

martedì 27 maggio 2014

18.00-19.00 SIMPOSIO 2
"THE OTHER SIDE OF THE MOON": L'INSUFFICIENZA
SURRENALICA



LA TERAPIA CON PLENADREN NELL'INSUFFICIENZA SURRENALICA PRIMARIA

Roberta Giordano

*Div. Endocrinologia, Diabetologia e Metabolismo;
Dip. Scienze Mediche; Università di Torino.*



Improved Cortisol Exposure-Time Profile and Outcome in Patients with Adrenal Insufficiency: A Prospective Randomized Trial of a Novel Hydrocortisone Dual-Release Formulation

G. Johannsson, A. G. Nilsson, R. Bergthorsdottir, P. Burman, P. Dahlqvist, B. Ekman, B. E. Engström, T. Olsson, O. Ragnarsson, M. Ryberg, J. Wahlberg, B. M. K. Biller, J. P. Monson, P. M. Stewart, H. Lennernäs, and S. Skrtic

(J Clin Endocrinol Metab 97: 473–481, 2012)

Design and setting: we conducted an **open, randomized, two-period, 12-wk crossover multicenter trial with a 24-wk extension at five university hospital centers.**

Patients: **64 adults** with **primary AI**; **11** had concomitant diabetes mellitus (**DM**).

Interventions: the same daily dose of hydrocortisone was administered as **once-daily (OD) dual release** (20 and 5 mg at 0800 h) or **thrice-daily dose (TID, 10 mg at 0800-1200-1600 h).**

TABLE 1. Demographics and baseline characteristics of patients with primary AI: ITT population and patients with concomitant DM

	ITT (n = 63)	DM ^a (n = 11)
Age (yr)	47.3 (13.7)	50.6 (16.4)
Sex		
Male	37 (58.7%)	8 (72.7%)
Female	26 (41.3%)	3 (27.3%)
Weight (kg)	79.6 (14.3)	90.8 (16.4)
BMI (kg/m ²)	26.2 (4.0)	29.2 (4.4)
SBP (mm Hg)	123.6 (19.7)	131.7 (15.3)
DBP (mm Hg)	75.8 (11.5)	75.3 (10.6)
Heart rate (beats/min)	65.5 (10.4)	65.7 (10.6)
Normal ECG	56 (88.9%)	10 (90.9%)
Tobacco use	11 (17.5%)	2 (18.2%)
Replacement dose (mg)		
20	8 (12.7%)	2 (18.2%)
25	6 (9.5%)	2 (18.2%)
30	37 (58.7%)	5 (45.5%)
40	12 (19.0%)	2 (18.2%)
Regimen before run-in		
BID	33 (55.0%)	7 (63.6%)
TID	27 (45.0%)	4 (36.4%)
Hypertension	11 (17.5%)	4 (36.4%)

Results are presented as n (%) for categorical variables and mean (SD) for continuous variables. BID, Twice daily; BMI, body mass index; ECG, electrocardiogram.

^a DM type 1, n = 9; DM type 2, n = 2.

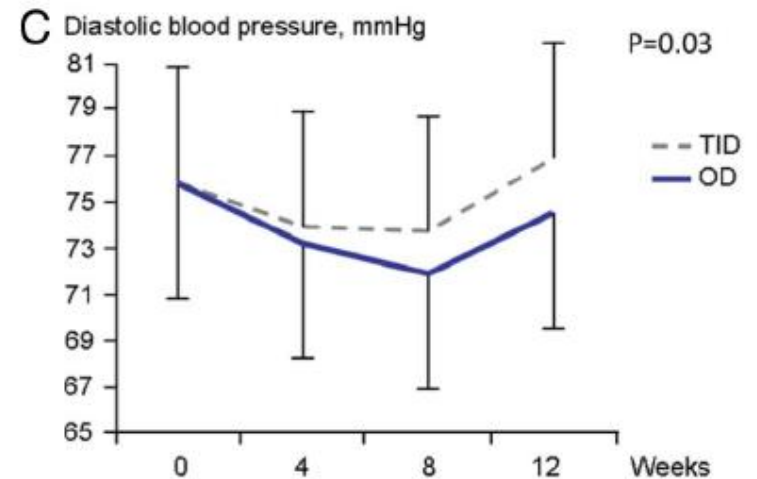
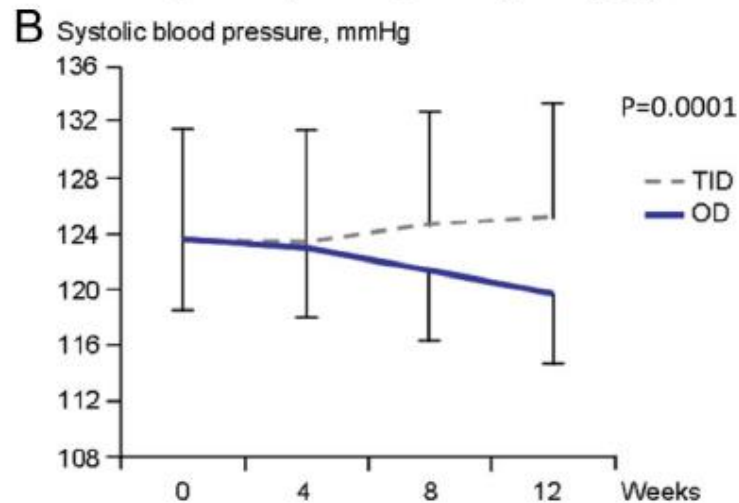
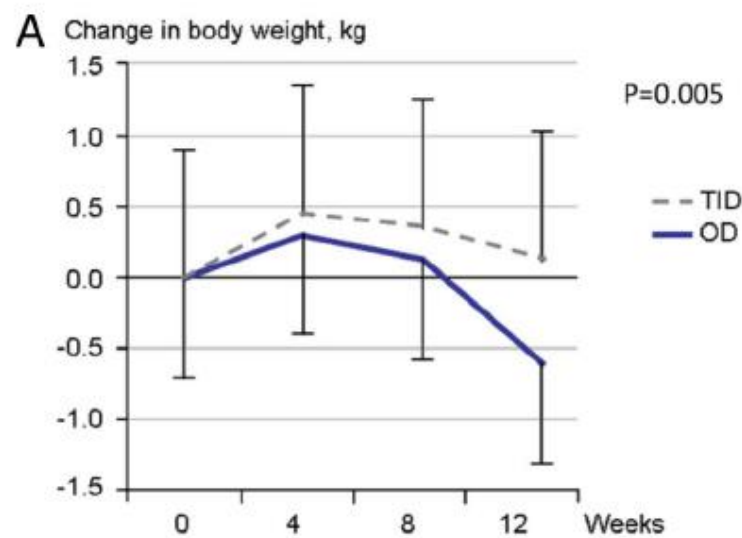


FIG. 3. Body weight and blood pressure in 64 patients with primary AI during 12 wk of OD and TID hydrocortisone replacement therapy. A, Mean (SD) change in body weight; B, mean (SD) systolic blood pressure; C, mean (SD) diastolic blood pressure. All *P* values are for the difference between OD and TID at 12 wk.

TABLE 3. Glucose, lipid, and bone metabolism in patients with primary AI during 12 wk OD and TID: safety population and the patients with concomitant DM

Variable	Safety population					DM population	
	Baseline, mean (sd)	12 wk OD, mean (sd)	12 wk TID, mean (sd)	OD minus TID at 12 wk	P value	OD minus TID at 12 wk	P value
HbA1c (%)	4.9 (1.1)	4.9 (0.9)	5.0 (1.1)	−0.1 (0.4)	0.0006	−0.6 (0.6)	0.0039
n	60	61	59	57		10	
Cholesterol (mmol/liter)	5.3 (1.1)	5.2 (1.0)	5.3 (0.9)	0.0 (0.4)	0.6729	−0.2 (0.2)	0.0938
n	63	57	57	51		8	
LDL-cholesterol (mmol/liter)	3.1 (1.0)	3.0 (0.9)	3.1 (0.9)	0.0 (0.3)	0.9131	−0.1 (0.1)	0.0625
n	63	57	57	51		8	
HDL-cholesterol (mmol/liter)	1.4 (0.4)	1.4 (0.4)	1.5 (0.4)	−0.1 (0.2)	<0.0001	−0.1 (0.1)	0.1875
n	63	57	57	51		8	
Triglycerides (mmol/liter)	1.5 (0.8)	1.6 (0.9)	1.4 (0.6)	0.2 (0.6)	0.0086	−0.2 (0.2)	0.0313
n	62	57	57	51		8	
PINP (μg/liter)	57.2 (28.3)	63.9 (34.8)	56.1 (29.2)	6.1 (15.5)	0.0036	5.8 (7.2)	0.0195
n	63	58	58	53		9	
Osteocalcin (μg/liter)	11.4 (5.6)	13.4 (6.5)	12.4 (5.4)	0.7 (4.5)	0.2337	0.5 (3.1)	0.6523
n	63	58	58	53		9	

P values are for comparisons of the difference between OD and TID (see *Subjects and Methods*).



... La nostra esperienza ...

Pazienti

• **15 pazienti (11 F e 4 M) con malattia di Addison in terapia sostitutiva convenzionale fissa (Idrocortisone 20 mg, 3 somministrazioni/dì; Florinef 0.025-0.1 mg/dì)**

Età: 20-61 anni

Durata di malattia: 3-42 anni

APS2 (n=13), APS 1 (n=1), AI (n=1)

3 pz. con DM1, 1 pz. con DM2

Nessuno pz. affetto da ipertensione arteriosa

Caso	Sesso	Età	Eziologia	Durata	DM
1	M	39	APS 2	29	
2	F	49	APS 2	10	
3	F	27	APS 1	10	
4	F	61	APS 2	11	Tipo 2
5	F	29	APS 2	7	Tipo 1
6	M	20	APS 2	11	Tipo 1
7	F	49	APS 2	3	
8	F	45	APS 2	6	Tipo 1
9	F	50	APS 2	7	
10	F	57	APS 2	33	
11	F	59	APS 2	7	
12	F	59	APS 2	42	
13	M	29	AI	11	
14	M	56	APS 2	18	
15	F	30	APS 2	23	

Valutazioni

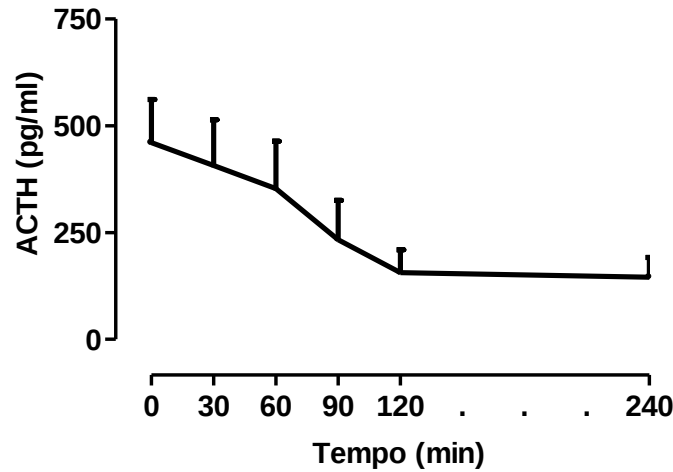
- **ACTH e cortisolo (ogni 30' per 120'. +240') ***
- **Peso (Kg)**
- **BMI (Kg/m²)**
- **Giro vita (cm)**
- **Glicemia a digiuno, HbA1C**
- **colesterolo tot, HDL, TG, LDL**
- **QoL (AddisonQoL 30 items, SF-36)**

0* → 1* → 3 → 6 → 12* mesi (11 pt)

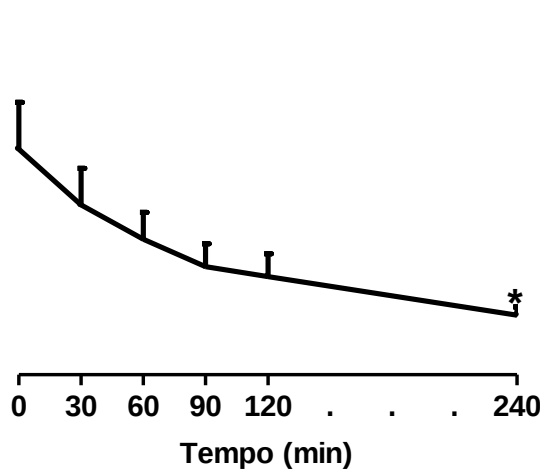
ACTH e cortisolo (media $\pm$ SEM) durante HC, PL 1 mese e 12 mesi

* $p < 0.05$ (vs HC)
** $p < 0.05$ (vs tempo 0')

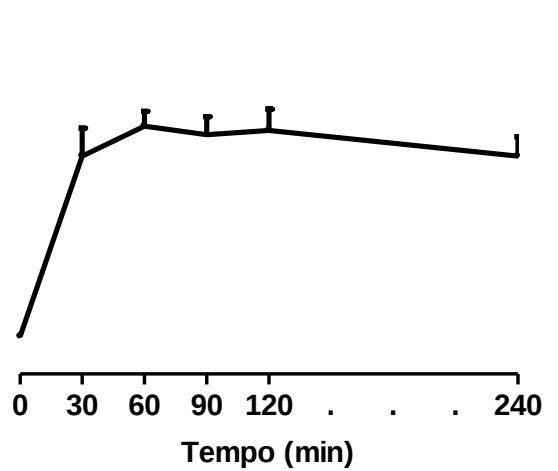
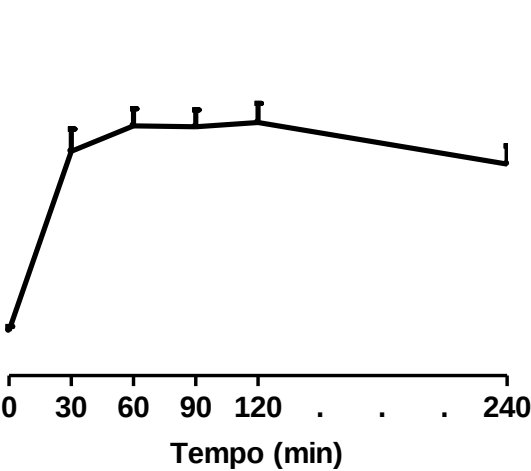
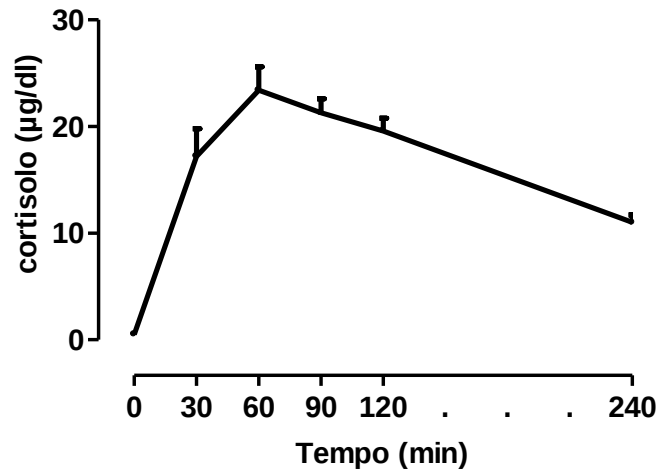
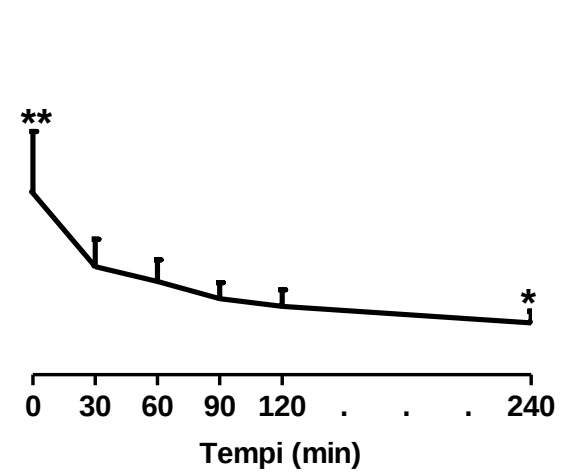
HC



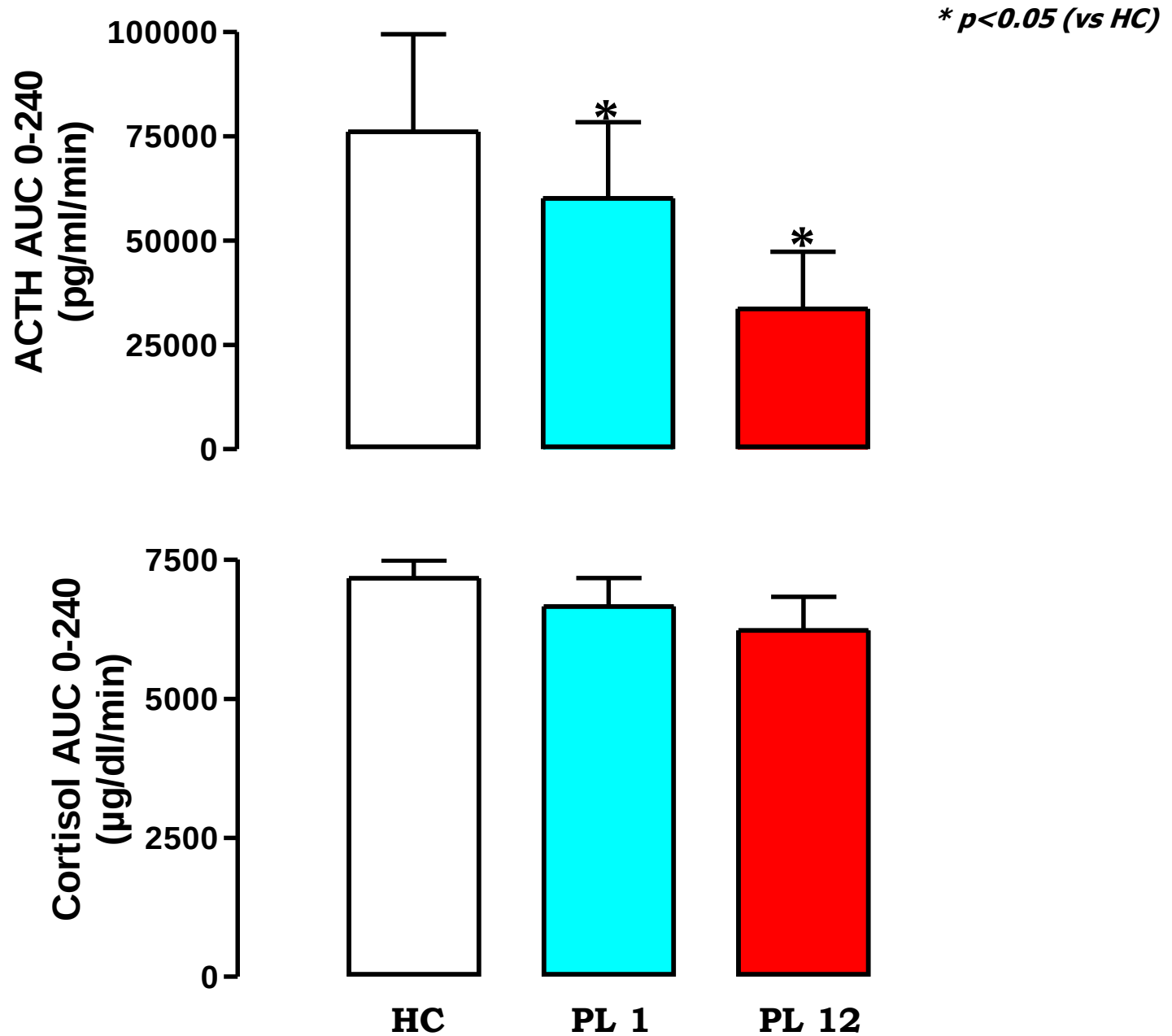
PL 1 mese



PL 12 mesi

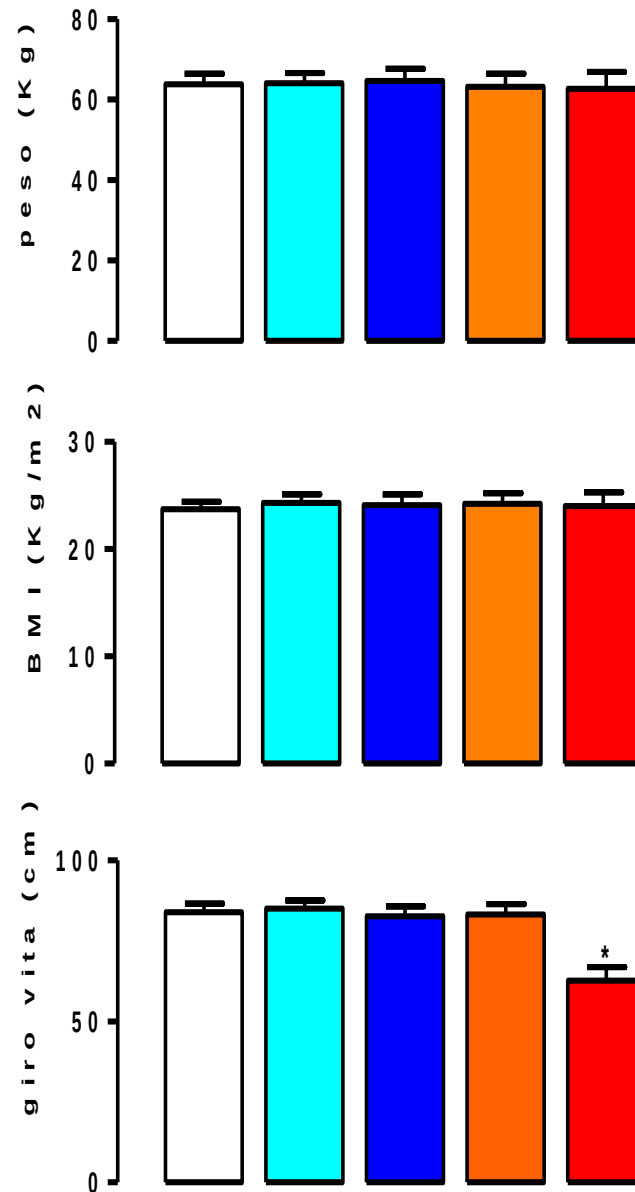


ACTH e cortisolo AUC (media $\pm$ SEM) durante HC, PL 1 mese (■) e 12 mesi(■)



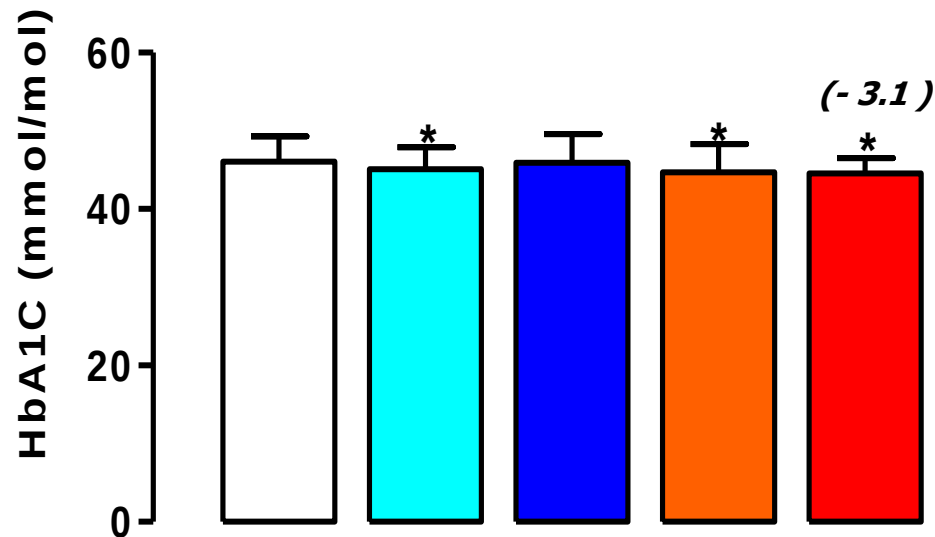
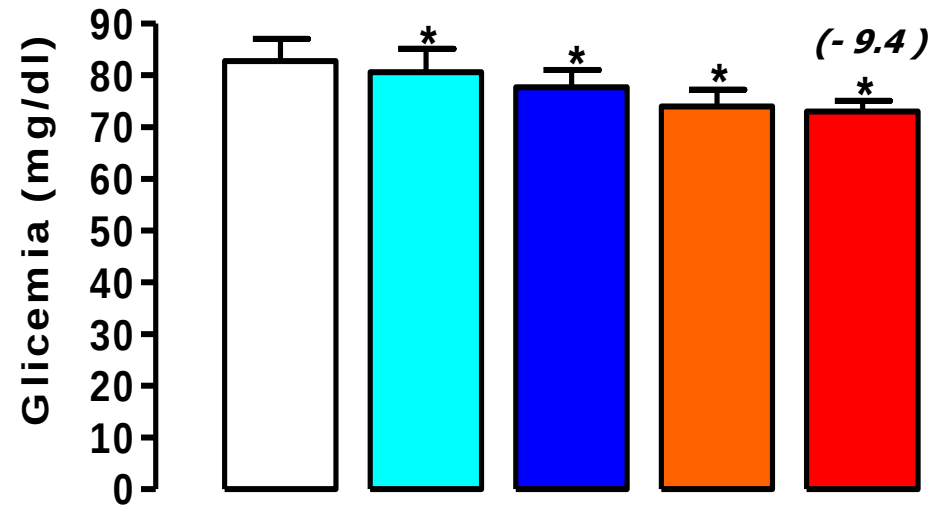
**Peso, BMI e giro vita (media $\pm$ SEM)
durante HC ($\square$), PL 1 mese ($\square$), 3 mesi ($\square$), 6 mesi ($\square$) e 12 mesi ($\square$)**

** $p < 0.05$ (vs HC)*

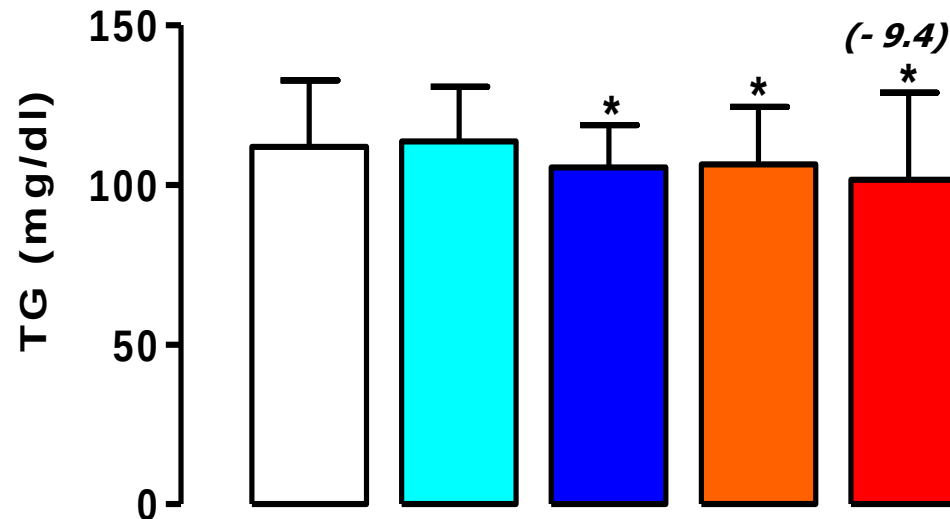
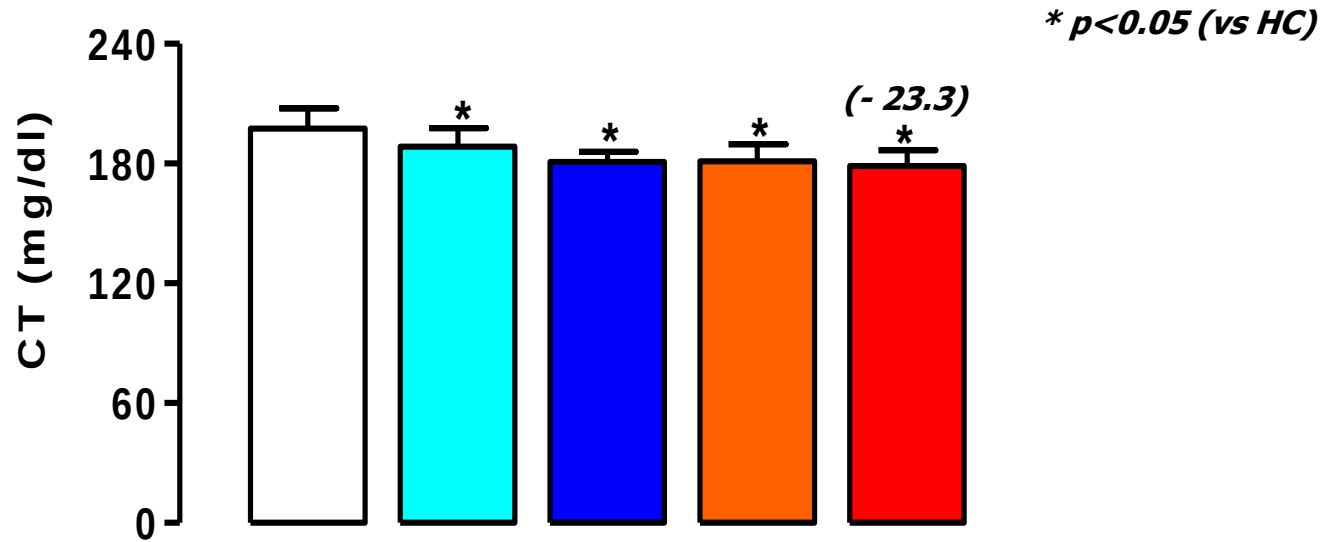


Glicemia ed HbA1C (media $\pm$ SEM)
durante HC (□), PL 1 mese (■), 3 mesi (■), 6 mesi (■) e 12 mesi (■)

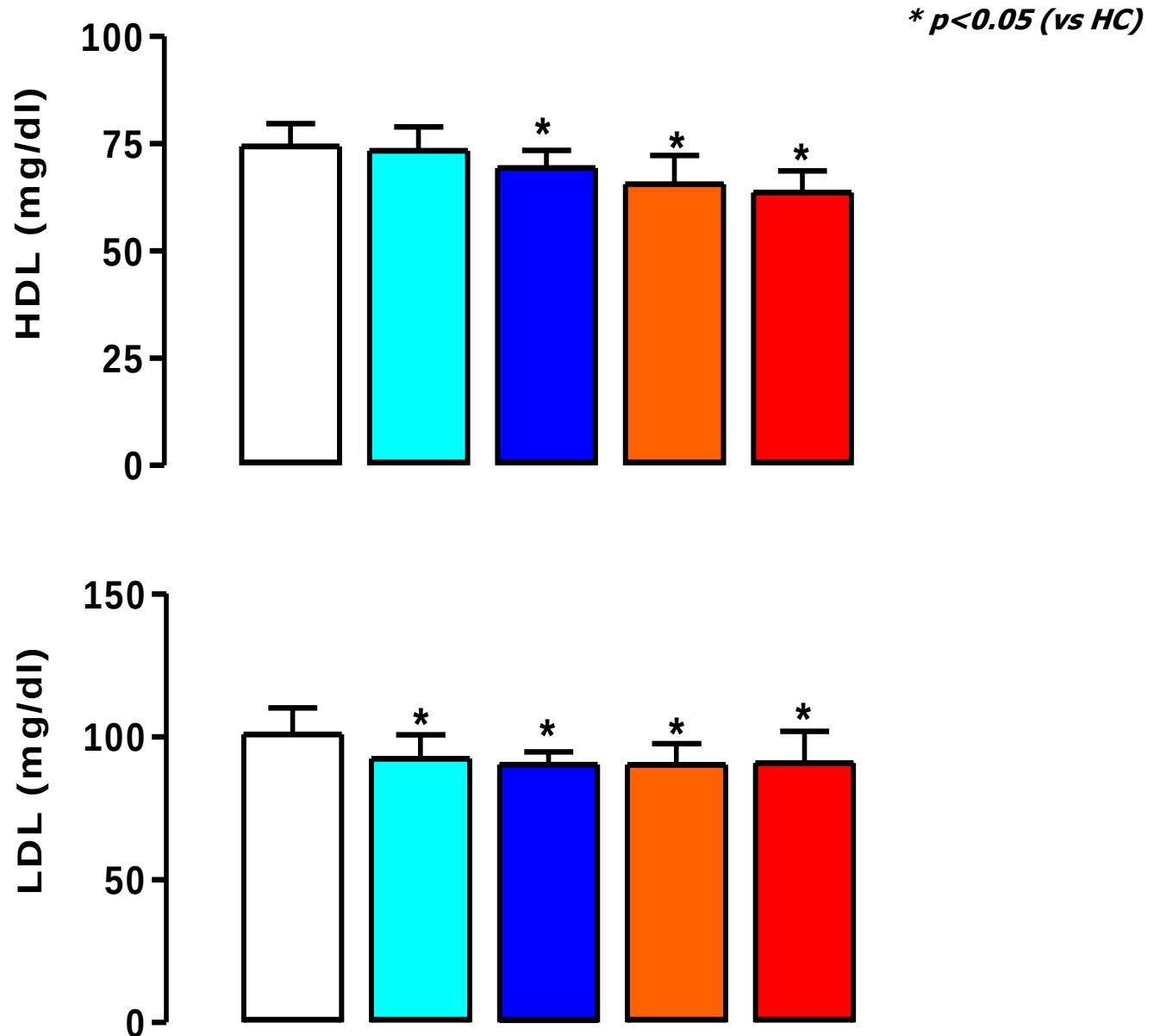
** $p < 0.05$ (vs HC)*



**Colesterolo tot e trigliceridi (media $\pm$ SEM)
durante HC ($\square$), PL 1 mese ($\square$), 3 mesi ($\square$), 6 mesi ($\square$) e 12 mesi ($\square$)**



Colesterolo HDL e LDL (media $\pm$ SEM)
durante HC (□), PL 1 mese (■), 3 mesi (■), 6 mesi (■) e 12 mesi (■)

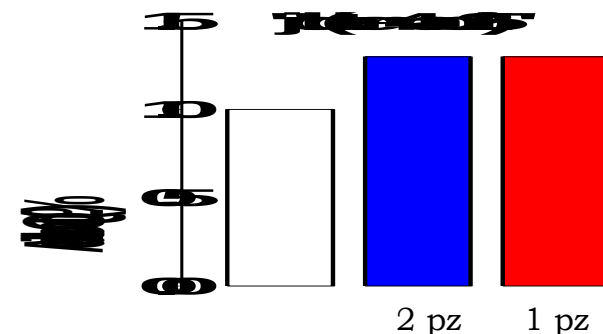
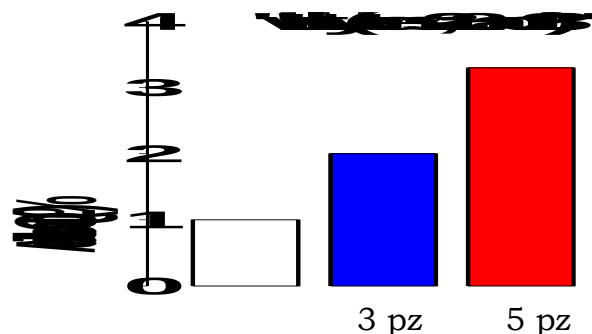
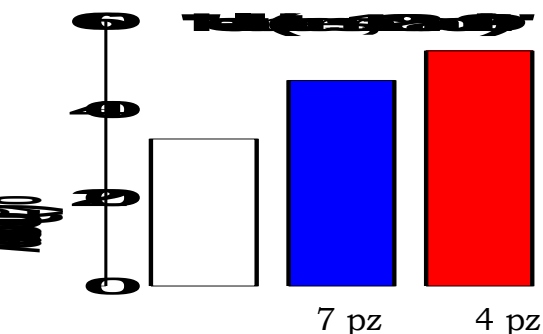


Addison QoL

	Item 1	Item 2	Item 4	Item 8	Item 25	Item 28	Item 29
HC	3.8±0.3	3.4±0.3	2.7±0.3	3.3±0.3	2.4±0.4	3.4±0.4	3.7±0.3
3 mesi	3.9±0.3	3.6±0.2	2.5±0.4	3.3±0.4	2.0±0.4	3.4±0.4	3.8±0.3
12 mesi	4.4±0.3	3.9±0.4	2.2±0.5	4.1±0.5	1.4±0.4	3.6±0.6	4.4±0.2

Item 1 (I feel good about my health), **item 2** (I can keep going during the day without feeling tired), **item 4** (I have to struggle to finish jobs), **item 8** (I feel rested when I wake up in the morning), **item 25** (my ability to work is limited), **item 28** (I feel full of energy), **item 29** (I feel physically fit)

Addison QoL (%)
durante HC (□), PL 3 mesi (■) e 12 mesi (■)



Compliance

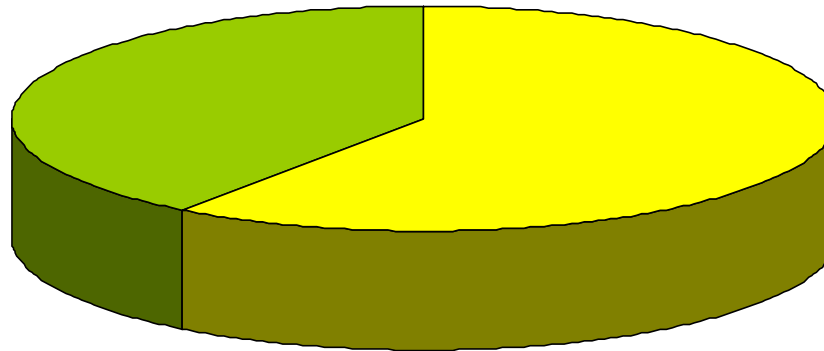
Circa il 93% dei pazienti ha preferito il PL rispetto HC (14/15 pz dopo 6 mesi, 10/11 pz dopo 12 mesi).

Nessun paziente ha finora sospeso la terapia.

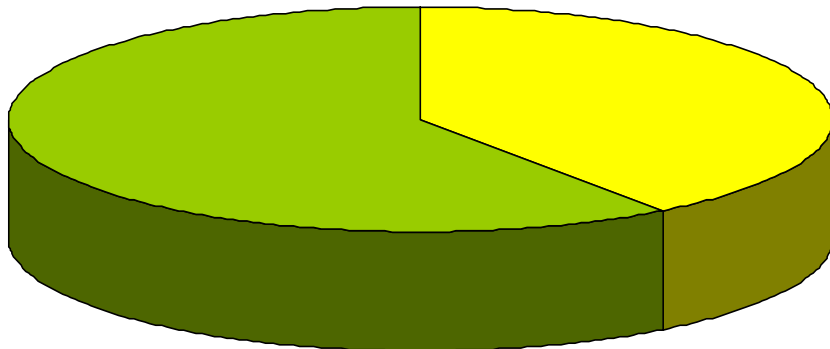
 *PL è simile ad HC*

 *PL è meglio di HC*

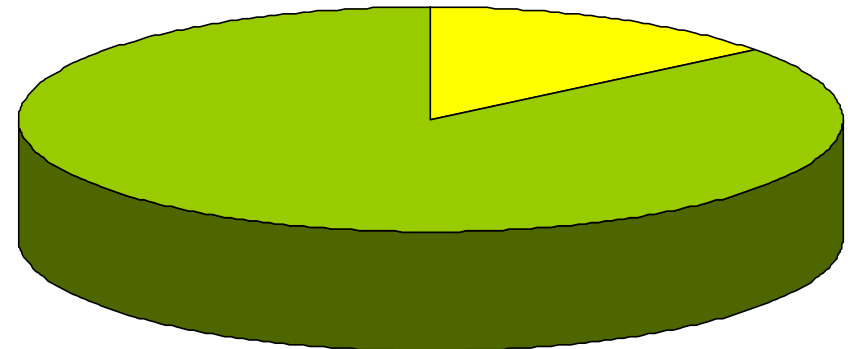
PL 1 mese



PL 3 mesi



PL 12 mesi



Eventi avversi:

- 4 pazienti con astenia nei primi 1-3 mesi
- 1 paziente con virosi (EBV)
- nessuna crisi ipocorticosurrenalica acuta
- nessun paziente ha richiesto ospedalizzazione

CONCLUSIONI

Questi **risultati**, seppure **preliminari**, dimostrano una certa **superiorità del nuovo preparato** rispetto alla terapia convenzionale, in termini di:

- capacità di ridurre i livelli medi di **ACTH** senza modificare i livelli medi di **cortisolemia**;
- migliorare** alcuni **parametri antropometrici** e soprattutto **metabolici**;
- **migliorare** la **QoL** e la **compliance** alla terapia.



... Grazie ...

