APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

2ª edizione

MANIFESTAZIONI CARDIOVASCOLARI E METABOLICHE IN REUMATOLOGIA

TORINO, 4-5 *aprile* 2014

Starhotels Majestic, corso Vittorio Emanuele II 54

SIMPOSIO
Rischio cardiovascolare e terapie reumatologiche

STEROIDI

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Meccanismi anti-infiammatori dei GCs

Azioni anti-infiammatorie ed immunosoppressive

- Riduzione della produzione di citochine (IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-11, IL-12, IFN-γ, TNF-α, GM-CSF)
- Riduzione della produzione di NO
- Riduzione della produzione di prostaglandine e leucotrieni
- Aumento della produzione di TGF-β
- Riduzione della sopravvivenza dei linfociti T, monociti, eosinofili
- Riduzione dell'espressione delle molecole di adesione cellulare (ELAM-1, E-selectin, ICAM-1, VCAM-1)
- Riduzione dell'attivazione dei linfociti T indotta da IL-2 e IFN-γ

Azioni anti-proliferative

Inibizione della sintesi del DNA e del turn-over cellulare

Azioni vasocostrittrici

Inibizione dell'azione dell'istamina e di altri mediatori vasodilatatori

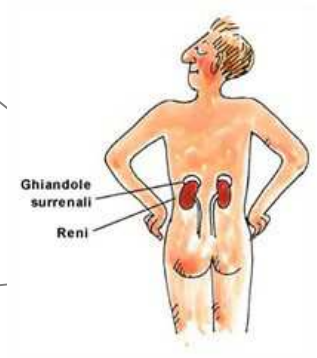
Effetti biologici dei glucocorticoidi

(mediazione risposta allo stress)

Aumento portata cardiaca e tono vascolare

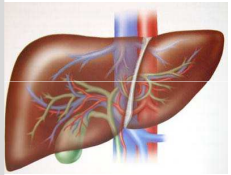
Aumento volemia, ritenzione Na, escrezione K

Azione anti-infiammatoria



+ Gluconeogenesi e glicogenolisi

- Uptake del glucosio e glicogenosintesi

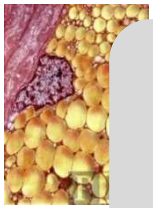


Sonno

Comportamento

Attività cognitive

Effetti catabolici su osso e tessuto connettivo



Lipolisi periferica, lipogenesi centrale

+ Proteolisi e glicogenolisi

- Uptake del glucosio e glicogenosintesi

Effetti biologici dei glucocorticoidi

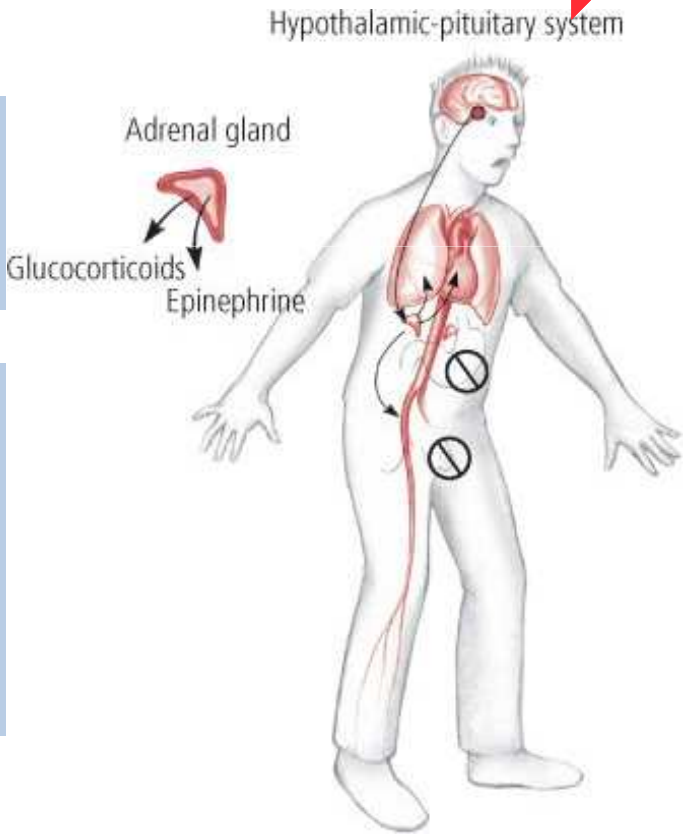
Fisiologia:

Esposizione cronica a un eccesso di glucocorticoidi

Patologia:

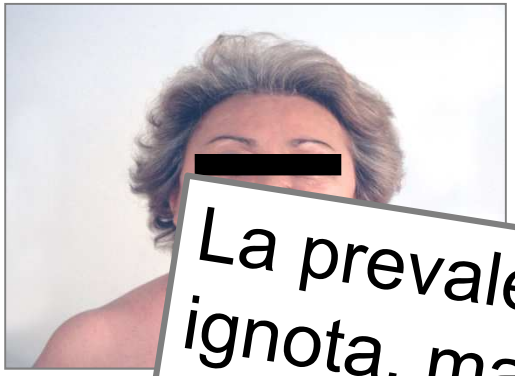
- Mantenimento omeostasi metabolica

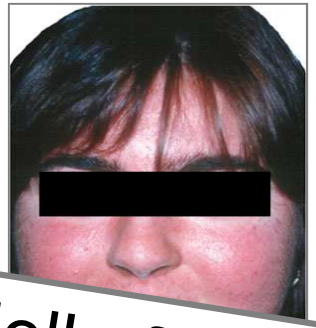
- **Risposta allo stress**
- Aumento substrati utilizzabili come fonti energetiche

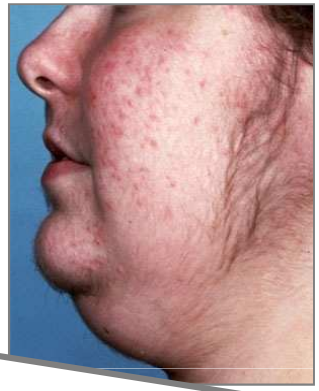


Fenomeni **maladattativi** (ipertensione, iperglicemia, dislipidemia, ...)
=
Sindrome di Cushing

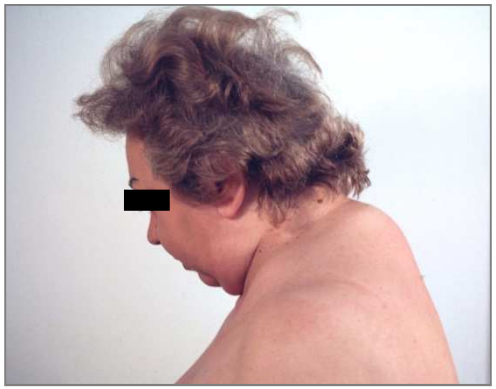
Sindrome di Cushing

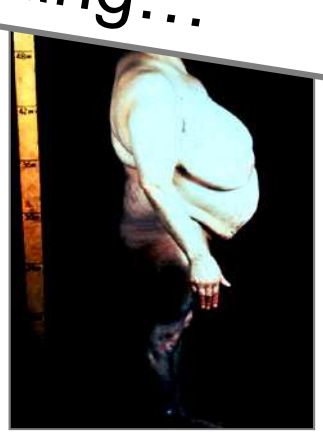


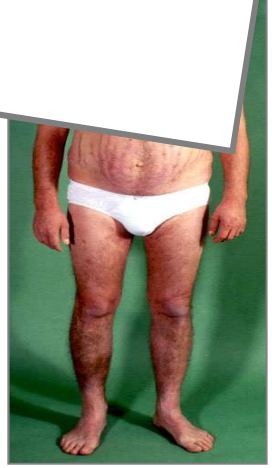




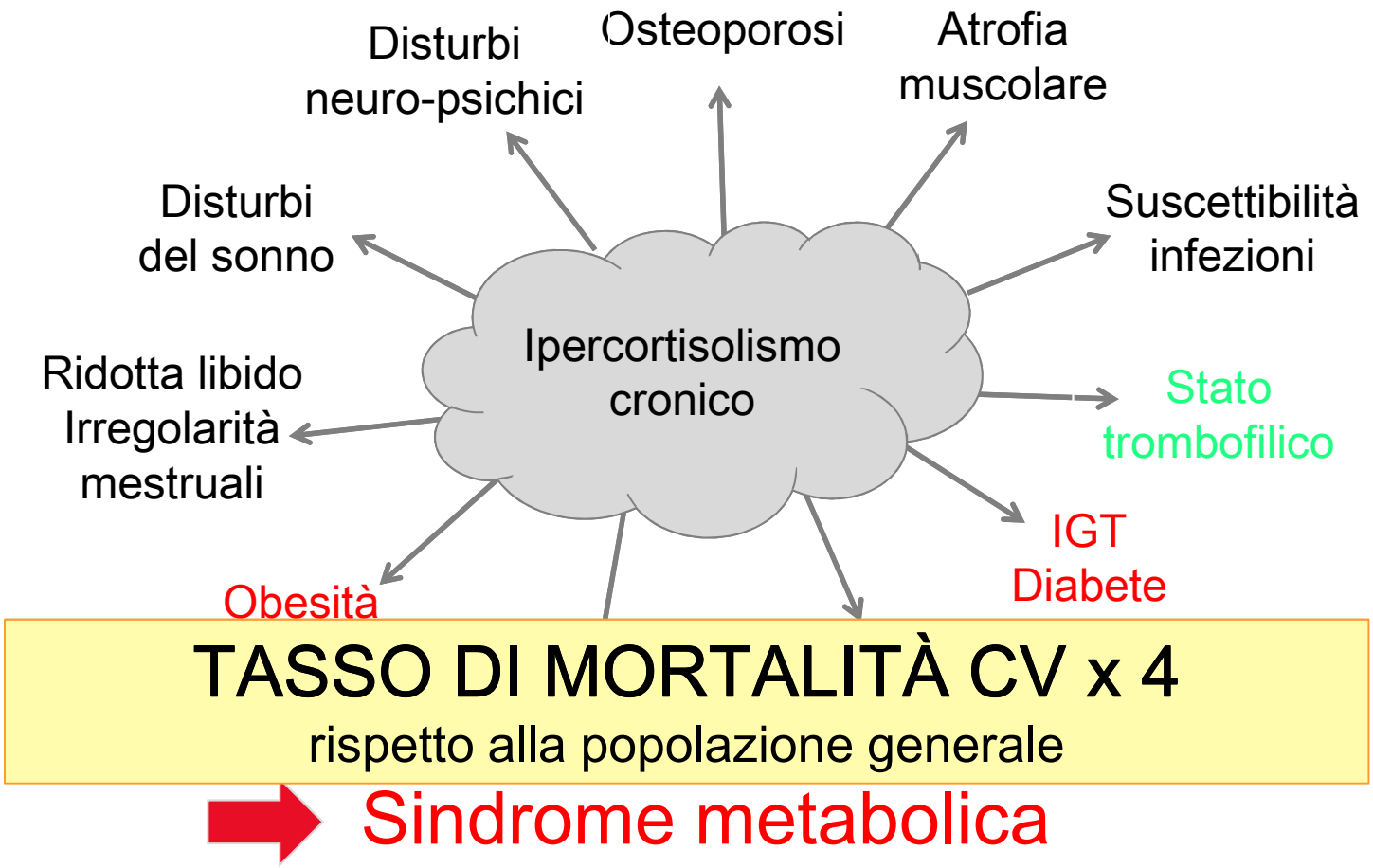
La prevalenza della forma iatrogena è ignota, ma è la forma più diffusa di sindrome di Cushing…







Sindrome di Cushing



Diagnosis and Complications of Cushing's Syndrome: a Consensus Statement
G Arnaldi, A. Angeli, AB Atkinson, X Bertagna, F Cavagnini, GP Chrousos et al
J. Clin. Endocrinol. Metab. 2003; 88, 5593-5602

Effetti cardiovascolari dei glucocorticoidi

Table 2 Cardiovascular effects of glucocorticoids.

Site of action	Via glucocorticoid receptors
Vascular smooth muscle	↑contractility e.g. to noradrenaline (185) ↓proliferation (138–140)
Er	
My	
Ma	
Nc	
	Dyslipidaemia Insulin resistance Glucose intolerance Prothrombotic

GR mediano:

…aumento contrattilità vasale…

…riduzione proliferazione, angiogenesi…

…effetto antinfiammatorio perivasale…

…protettivo su aterogenesi…

Published data show effects of corticosteroids to: ↑, increase; ↓, decrease; or ↕, either increase or decrease

Effetti cardiovascolari dei glucocorticoidi

Site of action	Via mineralocorticoid receptors

Ruolo controverso dei glucocorticoidi sul sistema CV

- **effetti metabolici in grado di aumentare i fattori tradizionali di rischio CV**
- **effetti complessi diretti su aterosclerosi e fibrosi cardiaca**

(sia protettivi sia di danno d'organo mediati da differenti tipi recettoriali)

Terapia steroidea in reumatologia:

"a *double-edge sw*

Effetto benefico o dannoso sul rischio cardiovascolare?

I

promuovono

la sindrome

meta

I GCs riducono

l'infiammazione

Tipo di steroide (emivita, affinità ai diversi R…)

Dose giornaliera

Dose cumulativa

Durata di esposizione

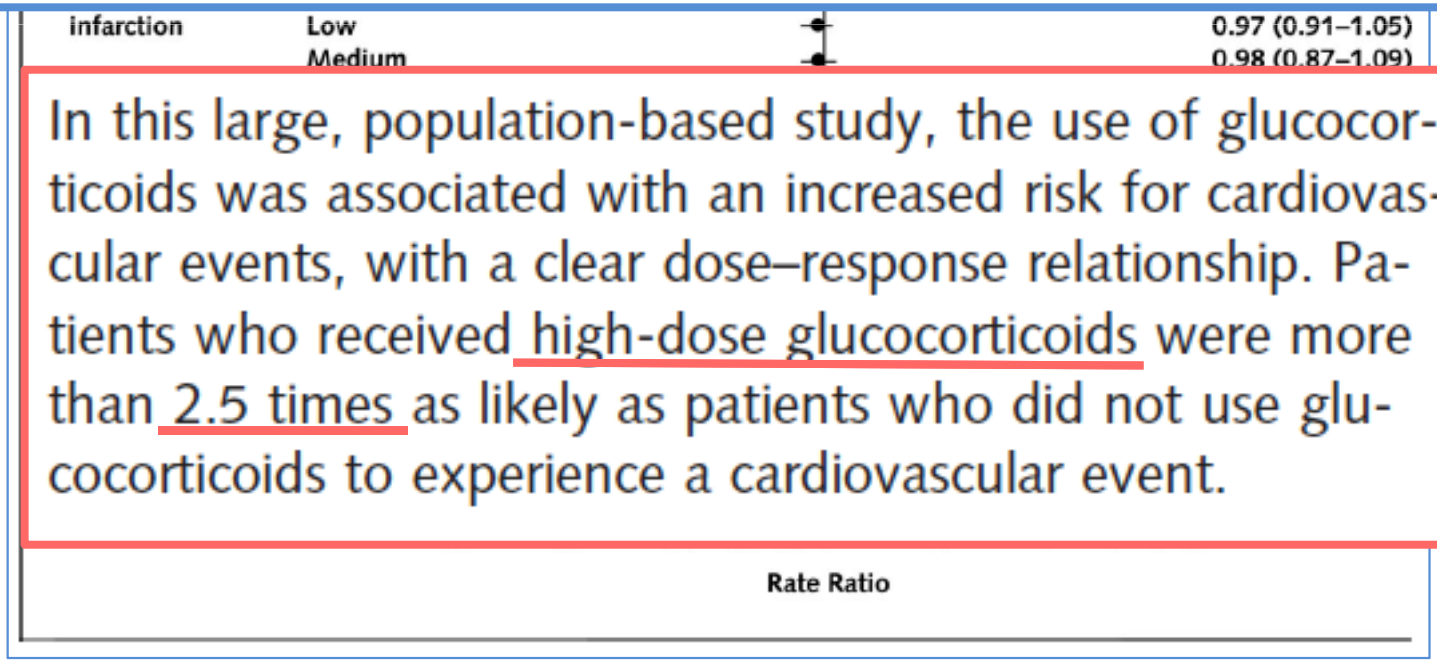
Timing di somministrazione

Taking Glucocorticoids by Prescription Is Associated with Subsequent Cardiovascular Disease

Li Wei, MB, MSc; Thomas M. MacDonald, MD, FRCPE; and Brian R. Walker, MD, FRCPE

Table 2. Influence of Dose of Glucocorticoids on All Cardiovascular Events

Steroid Exposure	Events, *n*	Unadjusted Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)*	Adjusted Rate Ratio (95% CI)†
Comparator	4383	1.00	1.00	1.00
Low dose	3521	1.30 (1.24–1.36)	1.00 (0.95–1.05)	1.00 (0.95–1.05)
Medium dose	1380	1.60 (1.50–1.70)	1.03 (0.96–1.10)	1.04 (0.95–1.14)
High dose	167	4.50 (3.86–5.25)	2.56 (2.18–2.99)	3.09 (2.51–3.80)



In this large, population-based study, the use of glucocorticoids was associated with an increased risk for cardiovascular events, with a clear dose–response relationship. Patients who received high-dose glucocorticoids were more than 2.5 times as likely as patients who did not use glucocorticoids to experience a cardiovascular event.

Ann Intern Med, 2004

Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study

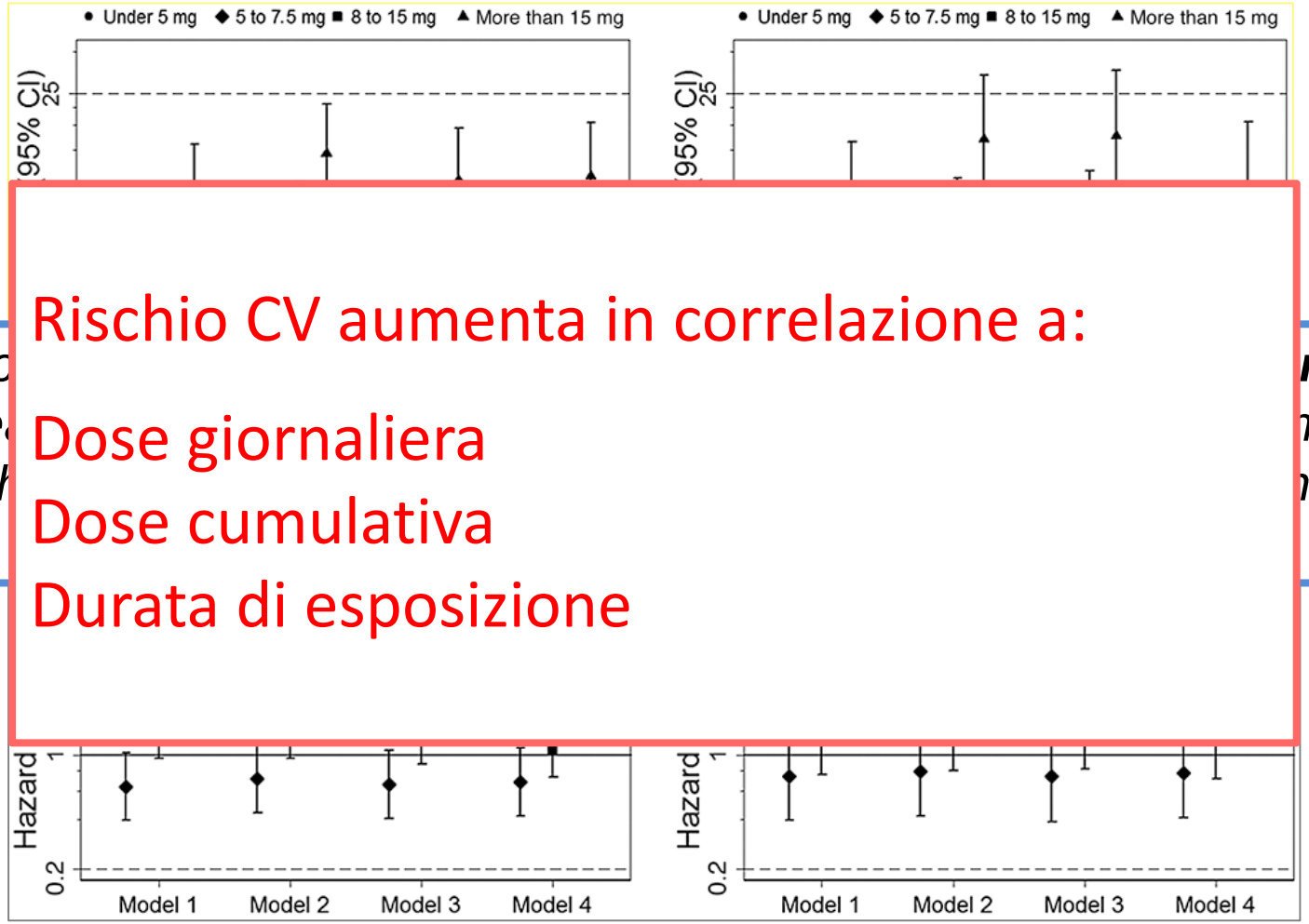
J. Antonio Aviña-Zubieta[1,2,3], Michal Abrahamowicz[4], Mary A. De Vera[2], Hyon K. Choi[2,3], Eric C. Sayre[2], M. Mushfiqur Rahman[2], Marie-Pierre Sylvestre[4,5], Willy Wynant[4], John M. Esdaile[1,2,3,6] and Diane Lacaille[1,2,3]

Conclusion. GCs are associated with an increased risk of MI in RA. Our results suggest a dual effect of GCs on MI risk, an immediate effect mediated through current dosage and a long-term effect of cumulative exposure.

1	Current use (yes/no)	1.94 (1.34, 2.80)	5175.4	1.68	1.14, 2.47)	5114.3
2	Current daily dose (5 mg)	1.17 (1.08, 1.27)	5177.8	1.14	1.05, 1.24)	5114.9
3	Total cumulative duration of use (year)	1.22 (1.09, 1.37)	5176.4	1.14	1.00, 1.29)	5116.9
4	Total past cumulative dose (1 g)	1.08 (1.04, 1.11)	5172.9	1.06	1.02, 1.10)	5113.6
5	Current daily dose (5 mg)	1.14 (1.04, 1.26)	5173.6	1.13	1.03, 1.24)	5114.9
	+Cumulative duration, year	1.18 (1.04, 1.33)		1.10	(0.97, 1.26)	

Rheumatology, 2013

Glucocorticoid Dose Thresholds Associated With All-Cause and Cardiovascular Mortality in Rheumatoid Arthritis



Rischio CV aumenta in correlazione a:

Dose giornaliera

Dose cumulativa

Durata di esposizione

del Rincòn I et al., *Arthritis Rheum*, 2014

Review

Cardiovascular risk induced by low-dose corticosteroids in rheumatoid arthritis: A systematic literature review

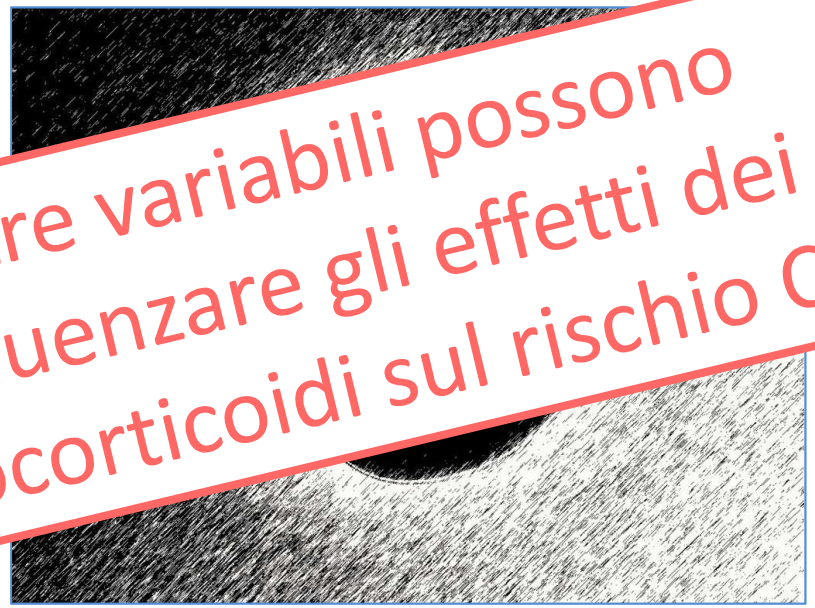
Adeline Ruyssen-Witrand[a,*], Bruno Fautrel[b], Alain Saraux[c], Xavier Le Loët[d], Thao Pham[e]

Joint Bone Spine 78 (2011) 23–30

the exposure to 1 to 3 years with LD-CT does not increase CV risk significantly in several RCT but longer exposure could increase the risk of major CV events. The risk is increased by two- to three-folds if prednisone is given with dosage > 10 mg per day. Since RA is already a risk factor for major CV events, the final objective of each physician should be stopping CT as soon as possible and give CT only for a short period at the very beginning of arthritis. The dose of prednisone should be also tailored according to the weight of patients.

Terapia steroidea in reumatologia:

"a *double-edge sword*"



Altre variabili possono influenzare gli effetti dei glucocorticoidi sul rischio CV?

Cardiovascular Death in Rheumatoid Arthritis

A Population-Based Study

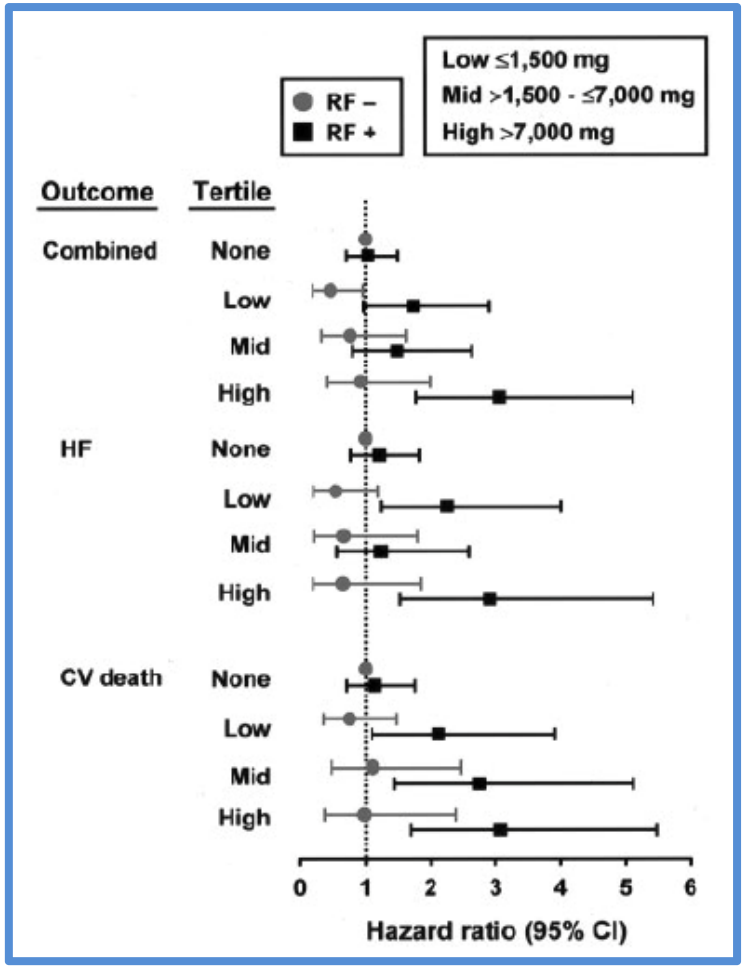
Hilal Maradit-Kremers, Paulo J. Nicola, Cynthia S. Crowson, Karla V. Ballman, and Sherine E. Gabriel

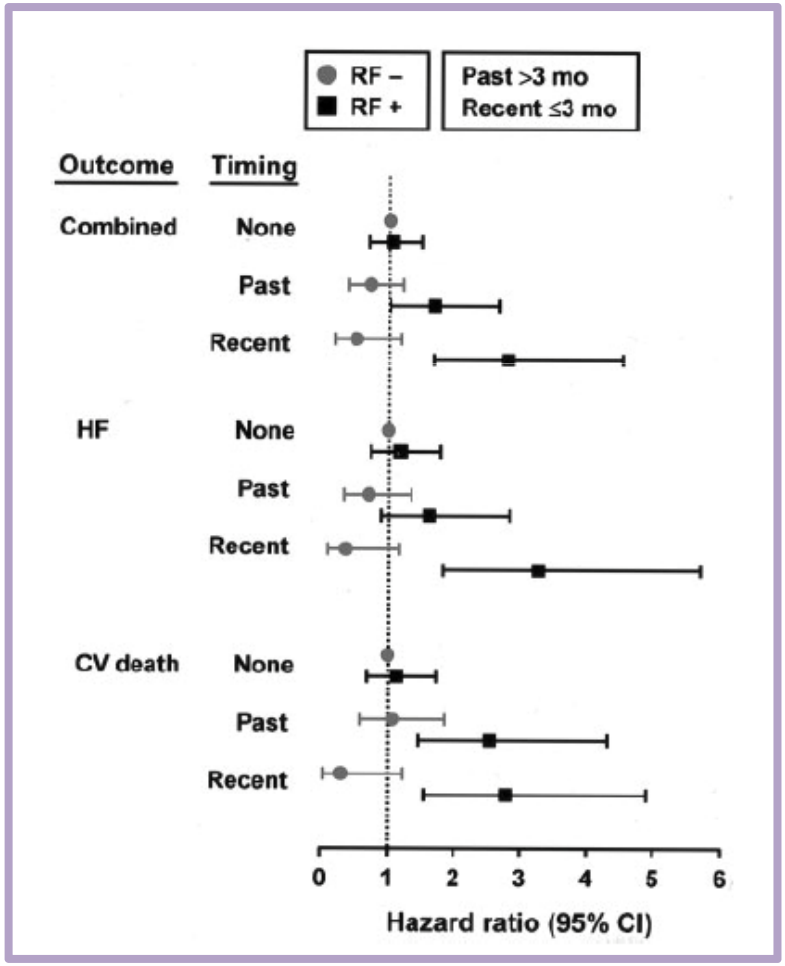
	No corticosteroids, HR (95% CI)*	Any corticosteroids, HR (95% CI)*
No personal history of CHD	1	1.78 (1.19–2.67)
Personal history of CHD	3.07 (1.91–4.95)	2.42 (1.37–4.26)

Arthritis & Rheumatism, 2005

Glucocorticoids and Cardiovascular Events in Rheumatoid Arthritis

A Population-Based Cohort Study



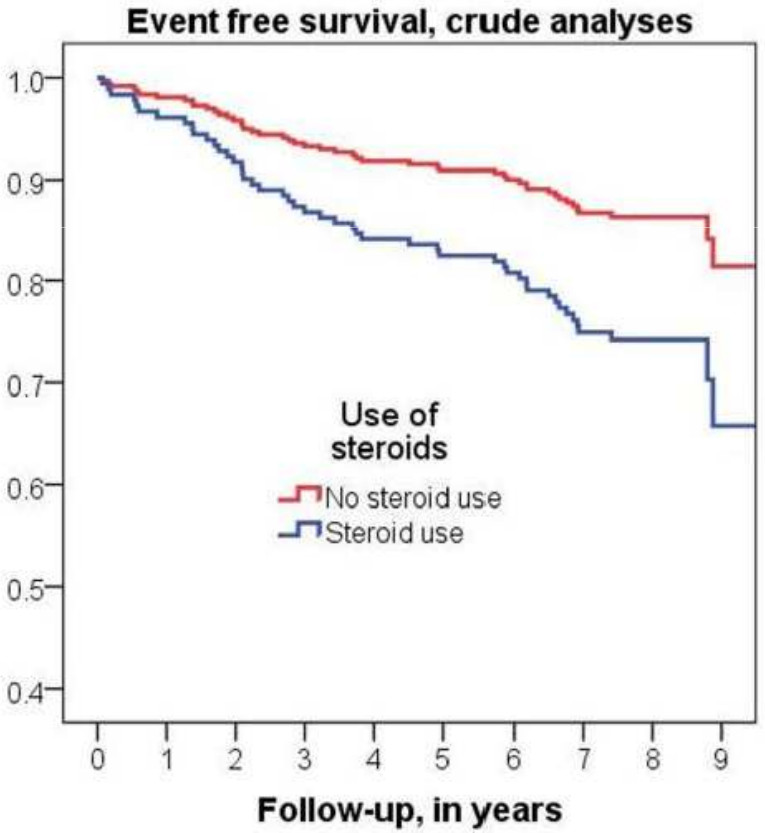


Davis JM III, *Arthritis & Rheumatism* 2007

Confounding by Indication Probably Distorts the Relationship between Steroid Use and Cardiovascular Disease in Rheumatoid Arthritis: Results from a Prospective Cohort Study

Alper M. van Sijl*, Maarten Boers, Alexandre E. Voskuyl, Michael T. Nurmohamed

Department of Rheumatology, VU University Medical Center, Amsterdam, the Netherlands

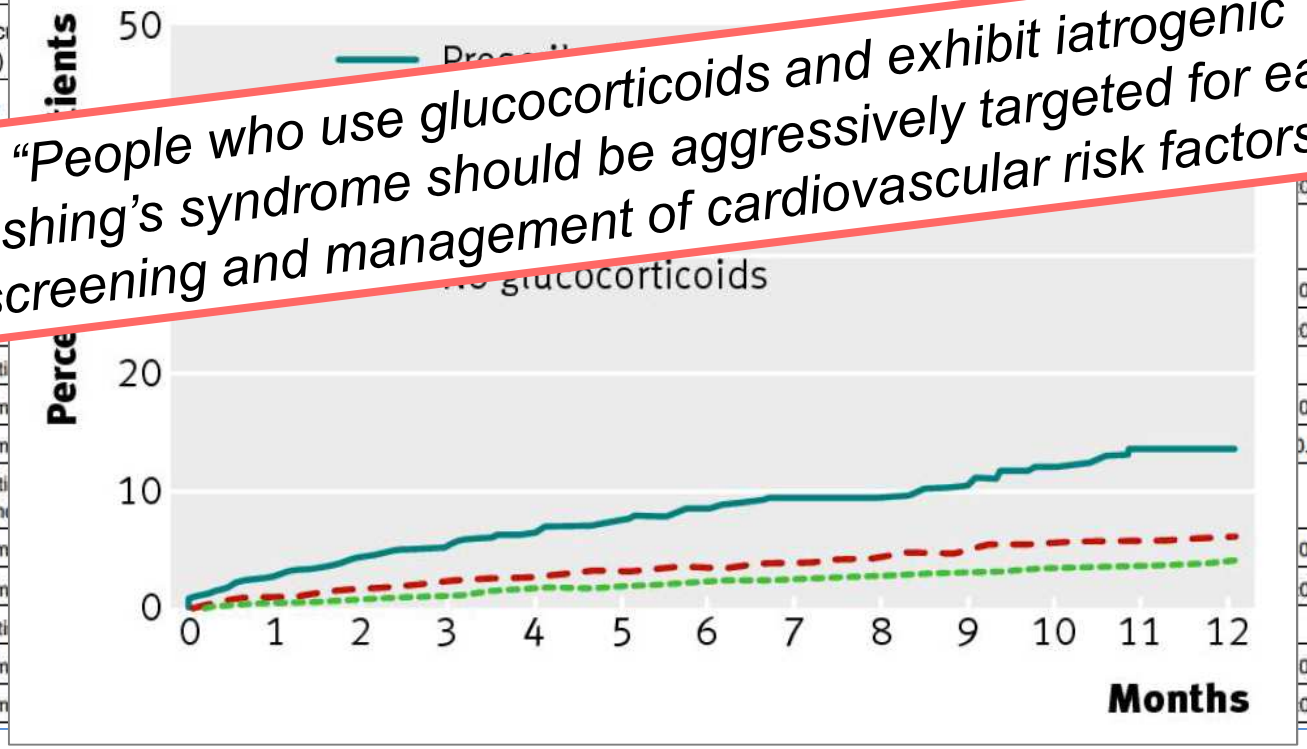


PLOS ONE, 2014

Risk of cardiovascular events in people prescribed glucocorticoids with iatrogenic Cushing's syndrome: cohort study

Table 5| Adjusted hazard ratios (95% confidence intervals) of cardiovascular events in patients with iatrogenic Cushing's syndrome

	Compared with patients without iatrogenic Cushing's syndrome (n=3231)				Compared with patients not prescribed glucocorticoids (n=3282)			
Cardiovascular events	Crude hazard ratio (95% CI)	P value	Adjusted hazard ratio* (95% CI)	P value	Crude hazard ratio (95% CI)	P value	Adjusted hazard ratio† (95% CI)	P value
All (n=341)	2.33 (1.73 to 3.14)	<0.001	2.74 (2.06 to 3.62)	<0.001	3.70 (2.63 to 5.22)	<0.001	4.16 (2.98 to 5.82)	<0.001
Coronary heart disease (n=1	1.96 (1.29 to 2.97)	0.002	2.27 (1.48 to 3.47)	<0.001	2.97 (1.91 to 4.64)	<0.001	2.68 (1.62 to 4.44)	
Cerebrovasc event (n=63)								
Heart failure								
Fasti								0.001
6 m								0.55
6 m								0.001
Fasti								
6 m								0.16
6 m								0.002
Fasti (mm								
6 m								0.08
6 m								0.001
Fasti								
6 m								0.31
6 m								0.001



"People who use glucocorticoids and exhibit iatrogenic Cushing's syndrome should be aggressively targeted for early screening and management of cardiovascular risk factors."

Fardet L et al., *BMJ* 2012

Clinical Features Associated with Glucocorticoid Receptor Polymorphisms

	In Vitro			Response to DEX		
	Trans-activation	Trans-repression	Cortisol levels	1 mg	0.25 mg	Phenotype (for details see Tables 1–4)
*TthIII*I	Not tested	Not tested	↑	=	=	Reduced risk of bipolar disorder, lower volume of hippocampus and amygdala, association with depression
ER22/23EK	↓	=	=	↓	=	Healthy metabolic profile, beneficial body composition, longevity, decreased risk of dementia, increased risk of depression
N363S	↑	=	=	=	↑	Increased BMI (in some studies), elevated cholesterol levels
*Bcl*I	Not tested	Not tested	=	↑	↑	More (abdominal) body fat, less lean mass, increased risk of depression
9β	=	↓	=	=	=/↓	Increased risk of myocardial infarction, higher hs-CRP levels, lower risk in *S. aureus* nasal carriage, beneficial body composition, increased risk of autoimmune diseases, e.g., RA, IBD

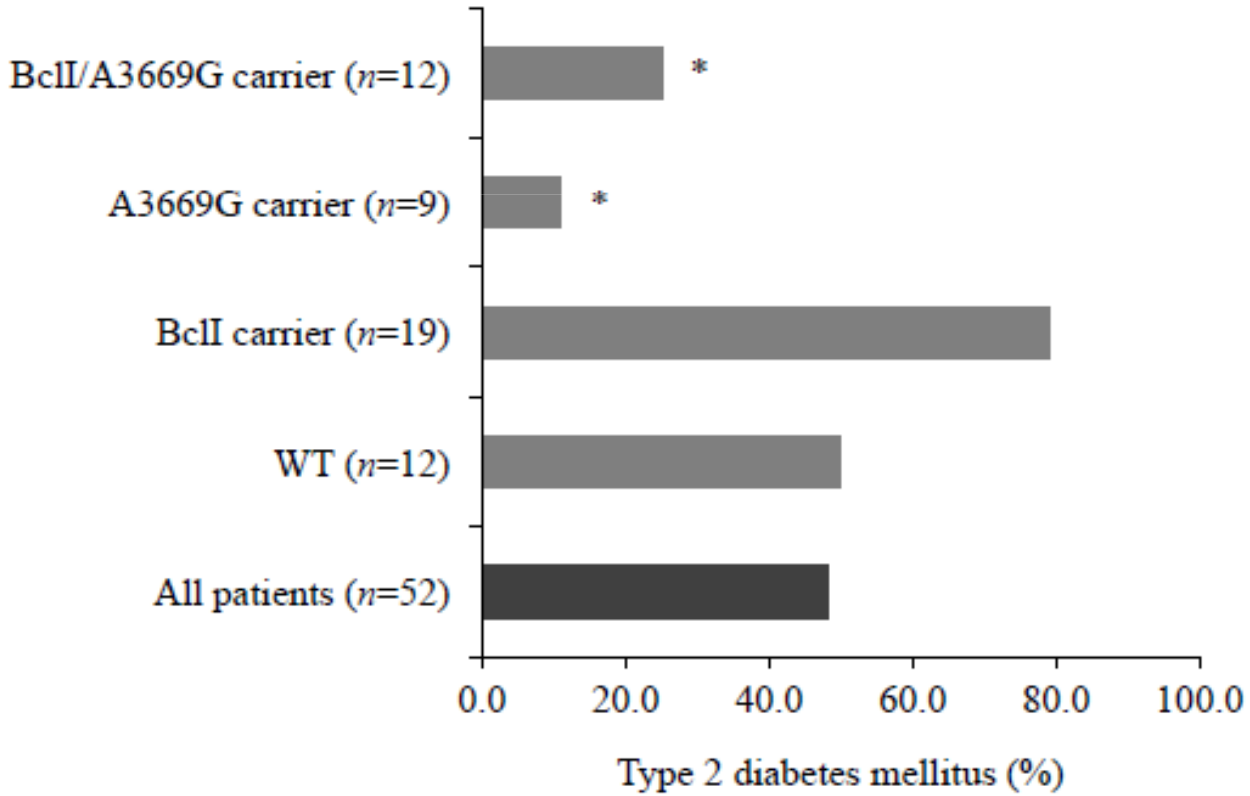
Abbreviations: DEX, dexamethasone; BMI, body mass index; hs-CRP, high sensitivity C-reactive protein; *S. aureus*, *Staphylococcus aureus*; RA, rheumatoid arthritis; IBD, inflammatory bowel disease. ↓, decrease; ↑, increase; =, no difference.

Manenschijn et al, , Ann. N.Y. Acad. Sci. 1179: 179–198 (2009)

Association of glucocorticoid receptor polymorphism A3669G with decreased risk of developing diabetes in patients with Cushing's syndrome

Laura Trementino, Gloria Appolloni, Carolina Concettoni, Marina Cardinaletti, Marco Boscaro and Giorgio Arnaldi

European Journal of Endocrinology (2012) **166** 35–42



Steroidi, terapie reumatiche e rischio CV

- **Gli steroidi rimangono una terapia cardine del trattamento delle patologie reumatiche**
- **L'effetto finale sul CVR deriva dal bilancio tra l'effetto anti-infiammatorio e**

Indicazioni ad utilizzare le minime dosi efficaci per il minimo tempo necessario

Indicazioni alla stratificazione del CVR pre-terapia ed ad un attento monitoraggio delle complicanze metaboliche (CVR) durante terapia

- **Anche per le basse dosi il CVR sembra aumentare per trattamenti prolungati (> 3 aa)**

REVIEW

A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy

>Basalmente:

Physical:	*Investigations:*
• Weight	• CBC
• Height	• Glucose (FPG, A1C, 2-h OGTT or casual PG)
• BMI	• Lipids (LDL-C, HDL-C, TC, non-HDL-C, TG, ± apo B)
• Blood pressure	• BMD

>Dopo l'inizio del trattamento:

Bone health (adults):

- Annual height measurement, and questionnaire fo
- BMD 1-year post GC initiation
  - → If stable: assess every 2–3 years
  - → If decreased: assess annually
- Lateral spine x-ray in adults ≥65 years to exam
- Use FRAX to estimate fracture risk
  - → Available at: http://www.sheffield.ac.uk/FR
- Consider referral to endocrinologist/rheumatol

Dyslipidemia and CV Risk (adults):

- Assess lipids 1 month after GC initiation, then every 6–12 months
- Assess 10-year CV risk using FRS

Hyperglycemia/Diabetes:

- Screen for classic symptoms at every visit: polyuria, polydipsia, weight loss
- Monitor glucose parameters:
  - → For at least 48 hours after GC initiation [38]
  - → Then every 3–6 months for first year; annually thereafter

Liu D et al., *J Allergy Clin Immunol*, 2013

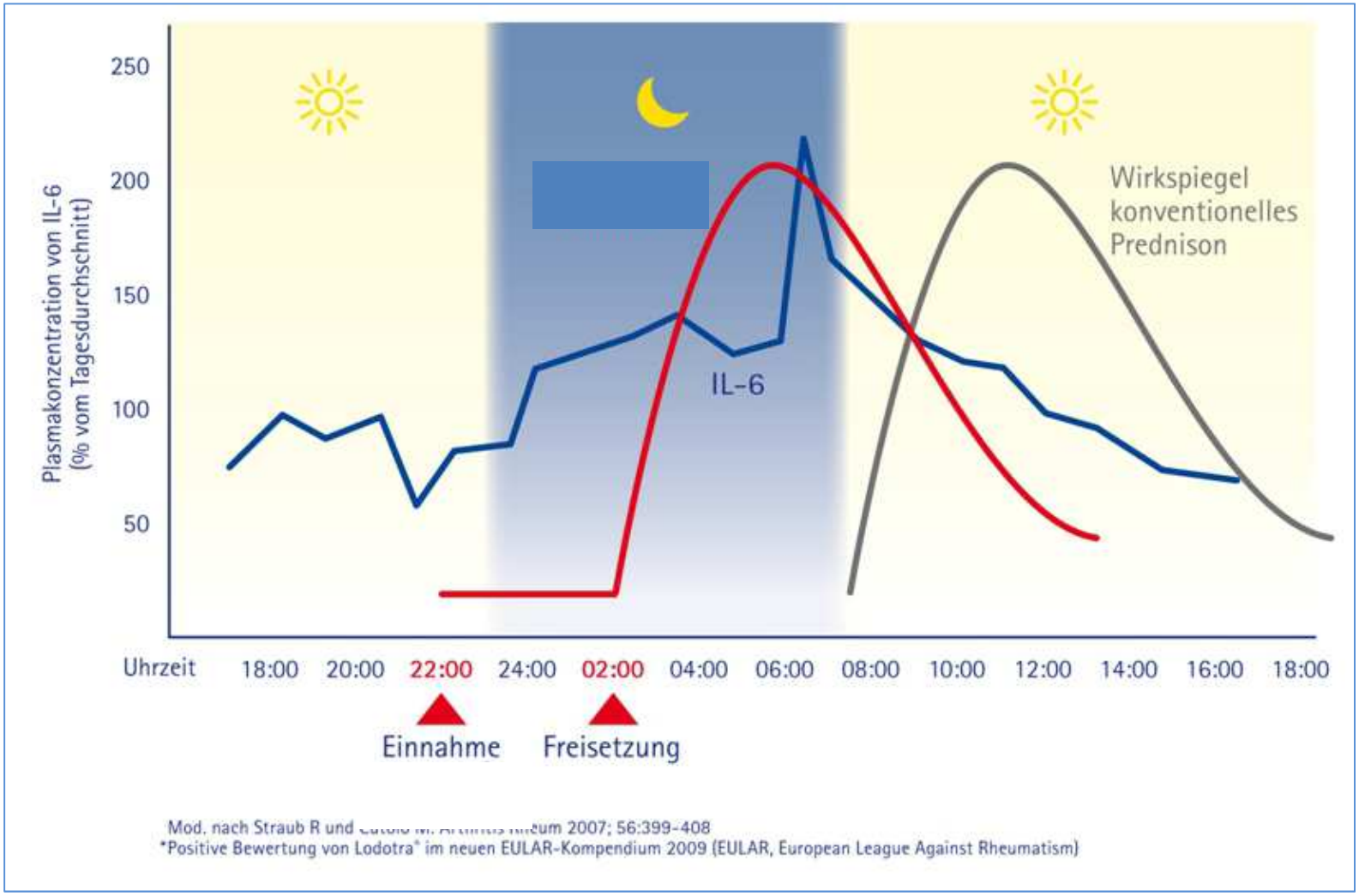
REVIEW

A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy

	Approximate equivalent dose* (mg)	Relative glucocorticoid activity	Relative mineralocorticoid activity	Duration of action (hours)	General therapeutic indications
Glucocorticoids					
Short-acting					
Hydrocortisone	20	1	1	8-12	• Relatively high mineralocorticoid activity makes it suitable for use in adrenal insufficiency
Cortisone	25	0.8	0.8	8-12	• Similar to hydrocortisone
Intermediate-acting					
Prednisone	5	4	0.8	12-36	• High glucocorticoid activity makes it useful for long-term treatment, and as an anti-inflammatory/ immunosuppressant
Prednisolone	5	4	0.8	12-36	• Similar to prednisone
Methylprednisolone	4	5	Minimal	12-36	• Anti-inflammatory/immunosuppressant
Triamcinolone	4	5	0	12-36	• Anti-inflammatory/immunosuppressant
Long-acting					
Dexamethasone	0.75	30	Minimal	36-72	• Anti-inflammatory/immunosuppressant; used especially when water retention is undesirable given its minimal mineralocorticoid activity • Usually reserved for short-term use in severe, acute conditions given its high potency and long-duration of action
Betamethasone	0.6	30	Negligible	36-72	• Similar to dexamethasone
Mineralocorticoids					
Fludrocortisone	**	10-15	125-150	12-36	• Used for aldosterone replacement

Liu D et al., *J Allergy Clin Immunol*, 2013

Prednisone a lento rilascio



Mod. nach Straub R und [illegible] 2007; 56:399-408
*Positive Bewertung von Lodotra® im neuen EULAR-Kompendium 2009 (EULAR, European League Against Rheumatism)

Review article

Why glucocorticoid withdrawal may sometimes be as dang… …e treatment itself

La preval… …settimana
1…
e…

…ica indotta da glucocorticoidi.

L'insufficienza surrenalica da sospensione della terapia steroidea è potenzialmente fatale, ma talvolta è ancora misconosciuta

…i bassi dosaggi e la breve durata del trattamento non la escludono!

Variazioni interindividuali nella funzionalità HPA …differenze genetiche nella …

Importanza della valutazione asse HPA alla sospensione della terapia …necessità di protocolli standardizzati…

Dinsen S et al., *Europ J Int Med* 2013

Pazienti con pregresso ipercortisolismo cronico:
aumento del rischio CV anche dopo anni dalla remissione…
…il rischio CV non è totalmente reversibile…
…follow up a lungo termine…

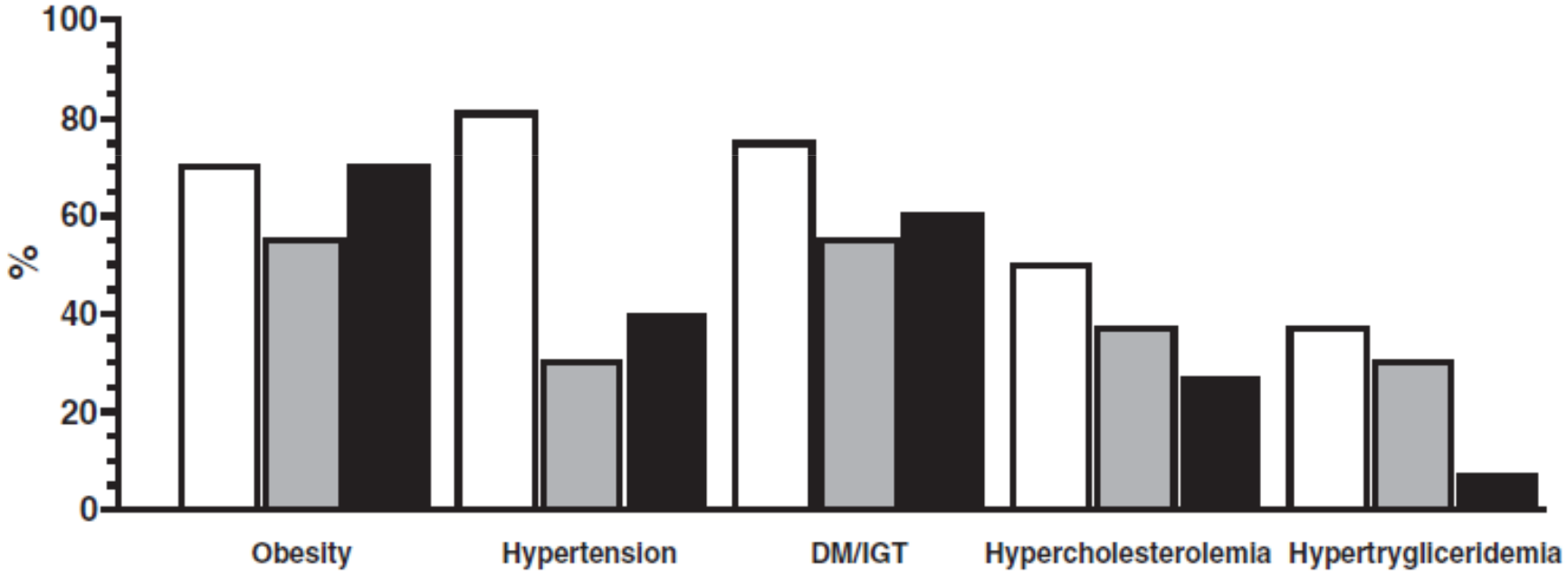


Figure 1. Prevalence of clinical manifestations of the metabolic syndrome in patients who have active Cushing's disease (*white bars*), patients in short-term remission (*gray bars*), and patients in long-term remission (*black bars*) from Cushing's disease. DM, diabetes mellitus; IGT, impaired glucose tolerance.

…Necessità di protocolli condivisi
per una gestione integrata
del paziente affetto da patologia reumatica
trattato con glucocorticoidi ….

…Grazie…

Dr.ssa Valentina D'Angelo