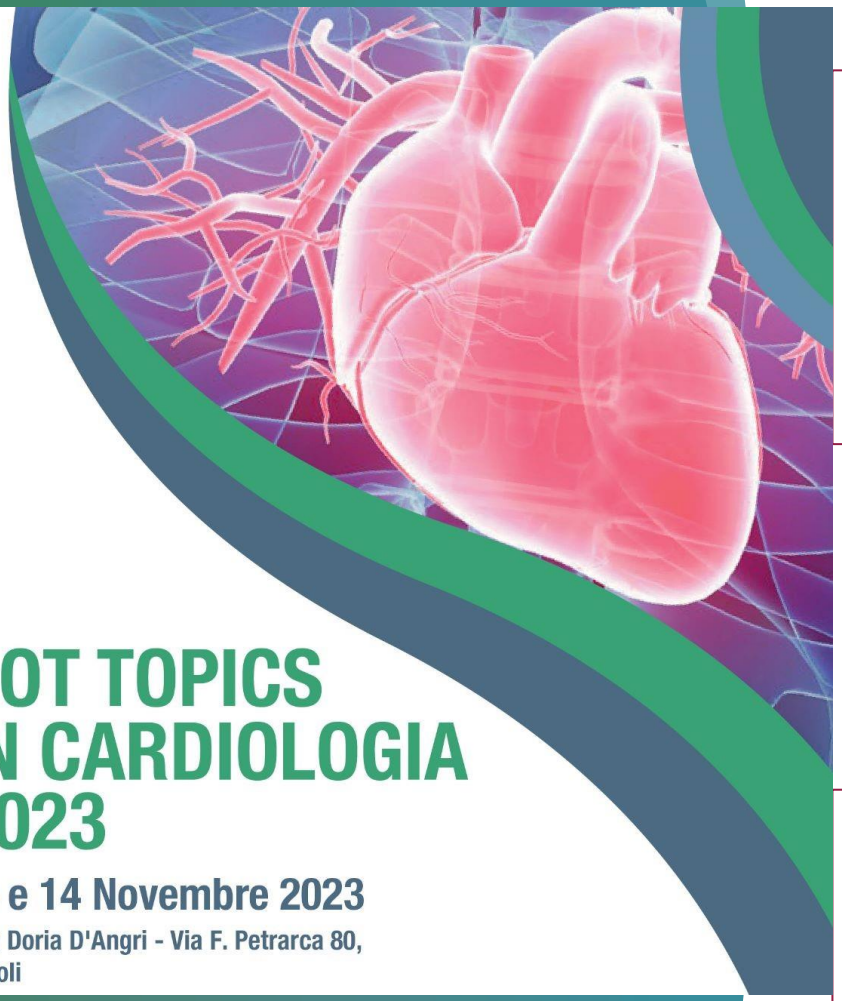


HOT TOPICS
IN CARDIOLOGIA
2023

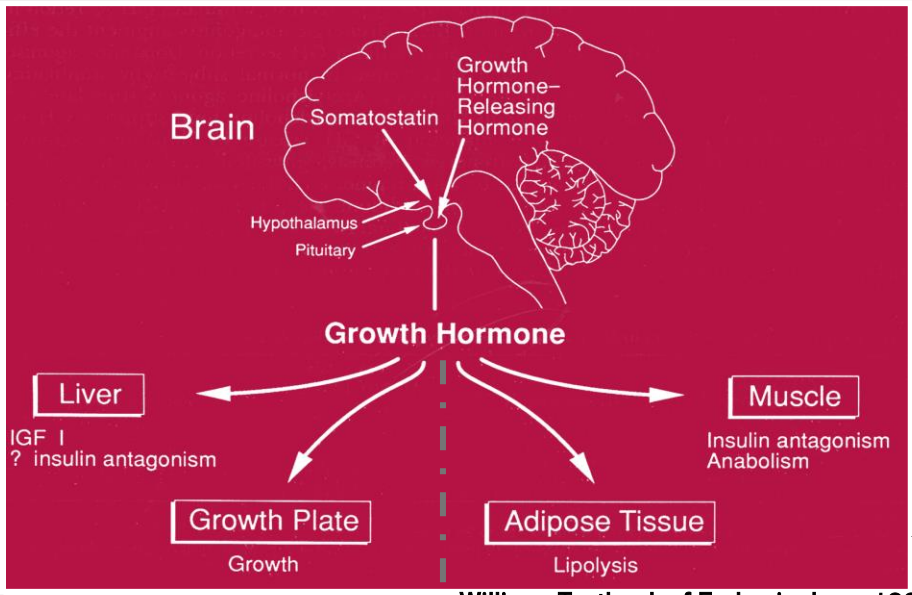
13 e 14 Novembre 2023

Villa Doria D'Angri - Via F. Petrarca 80,
Napoli

DEFICIT DI GH NELL'INSUFFICIENZA CARDIACA

Prof Antonio Cittadini

Dipartimento di Scienze Mediche Traslazionali –
Università delgi Studi di Napoli Federico II
Direttore di GENESIS – Centro Interdipartimentale di
Studio sulla Medicina di Genere



Williams Textbook of Endocrinology, 1992

Heart

Proc. Natl. Acad. Sci. USA
Vol. 81, pp. 935–939, February 1984
Medical Sciences

Tissue concentrations of somatomedin C: Further evidence for multiple sites of synthesis and paracrine or autocrine mechanisms of action

(insulin-like growth factor I/growth factor/growth hormone)

A. Joseph D'Ercole, Alan D. Stiles, and Louis E. Underwood

Department of Pediatrics, Division of Endocrinology, University of North Carolina School of Medicine, Chapel Hill, NC 27514

Communicated by Charles R. Park, October 24, 1983

The Journal of Biological Chemistry

Vol. 264, No. 17, Issue of June 15, pp. 9905–9910, 1989
Printed in U.S.A.

Regulation of Rat Growth Hormone Receptor Gene Expression*

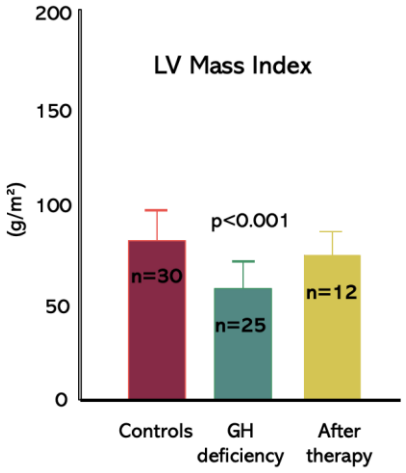
(Received for publication, November 22, 1988)

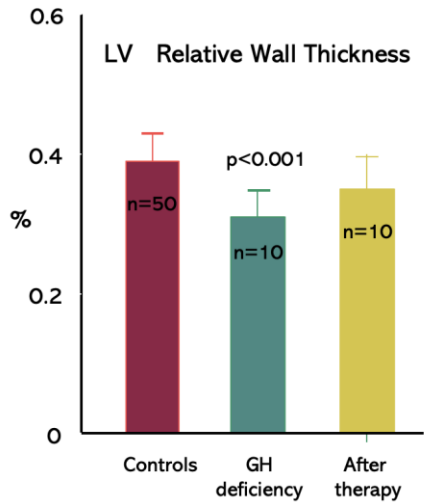
Lawrence S. Mathews‡, Bertil Enberg, and Gunnar Norstedt

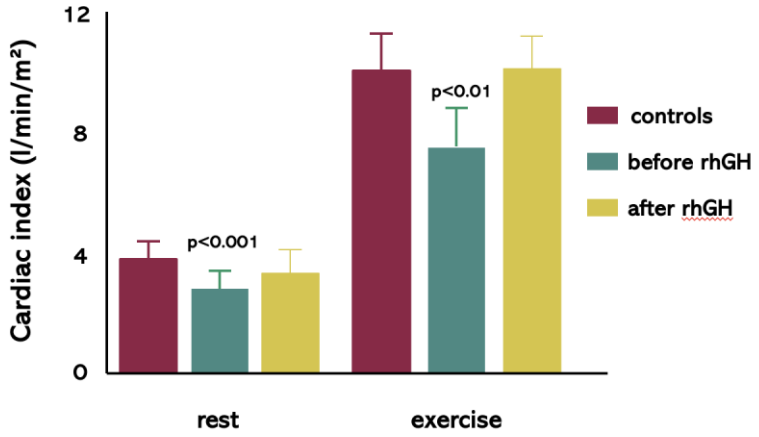
From the Center for Biotechnology and Department of Medical Nutrition, Huddinge University Hospital F82, S-141 86 Huddinge, Sweden

Growth Hormone Deficiency

Cardiac Atrophy







Acromegalic Cardiomyopathy

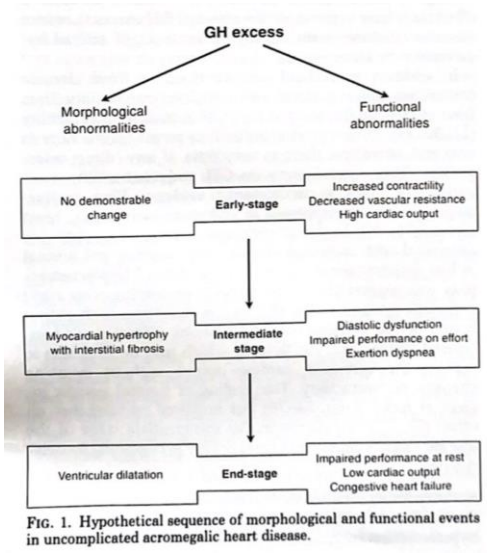
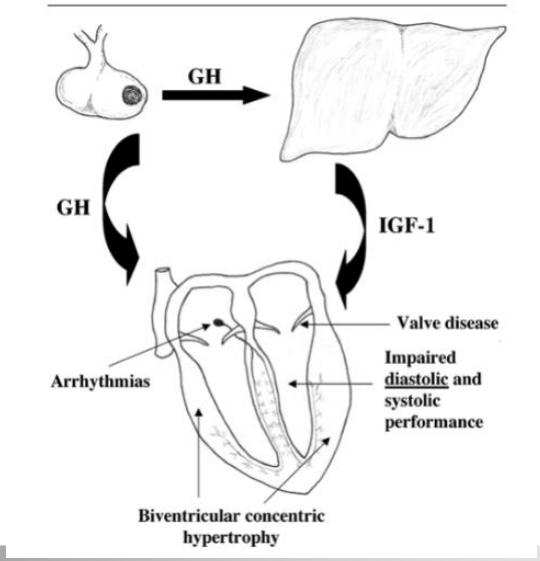


FIG. 1. Hypothetical sequence of morphological and functional events in uncomplicated acromegalic heart disease.



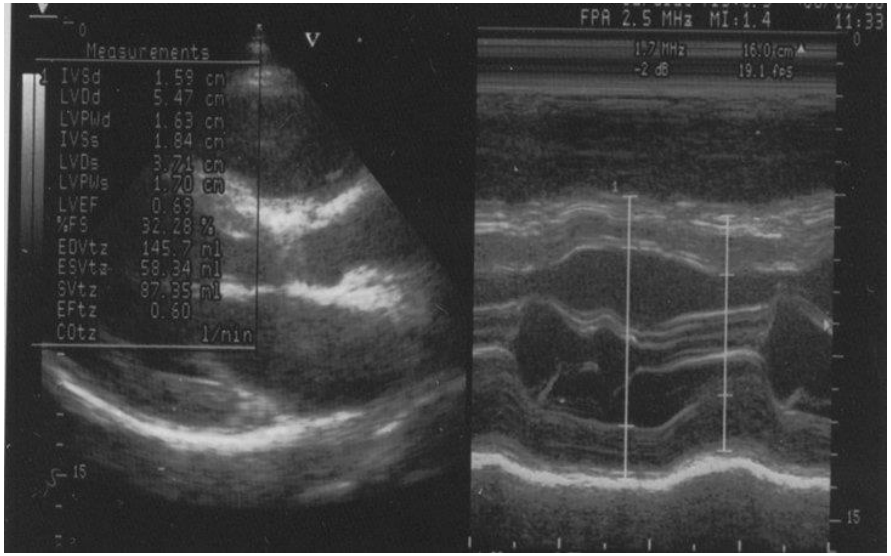
JOURNAL ARTICLE

Growth Hormone and the Heart

Get access >

Luigi Saccà ✉, Antonio Cittadini, Serafino Fazio

Endocrine Reviews, Volume 15, Issue 5, 1 October 1994, Pages 555–573,
https://doi.org/10.1210/edrv-15-5-555
Published: 01 October 1994



Beginning of the story: Rationale for a Growth Factor Approach to Heart Failure

Promotion of "physiological" cardiac growth

Mild concentric remodeling

No fibrosis, unchanged capillary density

Improvement of contractility

No re-expression of the fetal gene program

Metabolic advantages

Relatively low oxygen cost of contractility

e.g. wall stress reduction, Ca^{2+} sensitization

Stimulation of survival, anti-apoptotic pathways

Vascular reactivity

Skeletal muscle

Growth factor status in CHF

The New England
Journal of Medicine

Volume 334 MARCH 28, 1996 Number 13

A PRELIMINARY STUDY OF GROWTH HORMONE IN THE TREATMENT OF DILATED CARDIOMYOPATHY

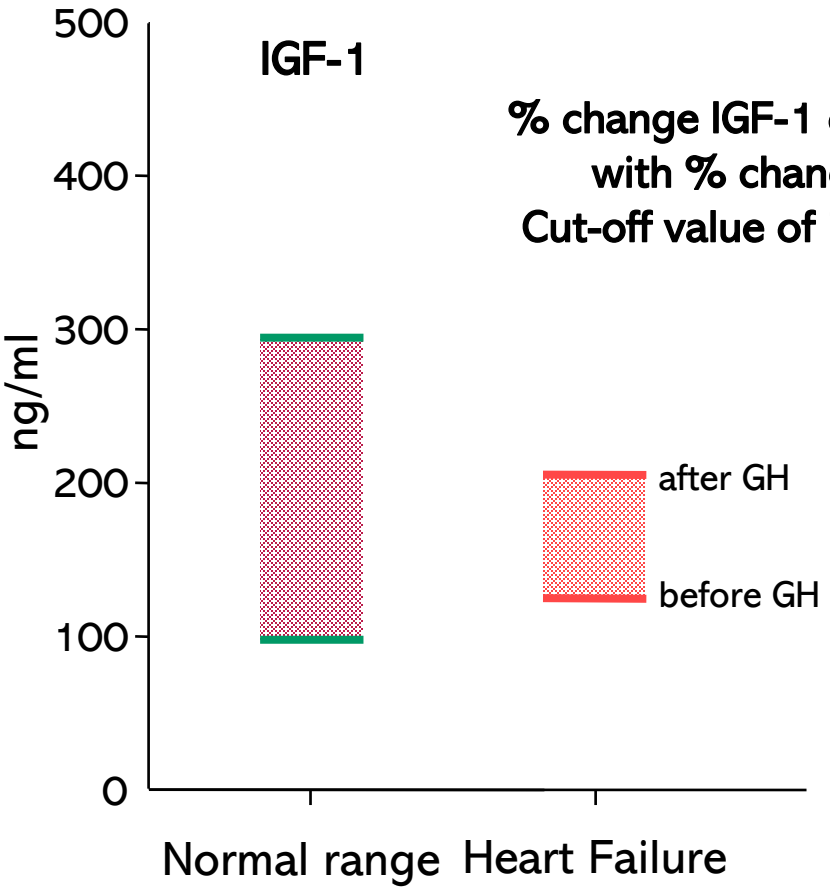
SERAFINO FAZIO, M.D., DOMENICO SABATINI, M.D., BRUNELLA CAPALDO, M.D., CARLO VIGORITO, M.D., ARTURO GIORDANO, M.D., RAFFAELE GUIDA, M.D., FRANCESCO PARDO, M.D., BERNADETTE BIONDI, M.D., AND LUIGI SACCÀ, M.D.

GH therapy in 147 patients with CHF

(in order of publication date)

1st author	Dose (IU/week)	Duration	No	Placebo	Benefit	IGF (ng/ml)
Cuneo	12 (IU/week) (84)	3 months	1	No	Yes	?
Fazio	4 IU/2nd day (14)	3 months	7	No	Yes	198 to 406
Frustaci	4 IU/ day (28)	3 months	5	No	No	?
Volterrani	0.1 IU/Kg/24h	24 hours	12	No	Yes	169 to 248
O'Driscoll	10+14 IU day (70+98)	1+7 weeks	2	No	Yes	?
De Luis Roman	16 IU/day (12)	1 year	1	No	Yes	?
Osterziel	2 IU/day (14)	3 months	50	Yes	No	134 to 211
Isgaard	2.6 IU day (mean 18)	3 months	22	Yes	No	175 to 425
Genth-Zotz	2 IU/day (14)	3 months	7	No	Yes	0.69 to 1.45 (UI/ml)
Adamopoulos	4 UI/2nd day(14)	3 months	12	No (R&C-O)	Yes	
Cittadini	2.5 UI/day	6 months	28	No (R&C)	Yes	94 to 146
Cittadini		48 months	28	No (R&C)	Yes	94 to 166

Pitfalls of GH trials in CHF: lack of evaluation of basal GH/IGF-1 status – heterogeneity of IGF-1 levels



Osterziel et al., Lancet 1998

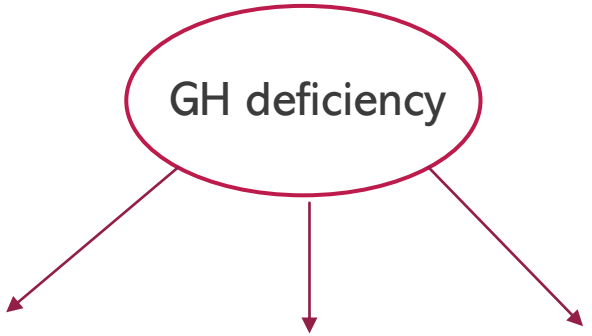
GH deficiency in Heart Failure

GH and IGF-1 are essential for preserving cardiac morphology and adult life performance.

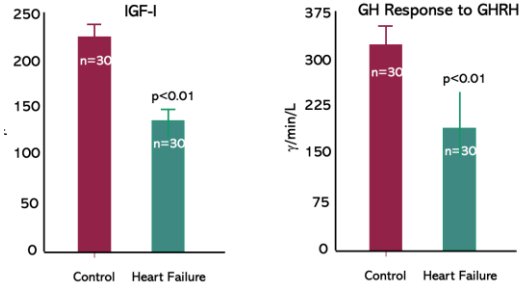
Approximately 30% of CHF patients, also display GH deficiency

Diagnosis: provocative tests, such as the insulin tolerance test (ITT) and the GH-releasing hormone (GHRH) + arginine (ARG) test

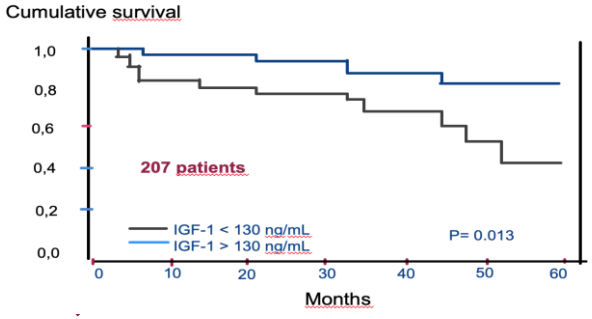
Patients with GH deficiency have impaired cardiac performance, increased peripheral vascular resistance (PVR), and reduced exercise capacity.



GH/IGF-1 status in CHF



IGF-1 and survival in CHF

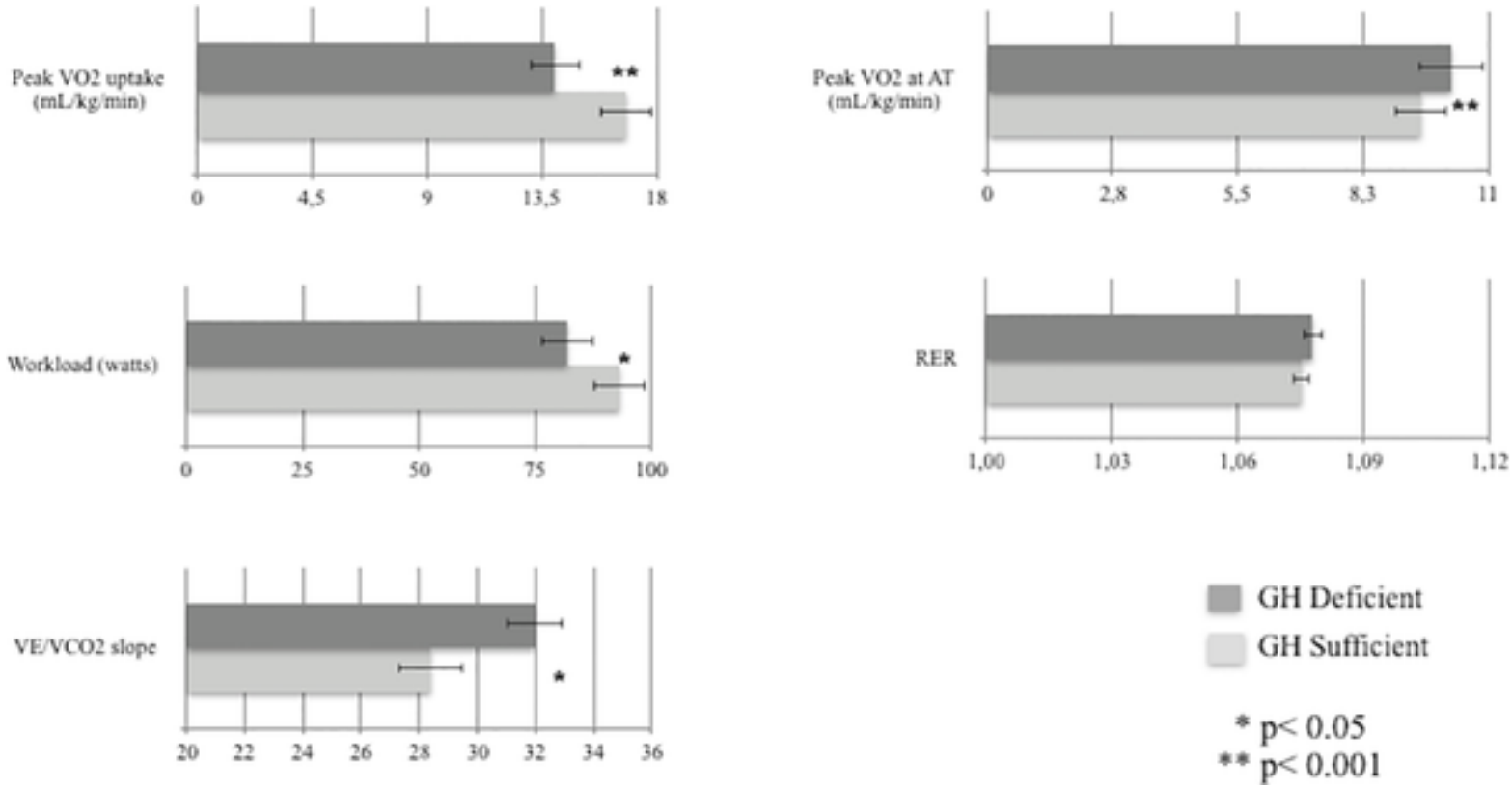


Increased mortality for cardiovascular disease

Adult GH deficiency criteria

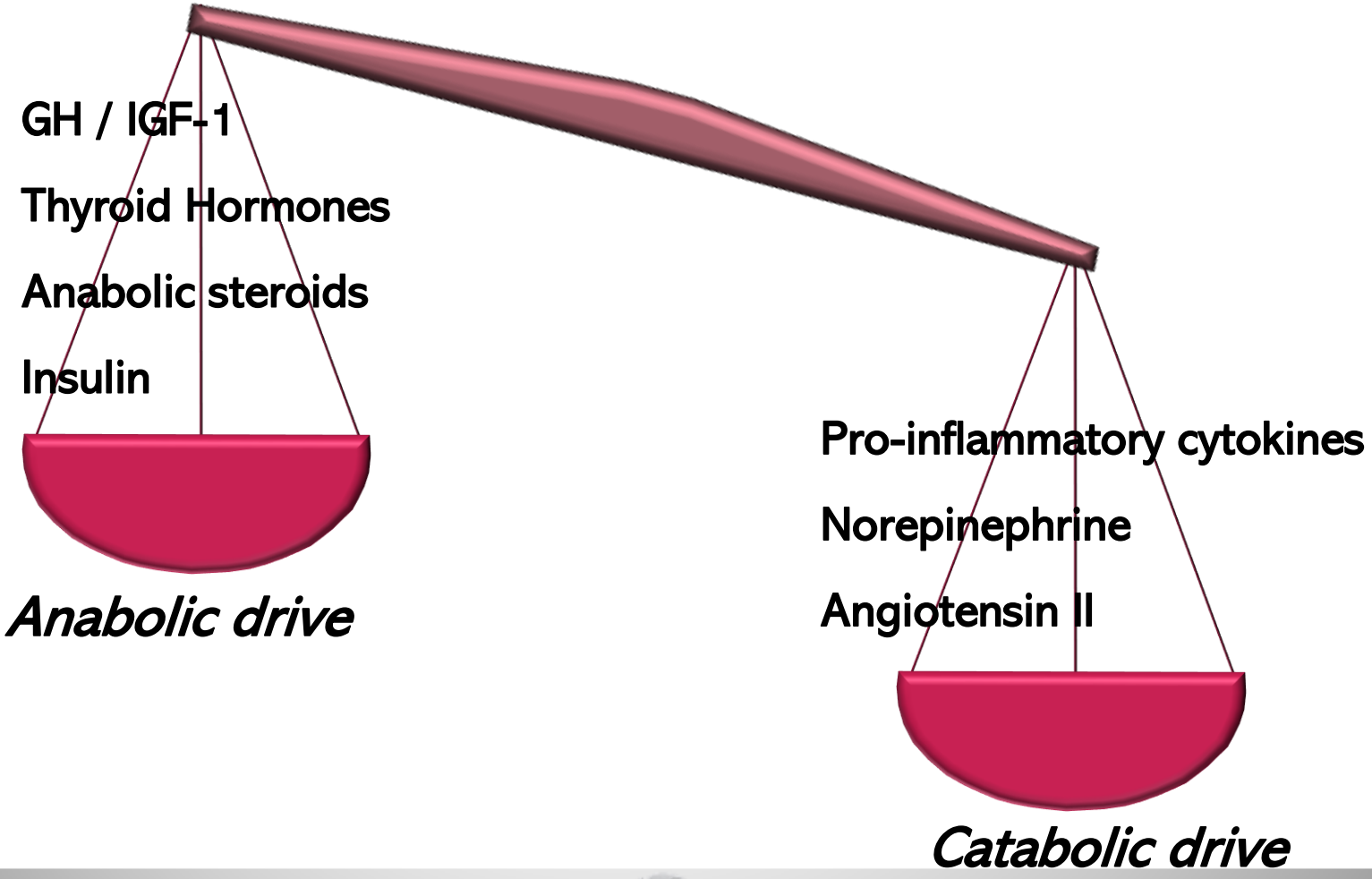
- In obese patients (BMI >30 kg/m2): use GHRH+arginine; GH deficiency if peak GH <4 µg/L
- in patients with BMI <29.9 kg/m2 and age >25 years: GH deficit if by insulin hypoglycemia test (ITT) GH <3 µg/L or by GHRH+arginine test GH <9 µg/L.

CPET parameters in GH sufficient and GH deficient patients with CHF



Arcopinto M. 2017, PLOS ONE 12(1): e0170058.

Paradigm shift:
HF as a Multiple Hormonal Deficiency Syndrome



Saccà L, Circ Heart Fail 2009

The T.O.S.CA. Registry

No large study focused on the relative role played by MHDS in the progression and survival of patients with heart failure until the T.O.S.CA. Registry .

The T.O.S.CA. Registry is a prospective multicenter observational study designed to evaluate the prevalence of MHDS in CHF patients and its impact on the outcomes of patients affected by CHF.

The T.O.S.CA Registry was set up in April 2013 and so far includes 19 centers from all over Italy.

Primary endpoint was a composite of all-cause mortality or cardiovascular hospitalization.

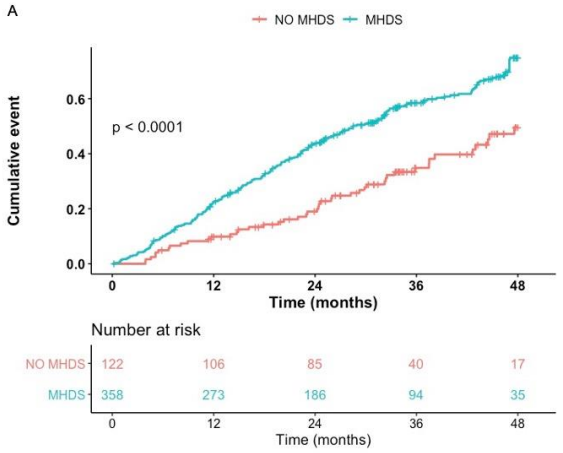
Secondary endpoint was the delta change in maximal oxygen consumption (peak VO2) from baseline.

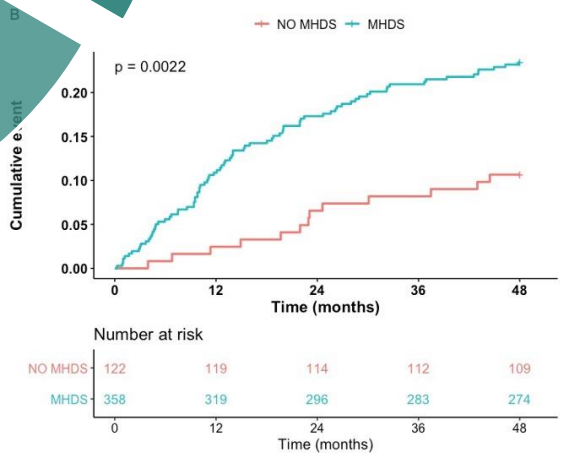
The T.O.S.CA. Registry results

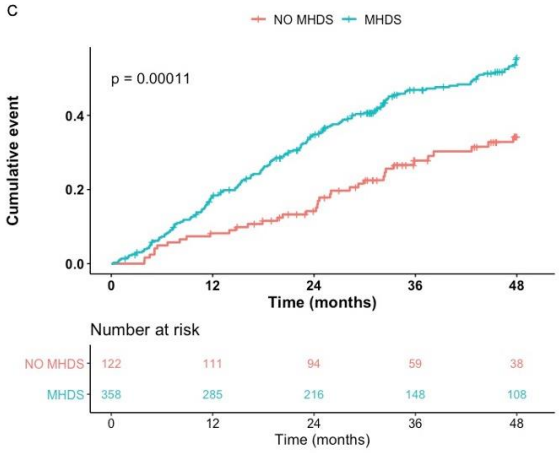
MHDS was independently associated with the primary endpoint and identified a group of patients with a higher mortality and graded relation between HDs and cumulative events.

MHDS or diabetes was diagnosed in 372 patients (77.5%).

A total of 271 events (97 deaths and 174 cardiovascular hospitalizations) were recorded, 41% in NO-MHDS and 62% in MHDS (P < 0.001).







Cittadini A, EJPC, Volume 28, Issue 15, December 2021.

GH: Short-term effects

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

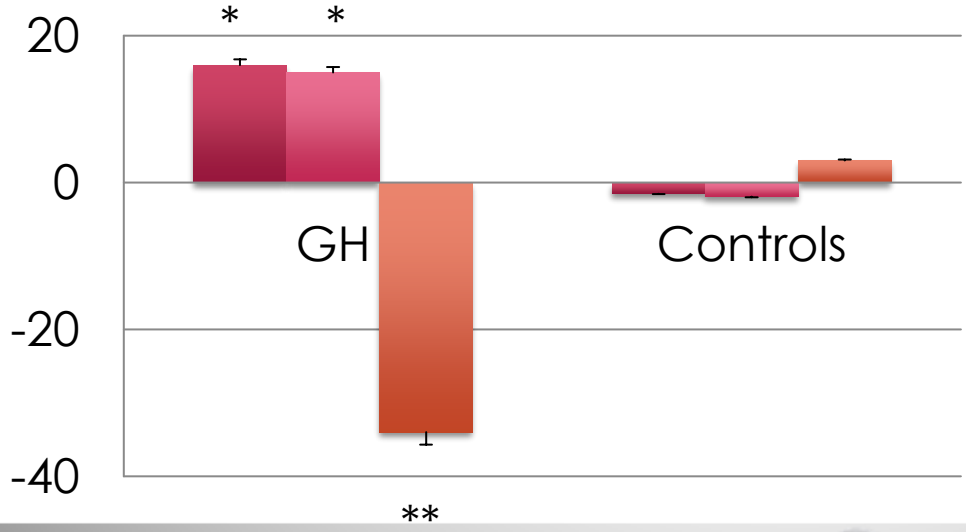
Growth Hormone Deficiency in Patients with Chronic Heart Failure and Beneficial Effects of Its Correction

Antonio Cittadini, Lavinia Saldamarco, Alberto Maria Marra, Michele Arcopinto, Guido Carlomagno, Massimo Imbriaco, Domenico Del Forno, Carlo Vigorito, Bartolomeo Merola, Ugo Oliviero, Serafino Fazio and Luigi Saccà

J. Clin. Endocrinol. Metab. 2009 94:3329-3336 originally published online Jul 7, 2009; , doi: 10.1210/jc.2009-0533

Study duration: 6 months

Treatment Effect (Delta change from baseline)



- Peak VO2 (ml/min/kg)
- Exercise duration(min)
- NT-proBNP (pg/ml)

** p<.01 vs. baseline and Δ controls*

*** p<0.05 vs. baseline and Δ controls*

GH: Long-term effects

JACC: Heart Failure
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 1, No. 4, 2013
ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2013.04.003

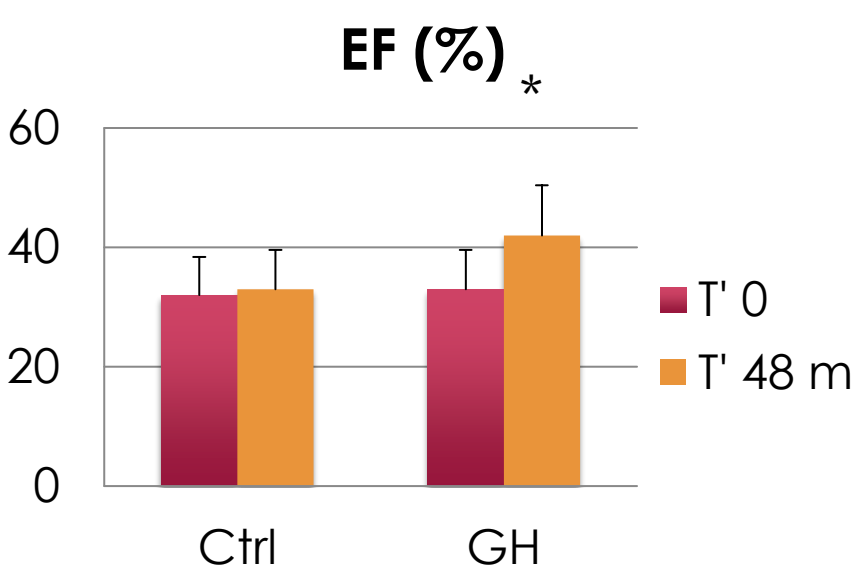
Growth Hormone Replacement Delays the Progression of Chronic Heart Failure Combined With Growth Hormone Deficiency

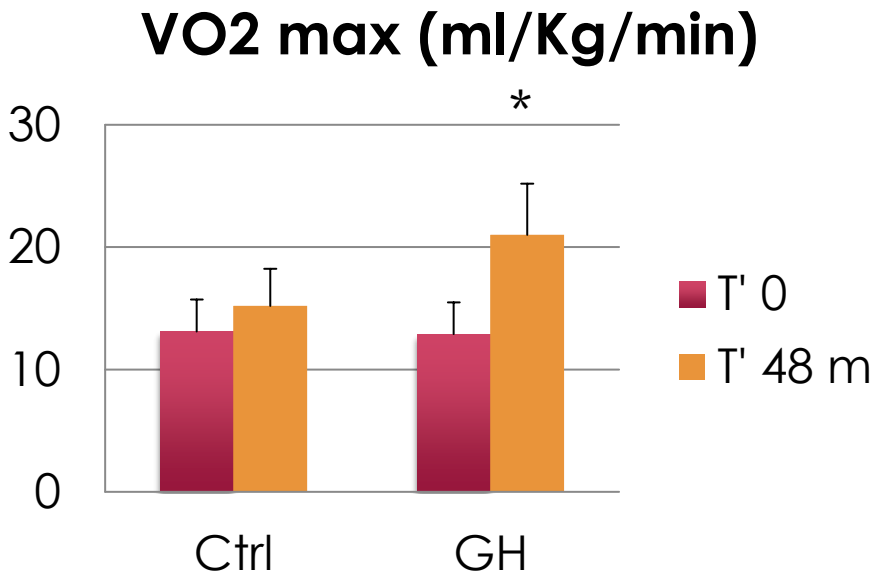
An Extension of a Randomized Controlled Single-Blind Study

Antonio Cittadini, MD,* Alberto M. Marra, MD,* Michele Arcopinto, MD,* Emanuele Bobbio, MD,* Andrea Salzano, MD,* Domenico Sirico, MD,* Raffaele Napoli, MD,* Annamaria Colao, MD,† Salvatore Longobardi, MD,‡ Ragavendra R. Baliga, MD,§ Eduardo Bossone, MD,|| Luigi Saccà, MD*

Naples, Rome, and Salerno, Italy; and Columbus, Ohio

Study duration: 4 years





Cittadini A et al, 2013 JACC HF

GRANT FOR GROWTH INNOVATION

GGI

GGI study: Treatment of Growth Hormone Deficiency Associated with Chronic Heart Failure: A Randomized, Double-Blind, Placebo-Controlled Study"

ClinicalTrials.gov
NCT03775993

Link
profitable solutions

64 CHF patients have been enrolled from July 2020 to July 2023

Two patients died from causes unrelated to treatment

17 patients are lost at follow up

No adverse events were recorded in the treatment arm

Data related to the endpoints considered are being processed and are very promising….

Future perspectives

ARTICLE IN PRESS

European Journal of Internal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

Chronic heart failure: An appropriate clinical context to search for GH deficiency?

ARTICLE INFO

Keywords
Chronic heart failure
Growth hormone deficiency

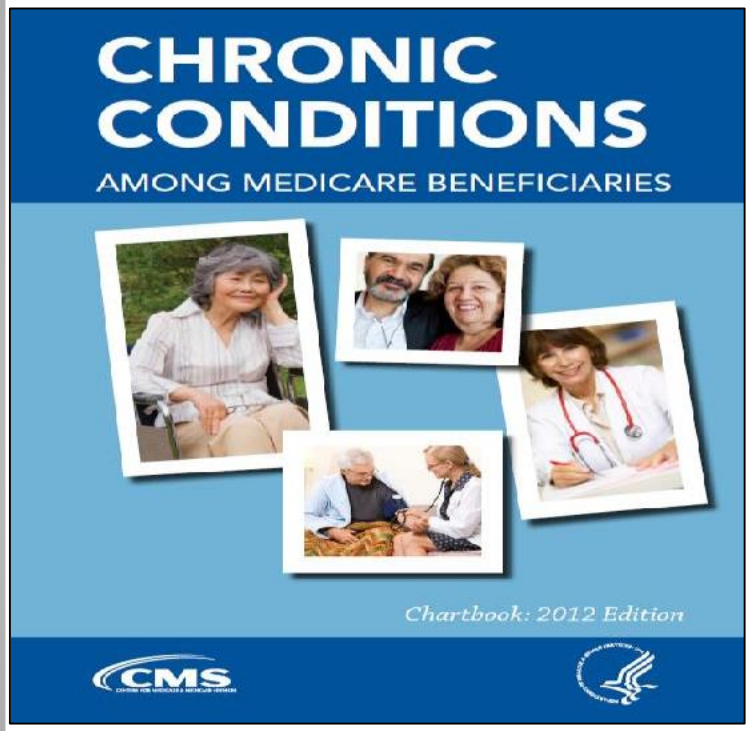
Cittadini A, De Luca MR, Saccà L, 2023

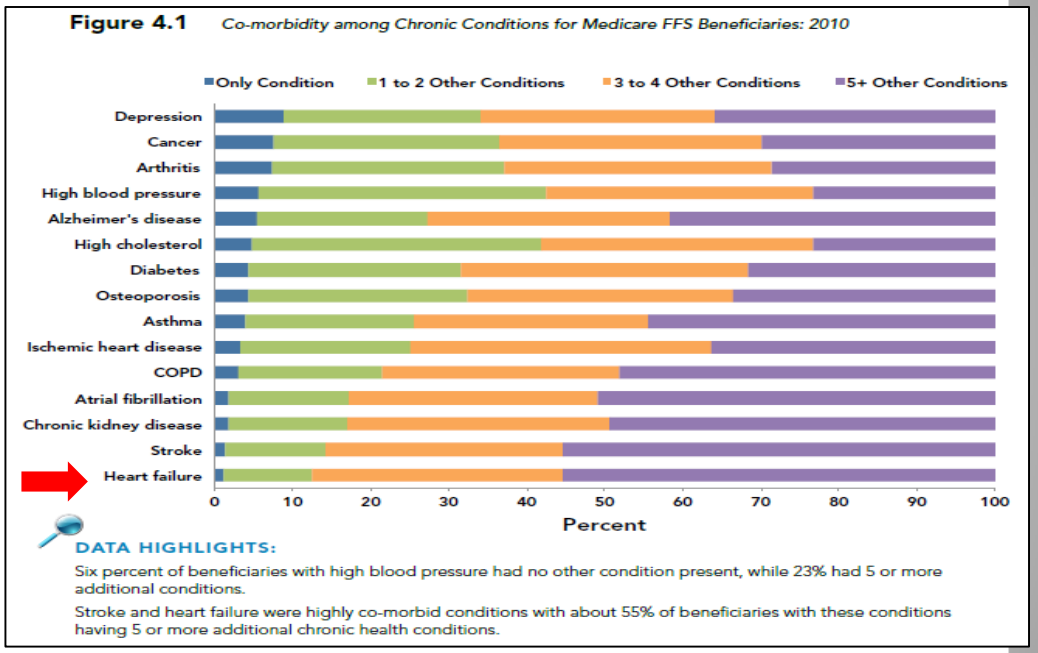
Key points

* Multiple hormone deficiency syndrome does not appear to be a mere epiphenomen since it significantly correlates with functional capacity and prognosis in patients with CHF
* Specifically, GH deficiency in CHF affects approximately 20-25% of patients and is associated with adverse LV remodeling, reduced cardiopulmonary performance, and increased mortality
* Emerging data support the hypothesis that GH replacement therapy in CHF is beneficial and that CHF is an appropriate context to search for GHD

Thus, the concept of treating patients with CHF “as a whole” with pharmacological doses of GH proved partly wrong. The emerging theory would be to identify a subset of patients with hormonal defects that could benefit from a replacement hormone therapy

Co-morbidity is universal!





http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Downloads/2012Chartbook.pdf

Endocrine Comorbidities

International Journal of Cardiology 225 (2016) 1–3

Contents lists available at ScienceDirect

International Journal of Cardiology

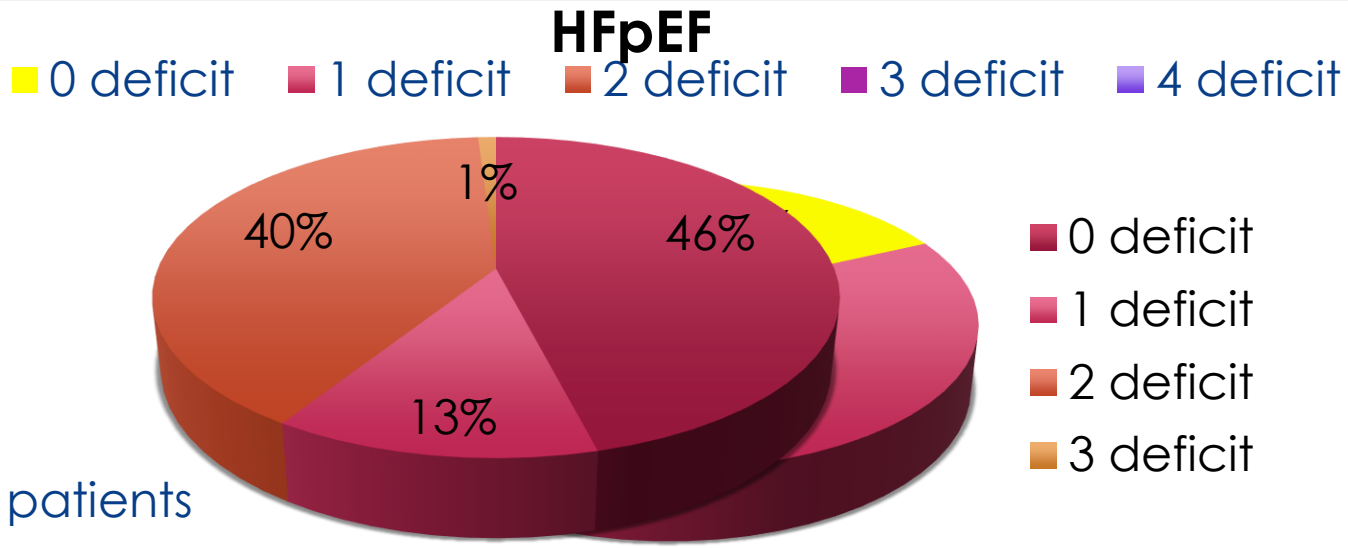
journal homepage: www.elsevier.com/locate/ijcard

Correspondence

Multiple hormone deficiency syndrome in heart failure with preserved ejection fraction

Andrea Salzano [a,1], Alberto Maria Marra [b,1], Francesco Ferrara [c], Michele Arcopinto [d], Emanuele Bobbio [a], Pietro Valente [a], Roberto Polizzi [a], Carlo De Vincentiis [d], Margherita Matarazzo [a], Lavinia Saldamarco [a], Francesco Saccà [e], Raffaele Napoli [a], Maria Gaia Monti [a], Roberta D'Assante [a], Andrea M. Isidori [f], Jorgen Isgaard [g], Nicola Ferrara [a], Pasquale Perrone Filardi [h], Francesco Perticone [i], Carlo Vigorito [a], Eduardo Bossone [c], Antonio Cittadini [a,j,*], on behalf of T.O.S.CA. investigators:

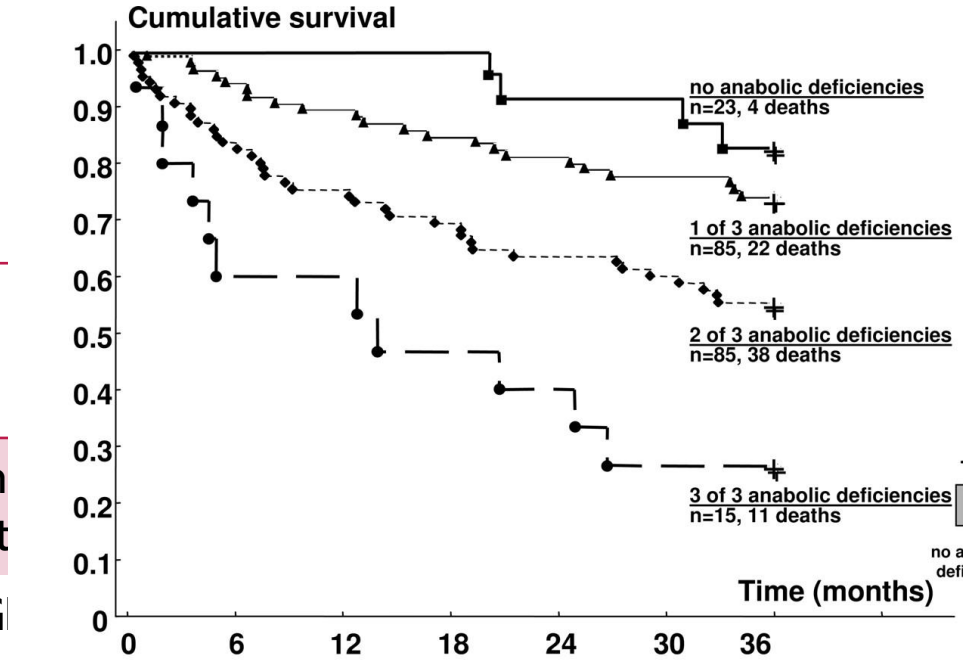
[a] Department of Translational Medical Science, Federico II University, Naples, Italy
[b] IRCCS S.D.N., Via Gianturco 113, 80143, Naples, Italy
[c] Department of Cardiology and Cardiac Surgery, University Hospital "Scuola Medica Salernitana", Salerno, Italy
[d] Department of Cardiac Surgery, IRCCS Policlinico San Donato, Milan, Italy
[e] Department of Neurological Sciences, University Federico II, Naples, Italy
[f] Department of Experimental Medicine, Sapienza University of Rome, Italy
[g] Department of Internal Medicine, Sahlgrenska Academy, University of Göteborg, Sweden
[h] Department of Advanced Biomedical Sciences, Federico II University, Naples
[i] Department of Medical and Surgical Sciences, Magna Graecia of Catanzaro University, Catanzaro, Italy
[j] Interdisciplinary Research Centre in Biomedical Materials (CRIB), University of Naples, Naples, Italy

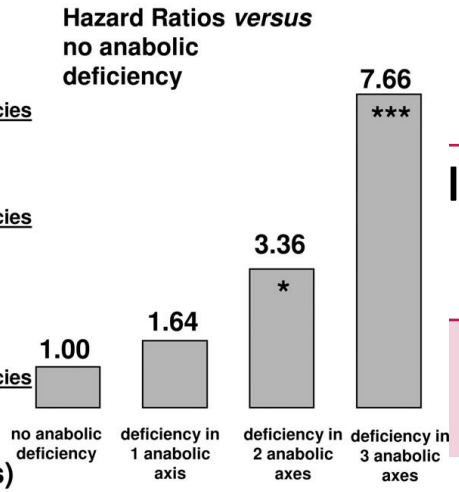


107 HFrEF patients

Salzano A et al, Int J Cardiol 2016

"Reverse" model in CHF and clinical

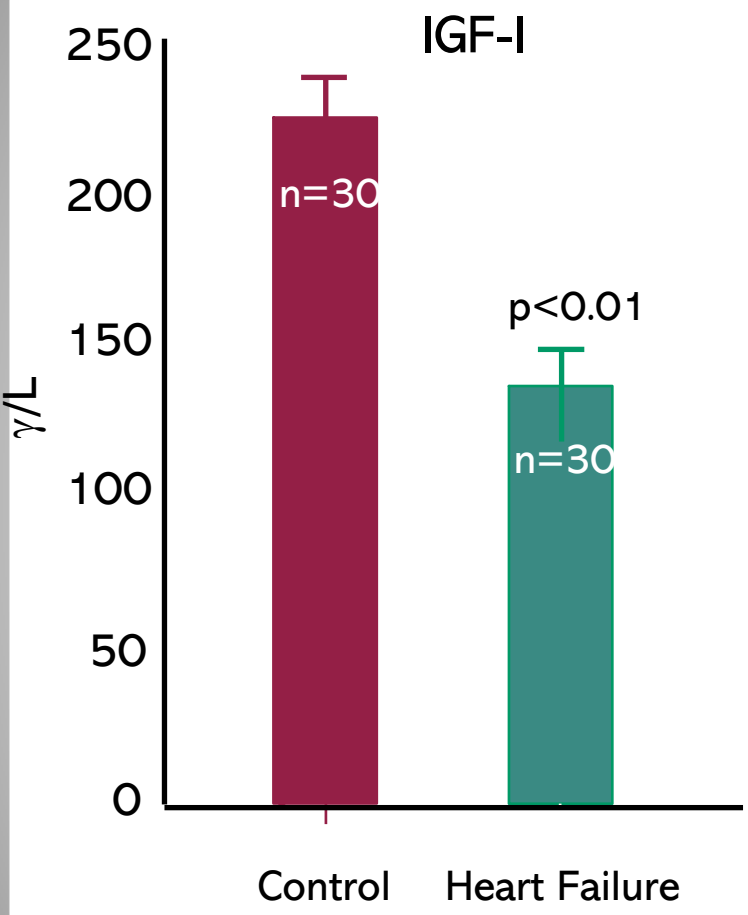


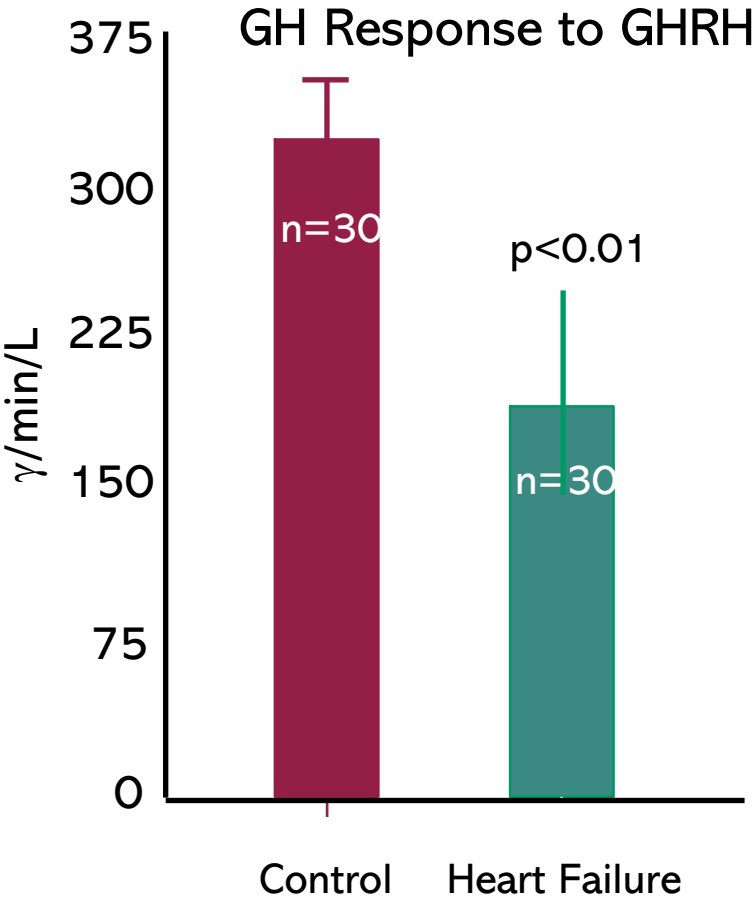


Insulin
Diabet
Low G
Low T
Low T

Jankowska et al, Circulation 2006

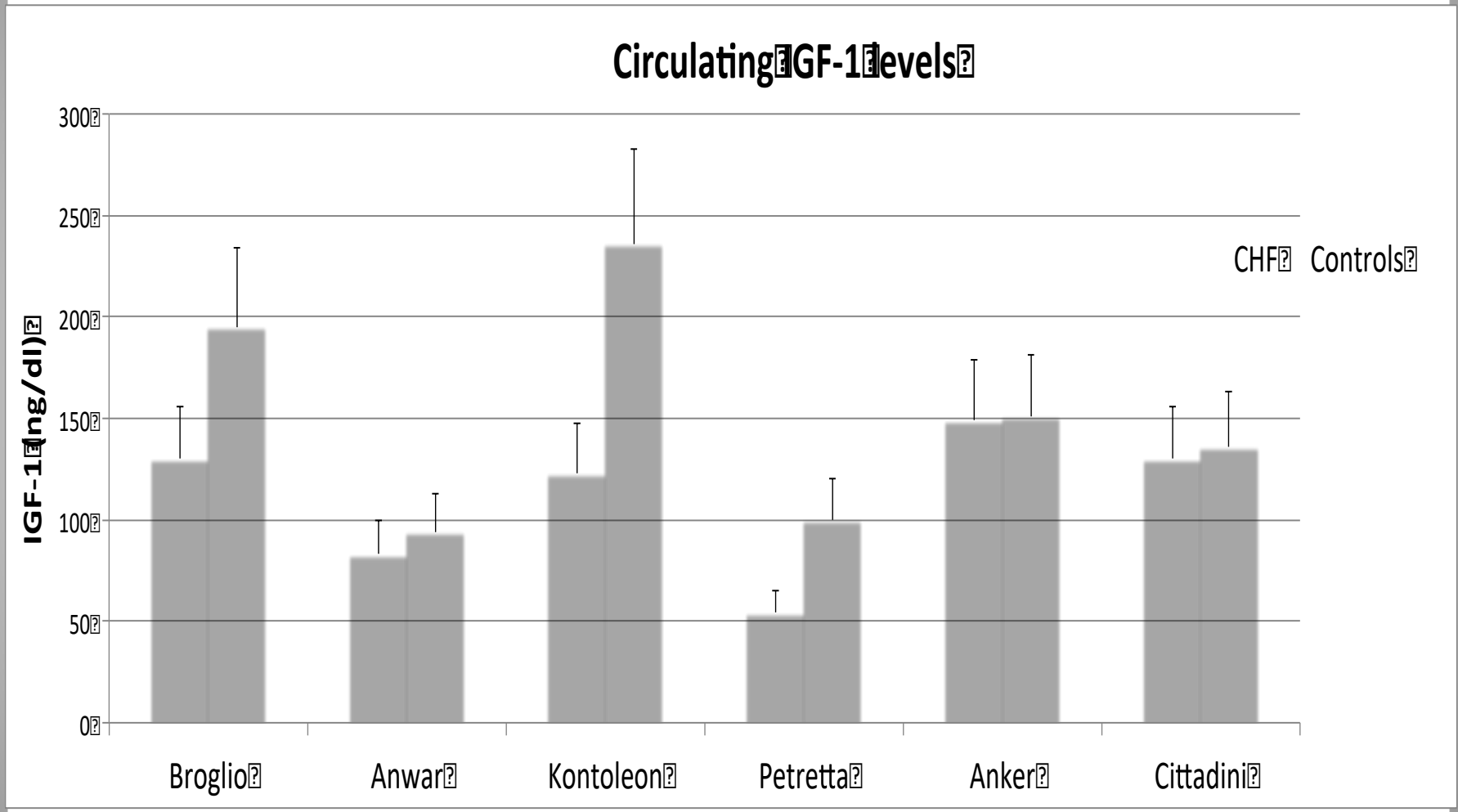
GH/IGF-1 status in CHF



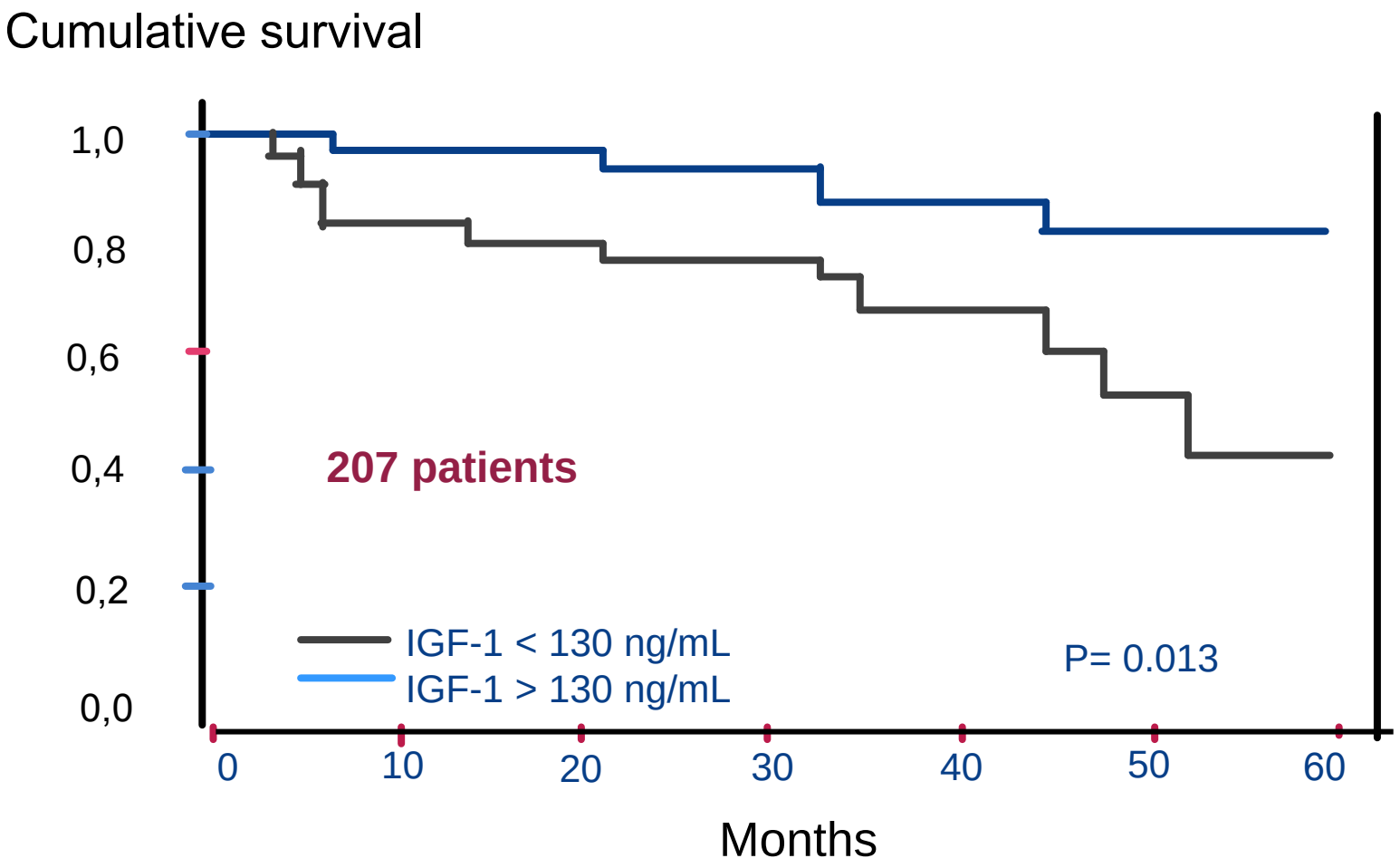


Broglio et al., Ann Endocrinol 1997

IGF-1 levels in CHF

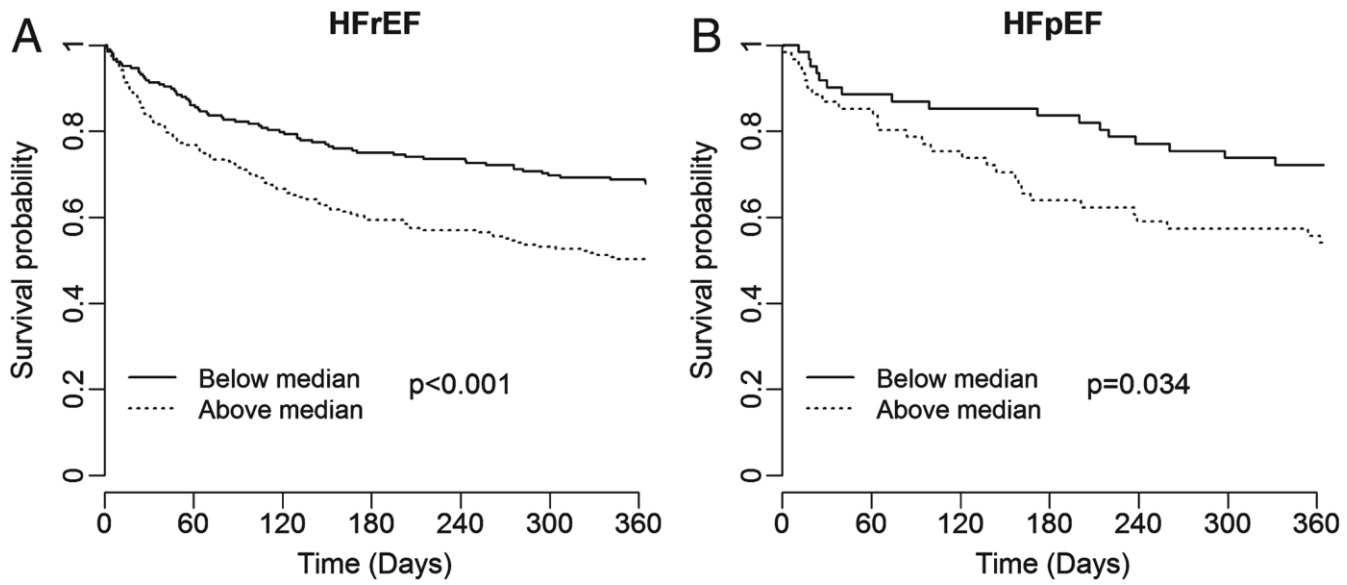


IGF-1 and survival in CHF



Cittadini A, Int J Cardiol 2014

Plasma growth hormone is a strong predictor of risk at 1 year in AHF



Plasma growth hormone is a strong predictor of risk at 1 year in acute heart failure. 2015; 18(3); 281-289

GH deficiency in CHF: prevalence and replacement therapy

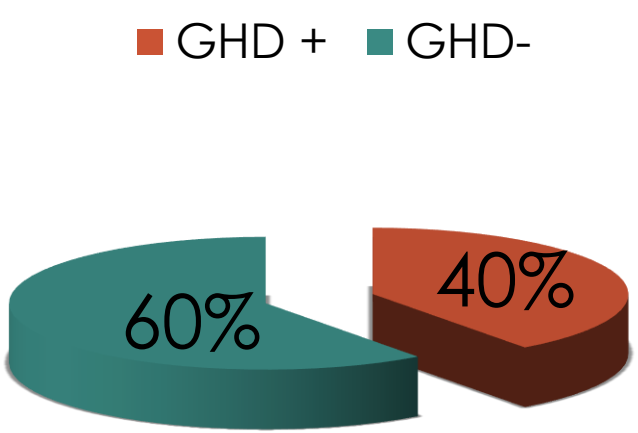
158 CHF patients NYHA class II-IV

GH stimulation test

66 GH Deficiency*

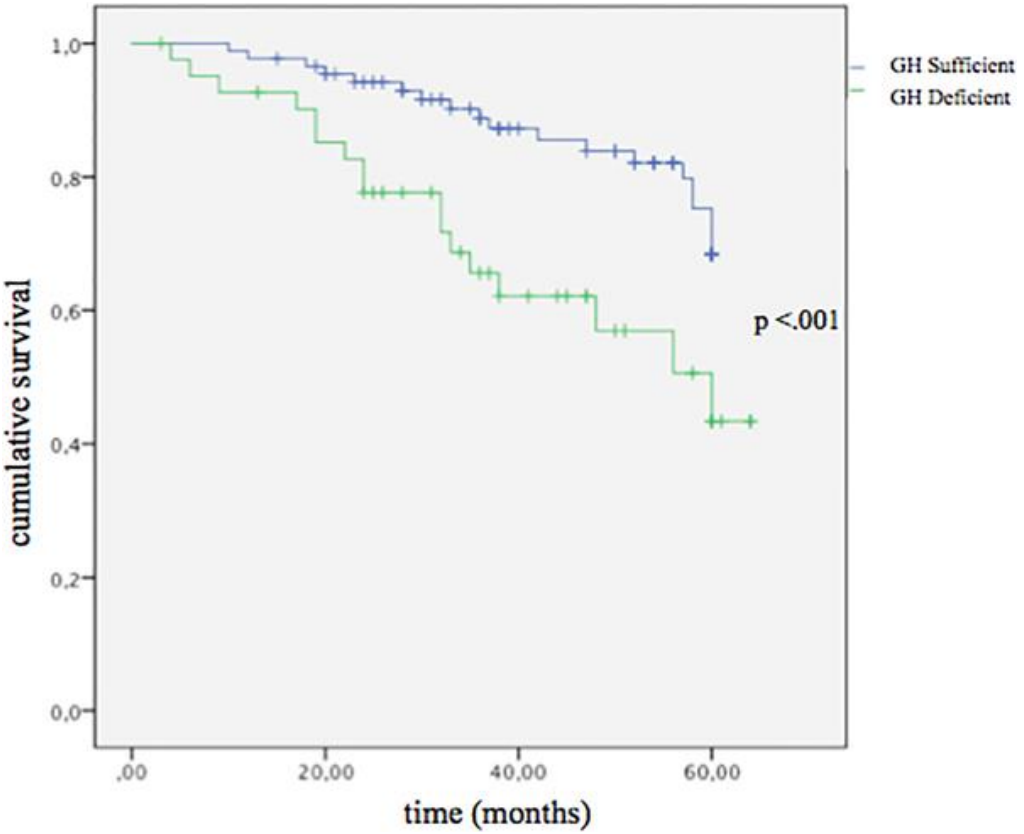
56 enrolled in our trial:

28 : GH administration (0.012 mg/kg every second day)
28 no therapy



In Italy, GH Deficiency is defined as a response to a GHRH+Arg stimulation test less than 9 ng/ml

Survival analysis according to GH status: Kaplan–Meier curve and log rank analysis



Arcopinto M. 2017, PLOS ONE 12(1): e0170058.

ESC Heart Failure Open Access

Short Communication | Open Access

Combined effects of growth hormone and testosterone replacement treatment in heart failure

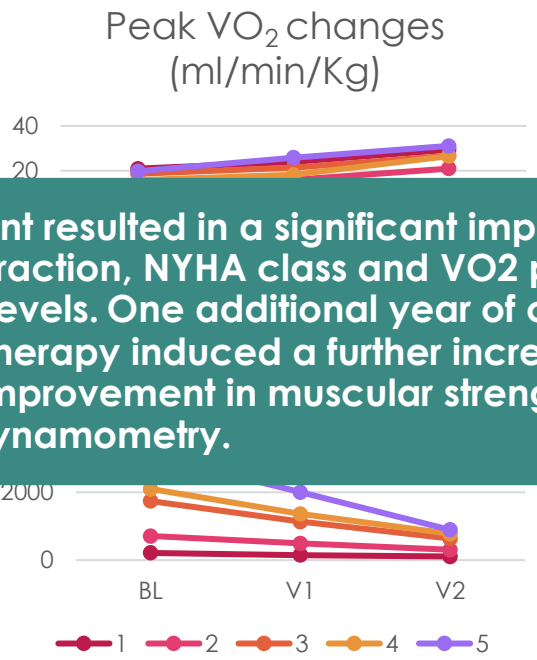
Andrea Salzano, Alberto M. Marra, Michele Arcopinto, Roberta D'Assante, Vincenzo Triggiani, Enrico Coscioni, Daniela Pasquali, Giuseppe Rengo, Toru Suzuki, Eduardo Bossone, Antonio Cittadini

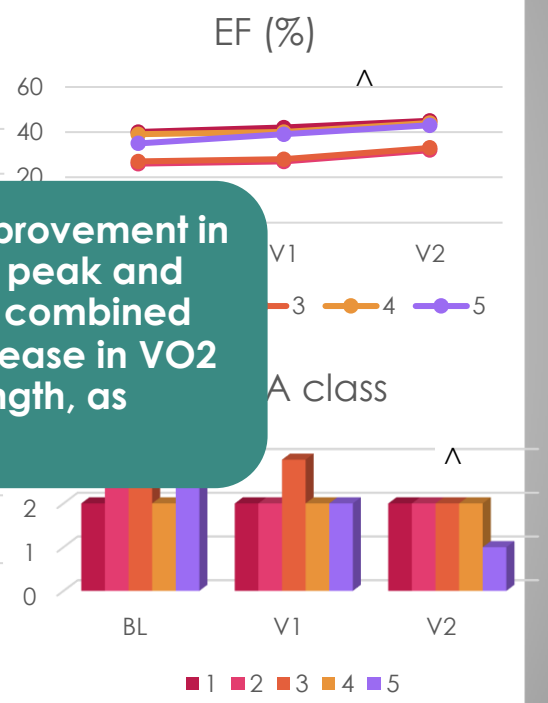
Five stable HFrEF with a concomitant diagnosis of growth hormone deficiency and testosterone deficiency

1 year of G
subcutaneous i
dose of 0.01
After 12 month
was added at a

One-year of GH treatment resulted in a significant improvement in left ventricular ejection fraction, NYHA class and VO2 peak and reduction in NT-proBNP levels. One additional year of combined GH and T replacement therapy induced a further increase in VO2 as well as a significant improvement in muscular strength, as assessed by handgrip dynamometry.

Changes in physical performance and various cardiovascular indexes were measured at baseline (BL), after 1 year of GH treatment (V1), and after 1 year of combined GH + T treatments (V2).





Adapted from Salzano A. ESC Heart Failure 2019; 6: 1216–

The T.O.S.CA. Registry methods

Thyroid hormones, insulin-like growth factor-1, total testosterone, dehydropianoandrosterone sulfate, insulin resistance, and the presence of diabetes were evaluated.

A MHDS was defined as the presence of >_2 hormone deficiencies (HDs).

Four hundred and eighty CHF patients with left ventricular ejection fraction (LVEF) ≤45%.

Median follow-up was of 36 months.

Variables	Cohort (n = 480)
Age (yr.)	63·7 ± 11·5
Sex (% male)	80.4
NYHA (% I/II/III/IV)	11/54/33/2
Aetiology (% ischemic)	52·7
Yr. of disease	7 [2-12]
Systolic blood pressure (mm/Hg)	121 ± 17
Diastolic blood pressure (mm/Hg)	74 ± 10
Type 2 Diabetes mellitus, n (%)	120 (25)
BMI (kg/m^2)	28·6 ±5·4
eGFR (, ml/min per 1.73 m^2)	86 ±41
NT pro BNP (pg/ml)	909 [284-2521]
Left Ventricular EF (%)	32·3 ± 7·2
Atrial fibrillation (%)	11·2
ICD (%)	36
CRT (%)	11·7
Medication (%)	
• B-blocker	87·5
• ACE-I/ARBs	86
• MRA	39
• Diuretics	69·4
• Amiodarone	15·8
• Digoxin	9·2
• Antiplatelets	49
• Antithrombotic	27·9
• Lipid-lowering medications	51·9
• Ivabradine	11
• Antidiabetics	15·2
• Insulin	10·6

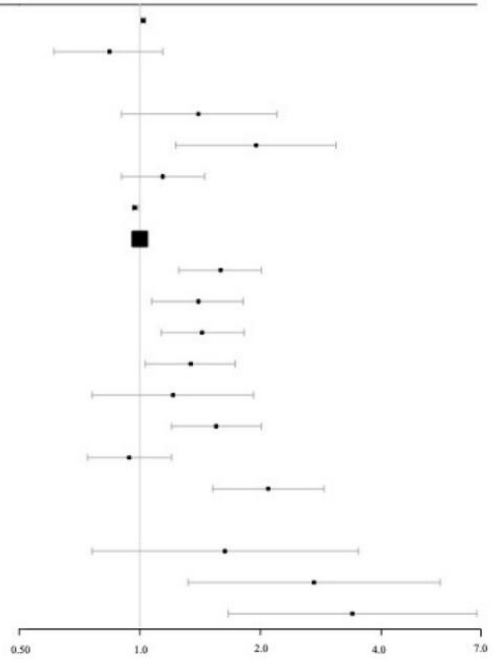
Cittadini A, EJPC, Volume 28, Issue 15, December 2021.

The T.O.S.CA. Registry results

In the univariate Cox proportional hazard regression analyses the advanced NYHA classes, LVEF, BNP, and anaemia were associated with mortality and cardiovascular hospitalization.

With regard to specific HD, testosterone deficiency IGF-1 deficit, and IR impairment were associated with the primary outcome.

Variables	HR	95% CI	p
Age (1yr)	1.02	1.01-1.03	0.001*
Sex (Female)	0.84	0.61-1.14	0.25
NYHA class			
II	1.40	0.90-2.20	0.14
III-IV	1.95	1.23-3.09	0.004*
Aetiology (Ischemic)	1.14	0.90-1.45	0.29
EF (%)	0.97	0.96-0.99	0.004*
BNP (1 pg/ml)	1.00	1.00-1.001	0.000*
Testosterone Deficiency	1.59	1.25-2.01	0.001*
DHEAS Deficiency	1.40	1.07-1.81	0.011*
IGF-1 Deficiency	1.43	1.13-1.82	0.003*
IR / DM	1.34	1.03-1.73	0.03*
Low-T3	1.21	0.76-1.92	0.42
DM	1.55	1.20-2.01	0.000*
IR	0.94	0.74-1.20	0.6
MHDS	2.09	1.52-2.88	0.000*
Number of HD			
1	1.63	0.76-3.51	0.21
2	2.73	1.32-5.61	0.006*
>=3	3.39	1.66-6.90	0.000*



Forest plot of univariate Cox proportional hazard regression analyses of the effect several variables on the primary endpoint (composite of all-cause mortality or cardiovascular hospitalization evaluated in the entire population *n* = 480)

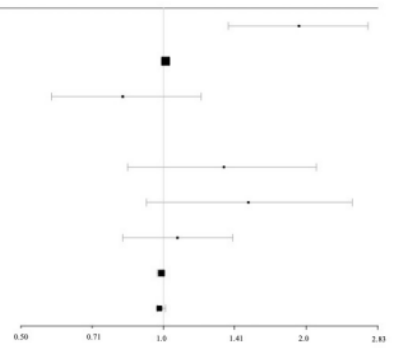
Cittadini A, EJPC, Volume 28, Issue 15, December 2021.

The T.O.S.CA. Registry results

In the multivariable Cox proportional hazard regression analyses, the presence of MHDS was significantly associated with the primary endpoint when adjusted for age, sex, NYHA class, aetiology, LVEF, BNP, and the presence of obesity, impaired eGFR, atrial fibrillation, and anaemia. In this model, also sex ,age and BNP were significantly associated with the outcome.

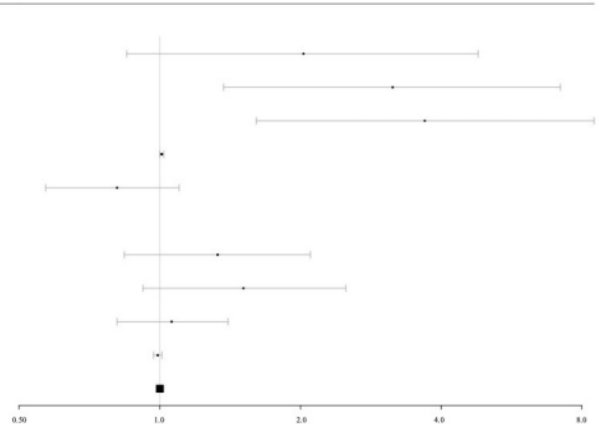
A

Variables	HR	95% CI	p
MHDS	1.93	1.37-2.7	<0.001*
Age (1 yr)	1.01	1.00-1.0	0.181
Sex (Female)	0.82	0.58-1.2	0.253
NYHA Class		Ref	
II	1.34	0.84-2.1	0.216
III-IV	1.51	0.92-2.5	1.101
Aetiology (Ischemic)	1.07	0.82-1.4	0.634
EF (%)	0.99	0.97-1.0	0.174
BNP (1 pg/ml)	0.98	0.97-1.01	0.075



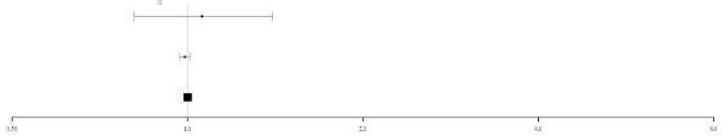
B

Variables	HR	95% CI	p
Number of HD			
1 HD	2.03	0.85-4.8	0.11*
2 HD	3.15	1.37-7.2	0.007*
≥3 HD	3.69	1.61-8.5	0.002*
Age (1 yr)	1.01	1.00-1.0	0.189
Sex (Female)	0.81	0.57-1.1	0.217
NYHA Class			
II	1.33	0.84-2.1	0.22
III-IV	1.51	0.92-2.5	0.1
Aetiology (Ischemic)	1.06	0.81-1.4	0.66
EF (%)	0.99	0.97-1.0	0.23
BNP (1 pg/ml)	1.00	1.00-1.0	0.14



C

Variables	HR	95% CI	p
Number of HD			
1 HD	2.03	0.85-4.8	0.11*
2 HD	3.15	1.37-7.2	0.007*
≥3 HD	3.69	1.61-8.5	0.002*
Age (1 yr)	1.01	1.00-1.0	0.189
Sex (Female)	0.81	0.57-1.1	0.217
NYHA Class			
II	1.33	0.84-2.1	0.22
III-IV	1.51	0.92-2.5	0.1
Aetiology (Ischemic)	1.06	0.81-1.4	0.66
EF (%)	0.99	0.97-1.0	0.23
lnBNP	1.00	1.00-1.0	0.14

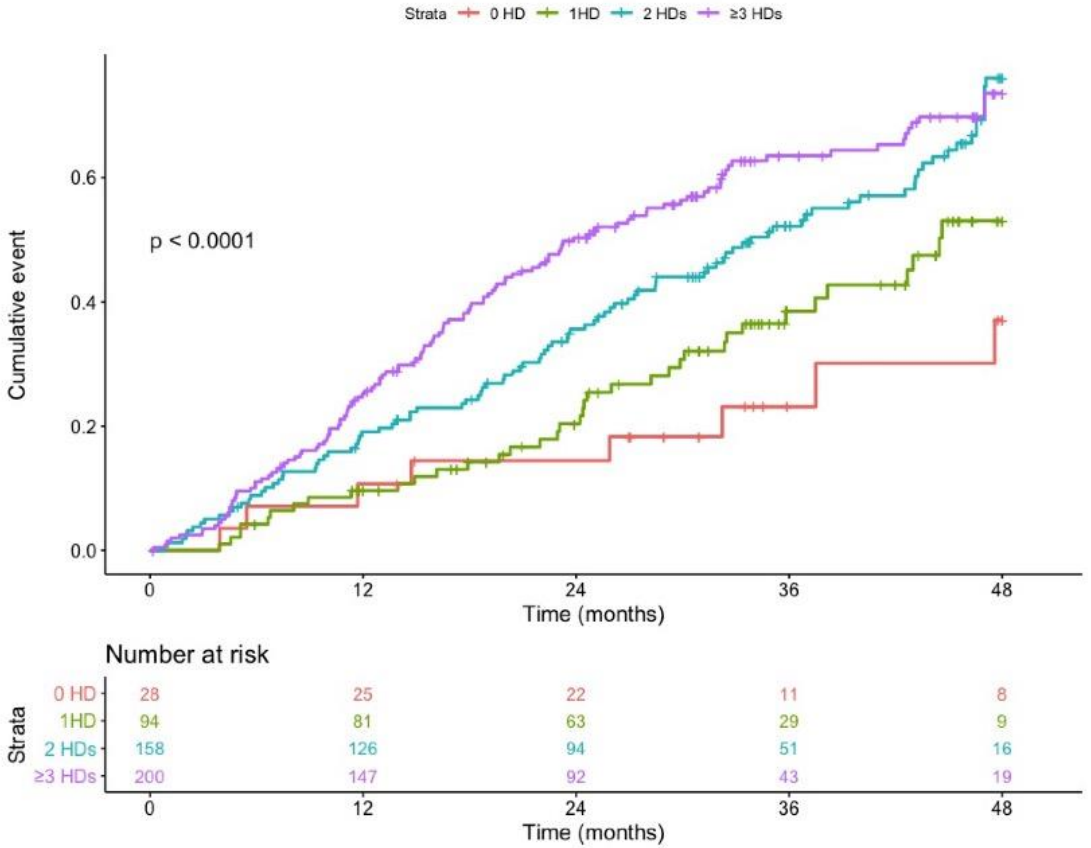


Cittadini A, EJPC, Volume 28, Issue 15, December 2021.

The T.O.S.CA. Registry results

The presence of TD, DHEAS-D, low IGF-1, or T2D, were independently associated with outcome (P< 0.001, P= 0.005, P< 0.001, and P< 0.001, respectively). Patients without HD had the best survival rate when compared with those with HD. Low T3 syndrome was not significantly associated with the primary endpoint.

Occurrence of the primary endpoint according to the number of hormonal deficiencies



Kaplan–Meier analysis of survival for all-cause mortality or cardiovascular hospitalization in patients with 0 (n = 28), 1 (n = 94), 2 (n = 158), three, or more than 4 (n = 200) hormonal deficiencies [1.35 (1.21–1.52), P < 0.001]

Cittadini A, EJPC, Volume 28, Issue 15, December 2021.

GGI Study design

This is a randomized, double-blind, and placebo-controlled study, with two parallel arms. The two groups have been randomized to either placebo or active treatment.

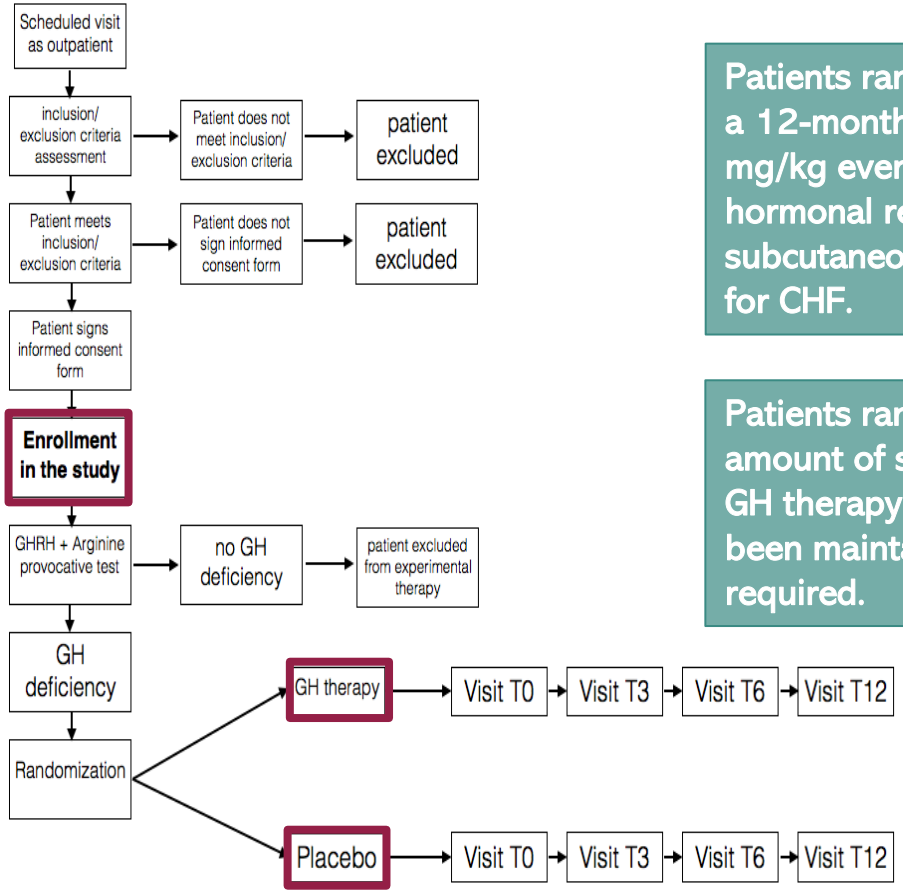
Inclusion criteria:

- CHF NYHA class I-III
- age ranged 10-80 years
- Stable and optimal therapy for at least three months
- LVEF 40% or less and LV end-diastolic dimension 55 mm or more
- Signed informed consent

Exclusion criteria:

- Inability to perform a bicycle exercise test
- Poorly controlled diabetes mellitus (Hb1Ac > 8.5) and/or active proliferative or severe non-proliferative diabetic retinopathy
- Active and/or history of malignancy
- Unstable angina o recent myocardial infarction (less than six months)
- Severe liver or kindey disease (serum creatinine levels > 2.5 mg/dl)

Study plan



Patients randomized to GH administration underwent a 12-month GH therapy at the initial dose of 0.012 mg/kg every second day (adjusted according to hormonal response and eventual adverse effects) subcutaneously, on top of standard medical therapy for CHF.

Patients randomized to placebo received an identical amount of saline employing the same device used for GH therapy for 12 months. The standard therapy has been maintained in all patients and modified only if required.

Planned assessment

	Screening	Visit T0	Visit T3	Visit T6	Visit T12
Medical history	X				
Physical examination/anthropometrics	X	X	X	X	X
Therapy/adverse event monitoring			X	X	X
EKG	X	X	X	X	X
Biochemistry	X	X	X	X	X
Test GHRH + Arginine		X			
Hormonal work up		X	X	X	X
Echocardiography		X		X	X
QoL tests		X		X	X
Cardiopulmonary Exercise test		X			X
Hand grip		X			X
Holter EKG 24 h		X			X

End points

The objective of the study is to determine whether treatment of GHD improves peak oxygen consumption (peak VO_2), a recognized surrogate end-point of CHF progression.

According to previous observations, we set a target **increase of peak VO_2 in the treated arm at 3 ml/kg/min at the end of the study (primary endpoint).**

Secondary end-points includes:

1. Hospitalizations
2. End-systolic LV volumes;
3. NT-proBNP levels;
4. QoL scores;
5. Muscle strength (handgrip

Statistical plan

Statistical plan

Assuming a significance level of 5% and an 80% study power, a sample of 28 patients in each arm of the study is sufficient to demonstrate an improvement in the primary variable (peak VO_2) by 3 ml/kg/min (primary end-point), assuming a standard deviation of 4 ml/kg/min for the object variable, in the group treated with GH compared with placebo. In addition, the drop-out rate of the recruited patients may be expected reasonably low (<15%), based on the documented good tolerability of GH in many previous studies in CHF (18) and observations coming from our previous studies. Therefore, we plan to recruit 64 patients to have at least 56 patients completing the study. Results will be analyzed with a "*per protocol*" approach. The *t* Student test for unpaired data will be used to compare the absolute difference of the variables of interest compared to baseline in the two groups (GH and placebo; treatment effect). Data will be preliminary tested for normal distribution and homoscedasticity.

The burden of Heart Failure

Chronic heart failure (CHF) is recognized worldwide as a major healthcare issue for its increasing prevalence and related extensive direct and indirect costs.

Prevalence

1-3% general adult population

Overall prevalence↑

Prevalence in HFrEF↔

Prevalence in HFpEF↑

Incidence

1-20 cases for 1000 person-years or per 1000 population

Incidence stable/declining↔

Incidence in HFrEF↓

Incidence in HFpEF↘

Mortality

Mortality remains high

30-day mortality ∽2-3%
1 year mortality ∽15-30 %
£ years mortality∽ 30-50%
5 years mortality ∽50-75%

CVD HFrEF↓
Non CVD HFpEF↑

Costs

Health care costs up to 25,500€ /year

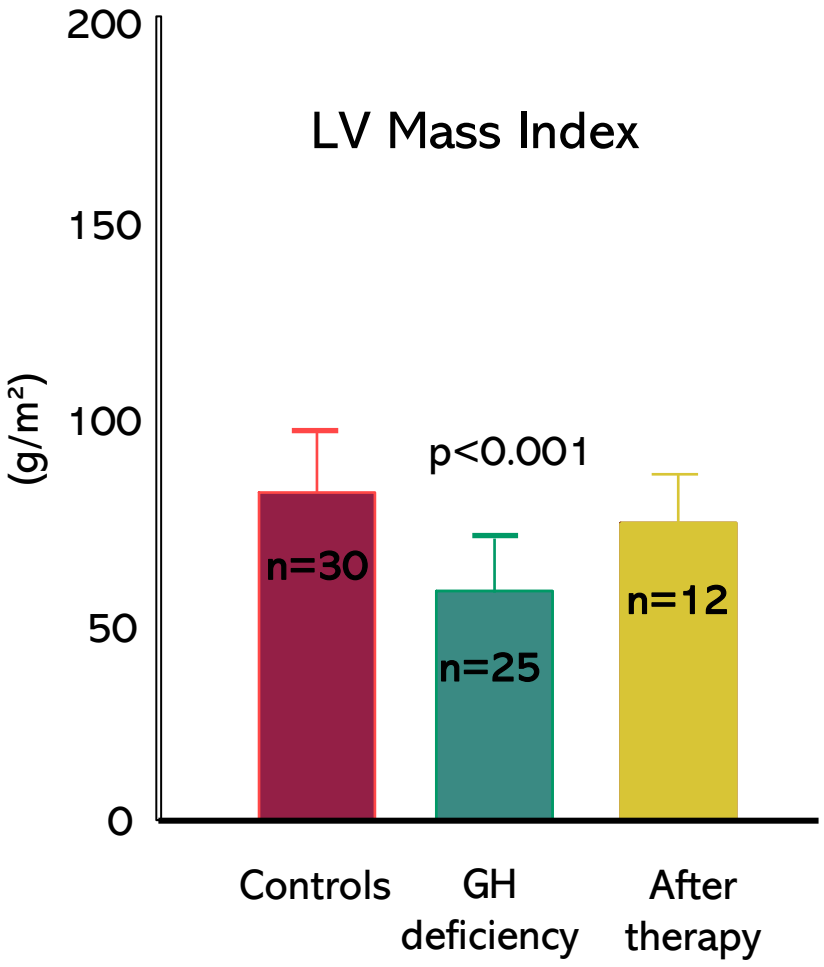
Increasing due to major demographic changes (>65 years)

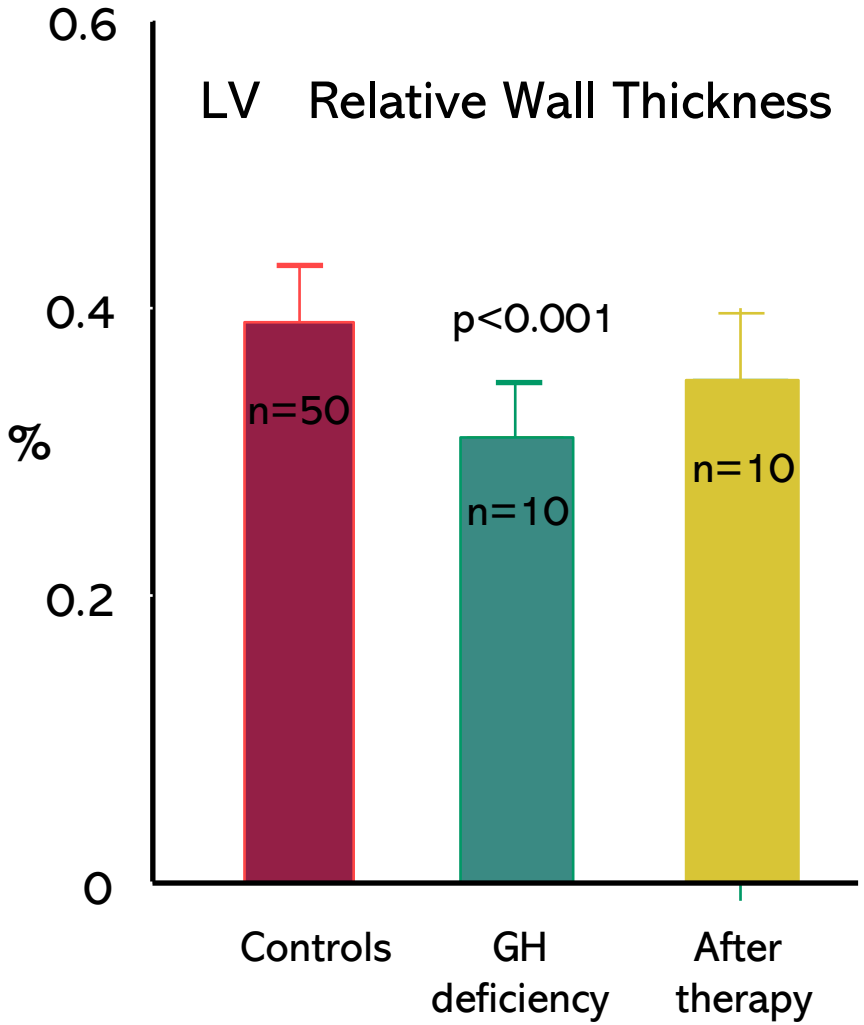
Main cost drivers:
-Direct costs (70%)
-Non CVD comorbidities
-Invasive procedures
-Medication/ diagnostics
-Outpatients visits

HFrEF: Heart Failure reduced Ejection Fraction
HFpEF: Heart Failure preserved Ejection Fraction
CVD: Chronic Vascular Disease

Adapted from Savarese G. Cardiovascular Research (2022) 00, 1–16

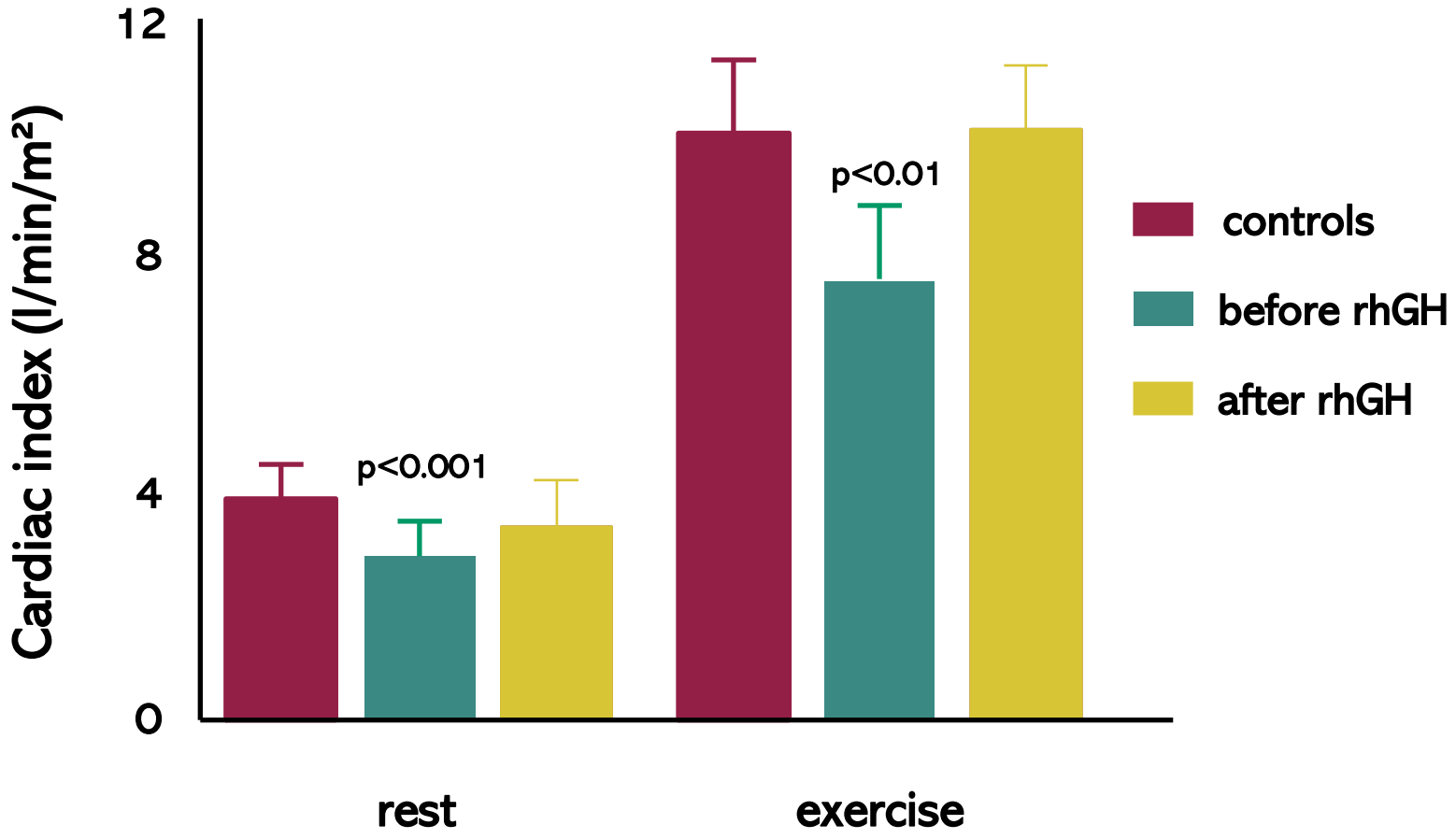
Growth Hormone Deficiency





Merola, Cittadini et al, JCEM 1993

Cardiac Performance in GH Deficiency

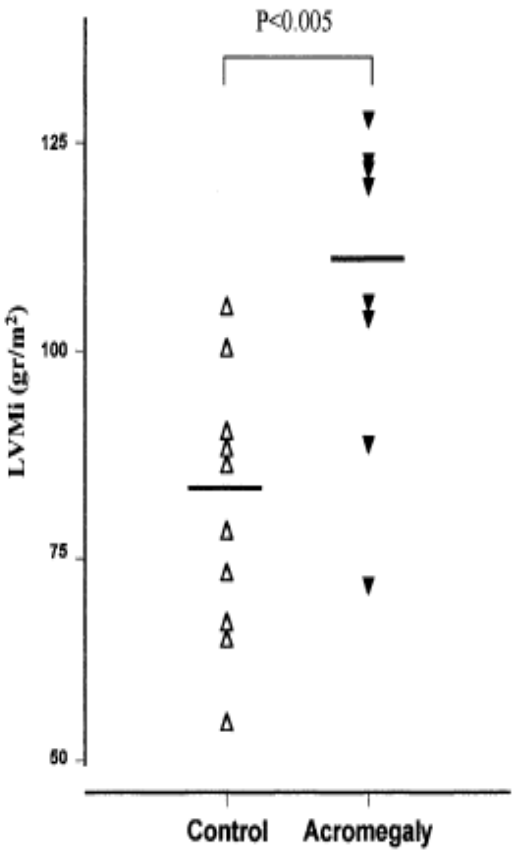


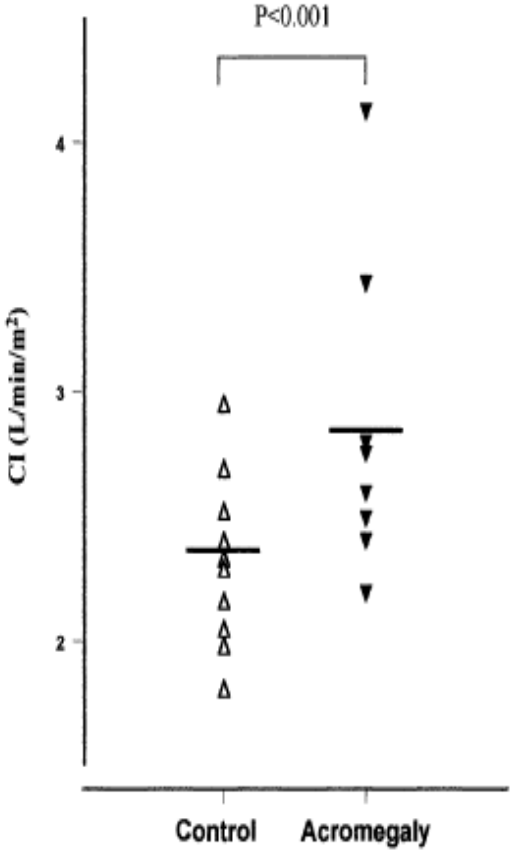
Acromegalic cardiomyopathy

- 10 patients with short duration of acromegalic disease (< 5 yrs) vs 10 healthy controls

	Controls (n = 10)	Patients (n = 10)
Systolic function		
SI (ml/m^2)	33 ± 2	39 ± 6[a]
CI (L/min·m^2)	2.30 ± 0.34	2.85 ± 0.57[b]
SVR (dyn·sec·cm^{-5})	1731 ± 225	1428 ± 248[b]
Diastolic function		
E (cm/sec)	77 ± 11	76 ± 15
A (cm/sec)	46 ± 7	49 ± 8
E/A ratio	1.70 ± 0.22	1.58 ± 0.32
MDT (msec)	156 ± 27	151 ± 24
IRT (msec)	82 ± 7	80 ± 14

[a] $P < 0.01$.
[b] $P < 0.001$ vs. controls.

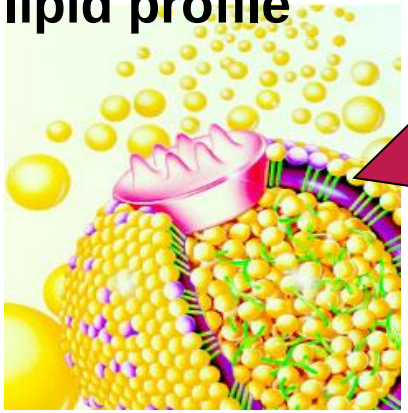




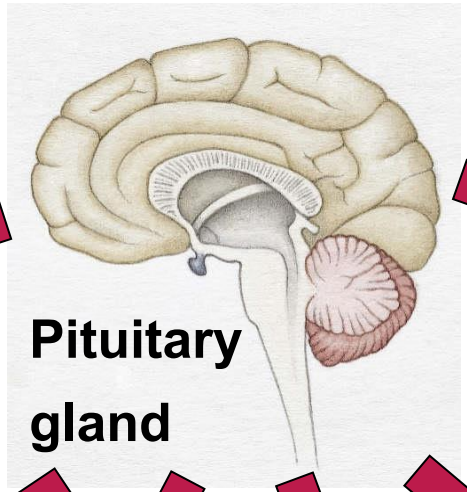
Fazio, Cittadini et al, JCEM 2000

Growth Hormone Deficiency

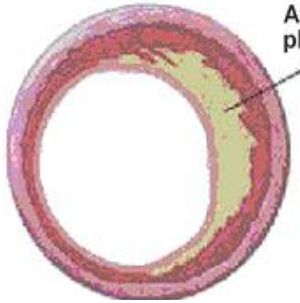
Atherogenic lipid profile



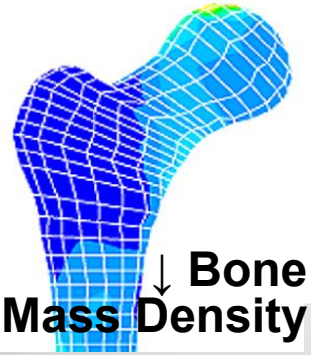
Cardiac Atrophy



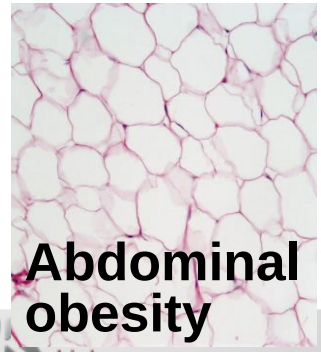
Pituitary gland



Atherosclerosis



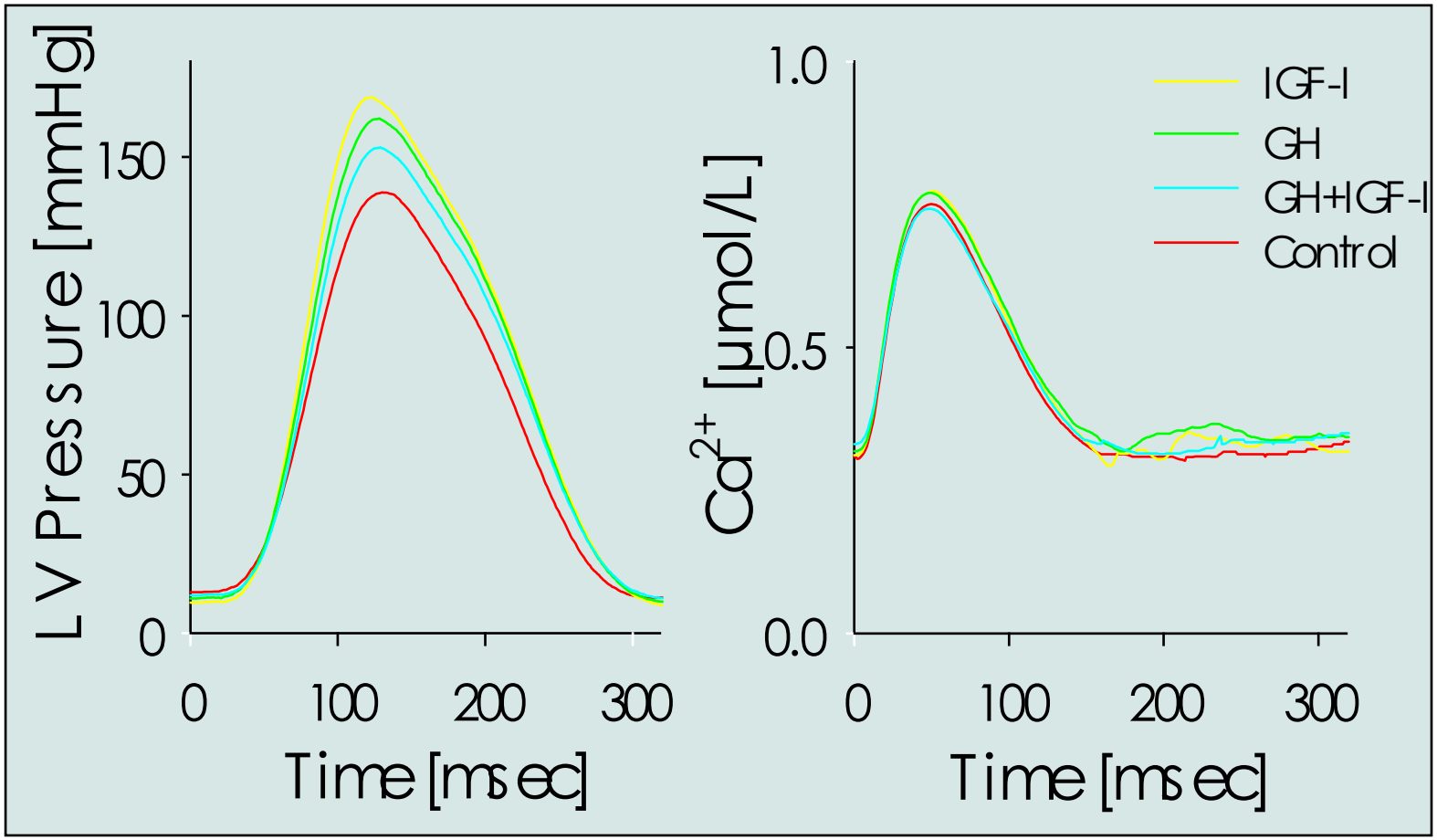
↓ Bone Mass Density



Abdominal obesity

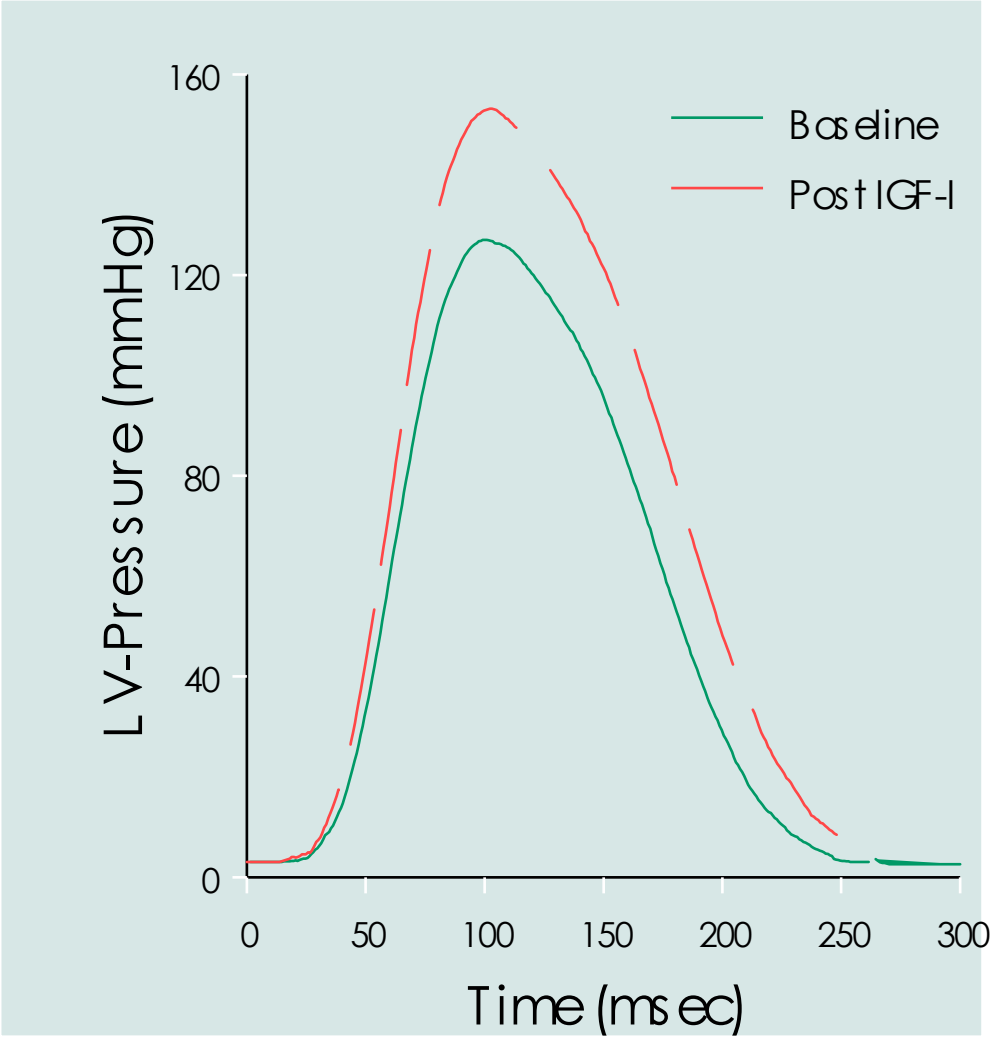
Hypertension

LV-Pressure and Calcium Transient



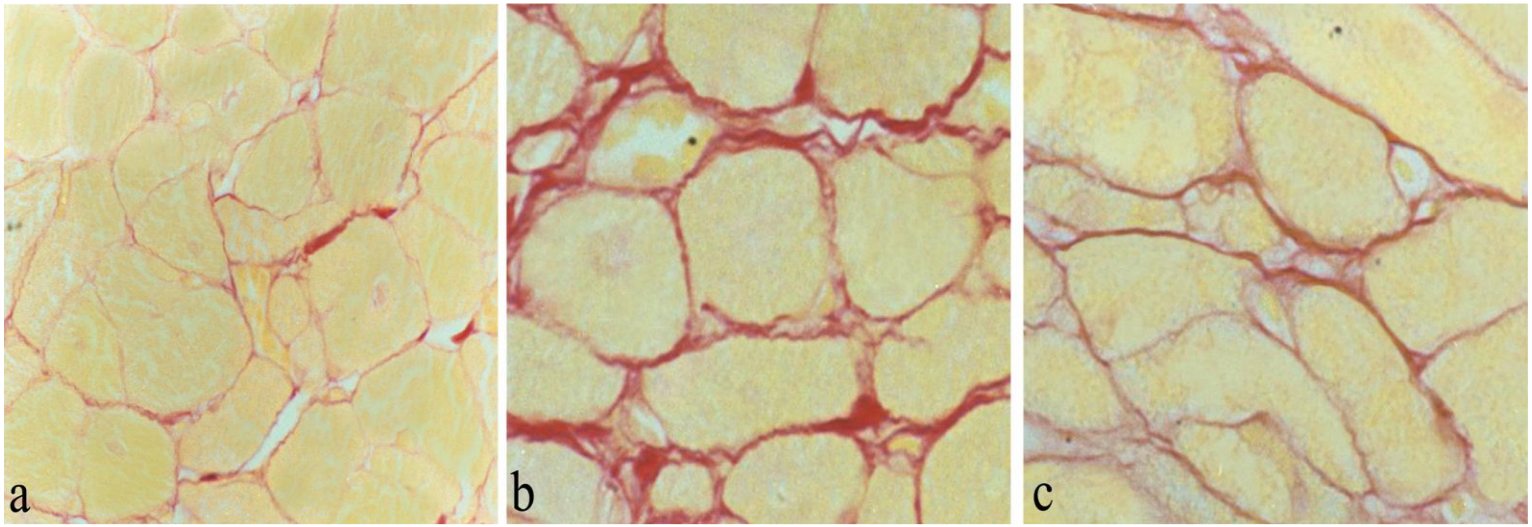
Stromer H, Cittadini et al, Circ Res 1996

Inotropic Effect of IGF-I



Cittadini et al, Circ Res 1998

GH-induced growth: interstitial fibrosis



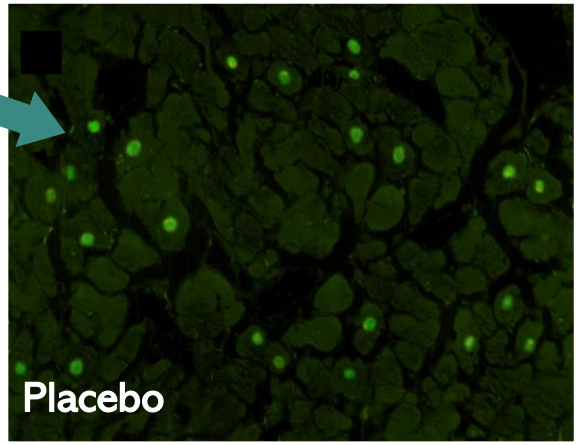
Control **Aortic banding** **GH**

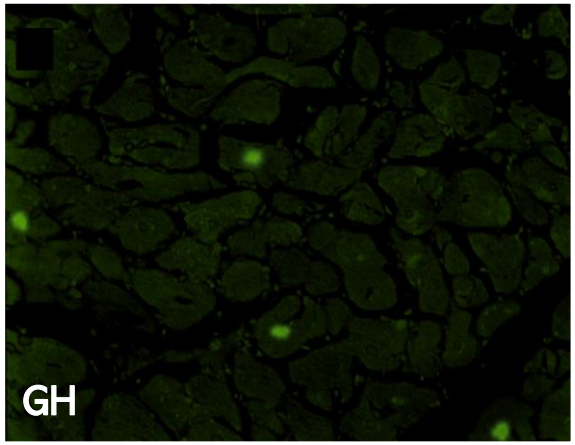
Similar results in mice overexpressing Akt E40K

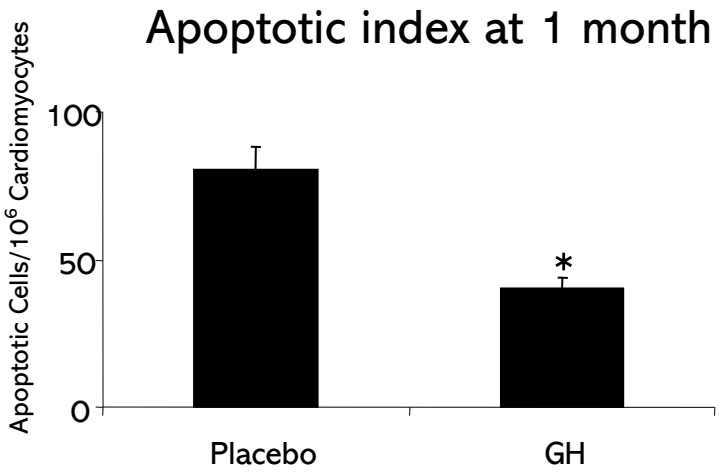
Cittadini et al, Growth Horm IGF Res. 2006

GH and apoptosis

Apoptotic Nuclei







Cittadini et al, JACC 2003

GH therapy in 147 patients with CHF

(in order of publication date)

1st author	Dose (IU/week)	Duration	No	Placebo	Benefit	IGF (ng/ml)
Cuneo	12 (IU/week) (84)	3 months	1	No	Yes	?
Fazio	4 IU/2nd day (14)	3 months	7	No	Yes	198 to 406
Frustaci	4 IU/ day (28)	3 months	5	No	No	?
Volterrani	0.1 IU/Kg/24h	24 hours	12	No	Yes	169 to 248
O'Driscoll	10+14 IU day (70+98)	1+7 weeks	2	No	Yes	?
De Luis Roman	16 IU/day (12)	1 year	1	No	Yes	?
Osterziel	2 IU/day (14)	3 months	50	Yes	No	134 to 211
Isgaard	2.6 IU day (mean 18)	3 months	22	Yes	No	175 to 425
Genth-Zotz	2 IU/day (14)	3 months	7	No	Yes	0.69 to 1.45 (UI/ml)
Adamopoulos	4 UI/2nd day(14)	3 months	12	No (R&C-O)	Yes	
Cittadini	2.5 UI/day	6 months	28	No (R&C)	Yes	94 to 146
Cittadini		48 months	28	No (R&C)	Yes	94 to 166