Altogether
to Beat
Cushing's
Syndrome

ABC

VIAGGIO ALLA (RI)SCOPERTA DELLA SINDROME DI CUSHING

seconda edizione

Capri \ 15-18 maggio 2013
Certosa di San Giacomo
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INTRODUZIONE AL LAVORO DEI GRUPPI DI STUDIO

1. LE VARIE FORME DELLA SINDROME DI CUSHING

8.30-10.30 **SESSIONE 1: IL CUSHING IPOFISARIO**
moderatori **Franco Mantero, Francesco Minuto**

8.30-9.00 IL TUMORE NON VISIBILE ED IL TUMORE AGGRESSIVO
Emanuela Arvat

9:00-9:30 IL RUOLO DELLA MODERNA RISONANZA MAGNETICA
Fabio Tortora

9:30-10.00 IL RUOLO ATTUALE DEL CATETERISMO DEI SENI PETROSI
Monica De Leo

10.00-10:30 discussione

10.30-11.00 pausa caffè

11.00-13.00 **SESSIONE 2: IL CUSHING ECTOPICO**
moderatori **Ettore Degli Uberti, Diego Ferone**

11.00-11.30 L'INQUADRAMENTO CLINICO-DIAGNOSTICO
Giovanni Vitale

11.30-12.00 L'APPROCCIO TERAPEUTICO
Manuela Albertelli

12.00-12.30 IL RUOLO DEGLI ANALOGHI DELLA SOMATOSTATINA E DEL PASIREOTIDE
Giorgio Arnaldi

12.30-13.00 discussione

13.00-14.30 pausa pranzo

14.30-16.30 **SESSIONE 3: IL CUSHING SURRENALICO**
moderatori **Massimo Mannelli, Salvatore Corsello**

14.30-15.00 L'ADENOMA SURRENALICO
Alfredo Scillitani

15.00-15.30 IL CARCINOMA SURRENALICO
Massimo Terzolo

15.30-16.00 L'IPERPLASIA BILATERALE DEL SURRENE
Paola Loli

16.00-16:30 discussione

16.30 -17.00 pausa caffè

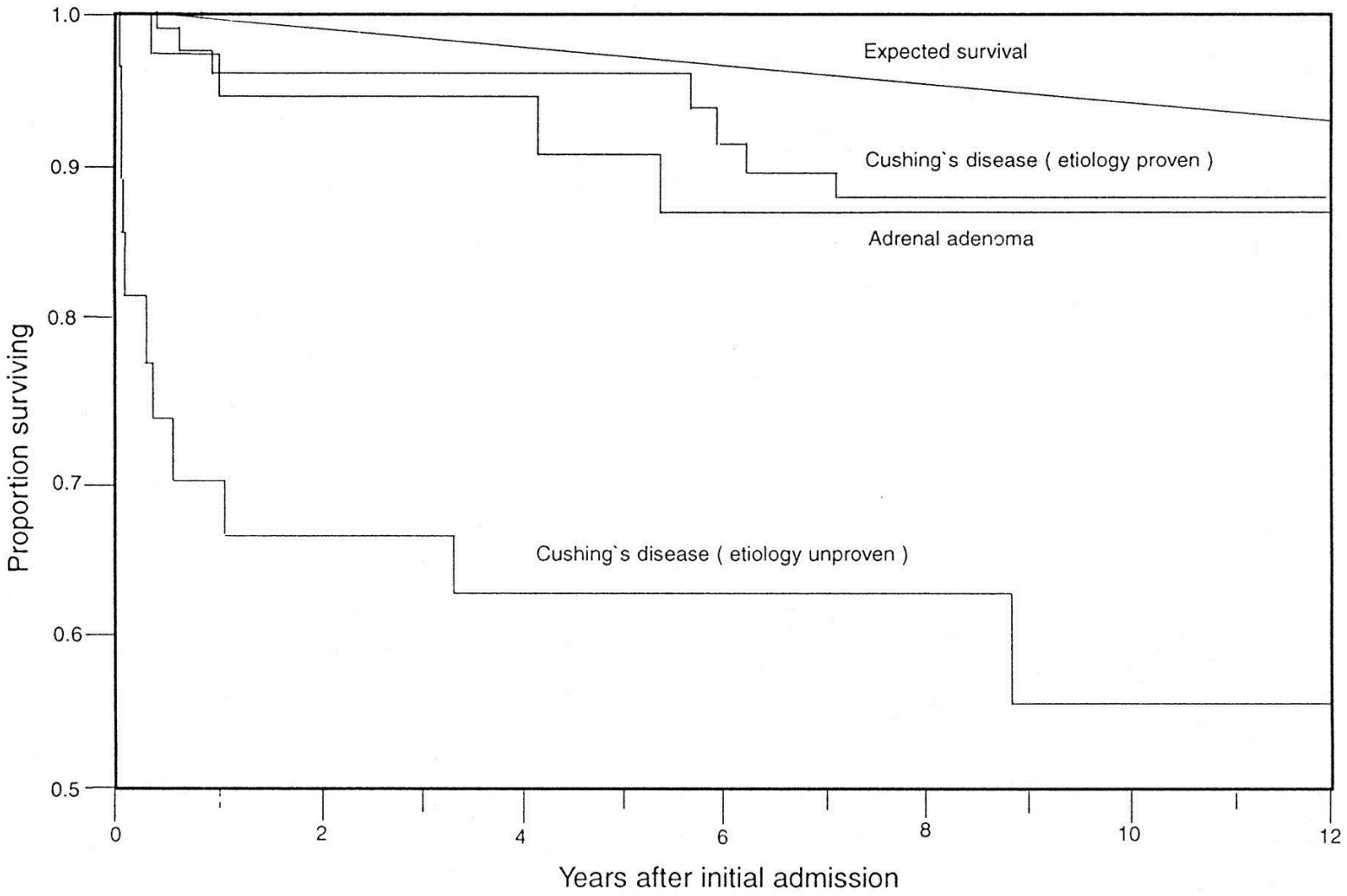
Annual incidence per million of Cushing's disease and adrenal adenoma by age and sex (cases per yr)

Age (yr)	Cushing's disease				Adrenal adenoma	
	Pituitary etiology proven		Pituitary etiology unproven			
	M	F	M	F	M	F
0–19	0.5 [4]	0.6 [4]	0 [0]	0 [0]	0 [0]	0.1 [1]
20–39	0.9 [8]	2.2 [19]	0.2 [2]	0.4 [3]	0 [0]	2.6 [22]
40–59	1.0 [7]	3.1 [22]	0.1 [1]	1.7 [12]	0.6 [4]	1.1 [8]
≥60	0.8 [4]	0.8 [5]	0 [0]	1.2 [8]	0 [0]	0.3 [2]
Total	0.8 [23]	1.7 [50]	0.1 [3]	0.8 [23]	0.1 [4]	1.1 [33]

M, Men; F, women. The number of patients is in *brackets*.

Lindholm J et al. JCEM 2001;86:117-123

Survival in patients with Cushing's disease (proven and unproven) and with adrenocortical adenoma.



Lindholm J et al. JCEM 2001;86:117-123

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Mortality and morbidity in Cushing's syndrome in New Zealand

Mark J. Bolland*, Ian M. Holdaway†, Juliet E. Berkeley‡, Sarina Lim§, Will J. Dransfield¶, John V. Conaglen§, Michael S. Croxson†, Greg D. Gamble*, Penny J. Hunt‡ and Robyn J. Toomath¶

	Entire cohort	Adrenal adenoma	Bilateral nodular hyperplasia	Pituitary macroadenoma*	Pituitary microadenoma*	Occult ectopic†	Probable ectopic
	$n = 253$	$n = 37$	$n = 9$	$n = 30$	$n = 158$	$n = 10$	$n = 9$
Age at presentation (year)	39 (15), range 5–75	41 (13)	41 (10)	45 (14)	36 (15)	33 (16)	53 (14)
Duration of symptoms (year)	2·0 [0–21]	0·1 [0–21]	0·2 [0–10]	0·2 [0–17]	0·2 [0–20]	0·1 [0–3]	0·1 [0–3]
Sex (% female)	76	89	78	73	77	30	56
Duration of follow-up (year)	6·4 [0–46]	3·1 [0–18]	5·7 [1·5–39]	6·9 [0–30]	7·5 [0–46]	6·8 [0–28]	8·1 [0–16]

Data are mean (SD) for normally distributed data, median [range] for nonnormally distributed data, or percentage.
*Pituitary macroadenoma ≥ 10 mm and pituitary microadenoma < 10 mm based on radiological imaging.
†Five bronchial carcinoid, three thymic carcinoid, one mediastinal neuroendocrine carcinoid and one medullary thyroid carcinoma.

Clin Endocrinol 2011

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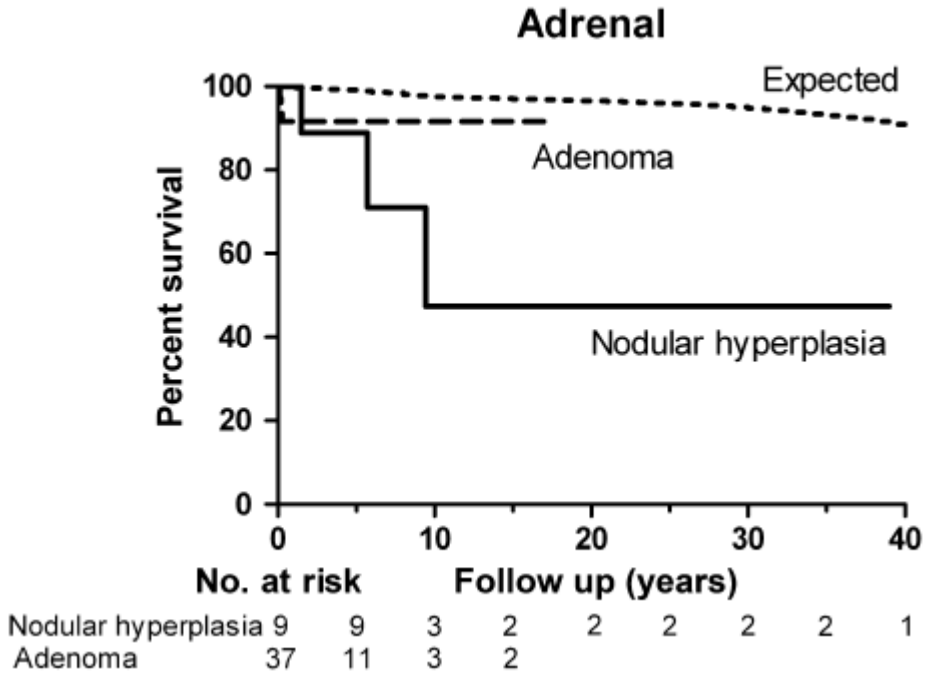

Kaplan–Meier plots showing the per cent survival over time of patients with Cushing's syndrome due to Adrenal Adenoma compared with the expected survival for the New Zealand population matched by age, gender and duration of follow-up

Clin Endocrinol 2011

Multisystem Morbidity and Mortality in Cushing's Syndrome: a Cohort Study

Several years elapse between onset of Cushing Syndrome and its diagnosis, mainly because the manifestations such as weight gain, hypertension, diabetes and menstrual cycle irregularities are nonspecific and common, even in combination.

Importantly, if symptoms of CS are treated, the underlying cortisol overproduction remains unaffected.

Exposure to supraphysiological cortisol levels exerts ramified harmful effects such as hypercoagulability, insulin resistance, hypertension, bone loss and immunosuppression.

It is assumed that some cortisol-related effects persist after CS is cured, as continued elevation of cardiovascular risk has been observed despite disease remission.

Mortality is increased approximately twofold in patients with CS, with the highest mortality risk occurring in patients with persistent disease.

Dekkers OM, JCEM 2013

Multisystem Morbidity and Mortality in Cushing's Syndrome: a Cohort Study

The present nationwide cohort study aimed to examine the risks faced by CS patients with respect to mortality, cardiovascular disease, fractures, peptic ulcers, and infections.

The source population consisted of the entire population of Denmark (7.6 million inhabitants from 1980 to 2010). Data were obtained from the Danish Civil Registration System (DCRS) and the Danish National Registry of Patients (DNRP).

All patients with an initial diagnosis of CS of pituitary or adrenal origin between 1980 and 2010 were eligible for inclusion. Patients who developed CS due to exogenous steroid treatment and patients with adrenal malignancies or ectopic CS were not included.

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Dekkers OM, JCEM 2013

Multisystem Morbidity and Mortality in Cushing's Syndrome: a Cohort Study

Table 2. Rates and hazard ratios with 95% confidence intervals (95% CI) for the risk of venous thromboembolism (VTE), acute myocardial infarction (AMI), stroke, heart failure, infections, ulcers, and fractures in patients with Cushing's syndrome (CS), stratified by follow-up time

Outcome	*Period (years before/after diagnosis)*	*Rate (95% CI) per 1,000 person-years in CS cohort*	*Rate (95% CI) per 1,000 person-years in control cohort*	*Hazard ratio (95% CI), age and sex-adjusted model*	*Hazard ratio (95% CI), fully adjusted model **
VTE	3 yr before	4.3 (1.1 – 9.3)	0.5 (0.4 – 0.7)	8.4 (3.0–23.4)	6.8 (2.4–19.3)
	1 yr after	15.3 (4.9 – 31.4)	0.9 (0.6 – 1.2)	20.6 (7.8–53.9)	17.1 (6.4–45.8)
	>1 to 30 yr after	1.9 (0.8 – 3.6)	1.3 (1.2 – 1.4)	1.6 (0.8–3.4)	1.4 (0.6–2.9)
AMI	3 yr before	2.1 (0.2 – 5.9)	0.9 (0.8 – 1.2)	2.2 (0.5–8.9)	2.1 (0.5–8.6)
	1 yr after	6.1 (0.7 – 16.9)	1.4 (1.0–1.8)	4.5 (1.1–18.4)	3.5 (0.8–14.7)
	>1 to 30 yr after	6.0 (3.8 – 8.8)	1.9 (1.8 – 2.1)	3.6 (2.4–5.5)	2.8 (1.8–4.4)
Stroke	3 yr before	5.3 (1.7 – 10.9)	1.1 (0.9 – 1.3)	5.0 (2.1–12.4)	4.5 (1.8–11.1)
	1 yr after	9.1 (1.8 – 22.0)	1.4 (1.1 – 1.9)	6.5 (2.0–21.0)	4.3 (1.3–14.2)
	>1 to 30 yr after	4.3 (2.5 – 6.7)	2.7 (2.5–2.8)	1.8 (1.1–3.0)	1.5 (0.9–2.5)
Heart failure	3 yr before	4.3 (1.1 – 9.3)	0.6 (0.5 – 0.8)	6.8 (2.5–18.6)	6.0 (2.1–17.1)
	1 yr after	6.1 (0.7 – 17.0)	0.9 (0.6–1.3)	6.7 (1.6–28.1)	3.1 (0.7–14.2)
	>1 to 30 yr after	1.6 (0.6 – 3.1)	1.9 (1.8 – 2.0)	1.0 (0.4–2.2)	0.8 (0.3–1.7)
Fractures	3 yr before	14.9 (7.9 – 24.0)	4.2 (3.8 – 4.7)	3.4 (2.0–6.0)	3.2 (1.9–5.6)
	1 yr after	20.1 (7.4 – 39.2)	4.6 (3.8 – 5.4)	4.3 (1.9–9.7)	3.8 (1.7–8.7)
	>1 to 30 yr after diagnosis	8.3 (5.5 – 11.6)	7.2 (6.9 – 7.4)	1.2 (0.8–1.7)	1.1 (0.8–1.6)
Infections	3 yr before	5.5 (1.8 – 11.3)	2.1 (1.8 – 2.4)	2.6 (1.1–6.4)	2.4 (1.0–5.9)
	1 yr after	51.7 (29.6 - 80.0)	2.4 (1.9–3.0)	22.3 (12.9–38.5)	17.8 (10.1–31.3)
	>1 to 30 yr after	12.7 (9.1 – 16.9)	3.7 (3.5 – 3.9)	3.7 (2.7–5.1)	2.9 (2.1–4.1)
Peptic ulcers	3 yr before	5.4 (1.7 – 11.0)	0.8 (0.6 – 1.0)	6.5 (2.6–16.0)	5.5 (2.2–13.9)
	1 yr after	12.3 (3.3 – 27.0)	1.0 (0.6 – 1.3)	12.5 (4.4–35.5)	8.9 (3.0–26.3)
	>1 to 30 yr after	1.9 (0.8 – 3.6)	1.6 (1.5 – 1.7)	1.3 (0.6–2.8)	1.1 (0.5–2.2)

* Model adjusted for age, sex, calendar time, cancer, diabetes, hypertension, chronic obstructive pulmonary disease, liver disease, and alcoholism-related diseases.

Dekkers OM, JCEM 2013

Multisystem Morbidity and Mortality in Cushing's Syndrome: a Cohort Study

Table 4. Preoperative *vs.* postoperative risk for venous thromboembolism (VTE), infections, and peptic ulcers

Outcome	*Period*	*Hazard ratio (95% CI), age- and sex- adjusted model*	*Hazard ratio (95% CI), fully adjusted model **
VTE	1 yr before operation	10.2 (3.1–33.5)	8.6 (2.5–29.3)
	Operation to 3 months postoperatively	59.9 (14.3–250.8)	58.8 (13.9–248.7)
	> 3 to 12 months pos to peratively	5.8 (0.8–43.6)	3.6 (0.4–28.6)
Infections	1 yr before operation	7.4 (3.0–18.5)	5.7 (2.2–14.4)
	Operation to 3 months postoperatively	53.5 (24.7–115.9)	38.2 (16.9–86.1)
	>3 to 12 months pos to peratively	14.1 (6.0–33.1)	8.3 (3.3–20.4)
Peptic ulcers	1 yr before operation	7.5 (1.8–31.7)	7.1 (1.6–31.3)
	Operation to 3 months postoperatively	13.9 (3.2–61.2)	9.9 (2.1–47.4)
	>3 to 12 months pos to peratively	8.9 (2.1–37.8)	6.1 (1.4–27.6)

* Model adjusted for age, sex, calendar time, cancer, diabetes, hypertension, chronic obstructive pulmonary disease, liver disease, and alcoholism-related diseases.

Dekkers OM, JCEM 2013

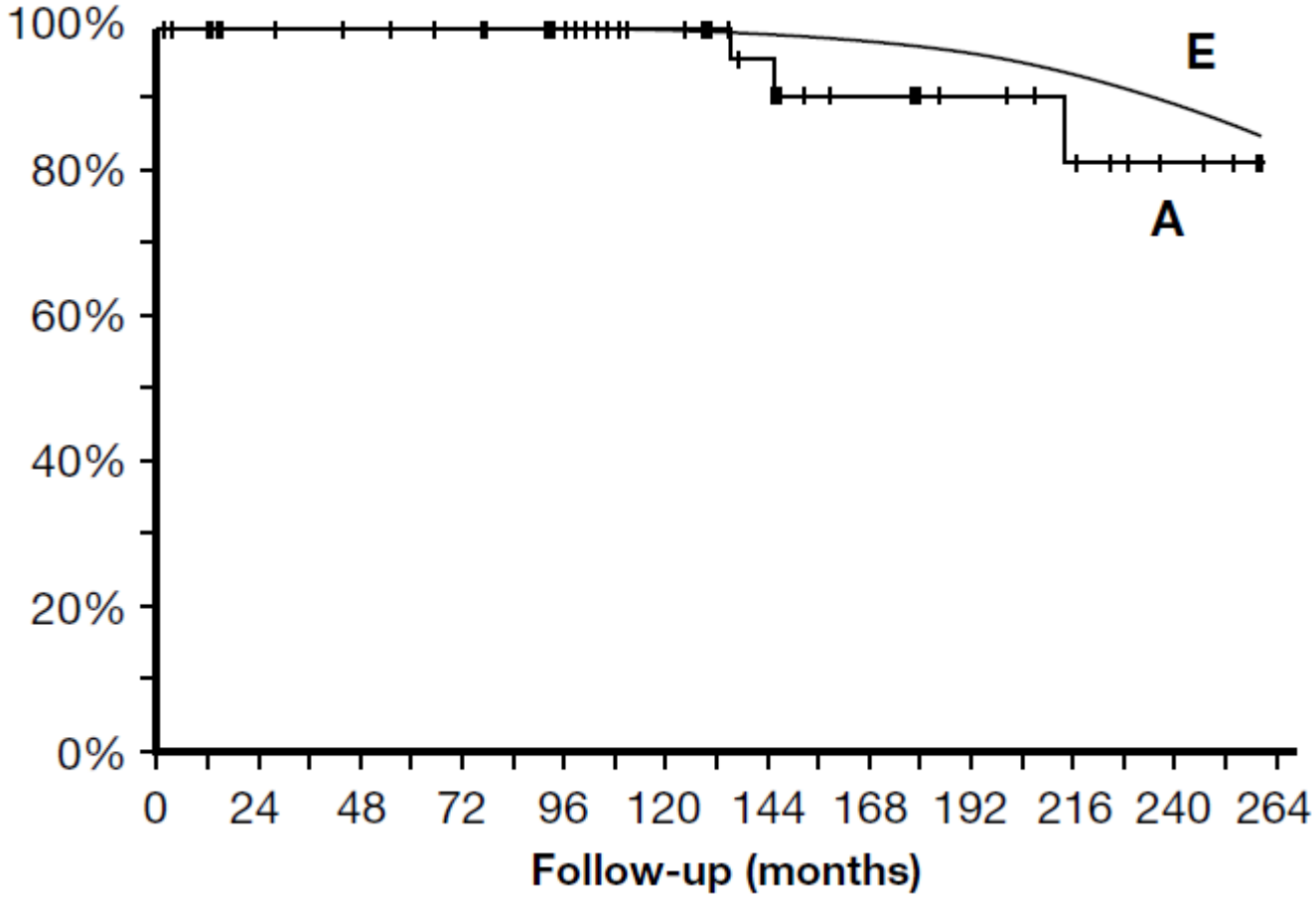
Multisystem Morbidity and Mortality in Cushing's Syndrome: a Cohort Study

Table 3. Hazard ratios with 95% confidence intervals (95% CI) for the risk of venous thromboembolism (VTE), acute myocardial infarction (AMI), stroke, heart failure, infections, ulcers, and fractures in patients with Cushing's syndrome (CS) 0–30 yr after diagnosis, stratified by age category and type of Cushing Syndrome

Outcome	*Patients* [lteq] *44 yr (n = 172)*	*Patients > 44 yr (n = 171)*	*Adrenal Cushing (n = 132)*	*Pituitary Cushing (n = 211)*
	Hazard ratio (95% CI), age and sex-adjusted model	*Hazard ratio (95% CI), age and sex-adjusted model*	*Hazard ratio (95% CI), age and sex-adjusted model*	*Hazard ratio (95% CI), age and sex-adjusted model*
Mortality	3.9 (2.6–6.1)	2.0 (1.5–2.6)	2.4 (1.6–3.5)	2.3 (1.7–3.0)
VTE	2.5 (0.9–6.9)	2.7 (1.3–5.4)	2.4 (0.9–6.5)	2.8 (1.4–5.6)
AMI	5.5 (2.4–12.6)	3.3 (2.1–5.3)	3.8 (1.9–7.8)	3.6 (2.2–5.9)
Stroke	2.0 (0.7–5.3)	2.1 (1.2–3.4)	1.9 (0.9–4.3)	2.1 (1.2–3.6)
Heart failure	1.1 (0.2–8.2)	1.3 (0.6–2.7)	1.2 (0.4–3.7)	1.3 (0.5–3.2)
Fractures	1.7 (1.1–2.8)	1.1 (0.7–1.8)	0.8 (0.4–1.8)	1.6 (1.1–2.4)
Infections	5.5 (3.7–8.1)	4.4 (3.1–6.4)	4.9 (3.1–7.7)	4.9 (3.5–6.8)
Peptic ulcers	0.6 (0.1–4.6)	2.5 (1.3–4.6)	2.5 (1.0–6.2)	1.7 (0.7–3.7)

Dekkers OM, JCEM 2013

Observed survival curve (A) in Cushing's patients after adrenalectomy for adrenocortical adenoma and expected survival curve (E) of age-matched control population



Iacobone M et al JEI 2005

Variations of blood pressure and body mass index before and after adrenalectomy according to the duration of the follow-up

	Patients (no.)	Hypertensive Patients (no.)	Systolic BP (mm/g) (mean±SD)	Diastolic BP (mm/g) (mean±SD)	BMI (mean±SD)	Obese Patients (no.)	Overweight Patients (no.)	Patients with abnormal BMI (%)
Before surgery	50	40	157.4±16.5	96.2±10.8	28.7±3.1	29	18	94
Follow-up: 1 yr	50	3	121±7.8	80±4.2	26.2±2.1	15	24	78
Follow-up: 3 yr	44	7	125±6	84.3±2.1	25.4±4.5	10	20	68
Follow-up: 6 yr	40	11	132±7.1	85.5±2.2	24.3±3.1	4	19	23
Follow-up: 10 yr	27	7	135±22	86±3.2	23.4±3	0	10	37

Iacobone M et al JEI 2005

Clinical features before and after adrenalectomy in a population of 50 patients with ACTH-independent hypercortisolism

	Before adrenalectomy	After adrenalectomy	*p* value
Hypertensive patients (no.)	40	17	<0.05
Systolic BP (mm/Hg) (in the 40 hypertensive patients before adrenalectomy) (mean±SD)	158.2±18.3	142±15.6	<0.001
Diastolic BP (mm/Hg) (in the 40 hypertensive patients before adrenalectomy) (mean±SD)	96.7±11.5	82.2±7.1	<0.001
Central obesity (no.)	48	1	<0.001
Mean BMI (Kg/m^2) (mean±SD)	28.7±3.1	23.4±2	<0.001
Patients with abnormal BMI (no.)	47	19	<0.001
Dyslipidemia (no.)	40	16	<0.05
Diabetes and glucose intolerance (no.)	48	8	<0.001
Asthenia (no.)	30	1	<0.001
Psychic symptoms (no.)	12	1	<0.001
Skin alterations (no.)	49	2	<0.001
Menstrual disorders (in 31 pre-menopausal women) (no.)	24	1	<0.001
BMD* (mg/cm^2) (mean±SD)	828±168	995±129	<0.001
T-score* (mean±SD)	–2.12±1.68	–0.59±1.24	<0.001
Patients with abnormal T-score (no.)*	13	6	<0.05

*Referred to 19 patients. BP: blood pressure; BMD: bone mass density.

Editrice Kurtis

Iacobone M et al JEI 2005

Bone Demineralization and Vertebral Fractures in Endogenous Cortisol Excess: Role of Disease Etiology and Gonadal Status

Libuse Tauchmanovà, Rosario Pivonello, Carolina Di Somma, Riccardo Rossi, Maria Cristina De Martino, Luigi Camera, Michele Klain, Marco Salvatore, Gaetano Lombardi, and Annamaria Colao

Variable	ACTH-secreting pituitary adenoma	Adrenal adenoma	Adrenal carcinoma	Ectopic ACTH excess	Controls
No. of subjects	37	18	15	10	80
Serum calcium (mmol/liter)	2.36 ± 0.13	2.38 ± 0.15	2.34 ± 0.14	2.39 ± 0.16	2.33 ± 0.11
Albumin (g/dl)	3.99 ± 0.44	4.06 ± 0.36	3.86 ± 0.5	4.28 ± 0.3	4.1 ± 0.3
Urinary calcium excretion (mg/24 h)	182 ± 95	215 ± 88	171 ± 44	192 ± 62	166 ± 73
iPTH (ng/liter)	43.4 ± 12	40.2 ± 14	38 ± 15	44.5 ± 13	41.2 ± 16
Osteocalcin (ng/ml)	1.5 ± 0.5[a]	2.3 ± 0.7	2.4 ± 0.9	1.2 ± 0.4[a]	8.9 ± 2.4[b]
ALP (U/liter)	153 ± 52	174.5 ± 58	185 ± 61	187 ± 49	168 ± 58
Creatinine (μmol/liter)	86 ± 8.6	88 ± 8.9	90 ± 9	87 ± 8.7	82 ± 9.8
Hydroxyprolinuria (μmol/m^2)	135 ± 41.5	129 ± 36	127.5 ± 32	137 ± 40	102 ± 16[b]
Lumbar Z score (SD)	−1.97 (−5.15 to −0.06)	−1.8 (−4 to −0.36)	−1.8 (−2.9 to 0.9)	−3.53 (−4.9 to −3.0)[c]	−0.03 ± 1.1[d]
Femoral Z score (SD)	−1.04 (−2.6 to 0.3)	−1.5 (−2.6 to 1.2)	−0.8 (−2.3 to 0.7)	−0.6 (−2.45 to −0.2)	0.05 ± 0.8[b]
Prevalence (%) of any vertebral fracture	29 (78%)	12 (67%)	10 (67%)	10 (100%)	1 (1.3%)[d]
Clinical fractures[e]	15 (52%)	6 (60%)	4 (40%)	7 (70%)	0 (0%)[b]
Multiple fractures[e]	25 (86%)	9 (75%)[f]	8 (80%)[f]	10 (100%)	0 (0%)[d]

Data are expressed as mean ± SD or median and range, as appropriate.

[a] $P < 0.05$ *vs.* all other groups of patients.

[b] $P < 0.05$ *vs.* all groups of patients.

[c] $P < 0.01$ *vs.* all other groups of patients.

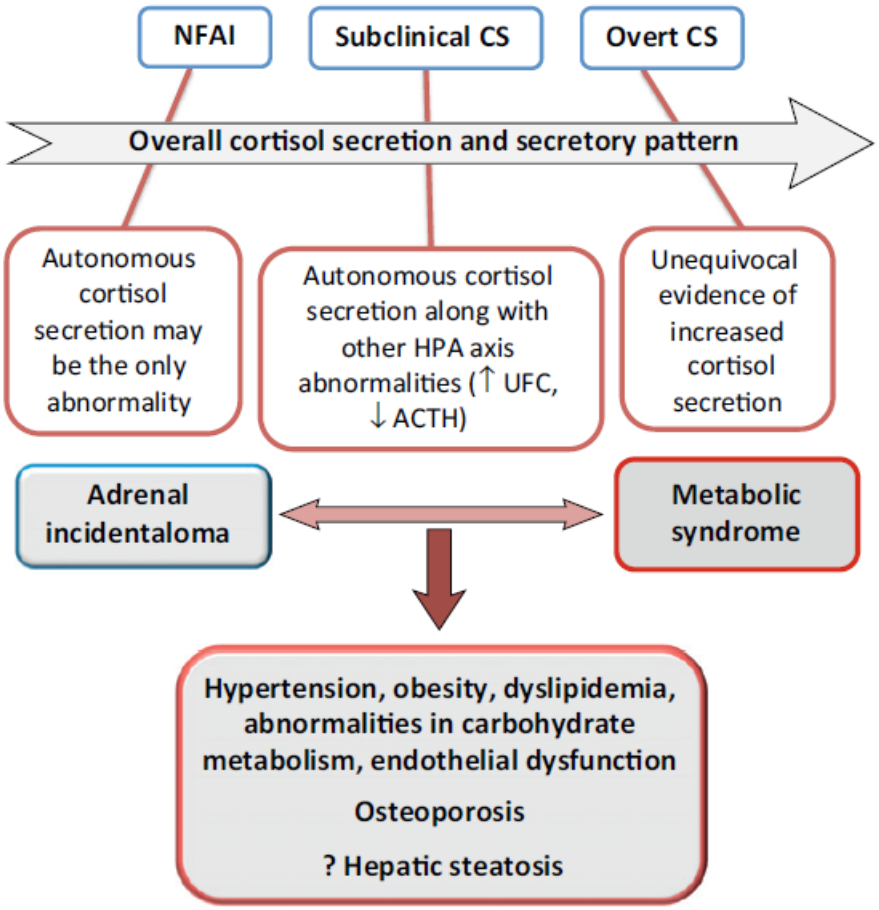
[d] $P < 0.01$ *vs.* all groups of patients.

[e] The percentage of clinical and multiple fractures was calculated as a subset of patients with any fracture. Reference ranges: calcium, 2.2–2.6 mmol/liter; ALP, 98–275 U/liter; creatinine, less than 133 μmol/liter; albumin, 3.6–5.2 g/dl; osteocalcin, 2–22 ng/ml; PTH, 10–75 ng/liter; hydroxyproline excretion, 60–190 μmol/m^2.

[f] $P < 0.05$ *vs.* ectopic ACTH hypersecretion.

Current status and controversies in adrenal incidentalomas

Adrenal incidentalomas, comorbidities, and their interrelations



NFAI: Non-functional adrenal incidentaloma
HPA: Hypothalamic–pituitary–adrenal
CS: Cushing syndrome
UFC: Urinary free cortisol
ACTH: Adrenocorticotropin

TRENDS in Endocrinology & Metabolism

Kaltsas G et al, TEM 2012

What is the frequency of incidental adrenal masses in the general population?

- **Clinical series:** 3% in middle age, 10% in the elderly
- **Male to female ratio:** 1.3 : 1.5
- **Autopsy series:** <1% below 30 years of age, 3% at 50 years, >7% around 70 years
- **Side**

right	53% (50-60)
left	37% (30-40)
bilateral	10% (7-15)

What are the causes of incidental adrenal masses in the general population?

	Average percentage in the literature	
• **Adenoma**	**63%**	**(33-96)**
not-secreting	75%	(52-97)
cortisol-secreting	9.5%	(1-29)
aldosterone-secreting	2.5%	(1.6-2.3)
estrogen/androgen-secreting	very rarely	
• **Pheochromocytoma**	**7%**	**(1.5-23)**
• **Carcinoma**	**6.5%**	**(1.2-11)**
• **Myelolipoma**	**8%**	**(7-15)**
• **Cyst**	**5%**	**(4-22)**
• **Ganglioneuroma**	**4%**	**(0-6)**
• **Metastases**		

TABLE 2. Accuracy of HPA axis secretion parameters in diagnosing SH

First author, year (Ref.)	No. of patients	CCR (SN/SP)	ACTH (SN/SP)	UFC (SN/SP)	DST (SN/SP)	DEX dose, DST cutoff	Gold standard criteria for SH diagnosis
Mantero, 2000 (9)	1004	43/83	79/85	76/88	73/90	1 mg, 5 μg/dl	≥2 out of CRH, CCR, ACTH, UFC, DST
Libè 2002 (52)	64	n.a.	41/96	33/96	91/98	1 mg, 5 μg/dl	≥2 out of CRH, CCR, ACTH, UFC, DST
Masserini, 2009 (32)	103	22.7/87.7	86.4/59.3	31.8/92.6	86.4/96.3	1 mg, 3 μg/dl	≥2 out of DST, ACTH, UFC
Nunes, 2009 (31)	48	77/69[a]	n.a.	n.a.	n.a.	1 mg, 2.2 μg/dl	DST plus ACTH or CCR
		77/68[b]				1 mg, 2.2 μg/dl	DST plus ACTH or CCR
Barzon, 2001 (67)	83	n.a.	n.a.	n.a.	44/100	1 mg, 5 μg/dl	Norcholesterol scintigraphy
					75/72	1 mg, 1.8 μg/dl	Norcholesterol scintigraphy
Valli, 2001 (48)	31	n.a.	n.a.	n.a.	58/83	1 mg, 5 μg/dl	Norcholesterol scintigraphy
					63/75	1 mg, 3 μg/dl	Norcholesterol scintigraphy
					100/67	1 mg, 2.2 μg/dl	Norcholesterol scintigraphy
Eller-Vainicher, 2009 (58)	60	64.1/81[d]	64.1/38	48.7/81	33.3/85.7	1 mg, 5 μg/dl	Postsurgical hypocortisolism
					59/52.4	1 mg, 3 μg/dl	Postsurgical hypocortisolism
					79.5/23.8	1 mg, 1.8 μg/dl	Postsurgical hypocortisolism
Morelli, 2010 (59)	231	n.a.	52.4/60.5	42.9/80	23.8/93.3	1 mg, 5 μg/dl	Prevalence of complications[e]
					52.4/81.4	1 mg, 3 μg/dl	Prevalence of complications[e]
					71.4/49.5	1 mg, 1.8 μg/dl	Prevalence of complications[e]
Eller-Vainicher 2010 (60)	55	65.2/65.6[c]	n.a.	n.a.	21.7/96.9	1 mg, 5 μg/dl	Metabolic improvement after surgery[f]
					91.3/56.3	1 mg, 2.0 μg/dl	Metabolic improvement after surgery[f]

CRH, Blunted response to CRH; CCR, altered circadian cortisol rhythm (elevated MSeC or MSaC levels); ACTH, low ACTH levels [<10 pg/ml (2.2 pmol/liter)]; UFC, 24-h UFC levels above the upper limit of the normal range; DST, reduced cortisol suppression after a DST; DEX, dexamethasone; n.a., data not available; SN, sensitivity (%); SP, specificity (%).

[a] MSaC levels [cutoff, 1.7 μg/liter (47 nmol/liter)].

[b] MSeC levels [cutoff, 4.9 μg/dl (135 nmol/liter)].

[c] MSeC [cutoff, 4.0 μg/dl (110 nmol/liter)].

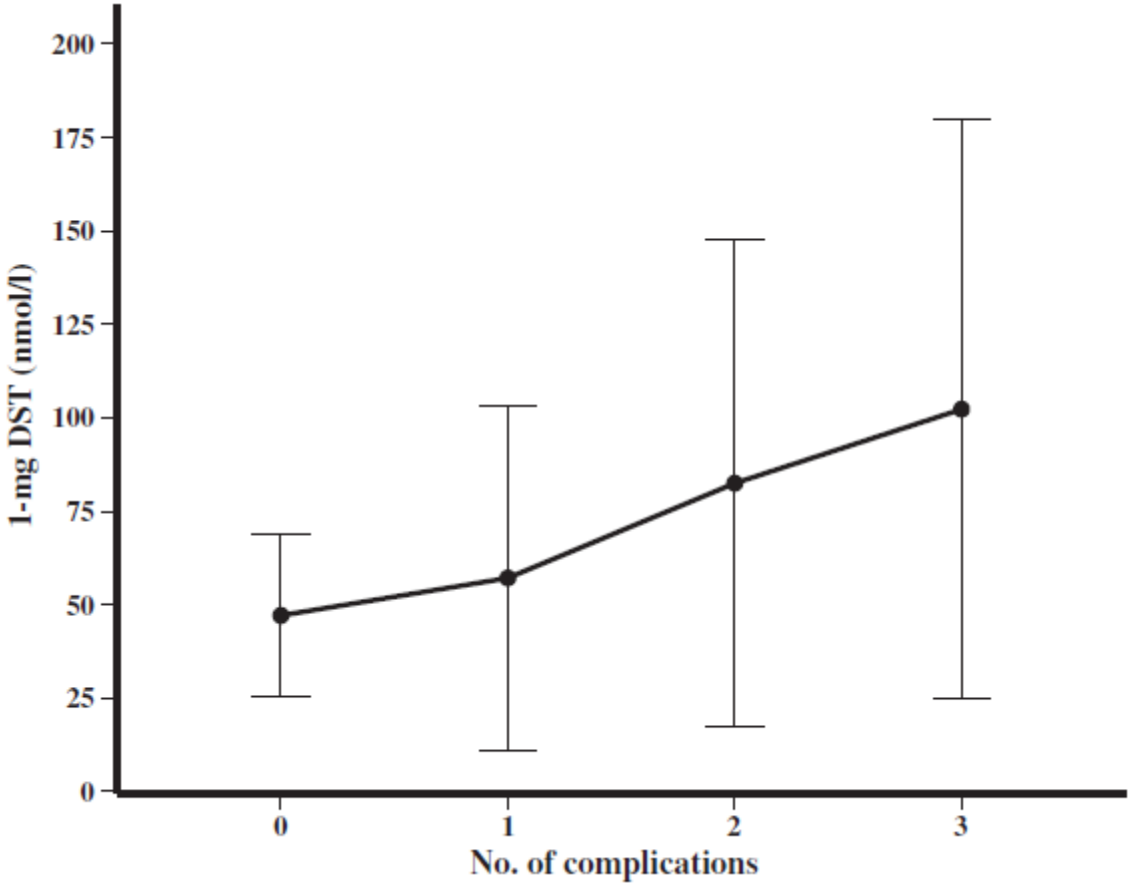
[d] MSeC [cutoff, 5.4 μg/dl (149 nmol/liter)].

[e] Concomitant presence of vertebral fractures, arterial hypertension, and type 2 diabetes mellitus.

[f] Improvement after surgery of at least two out of the following possible complications of SH: blood pressure, fasting glucose, body weight, and cholesterol levels.

Chiodini I JCEM 2011

Subclinical hypercortisolism: correlation between biochemical diagnostic criteria and clinical aspects



Morelli V et al Clin Endocrinol 2010

CLINICAL STUDY

Progressively increased patterns of subclinical cortisol hypersecretion in adrenal incidentalomas differently predict major metabolic and cardiovascular outcomes: a large cross-sectional study

Guido Di Dalmazi, Valentina Vicennati, Eleonora Rinaldi, Antonio Maria Morselli-Labate, Emanuela Giampalma[1], Cristina Mosconi[1], Uberto Pagotto and Renato Pasquali

Clinical outcomes in groups of patients with different patterns of cortisol secretion

	Secreting pattern				
	NSA (n=203)	ImP (n=71)	IMP (n=55)	SCS (n=19)	***P* value**[a]
Clinical outcomes					
Hypertension (n; %)	149 (73.4)	58 (81.7)	43 (78.2)	18 (94.7)	0.173
T2D (n; %)	31 (15.2)	13 (18.3)	18 (32.7)[b]	8 (42.1)[b,c]	0.004
CHD (n; %)	6 (2.9)	9 (12.6)[b]	6 (10.9)[d]	5 (26.3)[b]	0.002
Stroke (n; %)	1 (0.5)	2 (2.8)	3 (5.4)[d]	1 (5.2)	0.194
Osteoporosis (n; %)	30 (14.8)	7 (9.8)	8 (14.5)	9 (47.3)[b,e,f]	0.003
Osteoporotic fractures (n; %)	5 (2.5)	3 (4.2)	1 (1.8)	3 (15.8)[d]	0.056

[a]Comparisons of outcomes among the four groups (univariate logistic regression).
[b]Pairwise comparisons between groups (simple contrasts applied to the logistic regression): $P<0.01$ reference category, NSA.
[c]Pairwise comparisons between groups (simple contrasts applied to the logistic regression): $P<0.05$ reference category, ImP.
[d]Pairwise comparisons between groups (simple contrasts applied to the logistic regression): $P<0.05$ reference category, NSA.
[e]Pairwise comparisons between groups (simple contrasts applied to the logistic regression): $P<0.01$ reference category, ImP.
[f]Pairwise comparisons between groups (simple contrasts applied to the logistic regression): $P<0.01$ reference category, IMP.

EJE 2012

CLINICAL STUDY

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Odds ratios for T2D, CHD, osteoporosis, and osteoporotic fractures for potential risk factors in groups of patients with different patterns of cortisol secretion

	T2D			CHD			Osteoporosis			Osteoporotic fractures		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Risk factors												
IP-secreting pattern (IP vs NSA)	1.702	0.939–3.082	0.079	4.094	1.473–11.378	0.007	0.637	0.312–1.300	0.215	1.130	0.290–4.398	0.860
Age (1-year increase)	1.026	1.004–1.049	0.021	1.023	0.999–1.047	0.055	1.031	1.009–1.055	0.006	1.028	1.006–1.051	0.012
BMI (1 unit increase)	0.989	0.948–1.032	0.617	0.993	0.950–1.038	0.752	0.992	0.951–1.034	0.710	0.996	0.956–1.038	0.863
Gender (female vs male)	0.875	0.533–1.435	0.597	0.794	0.475–1.325	0.377	0.795	0.474–1.334	0.385	0.870	0.528–1.435	0.586
Family history of T2D (presence vs absence)	0.988	0.592–1.651	0.965	–	–	–	–	–	–	–	–	–
Hypertension (presence vs absence)	–	–	–	0.948	0.512–1.757	0.866	–	–	–	–	–	–
T2D (presence vs absence)	–	–	–	1.643	0.891–3.029	0.112	–	–	–	–	–	–
Dyslipidemia (presence vs absence)	–	–	–	0.875	0.531–1.442	0.600	–	–	–	–	–	–
Smoking status (smokers vs nonsmokers)	–	–	–	1.050	0.768–1.436	0.760	1.080	0.796–1.466	0.621	0.742	0.366–1.501	0.406
SCS-secreting pattern (SCS vs NSA)	3.443	1.181–10.038	0.024	6.104	1.407–26.490	0.016	5.940	1.793–19.677	0.004	6.530	1.292–32.994	0.023
Age (1-year increase)	1.059	1.006–1.116	0.029	1.045	0.989–1.103	0.116	1.043	0.987–1.103	0.132	1.054	1.002–1.108	0.040
BMI (1 unit increase)	0.962	0.872–1.060	0.434	0.965	0.872–1.068	0.489	1.015	0.917–1.123	0.774	0.988	0.894–1.092	0.810
Gender (female vs male)	0.807	0.285–2.286	0.686	0.757	0.258–2.220	0.613	1.872	0.557–6.286	0.310	1.160	0.395–3.406	0.788
Family history of T2D (presence vs absence)	0.869	0.284–2.654	0.805	–	–	–	–	–	–	–	–	–
Hypertension (presence vs absence)	–	–	–	2.932	0.341–25.177	0.327	–	–	–	–	–	–
T2D (presence vs absence)	–	–	–	2.736	0.926–8.085	0.069	–	–	–	–	–	–
Dyslipidemia (presence vs absence)	–	–	–	0.935	0.330–2.654	0.900	–	–	–	–	–	–
Smoking status (smokers vs nonsmokers)	–	–	–	0.764	0.379–1.538	0.450	0.664	0.317–1.395	0.280	0.742	0.366–1.501	0.406

IP, intermediate phenotype; SCS, subclinical Cushing's syndrome, using multivariate logistic regression analysis. The reference category is NSA.

EJE 2012

Long-term follow-up in adrenal incidentalomas: an Italian Multicentre Study

Methods. In this retrospective study all patients referred to 7 Italian Endocrine Centers for AI, without signs of hypercortisolism at baseline and with a ≥5 years follow-up (mean SD 82.5 32.1 months), were enrolled. The changes in weight, glucose and lipid metabolism, blood pressure control and the occurrence of CVE were obtained from 206 patients (144 F) .

Patients were classified as affected with subclinical hypercortisolism (SH) in the presence of cortisol after 1–mg dexamethasone suppression (1-mgDST) test >5 mcg/dl or ≥2 parameters out of low ACTH, increased urinary free cortisol and 1-mgDST >3 mcg/dl.

RESULTS	BASELINE (206)		FOLLOW-UP (206)	
	SH- (167)	SH+ (39)	SH- (167)	SH+ (39)
Age (yrs)	58.5 10.1 (25-79)	62.2 11* (25-78)	65.3 9.9 (35-86)	68.5 11.0 (35-91)
BMI (kg/m^2)	27.9±5.0 (17.3-44.7)	28.3±5.6 (19.4-47)	28.2±5.4 (17-52.1)	29.2±6.0 (19.3-49.6)
Bilateral adenomas n. (%)	18 (10.8)	11* (28.2)	22 (13.2)	12# (30.8)
Diameter of adenoma (cm)	2.2±0.7 (1.0-4.0)	2.8±0.9* (1.5-6.0)	2.5±0.9 (1.0-8.4)	3.1±1.0*# (1.6-6.2)
ACTH (pg/mL)	16.1±11.5 (2-78)	11.3±6.0* (3-28)	16.9±10.6 (1.4-72)	8.6±3.8*# (3.0-19.8)
1mg-DST (µg/dL)	1.6±0.8 (0.2-4.9)	3.5±2.1* (1.1-9.3)	1.6±0.8 (0.1-4.1)	4.9±2.2*#∞ (1.5-10.4)
UFC %	-42.0±36.0 (-90.9-134)	-14±68.5* (-85.7-266)	-39.6±34.4 (-93.3-111.4)	-14.1±50.7*# (-89.1-121.3)
Obese subjects n. (%)	46 (27.5)	13 (33.3)	54 (32.3)	18 (46.2)
Diabetic patients n. (%)	28 (16.8)	13* (33.3)	37 (22.2)	17*# (43.6)
Dyslipidemic patients n. (%)	70 (41.9)	21 (53.8)	90* (53.9)	27* (69.2)
Hypertensive patients n. (%)	90 (53.9)	26 (66.7)	105 (62.9)	34∞#* (87.2)
Patients with CVE n. (%)	10 (6.0)	8* (20.5)	22 new CVE	

*P<0.05 vs SH- at baseline; # P<0.05 vs SH- at follow-up;
∞ P<0.05 vs SH+ at baseline;

At the end of follow-up a new diagnosis of SH was made in 15 patients (7.3%) included in the SH+ group also for the basal analysis.

The adenoma size (baseline 2.3±0.8 cm) increased >2.5 cm in the 2.4% of cases.

The weight and glycaemic control, and LDL-cholesterol worsened in the 26% 25% and 13%, of patients respectively, with no differences between SH+ and SH-.

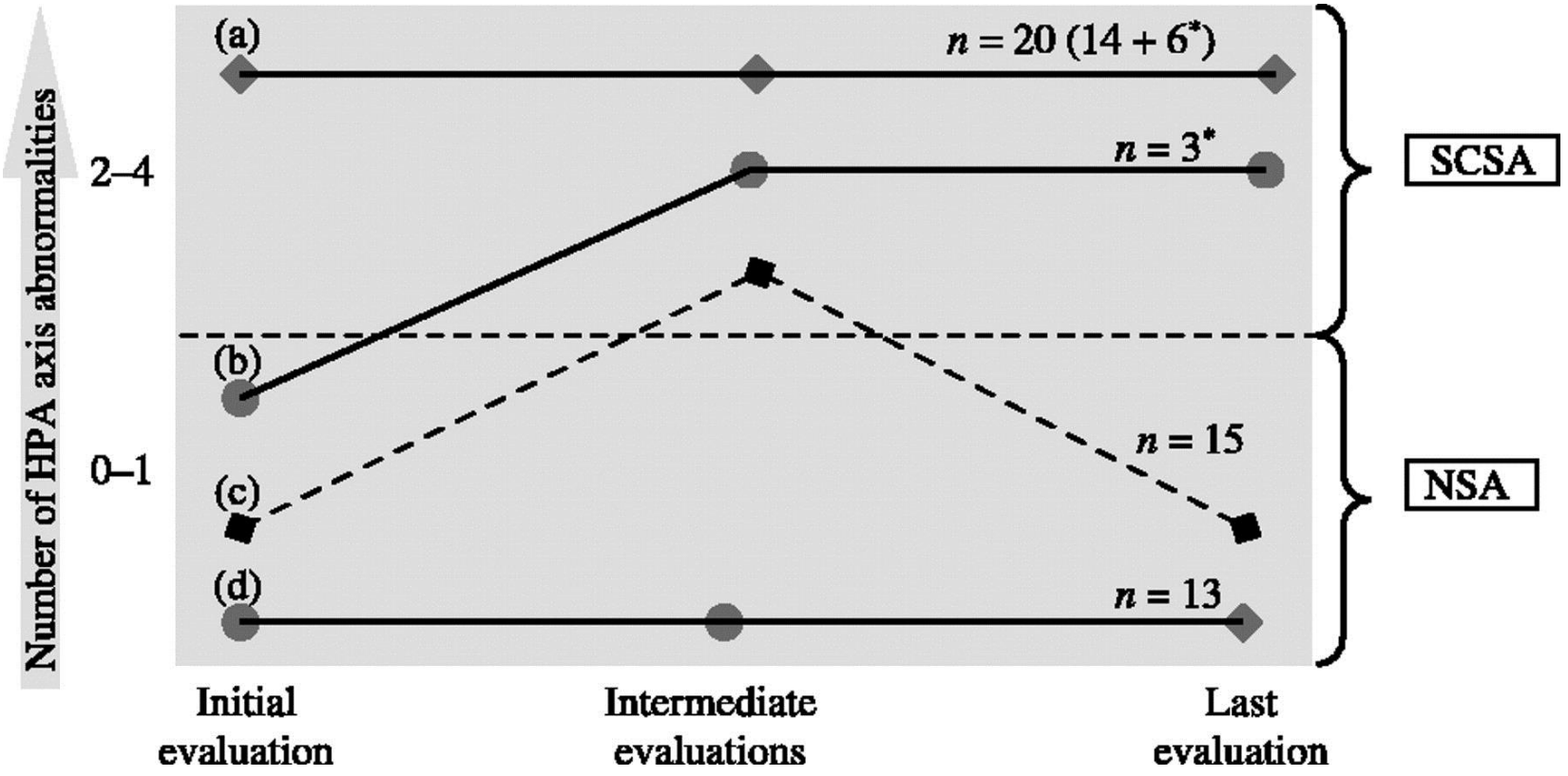
The blood pressure control worsened in the 46% of SH+ and 31% of SH- patients (P=0.07).

The logistic regression analysis showed that SH and T2DM were independently associated to the presence of CVE (OR 3.1, 95%CI 1.1-9.0 and OR 2.0, 95%CI 1.2-3.3 respectively, P<0.05) regardless of age.

8.4% in SH- vs 20.5% in SH+ patients (P=0.04).
The presence of SH was significantly associated with the occurrence of new CVE (OR 2.7, 95%CI 1.0-7.1 respectively, P=0.04), regardless of the worsening of blood pressure and the duration of follow-up.

Morelli V et al Copenhagen, ECE 2013

Figure 1 Illustration of hormonal evolution during follow-up.



Fagour C et al. Eur J Endocrinol 2009;160:257-264

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TABLE 4. Studies investigating the effect of the recovery from SH on blood pressure, body weight, fasting glucose, and bone

First author, year (Ref.)	Design	SH+ Surg (n)	SH+ Cons (n)	SH− Surg (n)	SH− Cons (n)	FU (months)	SH criteria	BP	BW	FG	Bone
Rossi, 2000, (18)	Prosp.	5	7	13	25	18–300	Cortisol >5.0 μg/dl after 1-mg DST plus 1 out of: high UFC, low ACTH, loss of F rhythm, blunted ACTH after CRH	↑[a]	–	↑[a]	–
Midorikawa, 2001 (46)	Prosp.	4	–	8	–	1	Cortisol >3.0 μg/dl after 1-mg DST and low ACTH	↕[a]	↓	↑[a]	–
Emral, 2003 (54)	Prosp.	3	1	3	57	n.a.	Cortisol >3.0 μg/dl and UFC reduction < 50% after 3-mg DST	↑	↑	↑	–
Bernini, 2003 (93)	Prosp.	6	–	9	–	12	Cortisol >5.0 μg/dl after 1-mg DST	↑[a]	↓	↑[a]	–
Erbil, 2006 (94)	Retrosp.	11	–	–	83	12	Cortisol >3.0 μg/dl after 1-mg DST and 8-mg DST	↕	↕	↕	–
Mitchell, 2007 (95)	Retrosp.	9	–	–	–	1–30	Cortisol >1.0 μg/dl after 1-mg DST plus 1 out of: high UFC, low ACTH, low DHEAS, lateralization with AVS, clinical signs	↑	↑	↑	–
Tsuiki, 2008 (96)	Retrosp.	10	12	–	–	7–19	Cortisol >3.0 μg/dl after 1-mg DST and ≥1.0 μg/dl after 8-mg DST plus 1 out of: low ACTH, loss of CCR, low DHEAS, AS uptake	↑	↓	↕	–
Toniato, 2009 (57)	Prosp. Rand.	23	22	–	–	24–204	Cortisol >5.0 μg/dl after 1-mg DST plus 1 out of: high UFC, low ACTH, loss of CCR rhythm, blunted ACTH after CRH	↑	–	↕	↓
Sereg, 2009 (97)	Retrosp.	5	8	42	70	109 ± 37	Cortisol >3.6 μg/dl after 1-mg DST and/or MSeC >5 μg/dl	↓	↓	↓	–
Chiodini, 2010 (61)	Retrosp.	25	16	30	37	18–54	2 out of: cortisol >3.0 μg/dl after 1-mg DST, low ACTH, high UFC	↑[a]	↑	↑	–

SH+, Patients with SH; SH−, patients without SH; FU, range of follow-up; Surg, number of surgically treated patients; Cons, number of patients followed up with conservative approach; BP, blood pressure; BW, body weight; FG, fasting glucose; CCR, altered circadian cortisol rhythm (elevated MSeC or MSaC levels); low ACTH, ACTH levels <10 pg/ml; high UFC, 24-h UFC levels above the upper limit of the normal range; DST, reduced cortisol suppression after a DST; Prosp., prospective; Retrosp., retrospective; Rand, randomized; Cortisol, serum cortisol; AVS, adrenal vein sampling; AS, adrenal scintigraphy; n.a., not available; ↑, improvement; ↕, possible improvement; ↓, stable; –, not evaluated. SI conversion factors: cortisol × 27.56; ACTH × 0.22.

[a] Improvement also in SH-treated subjects.

Chiodini I JCEM 2011

Risk of New Vertebral Fractures in Patients With Adrenal Incidentaloma With and Without Subclinical Hypercortisolism: A Multicenter Longitudinal Study

Clinical and Biochemical Modifications in Patients With and Without SH, at Baseline and After 2 Years of Follow-up

	Baseline		24 Months of follow-up	
	SH^+ (27)	SH^- (76)	SH^+ (27)	SH^- (76)
Age (years)	65.0 ± 8.7 (41–83)	62.7 ± 10.3 (28–80)	67.0 ± 8.5 (43–85)	64.9 ± 10.2 (30–82)
BMI (kg/m^2)	26.6 ± 4.3 (19.3–35.6)	27.5 ± 4.4 (20–39.8)	27.1 ± 4.2 (19.3–34.5)	27.9 ± 4.6 (20–41)
Diameter of adenoma (cm)	2.8 ± 1.0[a] (1.0–5.0)	2.1 ± 0.7 (0.3–3.8)	2.9 ± 1.0[c] (1.2–5.0)	2.2 ± 0.7 (1.0–4.1)
ACTH (pg/mL)	8.6 ± 3.7[a] (5–20.2)	16.9 ± 11.2 (5–62.8)	9.1 ± 3.5.0[c] (5–16)	18.0 ± 10.5 (5–57)
1-mg DST (μg/dL)	3.0 ± 1.2[a] (1.3–6.2)	1.5 ± 0.7 (0.5–4.6)	2.6 ± 1.0[c] (0.7–4.2)	1.4 ± 0.8 (0.4–5)
UFC (μg/24 hours)	66.8 ± 54.4[a] (11.4–263.5)	42.3 ± 26.9 (10.0–150.7)	58.3 ± 36.0[c] (11.0–138.6)	40.0 ± 19.6 (10.0–93.2)
LS BMD (*Z*-score)	0.01 ± 1.17 (−1.8–2.5)	0.03–1.38 (−2.8–4.1)	0.27 ± 1.37 (−2.0–3.6)	0.16 ± 1.45 (−2.6–4.6)
FN BMD (*Z*-score)	−0.04 ± 0.99 (−2.4–2.7)	0.07 ± 0.78 (−1.6–2.1)	0.00 ± 1.07 (−2.4–2.6)	0.11 ± 0.83 (−1.7–2.9)
SDI	1.11 ± 1.50 [b,d] (0–6)	0.58 ± 1.10 (0–4)	2.11 ± 1.85[c] (0–8)	0.79 ± 1.40 (0–6)
No. of patients with vertebral fractures (%)	15 [b,d] (55.6)	22 (28.9)	22[c] (81.5)	27 (35.5)
No. of new vertebral fractures (%)	—	—	13[c] (48.1)	10 (13.2)

Data are mean ± SD, with range in parentheses or absolute number with percentage in parentheses. BMI = body mass index; 1-mg DST = serum cortisol levels after 1-mg dexamethasone suppression test; UFC = urinary free cortisol; ACTH = adrenocorticotropic hormone; LS and FN BMD = bone mineral density measured by DXA at spine (L_1–L_4) and femoral neck, respectively; SDI = spinal deformity index, sum of the fracture grades of all vertebrae (T_4–L_4), assigning for each vertebra a visual semiquantitative grade of 0, 1, 2, or 3 for no fracture or mild, moderate, or severe fracture, respectively; SH^+ = subclinical hypercortisolism was diagnosed in the presence of two of the following: 1-mg DST > 3 μg/dL (82.7 nmol/L), UFC > 70 μg/24 hours (193.0 nmol/24 hours), and ACTH < 10 pg/mL (2.2 pmol/L); SH^- = patients without subclinical hypercortisolism.

[a] $p < .005$ SH^+ versus SH^- at baseline.

[b] $p < .05$ SH^+ versus SH^- at baseline.

[c] $p < .005$ SH^+ versus SH^- at follow-up.

[d] $p < .05$ SH^+ at baseline versus SH^+ at follow-up.

Morelli V et al JBMR 2011

Risk of New Vertebral Fractures in Patients With Adrenal Incidentaloma With and Without Subclinical Hypercortisolism: A Multicenter Longitudinal Study

Odds Ratio for New Vertebral Fractures for Potential Risk Factors Using Logistic Regression Analysis

	Odds ratio	*p* Value	95% confidence interval
Age (1-year increase)	1.037	0.474	0.939–1.146
Years since menopause (1-year increase)	1.023	0.609	0.929–1.130
Female versus male gender	1.644	0.645	0.199–13.592
BMI (1 kg/m^2 increase)	1.027	0.691	0.901–1.169
Lumbar spine BMD (1 *Z*-score unit decrease)	1.154	0.496	0.764–1.744
SH (presence versus absence)	12.264	0.001	4.118–36.529
Basal SDI	1.540	0.355	0.971–2.445

BMI = body mass index; LS and FN BMD = bone mineral density measured by DXA at spine (L_1–L_4); SH = subclinical hypercortisolism was diagnosed in presence of two of the following: 1-mg DST > 3 μg/dL (82.7 nmol/L), UFC > 70 μg/24 hours (193.0 nmol/24 hours), and ACTH < 10 pg/mL (2.2 pmol/L).

Morelli V et al JBMR 2011

Surgical Versus Conservative Management for Subclinical Cushing Syndrome in Adrenal Incidentalomas: A Prospective Randomized Study

…Over a 15-year period, 45 SCS patients were randomly selected to undergo surgery (n 23) or conservative management (n 22). All surgical procedures were laparoscopic adrenalectomies performed by the same surgeon.
All patients were followed up (mean, 7.7 years; range, 2–17 years) clinically by 2 experienced endocrinologists 6 and 12 months after surgery and then yearly, or yearly after joining the trial, particularly monitoring diabetes mellitus (DM), arterial hypertension, hyperlipidemia, obesity, and osteoporosis.

The study end point was the clinical outcome of SCS patients who underwent adrenalectomy versus those managed conservatively.

Results: All 23 patients in the surgical arm had elective surgery. Another 3 patients randomly assigned to conservative management crossed over to the surgical group due to an increasing adrenal mass3.5 cm. **In the surgical group**,
DM normalized or improved in 62.5% of patients (5 of 8), **hypertension in 67%** (12 of 18), **hyperlipidemia in 37.5%** (3 of 8), and obesity in 50% (3 of 6). No changes in bone parameters were seen after surgery in SCS patients with osteoporosis. On the other hand, **some worsening of DM, hypertension, and hyperlipidemia was noted in conservatively-managed patients**.

Toniato A et al Ann Surg 2009

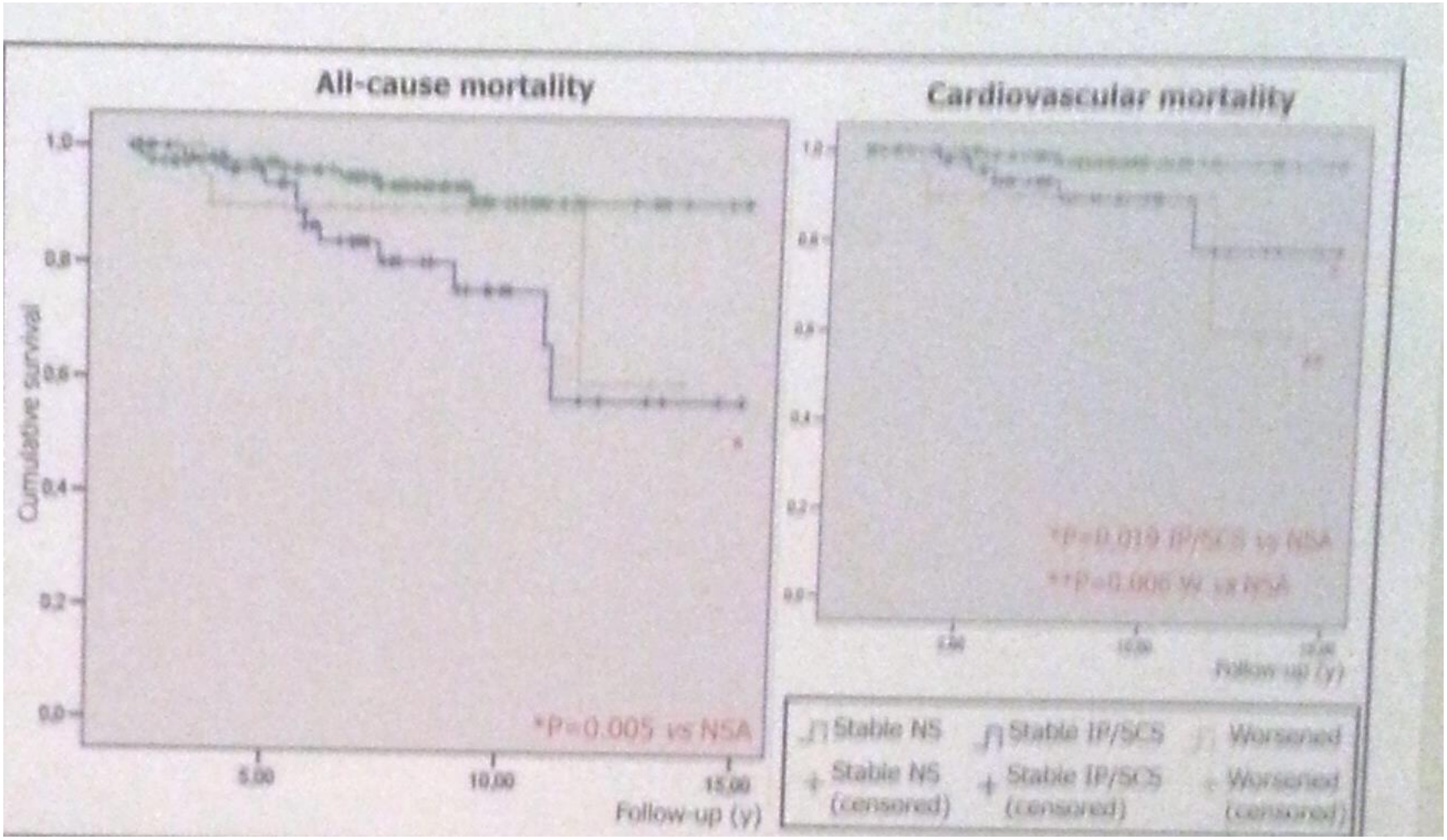
TABLE 3. Change of body weight, blood pressure, fasting glucose, and LDL cholesterol in treated and untreated patients with and without subclinical hypercortisolism

	SH+ treated (n = 25)	SH+ untreated (n = 16)	SH− treated (n = 30)	SH− untreated (n = 37)
Steady body weight, n (%)	15 (60.0)	10 (62.5)	21 (70)	25 (67.6)
Decreased body weight, n (%)	8 (32.0)[a,b]	2 (12.5)	3 (10.0)	2 (5.4)
Increased body weight, n (%)	2 (8.0)	4 (25.0)	6 (20.0)	10 (27.0)
Steady blood pressure, n (%)	11 (44.0)	8 (50.0)	17 (56.7)	21 (56.8)
Improved blood pressure, n (%)	14 (56.0)[b,c]	0 (0.0)	9 (30.0)[d]	5 (13.5)
Worsened blood pressure, n (%)	0 (0.0)[c]	8 (50.0)[e]	4 (13.3)	11 (29.7)
Steady fasting glucose, n (%)	13 (52.0)	10 (62.5)	26 (86.7)	30 (81.1)
Improved fasting glucose, n (%)	12 (48.0)[b,c]	0 (0.0)	3 (10.0)	3 (8.1)
Worsened fasting glucose, n (%)	0 (0.0)[c]	6 (37.5)[b,d]	1 (3.3)	4 (10.8)
Steady LDL cholesterol, n (%)	10 (40.0)	5 (31.2)	19 (63.3)	11 (29.8)
Improved LDL cholesterol, n (%)	9 (36.0)	3 (18.8)	8 (26.7)	9 (24.3)
Worsened LDL cholesterol, n (%)	6 (24.0)[a]	8 (50.0)[b]	3 (10.0)[f]	17 (45.9)

[a]P 0.05 vs. untreated SH patients. [b]P 0.01 vs. treated SH patients. [c]P 0.001 vs. untreated SH patients. [d]P 0.05 vs. untreated SH patients. [e]P 0.05 vs. treated SH patients. [f]P 0.001 vs. untreated SH patients.

Chiodini I et al, JCEM 2010

Mortality in long-term follow up patients with progressively Increased patterns of subclinical cortisol hypersecretion



Di Dalmazi G et al, Copenhagen ECE 2013