



LUNDS
UNIVERSITET

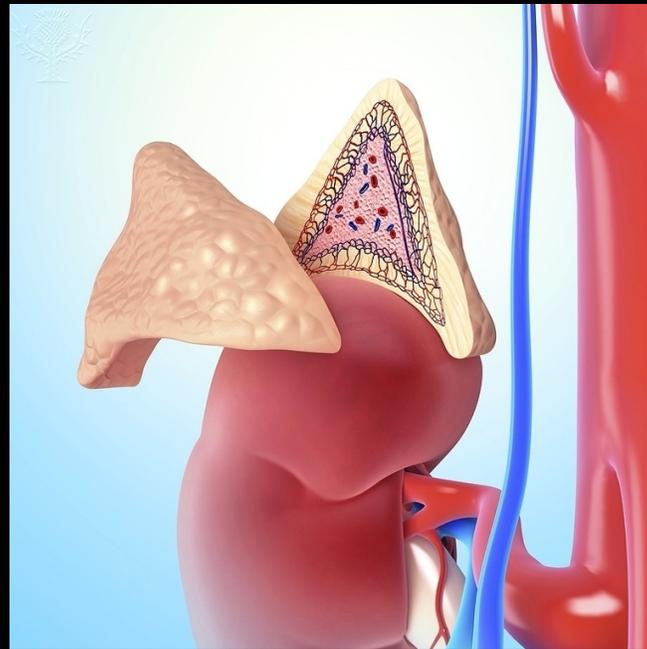
Autonom kortisolsekretion

Albin Kjellbom, Skånes universitetessjukhus



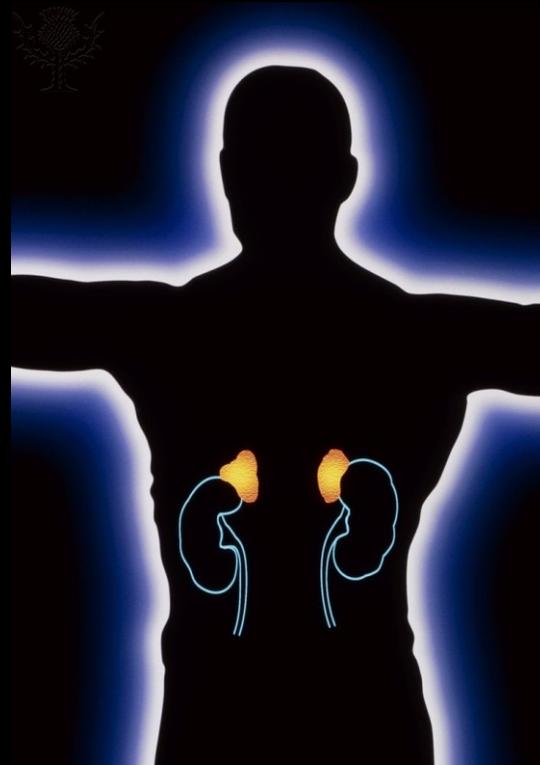
Autonom kortisolsekretion

”Vanligt endokrint tillstånd som medför en betydande risk att dö i förtid”



Agenda

- Bakgrund
- Definition och diagnostik av autonom kortisolsekretion (ACS)
- Mortalitet vid ACS
- Behandling
- Take home message



Acta med. scand. Vol. 184, pp. 211–214, 1968

ON THE PREVALENCE OF ADRENOCORTICAL ADENOMAS
IN AN AUTOPSY MATERIAL IN RELATION TO HYPERTENSION AND DIABETES

Hans Hedeland, Görel Östberg and Bernt Hökfelt

*From the Departments of Endocrinology and Pathology, Lund University Clinics,
General Hospital, Malmö, Sweden*

Abstract. A prospective study was performed on an autopsy material consisting of 739 consecutive cases over 20 years of age (391 females, 348 males) during a period of six months. The material included about 70% of the deaths in the city of Malmö (approximately 250,000 inhabitants). The adrenals were specially observed at autopsy for adenomas and hospital records were searched for hypertension and diabetes mellitus.



*

Postgrad Med J 1996; 72: 207–210 © The Fellowship of Postgraduate Medicine, 1996

Subclinical endocrinological disease

Series editor: Dr JWF Elte, Department of Internal Medicine, Sint Franciscus Gasthuis, Rotterdam, The Netherlands

**Adrenal incidentaloma: subclinical
Cushing's syndrome**

John Newell-Price, Ashley Grossman

Prevalens och etiologi av binjureincidentalom

~5 % av den vuxna befolkningen, kvinnor>män

~80-90 % barkadenom

~ 20-45 % autonom kortisolsekretion

~ 2 % primär aldosteronism

- Ingen risk för malign transformation
- Låg risk för utveckling av overt Cushings syndrom

Definition

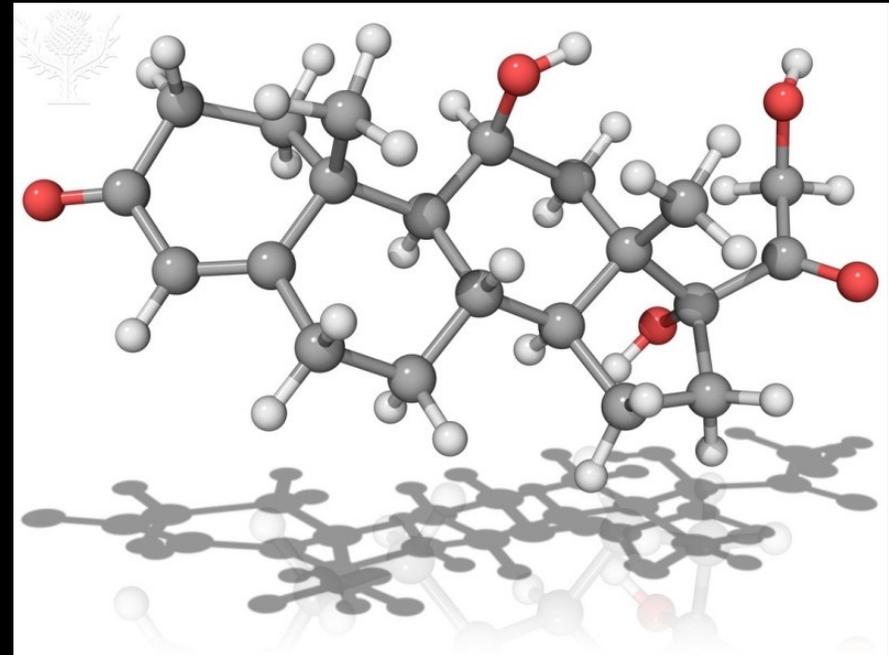
Subkliniskt Cushings syndrom – Subklinisk hyperkortisolism
Autonom kortisolsekretion (ACS) – Mild autonom kortisolsekretion (MACS)

European Society of Endocrinology, guidelines 2016

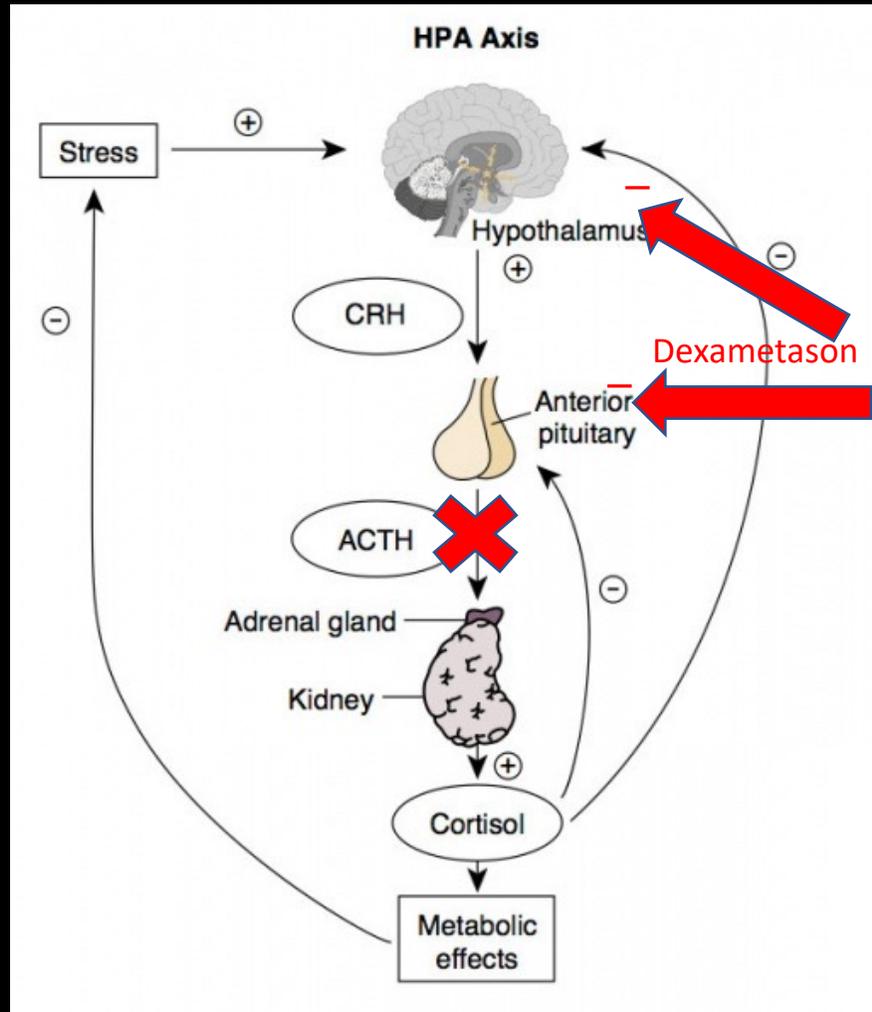
- 1-mg dexametasonhämningstest (DST)
 - p-kortisol:
 - <50 nmol/L utesluter ACS
 - 50-137 nmol/L "möjlig ACS"
 - ≥138 nmol/L ACS
- + ev annat diagnostiskt test

Diagnostik

- 1-mg dexametasonhämningstest
- *Salivkortisol vid midnatt*
- *Urinkortisol*
- *Lågt basalt ACTH*
- *DHEAS*
- *(Steroidprofil)*



Dexametasonhämningstest (DST)



1-mg DST

Felkällor t ex

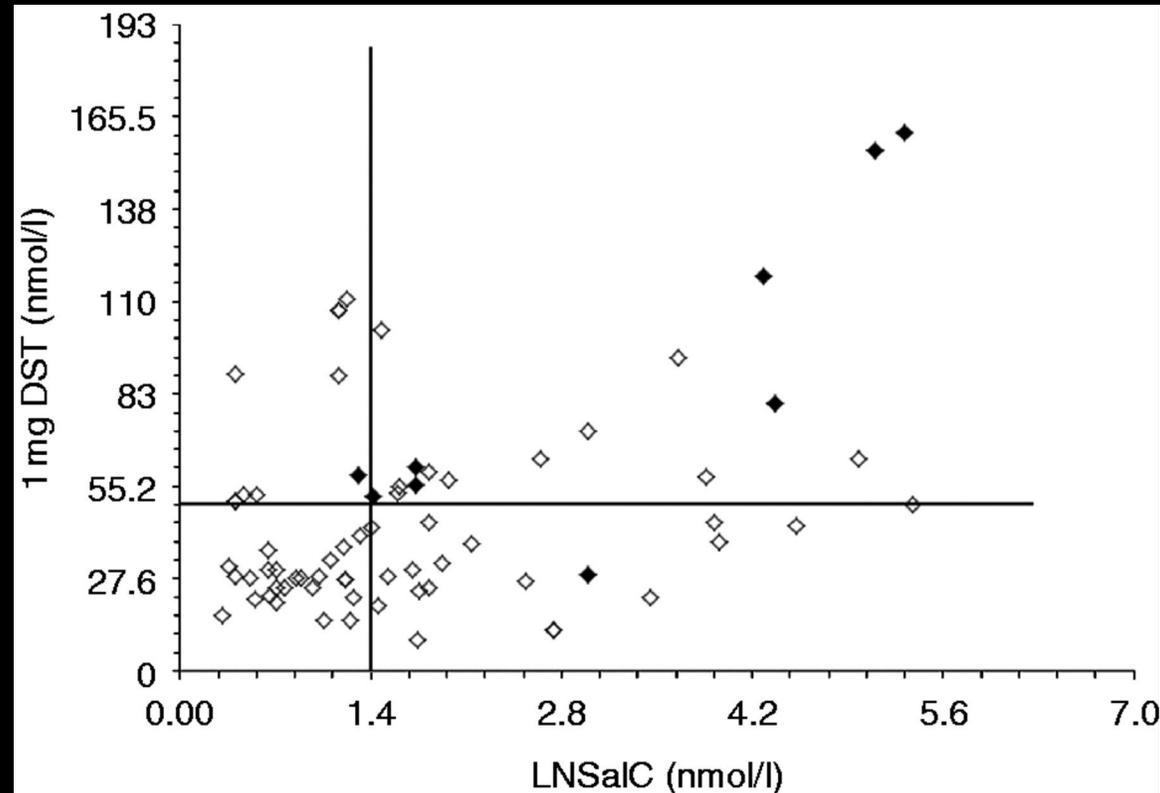
- Läkemedel
 - Inducerar CYP3A3
 - Östrogenbehandling
- Polymorfism i CYP3A3

Salivkortisol vid midnatt

CLINICAL STUDY

The role of salivary cortisol measured by liquid chromatography–tandem mass spectrometry in the diagnosis of subclinical hypercortisolism

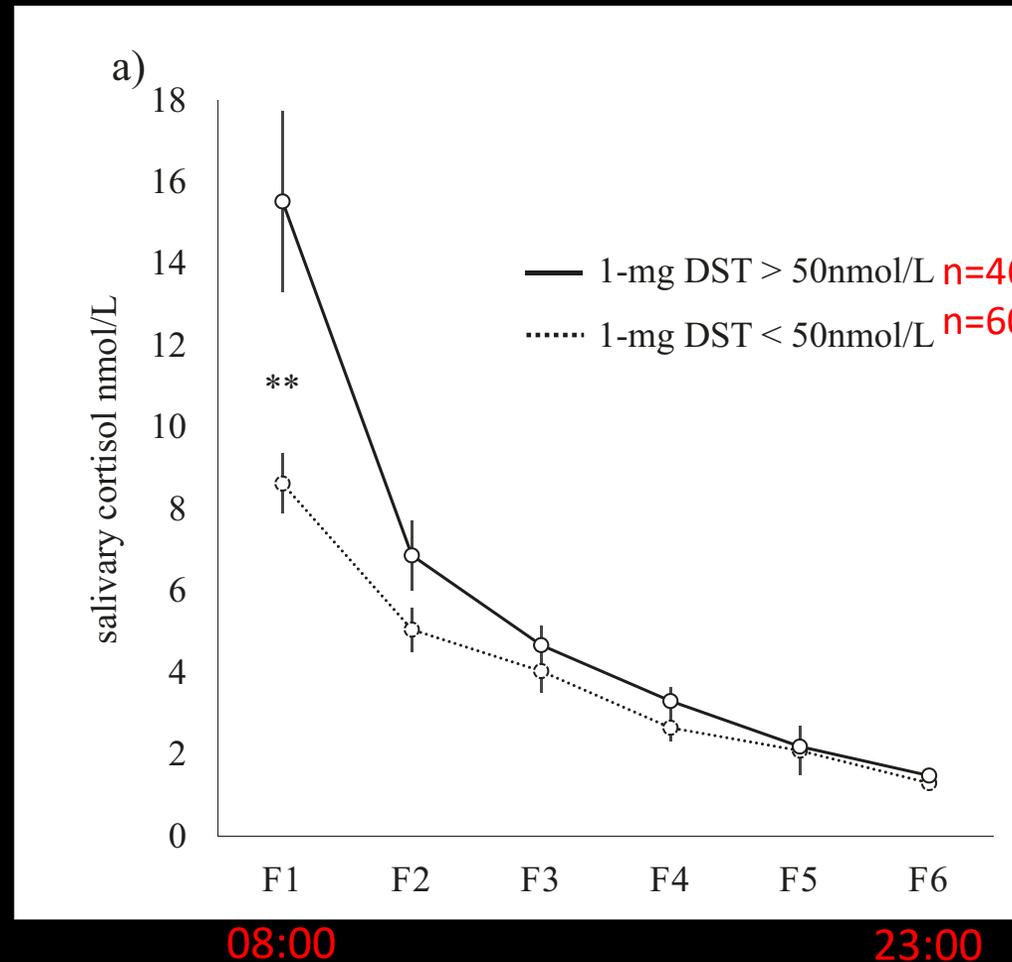
S Palmieri, V Morelli, E Polledri, S Fustinoni, R Mercadante, L Olgiati, C Eller Vainicher, E Cairoli, V V Zhukouskaya, P Beck-Peccoz and I Chiodini



*

Daily salivary cortisol and cortisone rhythm in patients with adrenal incidentaloma

Filippo Ceccato¹ · Mattia Barbot¹ · Nora Albiger¹ · Giorgia Antonelli² ·
Marialuisa Zilio¹ · Marco Todeschini¹ · Daniela Regazzo¹ · Mario Plebani² ·
Carmelo Lacognata³ · Maurizio Iacobone⁴ · Franco Mantero¹ · Marco Boscaro¹ ·
Carla Scaroni¹



24h-Urinkortisol

Appendix Table 5. Clinical Characteristics of ENSAT EURINE-ACT Study Participants With Unilateral Versus Bilateral Benign Adrenocortical Tumors*

Characteristic	NFAT + MACS (n = 1240)		NFAT Only (n = 649)		MACS Only (n = 591)	
	Unilateral Tumors (n = 955)	Bilateral Tumors (n = 285)	Unilateral Tumors (n = 542)	Bilateral Tumors (n = 107)	Unilateral Tumors (n = 413)	Bilateral Tumors (n = 178)
Median 24-hour UFC (IQR), nmol	127 (58-204)	174 (86-254)	124 (63-196)	177 (83-257)	127 (55-213)	168 (94-246)

Table 3. 24-Hour Steroid Metabolite Excretion in Persons With Benign Adrenocortical Tumors and Different Degrees of Cortisol Excess*

Steroid Metabolite Excretion	NFAT (n = 649)	MACS-1 (n = 451)	MACS-2 (n = 140)	Adrenal CS (n = 65)
Median cortisol excretion (IQR), µg/24 h	45 (28 to 65)	54 (32 to 82)	57 (33 to 92)	151 (76 to 344)
Change compared with NFAT (95% CI), %	-	23 (15 to 32)	33 (21 to 46)	131 (113 to 148)

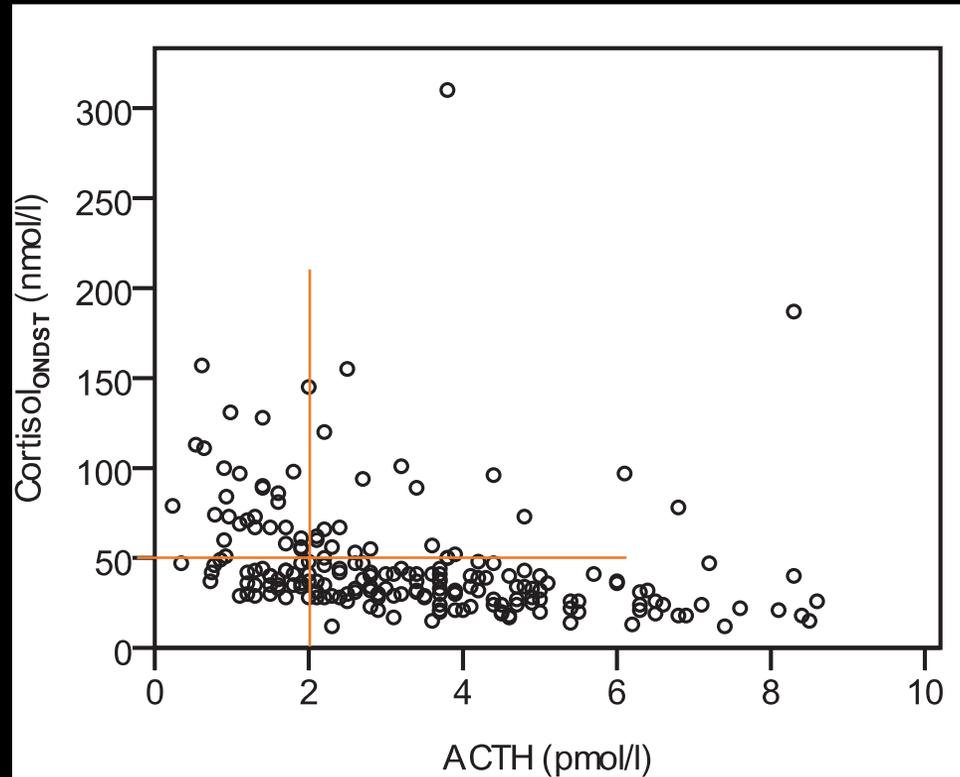
MACS-1: 50-138 nmol/L

MACS-2: >138 nmol/L

Lågt basalt ACTH

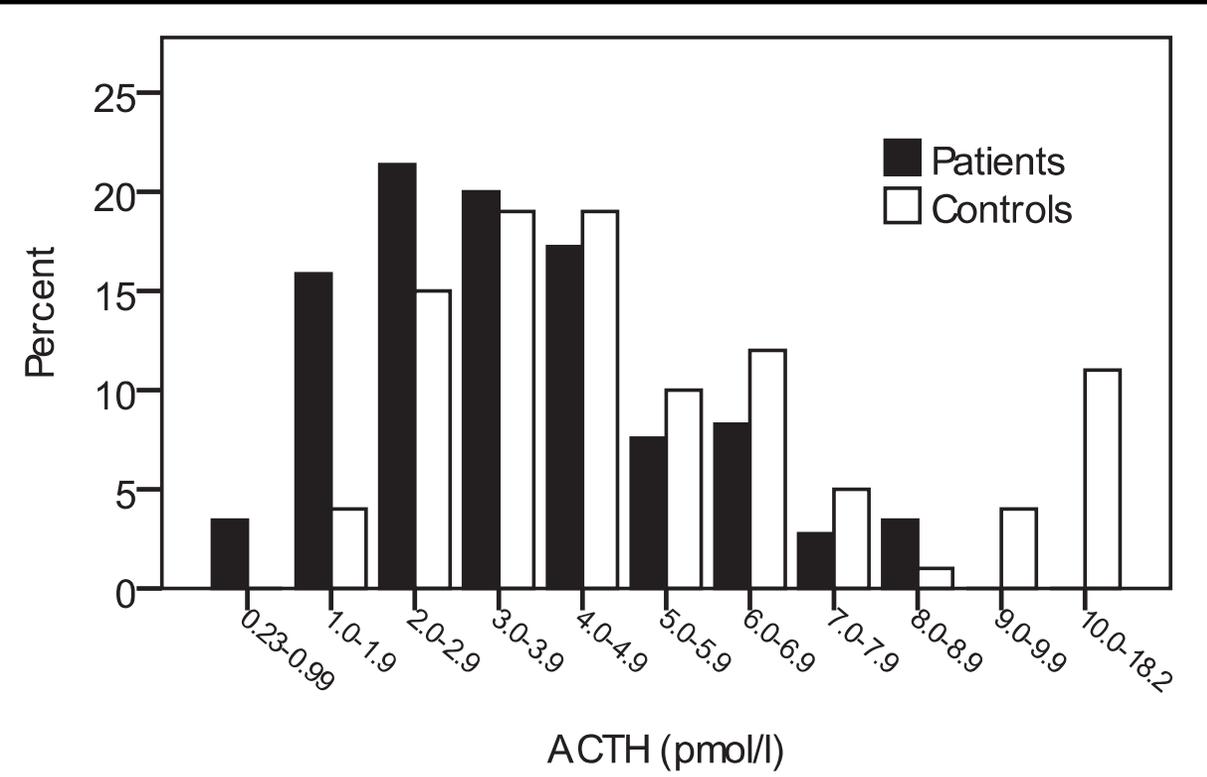
Suppressed ACTH Is Frequently Unrelated to Autonomous Cortisol Secretion in Patients With Adrenal Incidentalomas

Henrik Olsen,^{1,2} Albin Kjellbom,¹ Magnus Löndahl,^{1,2} and Ola Lindgren^{1,2}



Kortisol ≥ 50 nmol/L efter DST

- 53% lågt ACTH



Kortisol < 50 nmol/L efter DST

- 19% lågt ACTH vs 4% av kontroller

DHEAS

	Kappa index	Specific Po+ (%)	Specific Po- (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Considering the gold standard of ACS a DST > 50.0 nmol/L (1.8 µg/dL)							
UFC > 1931 nmol/24 h	0.086	24.5	75.0	15.8	91.7	54.5	63.4
ACTH < 2 pmol/L	0.235	51.4	72.0	48.7	74.4	54.4	69.8
LNSC > 157 nmol/L	0.179	35.8	76.4	25.0	90.9	63.3	65.9
Low sex- and age-adjusted DHEA-S	0.103	37.1	71.1	30.3	79.3	47.9	64.4

Mortalitetsrisk vid ACS



Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with intermediate phenotype or subclinical Cushing's syndrome: a 15-year retrospective study

Guido Di Dalmazi, Valentina Vicennati, Silvia Garelli, Elena Casadio, Eleonora Rinaldi, Emanuela Giampalma, Cristina Mosconi, Rita Golfieri, Alexandro Paccapelo, Uberto Pagotto, Renato Pasquali

Cortisol as a marker for increased mortality in patients with incidental adrenocortical adenomas

Miguel Debono, Mike Bradburn, Matthew Bull, Barney Harrison, Richard J Ross, John Newell-Price

Increased mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: a 13-year retrospective study from one center

Jekaterina Patrova ^{1,2,3} · **Magnus Kjellman**^{2,4} · **Hans Wahrenberg**^{1,5} · **Henrik Falhammar**^{1,2}

Annals of Internal Medicine

ORIGINAL RESEARCH

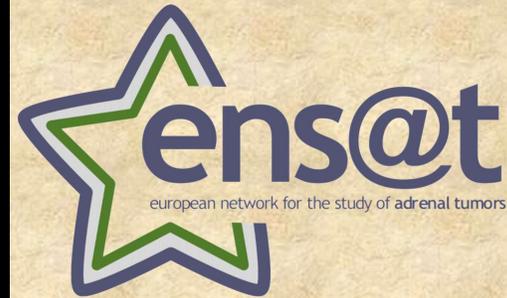
Association Between Mortality and Levels of Autonomous Cortisol Secretion by Adrenal Incidentalomas

A Cohort Study

Albin Kjellbom, MD; Ola Lindgren, MD; Shobitha Puvaneswaralingam, MD; Magnus Löndahl, MD; and Henrik Olsen, MD

YEAR IN REVIEW 2021

		
		
	<p>Original Perspectives on the Year's Most Important Clinical Topics in General Medicine from the Editors of NEJM Journal Watch</p>	



**ENS@T Award 2021 for
Research on
Non-Aldosterone Producing
Adenoma**

Albin Kjellbom

„Association between mortality and levels of autonomous cortisol
secretion by adrenal incidentalomas : a cohort Study “

eMeeting, 2nd of October 2021

G. Assié, president of ENS@T

Målsättning

- Är ACS en oberoende riskfaktor för död?
- Undersöka sambandet mellan mortalitet och olika nivåer av ACS

- Totalmortalitet
- Orsaksspecifik död

Metod

- Kohortstudie
- Konsekutiva patienter med AI (2005-2015)
- Förbestämda nivåer av kortisol efter DST (nmol/L);
 - <50
 - 50-82
 - 83-137
 - ≥ 138
- Utfallsdata från dödsorsaksregistret

Resultat

- 1048 patienter inkluderades
- 6,4 års uppföljningstid
- Medianålder 65 år
- 59 % kvinnor
- 45 % kortisol ≥ 50 nmol/L efter DST
- 170 dödsfall
- 151 MACE

Table 2. Adjusted HRs for All-Cause Mortality*

Variable	HR (95% CI) for All-Cause Mortality	
	Adjusted for the 6 Predefined Covariates	Additionally Adjusted for Medical History of Cancer and Diabetes
Sex (females vs. males)	0.66 (0.48-0.90)	0.65 (0.48-0.89)
Age (per year)	1.08 (1.06-1.10)	1.08 (1.06-1.10)
Previous cardiovascular disease (yes vs. no)	1.73 (1.24-2.42)	1.74 (1.25-2.42)
Smoker (yes vs. no)	1.78 (1.30-2.44)	1.79 (1.00-2.45)
eGFR <60 mL/min/1.73 m ² (yes vs. no)	1.56 (1.09-2.22)	1.51 (1.06-2.15)
Cortisol _{DST} 50-82 vs. <50 nmol/L	1.15 (0.78-1.70)	1.17 (0.79-1.73)
Cortisol _{DST} 83-137 vs. <50 nmol/L	2.30 (1.52-3.49)	2.33 (1.53-3.53)
Cortisol _{DST} ≥138 vs. <50 nmol/L	3.04 (1.86-4.98)	2.87 (1.74-4.74)
Medical history of cancer (yes vs. no)	Not included	1.40 (0.99-1.99)
Diabetes mellitus (yes vs. no)	Not included	1.59 (1.13-2.23)

Table 3. Predicted All-Cause Mortality at 2, 5, and 10 Years in 2 Patient Groups With Different Mortality Risk

Patient Group and Time Point	Mean Mortality (95% CI), %				Difference, %	
	Patients With Cortisol _{DST} <50 nmol/L	Patients With Cortisol _{DST} 50-82 nmol/L	Patients With Cortisol _{DST} 83-137 nmol/L	Patients With Cortisol _{DST} ≥138 nmol/L	Cortisol _{DST} 83-137 vs. <50 nmol/L	Cortisol _{DST} ≥138 vs. <50 nmol/L
Female, 65 y old, nonsmoker, no preexisting CVD, and eGFR ≥60 mL/min/1.73 m²						
2 y	0.5 (0.3-0.9)	0.6 (0.3-1.1)	1.1 (0.6-2.1)	1.5 (0.8-2.8)	0.6	1.0
5 y	3.1 (2.2-4.4)	3.6 (2.5-5.3)	7.1 (4.6-11.0)	9.3 (6.0-14.4)	4.0	6.2
10 y	8.9 (6.4-12.4)	10.2 (6.8-15.4)	19.4 (13.8-27.3)	24.8 (15.6-39.6)	10.5	15.9
Male, 70 y old, smoker, preexisting CVD, and eGFR ≥60 mL/min/1.73 m²						
2 y	3.5 (1.9-6.4)	4.0 (2.3-7.1)	7.8 (4.7-13.2)	10.2 (6.1-17.3)	4.3	6.7
5 y	19.9 (13.3-29.8)	22.6 (14.7-34.7)	40.0 (28.6-55.8)	49.1 (34.7-69.3)	20.1	29.2
10 y	47.8 (34.5-66.1)	52.7 (38.1-72.9)	77.6 (62.0-97.1)	86.1 (73.9-100.0)	29.8	38.3

Förhållandet mellan kortisol efter DST som kontinuerlig variabel och mortalitetsrisk

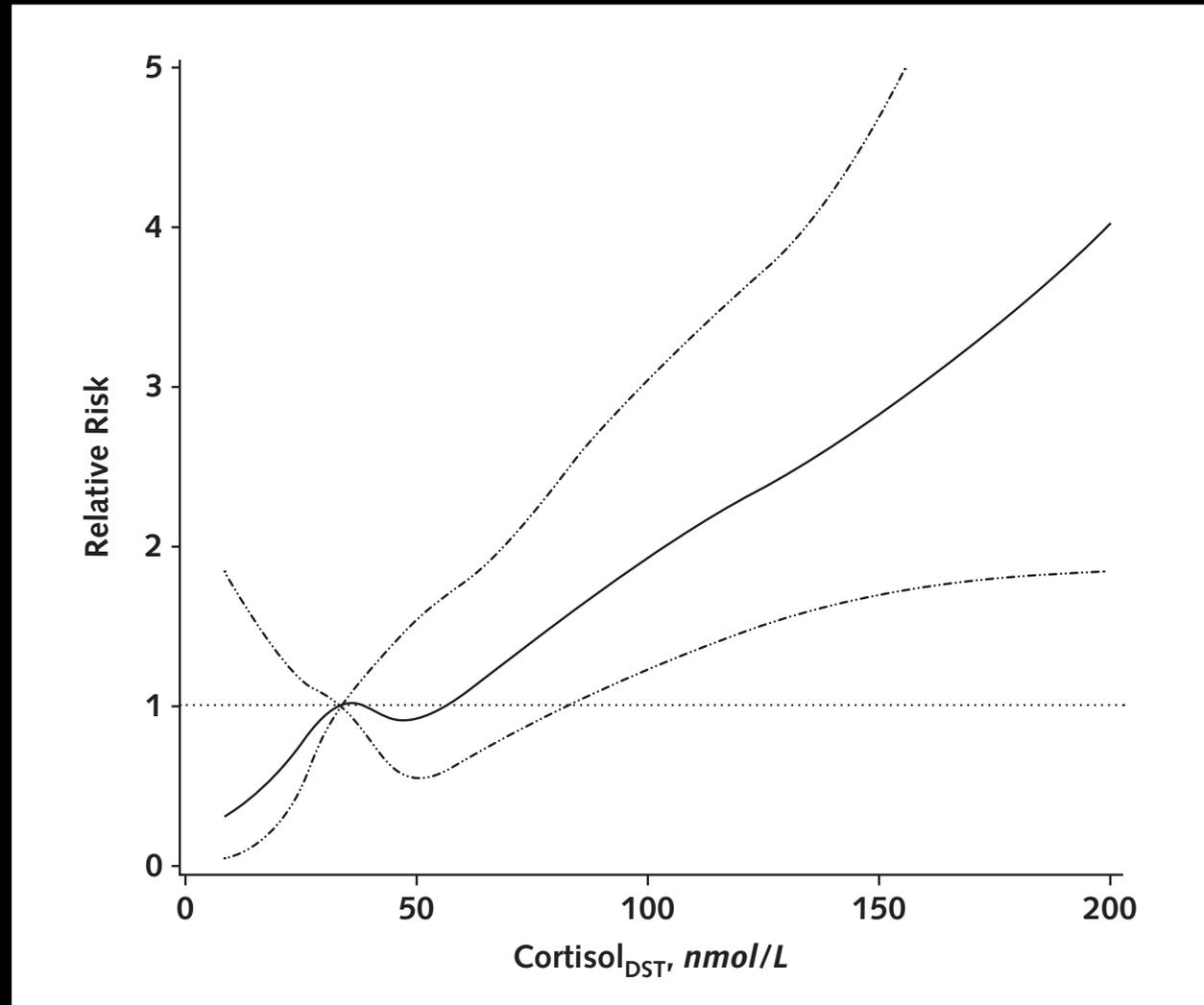


Table 4. Cause-Specific Mortality, According to CortisolDST Group*

Disease Category	Deaths, <i>n</i>	Cortisol_{DST} <50 nmol/L (<i>n</i> = 575)	Cortisol_{DST} 50-82 nmol/L (<i>n</i> = 272)	Cortisol_{DST} ≥83 nmol/L (<i>n</i> = 201)
Cardiovascular diseases	65	1.00	0.93 (0.48-1.80)	2.33 (1.27-4.28)
Cancer	51	1.00	1.67 (0.82-3.34)	2.00 (0.98-4.09)
Infectious diseases	6	1.00	1.32 (0.20-8.59)	1.45 (0.17-12.4)
Other diseases†	48	1.00	0.98 (0.47-2.05)	1.78 (0.88-3.61)

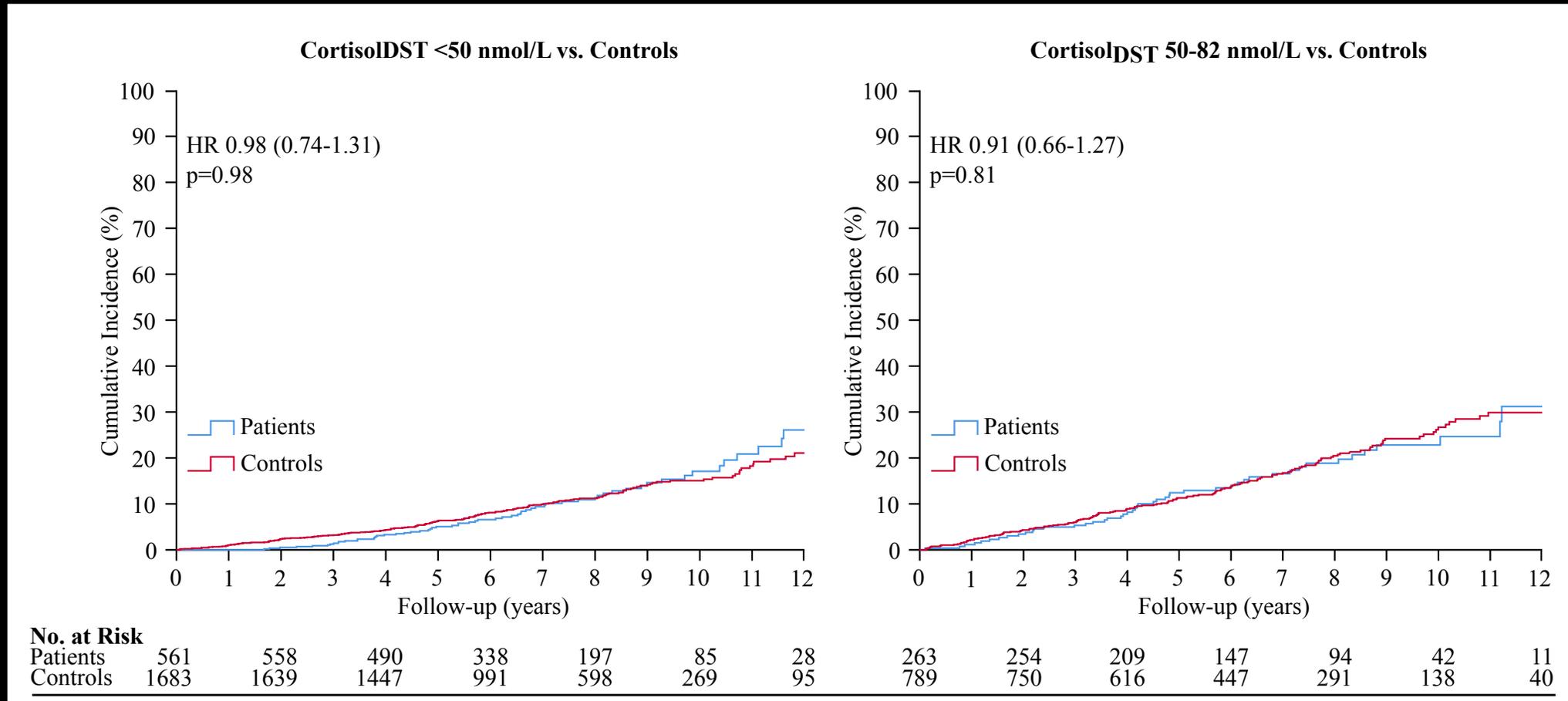
Svagheter

- ACS baserat på ett DST
- Uppföljningstid
- Dödsorsaksregistret

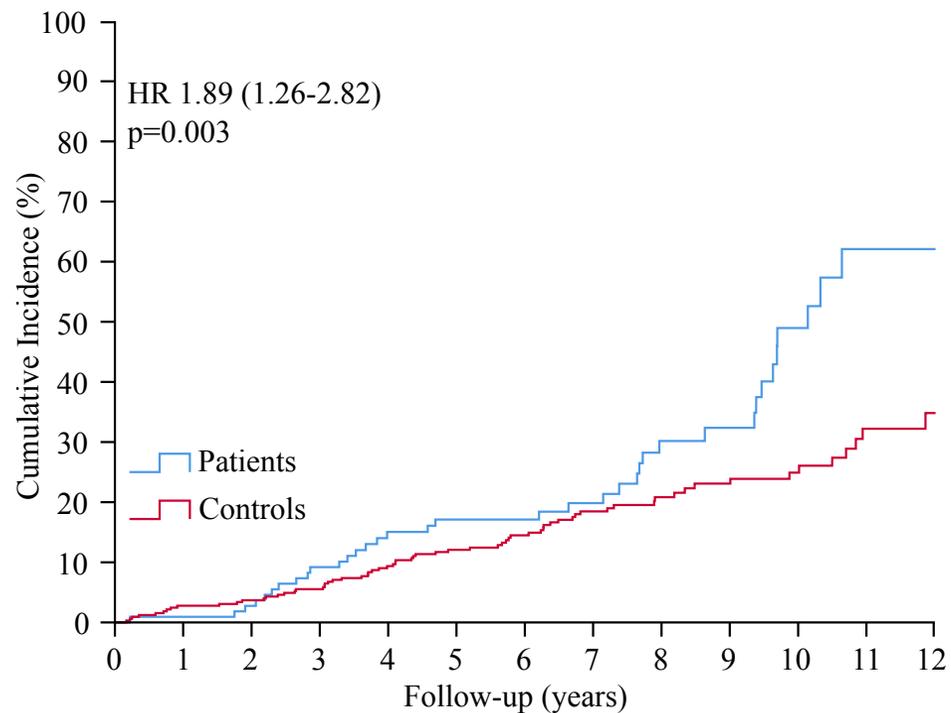
Slutsatser

- ACS är en oberoende riskfaktor för död
- Associationen mellan kortisol efter DST och mortslitesrisk är linjär
- Risken ser ut att bli kliniskt relevant vid kortisol ≥ 83 nmol/L

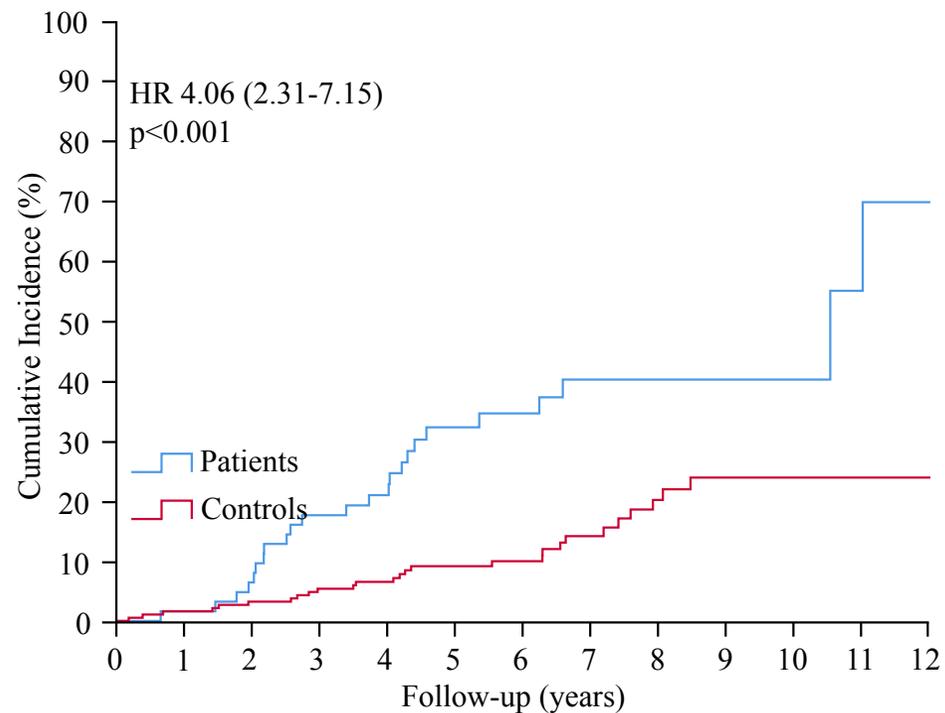
Mortalitetsrisk hos patienter med AI jmf med kontroller



Cortisol_{DST} 83-137 nmol/L vs. Controls



Cortisol_{DST} ≥138 nmol/L vs. Controls



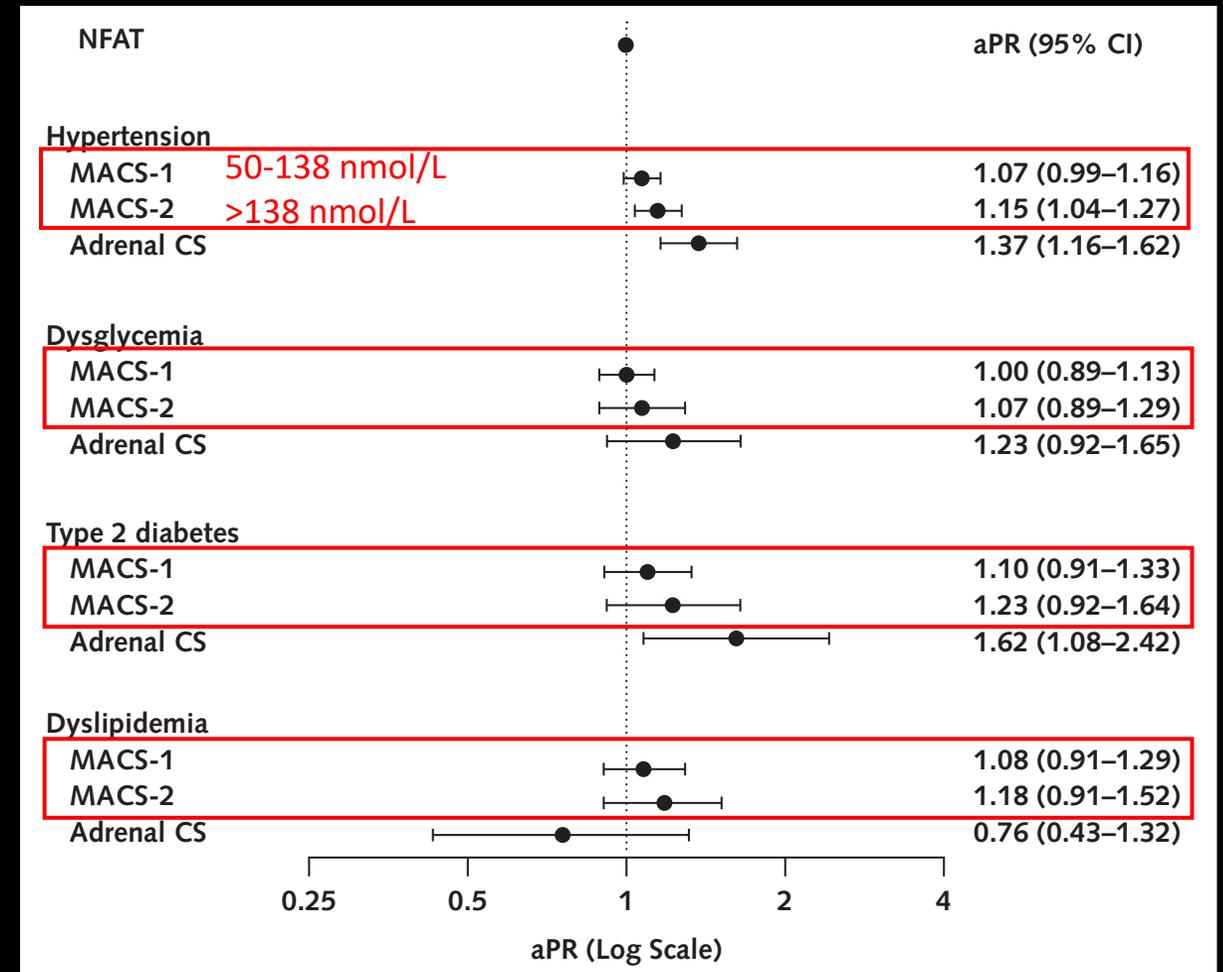
No. at Risk

Patients	109	106	84	63	35	14	3
Controls	327	314	273	200	119	66	25

Patients	62	58	43	25	13	4	1
Controls	186	179	149	92	47	14	12

Varför är ACS farligt?

- Mortalitetsrisken kan inte förklaras enbart av ökad förekomst av "klassiska" kardiovaskulära riskfaktorer
- Hyperkortisolism är associerat med
 - Vänsterkammerhypertrofi
 - Fibros i hjärtmuskeln
 - Förtjockad intima-media
 - Tromboembolism
 - ...



*

Behandlingsalternativ

- Sedvanlig behandling av kardiovaskulära riskfaktorer
- Adrenalektomi
- Läkemedel som påverkar steroidsyntes/glukokortikoidreceptorn



Kirurgi vs sedvanlig medicinsk behandling

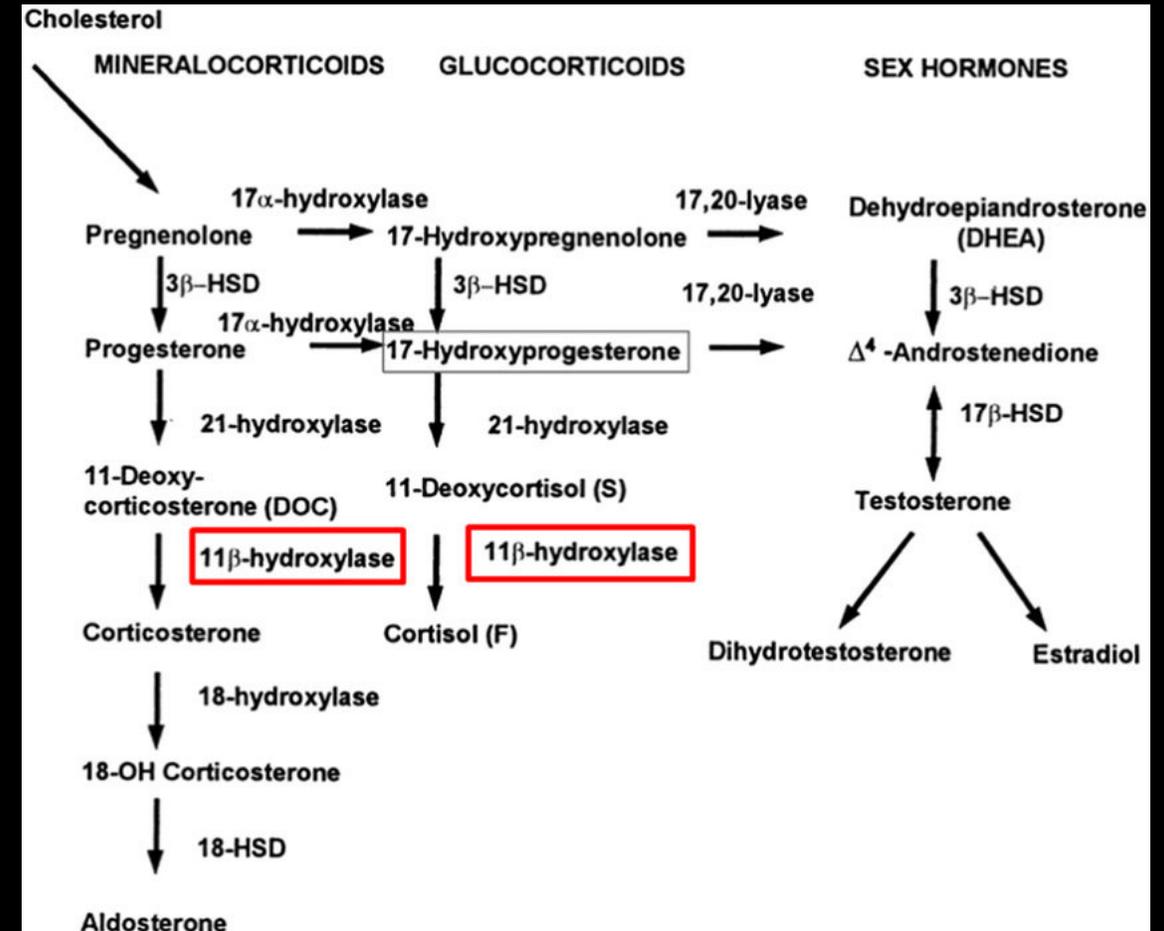
- Totalt ca 300 patienter studerade i ett tiotal studier
- Resultat, adrenalektomi kan ge blodtryckssänkning och minskad insulinresistens

Saknas randomiserade studier med hårda utfallsmått



Specifik farmakologisk behandling

- Metyrapon, 11 β -hydroxylashämmare
- Mifepriston /andra glukokortikoidreceptorhämmare



Kausalt samband?

Bradford Hill kriterierna

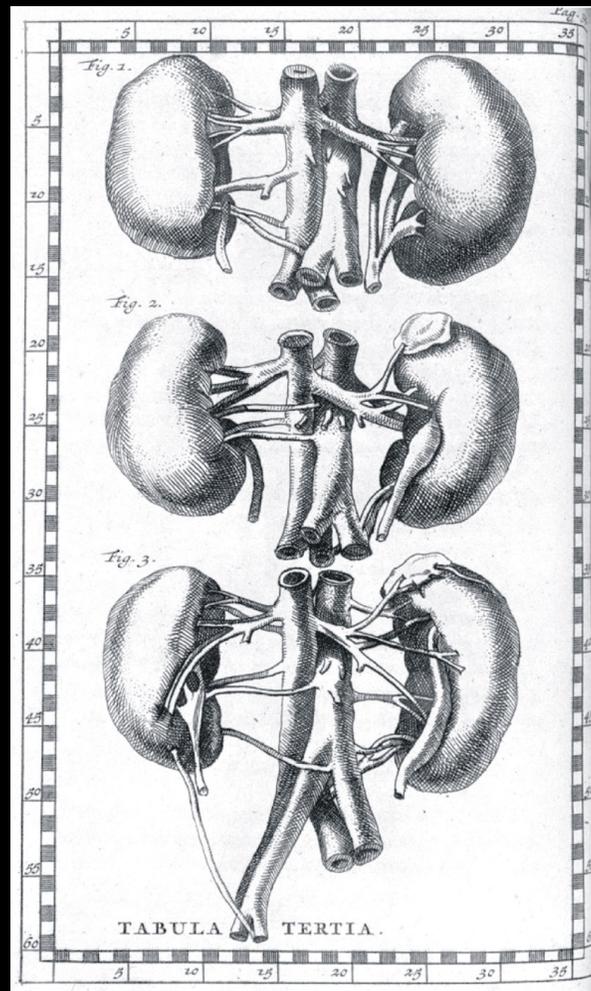
- Styrka – Associationens styrka
- Konsistens – Sambandet har observerats i olika populationer
- Specificitet – Saknas andra troliga förklaringar
- Temporalitet – Exponering före utfall
- Biologisk gradient - Dos-respons
- Plausibilitet – Trolig mekanism mellan exponering och utfall
- Koherens – Samstämmighet mellan epidemiologi och experiment
- **Experiment - Utfallet minskar om exponeringen upphör?**
- Analogi – Kausala samband för liknande faktorer



Take home message

- ACS är vanligt i befolkningen och "medför" en betydande mortalitetsrisk
- Kortisol efter DST är linjärt i förhållande till mortalitetsrisken
- Kortisol ≥ 83 nmol/L efter DST indikerar en kliniskt relevant riskökning
- Behandling... Oklart
 - Behandling av "klassiska" kardiovaskulära riskfaktorer
 - Väga in den nya kunskapen vid beslut om kirurgi

Frågestund



Referenser

- Araujo-Castro, M., A. García Cano, L. Jiménez Mendiguchía, H. F. Escobar-Morreale, and P. Valderrábano. 2021. 'Diagnostic accuracy of the different hormonal tests used for the diagnosis of autonomous cortisol secretion', *Sci Rep*, 11: 20539.
- Bancos, I., F. Alahdab, R. K. Crowley, V. Chortis, D. A. Delivanis, D. Erickson, N. Natt, M. Terzolo, W. Arlt, W. F. Young, Jr., and M. H. Murad. 2016. 'THERAPY OF ENDOCRINE DISEASE: Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing's syndrome: a systematic review and meta-analysis', *Eur J Endocrinol*, 175: R283-95.
- Belokovskaya, R., A. Ravikumar, D. Arumugam, S. Izadmehr, G. M. Goddard, E. B. Geer, and A. C. Levine. 2019. 'MIFEPRISTONE TREATMENT FOR MILD AUTONOMOUS CORTISOL SECRETION DUE TO ADRENAL ADENOMAS: A PILOT STUDY', *Endocr Pract*, 25: 846-53.
- Bovio, S., A. Cataldi, G. Reimondo, P. Sperone, S. Novello, A. Berruti, P. Borasio, C. Fava, L. Dogliotti, G. V. Scagliotti, A. Angeli, and M. Terzolo. 2006. 'Prevalence of adrenal incidentaloma in a contemporary computerized tomography series', *J Endocrinol Invest*, 29: 298-302.
- Bäcklund, N., G. Brattsand, M. Israelsson, O. Ragnarsson, P. Burman, B. Edén Engström, C. Høybye, K. Berinder, J. Wahlberg, T. Olsson, and P. Dahlqvist. 2020. 'Reference intervals of salivary cortisol and cortisone and their diagnostic accuracy in Cushing's syndrome', *Eur J Endocrinol*, 182: 569-82.
- Cambos, Sophie, and Antoine Tabarin. 2020. 'Management of adrenal incidentalomas: Working through uncertainty', *Best Practice & Research Clinical Endocrinology & Metabolism*, 34: 101427.
- Ceccato, F., C. Artusi, M. Barbot, L. Lizzul, S. Pinelli, G. Costantini, S. Niero, G. Antonelli, M. Plebani, and C. Scaroni. 2020. 'Dexamethasone measurement during low-dose suppression test for suspected hypercortisolism: threshold development with and validation', *J Endocrinol Invest*.
- Ceccato, Filippo, Mattia Barbot, Nora Albiger, Giorgia Antonelli, Marialuisa Zilio, Marco Todeschini, Daniela Regazzo, Mario Plebani, Carmelo Lacognata, Maurizio Iacobone, Franco Mantero, Marco Boscaro, and Carla Scaroni. 2018. 'Daily salivary cortisol and cortisone rhythm in patients with adrenal incidentaloma', *Endocrine*, 59: 510-19.
- Cohan, P., H. E. East, S. J. Galati, J. U. Mercado, P. J. Lim, M. Lamerson, J. J. Smith, A. L. Peters, and K. C. J. Yuen. 2019. 'Mifepristone Treatment in Four Cases of Primary Bilateral Macronodular Adrenal Hyperplasia (BMAH)', *J Clin Endocrinol Metab*, 104: 6279-90.
- Debono, M., M. Bradburn, M. Bull, B. Harrison, R. J. Ross, and J. Newell-Price. 2014. 'Cortisol as a marker for increased mortality in patients with incidental adrenocortical adenomas', *J Clin Endocrinol Metab*, 99: 4462-70.
- Debono, M., R. Chadarevian, R. Eastell, R. J. Ross, and J. Newell-Price. 2013. 'Mifepristone reduces insulin resistance in patient volunteers with adrenal incidentalomas that secrete low levels of cortisol: a pilot study', *PLoS One*, 8: e60984.
- Debono, M., R. F. Harrison, R. Chadarevian, C. Gueroult, J. L. Abitbol, and J. Newell-Price. 2017. 'Resetting the Abnormal Circadian Cortisol Rhythm in Adrenal Incidentaloma Patients With Mild Autonomous Cortisol Secretion', *J Clin Endocrinol Metab*, 102: 3461-69.
- Di Dalmazi, G., V. Vicennati, S. Garelli, E. Casadio, E. Rinaldi, E. Giampalma, C. Mosconi, R. Golfieri, A. Paccapelo, U. Pagotto, and R. Pasquali. 2014. 'Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with intermediate phenotype or subclinical Cushing's syndrome: a 15-year retrospective study', *Lancet Diabetes Endocrinol*, 2: 396-405.
- Elhassan, Y. S., F. Alahdab, A. Prete, D. A. Delivanis, A. Khanna, L. Prokop, M. H. Murad, M. W. O'Reilly, W. Arlt, and I. Bancos. 2019. 'Natural History of Adrenal Incidentalomas With and Without Mild Autonomous Cortisol Excess: A Systematic Review and Meta-analysis', *Ann Intern Med*, 171: 107-16.
- Fassnacht, M., W. Arlt, I. Bancos, H. Dralle, J. Newell-Price, A. Sahdev, A. Tabarin, M. Terzolo, S. Tsagarakis, and O. M. Dekkers. 2016. 'Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors', *Eur J Endocrinol*, 175: G1-G34.
- Genere, N., R. J. Kaur, S. Athimulam, M. A. Thomas, T. Nippoldt, M. Van Norman, R. Singh, S. Grebe, and I. Bancos. 2021. 'Interpretation of Abnormal Dexamethasone Suppression Test is Enhanced With Use of Synchronous Free Cortisol Assessment', *J Clin Endocrinol Metab*.
- Hedeland, H., G. Ostberg, and B. Hokfelt. 1968. 'On the prevalence of adrenocortical adenomas in an autopsy material in relation to hypertension and diabetes', *Acta Med Scand*, 184: 211-4.
- Hill, A. B. 1965. 'THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION?', *Proc R Soc Med*, 58: 295-300.
- Kjellbom, A., H. Olsen, O. Lindgren, and M. Löndahl. 2020. 'Mortality in patients with adrenal incidentalomas and autonomous cortisol secretion.' In *European congress of endocrinology*, 70 AEP23. Endocrine abstracts.
- Kjellbom, A., O. Lindgren, S. Puvaneswaralingam, M. Löndahl, and H. Olsen. 2021. 'Association Between Mortality and Levels of Autonomous Cortisol Secretion by Adrenal Incidentalomas : A Cohort Study', *Ann Intern Med*, 174: 1041-49.
- LIDDLE, GRANT W. 1960. 'TESTS OF PITUITARY-ADRENAL SUPPRESSIBILITY IN THE DIAGNOSIS OF CUSHING'S SYNDROME*', *The Journal of Clinical Endocrinology & Metabolism*, 20: 1539-60.
- Newell-Price, J., and A. Grossman. 1996. 'Adrenal incidentaloma: subclinical Cushing's syndrome', *Postgraduate Medical Journal*, 72: 207-10.
- Olsen, H., A. Kjellbom, M. Löndahl, and O. Lindgren. 2019. 'Suppressed ACTH Is Frequently Unrelated to Autonomous Cortisol Secretion in Patients With Adrenal Incidentalomas', *J Clin Endocrinol Metab*, 104: 506-12.
- Palmieri, S., V. Morelli, E. Polledri, S. Fustinoni, R. Mercadante, L. Olgiati, C. Eller Vainicher, E. Cairoli, V. V. Zhukouskaya, P. Beck-Peccoz, and I. Chiodini. 2013. 'The role of salivary cortisol measured by liquid chromatography-tandem mass spectrometry in the diagnosis of subclinical hypercortisolism', *Eur J Endocrinol*, 168: 289-96.
- Patrova, J., M. Kjellman, H. Wahrenberg, and H. Falhammar. 2017. 'Increased mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: a 13-year retrospective study from one center', *Endocrine*, 58: 267-75.
- Pivonello, R., I. Bancos, R. A. Feelders, A. Y. Kargi, J. M. Kerr, M. B. Gordon, C. N. Mariash, M. Terzolo, N. Ellison, and A. G. Moraitis. 2021. 'Relacorilant, a Selective Glucocorticoid Receptor Modulator, Induces Clinical Improvements in Patients With Cushing Syndrome: Results From A Prospective, Open-Label Phase 2 Study', *Front Endocrinol (Lausanne)*, 12: 662865.
- Pivonello, R., A. M. Isidori, M. C. De Martino, J. Newell-Price, B. M. Biller, and A. Colao. 2016. 'Complications of Cushing's syndrome: state of the art', *Lancet Diabetes Endocrinol*, 4: 611-29.
- Prete, A., A. Subramanian, I. Bancos, V. Chortis, S. Tsagarakis, K. Lang, M. Macech, D. A. Delivanis, I. D. Pupovac, G. Reimondo, L. V. Marina, T. Deutschbein, M. Balomenaki, M. W. O'Reilly, L. C. Gilligan, C. Jenkinson, T. Bednarczuk, C. D. Zhang, T. Dusek, A. Diamantopoulos, M. Asia, A. Kondracka, D. Li, J. R. Masjkur, M. Quinkler, GÅ Ueland, M. C. Denny, F. Beuschlein, A. Tabarin, M. Fassnacht, M. Ivović, M. Terzolo, D. Kastelan, W. F. Young, Jr., K. N. Manolopoulos, U. Ambroziak, D. A. Vassiliadi, A. E. Taylor, A. J. Sitch, K. Nirantharakumar, and W. Arlt. 2022. 'Cardiometabolic Disease Burden and Steroid Excretion in Benign Adrenal Tumors : A Cross-Sectional Multicenter Study', *Ann Intern Med*.
- Song, J. H., F. S. Chaudhry, and W. W. Mayo-Smith. 2008. 'The incidental adrenal mass on CT: prevalence of adrenal disease in 1,049 consecutive adrenal masses in patients with no known malignancy', *AJR Am J Roentgenol*, 190: 1163-8.
- Ueland, GÅ, P. Mæthlie, R. Kellmann, M. Bjørngaas, B. O. Åsvold, K. Thorstensen, O. Kelp, H. B. Thordarson, G. Mellgren, K. Løvås, and E. S. Husebye. 2017. 'Simultaneous assay of cortisol and dexamethasone improved diagnostic accuracy of the dexamethasone suppression test', *Eur J Endocrinol*, 176: 705-13.
- Wood, P. J., J. H. Barth, D. B. Freedman, L. Perry, and B. Sheridan. 1997. 'Evidence for the low dose dexamethasone suppression test to screen for Cushing's syndrome--recommendations for a protocol for biochemistry laboratories', *Ann Clin Biochem*, 34 (Pt 3): 222-9.

Table 1. Characteristics of Patients at Baseline, According to Cortisol_{DST} Group

Characteristic	Cortisol _{DST} <50 nmol/L (n = 575)	Cortisol _{DST} 50-82 nmol/L (n = 272)	Cortisol _{DST} 83-137 nmol/L (n = 119)	Cortisol _{DST} ≥138 nmol/L (n = 82)
Patient characteristics				
Median age (IQR), y	62.8 (54.4-69.6)	65.8 (60.6-73.9)	68.0 (60.7-75.1)	69.1 (61.3-74.6)
Female sex, n (%)	322 (56.0)	171 (62.9)	77 (64.7)	43 (52.4)
Median weight (IQR), kg*	80.5 (70.2-94.0)	77.6 (66.9-88.4)	78.8 (63.3-87.4)	71.0 (59.7-87.0)
Median BMI (IQR), kg/m ² †	28.2 (25.3-32.0)	26.9 (23.7-30.8)	27.0 (23.6-30.7)	25.7 (21.4-29.4)
Current smoker, n (%)	170 (29.6)	105 (38.6)	58 (48.8)	40 (48.8)
Median SBT (IQR), mm Hg	135 (125-149)	140 (130-150)	140 (130-150)	140 (125-155)
Median DBT (IQR), mm Hg	80 (70-85)	80 (70-85)	80 (70-85)	80 (70-85)
Comorbid conditions				
Hypertension, n (%)	257 (44.0)	160 (57.8)	80 (67.0)	57 (72.6)
Diabetes mellitus, n (%)	95 (16.5)	60 (22.1)	27 (22.7)	14 (15.0)
Cardiovascular disease, n (%)	98 (17.0)	63 (23.2)	33 (27.5)	22 (27.5)
Medical history of cancer, n (%)	92 (16.0)	48 (16.7)	27 (23.9)	21 (29.0)
Lipid-lowering treatment, n (%)	152 (26.9)	81 (30.0)	46 (40.4)	34 (46.8)
Heart failure, n (%)	11 (2.0)	15 (5.7)	8 (7.3)	7 (8.1)
Median eGFR (IQR), mL/min/1.73 m ²	86 (75->90)	78 (64->90)	75 (63->90)	76 (58-89)
eGFR <60 mL/min/1.73 m ² , n (%)	46 (8.0)	52 (18.3)	26 (22.0)	21 (25.8)
Hormones				
Median cortisol level (IQR), nmol/L‡	437 (346-551)	495 (397-603)	526 (422-620)	611 (437-715)
Median cortisol _{DST} (IQR), nmol/L	34 (27-41)	61 (55-69)	98 (90-109)	188 (159-265)
ACTH level <2.0 pmol/L, n (%)§	65 (15.9)	68 (33.0)	43 (48.9)	31 (53.4)
DHEAS level <1.04 μmol/L, n (%)	117 (21.5)	86 (33.6)	42 (38.2)	35 (43.8)
Imaging				
Bilateral adenomas, n (%)	67 (11.7)	47 (17.3)	32 (26.9)	23 (28.0)
Median adenoma size (IQR), mm¶	18 (14-24)	20 (16-26)	27 (21-33)	28 (22-39)
Follow-up				
Had surgery, n (%)	14 (2.4)	9 (3.3)	11 (9.2)	20 (24.4)
Died, n (%)	62 (10.8)	47 (17.3)	37 (31.1)	24 (29.3)
Median follow-up for mortality (IQR), y	6.6 (4.8-8.8)	6.4 (4.1-8.8)	6.6 (3.6-9.3)	4.1 (1.8-6.6)

ACTH = corticotropin; BMI = body mass index; cortisol_{DST} = plasma cortisol level after a 1-mg dexamethasone suppression test; DBT = diastolic blood pressure; DHEAS = dehydroepiandrosterone; eGFR = estimated glomerular filtration rate; IQR = interquartile range; SBT = systolic blood pressure.

* Available in the 4 patient groups in 559, 269, 118, and 82 patients, respectively.

† Available in the 4 patient groups in 558, 268, 118, and 81 patients, respectively.

‡ Available in the 4 patient groups in 393, 202, 90, and 60 patients, respectively.

§ Available in the 4 patient groups in 410, 206, 88, and 58 patients, respectively.

|| Available in the 4 patient groups in 543, 256, 110, and 80 patients, respectively.

¶ Adenoma size is for the largest if bilateral adenomas.

Appendix Table 3. Numbers of Patients Excluded According to the Exclusion Criteria*

Exclusion Criterion	Patients, n
Adenoma size <10 mm	97
Metastatic cancer	59
Not an adenoma	75
Pheochromocytoma	31
Primary aldosteronism	34
Treatment with systemic glucocorticoids	56
Treatment with inhaled glucocorticoids	111
Cushing syndrome	9
Dexamethasone test not done	46
Treatment with medication affecting dexamethasone metabolism	14
Treatment with estrogen	13
Total excluded	545

* Each patient is counted once, in the first applicable exclusion criterion appearing in this list.