Terapia cronica e monitoraggio

Roberta Giordano
SCDU Endocrinologia, Diabetologia e Metabolismo
Dipartimento di Medicina Interna
Università degli Studi di Torino

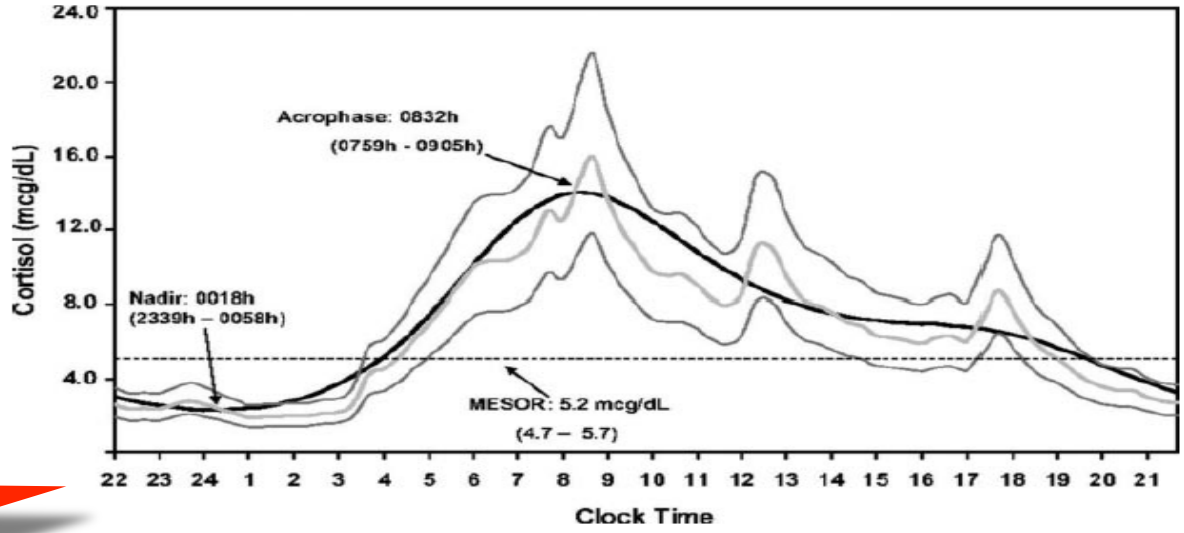
Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Shire
- Novartis

Terapia cronica glucocorticoidea

Morbidity
Mortality



PAI

3.1 We recommend glucocorticoid therapy in all patients w

HC 15-25 mg/day
CA 20-35 mg/day

3.2 W or cortisone ac l doses per day; the highest dose should be given in the morning at awakeni h after lunch; two-dose regimen) or at lunch and afternoon (three-dose regimen). Higher frequency regimens and size-based dosing may be beneficial in individual cases. (2|⊕⊕◯◯)

Two or three divided doses

3.3 As an alternative to hydrocortisone, we suggest using prednisolone (3–5 mg/d), administered orally once or twice daily, especially in patients with reduced compliance. (2|⊕◯◯◯)

3.4 W for the treatment of PAI because of risk of Cushingoid side effects due to difficulties in dose titration. (2|⊕⊕◯◯)

Against dexamethasone

J Clin Endocrinol Metab. 2016;101:364-389

SAI

2.1 W total daily dose vided doses should take the highest dose in the morning at awakening and gime) or the second and third at lunch and late afternoon, respectively (three-dose regime). (1|⊕⊕⊕◯)

HC 15-20 mg/day

Single or divided doses

2.2 We suggest using longer-acting GCs in selected cases (eg, n ce). (2|⊕◯◯◯)

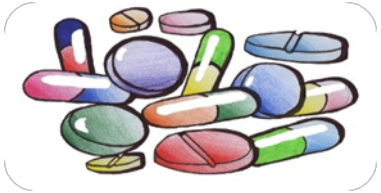
Longer acting GC

2.3 We recommend that clinicians teach all patients with AI regarding stress-dose and emergency GC administration and instruct them to obtain an emergency card/bracelet/necklace regarding AI and an emergency kit containing injectable high-dose GC. (1|⊕⊕⊕◯)

2.4 We recommend against using fludrocortisone in patients with secondary AI. (1|⊕⊕⊕◯)

J Clin Endocrinol Metab. 2016;101:3888-3921

Principali glucocorticoidi



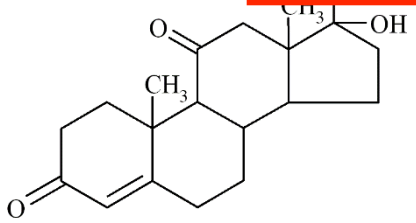
Steroide	Dose equivalente (mg)	Potenza relativa anti-infiammatoria	Potenza relativa mineralcorticoidea	Emivita plasmatica (h)	Emivita biologica (h)
Cortisone acetato	25	0.8	2	0.5	8-12
Idrocortisone	**20**	**1**	**2**	**1.5-2**	**8-12**
Metilprednisolone	4	5	0	1.5-3	18-36
Prednisone	5	4	1	1	18-36
Prednisolone	5	4	1	2-3.5	18-36
Triamcinolone	4	5	0	3.5-4	18-36
Betametasone	0.6-0.75	20-30	0	5.5	36-54
Desametasone	0.75	20-30	0	2-3.5	36-54

Farmaci:
+ *Rifampicina, carbamazepina, fenitoina, fenobarbital, mitotane*

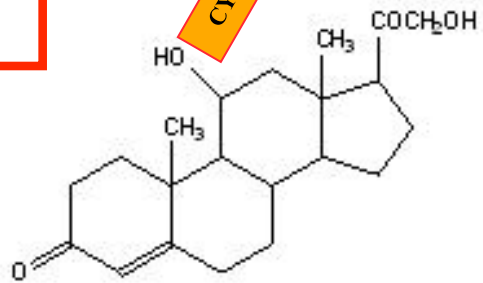
- Itraconazolo, ritonavir, nefazodone, claritromicina

6β-OHcortisolo

CYP3A4



11-β HSD1



CORTISONE

CORTISOLO

5β--reduttasi

5α--reduttasi

Deficit congenito

Epatopatie avanzate

Farmaci:
rhGH
PPARa agonisti (fibrati)
PPARγ agonisti
Flavonone
Carbenoxolone
Ac. glicirizzico
Ac. chenodesossicolico

ocortisolo

5α- diidrocortisolo

Tetraidrocortisone

(THE)

rocortisolo

(THF)

5β-tetraidrocortisolo

(allo-THF)

Altre interazioni …

Table 4 *Medications and food interacting with hydrocortisone and cortisone acetate*

Drugs that affect hydrocortisone metabolism	Hydrocortisone/cortisone acetate dose changes
Anti-epilepsy/ barbiturates	May need more
Antituberculosis	May need more
Antifungal drugs	May need to be changed
Etomidate	May need more
Topiramate	May need more
Grapefruit juice	May need less
Liquorice	May need less

Husebye ES et al, *J Internal Med* 2014; 104-115

Interactions between replacement hormones

Glucocorticoids and GH

2.19 We suggest testing HPA axis functionality before and after starting GH replacement in patients who are not receiving GC replacement and who have demonstrated apparently normal pituitary-adrenal function. (2|⊕◯◯◯)

Glucocorticoids and thyroid hormone

2.20 We suggest evaluating patients with CH for AI before starting L-T4 therapy. If this is not feasible, clinicians should prescribe empiric GC therapy in patients with CH who are starting L-T4 therapy until there is a definitive evaluation for AI. (2|⊕⊕◯◯)

Glucocorticoids and estrogen

2.21 We suggest that when clinicians assess adrenal reserve or the adequacy of HC replacement, they take into consideration that total serum cortisol level can be elevated due to the effects of estrogen on corticosteroid-binding globulin (CBG). (2|⊕⊕⊕◯)

Fleseriu M et al., *J Clin Endocrinol Metab. 2016;101:3888-3921*

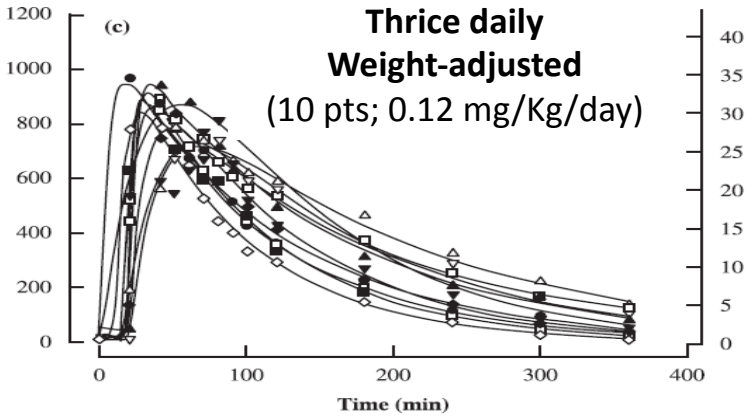
Modalità di somministrazione …

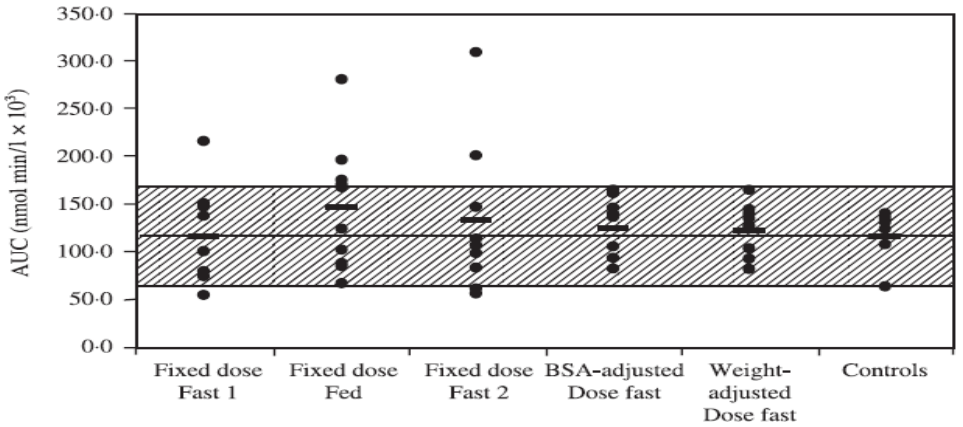
Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency

Clinical Endocrinology (2004) **61**, 367–375

Peak M. Mah*‡, Richard C. Jenkins*‡, Amin Rostami-Hodjegan†‡, John Newell-Price*, Anita Doane*, Victoria Ibbotson*, Geoffrey T. Tucker† and Richard J. Ross*

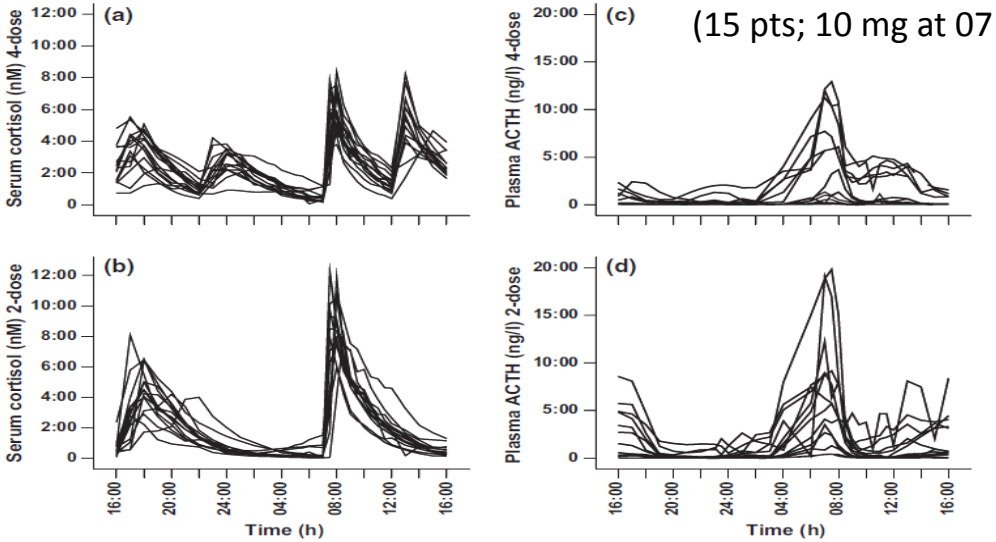
**Divisions of Clinical Sciences (North) and †Academic Unit of Molecular Pharmacology and Pharmacogenetics, University of Sheffield, UK*





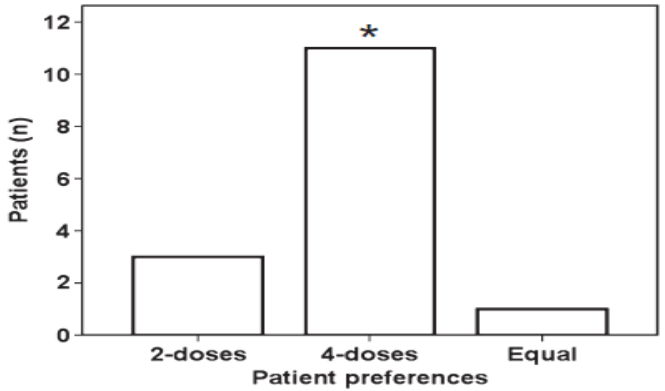
A randomized, double-blind, crossover study comparing two- and four-dose hydrocortisone regimen with regard to quality of life, cortisol and ACTH profiles in patients with primary adrenal insufficiency

Bertil Ekman*, Margareta Bachrach-Lindström†, Torbjörn Lindström*, Jeanette Wahlberg*, Johan Blomgren‡ and Hans J. Arnqvist§



Four times daily

(15 pts; 10 mg at 07:00+10 mg at 12:00+5 mg at 16:00+5 mg at 22:00/day)



Nella pratica clinica … in Europa …

1245 patients (84% PAI)

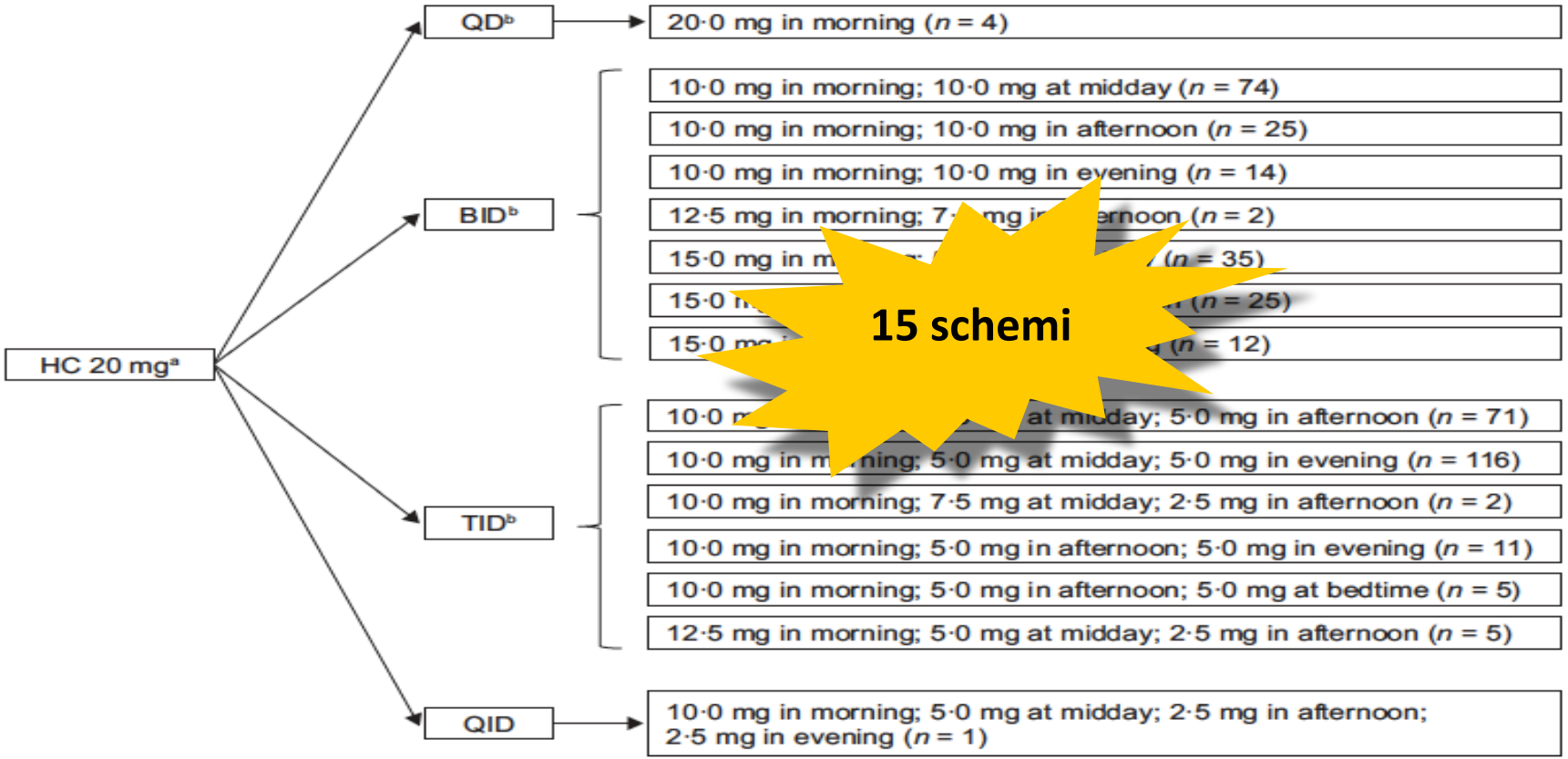
Forss M. et al., 2012; *BMC Endocrine Disorders*; 12:8

HC (80%) BID (48%) > TID (21%) > OD (12%)
Prednisone/prednisolone (10%)
Cortisone (3%)
Dexamethasone (3%)
Other (3%)

1166 patients (31% PAI)

Murray R. et al., 2017; *Clin Endocrinol*; 86:340-346

HC (88.5%) BID (48.7%) > TID (43.6%) > OD (5.5%) > four times (2.1%), 5-45 mg/day
Prednisone/prednisolone (5.1%)
Cortisone (4%)
Dexamethasone (0.1%)


HC 20 mg[a]
QD[b]
20·0 mg in morning (n = 4)
BID[b]
10·0 mg in morning; 10·0 mg at midday (n = 74)
10·0 mg in morning; 10·0 mg in afternoon (n = 25)
10·0 mg in morning; 10·0 mg in evening (n = 14)
12·5 mg in morning; 7·
mg i
ernoon (n = 2)
15·0 mg in m
(n = 35)
15·0
(n = 25)
15·0 m
(n = 12)
15 schemi
TID[b]
10·0 m
at midday; 5·0 mg in afternoon (n = 71)
10·0 mg in m
ning; 5·0 mg at midday; 5·0 mg in evening (n = 116)
10·0 mg in morning; 7·5 mg at midday; 2·5 mg in afternoon (n = 2)
10·0 mg in morning; 5·0 mg in afternoon; 5·0 mg in evening (n = 11)
10·0 mg in morning; 5·0 mg in afternoon; 5·0 mg at bedtime (n = 5)
12·5 mg in morning; 5·0 mg at midday; 2·5 mg in afternoon (n = 5)
QID
10·0 mg in morning; 5·0 mg at midday; 2·5 mg in afternoon;
2·5 mg in evening (n = 1)

Monitoraggio

3.5 We suggest monitoring glucocorticoid replacement using clinical assessment including body weight, postural blood pressure, energy levels, signs of frank glucocorticoid excess. (2|⊕⊕⊕◯)

3.6 We suggest against hormonal monitoring of glucocorticoid replacement and to adjust treatment only based on clinical response. (2|⊕⊕⊕◯)

J Clin Endocrinol Metab. 2016;101:364-389

Risk of hormonal over-replacement in hypopituitarism

Bone disease

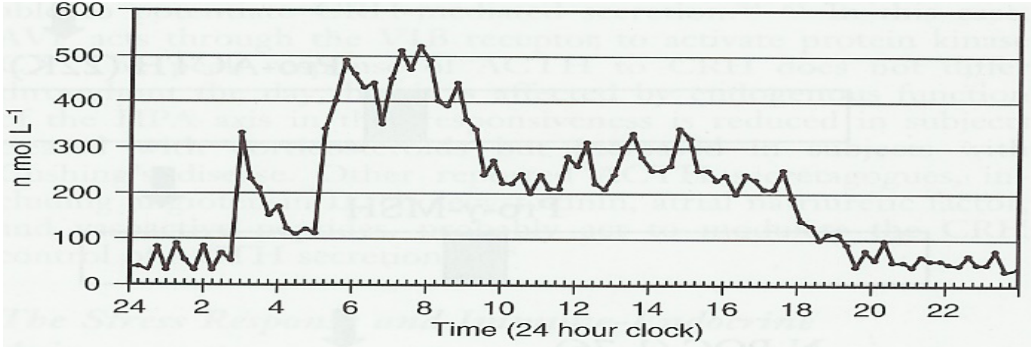
2.27 Clinicians should individually assess GC replacement and avoid over-replacement to reduce the risk of osteoporosis. We suggest low-dose HC replacement because this approach might be associated with increased bone formation and a positive bone-remodeling balance. (2|⊕⊕◯◯)

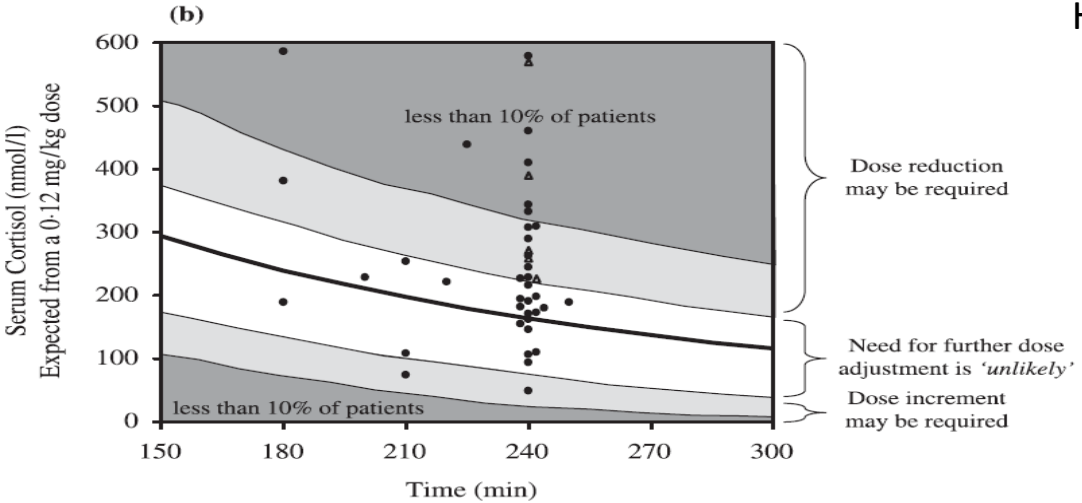
2.28 In men with hypopituitarism over-replaced with GC and at risk for fractures, we suggest vertebral fracture assessment (baseline plain spinal x-rays or dual-energy x-ray absorptiometry) to identify patients with unsuspected vertebral fractures. (2|⊕⊕◯◯)

2.30 In patients with central AI, we recommend using the lowest tolerable dose of HC replacement to potentially decrease the risks of metabolic and cardiovascular disease. (1|⊕⊕⊕◯)

J Clin Endocrinol Metab. 2016;101:3888-3921

Curve di cortisolemia





After HC assumption (90-120 min):

Morning **peak**: <650 nmol/l

Evening **peak**: <250 nmol/l

Feek et al. *Clin Endocrin* 1981; 14: 451-458

Peacey et al. *Clin Endocrinol* 1997; 46:255-261

Howlet et al. *Clin Endocrinol* 1997; 46:263-268

Mah et al. Clin Endocrinol 2004; 61:367-375

ACTH ?

«Outcome» clinici

Table 1. Baseline characteristics of patients in studies looking at the effect of glucocorticoid replacement regimens on clinical outcomes

	Outcome							GC treatment/mg/day			
First author, year	Bone	CV	QOL	Other	*n* (M : F)	Age/year mean ± SD or (range)	1°/2° adrenal failure	HC	Pred	Dex	CA
Valero, 1994[42]	X				30 (8 : 22)	M 55·1 ± 13; F 53·3 ± 12	1°	30	7·5		
Florkowski, 1994[44]	X				14 (5 : 9)	M 56·6; F 56	1°	25–30			
Zelissen, 1994[43]	X				91 (31 : 60)	M 42·4 ± 14; F 46·9 ± 14	1°	M 29·2; F 28·5			
Peacey, 1997[45]	X				32 (13 : 19)	52 ± 15·7	1° (12) 2° (20)	20/30			
Wichers, 1999[46]	X		X		9 (5 : 4)	44 (23–60)	2°	15/20/30			
Suliman, 2003[47]	X	X			9 (3 : 6)	52 ± 8·4	1° (8) 2° (1)	15/20		~0·5	
Malerbi, 1988[49]		X			6 (3 : 3)	Range 38–53	1°		5/7·5		37·5
Al-Shoumer, 1995[50]		X			8 (3 : 5)	Range 46–76	2°	15/20/30			
Dunne, 1995[51]		X			13 (7 : 6)	Range 21–58	2°	15/30			
McConnell, 2002[52]		X			15 (9 : 6)	45 ± 2·4	2°	20			
Lovas, 2002[53]			X		79 (35 : 44)	M 40·2 ± 2; F 48·8 ± 2	1°				40
Groves, 1988[54]			X		7 (3 : 4)	Range 22–65	1°	30–50			
Riedel, 1993[55]			X		14 (6 : 8)	45 (32–68)	1°	30			37·5
Weaver, 1994[57]				X	19 (6 : 13)	47 (24–60)	2°	0–40			
Flemming, 1999[62]				X	84 (34 : 50)	59 (20–87)	1° & 2°				

Abbreviations: cardiovascular (CV), quality of life (QOL), number in study (*n*), male (M), female (F), standard deviation (SD), primary (1°), secondary (2°), glucocorticoid (GC), hydrocortisone (HC), prednisolone (Pred), dexamethasone (Dex), cortisone acetate (CA).

Crown & Lightman, Clin Endocrinol 2005; 63:483-492

HRQoL

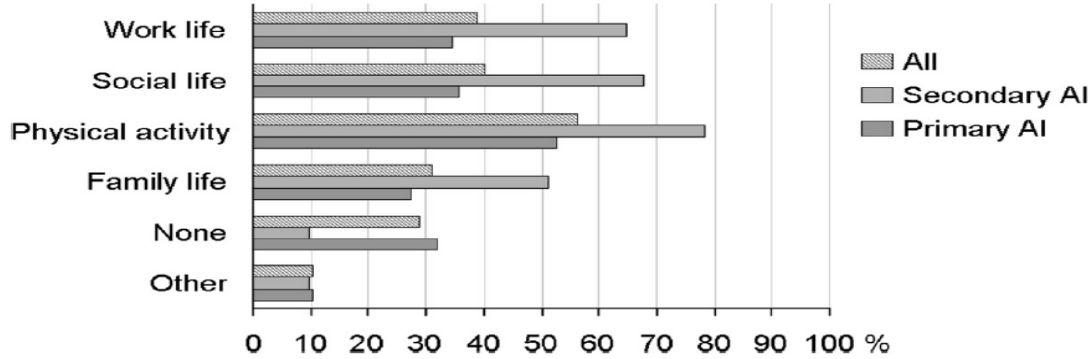


Figure 1 Change in activities due to adrenal insufficiency. Responses to the question "What activities do you need to alter due to your adrenal insufficiency"? in an international patient survey. A total of 1001 subjects responded to this question.

Table 3 Impact of adrenal insufficiency on quality of life (QoL) captured in an international survey

		Primary AI	Secondary AI	All
		n (%)	n (%)	n (%)
Impact on QoL	Yes	515 (60%)	99 (87%)	658 (64%)
	N	N = 857	N = 114	N = 1026
Degree of impacton QoL	A little	73 (14%)	10 (10%)	86 (13%)
	Intermediate	170 (33%)	16 (16%)	195 (30%)
	Quite a lot or very much	267 (52%)	73 (74%)	372 (57%)
	N	N = 510	N = 99	N = 653

Table 4 Fatigue in the morning and during the day reported by patients with adrenal insufficiency in an international patient survey

		Primary AI	Secondary AI	All
		n (%)	n (%)	n (%)
Fatigue experienced as a problem in the morning	Yes	438 (53%)	91 (81%)	571 (57%)
	N	N = 832	N = 113	N = 998
Fatigue experienced as a problem during the day	Yes	508 (61%)	99 (87%)	644 (65%)
	N	N = 830	N = 114	N = 995

Forss M et al., 2012; BMC Endocrine Disorders; 12:8

Mortalità: SAI (GC ?)

Glucocorticoid replacement and mortality in patients with nonfunctioning pituitary adenoma.
Zueger T et al. J Clin Endocrinol Metab. 2012;97(10):E1938-E1942

ACTH and gonadotropin deficiencies predict mortality in patients treated for nonfunctioning pituitary adenoma: long-term follow-up of 519 patients in two large European centres.
O'Reilly MW et al. Clin Endocrinol (Oxf). 2016;85(5):748-756

Higher glucocorticoid replacement doses are associated with increased mortality in patients with pituitary adenoma.
Hammarstrand C et al. Eur J Endocrinol. 2017;177(3):251-256

HC ≥0.35 mg/kg - 30 mg/daily – >20 mg or >0.30 mg/kg
(MR 57.9%- RR 3.79, 95% CI 1.49-9.67- HR 1.88, 95% CI 1.06-3.33 or HR 1.97, 95% CI 1.13-3.41)

ACTH deficiency, higher doses of hydrocortisone replacement, and radiotherapy are independent predictors of mortality in patients with acromegaly.
Sherlock M et al. J Clin Endocrinol Metab. 2009;94(11):4216-4223.

Total daily HC ≥ 25 mg/daily
(SMR 2.82, 95% CI 2.2-3.7)

Mortalità: PAI (da GC ?)

Reference	Total number of deaths			SMR/SIR (95% CI)
Bergthorsdottir *et al.*[11]	507			
		RR men	208	2·19 (1·91–2·51)
		RR women	299	2·86 (2·54–3·20)
		Cardiovascular mortality		
		RR men	103	1·97 (1·61–2·39)
		RR women	136	2·31 (1·94–2·74)
		Death from neoplastic disorder		
		RR men	36	1·61 (1·13–2·23)
		RR women	37	1·47 (1·03 –2·02)
		Death from respiratory disorder		
		RR men	15	1·74 (0·97–2·87)
		RR women	30	3·74 (2·52–5·34)
		Death from infectious disorder		
		RR men	6	6·57 (2·56–15·17)
		RR women	6	5·57 (2·04–12·13)
		Death in patients with concomitant DM compared with those without DM		
		RR men	NR	1·82 (1·29–2·06)
		RR women	NR	1·52 (1·11–2·07)
Bensing *et al.*[10]	1621	Overall mortality		
		SMR all	1621	2·7 (2·6–2·8)
		SMR men	653	2·5 (2·3–2·7)
		SMR women	968	2·9 (2·7–3·0)
		SMR no APS	1333	2·8 (2·6–2·9)
		SMR APS1	55	4·6 (3·5–6·0)
		SMR APS2	233	2·1 (1·9–2·4)
		Cancer		
		SIR all	333	1·3 (1·2–1·5)
		SIR no APS	275	1·4 (1·2–1·6)
		SIR APS1	13	2·3 (1·2–3·9)
		SIR APS2	45	0·9 (0·6–1·2)
Erichsen *et al.*[18]	132	Overall mortality		
		SMR all	132	1·15 (0·96–1·35)
		SMR men	55	1·18 (0·92–1·44)
		SMR women	77*	1·10 (0·80–1·39)
		SMR diagnosis before 40 years of age (all)	NR	1·50 (1·09–2·01)
		SMR diagnosis before 40 years of age (men)	23	2·03 (1·19–2·86)
		SMR diagnosis before 40 years of age (women)	NR	1·23 (0·70–1·76)

2006

(1987-2001)
1675 pts
RR 2.19-2.86
*> F e se **DM***

2008

(1964-2004)
3292 pts
RR 2.7
> se APS1

2009

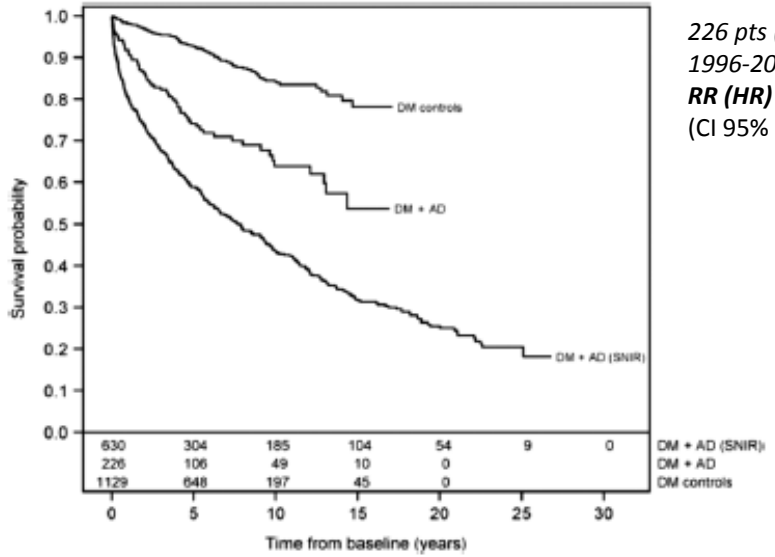
811 pts
RR 1. 15
> M, età 40 aa
***IA** (15%)*

Johannsson G et al. Clin Endocrinol 2015; 82:2-11

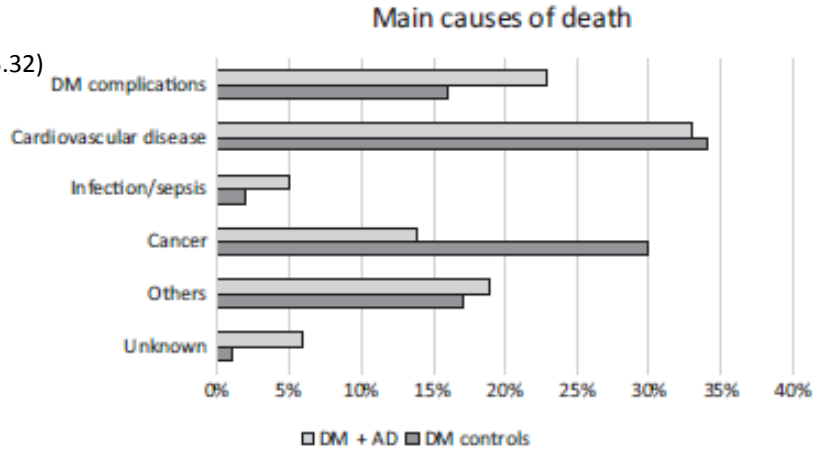
Mortality in patients with diabetes mellitus and Addison's disease: a nationwide, matched, observational cohort study

Dimitrios Chantzichristos[1,2], Anders Persson[3], Björn Eliasson[1,2,3], Mervete Miftaraj[3], Stefan Franzén[3], Ragnhildur Bergthorsdottir[1,2], Soffia Gudbjörnsdottir[1,2,3], Ann-Marie Svensson[3] and Gudmundur Johannsson[1,2]

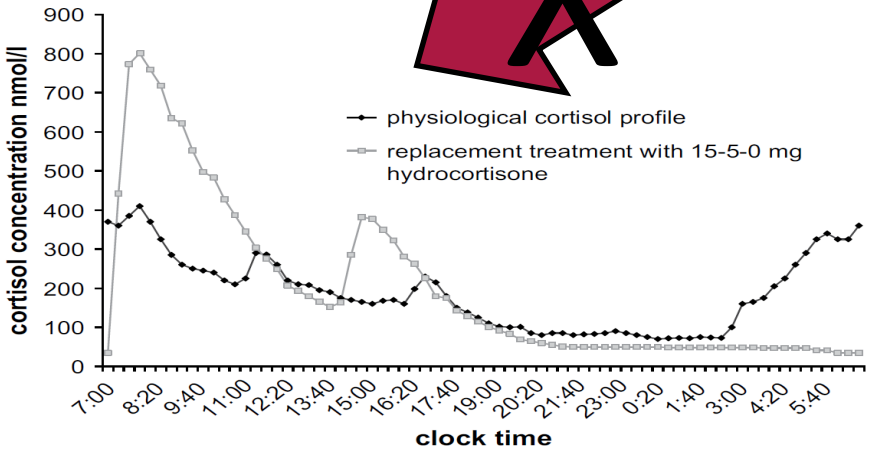
European Journal of Endocrinology (2017) **176**, 31–39



226 pts (vs 1129 DM)
1996-2012
RR (HR) 3. 89
(CI 95% 2.84-5.32)



Terapia GC "convenzionale"

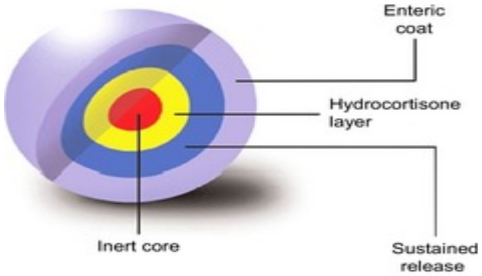


Morbilità
HRQoL
Mortalità

"Nuovi" GC

A hydrocortisone compound designed to restore a physiological cortisol peak at waking

CHRONOCORT (DIURF-006)



A hydrocortisone compound designed to allow a once morning daily intake

DUOCORT (PLENADREN)

(Duocort AB, Helsingborg, Sweden)

Improving glucocorticoid replacement therapy using a novel modified-release hydrocortisone tablet: a pharmacokinetic study

Gudmundur Johannsson[1], Ragnhildur Bergthor
and Stanko Skrtic[2]
Departments of [1]Endocrinology, Sahlgrenska Academy, Sahlgrenska University Hospital, Grona Straket 8 and [2]Clinical Pharmacology, Sahlgrenska

Randomised, controlled, two-way, cross-over, double-blind, PHASE I study
16 healthy subjects (9 male, 7 female), 18-65 years, BMI 18-27 Kg/m2
Duocort 5 mg, 20 mg, fasted, fed

Table 3 Plasma pharmacokinetic variables (mean ± S.D.) of hydrocortisone following oral single dose administration of a novel dosage form (5 and 20 mg) in fasted (5 and 20 mg) and fed state (20 mg) in healthy subjects ($n = 14$). The calculations of the pharmacokinetic variables are based on plasma concentrations determined with an immunoassay method. All pharmacokinetic variables, except for T_{max} and T_{200}, are presented as geometric mean and 95% confidence interval, while T_{max} and T_{200} are reported as median and range.

	5 mg (fasted)	**20 mg** (fasted)	**20 mg** (fed)
$AUC_{(0-24\ h)}$ (nmol h/l)	1178.8 (870.6–1487.1)	3634.0 (2739.8–4528.1)	4840.2 (3591.2–6089.3)
C_{max} (nmol/l)	253.1 (218.7–287.4)	614.2 (555–673.5)	496.1 (371.3–621)
C (0.25 h) (nmol/l)	76.5 (42.5–110.4)	98.5 (6.40–190.7)	39.0 (0–107.3)
T_{max} (min)	37.5[a] (25–90)	45[b] (20–90)	105[a,b] (30–360)
T (200 nmol/l) (min)	26 (15–46)	16.2[c] (6–35)	25[c] (6–130)
Terminal half-life 5–24 h (h)	2.99 (1.96–4.08)	3.68 (1.26–6.10)	2.68 (2.10–3.26)
Terminal half-life 5–14 h (h)	2.60 (2.14–3.05)	3.20 (2.46–3.95)	3.20 (0–6.63)
$AUC_{(0-infinity)}$ (nmol h/l)	1206.6 (892.3–1520.9)	3824.8 (2660.4–4989.2)	5054.5 (3833.5–6275.5)
% extrapolated AUC (%)	1.23 (0–2.54)	1.31 (0–6.0)	1.13 (0–4.56)

[a] $P < 0.001$; [b] $P < 0.05$; [c] $P < 0.05$ (but no significant difference if two extreme values are left out).

Ref.	type of study	n. patients	duration	results
Johannson G et al. 2012	Open, randomized, crossover, multicenter	64 PAI (11 DM, 11 Hypert.)	12 wk and 24 wk	Weight (-0.7 and -0.9 Kg) SBP (-5.5 mmHg) DBP (2.3 mmHg) HbA1C (-0.1%, -0.6% DM) QoL
Quinkler M et al. 2015	Open, prospective	26 PAI (15), 18 SAI (9), 6 CAH	202 days (85-498)	BMI (-0.4) HbA1C (-0.18%) QoL stabilized
Giordano R et al. 2016	Open, prospective, non-randomized	19 PAI	1,3,6 and 12 months	Waist (-4 cm) HbA1C (- 2 mmol/mol) Total Chol (-36 mg/dl) QoL
Guarnotta V et al. 2018	Retrospective	49 AI (13 PAI, 36 SAI)	36 months	BMI (-5 Kg/m2) Waist (-15 cm) HbA1C (-5 mmol/mol) HDL-C (+1 mmol/l)
Mongioi LM et al. 2018	Open	19 AI (10 PAI, 9 SAI)	3,6,9 and 12 months	HbA1C (-0.9% in PAI) QoL
Frara S et al. 2018	Retrospective observational	14 SAI	24 months	FPG (- 11 mg/dl) BMD (+ 10% lumbar, + 11.5% femoral neck)
Isidori AM et al. 2018	Single-blind, randomised, controlled	89 AI (44 PAI, 45 SAI) vs 25 HS 43 standard GC 46 DR-HC	24 wk	Weight (-4.0 Kg) BMI (-1.7 Kg/m2) Waist (-2.5 cm) HbA1C (-0.3%)

Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial

Lancet Diabetes Endocrinol 2018; 6: 173–85

Andrea M Isidori*, Mary Anna Venneri*, Chiara Graziadio, ... Gianfrilli, Carlotta Pozza, Patrizio Pasqualetti, Stefania Morrone, Ar...

After 12 and 24 weeks of DR-HC…
monocytes CD 14+CD16-↓, CD16+CD14-↑, NK CD16+ ↑

Circadian Rhythm of Glucocorticoid Administration Entrains Clock Genes in Immune Cells: A DREAM Trial Ancillary Study

Mary Anna Venneri,[1]* Valeria Hase...
Riccardo Pofi,[1,2] Chiara Graziadio,[1]
Mariarosaria Negri,[3] Fabio Naro,[4] A...
Rosario Pivonello,[3] and Andrea M. Isidori

J Clin Endocrinol Metab, August 2018, 103(8):2998–3009

After 12 weeks of DR-HC…
18 genes were restored to control levels (ARNTL, CLOCK, AANAT, CREB1, CREB3, MAT2A, PRKAR1A, PRKAR2A, PRKCB, **PER3**, TIMELESS, CAMK2D, MAPK1, SP1, **WEE1**, CSNK1A1, ONP3, **PRF1**)

Conclusioni (1)

La terapia GC convenzionale presenta alcuni limiti:

- ✓somministrazione 2-3 volte al dì (ridotta compliance);
- ✓non è in grado di mimare il ritmo circadiano del cortisolo;
- ✓non normalizza la QoL;
- ✓si associa ad una aumentata morbilità e mortalità (?).

La terapia GC "nuova" presenta alcuni vantaggi:

- ✓somministrazione unica (maggior compliance);
- ✓migliora la QoL;
- ✓si associa ad alterazioni "antropo-metaboliche-infiammatorie" favorevoli.

Conclusioni (2)

Il monitoraggio della terapia GC:

- ✓ prevede la ricerca di segni/sintomi di sovra-sottodosaggio;
- ✓ non dispone di marcatori biochimici “oggettivi”;
- ✓ è soggetto ad una variabilità inter-individuale (del paziente, del clinico, …).

… Grazie …