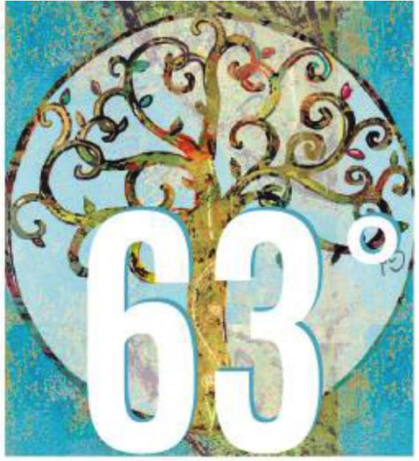

CONGRESSO NAZIONALE SIGG

GLI ANZIANI:
LE RADICI DA PRESERVARE

ROMA 28 novembre 01 dicembre 2018 Auditorium della Tecnica, Roma

Ruolo dell'Asse GH-IGF-1 nella Longevità

Prof. Antonio Cittadini
Professore Ordinario di Medicina Interna
Direttore della UO di Medicina Interna ad Indirizzo Metabolico e Riabilitativo
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DISCLOSURE INFORMATION

Antonio Cittadini

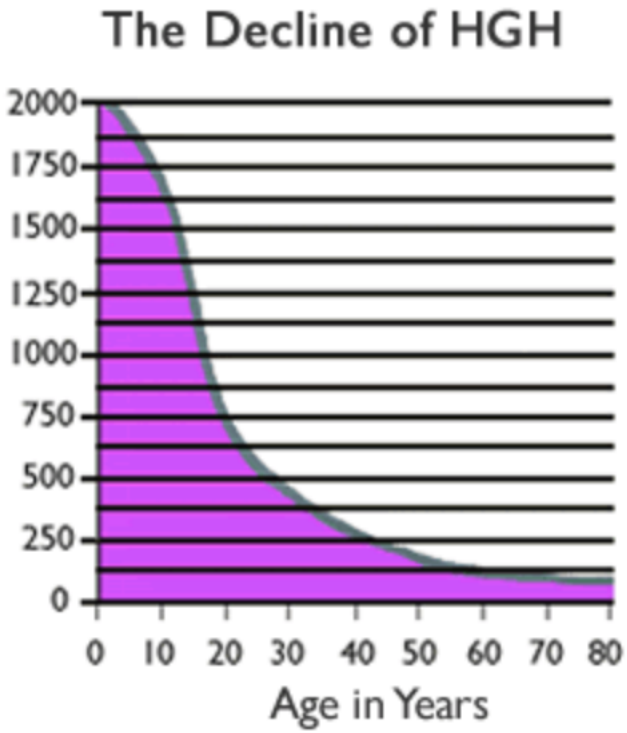
- Consults for: IRCSS SDN, Novo Nordisk
- Unrestricted grants: MerckSerono, Ipsen

Ageing and somatopause

Hormones

That Decrease With Age

- IGF-1 (HGH)
- Testosterone
- The Estrogens
- Progesterone
- DHEA



The New England

Journal of Medicine

Vol mber 1

D M.D.,

Journal of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci
2009. Vol. 64A, No. 10, 1039–1044
doi:10.1093/gerona/glp091

Advance Access publication on July 8, 2009

Statement by the Growth Hormone Research Society on the GH/IGF-I Axis in Extending Health Span

Michael O. Thorner

Design of Future Studies to Investigate Enhancement of Health Span

Given the expected demographic age shift in the world population, future clinical research in this area, with carefully designed, long-term studies, using validated outcome parameters, is strongly recommended. Until the results of such studies are available, the clinical use of GH or GHS in older adults, alone or in combination with testosterone, cannot be recommended.

Does GH accelerate aging?

Studies in GHD-GHR mice

Mutant mice with reduced somatotropic (GH/IGF-1) signaling and extended longevity

Mutation	Effects on somatotropic signaling	Reference
Ames dwarf; mutation of Prophet of pituitary factor1 (Prop1); $Prop1^{df}$	Failure of somatotroph differentiation; GH deficiency	Borg et al 1996
Snell dwarf; mutation of Pituitary factor 1; $Pit1^{dw}$	Failure of somatotroph differentiation; GH deficiency	Flurkey et al 2001
Little; mutation of GH releasing hormone receptor; $Ghrhr^{lit}$	GH deficiency	Flurkey et al 2001
Laron dwarf; Deletion of GH receptor/GH binding protein gene; Ghr/bp −/−	Deletion of GH receptors; GH resistance	Coschigano et al 2003
Midi-mice; hypomorphic IGF-1 mutation	Reduced IGF-1 levels	Sell and Lorenzini 2007
Heterozygous for deletion of IGF-1 receptor, Igfr +/−	Partial IGF-1 resistance	Holzenberger et al 2003
Deletion of Pregnancy associated plasma protein A; PAPP-A −/− (an IGFBP protease)	Reduced local (tissue) availability of IGF-1	Conover and Bale 2007

Abbreviations: GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP, insulin-like growth factor binding protein.

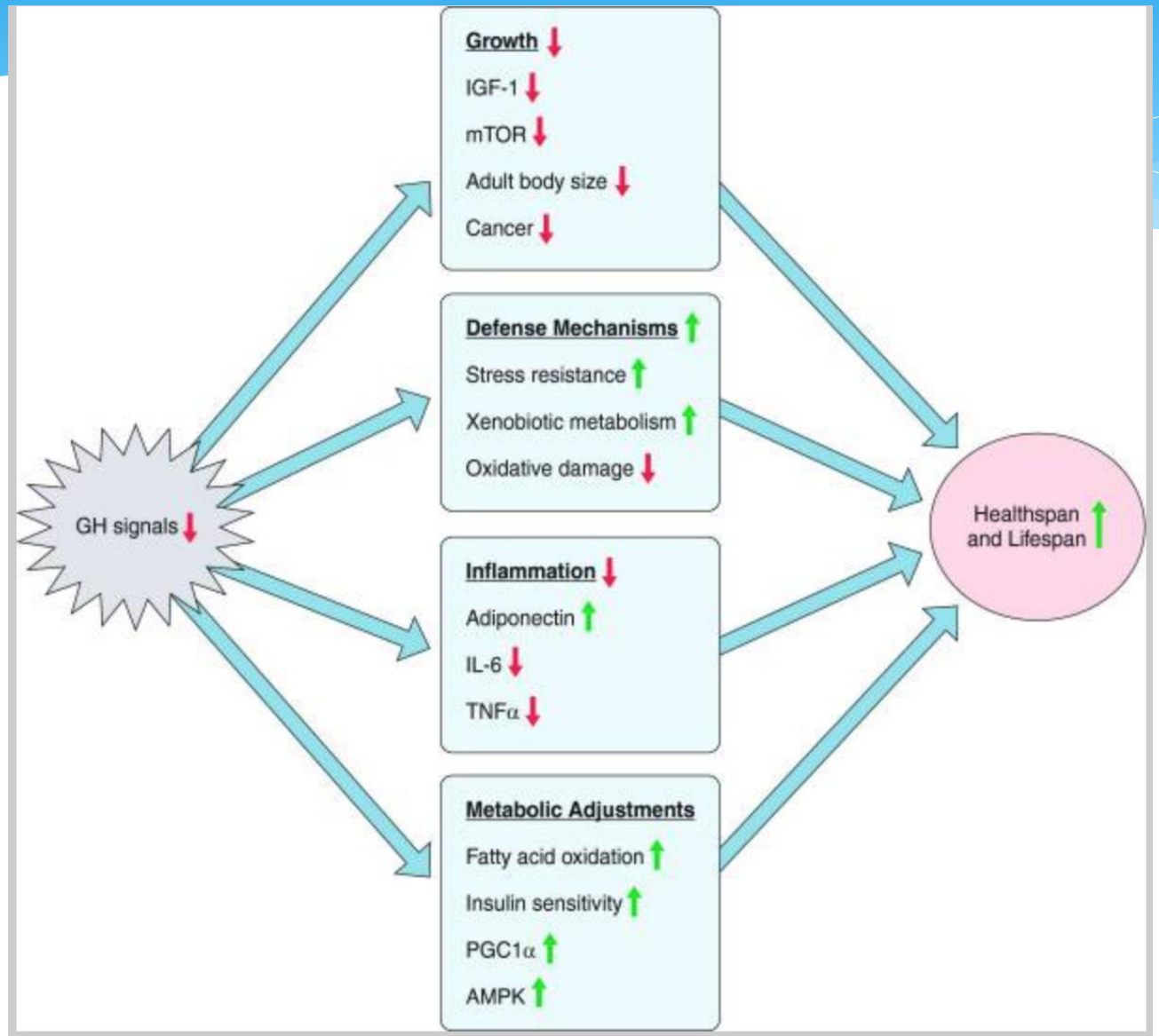
Does GH accelerate aging?

Studies in GHD-GHR mice

1. Extension of longevity reproducible and not limited to a particular laboratory, diet or genetic background
2. Lifespan is extended in both males and females
3. Extension of longevity is associated with a similarly extension of healthspan
4. The magnitude of increase in longevity exceeds the effects of most genetic, pharmachological, or dietary interventions that have antiaging effects in mice

Bartke A, WJMH 2018

Mechanisms involved in linking GH signaling with healthspan and lifespan



GH deficient /resistant mice and extended longevity

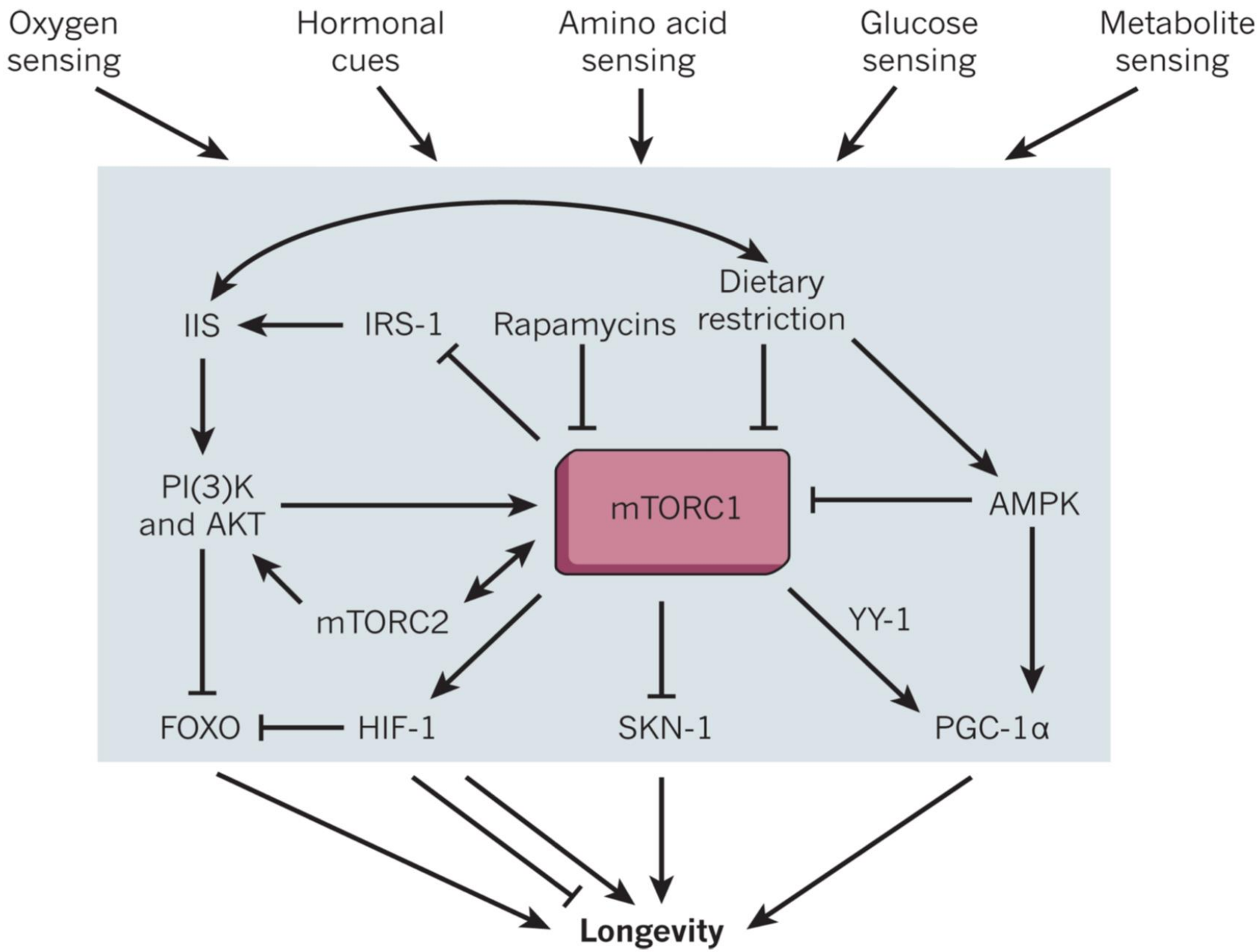
Improbable Mechanisms

1. Size (inverse correlation with lifespan in diverse species, but discordant data)
2. Insulin sensitivity (important, but IR does not preclude↑ lifespan)
3. Adiposity (mouse strain and GHD humans obesity, adipose tissue, particularly subcutaneous protective; Nether obesity nor a lean phenotype are a prerequisite for a long life)

Probable Mechanisms

1. Stress resistance (resistance to various cellular stress, such as heat, hypoxia, irradiation, glucose deprivation, accumulation of ROS) Autophagy or apoptosis. mTOR is central its long term activation induces cellular stress and accumulation of unfolded proteins, and is inhibited by caloric restriction and decresed GH/IGF-1 signaling
2. Tumour resistance (Enhanced GH/IGF-1 signaling associated with several types of cancers in mammals)

Junnila RK et al., Nat Rev Endocrinol 2013



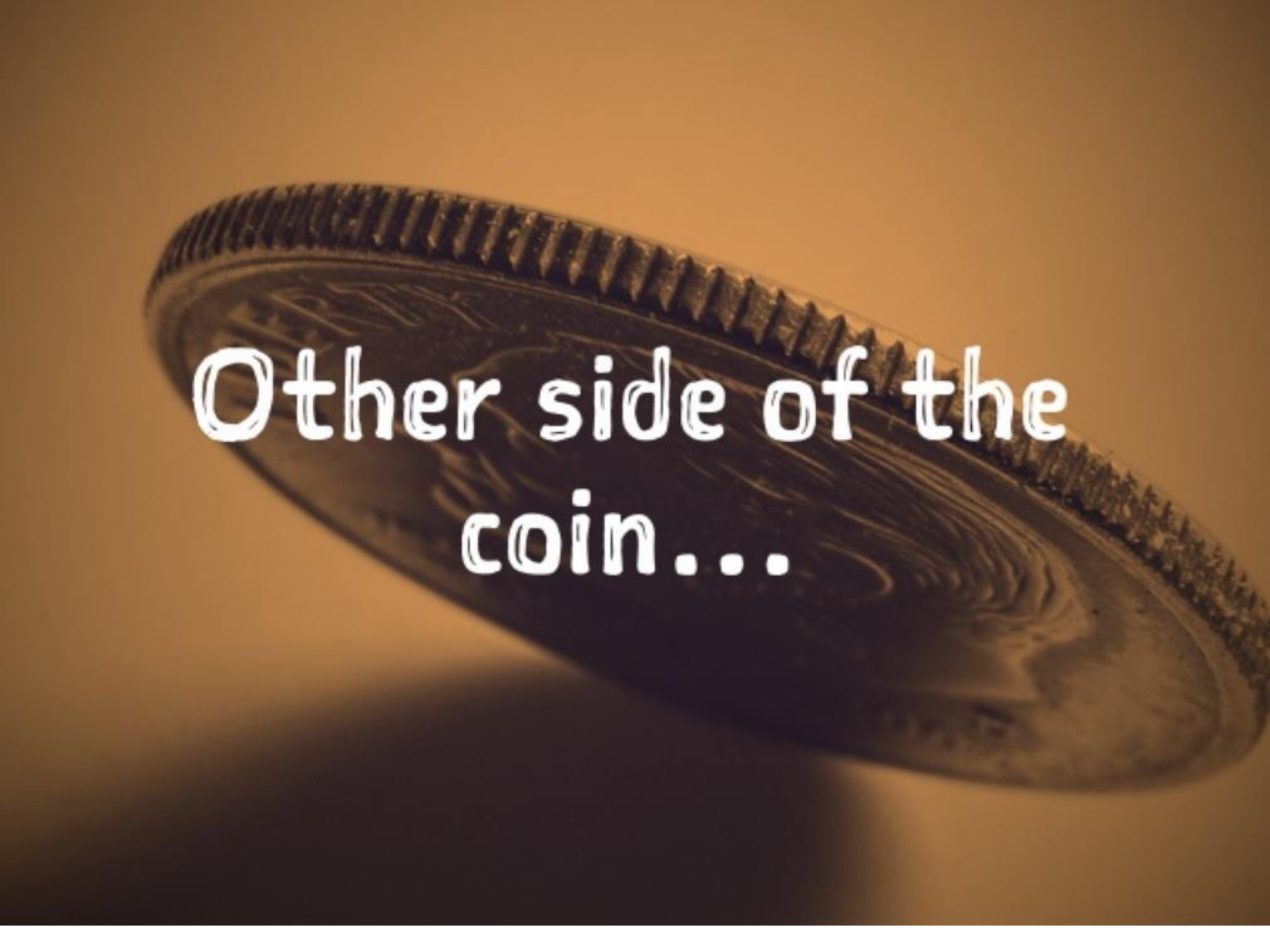
Johnson SC et al. , Nature 2013

Acromegalia

↑ Mortalità soprattutto x complicanze cardiovascolari e respiratorie, di circa 1.5-3 volte

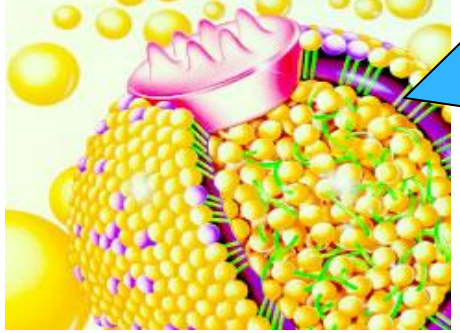
- Ipercalciuria
- Iperfostatemia
- Iperinsulinemia
- Diabete mellito (10%)
- Ipertensione arteriosa (30%)
- Cardiomegalia
- Insufficienza cardiaca congestizia (10-20%)
- Coronaropatia precoce

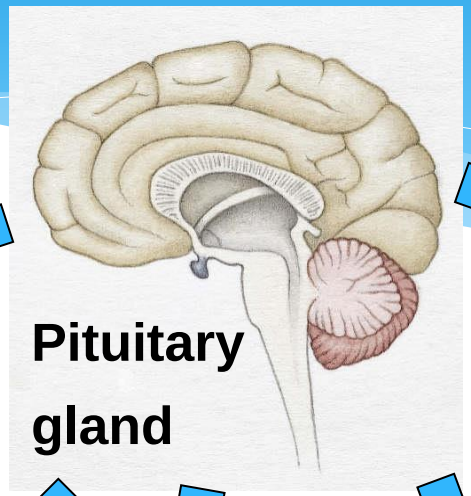
Saccà, Cittadini, Endocrin Rev 1994


Other side of the coin...

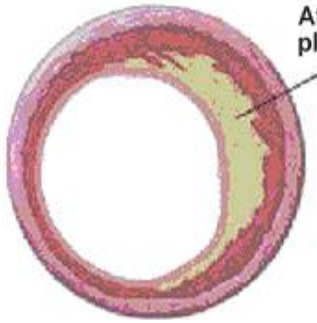
Growth Hormone Deficiency

Atherogenic lipid profile

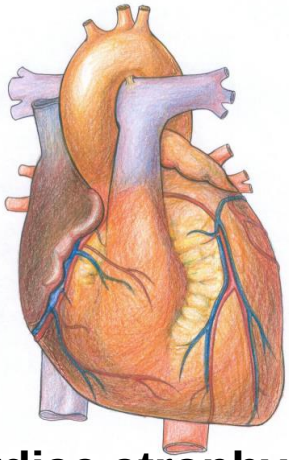




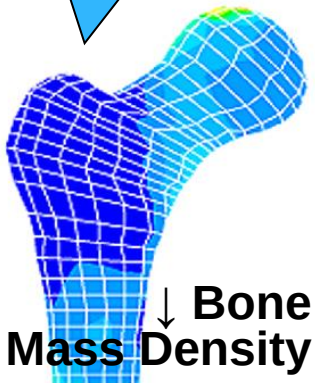
Pituitary gland



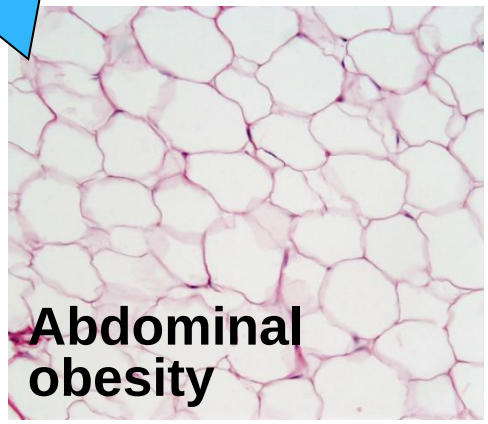
Atherosclerosis



Cardiac atrophy & dysfunction



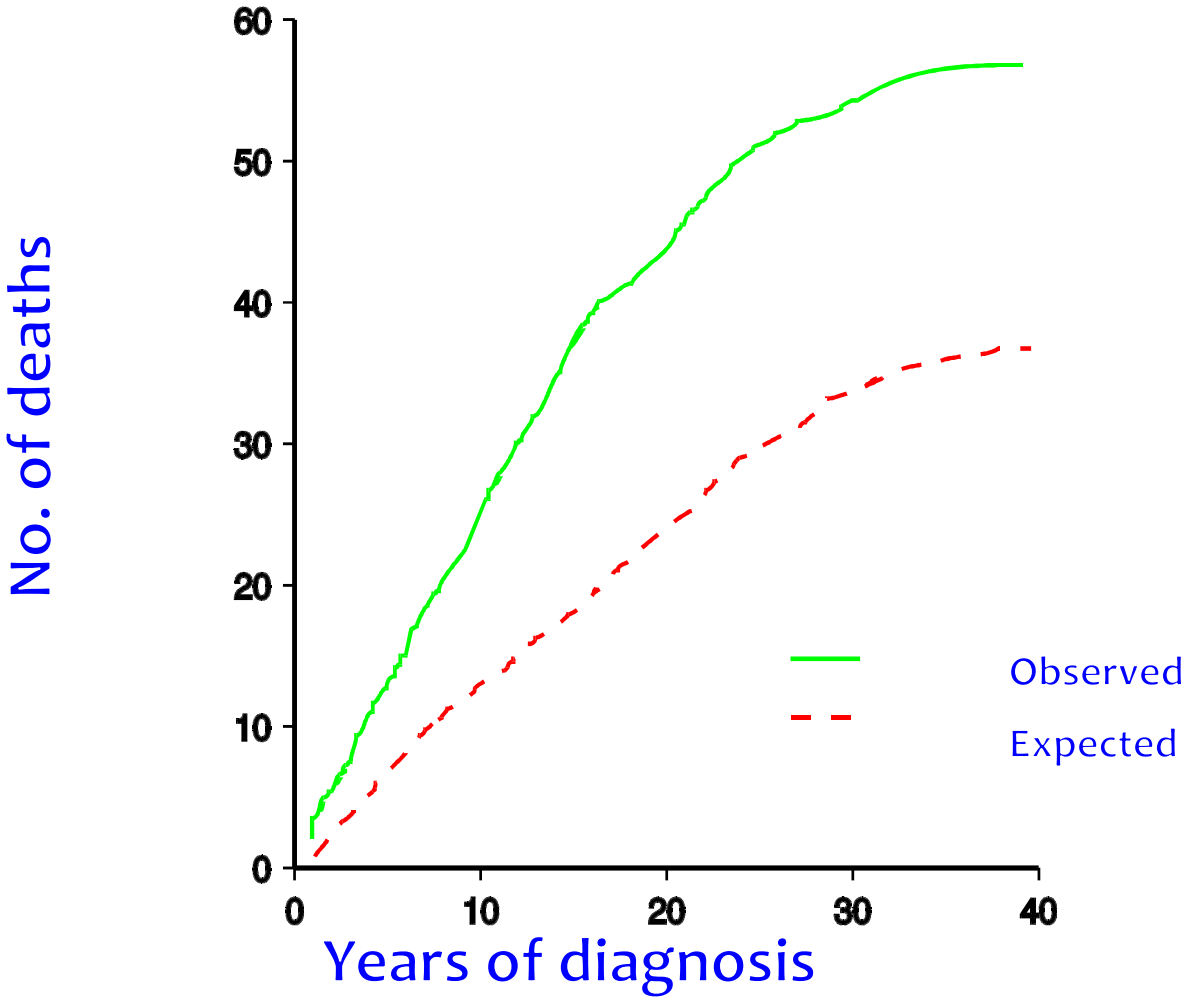
↓ Bone Mass Density



Abdominal obesity

Saccà, Cittadini, Endocrin Rev 1994

Mortality from Cardiovascular Disease in Hypopituitarism



Rosén and Bengtsson, Lancet 1990

Mortality from Cardiovascular Disease and Malignacy in Hypopituitarism

- Hypopituitary females have a high incidence of cardiovascular morbidity and an increased prevalence of cardiovascular risk factors, *Bulow B et al. JCEM 2000*

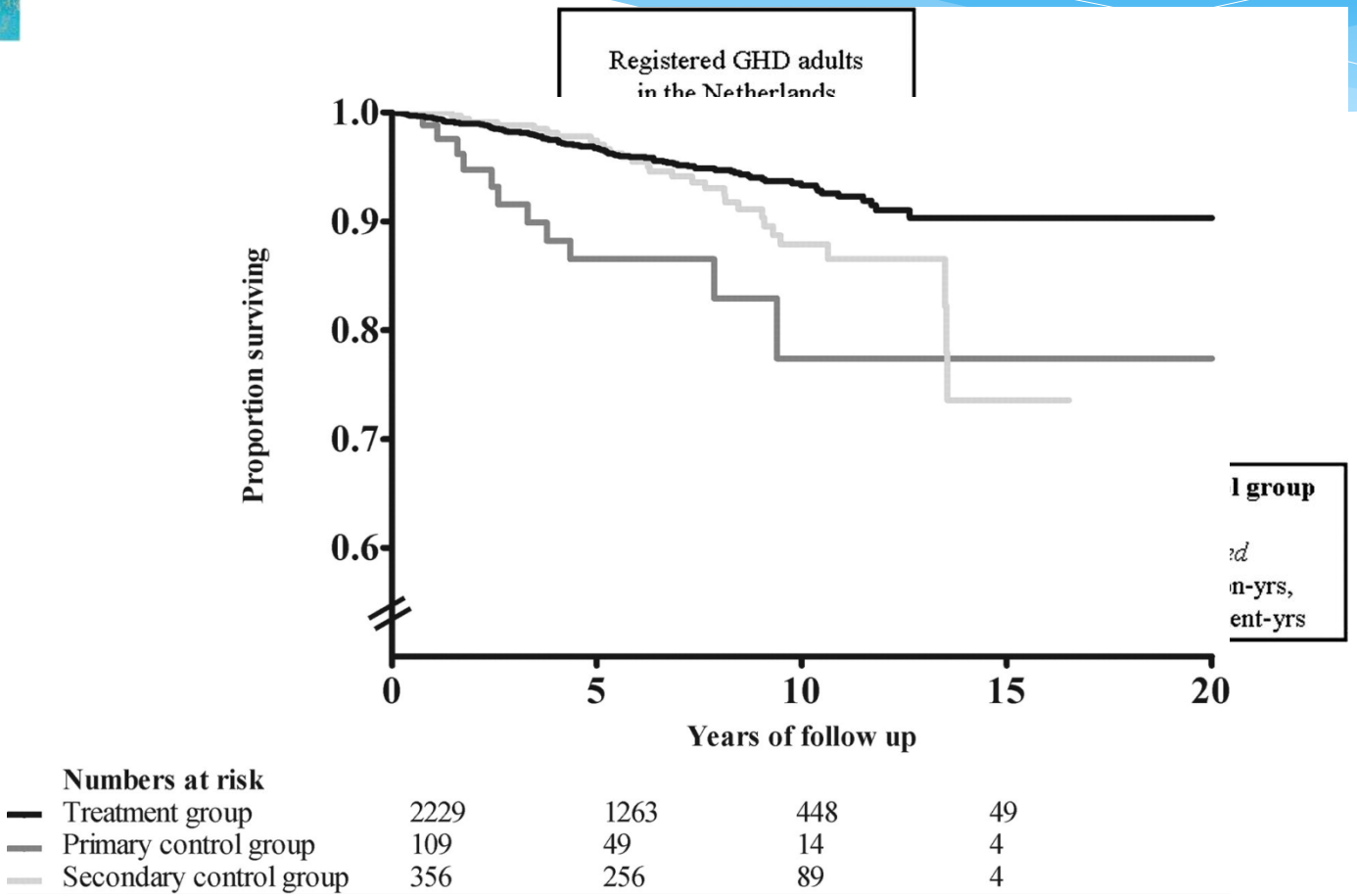
- Svensson et al in 1,411 hypopitutary patients showed increased incidence of MI, cerebrovascular disease, malignancy, and death compared to general population while GH treated HYP had an overall malignancy and mortality rate comparable to that of the general population *JCEM 2004*

GH deficiency: clinical status and replacement therapy

Signs/symtoms of GH deficiency	*Benefits*
↑ Fat mass	↓ Fat mass
↓ Lean mass	↑ Lean mass
↓ Bone density	↑ Bone density
↓ Exercise & skeletal muscle	↑ Exercise & muscle
Atherogenic lipidic profile	Improvement
Atherosclerosis	Improvement
↓ Quality of life	↑ Quality of life
↓Survival	????

Cittadini A et al. , JCEM, Am J Physiol 1996-1997

GH therapy and mortality in GHD



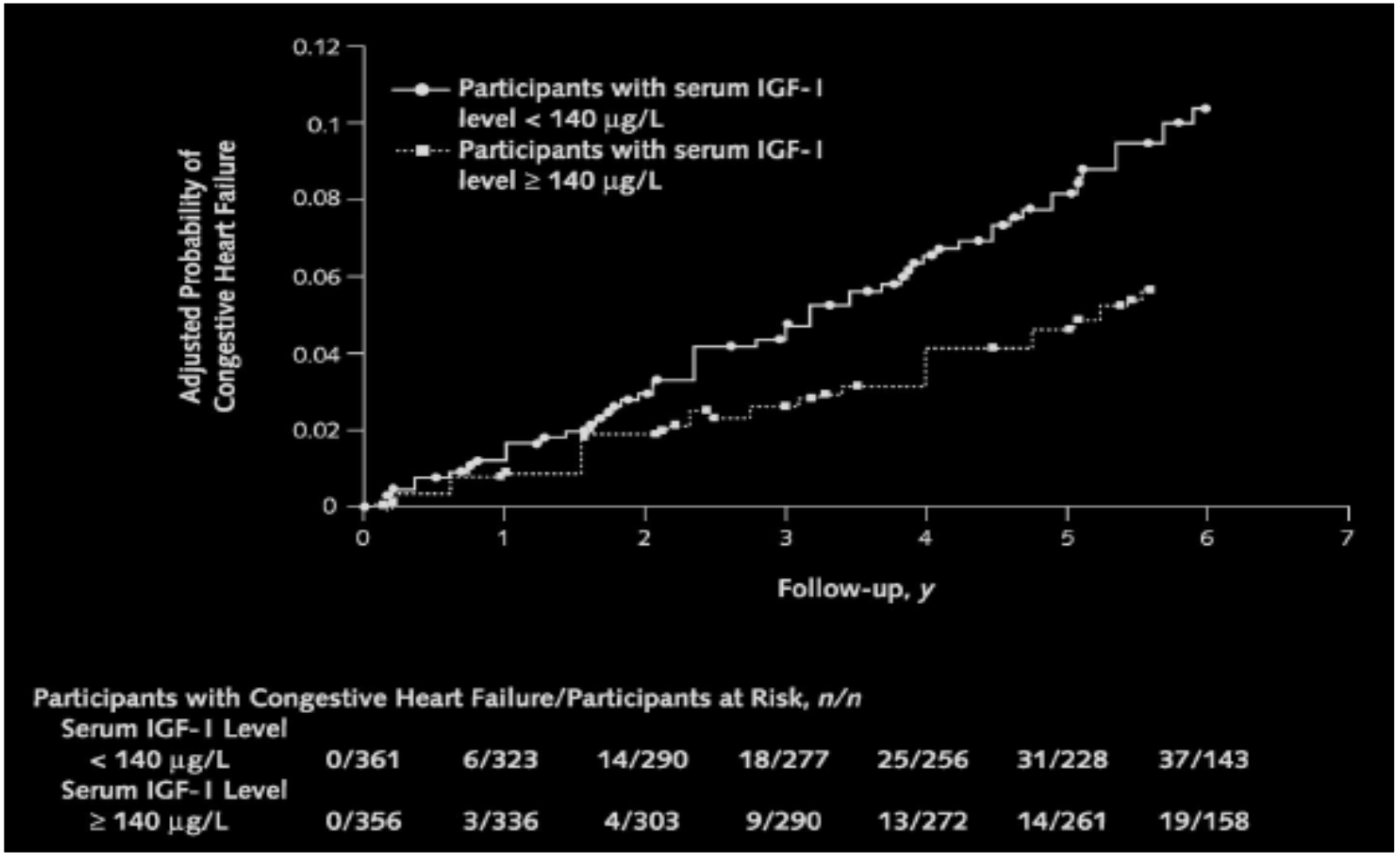
From: Does Growth Hormone Replacement Therapy Reduce Mortality in Adults with Growth Hormone Deficiency? Data from the Dutch National Registry of Growth Hormone Treatment in Adults

J Clin Endocrinol Metab. 2011;96(10):3151-3159. doi:10.1210/jc.2011-1215

Low IGF-1 and IHD in normals

- Danish prospective study on a sample of 4,807 individuals aged 30-60 yrs without disease at the enrollment. *Low serum IGF-I is associated with increased risk of ischemic heart disease, Juul A et al. Circulation 2002*

Serum IGF-I and Risk of CHF in Elderly Individual Without a Previous Myocardial Infarction: the Framingham Heart Study

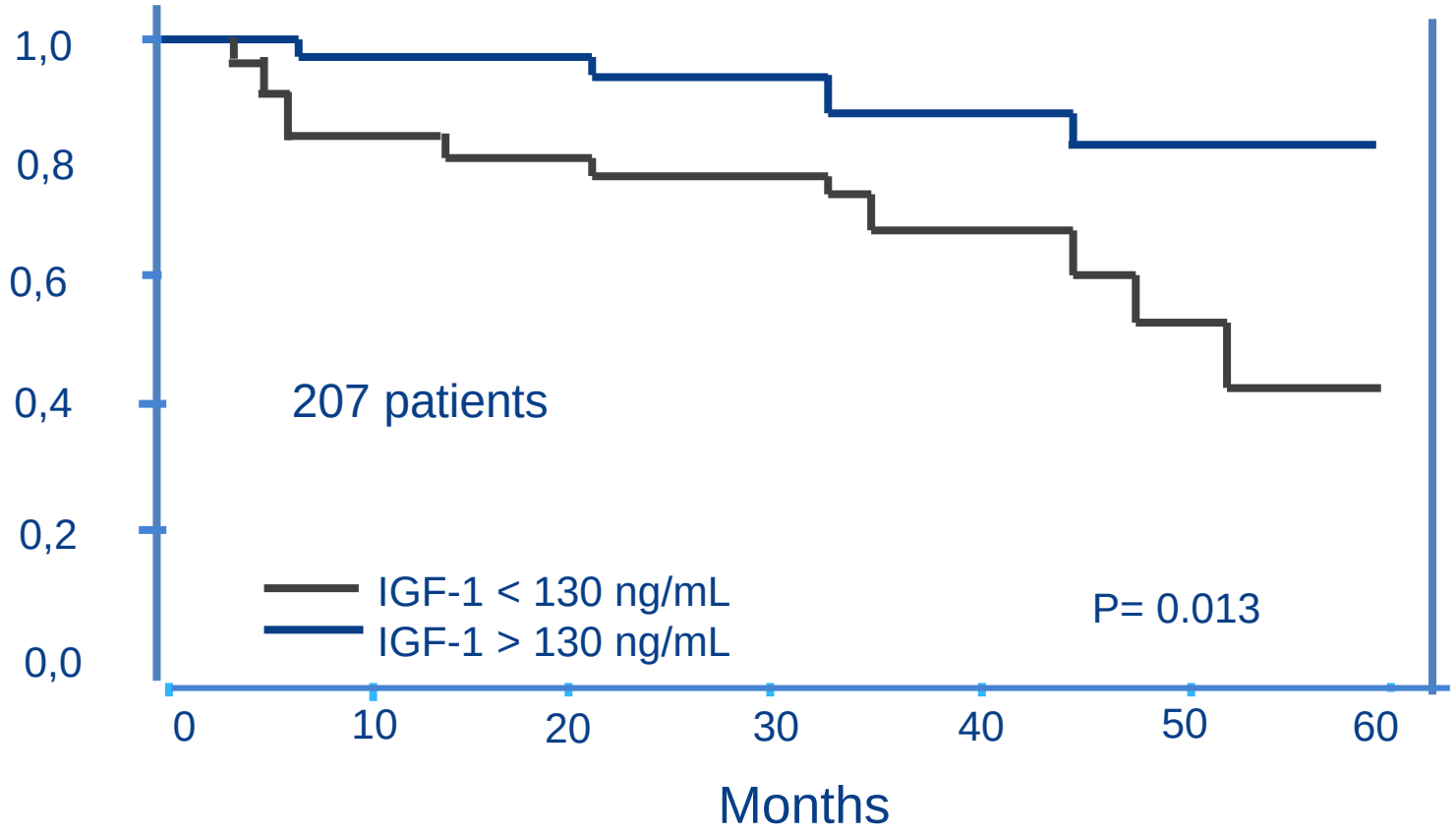


Participants with Congestive Heart Failure/Participants at Risk, *n/n*							
Serum IGF-I Level < 140 µg/L	0/361	6/323	14/290	18/277	25/256	31/228	37/143
Serum IGF-I Level ≥ 140 µg/L	0/356	3/336	4/303	9/290	13/272	14/261	19/158

Vasan et al, Ann Intern Med 2003

IGF-1 and survival in CHF

Cumulative survival



Cittadini A, Int J Cardiol 2014

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

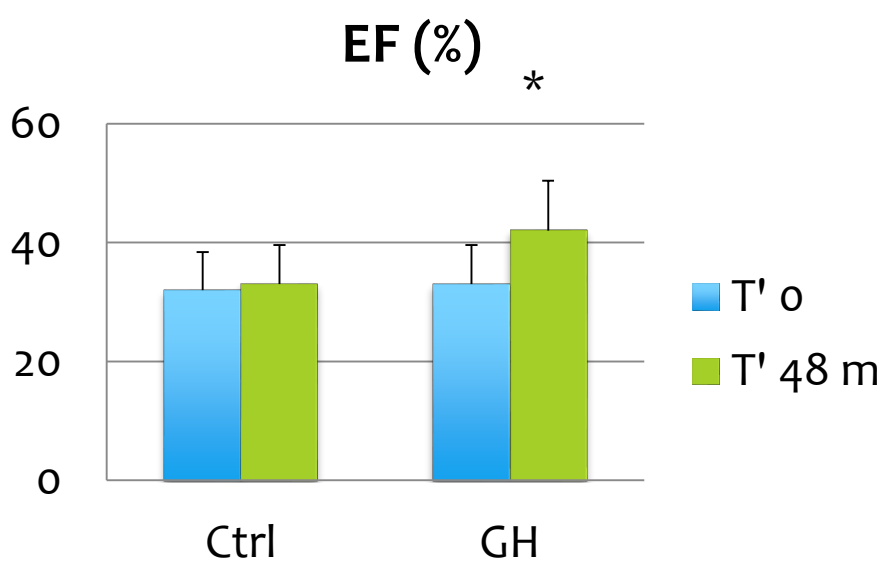
Growth Hormone Replacement Delays the Progression of Chronic Heart Failure Combined With Growth Hormone Deficiency

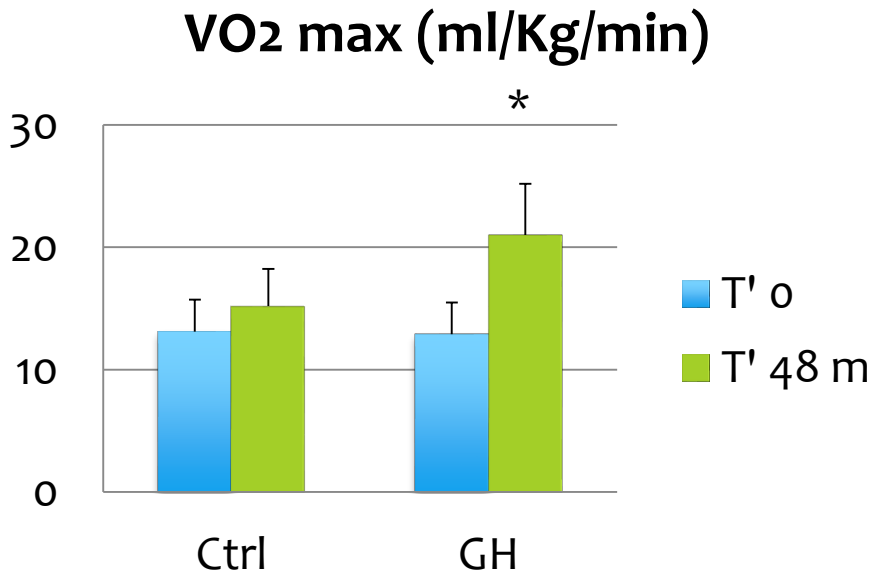
An Extension of a Randomized Controlled Single-Blind Study

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

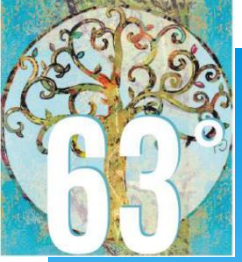




Cittadini A et al, 2013 JACC HF

Summary

1. Animal studies suggest that a reduction of the GH/IGF-I axis extends life span
2. On the other hand, epidemiological human data do not support this hypothesis
3. Hypopituitarism with uncorrected GH deficiency in humans is associated with increased cardiovascular morbidity and mortality
4. All explanations for this apparent discrepancy proved inconclusive
5. This is likely the results of the complexity of the GH/IGF-1 axis, the inhomogeneity of animal and human models of GH excess and deficiency, and of the broad variety of mechanisms involved in ageing



Unanswered questions

1. At what point in the lifespan and for what duration and magnitude would attenuating the GH/IGF-1 pathway impact aging?
2. Does an early decline in somatotropic hormones reflect premature aging or enhanced adaptation to and protection from the consequences of aging?
3. Are there organ systems in older adults that might suffer detrimental effects from reduced IGF-1 signaling?
4. How are these effects from reduced to differ between males and females?
5. Is it a reduction in GH, IGF-1, or both that is necessary to achieve these effects?
6. What is the contribution of environmental factors, such as nutrition, to the function of the somatotropic axis?

Milman Set al, 2016 Cell Metab

Conclusions

1. Although widely employed GH is NOT recommended as anti aging therapy
2. GH replacement therapy is safe and effective in GHD
3. Future basic studies focused on the attenuation of specific intracellular pathways depending on the GH/IGF-1 axis are eagerly awaited to unravel potential anti aging approaches

My team

Aristotelian Syllogism

1. Major premise: GH deficiency and low circulating IGF-1 levels are associated with increased cardiovascular morbidity and mortality
2. Minor premise: approximately 20-40% of CHF patients display GH deficiency and/or reduction of IGF-1 levels
3. Conclusion = 20-40% of CHF patients exhibit an "*excess* " cardiovascular mortality compared with non GH deficient CHF patients

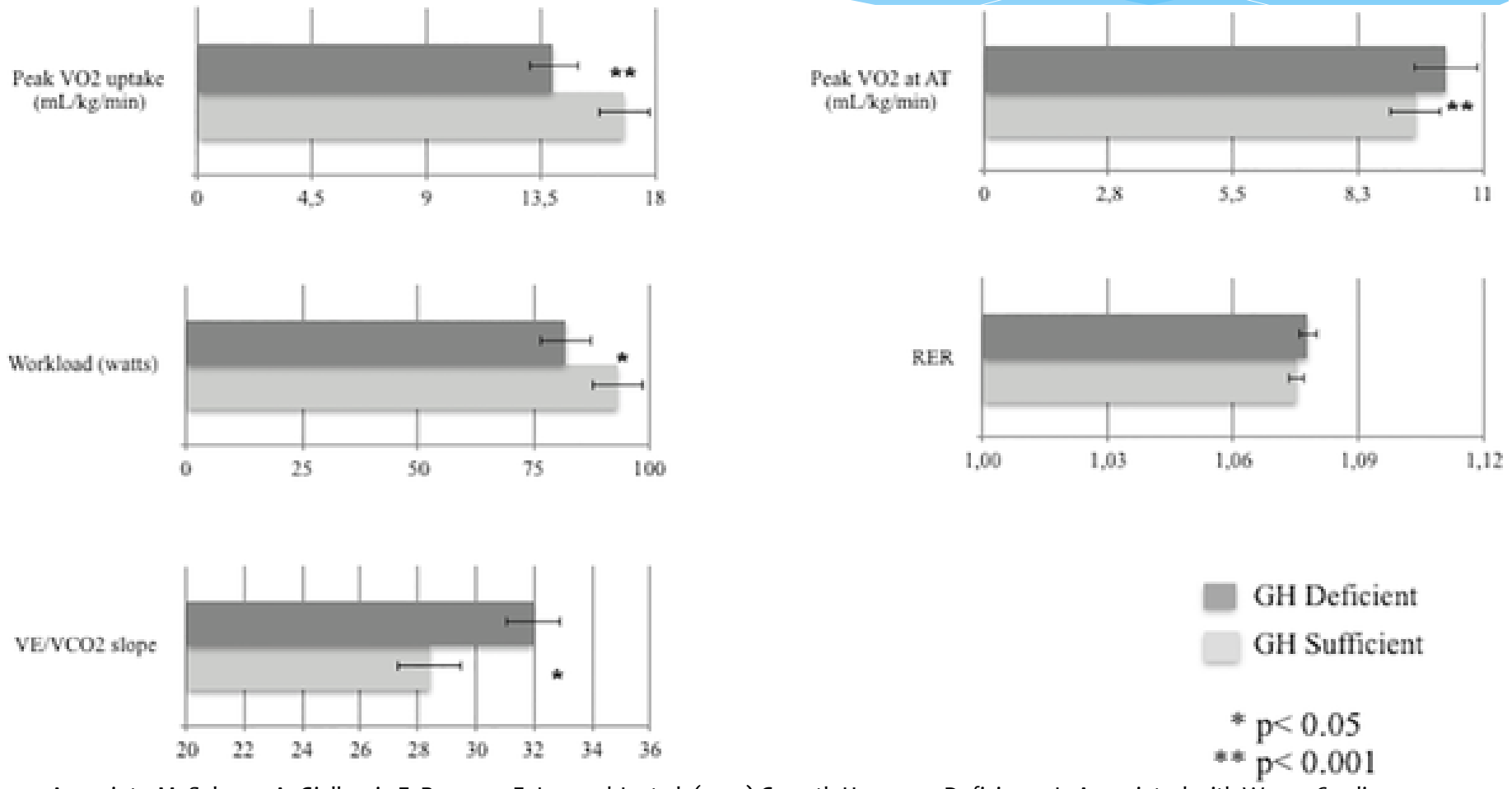
The New England Journal of Medicine

Volume 334 MARCH 28, 1996 Number 13

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

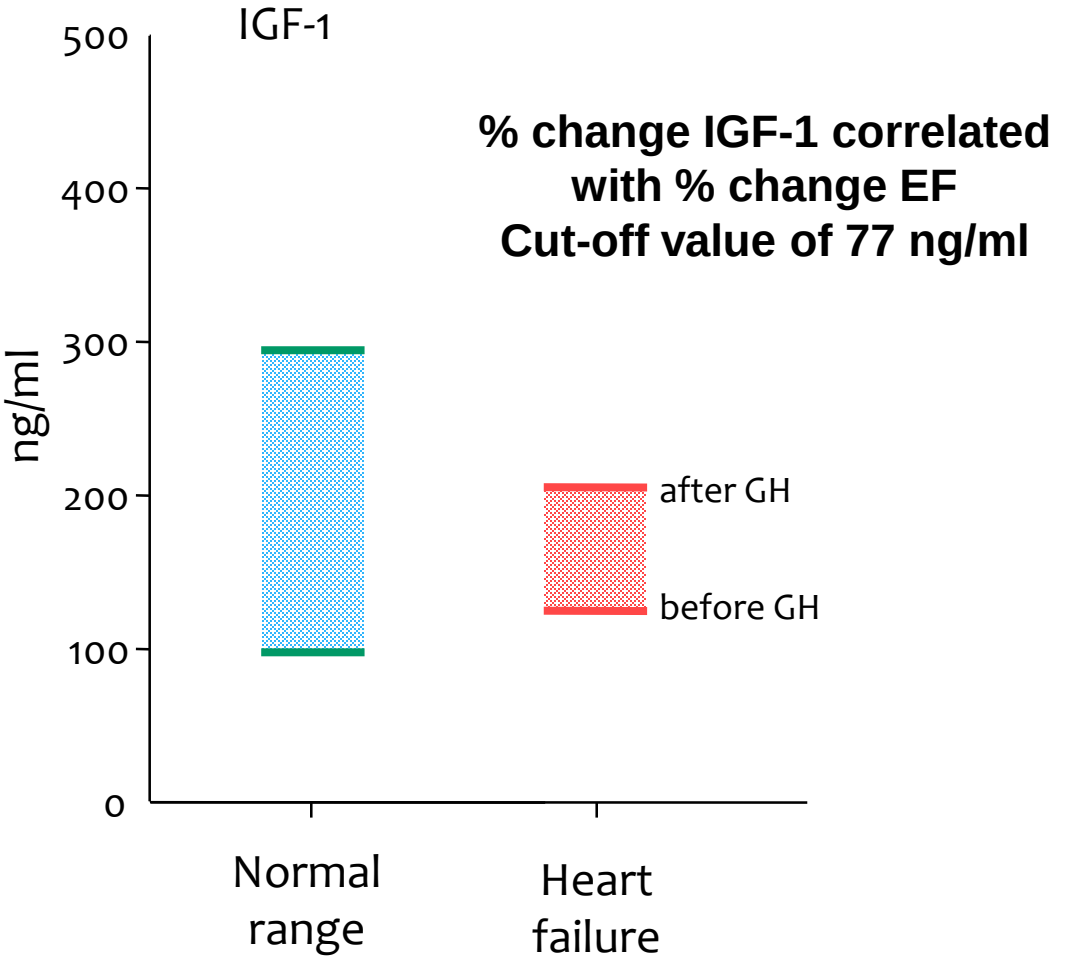
SERAFINO FAZIO, M.D., DOMENICO SABATINI, M.D., BRUNELLA CAPALDO, M.D., CARLO VIGORITO, M.D., ARTURO GIORDANO, M.D., RAFFAELE GUIDA, M.D., FRANCESCO PARDO, M.D., BERNADETTE BIONDI, M.D., AND LUIGI SACCÀ, M.D.

CPET parameters in GH sufficient and GH deficient patients with CHF



Arcopinto M, Salzano A, Giallauria F, Bossone E, Isgaard J, et al. (2017) Growth Hormone Deficiency Is Associated with Worse Cardiac Function, Physical Performance, and Outcome in Chronic Heart Failure: Insights from the T.O.S.CA. GHD Study. PLOS ONE 12(1): e0170058. https://doi.org/10.1371/journal.pone.0170058
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0170058

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

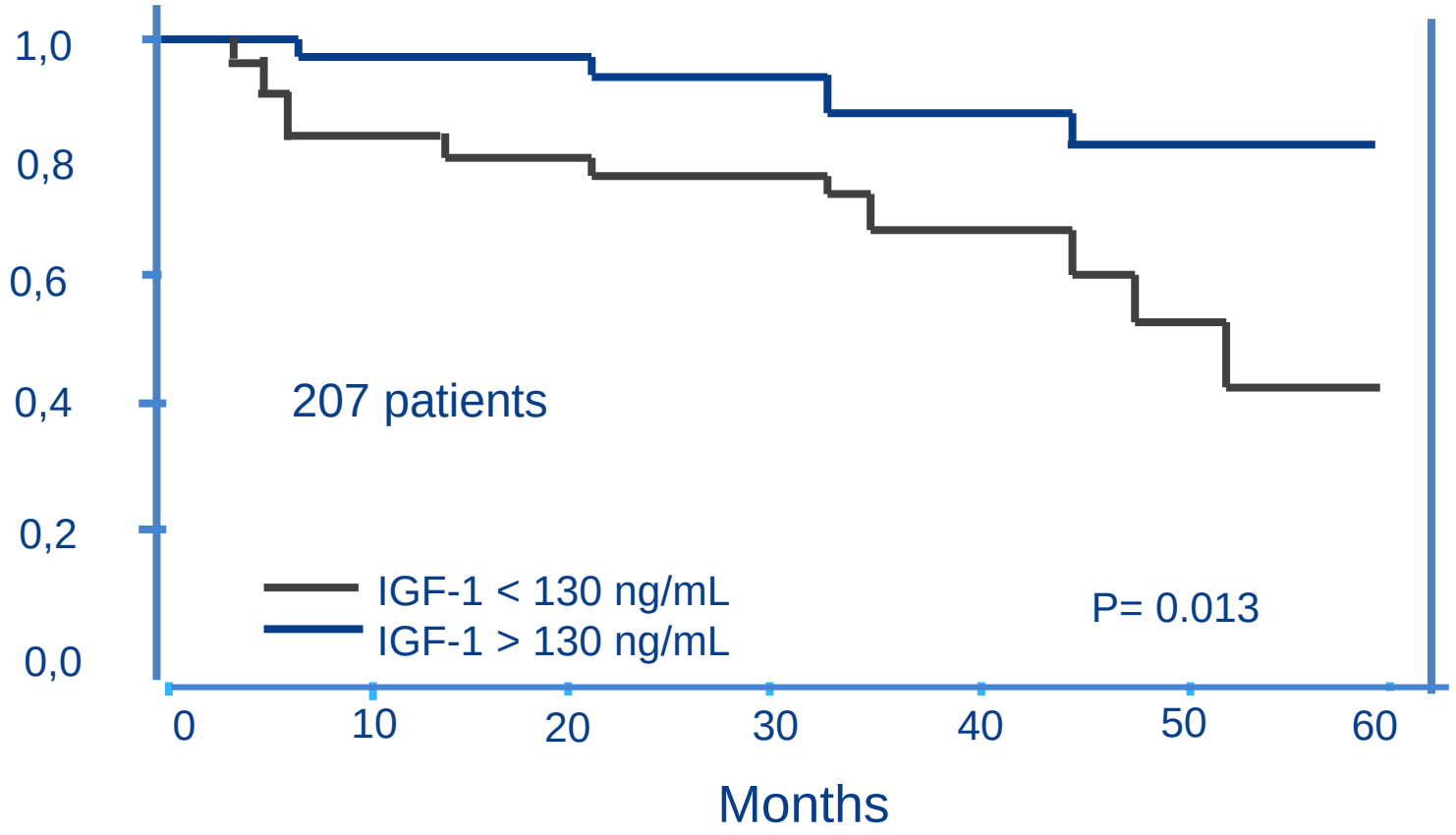


Osterziel et al., Lancet 1998

GRANT FOR GROWTH INNOVATION

IGF-1 and survival in CHF

Cumulative survival

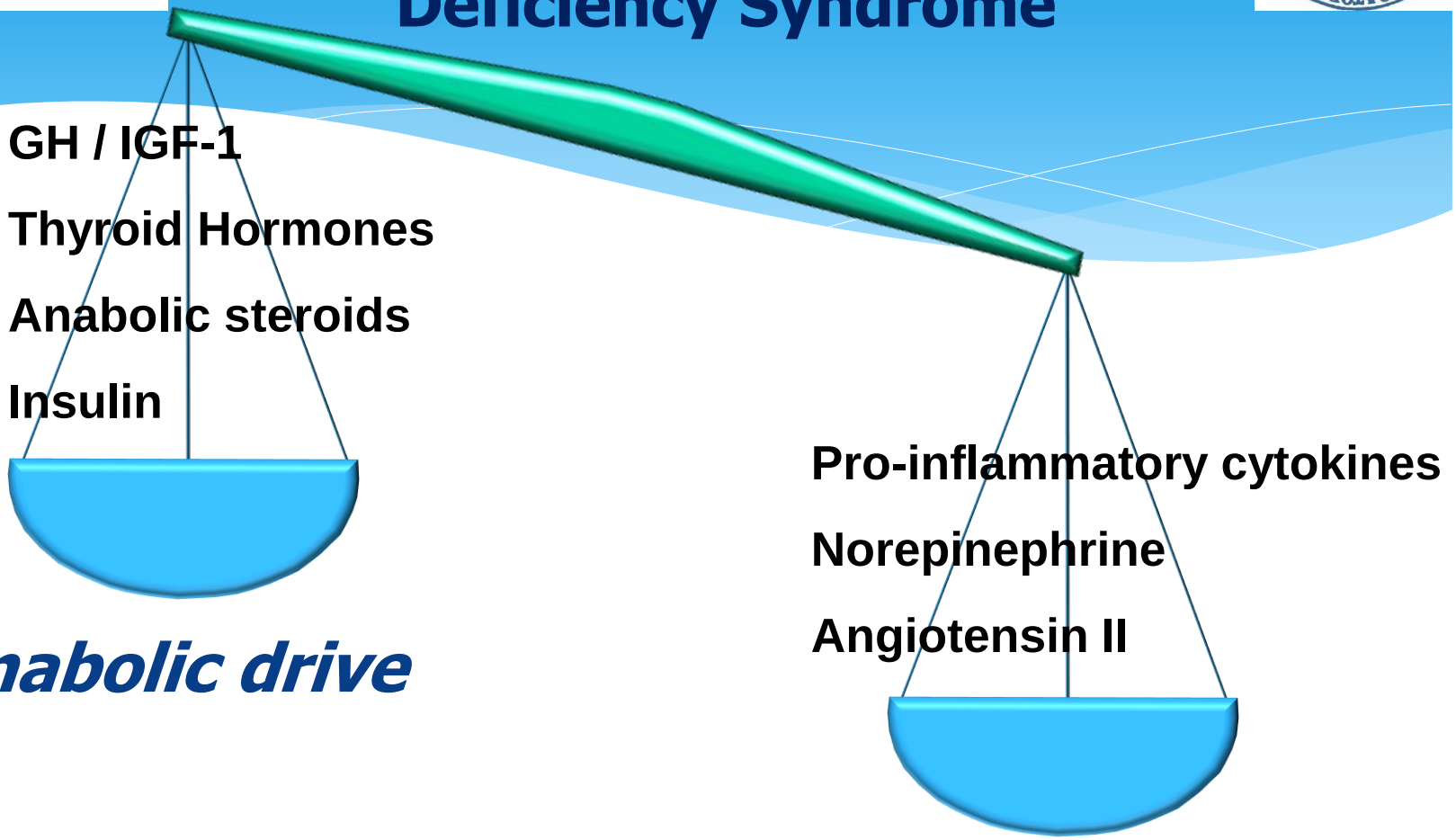


Cittadini A, Int J Cardiol 2014

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
Flow-mediated Vasodilation		X			X
Hand grip		X			X
Holter EKG 24 h		X			X

Paradigm shift: HF as a Multiple Hormonal Deficiency Syndrome



Saccà L, Circ Heart Fail 2009

Characteristics of GH-resistant and/or GH-deficient mice believed to contribute to their extended longevity

- Increased whole animal insulin sensitivity (40, 202)
- Mild hypoglycemia (43, 125)

Stress resistance and oxidative damage

- Cellular resistance to a variety of oxidative, cytotoxic and metabolic stresses (175, 253)
- Improved antioxidant defense mechanisms; reduced ROS production (49, 235)
- Greater capacity for xenobiotic metabolism (7)
- Reduced oxidative damage to macromolecules (49, 256)
- Reduced mutation rate (104)

Growth, tissue maintenance, and cancer

- Reduced hepatic IGF-I expression and circulating IGF-I levels (20, 340)
- Preserved local IGF-I signaling (including the brain and the heart) (200, 288)
- Reduced mTOR-mediated translation and cell size (40, 127, 265)
- Delayed onset and reduced severity of neoplastic disease (133, 134, 312)
- Delayed maturation; reduced adult body size (20, 147, 334)
- Improved maintenance of stem cells (246)
- Organ-specific alterations in apoptosis (106, 150)

Cardiovascular function

- Reduced blood pressure (179)
- Reduced cardiac extracellular collagen (127)
- Rheological advantages of reduced body size (254)

Other potential mechanisms

- Delayed immune system aging (100)
- Altered *N*-glycosylation (308)
- Altered profile of expression of multiple genes and micro RNAs (8, 25, 77, 211, 305)

GRANT FOR GROWTH INNOVATION

GGI

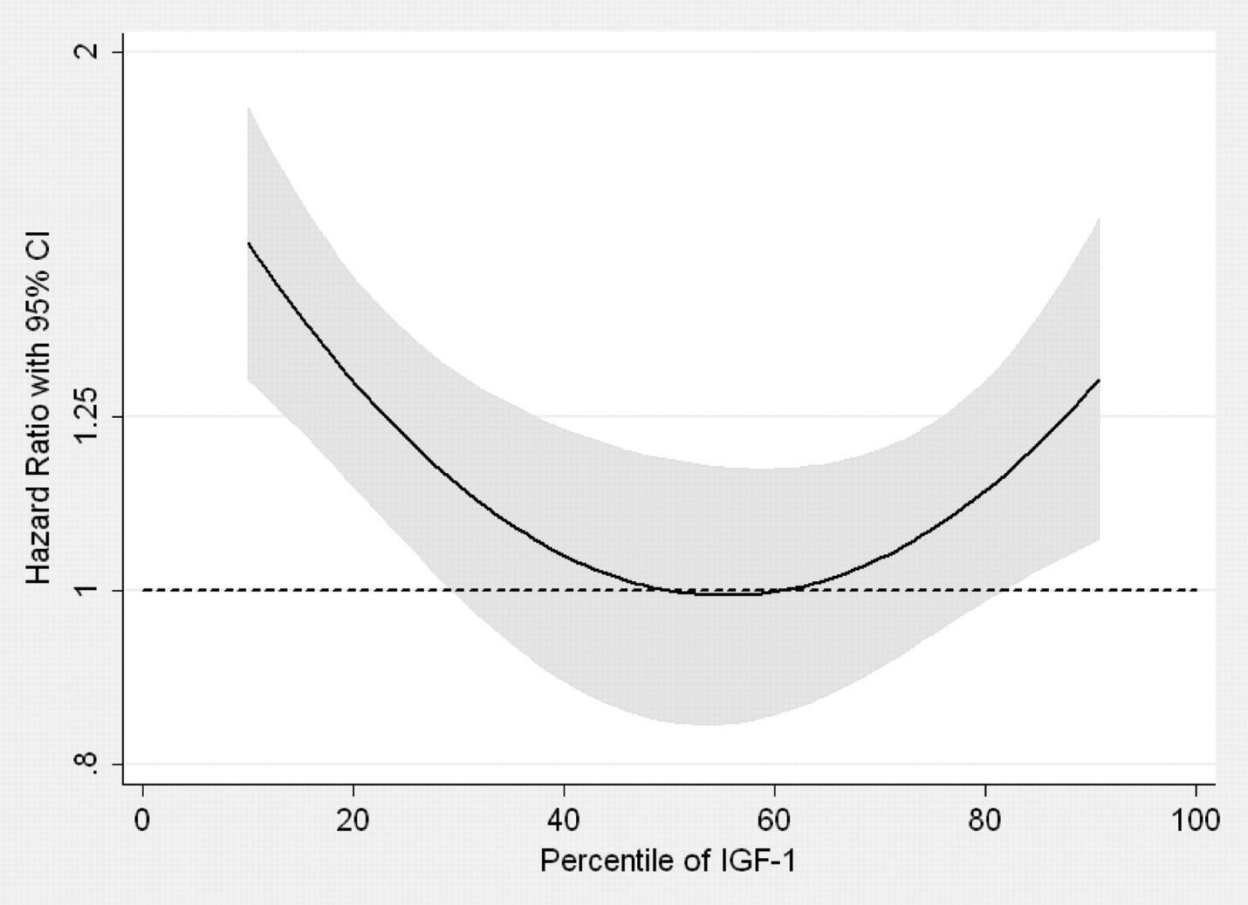
GH therapy in 147 patients with CHF

(*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

IGF-1 and mortality

(*meta-analysis and dose-response meta-regression*)



From: Meta-Analysis and Dose-Response Metaregression: Circulating Insulin-Like Growth Factor I (IGF-I) and Mortality

J Clin Endocrinol Metab. 2011;96(9):2912-2920. doi:10.1210/jc.2011-1377

Burgers AMG et al. , JCEM 2011

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Mild hypoglycemia

Delayed immune system aging

Stress resistance and oxidative damage

Cellular resistance to oxidative, cytotoxic, and metabolic stresses

Improved antioxidant defense mechanisms, ↓ ROS production

↑ Xenobiotic metabolism

↓ Oxidative damage to macromolecules

↓ Mutation rate

Growth, tissue maintenance, and cancer

↓ Hepatic IGF-1 production and circulating IGF-1 levels

Preserved local IGF-1 signaling

↓ mTOR-mediated translation and cell size

Delayed onset and reduced severity of neoplastic disease

Delayed maturation; reduced adult body size

Improved maintenance of stem cells

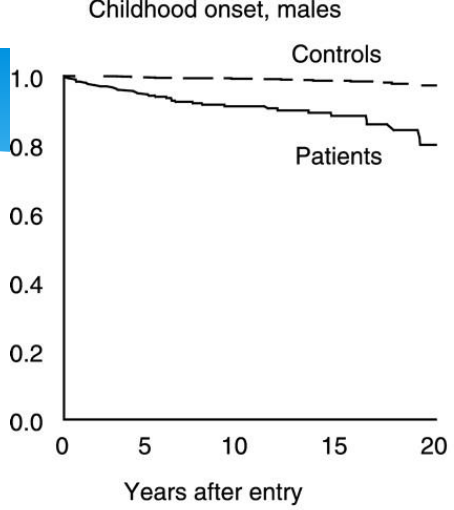
Organ specific alterations ion apoptosis

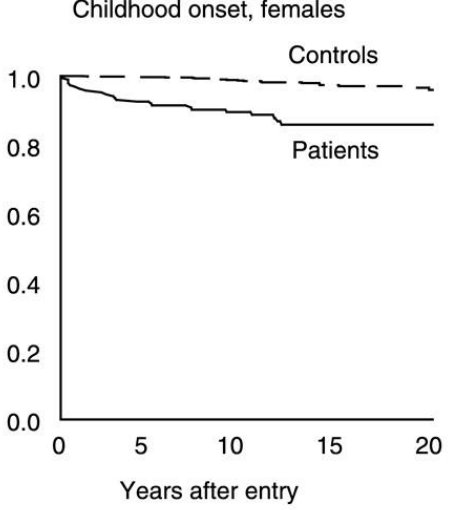
Cardiovascular function

↓ Blood pressure

↓ Cardiac extracellular collagen

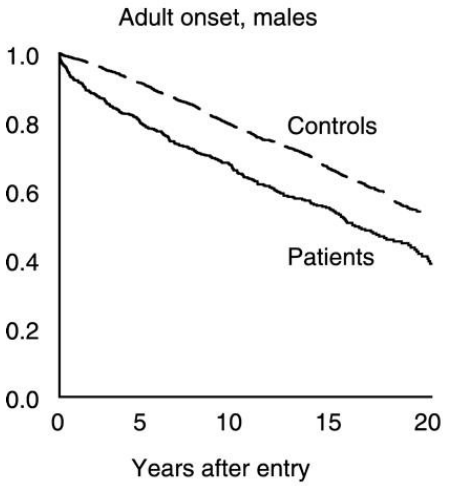
Rheological advantages of reduced body size

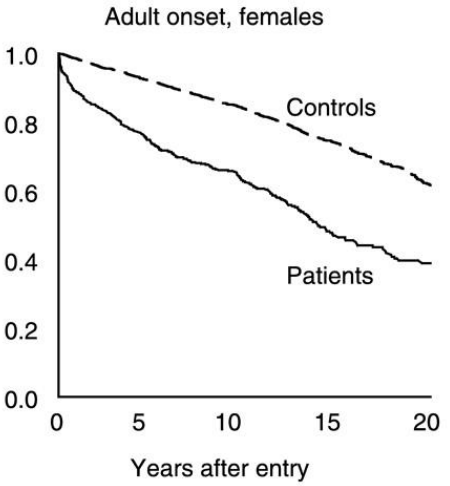




Number of patients/controls

299	269	179	97	32		187	169	117	60	25
1332	1279	881	491	178		872	848	597	334	159

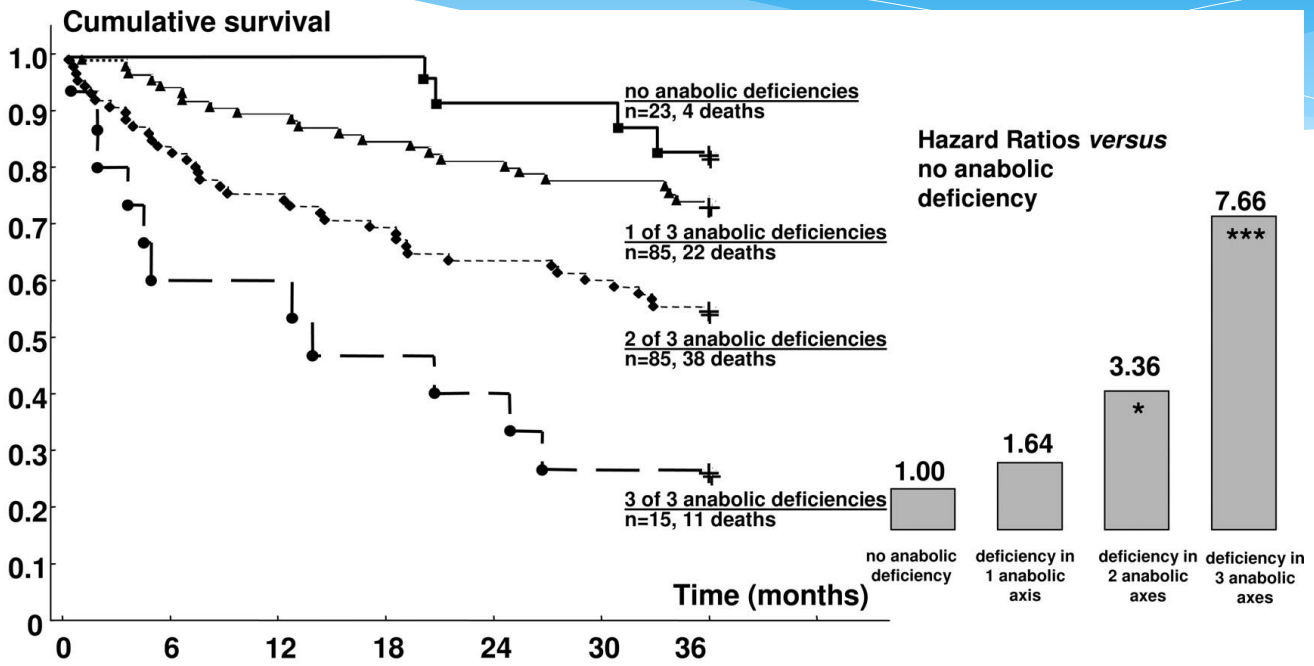




Number of patients/controls

732	550	302	160	54		576	412	244	106	48
3200	2748	1613	857	338		2610	2321	1526	836	387

CHF and Anabolic Deficiency

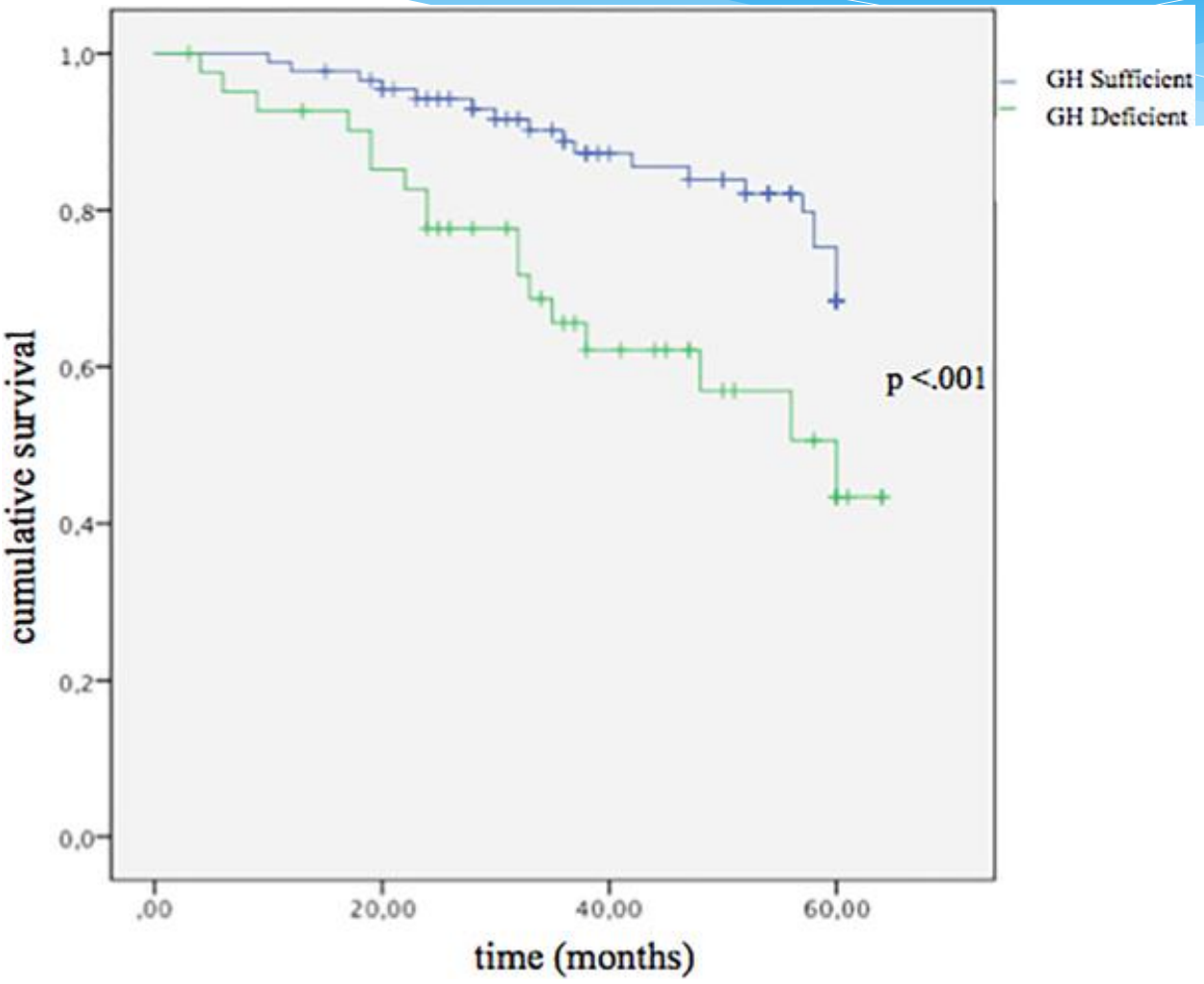


Men with no anabolic deficiency				
At risk	23	23	21	19
Deaths	–	0	2	4
Men with deficiency in 1 anabolic axis				
At risk	85	76	69	63
Deaths	–	9	16	22
Men with deficiency in 2 anabolic axes				
At risk	85	64	54	47
Deaths	–	21	31	38
Men with deficiency in 3 anabolic axes				
At risk	15	9	6	4
Deaths	–	6	9	11

Ewa A. Jankowska et al. Circulation. 2006;114:1829-1837

American Heart Association.

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



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