FOCUS ON

TERAPIA DELL'INSUFFICIENZA SURRENALICA: VERSO UNA MIGLIORE QUALITA' DELLA VITA

Nuove prospettive terapeutiche: quali vantaggi?

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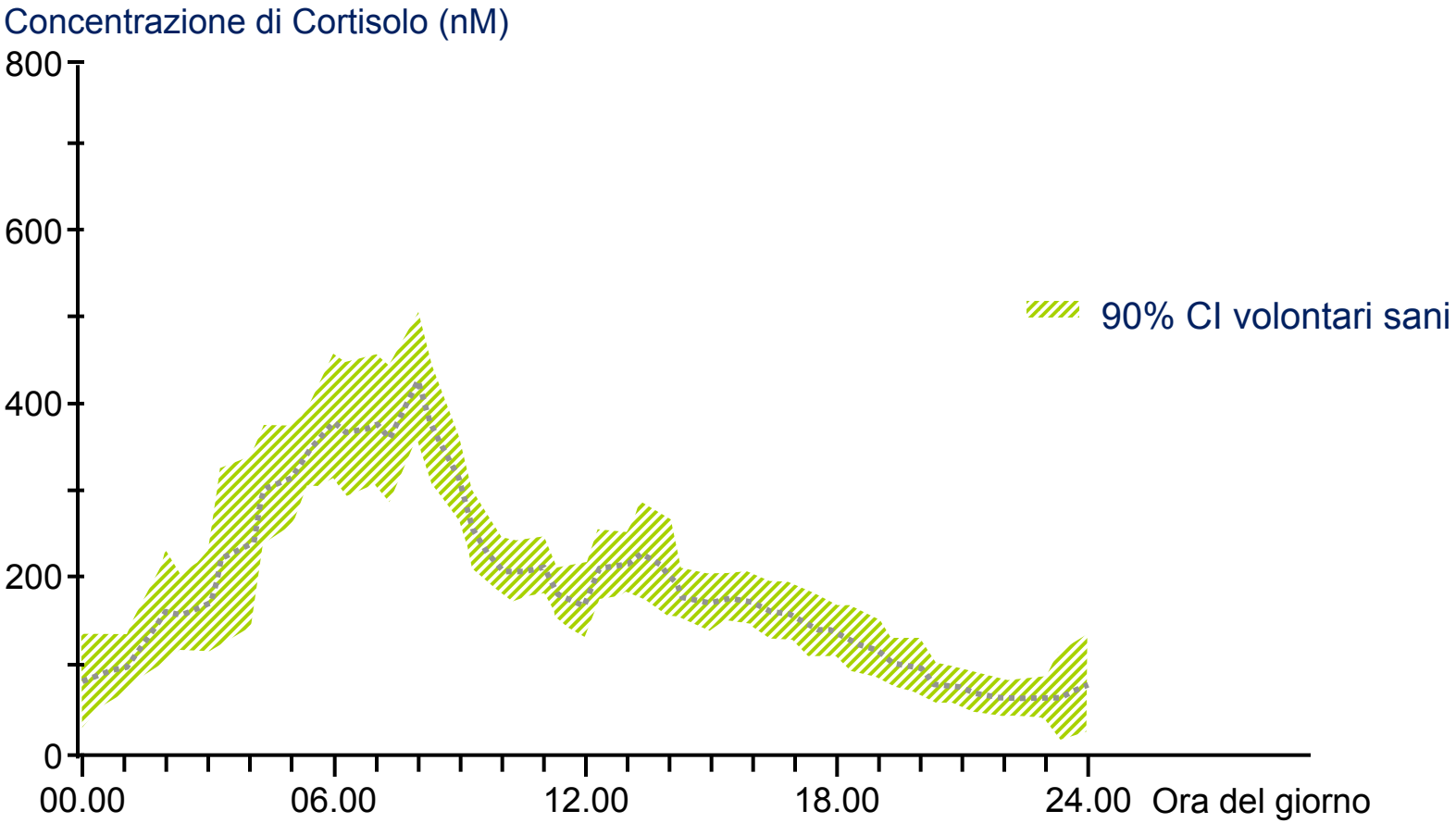
Insufficienza corticosurrenalica

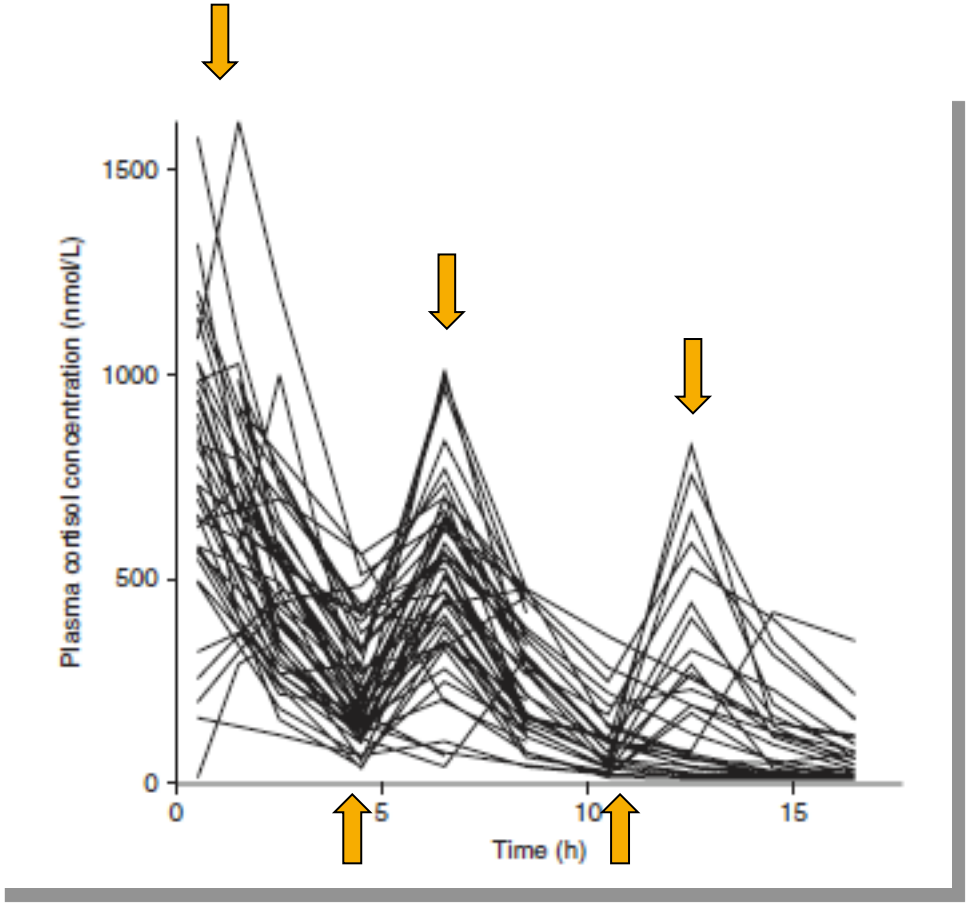
- Malattia potenzialmente letale
  - Mortalità ad un anno in pazienti non trattati >80%
- Nel corso degli ultimi 50 anni non c'è stato sviluppo di nuovi preparati per la terapia sostitutiva con glucocorticoidi
- L'attuale terapia con glucocorticoidi non è documentata in trial clinici strutturati
  - Non vi è consenso internazionale sulle dosi e regimi terapeutici ottimali

Ritmo circadiano del cortisolo in volontari sani



Vgontzas AN, et al. J Clin Endocrinol Metab 2001;86:3787-94

PK Profiles with Current Hydrocortisone Replacement Therapy



7.30:AM **5.30:PM** **10.30:PM**

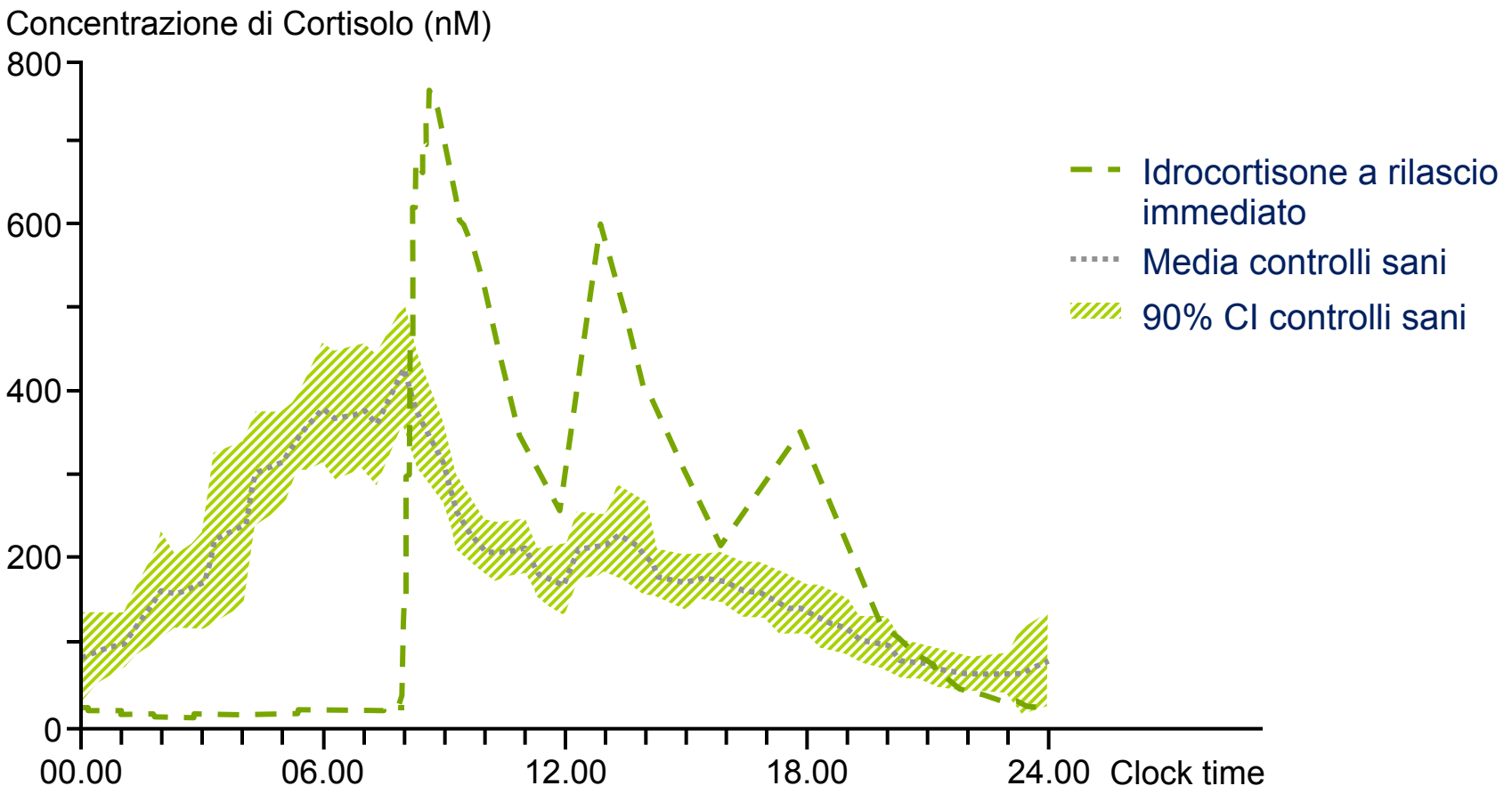
Adrenal insufficiency	(n)
Primary	20
Secondary	30
Doses per day (n)	
1	4
2	24
3	22

Mean dose: 25mg/day (SD:6)
Range:15–50 mg/day

13 different dosing regimens used

Simon N et al. Clin Pharmacokinet 2010; 49; 455-63

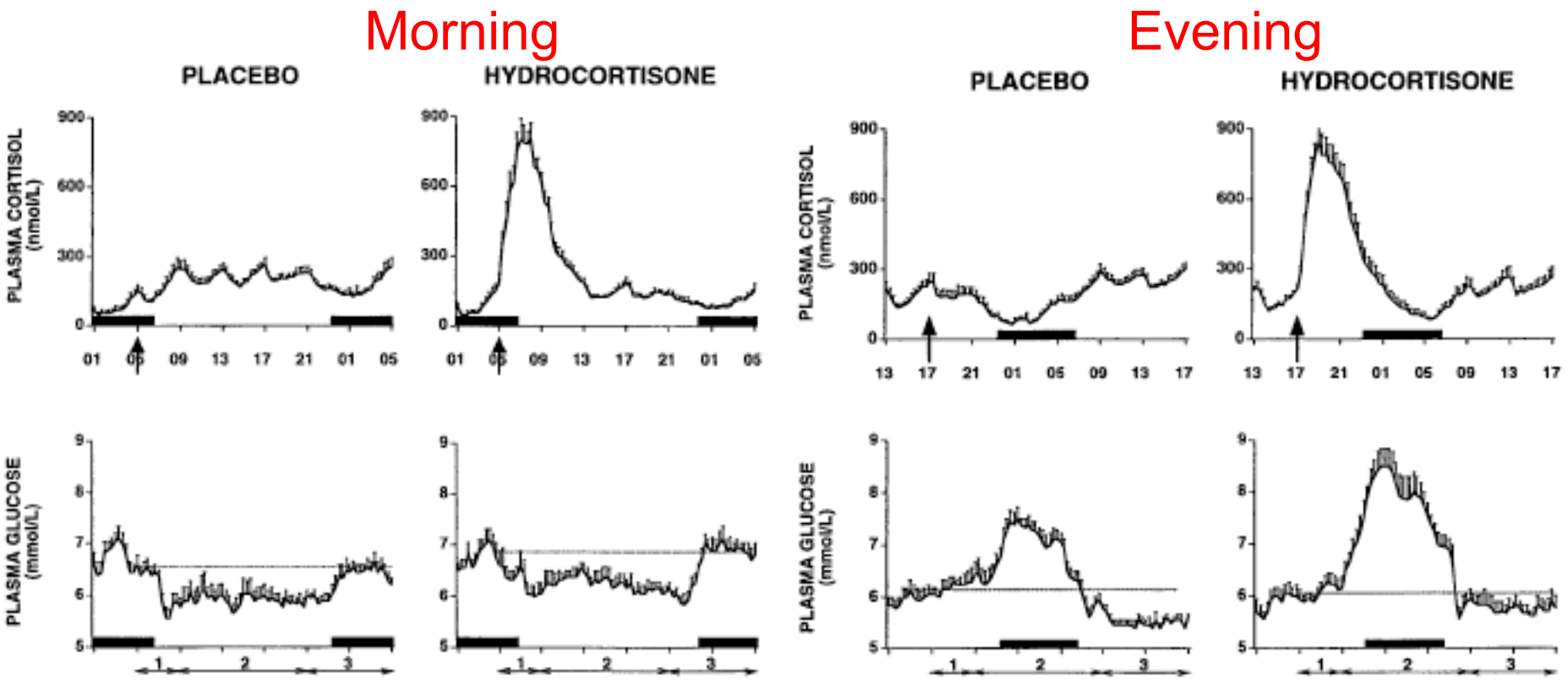
Trattamento subottimale con attuali preparazioni di idrocortisone (tre somministrazioni/die)



Vgontzas AN, et al. J Clin Endocrinol Metab 2001;86:3787-94

Johannsson et al. J Clin Endocrinol Metab. 2012;97:473-81

Metabolic Effects of Cortisol Are More Pronounced in the Evening Than in the Morning



Plat L *et al.* J Clin Endocrinol Metab 1999; 84: 3082–3092

Outcome negativi associati all'attuale terapia sostitutiva dell'insufficienza corticosurrenalica

Terapia sostitutiva convenzionale con glucocorticoidi

- Mortalità prematura
- Alta frequenza di ospedalizzazioni/ infezioni
- Ridotto benessere e qualità percepita della vita
- Alterato profilo metabolico
- Ridotta densità minerale ossea

Bergthorsdottir et al. JCEM 2006, Smans LCCJ et al. ECE 2011, Hahner et al. JCEM 2007, Filipsson et al. JCEM 2007, Zelissen et al. Ann Intern Med 1994; Lövås et al EJE 2009

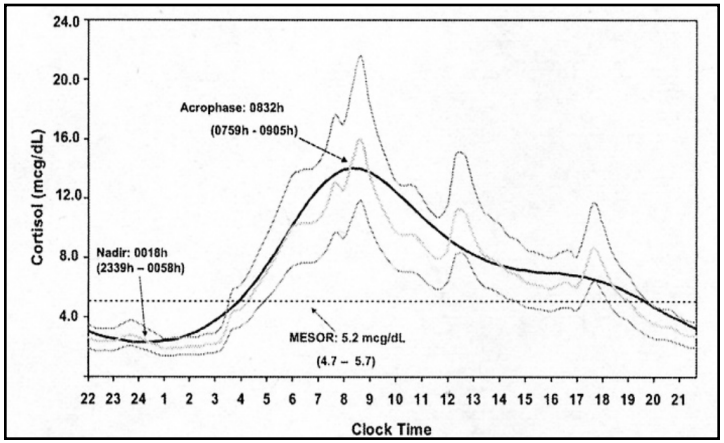
I limiti dell'attuale terapia sostitutiva

Somministrazioni giornaliere multiple

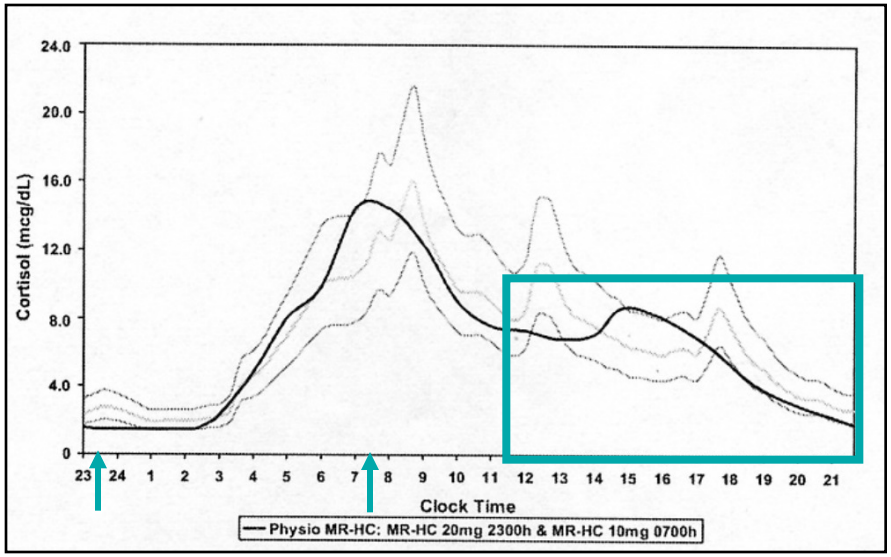
- Alternanza di picchi e decrementi non fisiologici della cortisolemia ogni giorno
- Variabilità nel timing della dose assunta
  - Aumenta la variabilità da giorno a giorno del profilo di esposizione al cortisolo
- Assunzioni mancate – problemi di sicurezza ed efficacia

A Modified-release Hydrocortisone preparation

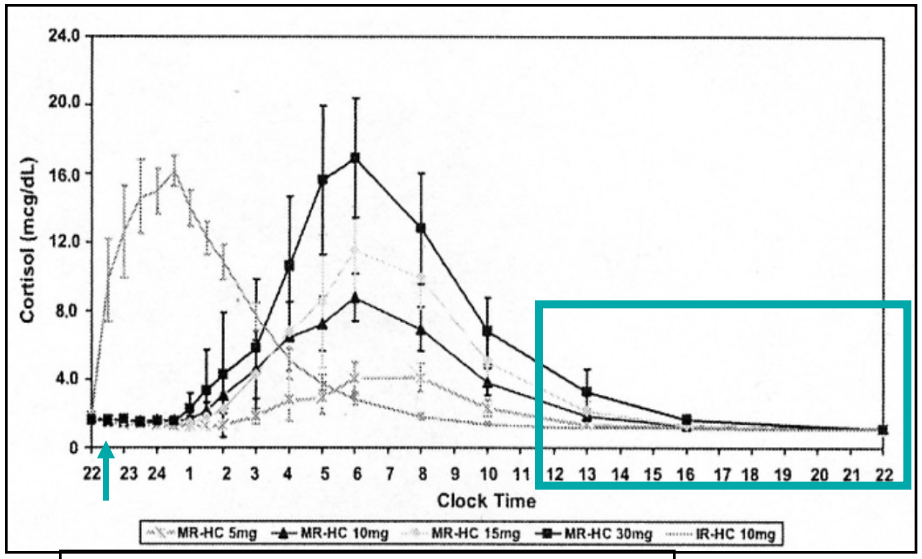
Roma,
9-11 novembre 2012



Circadian Profile of cortisol



2 doses at 22:00 and at 07:00



1 dose at 22:00

Modified-Release Hydrocortisone to Provide Circadian Cortisol Profiles

JCEM 94:1548;2009

Miguel Debono, Cyrus Ghobadi, Amin Rostami-Hodjegan, Hiep Huatan, Michael J. Campbell, John Newell-Price, Ken Darzy, Deborah P. Merke, Wiebke Arlt, and Richard J. Ross

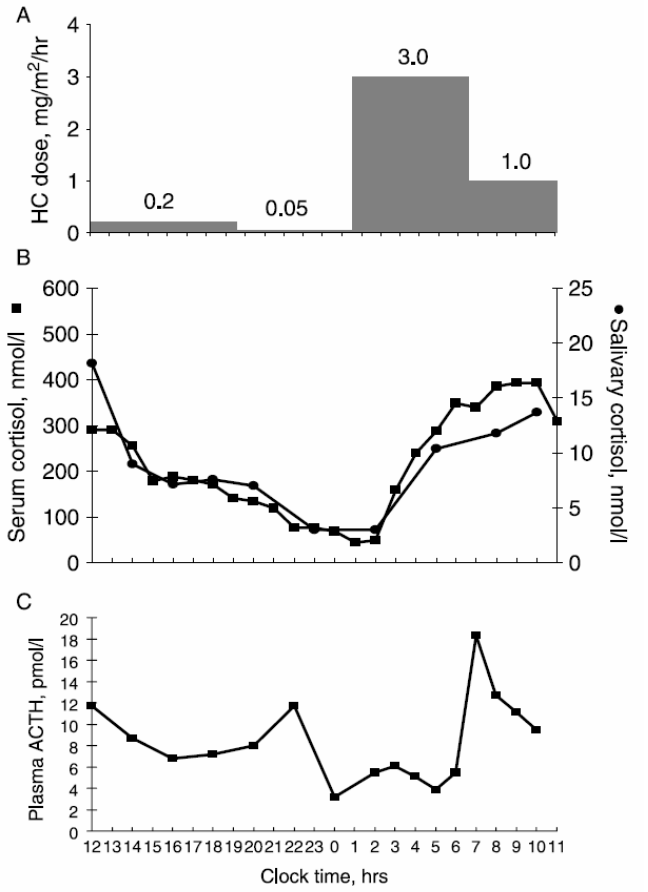
Continuous subcutaneous HC infusion

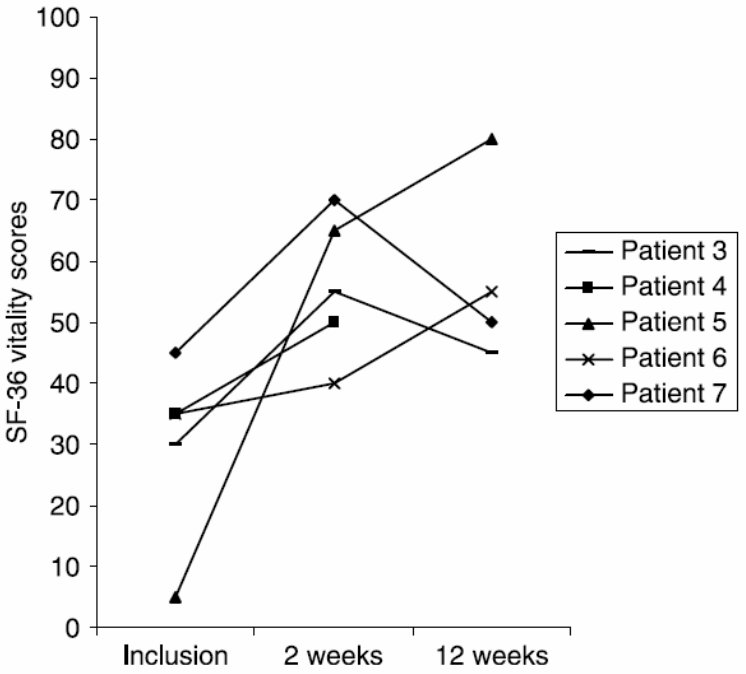
European Journal of Endocrinology (2007) **157** 109–112 ISSN 0804-4643

CLINICAL STUDY

Continuous subcutaneous hydrocortisone infusion in Addison's disease

Kristian Løvås[1,2] and Eystein S Husebye[1,2]

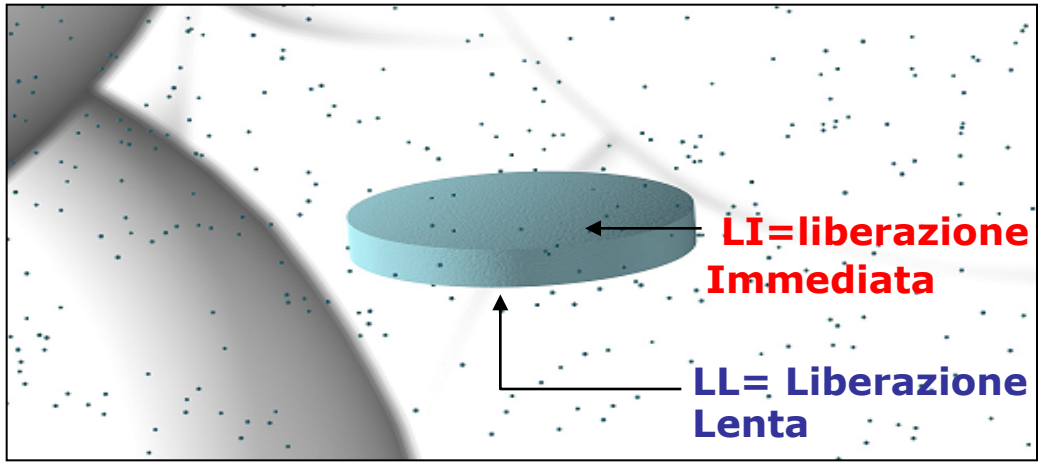




A dual-release hydrocortisone preparation

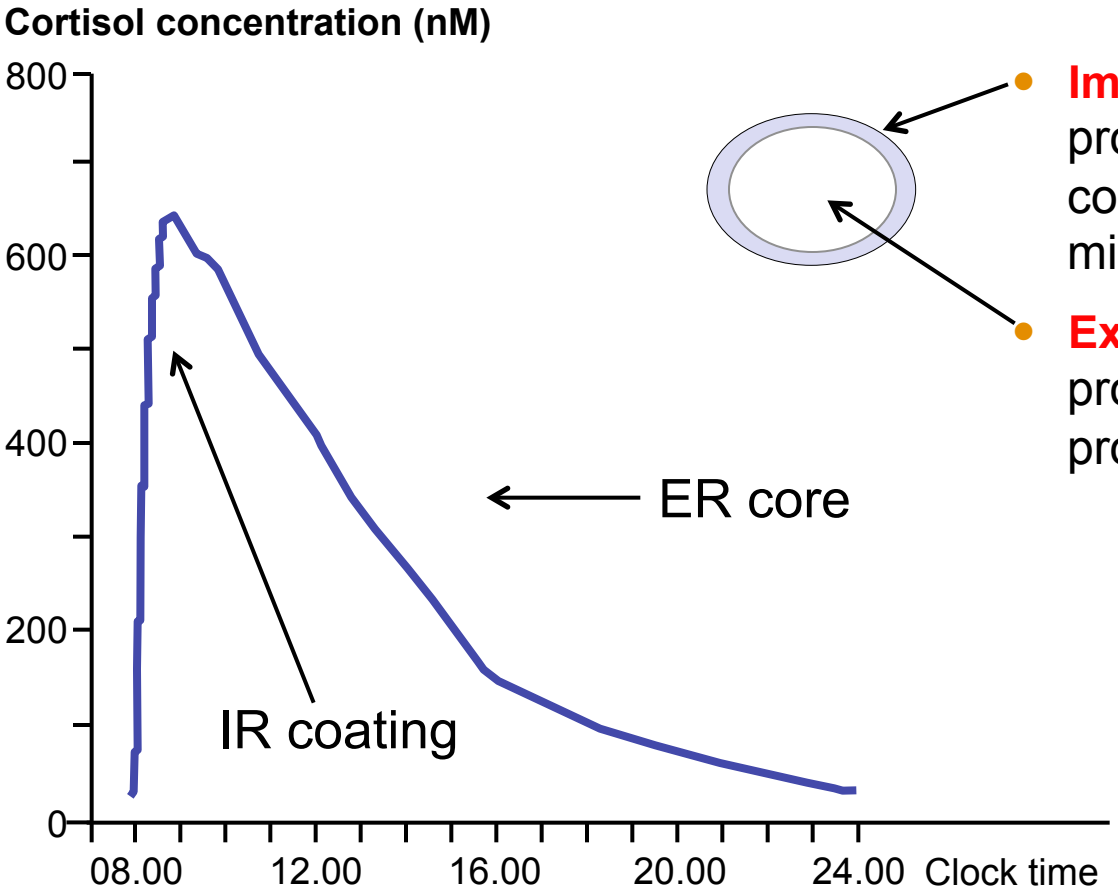
- rivestimento esterno (LI)
- Nucleo centrale (LL)

Ø 8 mm



- Unica somministrazione al risveglio
- La liberazione immediata seguita dalla liberazione lenta mima il ritmo circadiano del cortisolo
- La notte il cortisolo è basso
- L'assorbimento è costante
- Due posologie da: 20mg e 5mg

Hydrocortisone Release Profile



- **Immediate release (IR) coating** provides physiological morning cortisol concentrations within 20 minutes after intake
- **Extended release (ER) core** provides a smooth serum cortisol profile over the day

Johannsson G et al. *Eur J Endocrinol* 2009;161:119–130

Patient Demographics in Registrative Phase II/III trial

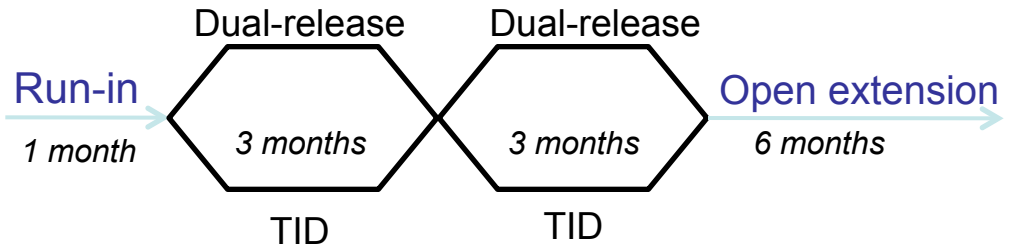
N=63 (All patients with at least one PK measurement)

Male/Female	58.7% / 41.3%
Age	Mean: 47.3 years (SD:13.7 years)
Body mass index (BMI)	Mean: 26.2 kg/m^2 (SD: 4.0 years)
Replacement dose at run-in	
20 mg/day	12.7%
25 mg/day	9.5%
30 mg/day	58.7%
40 mg/day	19.0%
BID (twice daily)	55.0%
TID (thrice daily)	45.0%
Hypertension	17.5%
Diabetes mellitus	17.5%

Table 1 in Johannsson et al. J Clin Endocrinol Metab. 2012;97:473-81

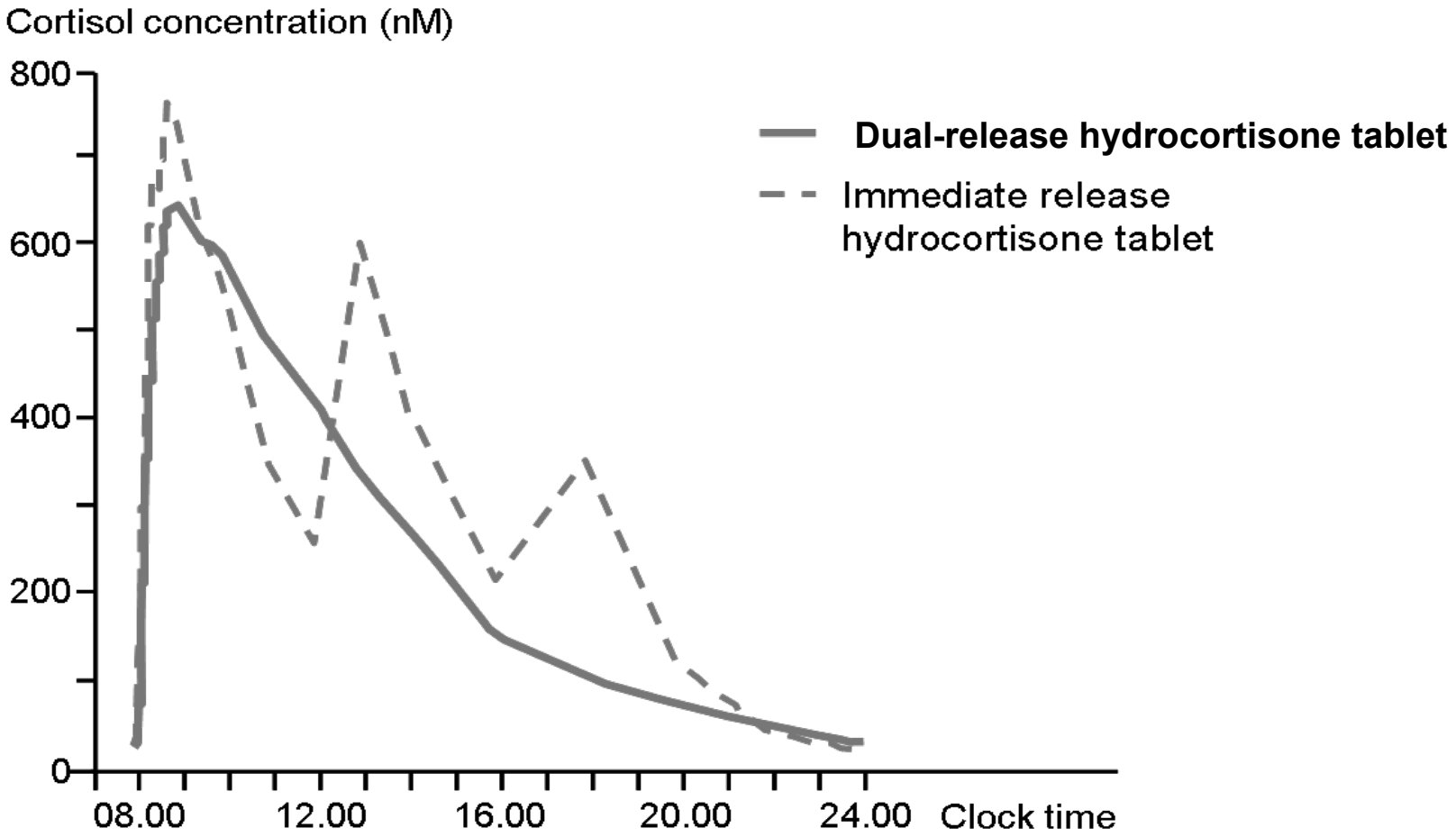
Phase II/III Study in Patients with Primary Adrenal Insufficiency

- Pivotal, EMA protocol assistance
- Multicenter, randomized controlled trial in patients with primary AI
- N=64 randomized
- 2-way cross-over for 12 w
- Dual-release vs TID tablets same dose was compared
- No dosage changes allowed
- Objectives:
  - PK (1º)
  - Safety and QoL



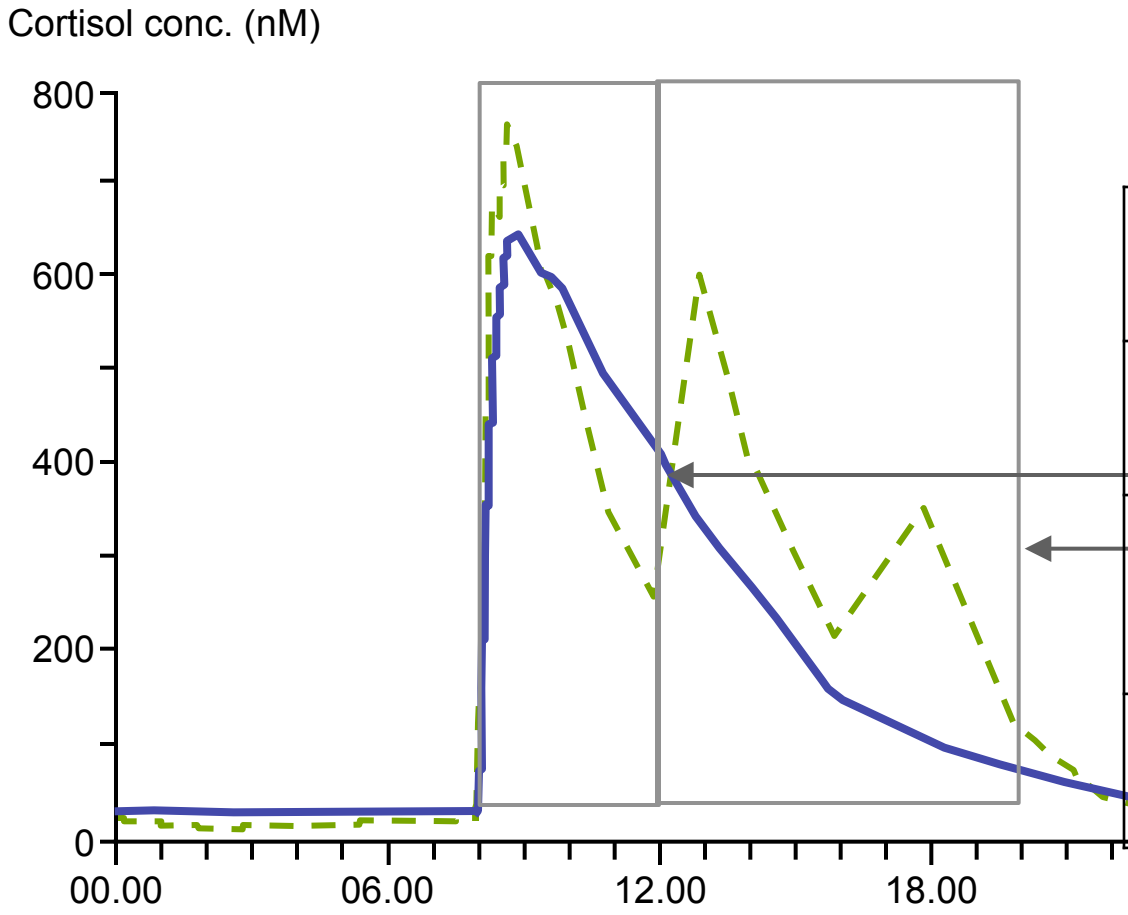
Johannsson G et al. *J Clin Endocrinol Metab* 2012;97:473–481

Dual-release vs. Immediate Release Hydrocortisone TID



Johannsson et al. J Clin Endocrinol Metab. 2012;97:473-81

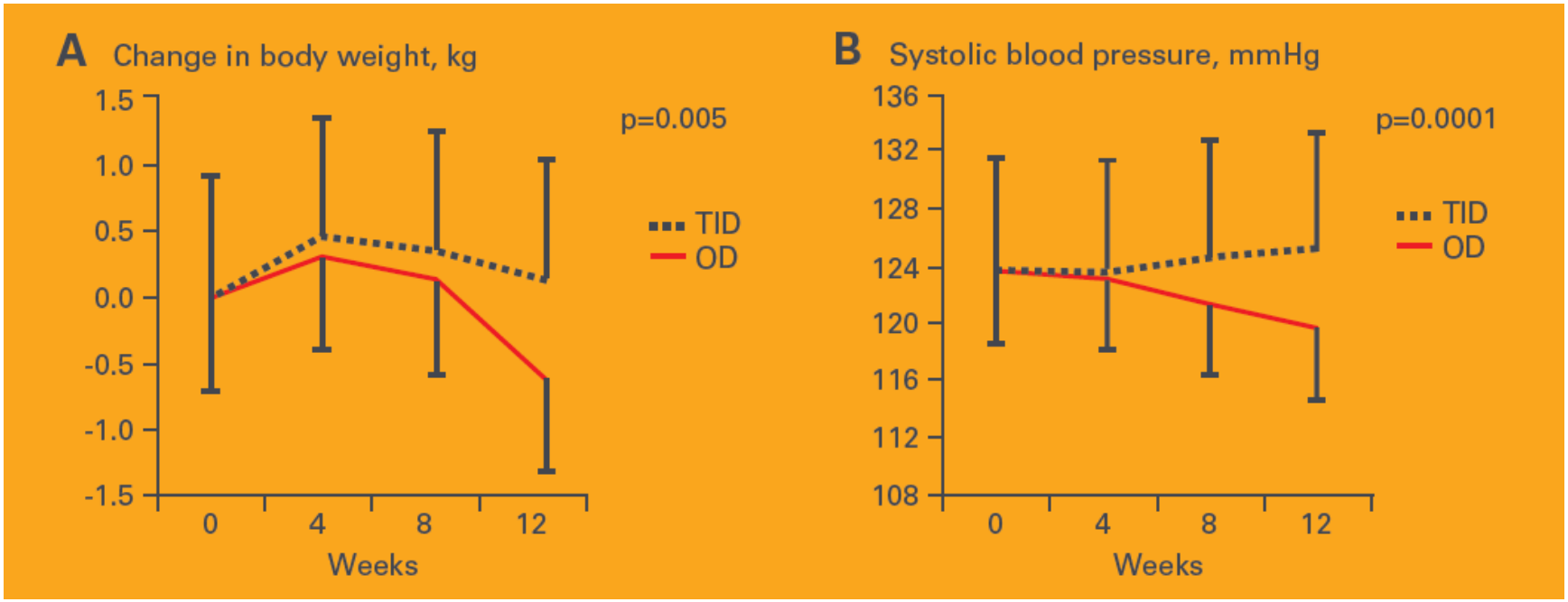
Improved Serum Cortisol Profile with Dual-Release HC tablet



0-24 h (8 AM-8 AM)	Total exposure 19% lower on Dual-release than TID
0-4 h (8 AM-12.00)	Morning exposure 6% higher on Dual-release than TID
4-12 h (12.00-8 PM)	Afternoon and early evening exposure 38% lower on Dual-release than TID
12-24 h (8 PM-8AM)	Night exposure 41% lower on Dual-release than TID

Johannsson G et al. *J Clin Endocrinol Metab* 2012;97:473–481

Lower Body Weight and Systolic Blood Pressure on Dual-Release HC at 12 Weeks



12 weeks: -0.7 kg; p=0.005

at 12 weeks: -5.5 mm Hg; p=0.0001

Johannsson G et al. *J Clin Endocrinol Metab* 2012;97:473–481

Metabolic Safety Variables in patients with T1DM

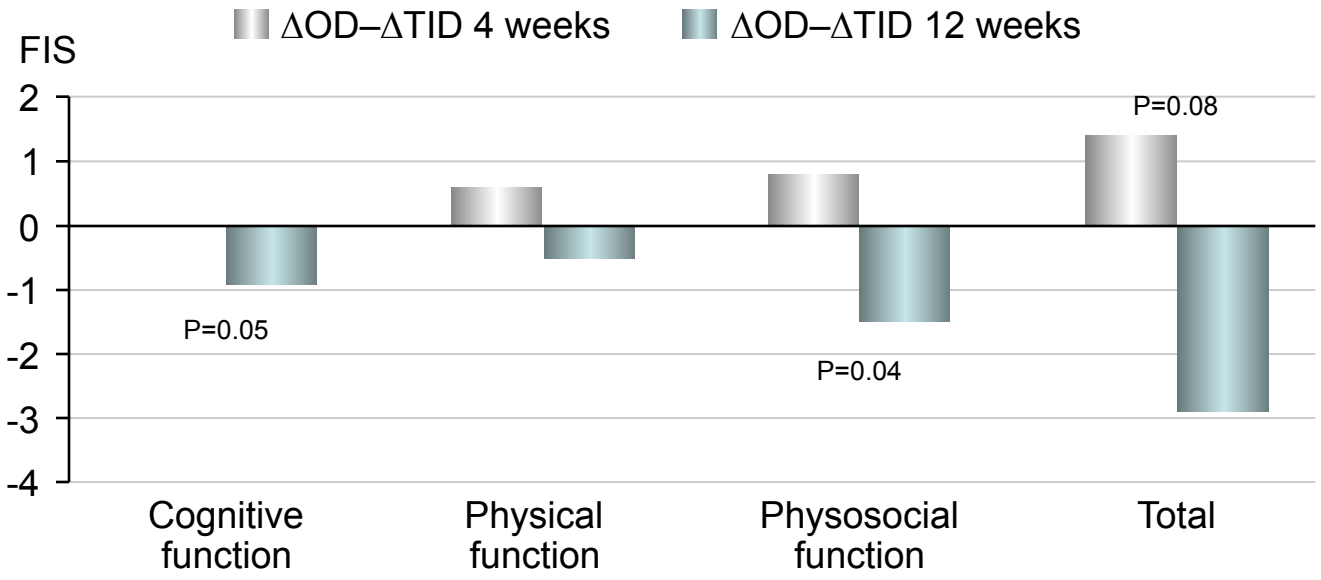
Difference Dual Release HC – TID, diabetics at 12 weeks, n=11

	(mean ± SD)	
HbA1c	**-0.6 ± 0.6 %**	**p<0.01**
Body weight	-0.5 ± 1.1 kg	p=0.13
SBP	-10.3 ± 11.6 mm Hg	p<0.05
DBP	-3.5 ± 6.7 mm Hg	p=0.17

Johannsson G et al. *J Clin Endocrinol Metab* 2012;97:473–481

Significant QoL Improvement Already at 12w

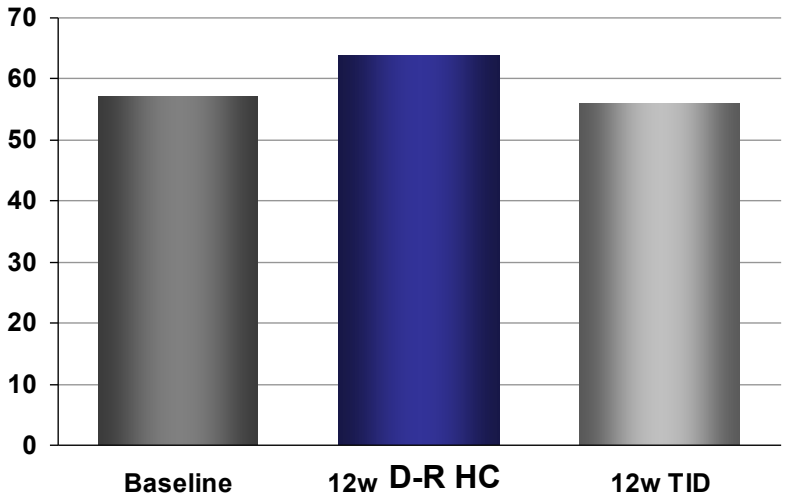
- Consistent changes in QoL in favour of Dual-Release HC
- Well-being (p=0.03) (PGWB)
- Moodiness evening (p=0.04) and total (p=0.04) (VAS)



Johannsson G et al. *J Clin Endocrinol Metab* 2012;97:473–481

Effect on Bone Formation Markers

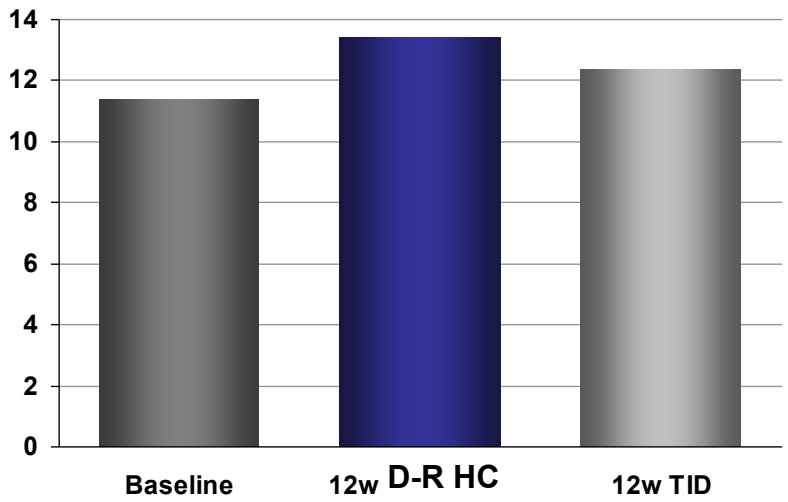
PINP (µg/L)



Dual-release HC – TID= 6.1 ± 15.5 µg/L, p<0.01

Amino-terminal type I collagen propeptide (PINP)

Osteocalcin (µg/L)

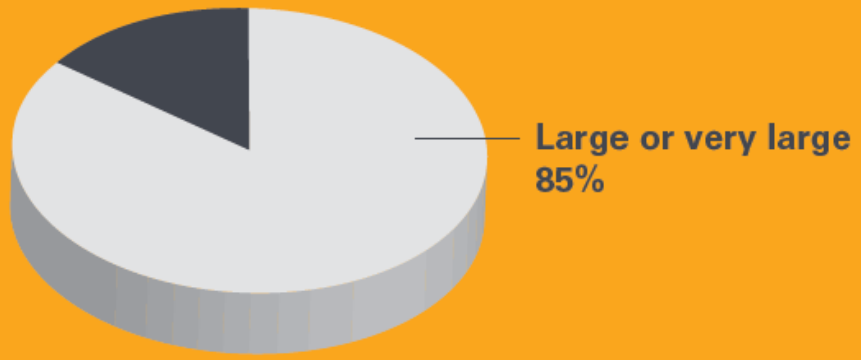


Dual-release HC – TID = 0.7 ± 4.5 µg/L, p=0.2

Johannsson G et al. *J Clin Endocrinol Metab* 2012;97:473–481

85% of the Patients Preferred Dual-Release HC to TID

Of the patients participating in the 12 weeks cross-over study 85% reported the benefit of the Dual-Release HC preparation to be large or very large

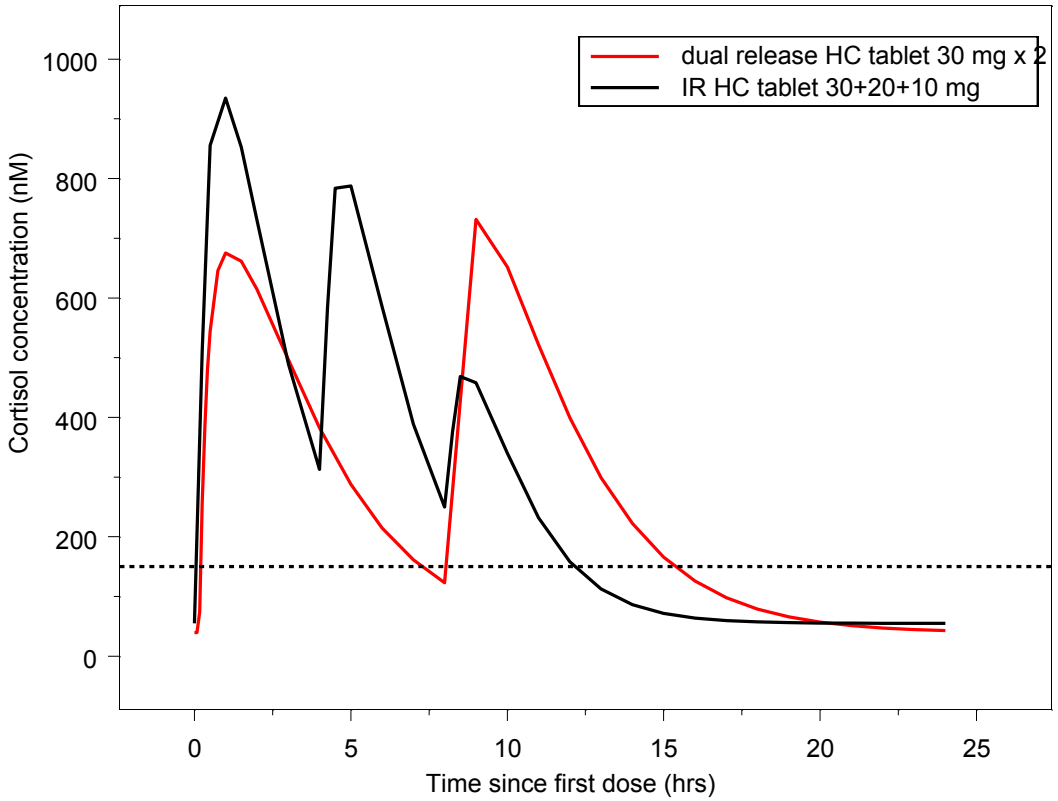


Johannsson et al. J Clin Endocrinol Metab. 2012;97:473-81

Profilo di sicurezza del Dual-Release HC

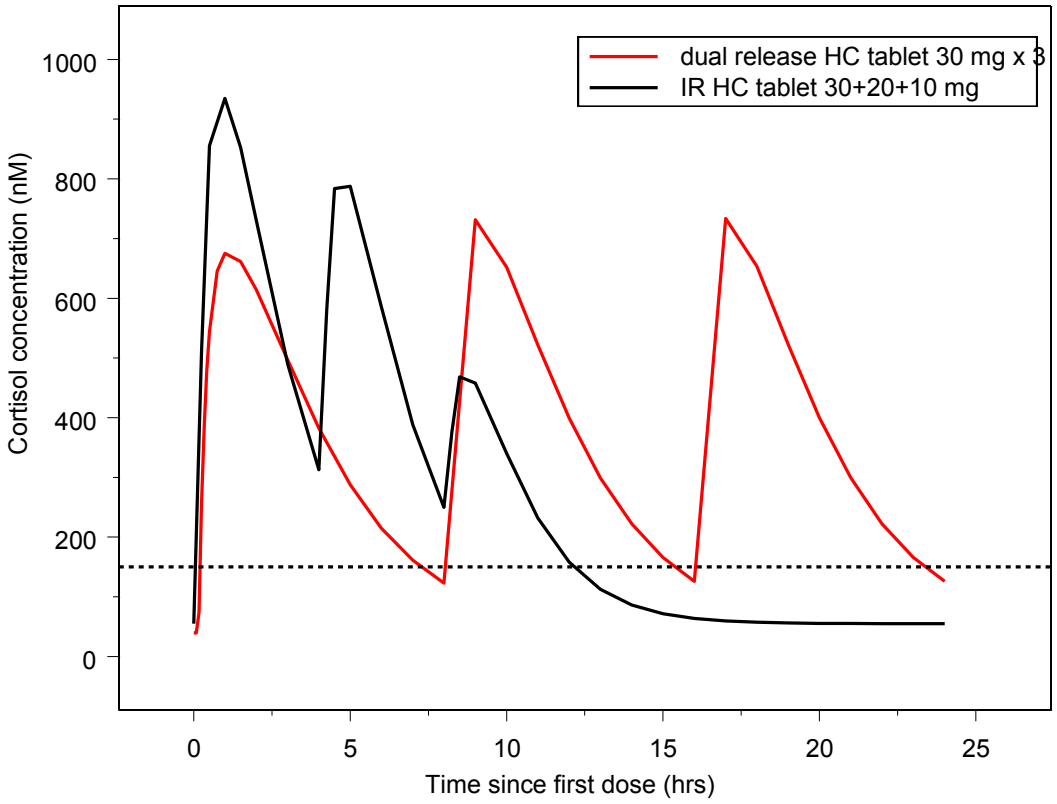
- Globalmente la frequenza e tipo di reazioni avverse, dopo un'iniziale fase di adattamento, sono risultate simili per la Dual-Release HC e la TID nello studio di 12 settimane
- Gli avventi avversi più comuni sono stati nasofaringite, affaticamento, gastroenterite ed influenza con infezioni osservate nel 43.8% dei pazienti in trattamento con Dual-Release HC e 39.1% in trattamento con idrocortisone TID
- La percentuale di giorni con incremento della dose di idrocortisone è stata bassa sia per il Dual-Release HC che per TID
- Sono disponibili dati a lungo termine (oltre 3 anni) sul livello di sicurezza della preparazione di Dual-Release HC

Dual-Release HC tablet Dosing During Intercurrent Illness vs TID IR HC



Simonsson et al, data presented as poster at ICE/ECE congress Florence 2012

Dual-Release HC tablet Dosing During Intercurrent Illness vs TID IR HC



Simonsson et al, data presented as poster at ICE/ECE congress Florence 2012

Dual-release HC preparation

- La preparazione a doppio rilascio contiene idrocortisone per la terapia sostitutiva dell'insufficienza corticosurrenalica primitiva e secondaria **negli adulti (esclusi pazienti con aumentata mobilità intestinale o con concomitanti infezioni retrovirali)**.
- E' somministrata **una volta sola** al giorno al mattino
- Sono disponibili compresse da 5 mg e 20 mg
- La dose orale sostitutiva deve essere personalizzata. Normalmente la dose di mantenimento oscilla tra 20 e 30 mg al giorno, ma dovrebbe essere utilizzata la dose minima necessaria
- E' disponibile in Italia dal mese di Settembre grazie alla legge 648/1996 che rende disponibili farmaci innovativi già in commercio in altre nazioni europee, a carico del SSN