



Acromegalia e Comorbilità Cometa & Heart

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COMETA

COMORBIDITIES EVALUATION AND TREATMENT IN ACROMEGALY

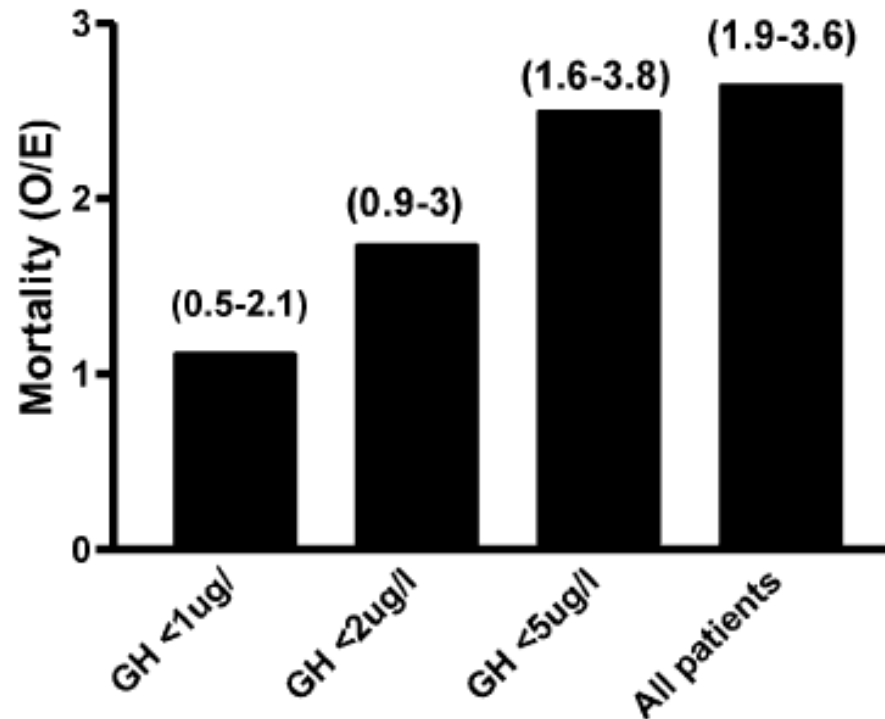
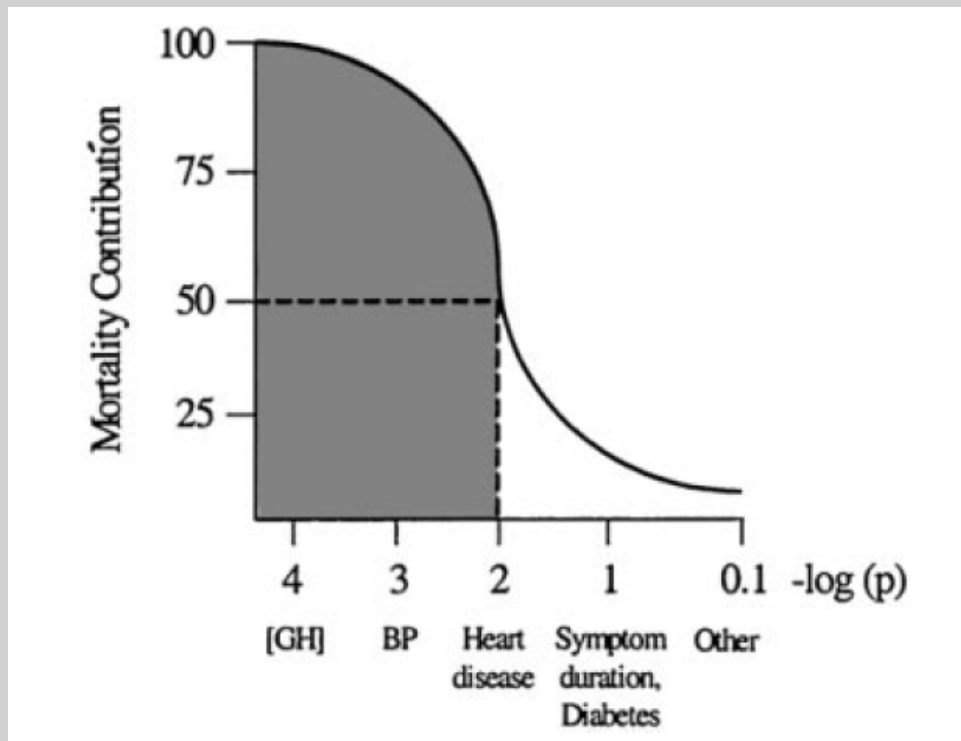


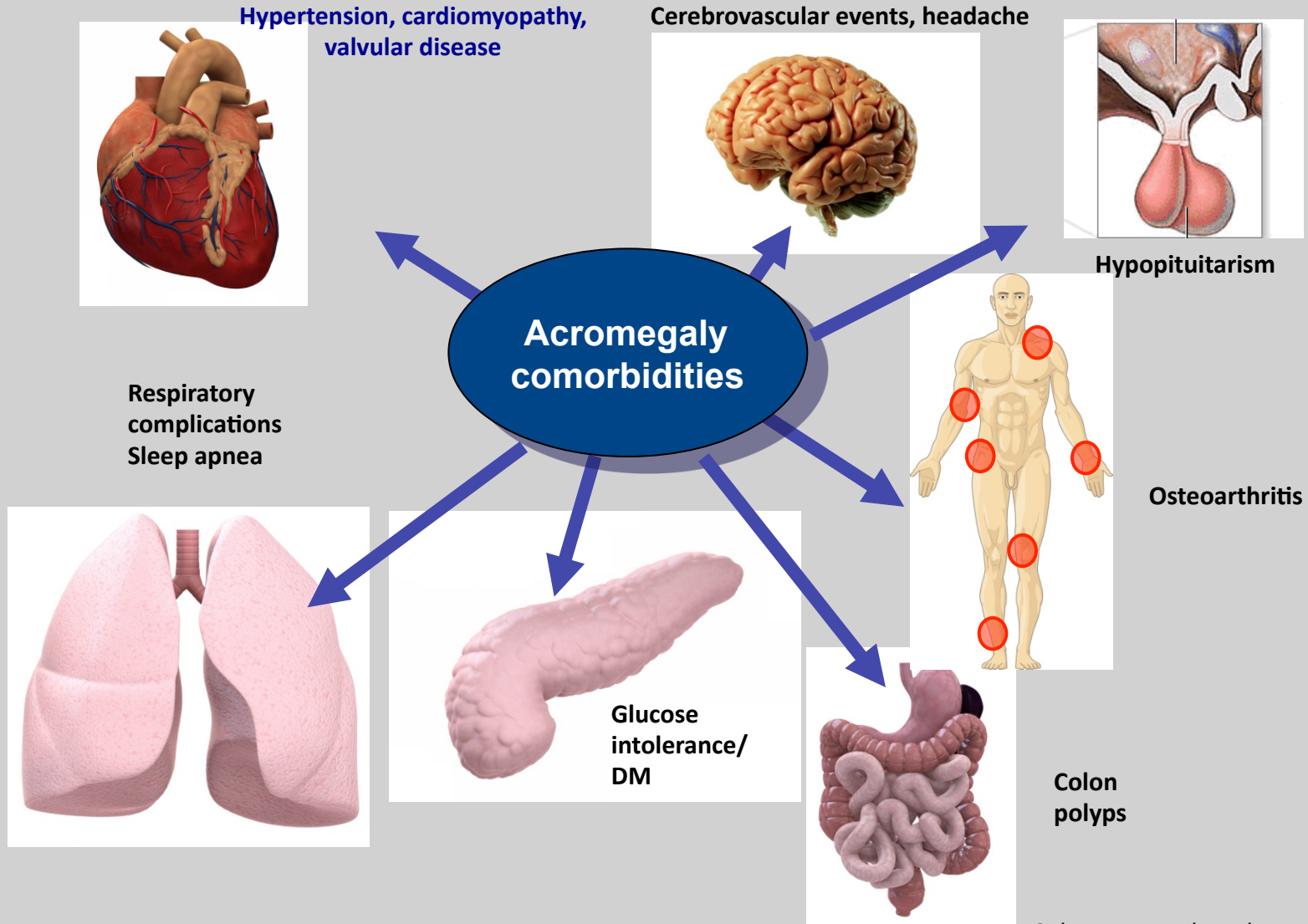
Fig. 1. Observed compared with expected mortality (with 95% CI values) in acromegalic patients according to last post-treatment serum growth hormone level [13].

Acromegalia & Mortalità

Acromegaly: outcome determinants			
Causes of death	%	Survival determinants	<i>P</i>
Cardiovascular	60	Last GH	<0.0001
Respiratory	25	Hypertension	<0.02
Malignancy	15	Cardiac disease	<0.03
		Diabetes	<0.03
		Symptom duration	<0.04



Background - comorbidità



➤ Riduzione mortalità

- To reduce mortality to general population levels
- Biochemical goal: control GH and/or IGF-I level
- Early diagnosis and prompt treatment

➤ Controllo massa tumorale

➤ Trattamento delle comorbidità

- Ipertensione, disfunzione cardiaca, diabete, osteoartriti, sleep apnea
- Gestite e monitorate rigorosamente come nella popolazione generale

Cardiomiopatia acromegalica

1. Il cuore esprime un elevato numero di recettori per il GH e IGF-I.
2. GH agisce direttamente a livello miocardico attivando l'espressione precoce dell' oncogene c-myc e di altri fattori di crescita.
3. GH stimola la trascrizione dell' mRNA per IGF-1 che a sua volta induce la crescita e l'aumento della contrattilità dei miociti e l'espressione di geni muscolo specifici.
4. La trascrizione dell' mRNA per IGF-1 è stimolata anche da meccanismi GH indipendenti (sovraccarico di pressione e di volume).

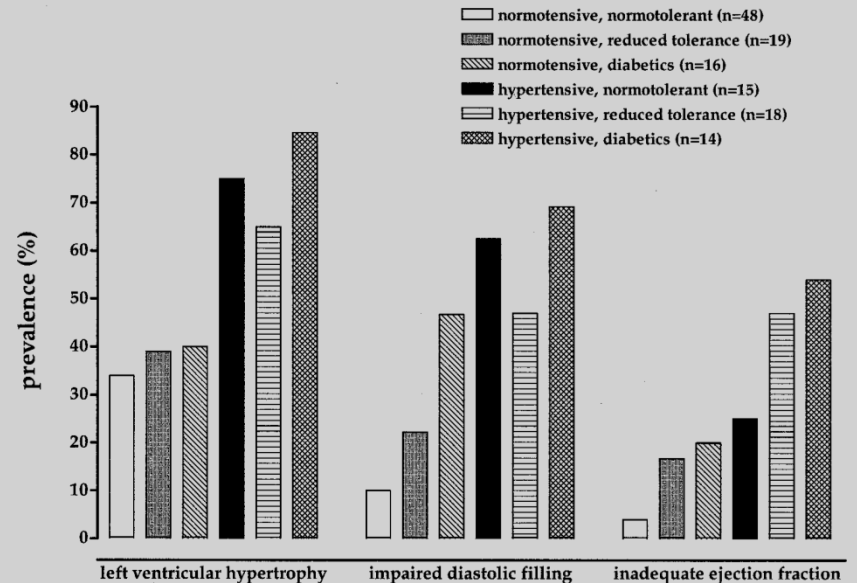
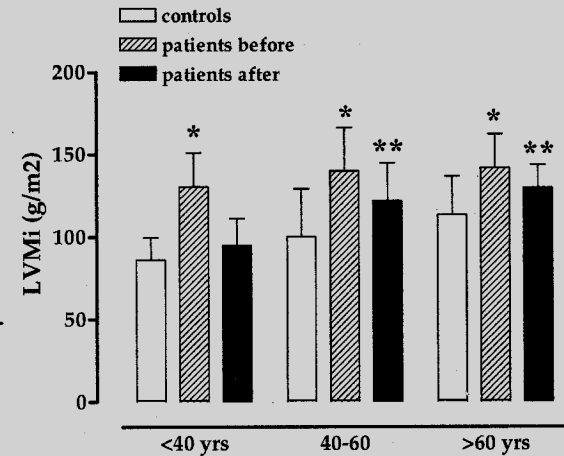
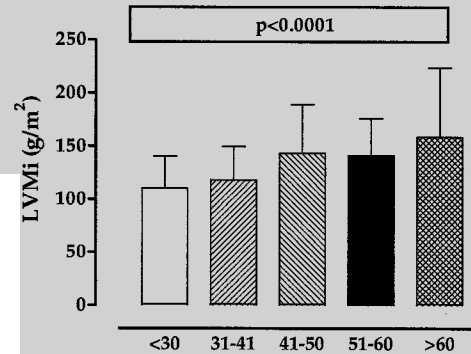
Correla
Con età e durata
di malattia

Ixtensione e/o DM
aumentano la prevalenza

E' presente anche

◆ in età giovanile

◆ in assenza di ixtensione e/o DM



- ❖ Battiti ectopici,
- ❖ FAP
- ❖ TPSV
- ❖ SSS
- ❖ TV
- ❖ Blocchi di branca

Più frequenti durante esercizio fisico

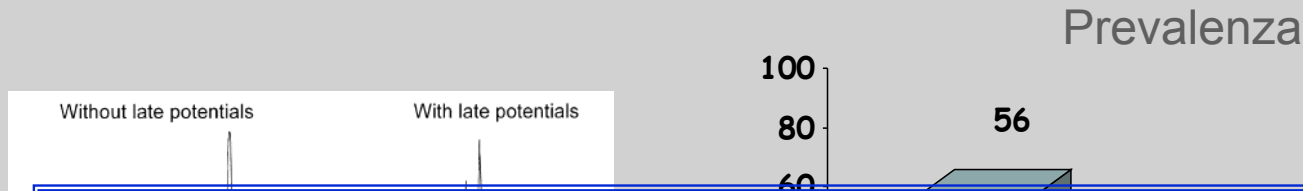
La guarigione ripristina la normalità?

**40% dei pazienti acromegalici
=
disturbi del ritmo**

Occurrence of ventricular late potentials in patients with active acromegaly

B. L. Herrmann*, C. Bruch†, B. Saller*, S. Ferdin*,
N. Dagres†, C. Ose‡, R. Erbel† and K. Mann*

Potenziali tardivi= fattore predittivo per aritmia

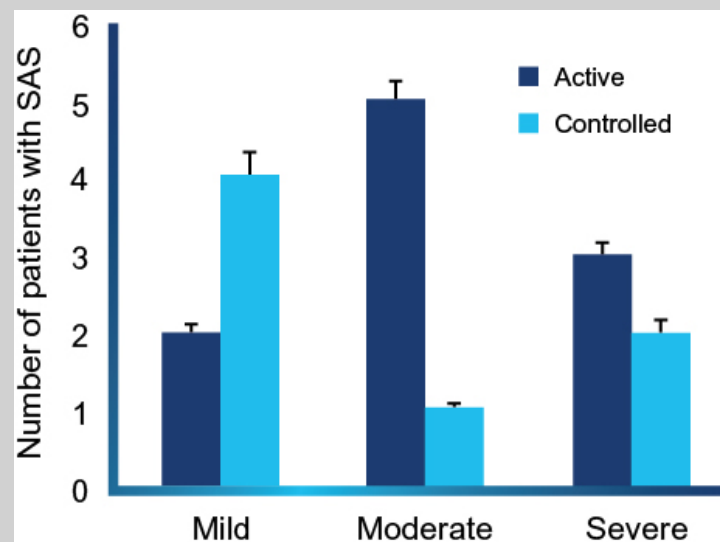


Late potentials were **not related** to **muscle mass index**.
The association of disease activity with the detection of late potentials **was independent** of **age, gender, duration** of the disease and **body mass index**

	Acromegaly	Controls	P
QRS duration (ms)	115 ± 11	109 ± 7	0.0027
RMS 40 (µV)	29 ± 15	42 ± 19	0.0002
LAS 40 (ms)	37 ± 8	30 ± 4	0.0004

- Sottostimata
 - Prevalenza superiore al 70%
- Tutti i pazienti necessitano attenta valutazione
 - Sintomi
 - Strumentali
- Necessaria una maggiore compliance per CPAP e altri dispositivi
- Consulenza maxillo-faciale?

Il miglioramento SAS è solo parzialmente dipendente dal compenso ormonale



Cardiopatia-CVD

Sindrome apnee notturne (SAS)

Diabete Mellito

Ossa e articolazioni

Poliposi intestinale

Qualità di vita (QoL)

Ipogonadismo/sexualità

Altro...



Roma,
settembre 2012

Assessment of the awareness and management of cardiovascular complications of acromegaly in Italy. The COM.E.T.A. (COMorbidity Evaluation and Treatment in Acromegaly) Study

A. Giustina¹, T. Mancini², P.F. Boscani³, E. de Menis⁴, E. degli Uberti⁵, E. Ghigo⁶, E. Martino⁷, F. Minuto⁸, and A. Colao⁹; for the COM.E.T.A. (COMorbidity Evaluation and Treatment in Acromegaly) Italian Study Group*

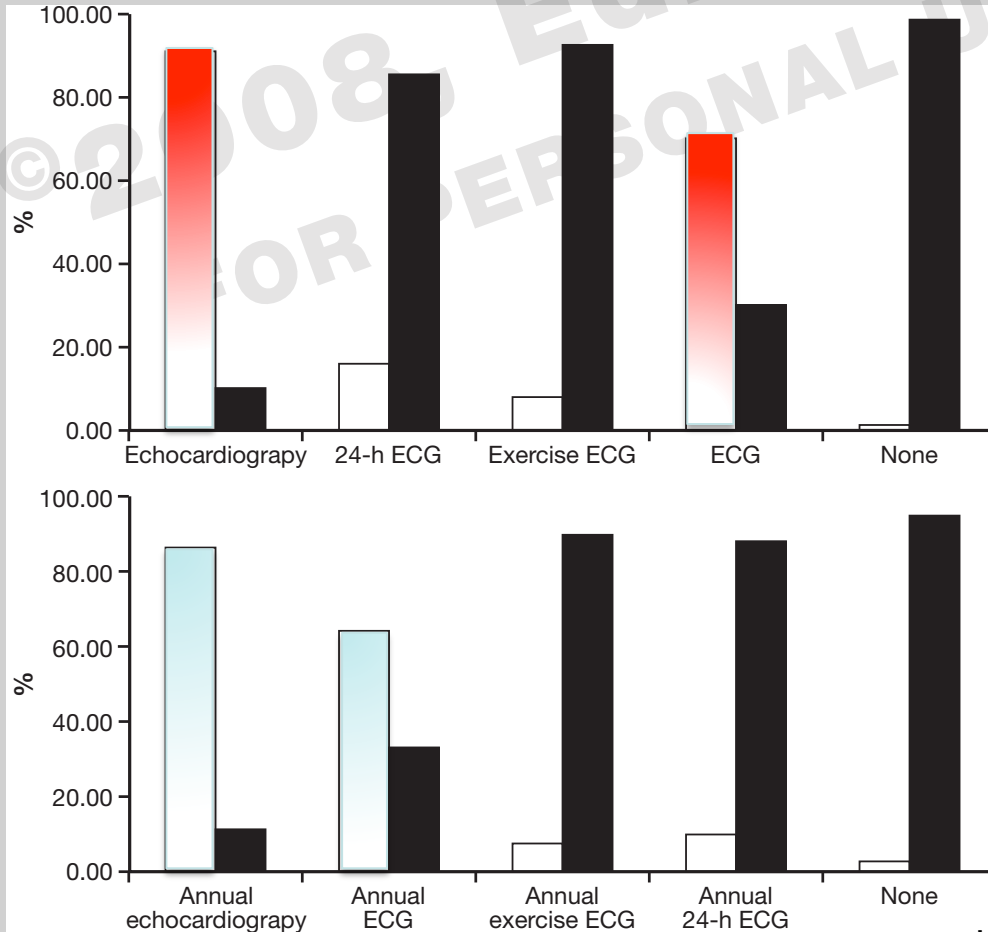
The aim of this work coordinated by the Italian Study group on co-morbidities evaluation and treatment in acromegaly (COM.E.T.A.) was **to assess**, on a national basis, the application in the clinical practice of the Versailles criteria for **diagnosis and treatment of cardiovascular comorbidities** in acromegaly



J. Endocrinol. Invest. 31: 731-738, 2008

Assessment of the awareness and management of cardiovascular complications of acromegaly in Italy. The COM.E.T.A. (COMorbidities Evaluation and Treatment in Acromegaly) Study

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Evaluation of acromegalic cardiomyopathy at diagnosis.

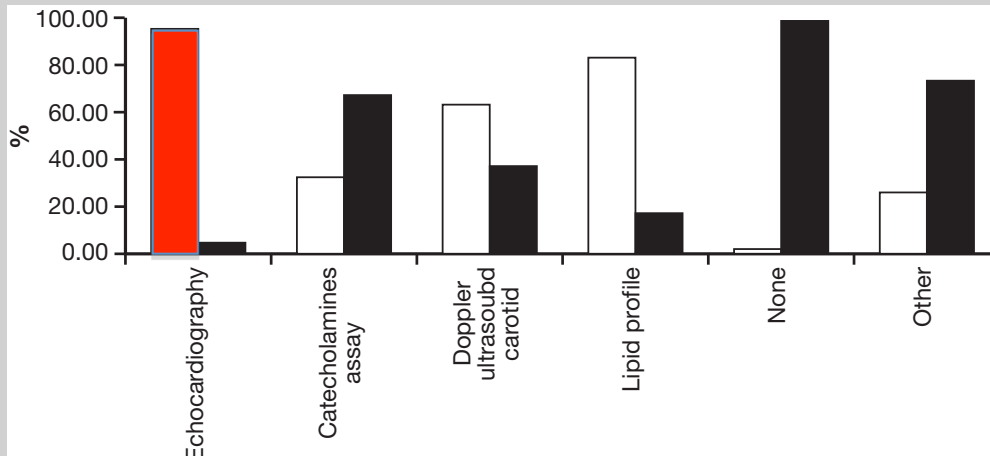
Black bars represent negative responses.

Evaluation of acromegalic cardiomyopathy during follow up.

Black bars represent negative responses. ECG: electrocardiogram.

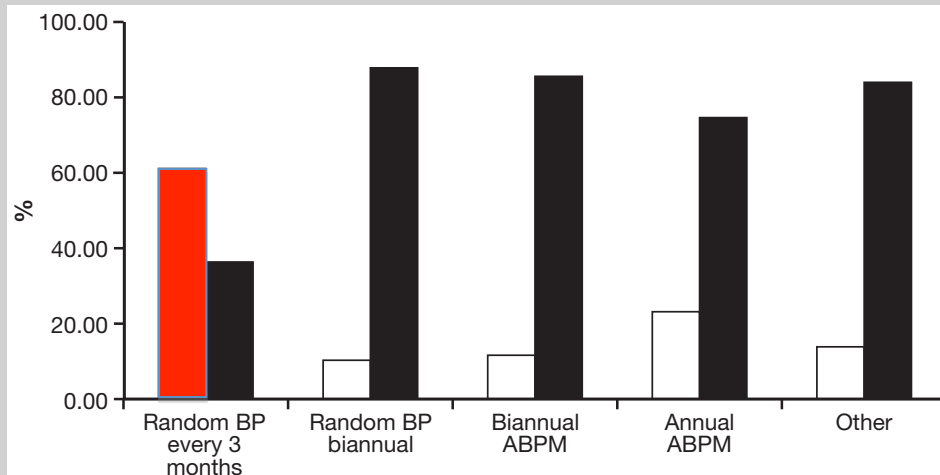
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Instrumental and laboratory assessments with acromegaly in hypertensive patients at diagnosis.

Black bars represent negative responses.



Instrumental assessments for the follow up of hypertension in acromegalic patients.

Black bars represent negative responses. BP: blood pressure; ABPM: ambulatory blood pressure monitoring.



In conclusion, the results of this national survey among Italian endocrinologists concerning the awareness and the management of cardiovascular complications in acromegaly suggest that available **international guidelines have been generally well perceived** and apparently translated into clinical practice. Specifically:

1. echocardiography is considered the **mainstay** for the diagnosis and follow-up of cardiovascular complications of acromegaly;

2. ABPM and blood lipid assessment are performed in most hypertensive acromegalic patients;

3. most endocrinologists directly manage hypertension in acromegaly and are aware of the uncertainty of the effect of the control of the GH/IGF-I axis on blood pressure levels;

4. ACE inhibitors and ARB are first choice anti-hypertensive treatment;

5. approximately half of the centers consider somatostatin analogs of paramount relevance for biochemical control of disease and of its cardiovascular comorbidities such as hypertension and left ventricular hypertrophy;

6. awareness that **left ventricular hypertrophy and heart failure** are the most relevant cardiovascular complications in acromegalic patients is high although the prognostic relevance of other cardiac complications (ischemic, arrhythmic, and valvular) is less well perceived.

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Assessment of the awareness and management of sleep apnea syndrome in acromegaly. The COM.E.TA (Comorbidities Evaluation and Treatment in Acromegaly) Italian Study Group

E. De Menis¹, A. Giustina², A. Colao³, E. Degli Uberti⁴, E. Ghigo⁵, F. Minuto⁶, F. Bogazzi⁷, R. Drigo⁸, A. Cattaneo⁹, and G. Aimaretti¹⁰; for the COM.E.T.A. (COMorbidities Evaluation and Treatment in Acromegaly) Italian Study Group*

The aim of this second national investigation was to assess among Italian Endocrine Centers **the awareness**, the **diagnostic tools and treatment of SAS** in acromegaly and to compare the results to international guidelines



Assessment of the awareness and management of sleep apnea syndrome in acromegaly. The COM.E.TA (Comorbidities Evaluation and Treatment in Acromegaly) Italian Study Group

E. De Menis¹, A. Giustina², A. Colao³, E. Degli Uberti⁴, E. Ghigo⁵, F. Minuto⁶, F. Bogazzi⁷, R. Drigo⁸, A. Cattaneo⁹, and G. Aimaretti¹⁰; for the COM.E.T.A. (COMorbidities Evaluation and Treatment in Acromegaly) Italian Study Group*

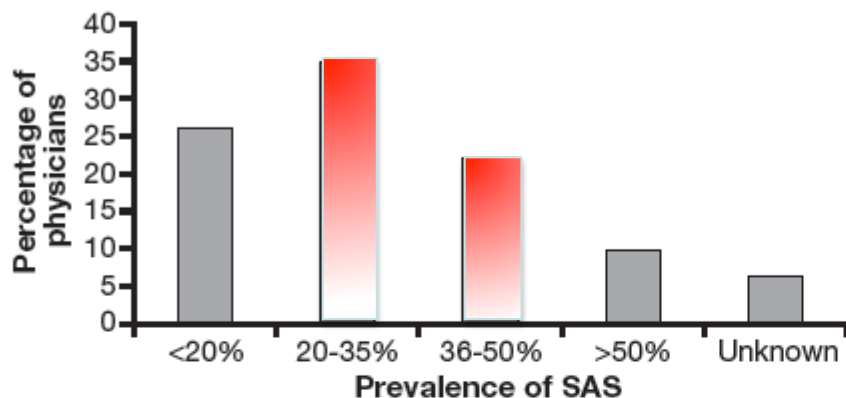


Fig. 1 - Physicians' estimated prevalence of sleep apnea syndrome (SAS) in acromegalic patients.

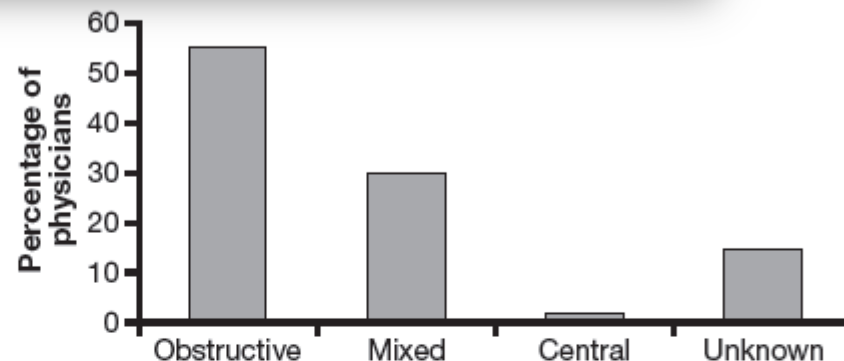


Fig. 2 - Type of sleep apnea syndrome (SAS).

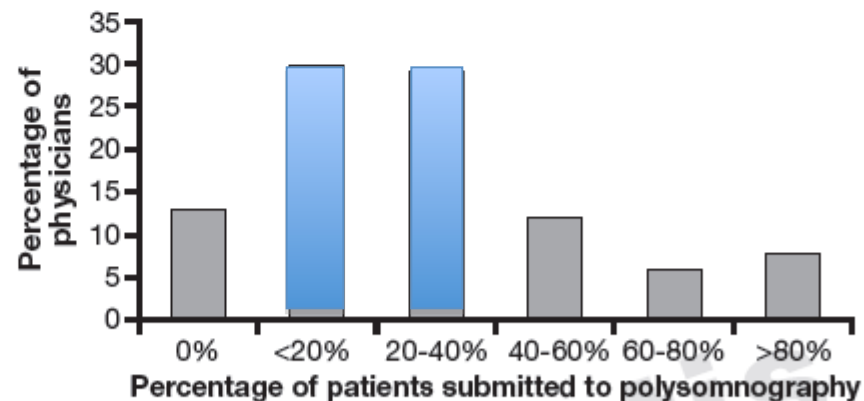


Fig. 3 - Percentage of patients who were reported to be submitted to polysomnography.

Assessment of the awareness and management of sleep apnea syndrome in acromegaly. The COM.E.TA (Comorbidities Evaluation and Treatment in Acromegaly) Italian Study Group

E. De Menis¹, A. Giustina², A. Colao³, E. Degli Uberti⁴, E. Ghigo⁵, F. Minuto⁶, F. Bogazzi⁷, R. Drigo⁸, A. Cattaneo⁹, and G. Aimaretti¹⁰; for the COM.E.T.A. (COMorbidities Evaluation and Treatment in Acromegaly) Italian Study Group*

- 1) Most centers manage directly acromegalic patients but **diagnosis and treatment of SAS** is performed in **collaboration** with other specialists
- 2) SAS is believed to be a **frequent complication** of acromegaly and **PSG** is considered the **best diagnostic tool** but **only few patients undergo** this evaluation in clinical practice
- 3) **Treatment of SAS** is considered **central** for improvement of other acromegalic co-morbidities, i.e. hypertension and arrhythmias
- 4) **GH/IGF-I** normalization is thought **to decrease the severity** of SAS
- 5) **C-PAP** is the **treatment of choice** of SAS



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E. De Menis¹, A. Giustina², A. Colao³, E. Degli Uberti⁴, E. Ghigo⁵, F. Minuto⁶, F. Bogazzi⁷, R. Drigo⁸, A. Cattaneo⁹, and G. Aimaretti¹⁰; for the COM.E.T.A. (COMorbidities Evaluation and Treatment in Acromegaly) Italian Study Group*

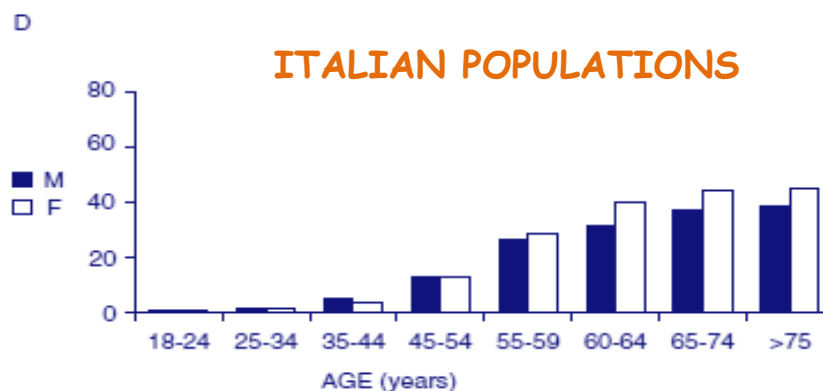
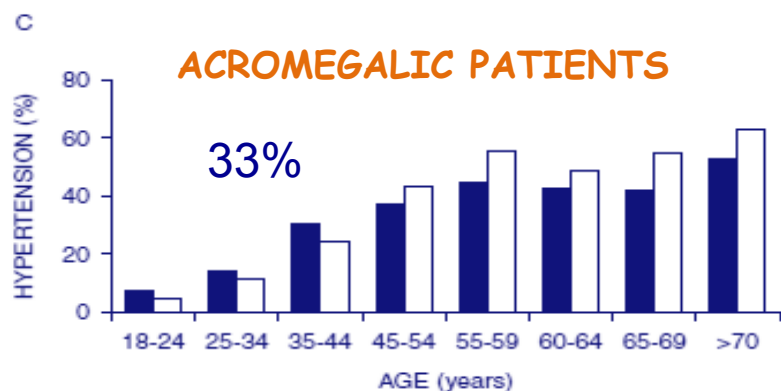
Our survey shows that Italian endocrinologists underestimate the frequency of SAS and patients are quite often evaluated for SAS only in the presence of overt clinical symptoms. PSG and specialist consultation are considered the gold standard for diagnosis, but only few patients actually undergo PSG. SAS treatment is considered substantial for improvement of some acromegalic comorbidities and QoL. GH/IGF-I control improves SAS and, if SAS persists, C-PAP is the cornerstone of therapy. In conclusion strategies to improve awareness of SAS in acromegaly among endocrinologists are needed as well as involvement of sleep specialists. This may lead to a better outcome of this complication using cost-effective diagnostic tools and increasing adherence of patients to specific therapy.

Table 1. Prevalence of hypertension in acromegaly

Authors	Reference	N patients	Hypertensive patients		Age (yr)	
			N	(%)	Range	(Mean)
Gordon et al. (1962)	[11]	100	18	18	–	–
McGuffin et al. (1974)	[12]	57	13	23	30–75	(47)
Wass et al. (1977)	[13]	73	29	40	18–72	–
Jadresic et al. (1982)	[14]	155	49	32	–	(44.5)
Nabarro (1987)	[2]	256	78	30.5	–	–
Rodrigues et al. (1989)	[15]	34	9	26	35–72	(56)
Kraatz et al. (1990)	[16]	158	49	31	–	(51)
Molitch (1992)	[17]	639	147	23	–	–
Ezzat et al. (1994)	[18]	500	255	51	7–77	(46)
Rajaasooriya et al. (1994)	[4]	151	49	32.5	3–75	(41)
Ohtsuka et al. (1995)	[19]	64	24	37.5	–	(48)
Lopez-Velasco et al. (1997)	[20]	39	13	33.3	24–74	(50)
Minniti et al. (1998)	[21]	40	17	42.5	27–70	(48.6)
Colao et al. (2000)	[22]	130	46	35.4	17–80	(48)
Weiss et al. (2000)	[23]	55	21	38.2	22–67	(50.7)
Pietrobelli et al. (2001)	[24]	25	14	56	23–72	(47)
Jaffrain-Rea et al. (2001)	[25]	65	33	51.5	–	(47.5)
Otsuki et al. (2001)	[26]	21	12	57	22–68	(52)
Total		2562	876	34.2		

Predictors of morbidity and mortality in acromegaly: an Italian survey

M Arosio, G Reimondo¹, E Malchiodi², P Berchiolla³, A Borraccino³, L De Marinis⁴, R Pivonello⁵, S Grottoli⁶, M Losa⁷, S Cannavò⁸, F Minuto⁹, M Montini¹⁰, M Bondanelli¹¹, E De Menis¹², C Martini¹³, G Angeletti¹⁴, A Velardo¹⁵, A Peri¹⁶, M Faustini-Fustini¹⁷, P Tita¹⁸, F Pigliaru¹⁹, G Borretta²⁰, C Scaroni²¹, N Bazzoni²², A Bianchi⁴, M Appetecchia²³, F Cavagnini²⁴, G Lombardi⁵, E Ghigo⁶, P Beck-Peccoz², A Colao⁵ and M Terzolo¹ for the Italian Study Group of Acromegaly*



A Consensus on Criteria for Cure of Acromegaly

A. Giustina, P. Chanson, M. D. Bronstein, A. Klibanski, S. Lamberts, F. F. Casanueva, P. Trainer, E. Ghigo, K. Ho and S. Melmed

J. Clin. Endocrinol. Metab. 2010 95:3141-3148 originally published online Apr 21, 2010; , doi: 10.1210/jc.2009-2670

Optimal control of comorbidities should be achieved with the most effective treatments for **both acromegaly and the specific comorbidities (SR)** (45, 59–61).

Cardiovascular disease, hypertension, diabetes, sleep apnea, and arthralgia are all improved, although only partial regression may occur, in patients with normalized GH levels (MQ) (59, 62). **Cardiovascular risk factors** should be actively **identified and treated (SR)** (52).

Obstructive sleep apnea is a comorbidity that may occur in 25–60% of patients. Sleep quality and disturbances in patients with acromegaly require detailed assessment and appropriate referral for management (SR) (63).

Hypertension in acromegaly and in the normal population: prevalence and determinants

Giovanni Vitale, Rosario Pivonello, Renata S. Auriemma, Ermelinda Guerra, Francesco Milone, Silvia Savastano, Gaetano Lombardi and Annamaria Colao

Clin Endo 2005

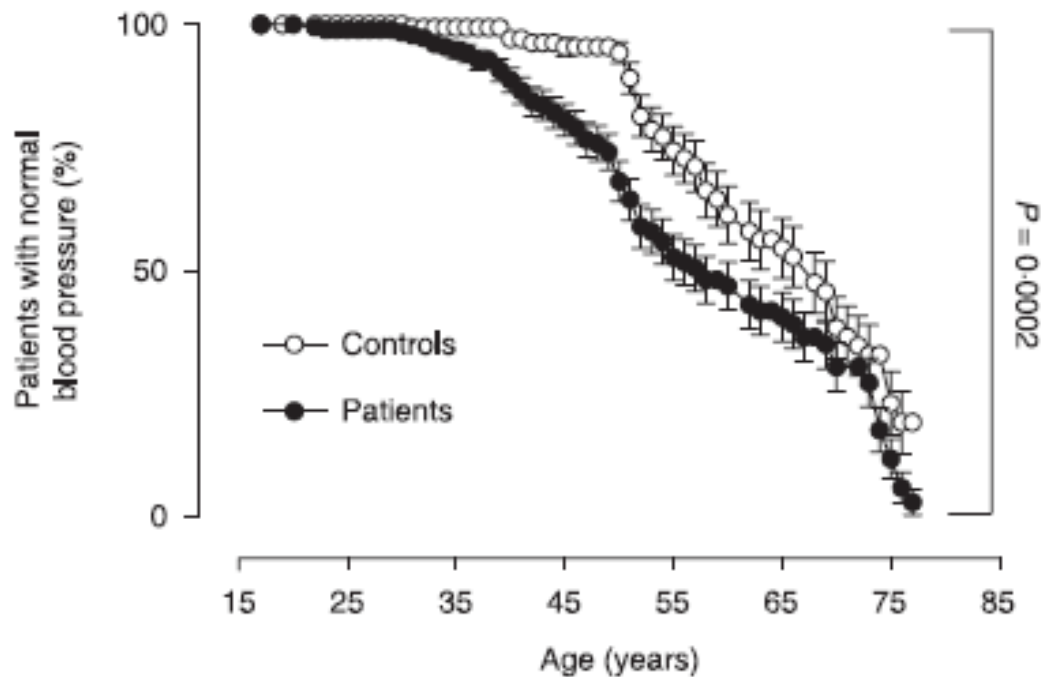


Fig. 3 The risk of developing hypertension according to age in the 200 patients with acromegaly and in the 200 controls. The hazard ratio for hypertension in patients with acromegaly was 1.9 (95% CI 1.4–2.7).

HR ixtensione
in
acromegalia
=
1.9

Possibili fattori patogenetici coinvolti nello sviluppo dell'ipertensione nell'acromegalia

-
- Expansion of plasma volume
(GH/IGF-I system on the kidney)
 - Reduced ANP secretion
 - Hyperinsulinaemia
 - Sympathetic system hyperactivity
 - Cardiac hyperkinesia
 - GH and IGF-I as cardiovascular growth factors
-

Misurazione pressoria rilevazione random vs ABPM

BP value	Clinical BP	24-h-BP	Daytime BP	Nighttime BP
SBP (mmHg)	136.1±16.3	131.1±21.5	137.8 ± 20.9	118 ± 23.2
DBP (mmHg)	88.8 ± 8.1	74.6± 10.6	78.6 ± 11.5	66.7± 10.9

Prevalenza ipertensione 42 % (clinical BP) vs 17 % (ABPM)

Protocollo di studio

Effetti del controllo della secrezione di GH e di IGF-I sulla pressione arteriosa e sul ritmo cardiaco in pazienti con acromegalia attiva



Obiettivo primario:

Valutare in pazienti con **acromegalia attiva** gli effetti della secrezione di GH e IGF-I **sulla pressione arteriosa** dopo **24±2 settimane** di dosi titolate di **lanreotide Autogel 120 mg** secondo la programmazione di trattamento individualizzato per ogni singolo paziente.



Obiettivi secondari:

Valutare in pazienti con acromegalia attiva in terapia a dosi titolate di lanreotide Autogel 120 mg:

- 1) gli effetti della secrezione di GH e IGF-I **sulla pressione arteriosa** dopo **50±2 settimane**.
- 2) gli effetti del controllo della secrezione di GH e IGF-I sul **ritmo e sull'ipertrofia cardiaca**.
- 3) la percentuale di **pazienti ben controllati** dopo 50±2 settimane di trattamento
- 4) il numero di pazienti che richiedono **variazione della terapia antipertensiva** per incremento o riduzione dei valori pressori a 24±2 e 50±2 settimane.
- 5) cambiamenti della **qualità di vita** (AcroQoL).
- 6) **il grado di soddisfazione** del paziente alla terapia medica.
- 7) i **costi del trattamento** con SSA e farmaci antipertensivi.

Lo studio multicentrico, aperto, con un singolo braccio

Centri coinvolti n. 24
Centri attivi n. 11



- 1) Monitoraggio ambulatoriale 24 ore della pressione arteriosa (ABPM); *riduzione di almeno 4 mmHg di pressione arteriosa rispetto al basale rappresenta l'end-point principale di efficacia*
- 2) Holter ECG 24 ore
- 3) Ecocardiogramma (IVsx)
- 4) GH < 2.5 ng/ml; IGF-I di norma x età
- 5) Questionario x Sintomi di malattia
- 6) Questionario soddisfazione

Soggetti

M e F 18 e 75 anni

Acromegalia attiva di **nuova diagnosi**

Acromegalia attiva già **operata o sottoposta a RT**

Acromegalia con **trattamento** in atto o pregresso con **analoghi della somatostatina senza adeguato controllo** della malattia

Ipertensione arteriosa in stabile controllo

Consenso scritto informato

Pazienti arruolati al 07/11/2012
n. 20

Risultati in corso di elaborazione



Take home message

I dati della letteratura suggeriscono che nell' acromegalia

- 1) L' ipertensione arteriosa ha **patogenesi multifattoriale**
- 2) La **cronica esposizione** ad una ipersecrezione di **GH/IGF-I facilita** lo sviluppo dell' ipertensione (*probabilmente tramite un aumentato riassorbimento renale di sodio - ridotta secrezione di ANP e conseguente espansione dei fluidi*)
- 3) La **disfunzione simpatica** può avere un ruolo nello **sviluppo/mantenimento** degli elevati livelli pressori
- 4) Il **controllo ormonale** di malattia, indipendentemente da come ottenuto (NCH, RT, SSA) si **associa ad una riduzione dei livelli pressori**
- 5) La **misurazione pressoria tramite ABPM** è la metodica **più affidabile** per diagnosticare l' ipertensione (la misurazione clinica sovrastima)

Nell' acromegalia

- 1) La **diagnosi** di ipertensione arteriosa dovrebbe essere effettuata con **ABPM**
- 2) Il **controllo pressorio** può essere ottenuto con approccio **multi-fattoriale**
 - a) Controllando l' **ipersecrezione di GH/IGF-I**
 - b) Utilizzando preferenzialmente **Beta-bloccanti, ACE-inibitori/Sartani, diuretici sodio-disperdenti**

Grazie
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tra
AMICI
(e Prénom)



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