Altogether to Beat Cushing's Syndrome

DIPARTIMENTO DI MEDICINA CLINICA E CHIRURGIA
UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

16.30-17-30 **SESSION 2: A PECULIAR ASPECT OF COMPLICATIONS: HYPERGLICAEMIA AND DIABETES MELLITUS IN CUSHING'S SYNDROME**

THE DIABETES DURING "TREATMENT" OF CUSHING'S SYNDROME

Viaggio alla (ri)scoperta della Sindrome di Cushing 4ª Edizione / 4th Edition

Journey to the (re)discovery of Cushing's Syndrome

Napoli, 5-7 May 2015

Laura Trementino

Clinica di Endocrinologia
Università Politecnica delle Marche
Ancona

THE DIABETES DURING "TREATMENT" OF CUSHING'S SYNDROME

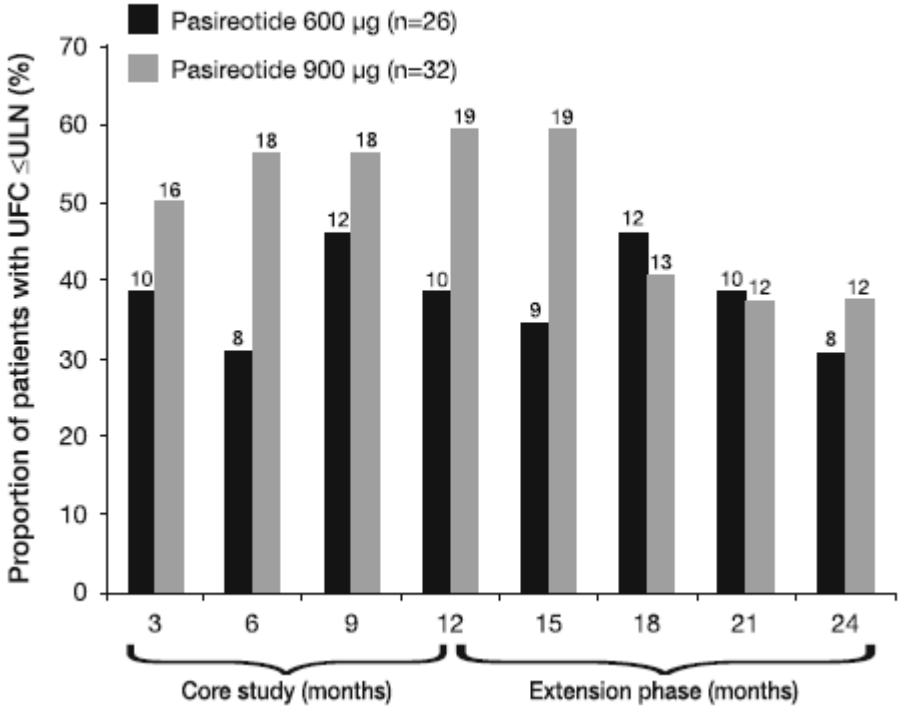
1. Pre-existing diabetes/prediabetes worsening or new onset diabetes during pasireotide treatment

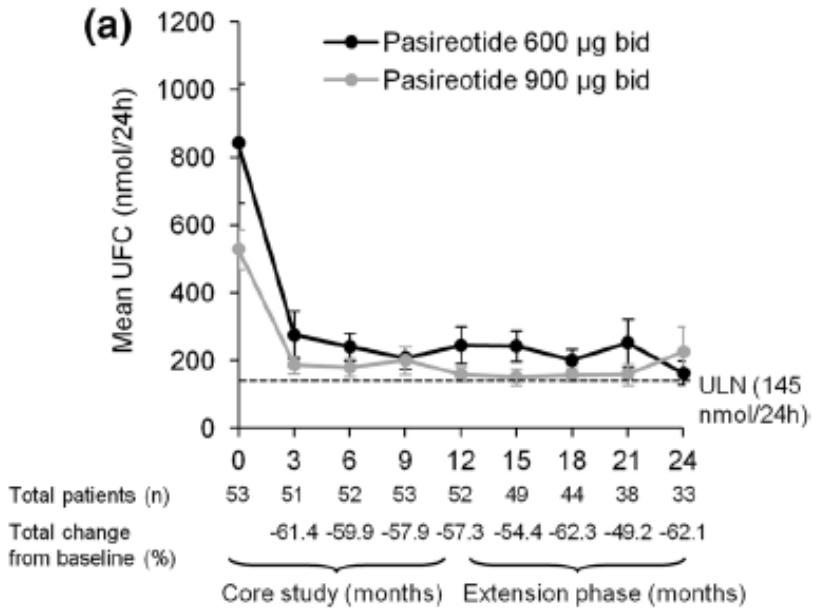
2. Pre-existing diabetes/prediabetes improvement during medical treatment and disease control

THE DIABETES DURING "TREATMENT" OF CUSHING'S SYNDROME

1. Pre-existing diabetes/prediabetes worsening or new onset diabetes during pasireotide treatment

Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial





Reduction in mean UFC and improvements in clinical signs of Cushing's disease maintained over 24 months

of pasireotide treatment

Pituitary
DOI 10.1007/s11102-014-0618-1

J. Schopohl

Published online: 24 December 2014

Safety: most frequent study drug-related AEs (≥ 5%)

Adverse Event	Pasireotide 600 μg Twice Daily (N=82)		Pasireotide 900 μg Twice Daily (N=80)		Overall (N=162)	
	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades
	number of patients (percent)					
Diarrhea	3 (4)	48 (59)	2 (2)	46 (58)	5 (3)	94 (58)
Nausea	1 (1)	38 (46)	3 (4)	46 (58)	4 (2)	84 (52)
Hyperglycemia	8 (10)	31 (38)	13 (16)	34 (42)	21 (13)	65 (40)
Cholelithiasis	1 (1)	25 (30)	1 (1)	24 (30)	2 (1)	49 (30)
Headache	1 (1)	23 (28)	2 (2)	23 (29)	3 (2)	46 (28)
Abdominal pain	1 (1)	19 (23)	2 (2)	20 (25)	3 (2)	39 (24)
Fatigue	1 (1)	12 (15)	2 (2)	19 (24)	3 (2)	31 (19)
Diabetes mellitus	6 (7)	13 (16)	6 (8)	16 (20)	12 (7)	29 (18)
Nasopharyngitis	0	10 (12)	0	11 (14)	0	21 (13)
Alopecia	0	10 (12)	0	10 (12)	0	20 (12)
Asthenia	2 (2)	13 (16)	2 (2)	5 (6)	4 (2)	18 (11)
Glycated hemoglobin elevation	1 (1)	10 (12)	0	8 (10)	1 (1)	18 (11)
ALT elevation	1 (1)	11 (13)	3 (4)	6 (8)	4 (2)	17 (10)
GGT elevation	4 (5)	10 (12)	2 (2)	7 (9)	6 (4)	17 (10)
Peripheral edema	0	9 (11)	0	8 (10)	0	17 (10)
Upper abdominal pain	0	10 (12)	0	6 (8)	0	16 (10)
Decreased appetite	0	7 (9)	0	9 (11)	0	16 (10)
Hypercholesterolemia	0	7 (9)	0	9 (11)	0	16 (10)
Hypoglycemia	3 (4)	12 (15)	0	3 (4)	3 (2)	15 (9)
Type 2 diabetes mellitus	4 (5)	10 (12)	3 (4)	5 (6)	7 (4)	15 (9)
Anxiety	0	5 (6)	0	9 (11)	0	14 (9)
Influenza	0	9 (11)	0	5 (6)	0	14 (9)
Insomnia	0	3 (4)	0	11 (14)	0	14 (9)
Myalgia	1 (1)	10 (12)	0	4 (5)	1 (1)	14 (9)

73% of patients had at least one hyperglycemia-related AE (6% discontinued study drug).

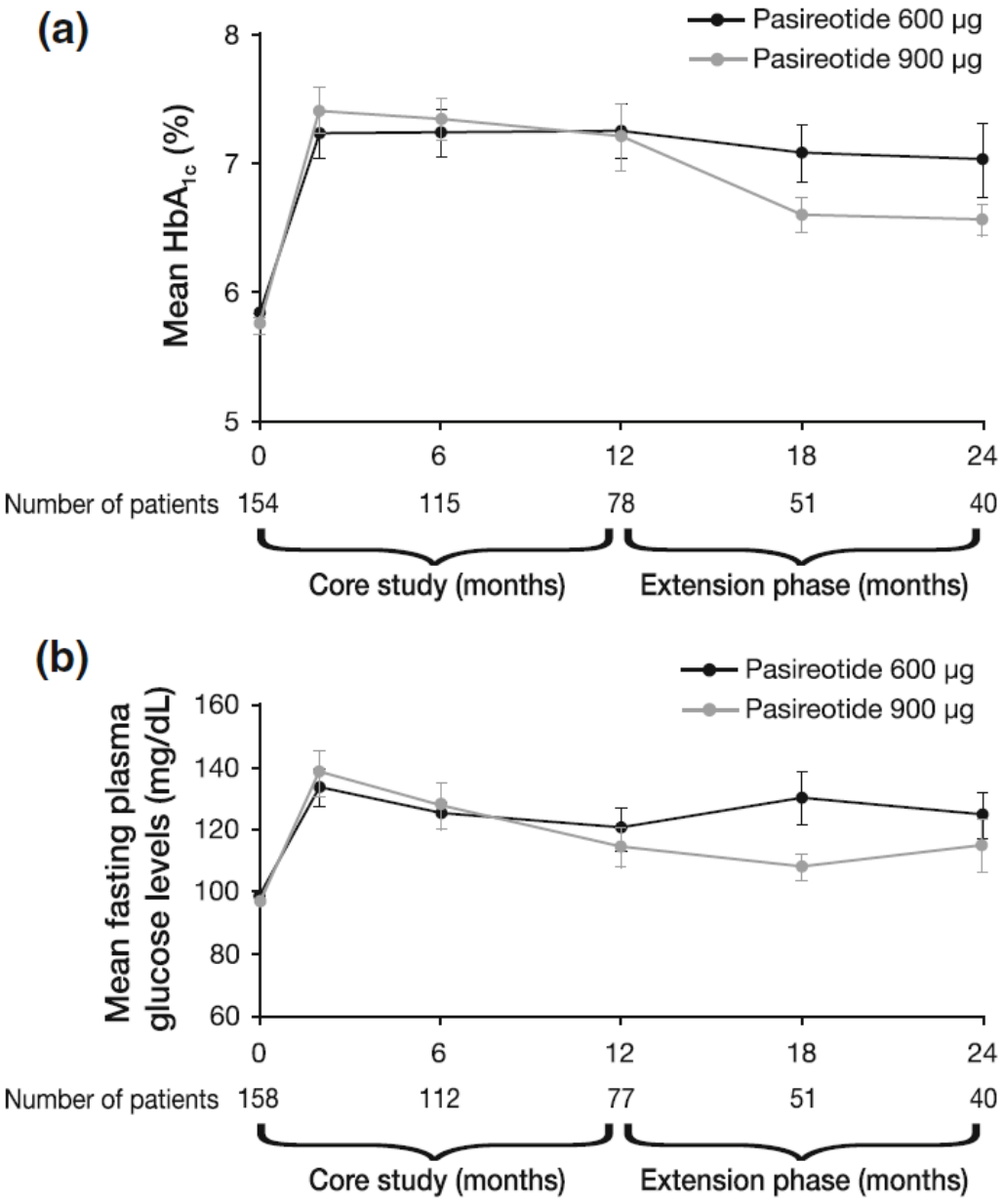
48% new onset diabetes mellitus

45% of patients started a new anti-diabetic medication

Safety profile at month 12 similar to that at month 24

Colao et al., N Engl J Med 2012

Changes in glycemia

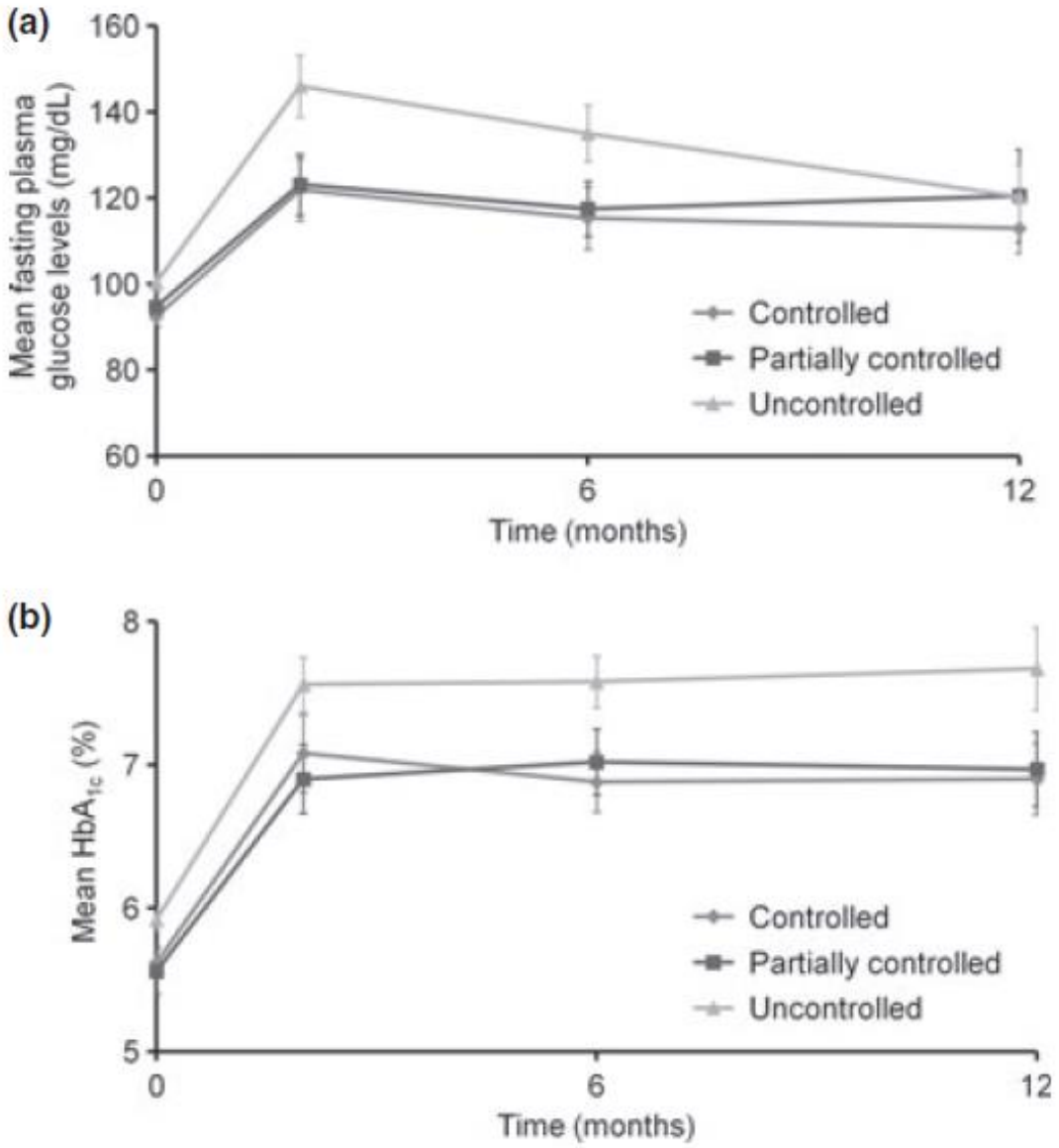


- **Glucose and HbA1c levels increased soon** after the initiation of pasireotide to stabilize thereafter
- **Preexisting diabetes or impaired glucose tolerance increased the risk of hyperglycemia-related AEs**

Pituitary
DOI 10.1007/s11102-014-0618-1

Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: results from a Phase III study

FPG and HbA1c increased from baseline irrespective of decreases of UFC



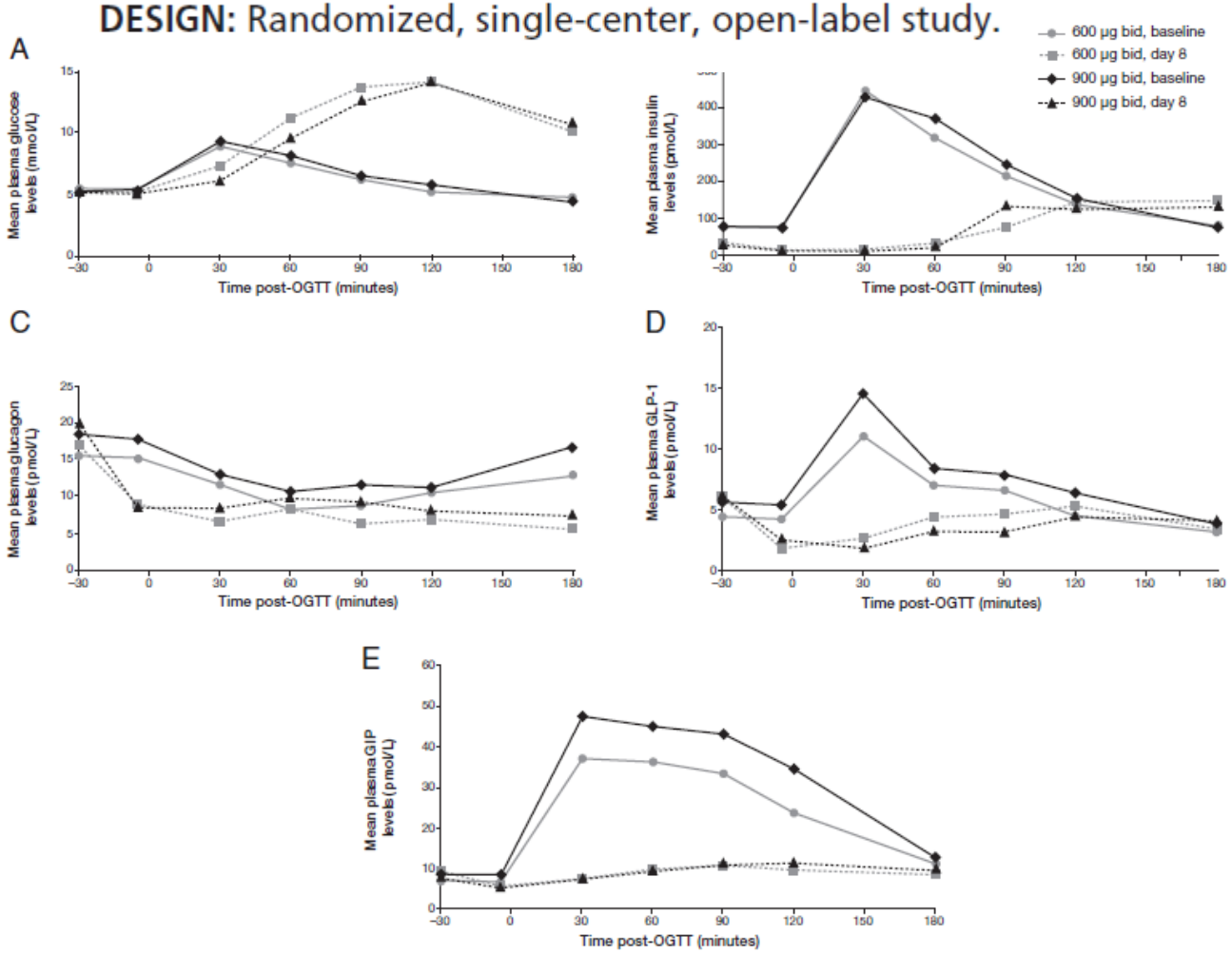
R. *Pivonello* et al.

Clinical Endocrinology (2014)

Hyperglycemia associated with pasireotide:results from a mechanistic study in healthy volunteers

Robert R Henry,[1,2] Thoedore P Ciaraldi,[1,2] Debra Armstrong,[1] Paivi Burke,[1] Monica Ligueros-Saylan,[3], and Sunder Mudaliar[1,2]

DESIGN: Randomized, single-center, open-label study.



Pasireotide reduces insulin secretion and incretin response, with modest suppressive effect on glucagon secretion and without affecting insulin sensitivity

J Clin Endocrin Metab. First published ahead of print June 3, 2013 as doi:10.1210/jc.2013-1771

Limitations of supporting study

- Healthy subjects (BMI ≤25 Kg/m^2, no family hystory of diabetes, no baseline diabetes/impaired glucose tolerance) → Cushing's disease ?

- Short-term study (Long-term changes in glucose metabolism?)

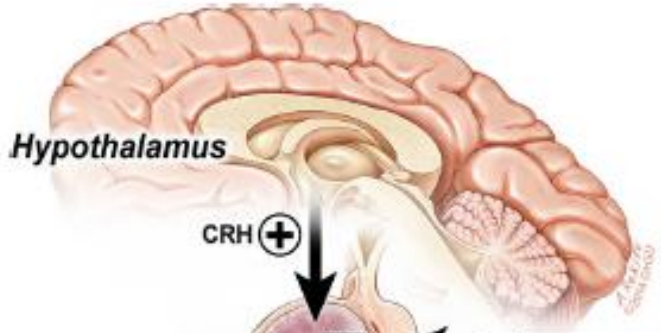
Our 10-year experience with pasireotide in CD

Patient	GLYCEMIC STATUS			Months of	Δ HbA1c	GLUCOSE LOWERING INTERVENTIONS	GLYCEMIC	UFC
	Baseline	Month 3	Last FU	treatment	(%)		CONTROL	at last FU
1	DM	DM	DM	24	+2.6	metformin→DPP-4 inhibitor→GLP-1 analog→ GLP-1 analog + detemir→ basal-bolus insulin	PC	Reduced
2	Pre-DM	NGT	DM	24	+1.6	diet and lifestyle	T	Reduced
3	DM	Pre-DM	Pre-DM	48	+1.3	diet and lifestyle	T	Reduced
4	NGT	NGT	DM	60	+1.2	diet and lifestyle	T	Normalized
5	NGT	NGT	DM	18	+1.6	diet and lifestyle	T	Reduced
6 (Ref. 17)	DM*	DM	DM	72	0	basal-bolus insulin→metformin + DPP-4 inhibitor	PC	Normalized
7	NGT	NGT	NGT	4	0	diet and lifestyle	T	Normalized
8	NGT	DM	DM	18	+1.8	metformin	PC	Reduced
9	DM	DM	DM	72	+2	metformin + glimepiride→glimepiride	PC	Reduced
10	Pre-DM	DM	DM	12	+0.7	diet and lifestyle	T	Normalized
11	DM	DM	DM	6	+1.3	metformin + DPP-4 inhibitor + glargine→ metformin + DPP-4 inhibitor	PC	Normalized
12	DM	DM	DM	8	+0.3	metformin	T	Normalized
13	DM*	DM	DM	3	+1.6	metformin + glargine→metformin + glargine	T	Unchanged
14	NGT	DM	DM	6	+0.8	metformin + glimepiride	T	Reduced
15	Pre-DM	DM	DM	3	+2.4	diet and lifestyle	UC	Unchanged
16	NGT	DM	DM	9	+0.9	diet and lifestyle	T	Normalized
17	Pre-DM	DM	DM	9	+2.2	glimepiride	UC	Normalized
18	NGT	Pre-DM	Pre-DM	3	+0.7	diet and lifestyle	T	Reduced
19	DM	DM	DM	6	+1.4	diet and lifestyle	PC	Normalized
20	Pre-DM	DM	DM	6	+1.7	diet and lifestyle	PC	Normalized

THE DIABETES DURING "TREATMENT" OF CUSHING'S SYNDROME

2. Pre-existing diabetes/prediabetes improvement during medical treatment and disease control

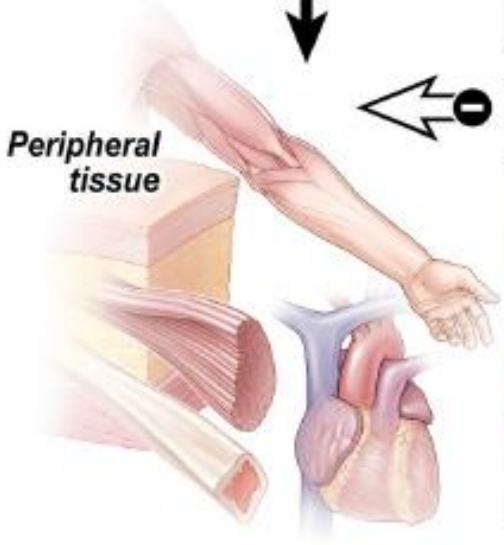
Medical treatment in Cushing's syndrome



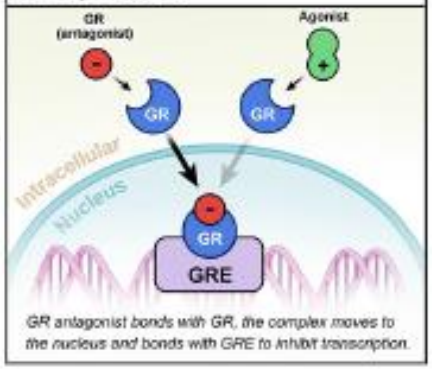
Neuromodulators of ACTH release
SRLs (Pasireotide)
DAs (Cabergoline)

ACTH

Adrenal steroidogenesis inhibitors
Ketoconazole
Metyrapone
Mitotane
Etomidate
LCI699 *(in clinical trials)*
Normocort *(in clinical trials)*

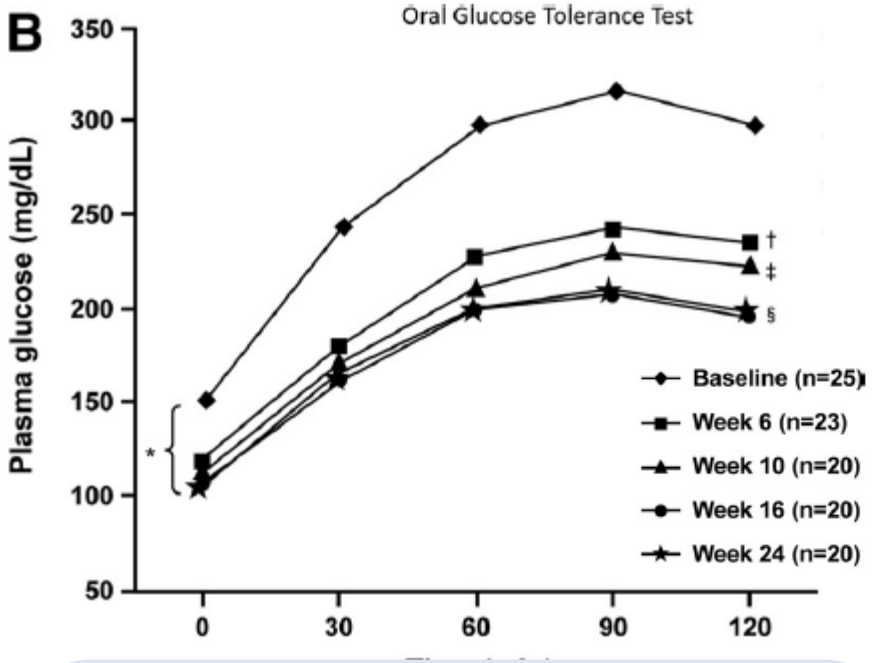


Glucocorticoid receptor blocker
Mifepristone

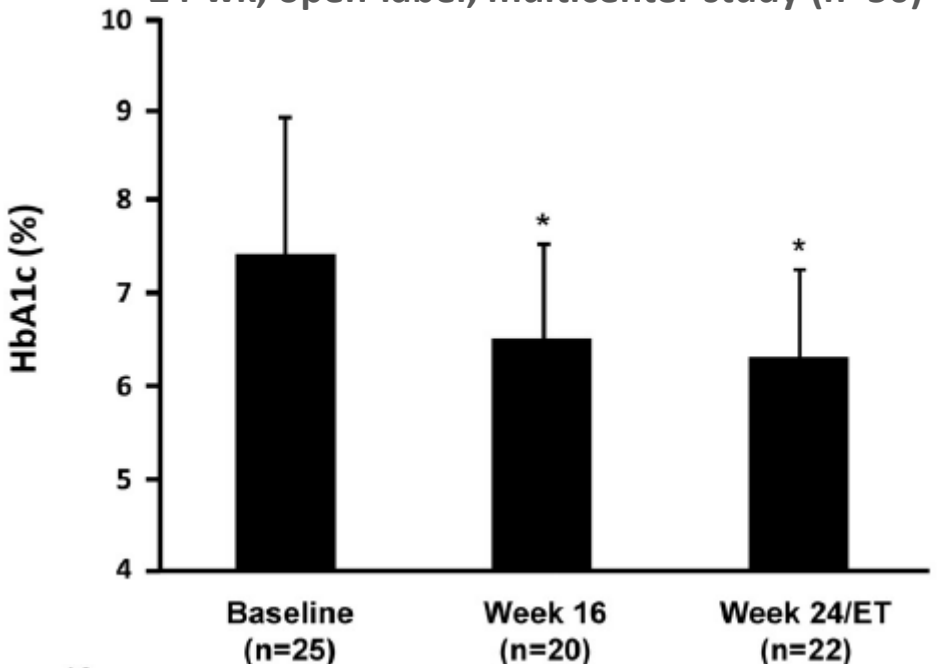


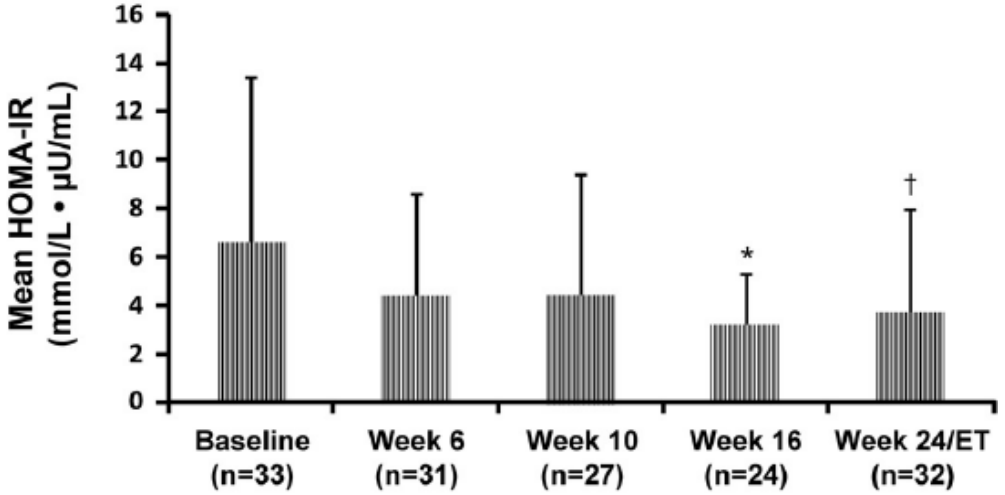
Fleseriu M. & Petersenn S., Pituitary 2015

Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome



24-wk, open-label, multicenter study (n=50)





U.S. FDA-approved to treat hyperglycemia in adults patients with CS and type 2 DM or glucose intolerance not candidates for surgery or who have not responded to prior surgery

J Clin Endocrinol Metab, June 2012, 97(6):2039–2049

Ketoconazole in Cushing's Disease: Is It Worth a Try?

Median dose 600 mg/die
- **49.3% Normal UFC**
- **25.6% UFC decrease ≥50%**
- **25.4% unchanged UFC**

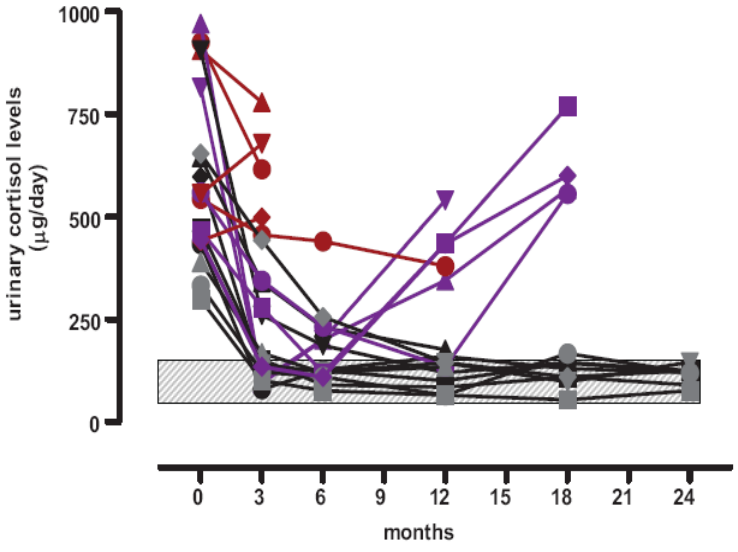
200 patients

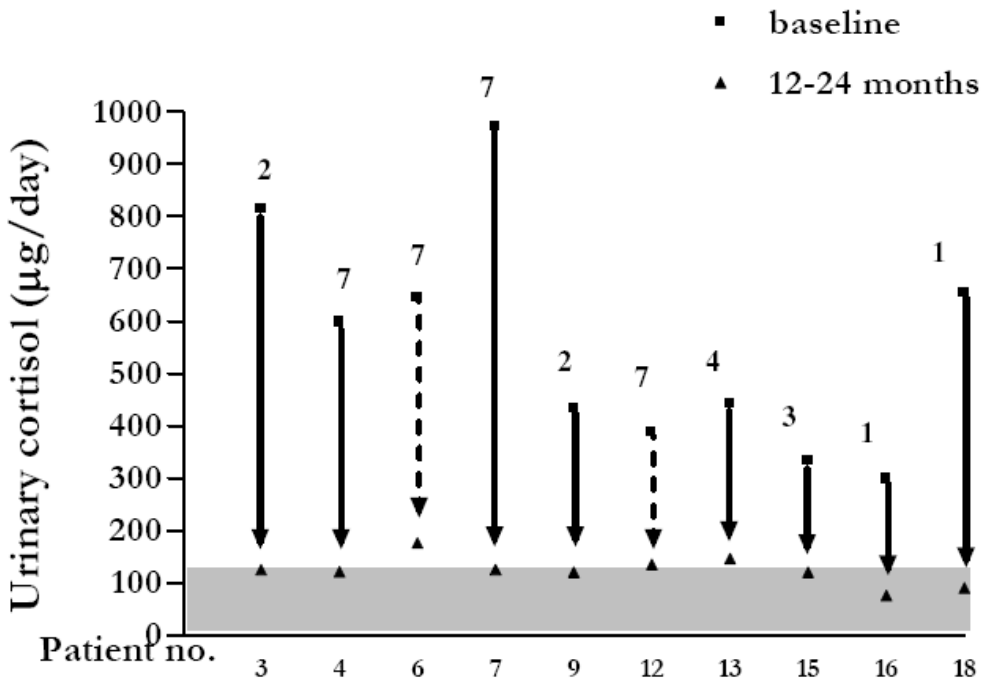
40 as a presurgical treatment	32 as a primary treatment (CI or refusal to surgery)	128 as a secondary treatment - Unsuccesful surgery (n=93) - Following radiotherapy (n=35)
Antisecretory efficacy (n=39) - 19 Controlled (48.7%) - 14 Partially controlled (35.6%) - 6 Uncontrolled (15.4%)	**Antisecretory efficacy (n=32)** - 16 Controlled (50%) - 9 Partially controlled (28.1%) - 7 Uncontrolled (21.8%)	**Antisecretory efficacy (n=126)** - 62 Controlled (49.2%) - 28 Partially controlled (22.2%) - 36 Uncontrolled (28.5%)

	Initial	Improved		Initial	Improved		Initial	Improved
Clinical signs	38	42.1%	Clinical signs	28	67.8%	Clinical signs	106	50%
Hypertension	26	50%	Hypertension	23	34.8%	Hypertension	67	41.8%
Hypokalemia	13	38.4%	Hypokalemia	7	28.6%	Hypokalemia	19	42.1%
Diabetes	16	50%	Diabetes	12	58.3%	Diabetes	27	59.2%

Tolerance data in 190 patients

The Medical Treatment of Cushing's Disease: Effectiveness of Chronic Treatment with the Dopamine Agonist Cabergoline in Patients Unsuccessfully Treated by Surgery





- Short-term (3 months) response: 75% (15/20). 35% (7/20) normalized
- Long-term (12-24 months) response: 40% (8/20) normalized
- Cabergoline dose ranging from 1 and 7 mg/wk, mean 6 mg/wk (1 year) and mean 3.5 mg/wk (2 year)

TABLE 3. Clinical, biochemical, and radiological features of patients with CD long-term responsive to cabergoline treatment

Parameter	Baseline (10 patients)	12-month treatment (10 patients)	24-month treatment (8 patients)	*P* value
Body mass index (kg/m^2)	28.2 ± 0.9	28.0 ± 0.8	27.1 ± 0.7[a]	0.011
Waist to hip ratio	1.12 ± 0.06	1.03 ± 0.06[b]	1.01 ± 0.06[a]	0.002
Systolic blood pressure (mm Hg)	141.5 ± 4.4	118.0 ± 5.1[a]	123.1 ± 4.4[a]	0.015
Diastolic blood pressure (mm Hg)	91.0 ± 2.5	75.0 ± 3.8[b]	80.0 ± 3.4[a]	0.002
Heart rate (beats/min)	71.5 ± 2.3	79.7 ± 2.2[a]	76.9 ± 2.1	0.368
Fasting serum glucose (mg/dl)	128.2 ± 8.1	115.0 ± 3.2	106.0 ± 5.2[a]	0.002
Fasting serum insulin (μU/ml)	10.9 ± 1.5	8.4 ± 1.0[b]	7.2 ± 1.0[a]	0.002
HOMA-IR	3.47 ± 0.66	2.37 ± 0.29[b]	1.88 ± 0.29[a]	0.001
HOMA-B (%)	66.6 ± 9.2	61.0 ± 8.7	67.8 ± 11.3	0.607
Plasma ACTH (pg/ml)	62.4 ± 6.1	45.4 ± 3.6[b]	35.6 ± 3.2[a]	0.002
Serum cortisol (μg/liter)	236.2 ± 17.6	160.2 ± 6.0[b]	144.6 ± 10.5[a]	0.002
Urinary cortisol (μg/d)	558.1 ± 69.1	118.5 ± 12.2[b]	115.4 ± 7.8[a]	0.002
Tumor volume (mm^3)	224.3 ± 31.9	158.1 ± 46.2[a]	133.7 ± 56.7[a]	0.084

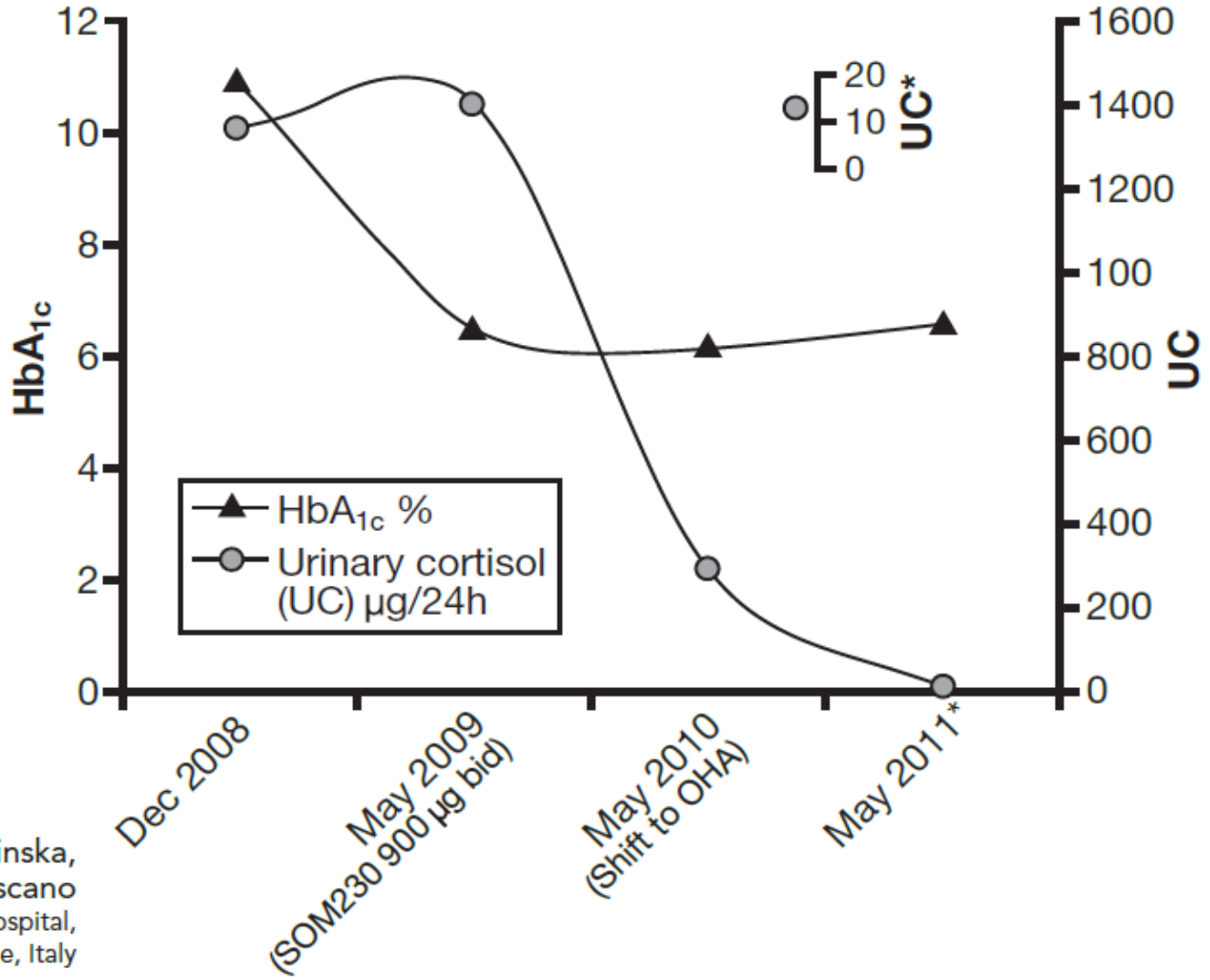
Prevalence of DM and IGT decreased from 25 to 10% and 37.5 to 20% respectively

Direct beneficial effect of dopamine agonists on glucose tolerance

J. Endocrinol. Invest. 34: 731-732, 2011

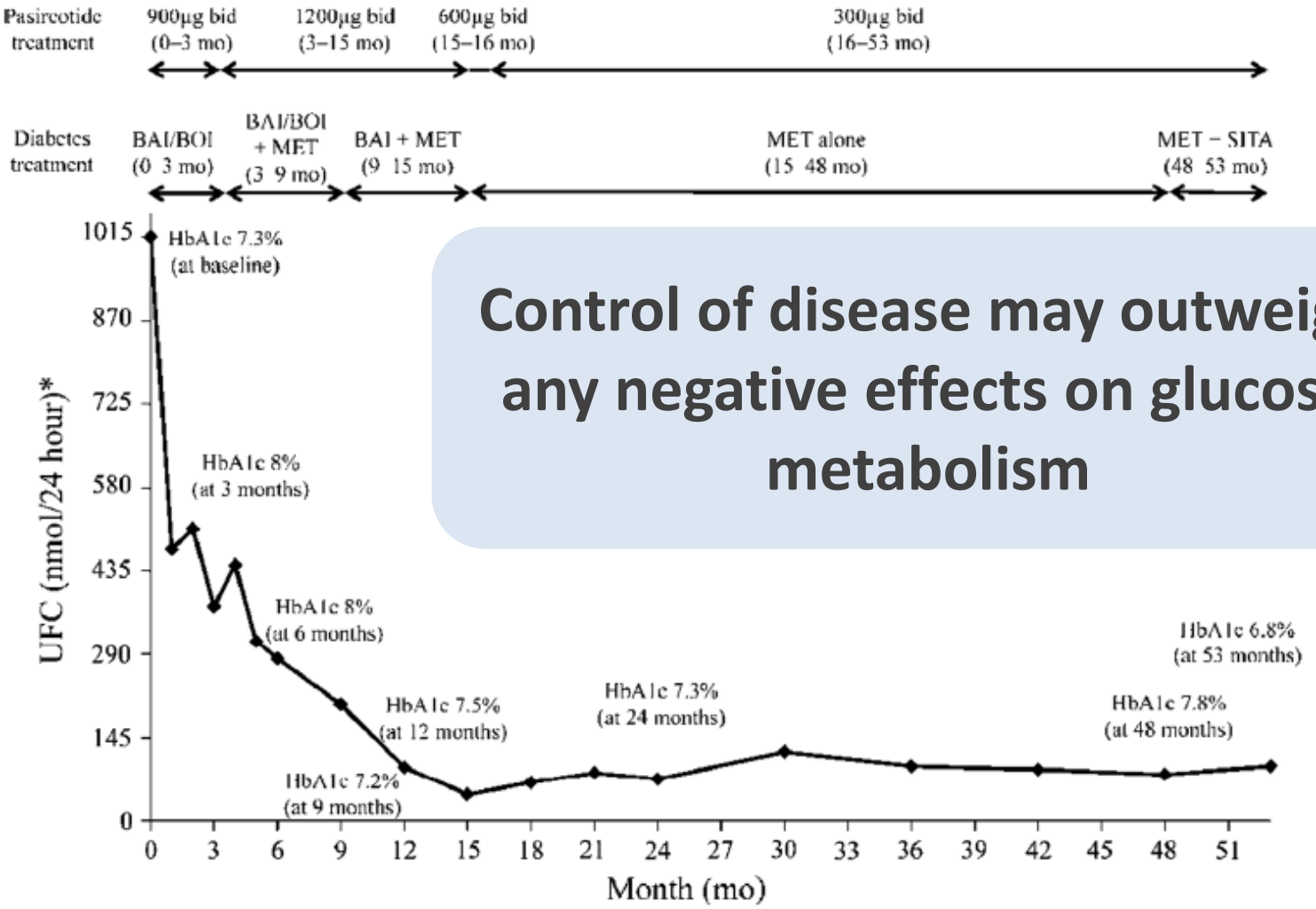
LETTER TO THE EDITOR

SOM230 in Cushing's disease complicated by poorly controlled diabetes mellitus



C. Fiorentino, C. Motta, D.T. Wolosinska, S. Monti, F. Mori, and V. Toscano
Division of Endocrinology, S. Andrea Hospital, "Sapienza" University of Rome, Rome, Italy

Up-to 5-year efficacy of pasireotide in a patient with Cushing's disease and pre-existing diabetes: literature review and clinical practice considerations

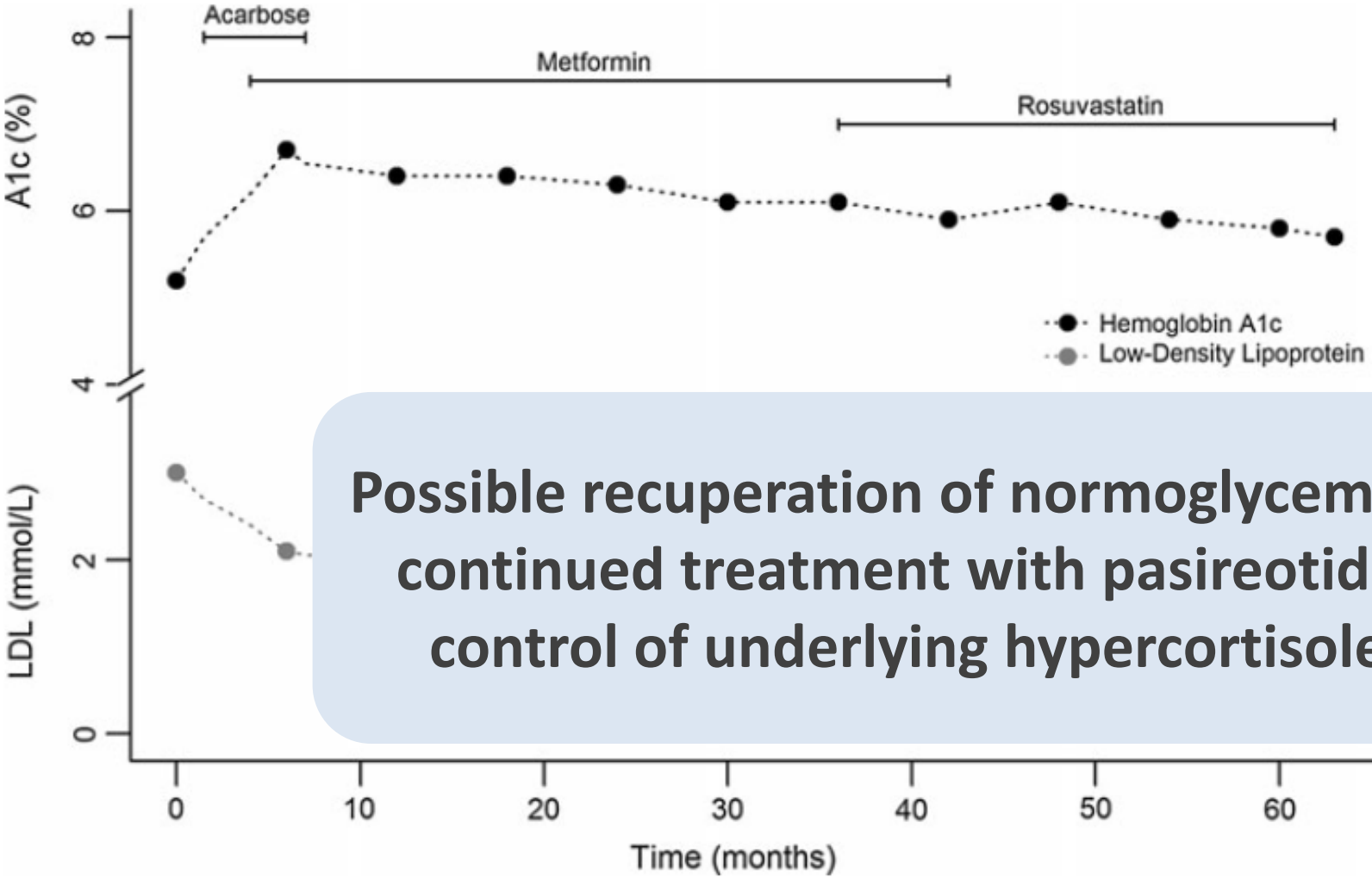


Control of disease may outweigh any negative effects on glucose metabolism

Pituitary
DOI 10.1007/s11102-014-0582-9

Laura Trementino · Marina Cardinaletti · Carolina Concettoni · Giorgia Marcelli · Marco Boscaro · Giorgio Arnaldi

Pasireotide monotherapy in Cushing's disease: a single-centre experience with 5-year extension of phase III Trial



Possible recuperation of normoglycemia after continued treatment with pasireotide and control of underlying hypercortisolemia

Pituitary
DOI 10.1007/s11102-013-0539-4

Jessica MacKenzie Feder · Isabelle Bourdeau · Sophie Vallette · Hugues Beauregard · Louis-Georges Ste-Marie · André Lacroix

THE DIABETES DURING "TREATMENT"
OF CUSHING'S SYNDROME

Literature data and clinical practice considerations:

1. **Hyperglycemia** is a frequent complication of **pasireotide** treatment but probably the **clinical impact of this AE is overestimated**

2. **Effective medical treatment can determine the improvement of a pre-existing diabetes**, in the medium-long term **even during pasireotide treatment**

thank you!