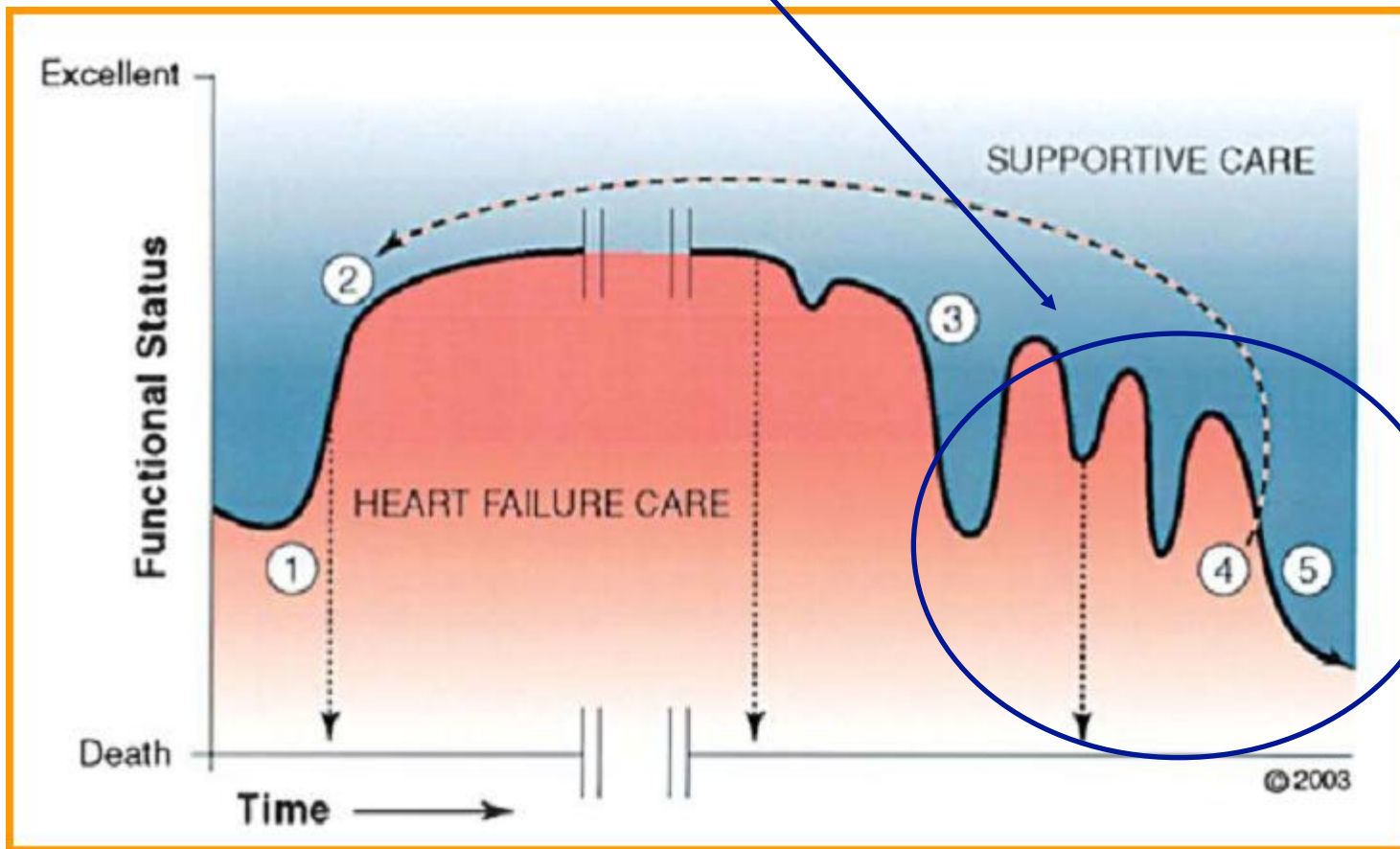
Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

Deficit di GH/IGF-1



Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

Deficit di GH/IGF-1



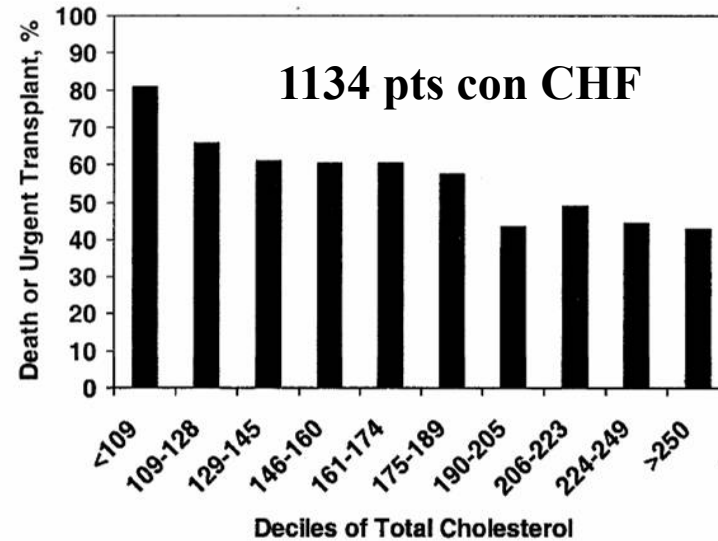
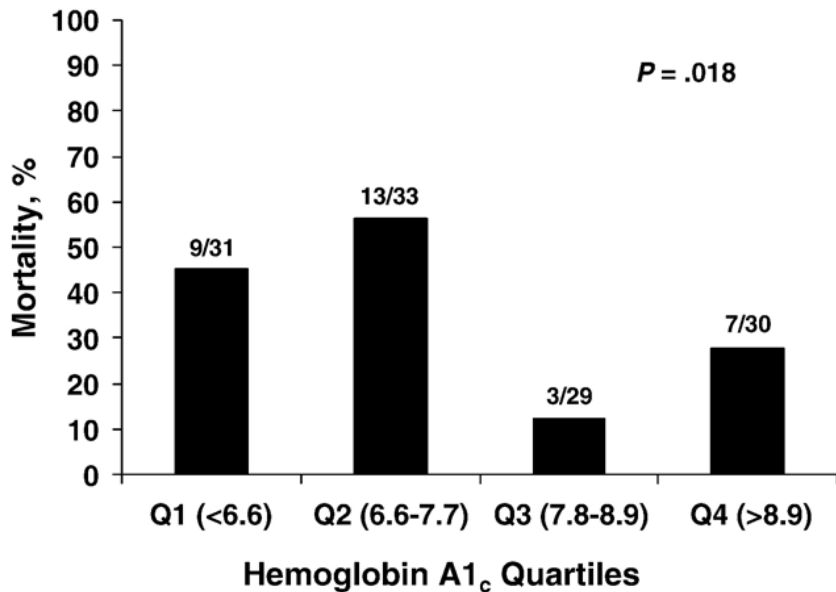
Viewpoint

Reverse Epidemiology of
Conventional Cardiovascular Risk
Factors in Patients With Chronic Heart Failure

Kamyar Kalantar-Zadeh, MD, MPH,*† Gladys Block, PhD,† Tamara Horwich, MD,‡
Gregg C. Fonarow, MD, FACC‡
Torrance, Berkeley, and Los Angeles, California

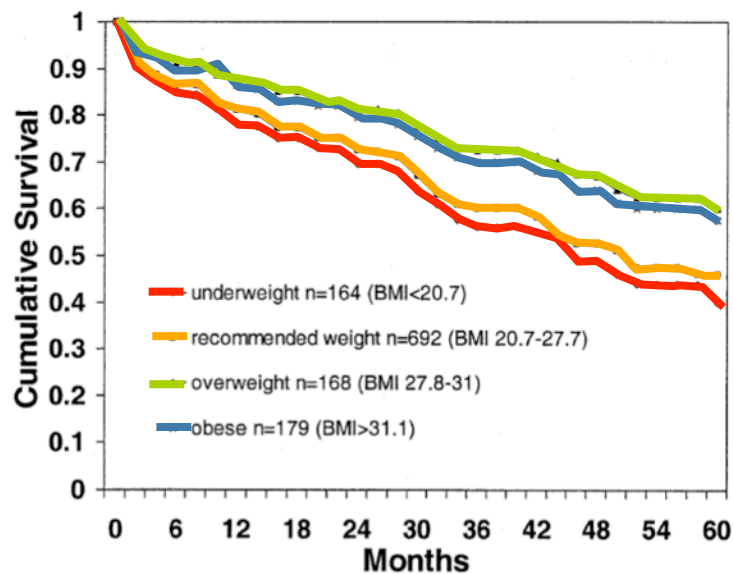
Reverse epidemiology of conventional cardiovascular risk factors is observed in CHF and may have a bearing on the management of these patients; thus, it deserves further investigation. (J Am Coll Cardiol 2004;43:1439–44) ©

Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo



Eshaghian S et al. Am Heart J 2006;151:91

Horwich et al J cardiac Fail 2002;8:216-24



Horwich et al

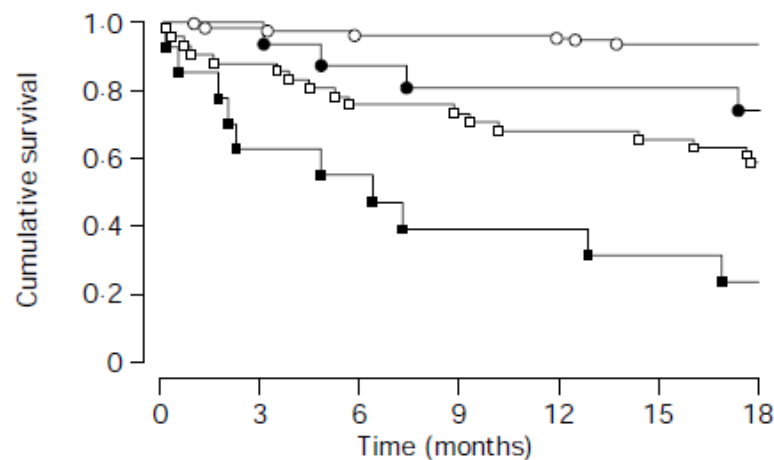
J Am Coll Cardiol 2001;38:789

Cachessia cardiaca

Patients with cardiac cachexia were defined as those with documented non-oedematous and non-intentional weight loss of more than 7.5% of the previous normal nonoedematous weight over a period of at least 6 months.

Variable	p (likelihood ratio test)	Hazard ratio (95% CI)
Cachexia plus peak VO₂		
Cachexia	0.0012	3.01 (1.54-5.86)
Peak VO ₂ <14 mL kg ⁻¹ min ⁻¹	<0.0001	6.58 (3.24-13.35)
Cachexia plus NYHA class		
Cachexia	0.0063	2.54 (1.30-4.97)
NYHA class III/IV	0.0001	6.44 (2.48-16.73)
Cachexia plus exercise time		
Cachexia	0.0012	3.20 (1.58-6.48)
Exercise time (min)	0.0008	0.80 (0.70-0.91)
Cachexia plus LVEF		
Cachexia	0.0027	3.37 (1.52-7.46)
LVEF ≤25% (n=115)	0.0073	3.20 (1.37-7.47)
Cachexia plus age		
Cachexia	0.0003	3.46 (1.76-6.81)
Age	0.27	1.02 (0.99-1.05)
Cachexia plus plasma sodium		
Cachexia	0.0003	3.82 (1.86-7.81)
Plasma sodium	0.62	0.98 (0.89-1.07)
Cachexia plus NYHA class plus peak VO₂		
Cachexia	0.0045	2.63 (1.35-5.12)
NYHA class III/IV	0.0065	3.89 (1.46-10.38)
Peak VO ₂ <14 mL kg ⁻¹ min ⁻¹	<0.0001	4.63 (2.24-9.59)

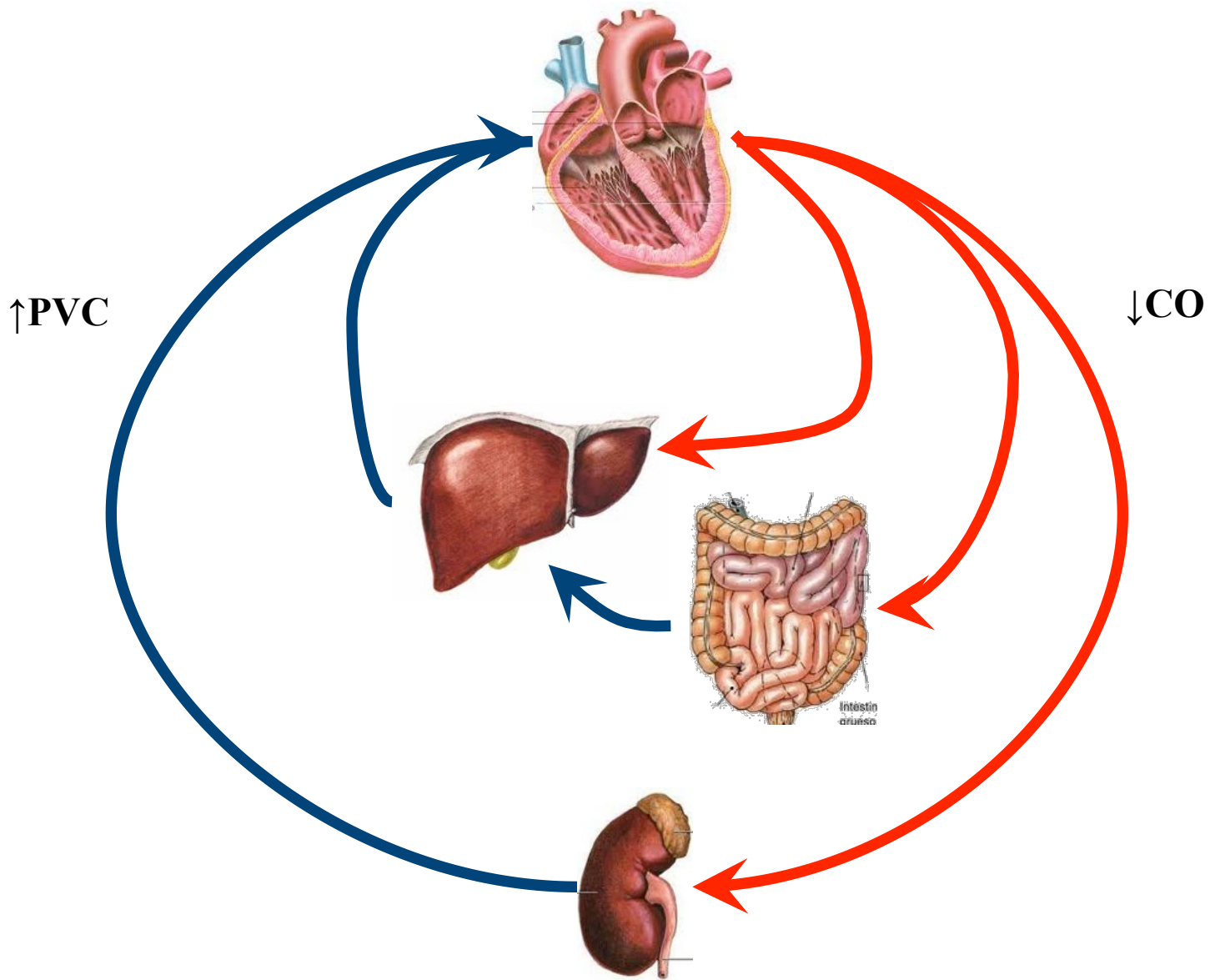
Table 3: Multivariate analysis—predictors of 18-month mortality in 171 patients with CHF (Cox proportional hazard)



At risk	159	149	142	133
Deaths	12	22	29	38

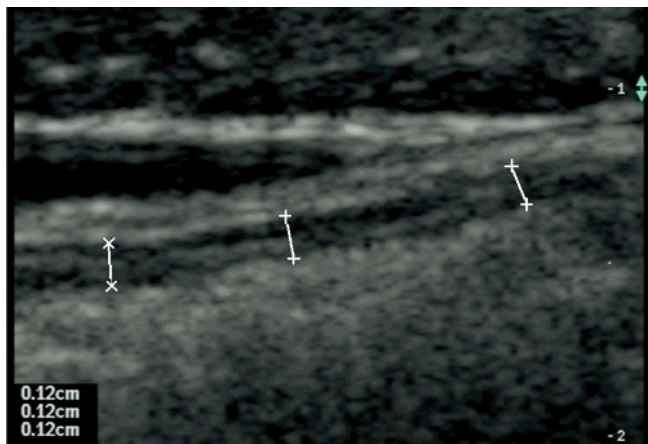
- Cachectic and peak VO₂ <14 mL kg⁻¹ min⁻¹ (n=13, 10 deaths)
- Non-cachectic and peak VO₂ <14 mL kg⁻¹ min⁻¹ (n=40, 17 deaths)
- Cachectic and peak VO₂ ≥14 mL kg⁻¹ min⁻¹ (n=15, 4 deaths)
- Non-cachectic and peak VO₂ ≥14 mL kg⁻¹ min⁻¹ (n=103, 7 deaths)

Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

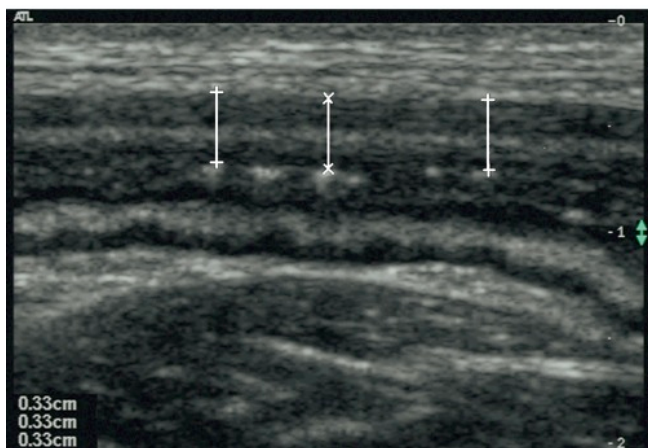


Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

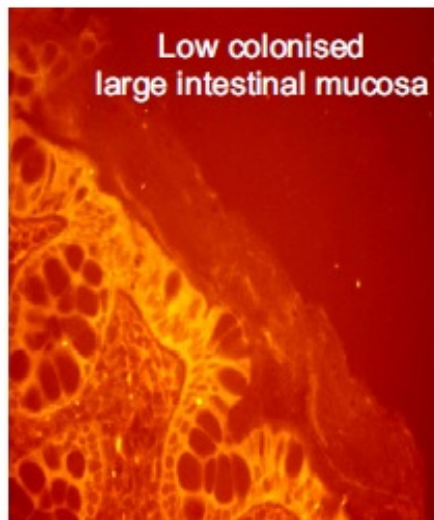
Control



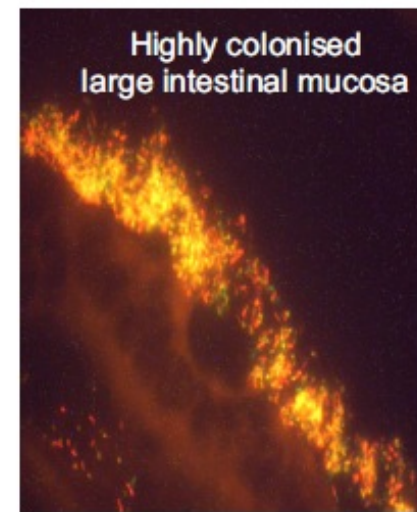
CHF patient



Effetti sulla mucosa intestinale

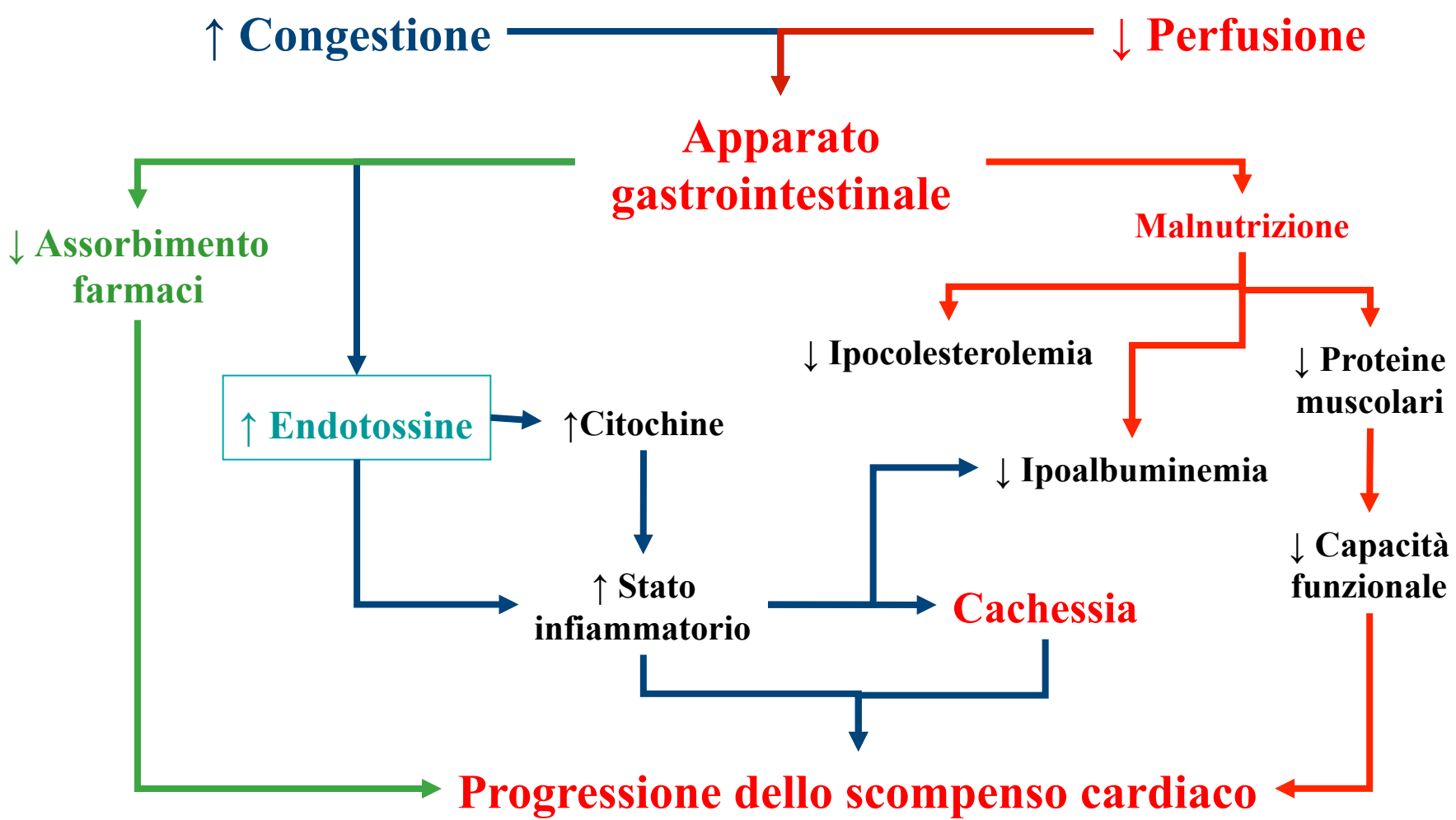


Control subject

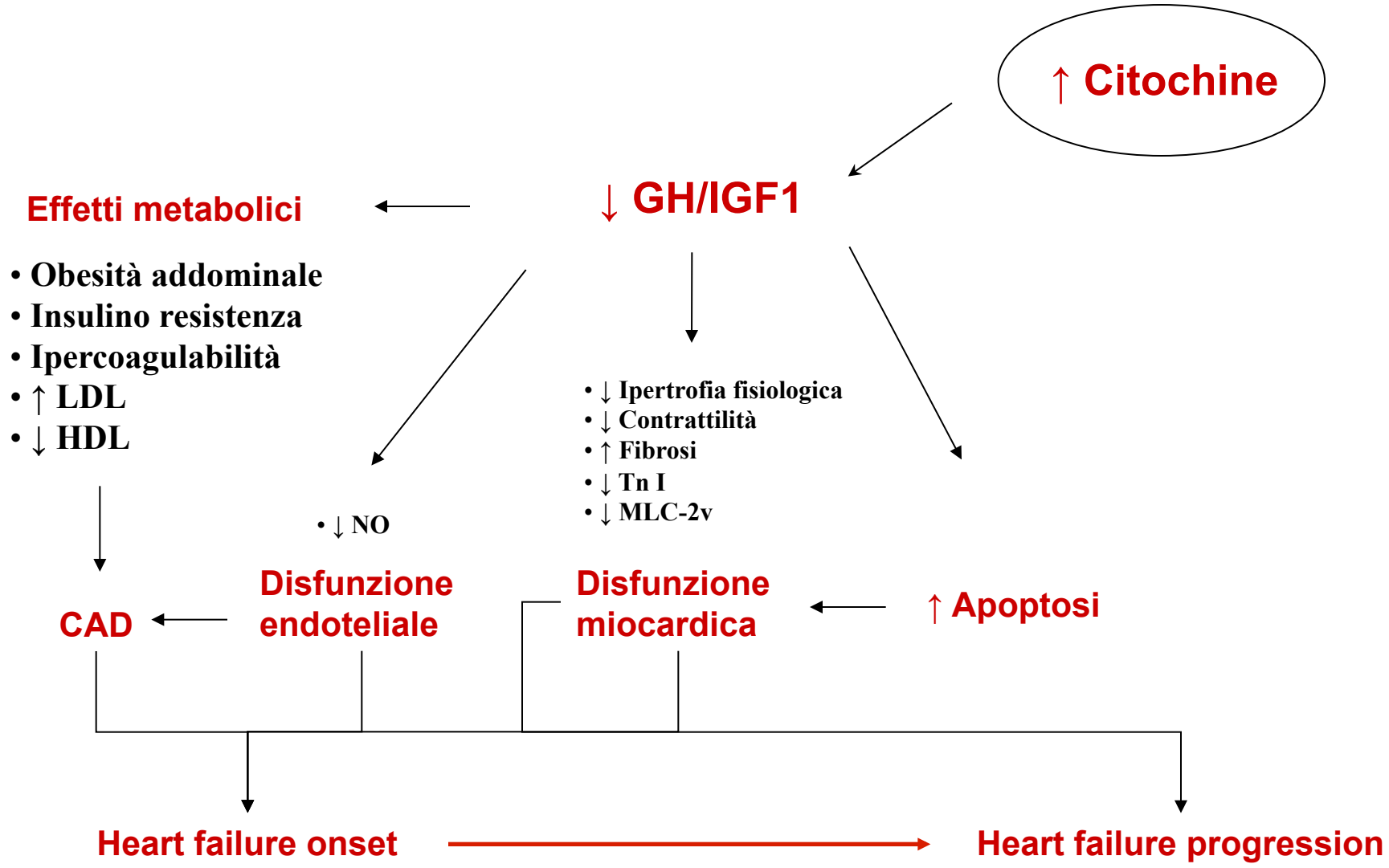


CHF patient

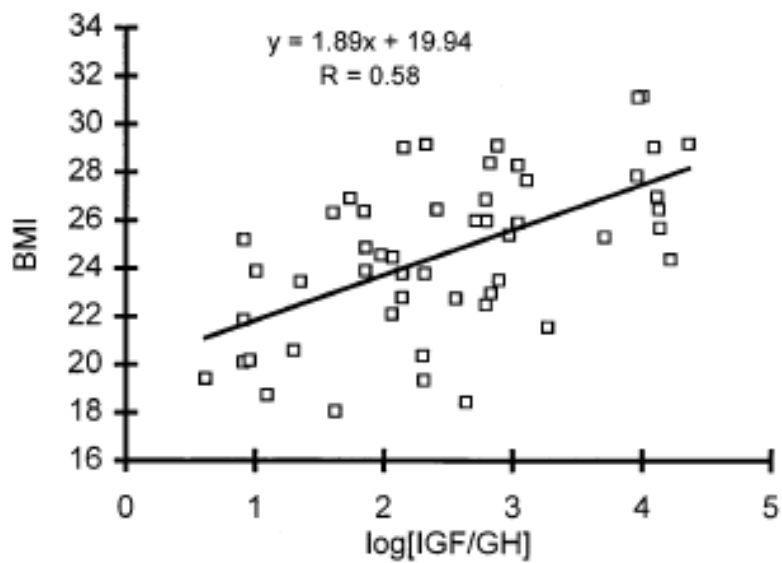
Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo



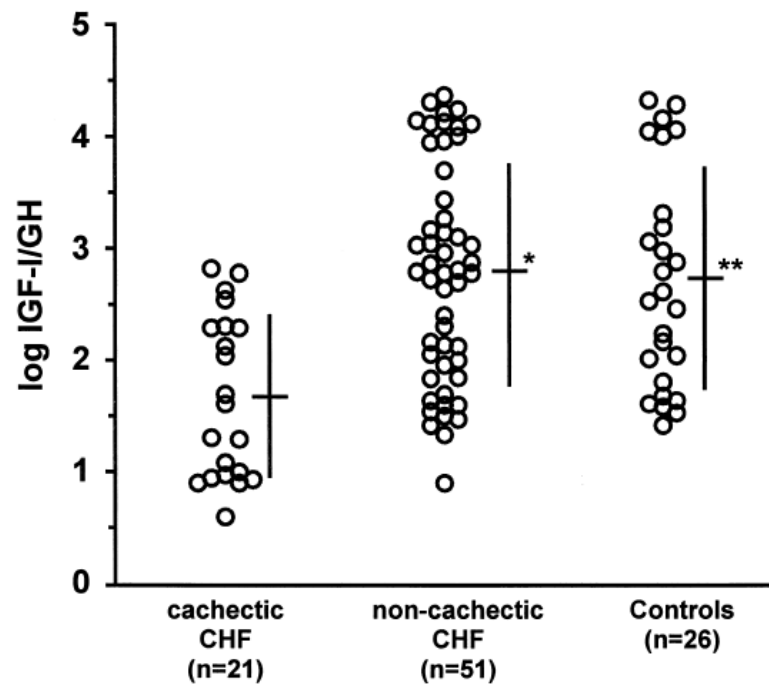
Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo



Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

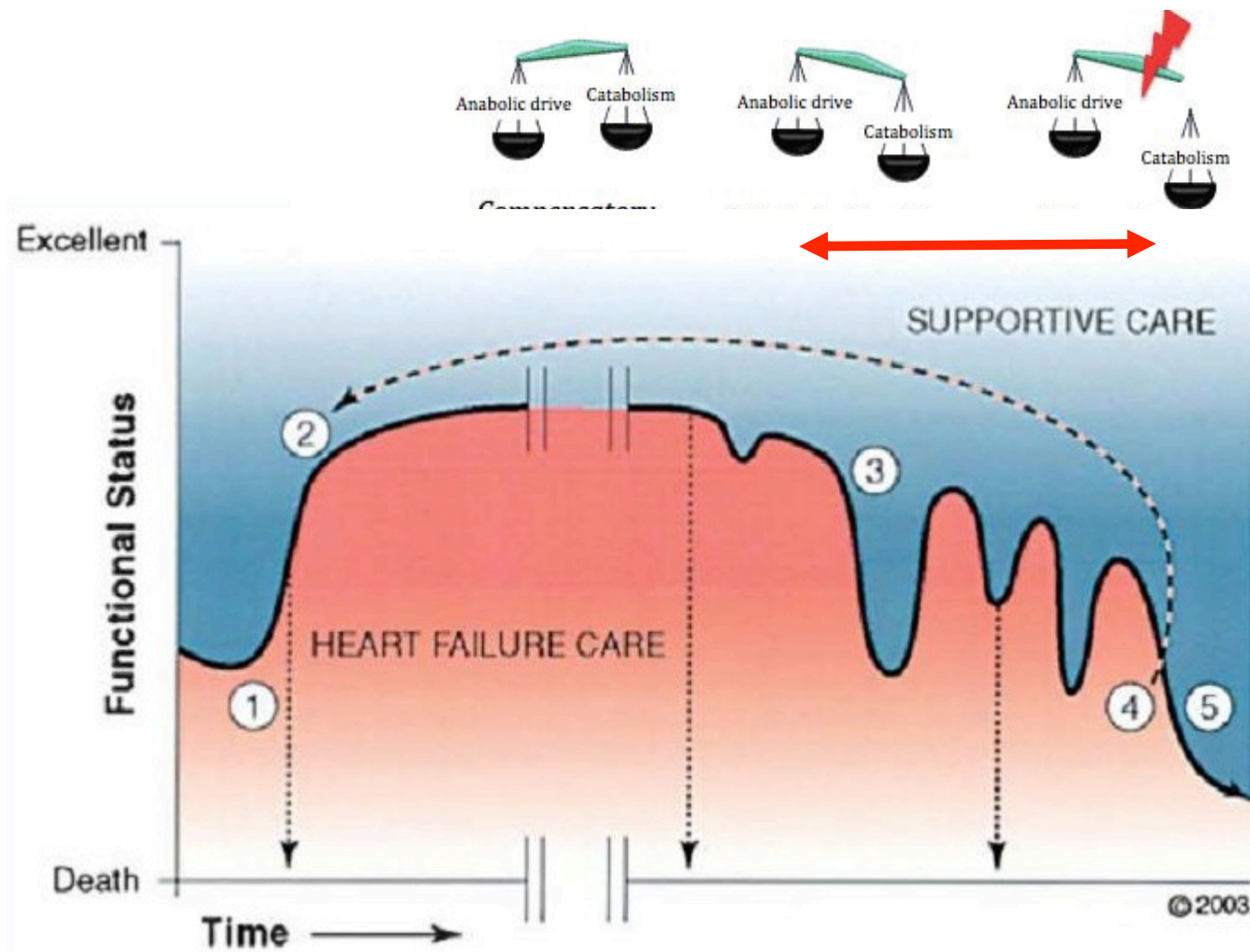


Niebauer et al. J Am Coll Cardiol 1998;32:393-7



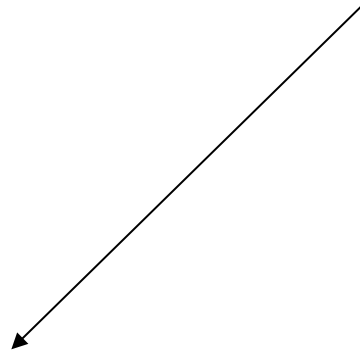
Anker et al. J Am Coll Cardiol 2001;38:443-52

Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo



Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

↓ **GH/IGF1**



Marcatore di prognosi

Stratificazione prognostica

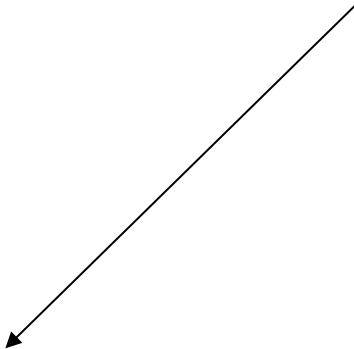
Table 17
Conditions associated with a poor prognosis in heart failure

Demographics	Clinical	Electrophysiological	Functional/exertional	Laboratory	Imaging
Advanced age ^a	Hypotension ^a	Tachycardia Q waves	Reduced work, low peak VO ₂ ^a	Marked elevation of BNP/NT pro-BNP ^a	Low LVEF ^a
Ischaemic aetiology ^a Resuscitated sudden death ^a	NYHA functional class III–IV ^a Prior HF hospitalization ^a	Wide QRS ^a LV hypertrophy Complex ventricular arrhythmias ^a		Hyponatraemia ^a Elevated troponin ^a Elevated biomarkers, neurohumoral activation ^a	
Poor compliance	Tachycardia	Low heart rate variability Atrial fibrillation	Poor 6-minute walk distance	Elevated creatinine/BUN	Increased LV volumes
Renal dysfunction	Pulmonary rales	T-wave alternans	High VE/VCO ₂ slope Periodic breathing	Elevated bilirubin Anaemia	Low cardiac index
Diabetes Anaemia	Aortic stenosis Low body mass index			Elevated uric acid	High LV filling pressure Restrictive mitral filling pattern, pulmonary hypertension Impaired right ventricular function
COPD	Sleep-related breathing disorders				
Depression					

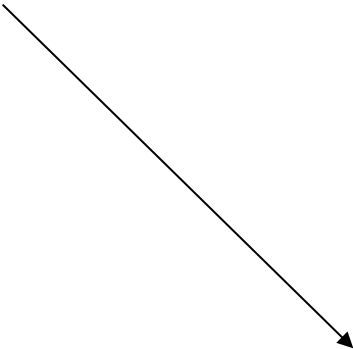
^a Powerful predictors.

Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

↓ **GH/IGF1**



Marcatore di prognosi



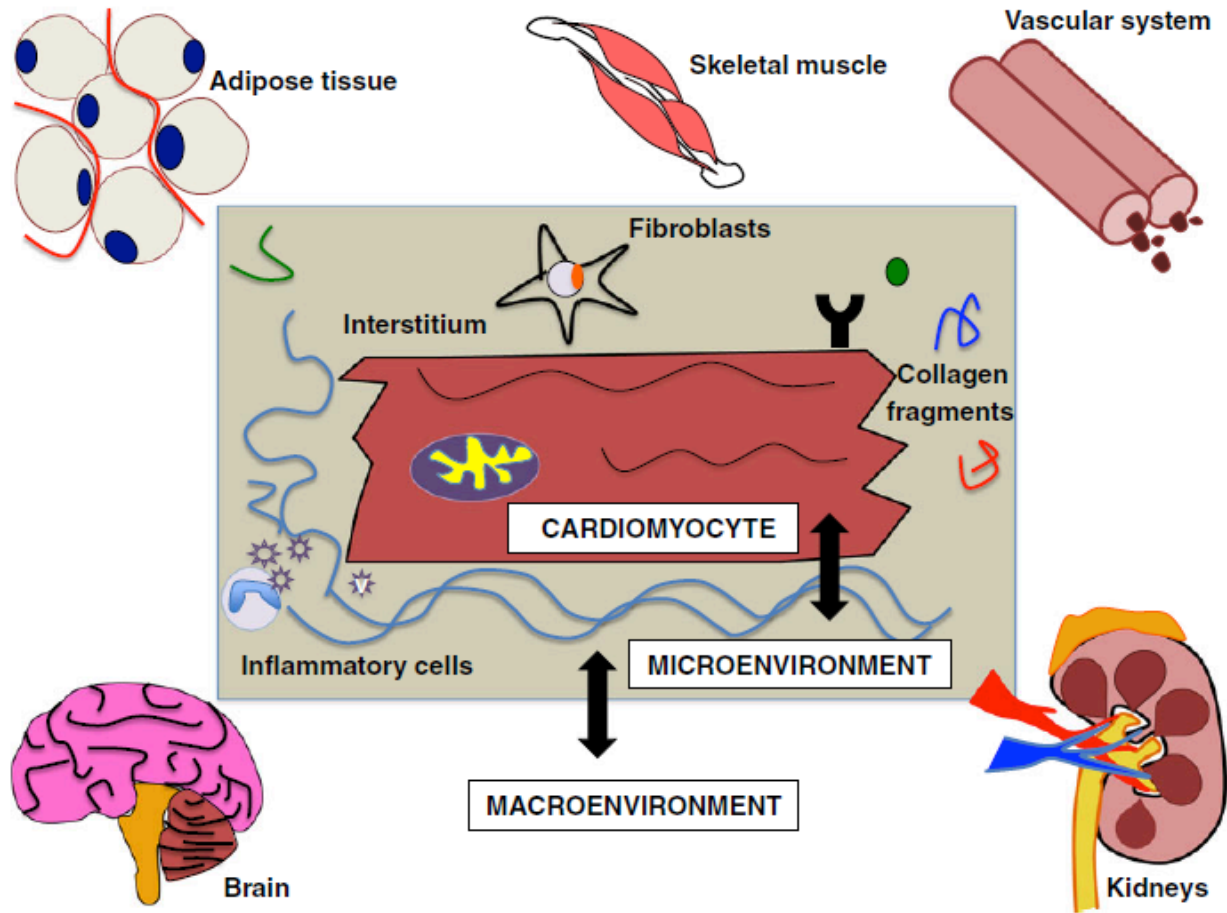
Mediatore di prognosi

Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

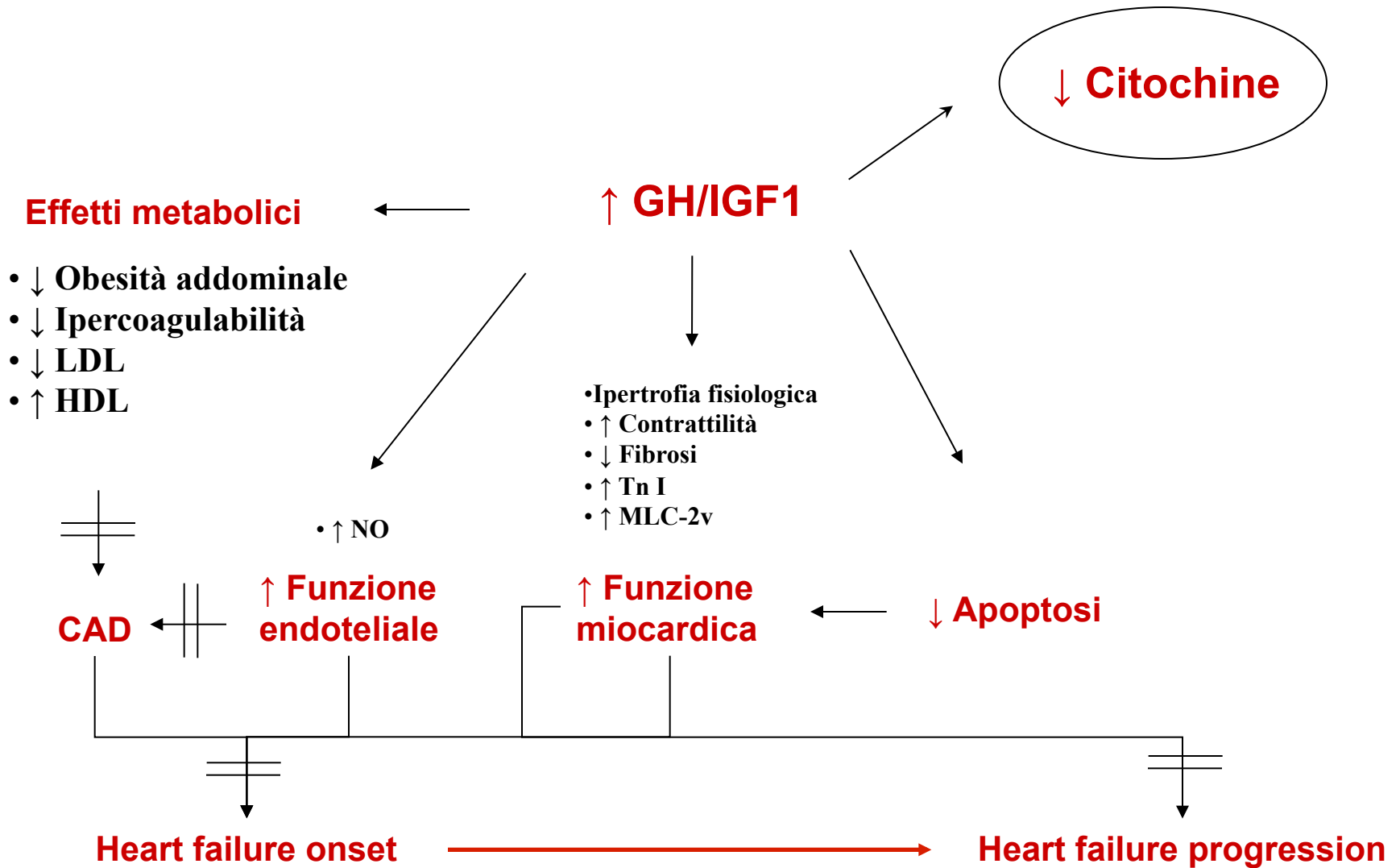
Cardiomyocyte	Microenvironment	Macroenvironment
<p>Stretch</p> <p>NT-proBNP / BNP*</p> <p>ANP*</p> <p>Soluble ST2*</p> <p>Injury</p> <p>TnI-T*</p> <p>Apoptosi</p> <p>Heart-type fatty acid binding protein*</p> <p>Soluble apoptosis-stimulating fragment*</p> <p>Myostatin</p>	<p>Interstitial</p> <p>MMPs* TIMPs*</p> <p>PIIINP*</p> <p>Galectin-3*</p> <p>Fibrosis</p> <p>Citokyne</p> <p>Osteoprotegerin*</p> <p>Pentraxin-3*</p> <p>Cardiotrophin-1</p> <p>Oxidative stress</p> <p>Myeloperoxidase*</p> <p>Ox-LDL</p>	<p>Myocardial energetics</p> <p>Adipokines (adiponectin)*</p> <p>Neurohormones</p> <p>ADM / Mid-reg proADM</p> <p>Copeptin*</p> <p>Cardiorenal syndrome</p> <p>NGAL</p> <p>Beta-trace protein*</p> <p>Cystatin C*</p> <p>KIM-1</p> <p>Others</p> <p>GDF-15*</p> <p>Follistatin-like 1</p>

* Biomarker shown to have predictive abilities in cardiovascular outcomes

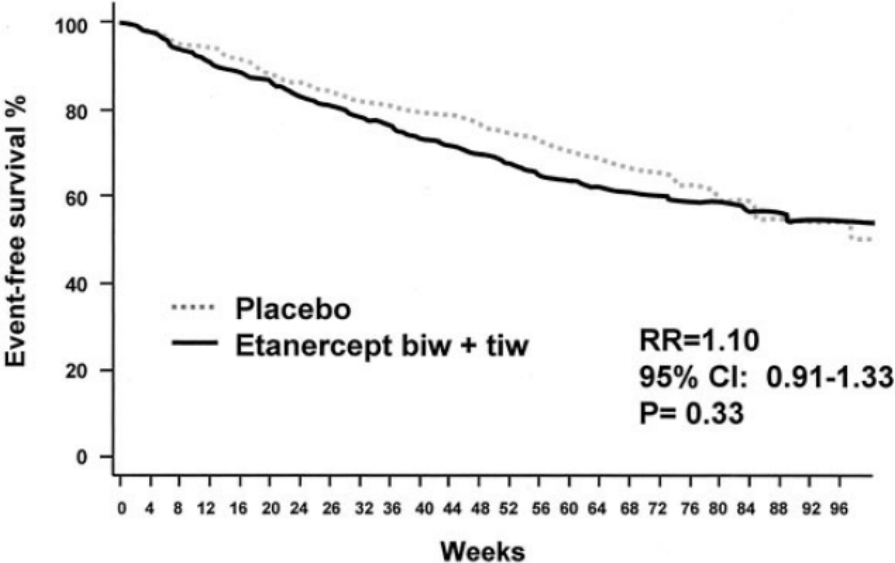
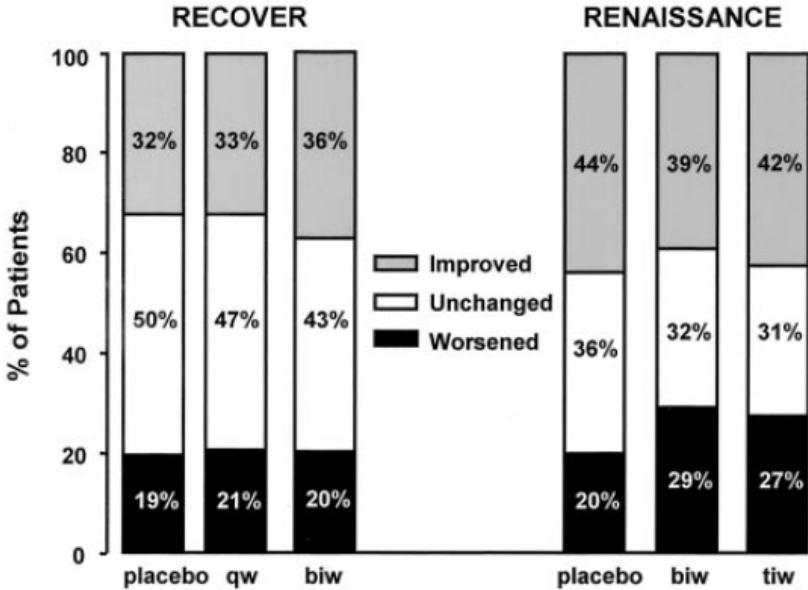
I marcatori biumorali



Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

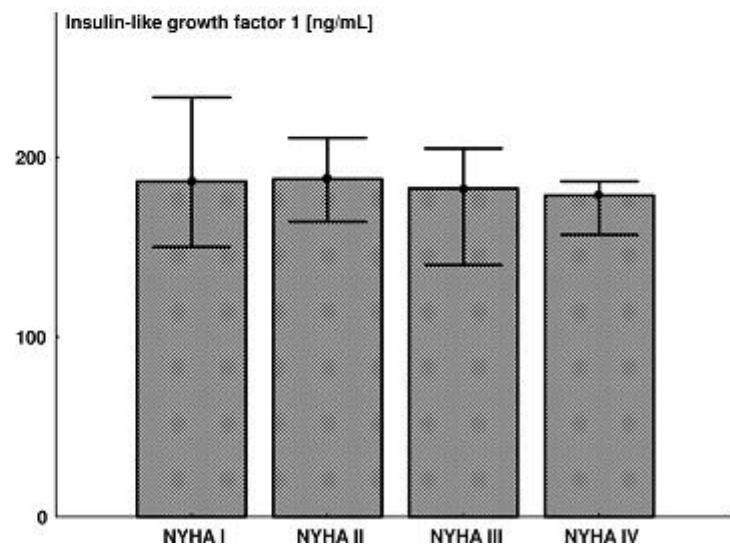
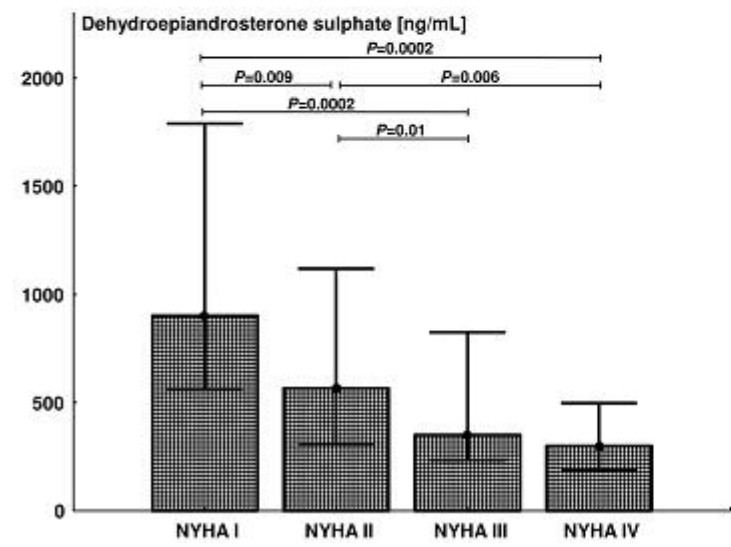
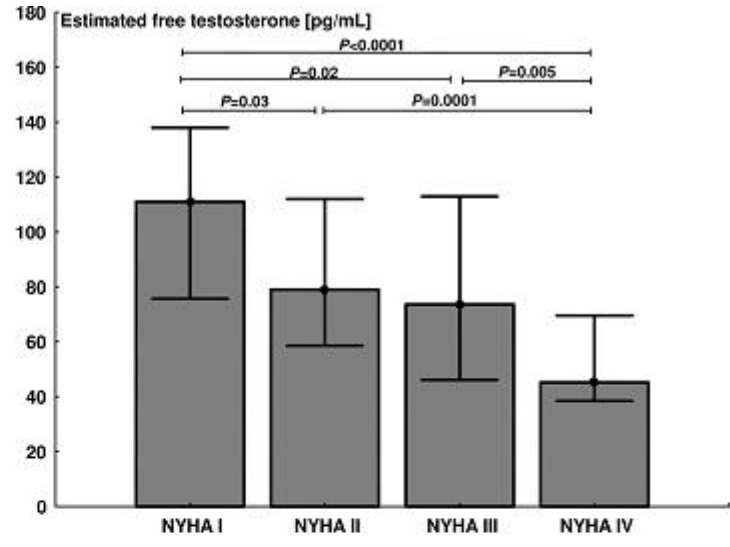
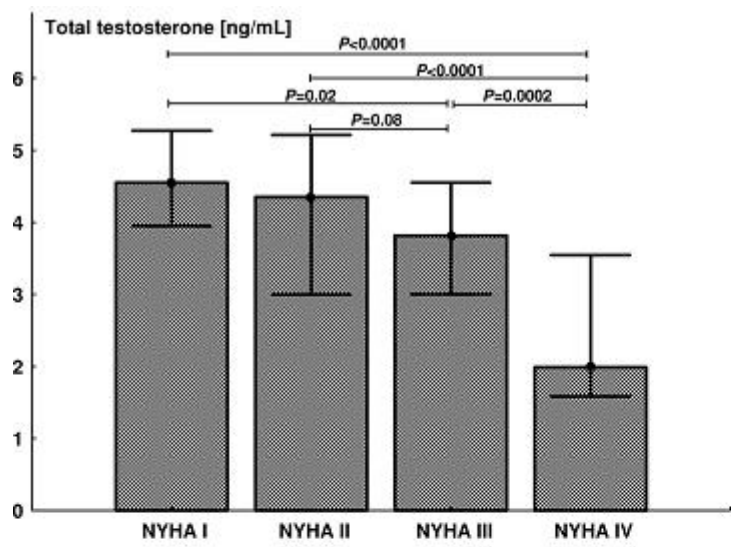


RECOVER – RENAISSANCE trials (Etanercept: antagonista TNF)

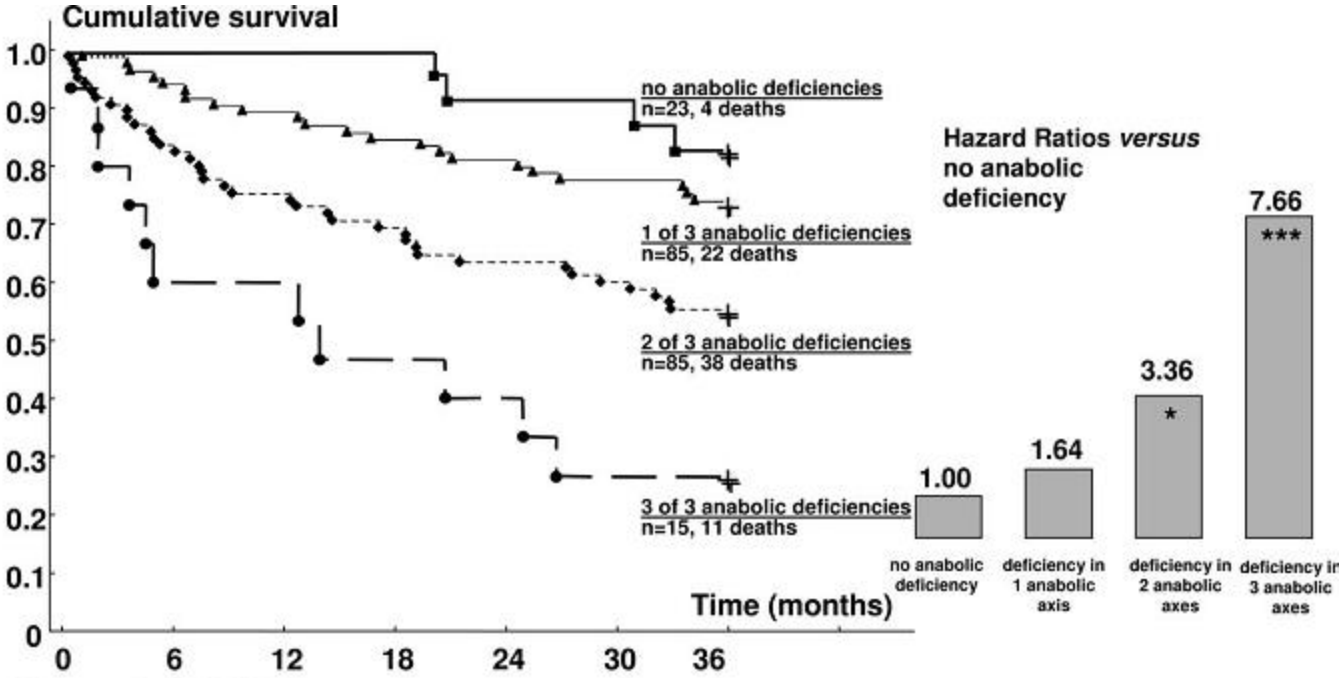


Placebo: 682 660 632 620 603 510 418 352 317 299 270 243 222 198 181 149 135 118 101 79 61 49 35 23 17
Etanercept biw + tiw: 991 962 922 885 855 751 627 548 502 459 416 376 343 302 275 243 212 192 172 151 111 85 68 46 31

Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo



Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo



Model With a Number of Anabolic Deficiencies				
Variables	Units	HR	95% CI	P
No. of anabolic deficiencies	0/1/2/3	1.78	1.29-2.45	0.0004
Age	1 year	1.04	1.01-1.07	0.02
NYHA class	I/II/III/IV	1.59	1.09-2.33	0.02
LVEF	1%	0.94	0.91-0.98	0.002
Plasma NT-proBNP	500 pg/mL	1.02	0.99-1.04	0.12
GFR	5 mL · min ⁻¹ · 1.73 m ⁻²	0.93	0.85-1.01	0.09
Hemoglobin	1 g/dL	0.88	0.77-1.01	0.07

Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo

First Name (Reference)	Year of Publication	Study Design	Patients Enrolled	Age (mean±SD)	Target Dose (IU/wk)	IGF-1 Increase (%)	Therapy Duration (Months)	Main Results
Fazio S [115]	1996	Open	7	46 ± 9	14	105.1	3	First evidence of inverse LV remodeling with GH therapy
Frustaci A [116]	1996	Open	5	32 ± 8.1	28	NA	3	Mild inverse LV remodeling Worsening tachyarrhythmia
Isgaard J [117]	1998	Double-blind placebo-controlled	PL:11 GH:11	60 ± 11.3	0.25 IU/kg-wk up to 28	137.1	3	No morpho-functional cardiac effect Good tolerability
Osterziel K [120, 119]	1998, 2001	Double-blind placebo-controlled	50	54 ± 10	14	78.8	3	No improvement in clinical status IGF-1-related increase in LV mass and LVEF
Genth-Zotz S [124]	1999	Open	7	55 ± 9	14	110.1	3	Attenuation of LV remodeling Improvement in hemodynamics and exercise capacity [peak VO ₂]
Jose VJ [138]	1999	Open	6	NA	7	NA	6	Improvement in the symptomatic class
Spallarossa P [132]	1999	Parallel	20	62.1 ± 8	0.14 IU/kg-wk	89	6	Increased in exercise duration No LV morphologic modifications
Smit JW [131]	2001	Parallel	22	65.5 ± 8.5	14	36.7	6	No effect on LV mass and function
Napoli R [118]	2002	Placebo-controlled	16	54.5±11.3	14	85.5	3	Increase in VO ₂ max
Acevedo M [112]	2003	Placebo-controlled	19	57.7±4.5	0.245 IU/kg-wk	40.1	2	No significant changes in LVEF, exercise capacity and/or neurohormonal status.
Adamopoulos S [113]	2003	Cross-over	12	50 ± 13.8	14	NA	3	Inverse LV remodeling Reduction in TNF-α levels
Cittadini A [114]	2003	Double-blind placebo-controlled	10	38.9±10.6	0.21 IU/kg-wk	NA	3	Heart failure related to muscular dystrophy. Reduction of NT-proBNP
Fazio S [139]	2007	Double-blind placebo controlled	22	PL:57±11 GH:54±10	14	101±18	3	Increased in exercise performance [exercise duration, VO ₂ max, anaerobic threshold]
Cittadini A [72]	2009	Randomized, single-blind, controlled trial	28	62 ± 2	17.5	74%	6	Patient with GH Deficiency. Improvement in exercise capacity, vascular reactivity, LV function, and indices of quality of life

Conclusioni

- **Lo scompenso cardiaco è una sindrome clinica ad elevato impatto socio-economico ed a prognosi ancora infausta nonostante i notevoli progressi nella terapia degli ultimi decenni**
- **Negli ultimi anni è diventato sempre più evidente il peso di patologie non cardiovascolari sulla storia naturale dello scompenso cardiaco**
- **Tra tali condizioni sicuramente il deficit di GH appare di particolare rilevanza nella fisiopatologia dello scompenso cardiaco. Gli studi futuri dovranno confermare i risultati preliminari che evidenziano i benefici derivanti dalla correzione di tale deficit nello scompenso cardiaco**

Deficit di GH nello scompenso cardiaco: Il punto di vista del cardiologo



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doi:10.1093/eurheartj/ehs104

ESC GUIDELINES

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

Recommendations	Class ^a	Level ^b	Ref ^c
It is recommended that patients with heart failure are enrolled in a multidisciplinary-care management programme to reduce the risk of heart failure hospitalization.	I	A	236, 259, 264

