INFLUENCIA DE LOS TRATAMIENTOS DEL LUPUS EN LA ENFERMEDAD CARDIOVASCULAR

Jose Gabriel Erdozain Castiella
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¿DÓNDE ESTAMOS?

Patrón bimodal de mortalidad

Urowitz MB et al. Am J Med 1976;60:221-5

Eventos vasculares, ICC y muerte súbita: 30% de las muertes tardías en la cohorte de Toronto

Nikpour M et al. Rheum Dis Clin North Am 2005;31:329-54

¿DÓNDE ESTAMOS?

American Journal of Epidemiology

Vol 145, No 5
Printed in U.S.A.

Age-specific Incidence Rates of Myocardial Infarction and Angina in Women with Systemic Lupus Erythematosus: Comparison with the Framingham Study

Susan Manzi,[1] Elaine N Meilahn,[2] Joan E Rairie,[1] Claudia G. Conte,[1] Thomas A. Medsger, Jr.,[1] Linda Jansen-McWilliams,[2] Ralph B. D'Agostino,[3] and Lewis H. Kuller[2]

52 veces más posibilidades de sufrir un IAM en mujeres con LES de 35-44 años, comparado con mujeres sanas.

¿DÓNDE ESTAMOS?

ARTHRITIS & RHEUMATISM
Vol. 42, No. 2, February 1999, pp 338–346

PREMATURE MORBIDITY FROM CARDIOVASCULAR AND CEREBROVASCULAR DISEASES IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

MICHAEL M. WARD

2 veces más posibilidades de sufrir un ACV en mujeres con LES 18-44 años.

¿DÓNDE ESTAMOS?

Table 4. Relative risk of vascular outcomes in systemic lupus erythematosus compared with those expected based on Framingham models*

Outcome	Observed number of events	Expected number of events	Observed: expected ratio	95% CI
Nonfatal myocardial infarction	17	1.7	10.1	5.8–15.6
Death due to coronary heart disease	12	0.7	17.0	8.1–29.7
Overall coronary heart disease	34	4.5	7.5	5.1–10.4
Stroke	16	2.0	7.9	4.0–13.6

* 95% CI = 95% confidence interval.

Esdaile JM et al. Arthritis Rheum 2001;44:2331-7

¿El tratamiento del LES realmente influye en la enfermedad cardiovascular?

¿Cuánta culpa tiene?

CORTICOIDES

Se han relacionado con múltiples efectos adversos

¿Dosis dependiente?

CORTICOIDES

Ann Intern Med. 2004;141:764-770. www.annals.org ARTICLE

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

Dosis bajas: tópico o inhalado.

Dosis medias: < 7,5 mg/dia de prednisona.

Dosis altas: ≥ 7,5 mg/dia de prednisona.

CORTICOIDES

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

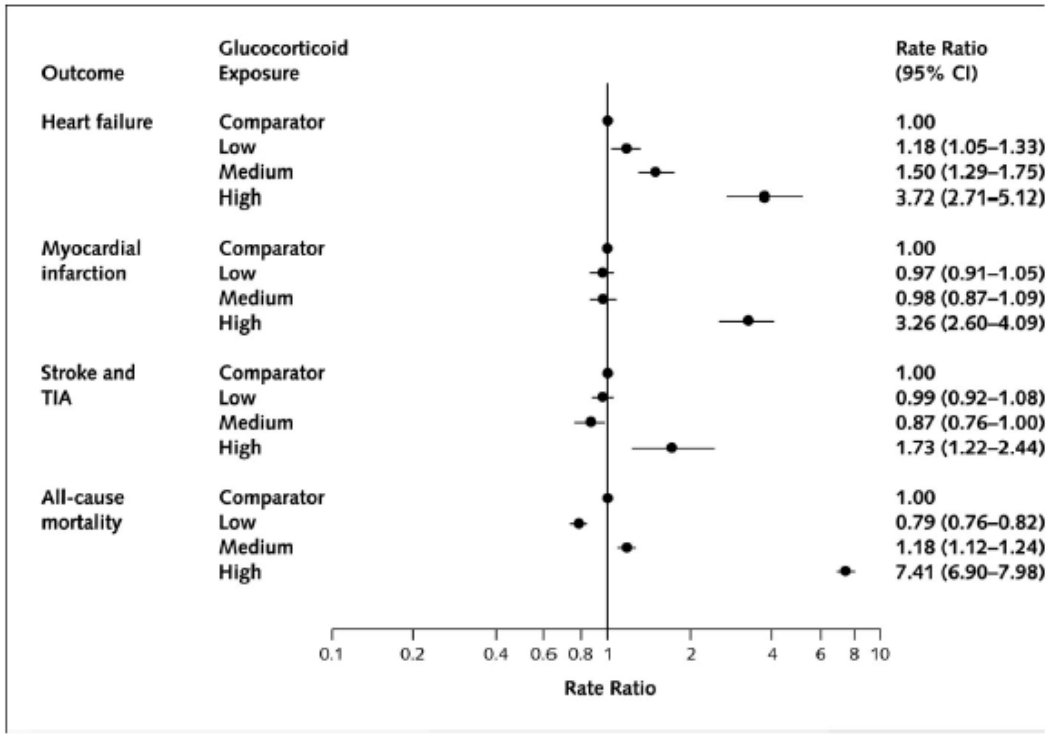
Steroid Exposure	Events, *n*	Unadjusted Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)*	Adjusted Rate Ratio (95% CI)†
Comparator	4383	1.00	1.00	1.00
Low dose	3521	1.30 (1.24–1.36)	1.00 (0.95–1.05)	1.00 (0.95–1.05)
Medium dose	1380	1.60 (1.50–1.70)	1.03 (0.96–1.10)	1.04 (0.95–1.14)
High dose	167	4.50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

* Adjusted for age; sex; social deprivation; use of angiotensin-converting enzyme inhibitors, anticoagulants, antiplatelets, α-blockers, β-blockers, calcium-channel blockers, cardiac glycosides, diuretics, nitrates, lipid-lowering drugs, hormone replacement therapy and oral contraceptives, nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, and bronchodilators during the follow-up; noncardiovascular hospitalization in the past 6 months; diabetes mellitus; cancer; and renal disease.
† Results of matched cohorts.

Wei L et al. Ann Intern Med 2004;141:764-70

CORTICOIDES

Figure. **Glucocorticoid use with different cardiovascular diseases.**



TIA = transient ischemic attack.

Wei L et al. Ann Intern Med 2004;141:764-70

CORTICOIDES

Table 5. Relative risk of damage in SLE associated with cumulative prednisone, high-dose prednisone, and pulse methylprednisolone

Damage item	Cumulative prednisone*		High dose prednisone†		Pulse methylprednisolone‡	
	Adjusted RR (95% CI)	*P*	Adjusted RR (95% CI)	*P*	Adjusted RR (95% CI)	*P*
Osteoporotic fracture	2.5 (1.7, 3.7)	0.0001	0.8 (0.7, 1.0)	0.08	1.3 (1.0, 1.8)	0.07
Coronary artery disease	1.7 (1.1, 2.5)	0.008	1.0 (0.8, 1.2)	0.9	1.1 (0.7, 1.8)	0.8
Cataracts	1.9 (1.4, 2.5)	0.0001	0.9 (0.8, 1.1)	0.3	1.0 (0.7, 1.4)	0.9
Avascular necrosis	1.1 (0.8, 1.5)	0.6	1.2 (1.1, 1.4)	0.0002	1.2 (0.9, 1.6)	0.2
Stroke	0.9 (0.5, 1.5)	0.7	1.2 (1.0, 1.5)	0.02	0.9 (0.5, 1.5)	0.7
Diabetes mellitus	1.4 (0.8, 2.4)	0.2	1.0 (0.9, 1.3)	0.5	0.8 (0.4, 1.6)	0.6
Hypertension	1.0 (0.7, 1.3)	0.9	1.1 (0.9, 1.2)	0.3	1.0 (0.8, 1.3)	0.9
Pulmonary fibrosis	1.6 (1.0, 2.8)	0.1	1.1 (0.8, 1.3)	0.7	0.7 (0.3, 1.9)	0.5
Venous insufficiency	1.1 (0.5, 2.1)	0.9	1.1 (0.9, 1.5)	0.4	No events	–
Cognitive impairment/psychosis	1.3 (0.6, 2.9)	0.5	1.1 (0.9, 1.4)	0.3	1.5 (1.1, 2.0)	0.02
Renal failure	1.3 (0.8, 2.1)	0.3	1.0 (0.8, 1.2)	0.7	1.3 (0.8, 2.0)	0.3
Joint deformity/erosion	1.2 (0.8, 1.7)	0.4	0.9 (0.8, 1.1)	0.5	1.3 (0.9, 1.8)	0.1
Scarring alopecia	1.5 (0.9, 2.6)	0.1	0.7 (0.4, 1.1)	0.09	1.2 (0.8, 1.7)	0.4
Pulmonary hypertension	0.7 (0.3, 1.5)	0.4	1.2 (0.9, 1.5)	0.3	1.0 (0.5, 1.8)	0.9
Malignancy	1.1 (0.6, 2.0)	0.8	0.4 (0.1, 2.0)	0.3	1.0 (0.4, 2.5)	0.9

* Adjusted RR = risk ratio associated with a cumulative prednisone dose of 36.5 gm, adjusted for age, sex, race, high-dose prednisone and pulse methylprednisolone. 95% CI = 95% confidence interval.

† Adjusted RR = risk ratio associated with each 2-month exposure to ≥60 mg prednisone, adjusted for age, sex, race, cumulative prednisone dose and pulse methylprednisolone.

‡ Adjusted RR = risk ratio associated with each pulse of methylprednisolone (1,000–3,000 mg intravenously), adjusted for age, sex, race, high-dose prednisone and cumulative prednisone dose.

Zonana-Nacach A et al. Arthritis and Rheumatism 2000;43:1801-8.

CORTICOIDES

Table 4. Hazard ratio of organ damage (n = 141) by cumulative average dose of prednisone.

Cumulative Average Prednisone Dose (mg/mo)		% of Patient-mos	No. of Events	Unadjusted Model HR	Unadjusted Model 95% CI	Conventionally-Adjusted Model* HR	Conventionally-Adjusted Model* 95% CI	Weighted Model* HR	Weighted Model* 95% CI
0		35.9	34	Ref		Ref		Ref	
> 0–180	0-6	37.0	49	1.58	1.00, 2.50	2.01	1.11, 3.63	1.16	0.54, 2.50
> 180–360	6-12	14.9	29	2.10	1.24, 3.55	2.46	1.17, 5.16	1.50	0.58, 3.88
> 360–540	12-18	6.7	18	3.04	1.67, 5.53	3.54	1.55, 8.12	1.64	0.58, 4.69
> 540	>18	5.5	21	4.19	2.35, 7.47	4.10	1.74, 9.65	2.51	0.87, 7.27

*Adjusted for age, sex, race/ethnicity, baseline prednisone dose, baseline SLE activity, baseline organ damage, and time-varying covariates. HR: hazard ratio.

Thamer M et al. J Rheumatol 2009;36:560-4.

CORTICOIDES

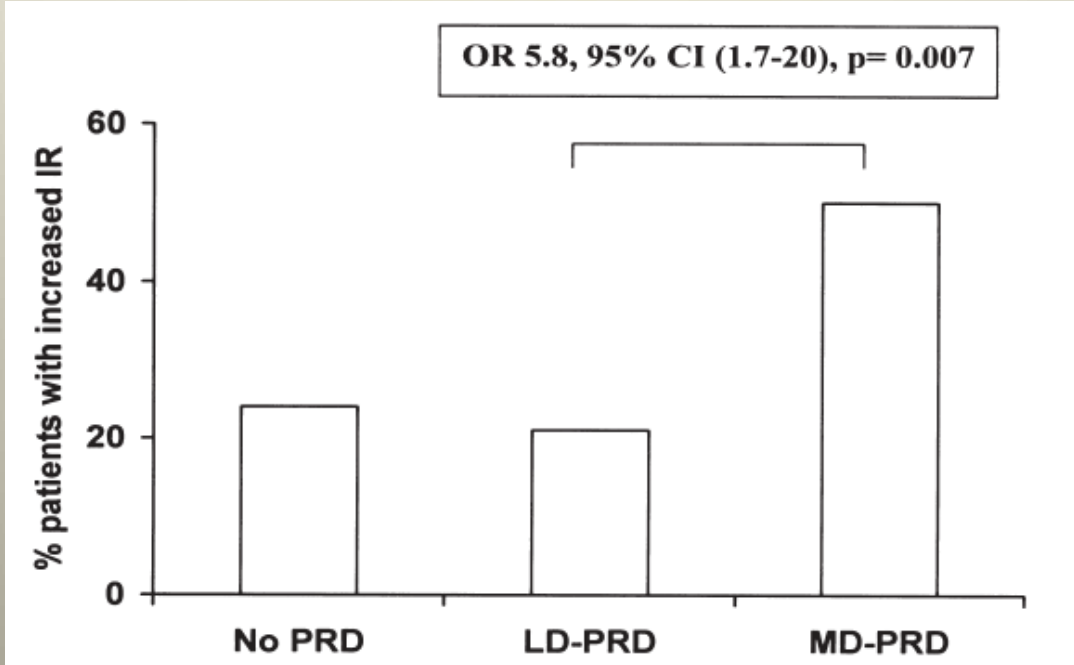


Fig. 1. Percentage of SLE patients with increased insulin resistance (IR) according to prednisone dose. No PRD: prednisone nonusers. LD-PRD: low-dose prednisone group; MD-PRD: medium-dose prednisone group.

Dosis bajas: ≤ 7,5 mg/dia de prednisona

Sabio JM et al. Clin Exp Rheumatol 2010;28:483-9

CORTICOIDES

- Revisión sistemática en pacientes con AR

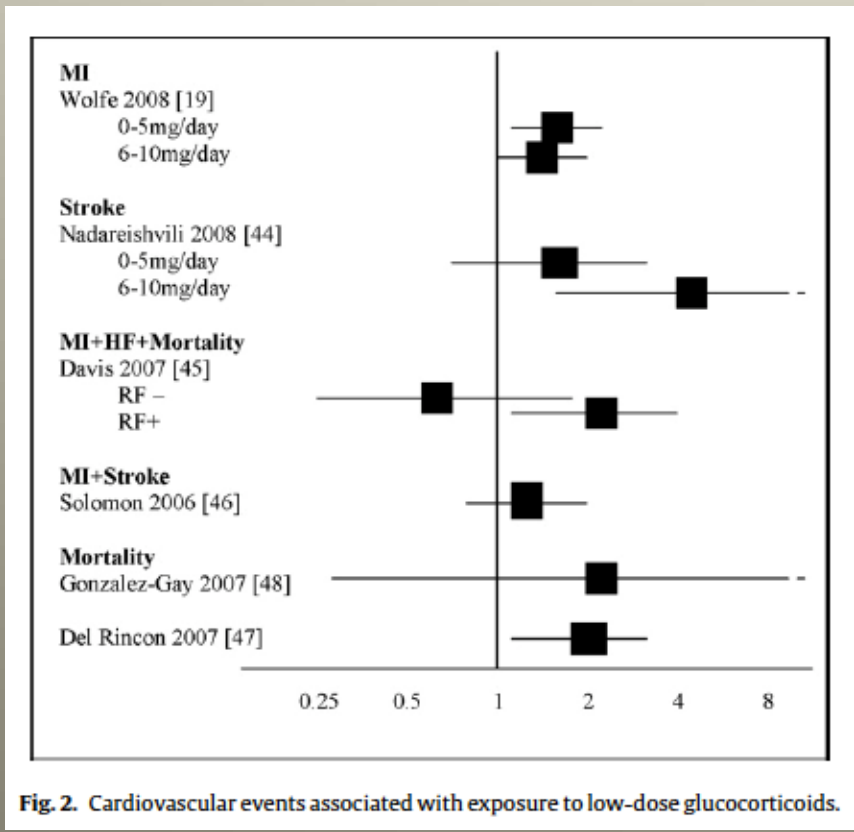


Fig. 2. Cardiovascular events associated with exposure to low-dose glucocorticoids.

1. Exposición de 1 a 3 años a dosis bajas (<10 mg/dia) no aumenta el riesgo evento vascular.
2. Se detecta una tendencia a tener mayor riesgo de sufrir un evento vascular.
3. No encuentra asociación entre dosis bajas y aterosclerosis.
4. Dosis < 5mg/dia podrían aumentar la resistencia a la insulina.

Ruyssen-Witrand et al. Joint Bone Spine 2010, doi:10.1016

CORTICOIDES

Table 2. Characteristics of Patients with Systemic Lupus Erythematosus, According to the Presence or Absence of Plaque.*

Characteristic	No Plaque (N=124)	Plaque (N=73)	P Value
Age (yr)	39±11	52±12	<0.001
White race (%)	47.6	67.1	0.008
Postmenopausal (%)	35.0	72.0	<0.001
Body-mass index	25.8±7.0	26.4±6.6	0.53
Systolic blood pressure (mm Hg)	107±15	116±21	<0.001
Current smoker (%)	16.2	12.7	0.51
Hypertension (%)	24.2	37.0	0.06
Diabetes (%)	1.7	7.1	0.06
Prednisone use (%)	92.6	84.9	0.09
5-yr daily dose of prednisone (mg)	11.9±6.9	6.9±6.8	0.002
Duration of corticosteroid use (mo)	67±75	91±94	0.24
Azathioprine use (%)	36.4	24.2	0.10
Cyclophosphamide use (%)	26.0	9.6	0.005
Hydroxychloroquine use (%)	82.3	63.0	0.003

Roman M et al. NEJM 2003;349:2399-406.

CORTICOIDES

Table 1. Current knowledge on the relationship between clinical dosing and cellular actions of glucocorticoids

Terminology*	Clinical application†	Genomic actions (receptor saturation)‡§	Nongenomic actions§	
			Nonspecific	cGCR-mediated
Low dose (≤7.5 mg/day)	Maintenance therapy for many rheumatic diseases	+ (<50%)	–	?
Medium dose (>7.5 to ≤30 mg/day)	Initial treatment for primary chronic rheumatic diseases	++ (>50 to <100%)	(+)	(+)
High dose (>30 to ≤100 mg/day)	Initial treatment for subacute rheumatic diseases	++(+) (almost 100%)	+	+
Very high dose (>100 mg/day)	Initial treatment for acute and/or potentially life-threatening exacerbations of rheumatic diseases	+++ (almost 100%)	++	+(+?)
Pulse therapy (≥250 mg for 1 or a few days)	For particularly severe and/or potentially life-threatening forms of rheumatic diseases	+++ (100%)	+++	+(++?)

* Values represent mg of prednisone equivalent per day. See ref. 9 for further information.
† See ref. 9.
‡ See ref. 10.
§ cGCR = cytosolic glucocorticoid receptor; ? = unknown; – = not relevant; (+) = perhaps relevant, but of minor importance; + = relevant; +(+?) = relevant or perhaps even very relevant; +(++?) = relevant or perhaps even very or most relevant; ++ = very relevant; ++(+) = very relevant to most relevant; +++ = most relevant.

Buttgereit F et al. Arthritis and Rheumatism 2004;50:3408-17

ANTIPALÚDICOS

- Efecto en mortalidad
- Efecto en trombosis
- Diabetes Mellitus
- Síndrome Metabólico
- Efecto en desarrollo de aterosclerosis

ANTIPALÚDICOS: SUPERVIVENCIA

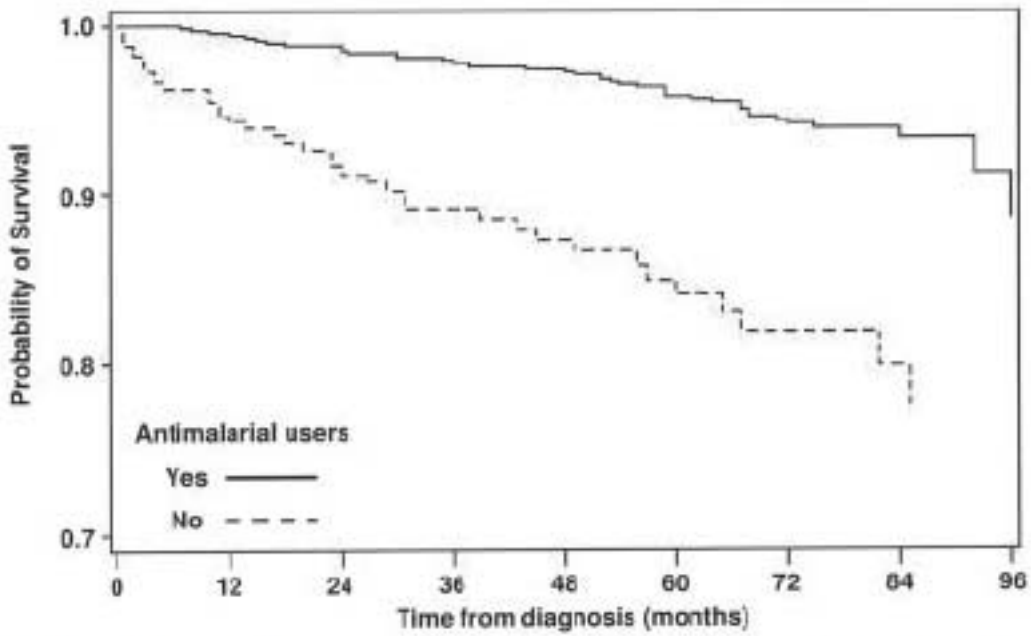
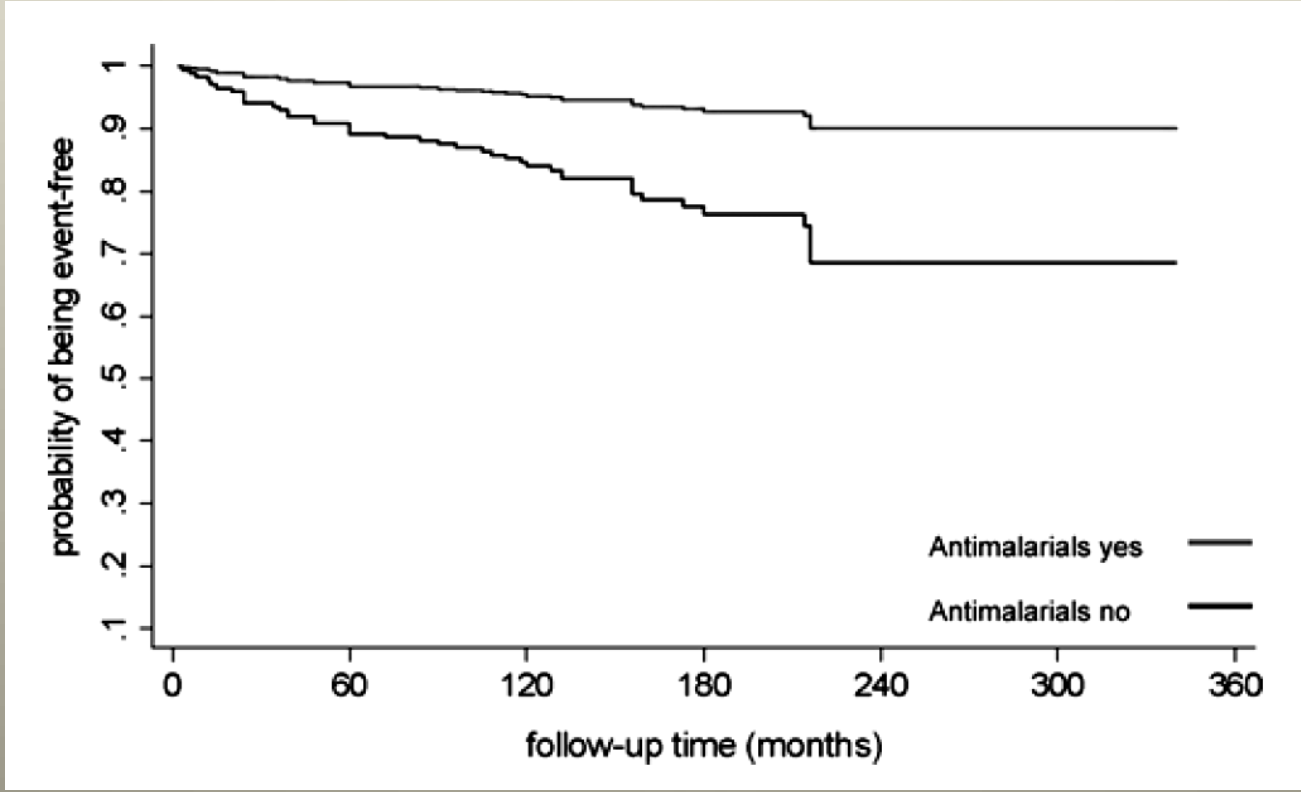


Figure 1. Kaplan-Meier survival curves showing time-dependent survival rates according to duration of antimalarial use in the entire cohort of patients with systemic lupus erythematosus.

Reducción de la mortalidad de un 38%

Shinjo SK et al. Arthritis Rheum 2010;62:855-62

ANTIPALÚDICOS: TROMBOSIS

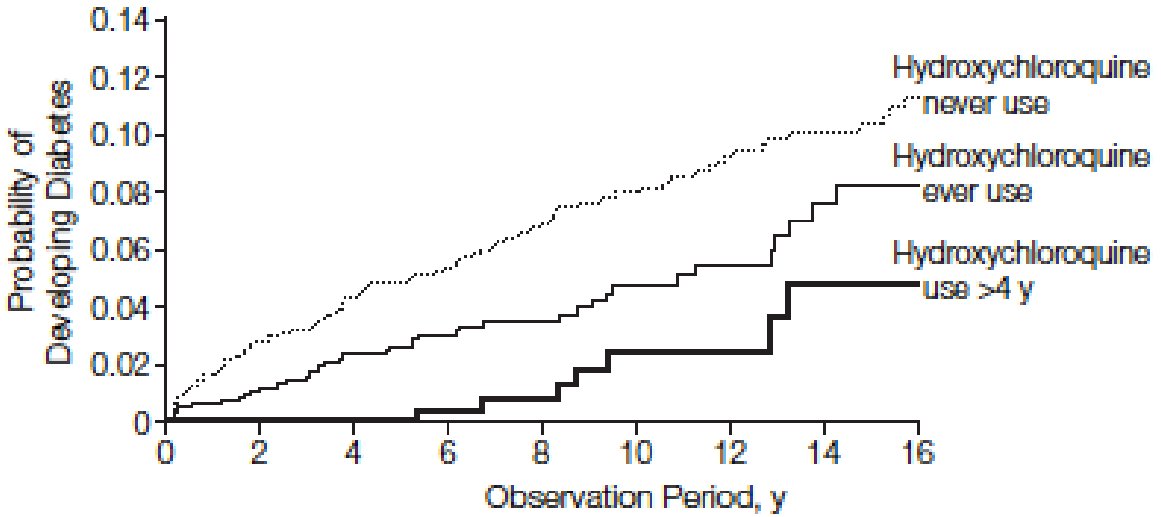


Disminución del 70% del riesgo de trombosis

Ruiz-Irastorza G et al. Lupus 2006;15:577-83.

ANTIPALÚDICOS: DM

Figure. Probability of Developing Diabetes in Rheumatoid Arthritis Patients According to Hydroxychloroquine Use



Wasko M et al. JAMA 2007;298:187-93

ANTIPALÚDICOS: SD. METABÓLICO

Table 5 Variables associated with metabolic syndrome in patients with SLE, using logistic regression

Explanatory variable	*β coefficient*	*Odds ratio*	*95% confidence interval*	P
Educational level	−0.180	0.835	0.749–0.930	<0.001
Triglycerides	0.023	1.024	1.011–1.036	<0.001
HDL cholesterol	−0.066	0.936	0.906–0.968	<0.001
C3	0.016	1.017	1.001–1.032	0.032
Hydroxychloroquine use	−1.649	0.192	0.061–0.605	0.003

The sensitivity and specificity of the model were 0.80 and 0.89, respectively, for a cut off of 0.20.

Sabio JM et al. Lupus 2008;17:849-59

ANTIPALÚDICOS: ATEROSCLEROSIS

Table 2. Characteristics of Patients with Systemic Lupus Erythematosus, According to the Presence or Absence of Plaque.*

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Roman M et al. NEJM 2003;349:2399-406.

ARD

Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review

Guillermo Ruiz-Irastorza, Manuel Ramos-Casals, Pilar Brito-Zeron and Munther A Khamashta

Ann Rheum Dis published online 4 Jun 2009;
doi:10.1136/ard.2008.101766

Table 5 Effects of antimalarials in patients with systemic lupus erythematosus (SLE) graded according to the quality of evidence[7]

Quality of evidence	AM
High:	
Reduction of SLE activity (also in pregnancy)	CQ/HCQ
Reduction of mortality	CQ/HCQ
Moderate:	
Increase in BMD	HCQ
Protective effect on thrombotic events	CQ/HCQ
Protective effect on irreversible organ damage	HCQ
Low:	
Reduction of severe flares	HCQ
Adjuvant effect for achieving LN remission	HCQ
Beneficial effect on serum lipid levels	CQ/HCQ
Protective effect on osteonecrosis	HCQ
Delaying the evolution to SLE	HCQ
Protective effect on cancer	CQ/HCQ
Very low:	
Reduction of 1–25 $(OH)_2$ vitamin D levels	HCQ
Reduction of atherosclerosis	CQ/HCQ

AM, antimalarial; BMD, bone mineral density; CQ, chloroquine; HCQ, hydroxychloroquine; LN, lupus nephritis.

AINES:

Se relacionan con ICC y desarrollo de HTA en población general

Page J et al. Arch Intern Med 2000;160:777-84
Johnson AG et al. Ann Intern Med 1994;121:289-300

INMUNOSUPRESORES:

La azatioprina es un factor de riesgo independiente para engrosamiento medio y máximo de la intima media.

Schanberg LE et al. Arthritis Rheum 2009;60:1496-1507

BIOLÓGICOS (RITUXIMAB):

Mejoría del perfil lipídico a largo plazo

Pego-Reigosa JM et al. Rheumatology 2010;49:691-6

Mejoría de la disfunción endotelial y aterosclerosis carotídea

Kerekes G et al. Clin Rheumatol 2009;28:705-10.

QUE ME PUEDE QUEDAR CLARO

Controlar los factores de riesgo vascular

Controlar la actividad de la enfermedad, con los fármacos más seguros:

- antipalúdicos
- corticoides: dosis bajas (< 7,5 mg/dia)
- inmunosupresores


LA POTENZA E' NULLA SENZA CONTROLLO.
SE VUOI GUIDARE GUIDA DAVVERO.
PIRELLI