SESSION 4: A CHALLENGE IN THE MANAGEMENT OF CUSHING'S SYNDROME: SUBCLINICAL CUSHING'S SYNDROME

Chairs: Franco Grimaldi, Renato Pasquali

9:00-9:15 THE WORK-UP OF ADRENAL INCIDENTALOMA
Maria Cristina De Martino

9:15-9:30 THE ENIGMA OF THE DIAGNOSIS OF SUBCLINICAL CUSHING
Massimo Mannelli

9:30-9:45 THE TREATMENT OF ADRENAL INCIDENTALOMA AND SUBCLINICAL CUSHING
Iacopo Chiodini

9:45-10:00 Discussion

Effect of the recovery from subclinical hypercortisolism

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]	↑	↑	–

Chiodini I, J Clin Endocrinol Metab 2011

Beneficial Metabolic Effects of Prompt Surgical Treatment in Patients with an Adrenal Incidentaloma Causing Biochemical Hypercortisolism

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, J Clin Endocrinol Metab 2010

Table 3 Sensitivity, specificity, positive and negative predictive values, and accuracy of the different SH criteria are able to predict the improvement of at least two parameters among body weight, blood pressure, fasting glucose, and LDL cholesterol levels after removal of an adrenal incidentaloma. Data are expressed as percentage.

Criterion	SN	SP	PPV	NPV	AC	*P*
I: 2 parameters out of 1 mg-DST >3.0 μg/dl, UFC >70.0 μg/24 h, ACTH <10 pg/ml	65.2	68.8	60.0	73.3	67.3	0.013
II: 2 parameters out of 1 mg-DST >2.0 μg/dl[a], UFC >70.0 μg/24 h, MSC >4.0 μg/dl	65.2	65.6	57.7	72.4	65.5	0.024
III: 1 mg-DST >2.0 and MSC >4.0 μg/dl	78.3	68.8	64.3	80.5	72.7	0.014
IV: 1 mg-DST >2.0 μg/dl[a]	91.3	56.3	60.0	90.0	70.9	0.0001
V: 1 mg-DST ≥5.0 μg/dl	21.7	96.9	83.3	63.3	65.5	0.070

LDL, low-density lipoprotein; SH, subclinical hypercortisolism; SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; AC, accuracy; AI, adrenal incidentaloma; ACTH (SI conversion factor×0.22); 1 mg-DST, cortisol after 1 mg overnight dexamethasone-suppression test (SI conversion factor×27.56); UFC, urinary free cortisol (SI conversion factor×2.76); MSC, midnight serum cortisol (SI conversion factor×27.56).
[a]Cut-off obtained by ROC analysis (see section Methods).

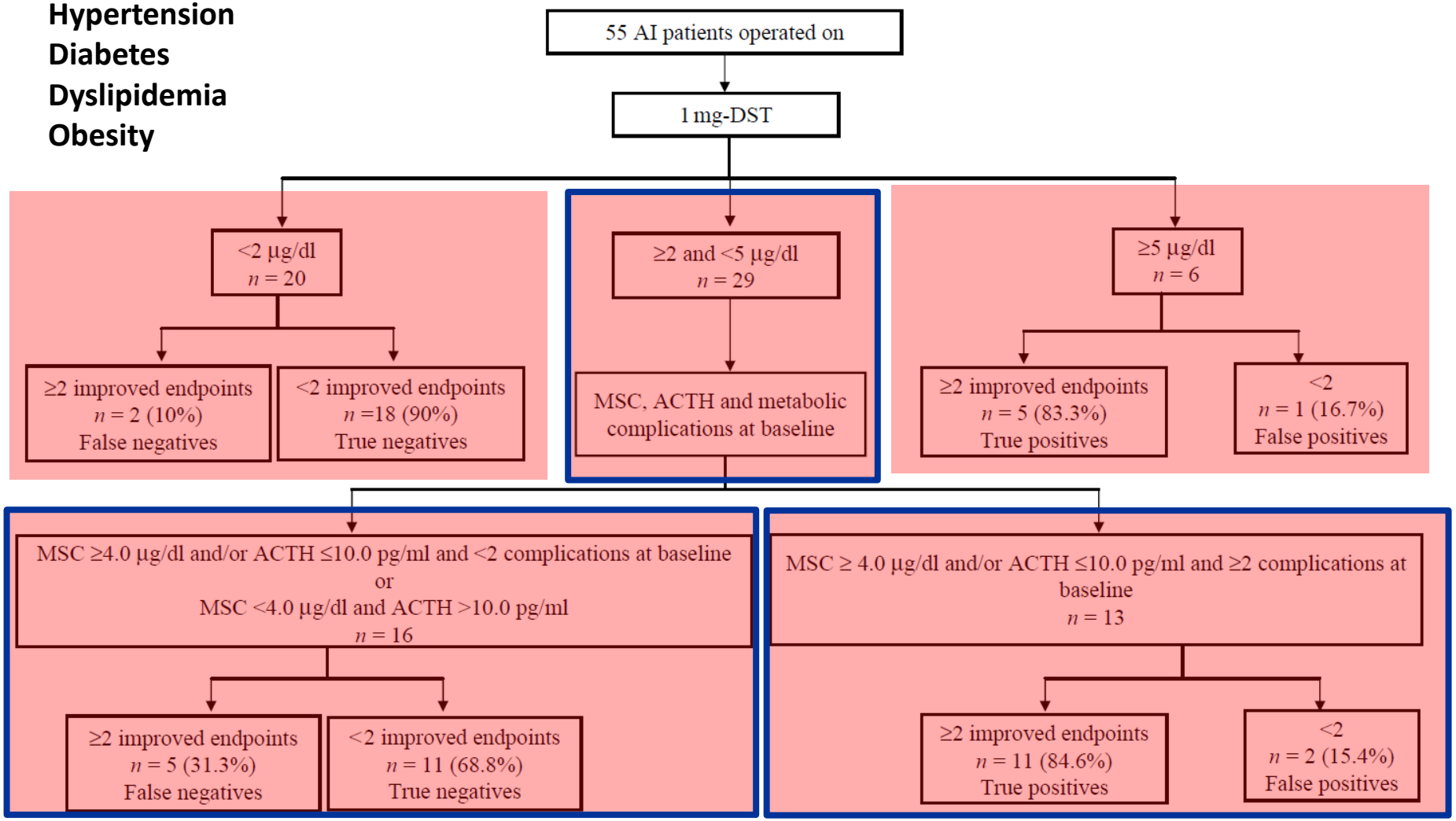
The DST-UFC-ACTH combination criterion was confirmed to be useful because it showed the best accuracy also in predicting the worsening of the endpoints (sensitivity, 55.6%; specificity, 82.9%), in the conservatively treated subjects.

Eller Vainicher C. et al, EJE 2010

How to predict who can benefit from surgery

End-points:

Hypertension
Diabetes
Dyslipidemia
Obesity



Using this protocol in 45 out of the 55 (81.2%) treated AI patients the improvement after surgery of >2 endpoints was correctly predicted before surgery.

Eller Vainicher et al, EJE 2010

Surgery in SH: why yes?

Even though:

- prospective randomized trials comparing surgically treated and conservatively treated with and without SH are lacking,
- the diagnosis of SH is not accurate in predicting the outcome after surgery .....

Available data suggest that:

- surgery positively affects blood pressure and glucose metabolism,
- the optimization of the medical therapy is not completely free of adverse events
- adrenal surgery is becoming increasingly safer by endoscopic procedures.
- SH seems to be associated with increased cardiovascular events and mortality

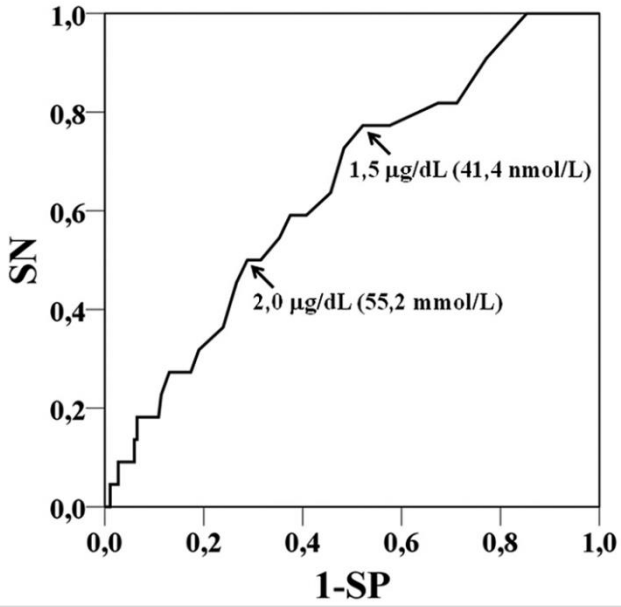
Finally, because patients with SH seem to worsen if not surgically treated, the economic costs of surgery have to be compared with those of curing the possible consequences of SH (i.e. chronic complications of diabetes and hypertension and fractures).

Chiodini I, J Clin Endocrinol Metab 2011

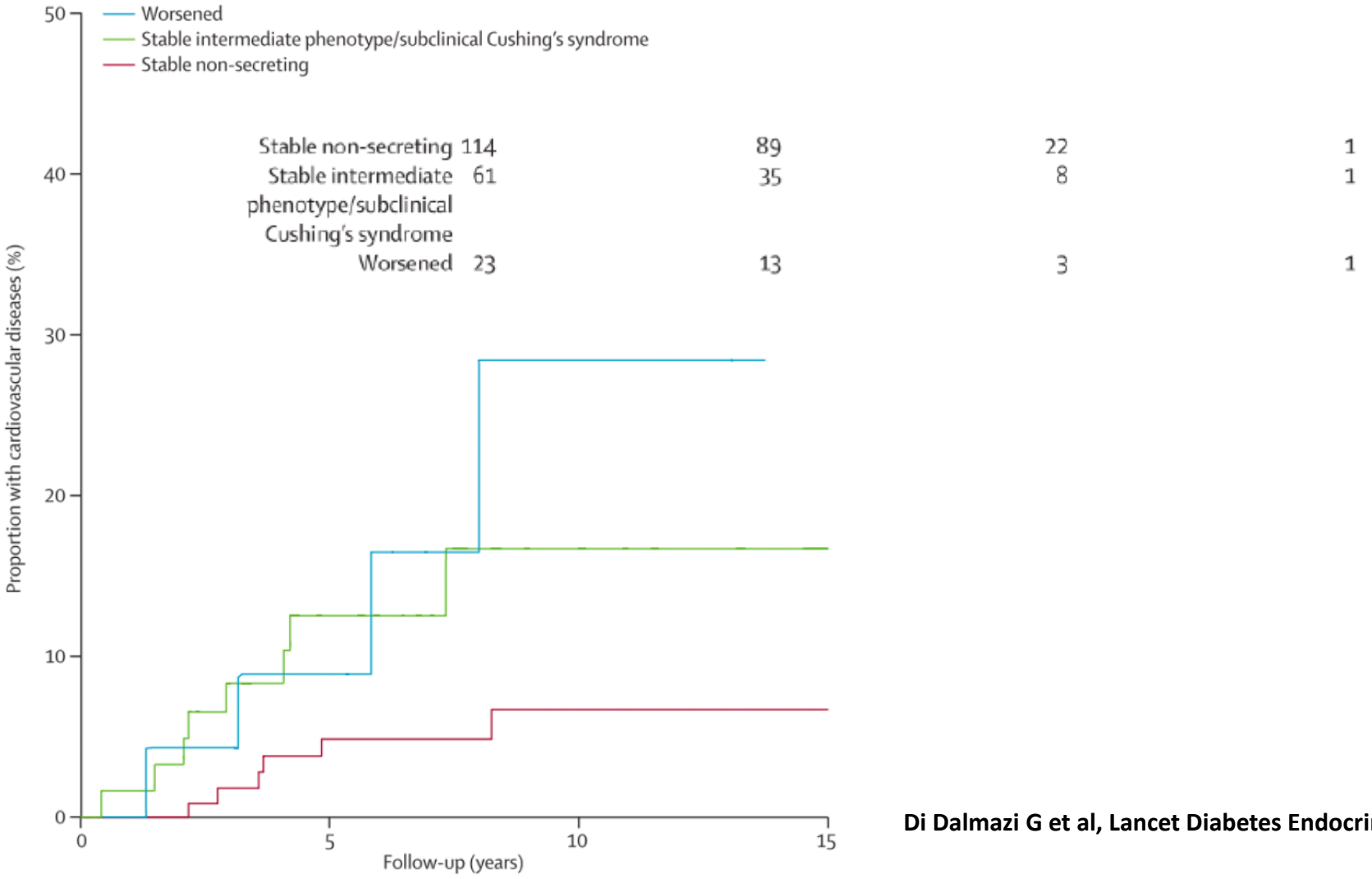
RISK OF CARDIOVASCULAR EVENTS IN ENDOGENOUS SUBCLINICAL HYPERCORTISOLISMS

Morelli V et al, J Clin Endocrinol Metab 2014

	SH+ Group	SH− Group	*P*
n	39	167	
Duration of follow-up, mo	79.4 ± 25.2	83.2 ± 33.6	.826
New CVE	8 (20.5)	14 (8.4)	.040
New CVE in CVE− patients at baseline	4 (10.0)	11 (6.6)	.343
Increased body weight[a]	13 (33.3)	40 (24.0)	.229
Worsened blood pressure control[b]	18 (46.2)	52 (31.1)	.070
Worsened glycemic control[c]	12 (30.8)	39 (23.4)	.334
Worsened LDL[c]	7 (17.9)	20 (12.0)	.303

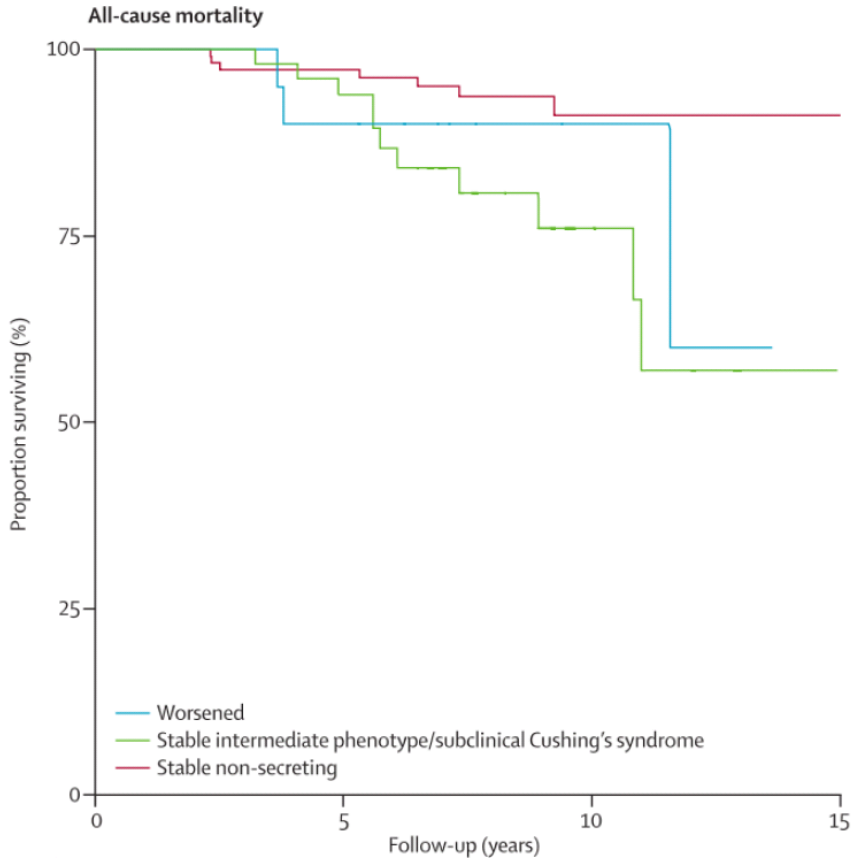


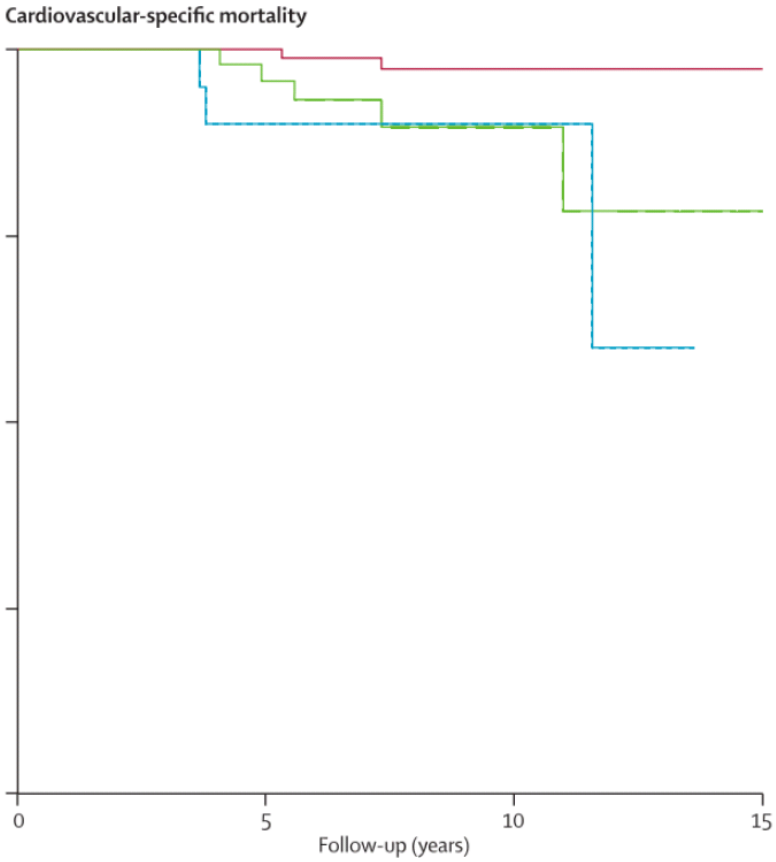
CARDIOVASCULAR EVENTS AND MORTALITY IN PATIENTS WITH ADRENAL INCIDENTALOMAS



Di Dalmazi G et al, Lancet Diabetes Endocrinol. 2014

CARDIOVASCULAR EVENTS AND MORTALITY IN PATIENTS WITH ADRENAL INCIDENTALOMAS



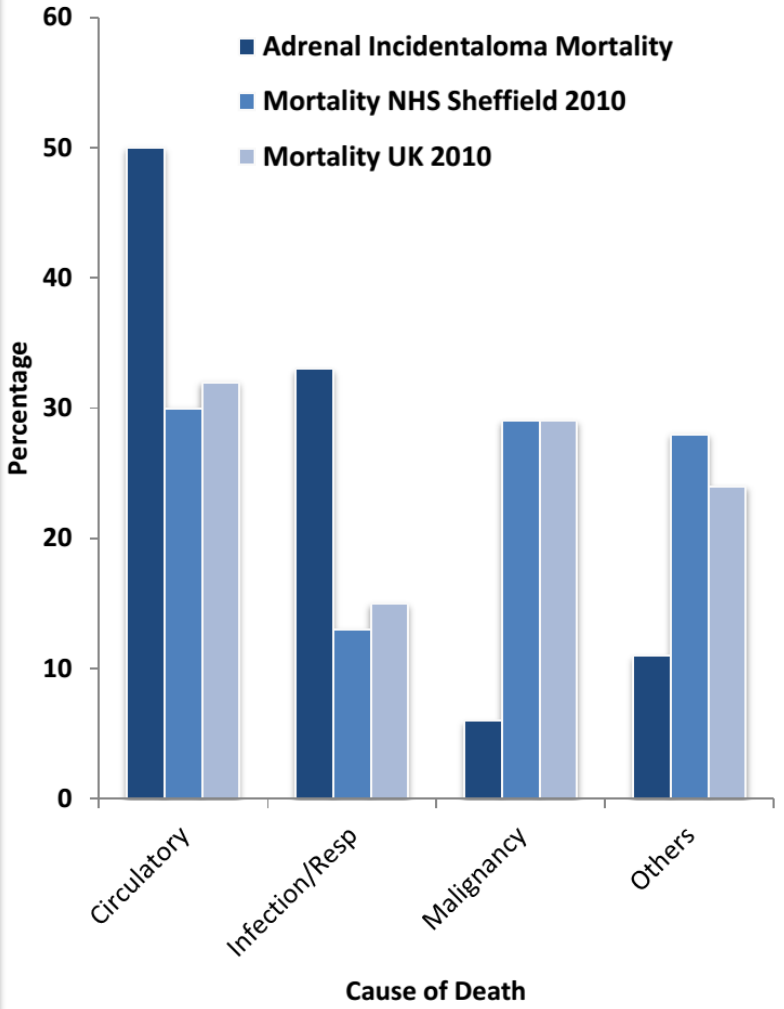


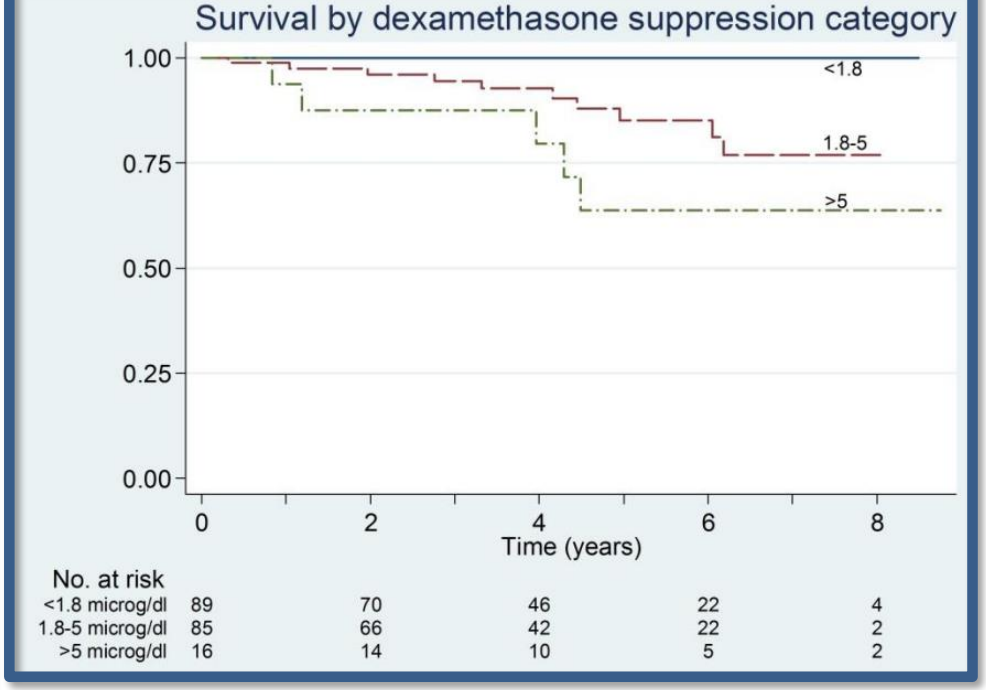
Stable non-secreting	114	94	25	3	114	93	24	3
Stable intermediate phenotype/subclinical Cushing's syndrome	61	41	9	1	61	42	10	1
Worsened	23	16	4	1	23	15	4	1

Di Dalmazi G et al, Lancet Diabetes Endocrinol. 2014

CORTISOL AS A MARKER FOR INCREASED MORTALITY IN PATIENTS WITH INCIDENTAL ADRENOCORTICAL ADENOMAS

Newell-Price et al, J Clin Endocrinol Metab 2014





- January 2005 and July 2013
- 206 patients with a benign adrenocortical adenoma
- Follow up of 4.2±2.3 years
- 18 deaths

THE TREATMENT OF ADRENAL INCIDENTALOMA AND SUBCLINICAL HYPERCORTISOLISM: TAKE HOME MESSAGES

- The choice of patients who need surgery may depend on the presence of possible complications.
- The recovery from SH seems to lead to a metabolic improvement.
- Patients who do not undergo surgery need a careful follow-up.
- Only a study, in which a large sample of consecutive patients with adrenal incidenaloma with possible subclinical hypercortisolism (i.e, 1mgDST between 1.8 and 5 mcg/dL) will be randomized to surgery or follow up, may answer to the questions:

- Is surgery useful in patients with adrenal incidentaloma and subclinical hypercortisolism ?
- Who has to be operated on?

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THANK YOU