TOP 5
Síndrome Antifosfolípido

VII Reunión GEAS

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CONCISE REPORT

Postural tachycardia syndrome (POTS) and other autonomic disorders in antiphospholipid (Hughes) syndrome (APS)

JR Schofield[1], S Blitshteyn[2], Y Shoenfeld[3,4] and GRV Hughes[5]

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-15 pacientes con diagnóstico de SAF y trastorno disautonómico.

Mesa basculante	**Respiración profunda**	**Valsalva**	**Hand grip test**	**QSART**

8 POTS, 8 NCS, 3 OH, 1 IST, 1 CRPD

6 de los pacientes presentaron más de 1 trastorno disautonómico simultáneo.

Lupus (2014) 23, 697–702

Síntomas poco específicos, muy diversos… su diagnóstico supone un desafio

- **Importancia de valorar la presencia de disfunción del SNA en pacientes con SAF:**

  - Desde disfunción leve compatible con vida normal hasta cuadros que incapacitan o incluso ponen en riesgo la vida del paciente.

  - Posibilidad de tratamiento con el fin de restablecer el balance simpático-parasimpático.

  - Nos permiten vigilar la aparición de manifestaciones disautonómicas evolutivamente más graves.

A Pilot Open-Label Phase II Trial of Rituximab for Non-Criteria Manifestations of Antiphospholipid Syndrome

Doruk Erkan,[1] JoAnn Vega,[2] Glendalee Ramón,[2] Elizabeth Kozora,[3] and Michael D. Lockshin[1]

- Objetivo primario: evaluación seguridad
- Objetivos secundarios
  - -Efecto del RTX sobre el perfil de AAF
  - -Eficacia sobre las manifestaciones no incluidas en los criterios de Sidney
- 19 pacientes
- Trombopenia, enfermedad valvular cardíaca, úlceras cutáneas, nefropatía, y disfunción cognitiva.

ARTHRITIS & RHEUMATISM
Vol. 65, No. 2, February 2013, pp 464–471

Resultados

Seguridad:

12 reacciones adversas graves no relacionadas con la infusión

49 reacciones adversas leves

Perfil de AAF:

Todos los pacientes con positividad basal para AL, aCL, y anti- B2 GPI siguieron siendo positivos a las sem 24 y 52.

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Efectos clínicos

Table 1. Baseline characteristics of and clinical outcomes in the study patients*

Patient/ age/sex	APS	Inclusion criteria/duration	Previous medications†	Concomitant medications‡	Response at 24 wks	Observations at 24–52 wks§	Observations after 52 wks (duration from study completion to time of report)¶
1/61/M	No	Skin ulcer (PG)/36 mos	CS, WAR, LMWH, AZA	ASA, PTX, HCQ, MMF	RC	Active ulcers	–
2/25/M	No	Cardiac valve disease/3 mos	–	–	NR	–	No change (6 mos)
3/32/M	No	Thrombocytopenia/3 mos	–	ASA, HCQ	ET	–	–
		Cardiac valve disease/1 wk			ET	–	–
		Cognitive dysfunction/48 mos#		–	ET	–	–
4/40/F	No	Thrombocytopenia/6 mos	CS, IVIG, WinRho	–	CR	No change	Recurrence (4 mos)
5/38/F	PM	Thrombocytopenia/8 mos	CS, IVIG	ASA, HCQ	PR	No change	–
		Cognitive dysfunction/24 mos#			CR	–	–
6/24/F	VE	Thrombocytopenia/5 mos	CS, WinRho	WAR	NR	–	–
7/61/F	No	Cognitive dysfunction/6 mos#	–	ASA, HCQ, STN	CR	–	–
8/53/M	No	Cognitive dysfunction/10 mos#	–	WAR, HCQ, MMF	PR	–	–
9/46/F	VE + PM	Cognitive dysfunction/12 mos#	CS	ASA, WAR	CR	–	–
10/20/F	VE	Skin ulcer (LV)/2 mos	CS	HCQ, STN, WAR	CR	No change	–
11/45/M	VE	Skin ulcer (PG)/5 mos	CS, IVIG	WAR	CR**	Active ulcers	–
12/46/F	VE + PM	Thrombocytopenia/12 yrs	CS, TPO	HCQ, CPG, WAR	ET††		
		Cardiac valve disease/3 mos			ET	–	–
13/52/M	VE	Cardiac valve disease/1 mo	–	STN, WAR	NR	–	Improved (17 mos)‡‡
14/38/M	VE	Skin ulcer (PG)/1.5 mos	–	HCQ, WAR	CR	No change	–
15/22/M	No	aPL nephropathy/2 mos	CS	ACE inhibitor	ET	–	–
16/61/F	VE	Skin ulcer (PG)/22 mos	CS	ASA, STN	PR	Recovered	–
17/20/F	No	aPL nephropathy/35 mos	CS, MMF	ACE	PR	No change	–
18/45/F	PM	Cognitive dysfunction/3 mos#	–	ASA, HCQ	NR	–	–
19/41/F	PM	Cardiac valve disease/25 mos	–	ASA	NR	–	Improved (5 mos)§§

Efectos clínicos

- Trombocitopenia: RC 1, RP 1, NR 1. ET 2
- Alteraciones valvulares: NR en sem 24. Sin embargo, mejoría posterior en 2/3 pacientes.
- Úlceras cutáneas: 3 RC , 1 RP, 1 ReC.
- Nefropatía: 1 RP. ET 1
- Disfunción cognitiva: 3 RC, 1 RP, 1 NR. ET 1

Original article

GAPSS: the Global Anti-Phospholipid Syndrome Score

Savino Sciascia[1,2], Giovanni Sanna[1,3], Veronica Murru[1], Dario Roccatello[2], Munther A. Khamashta[1,2] and Maria Laura Bertolaccini[1]

Abstract

Objective. To develop and validate a risk score [global APS score (GAPSS)] derived from the combination of independent risk for thrombosis and pregnancy loss (PL), taking into account the aPL profile, conventional cardiovascular risk factors and the autoimmune antibody profile.

Methods. This cross-sectional study included 211 consecutive SLE patients. Data on clinical manifestations, conventional cardiovascular risk factors, aPL profile, ANAs, ENA and anti-dsDNA were collected. Long-term low-dose aspirin, oral anticoagulant and HCQ treatment were also included in the analysis. Patients were randomly divided into two sets by a computer-generated randomized list. We developed GAPSS in the first set of patients ($n = 106$), assigning the risk factors identified by multivariate analysis weighted points proportional to the β-regression coefficient values. GAPSS was validated in the second set of patients ($n = 105$). The relationship between GAPPS and thrombosis and/or PL was analysed.

Results. In the first set, higher values of GAPSS were seen in patients who experienced thrombosis and/or PL compared with those without clinical events [GAPSS 9.3 (4.8) (range 1–19) and 5.3 (4) (range 0–16), $P < 0.001$]. Also taken separately, patients who experienced thrombosis or PL showed higher GAPSS compared with those without clinical events [GAPSS 9.6 (4.8) (range 1–19) *vs* 4.9 (5) (range 0–14), $P = 0.027$ for thrombosis; 7.3 (5) *vs* 3.9 (5.1) (range 0–16), $P = 0.024$ for PL, respectively]. In the second set, the results were similar, with statistically higher values of GAPSS in patients with a clinical history of thrombosis and/or PL compared with those without events [GAPSS 9.5 (5.6) (range 0–20) and 3.9 (4.1) (range 0–17), $P < 0.001$). Higher values were also seen when subclassifying the patients according to the clinical manifestation, thrombosis or PL [GAPSS 9.5 (5.6) (range 0–20) *vs* 4.8 (5.4) (range 0–17), $P = 0.036$ for thrombosis; 7.9 (3.3) *vs* 3.8 (5.4) (range 0–16), $P = 0.037$ for PL, respectively).

Conclusion. These data propose a substantial improvement in risk prediction of thrombosis or PL in SLE based on assessment of the GAPSS, a quantitative scoring system.

Key words: antiphospholipid antibodies, pregnancy loss, thrombosis, Hughes syndrome, prothrombin.

Global Anti-Phospholipid Syndrome Score

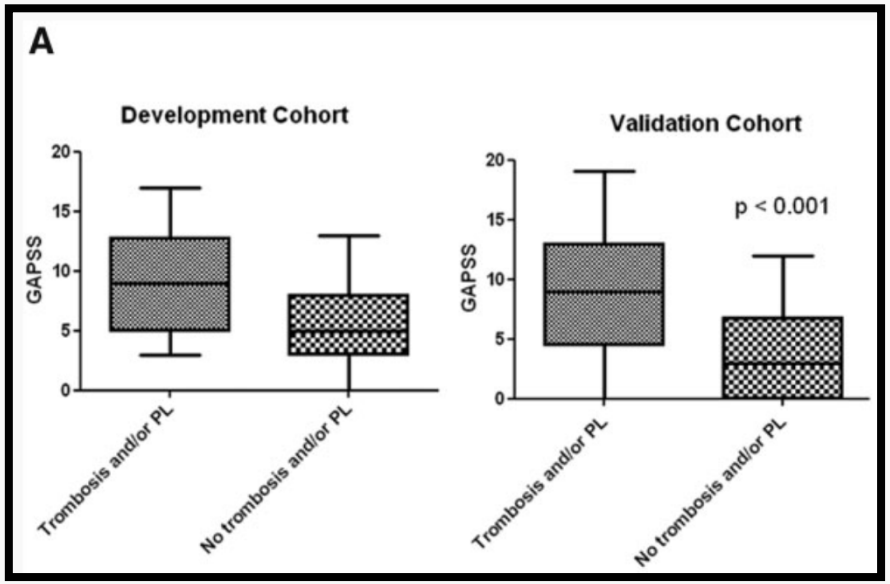
TABLE 2 Univariate logistic regression analysis for the development cohort

	OR (95% CI)	*P*
Conventional risk factors (⩾1)	1.84 (0.782, 4.253)	0.19
Smoking	0.823 (0.353, 1.920)	0.08
Oral contraceptive pill	0.558 (0.160, 1.950)	0.21
Hyperlipidaemia	2.492 (1.28, 5.918)	0.036
Arterial hypertension	1.831 (1.099, 8.280)	0.035
Diabetes	1.831 (0.81, 21.938)	0.6
HRT	3.55 (0.655, 13.23)	0.15
Anti-dsDNA	1.63 (0.738, 3.59)	0.53
ENA	1.304 (1.127, 2.780)	0.039
Anti-RO/SSA	0.471 (0.188, 9.178)	0.31
Anti-LA/SSB	1.885 (0.315, 7.482)	0.27
Anti-RNP	1.324 (1.116, 6.09)	0.047
Anti-Sm	0.369 (0.124, 2.0979)	0.61
aCL IgG/IgM	3.998 (1.987, 10.448)	0.023
Anti-β2GPI IgG/IgM	3.98 (1.462, 10.892)	0.049
aPT IgG/IgM	2.778 (1.037, 7.47)	0.034
aPS/PT IgG/IgM	2.133 (1.368, 7.128)	0.006
aProtS IgG	1.424 (0.177, 8.22)	0.19
aPE IgG/IgM	1.997 (0.457, 2.193)	0.22
LA	1.885 (1.116, 8.507)	0.031
LDA	0.379 (0.141, 3.193)	0.47
HCQ	0.63 (0.438, 3.98)	0.32
OA	0.55 (0.122, 1.71)	0.67

TABLE 3 Multivariate logistic regression analysis for the development cohort and scoring system

	β-coefficient	GAPSS[a]
Hyperlipidaemia	1.73	3
Arterial hypertension	0.54	1
aCL IgG/IgM	2.63	5
Anti-β2GPI IgG/IgM	2.02	4
aPS/PT IgG/IgM	1.78	3
LA	2.35	4

Global Anti-Phospholipid Syndrome Score



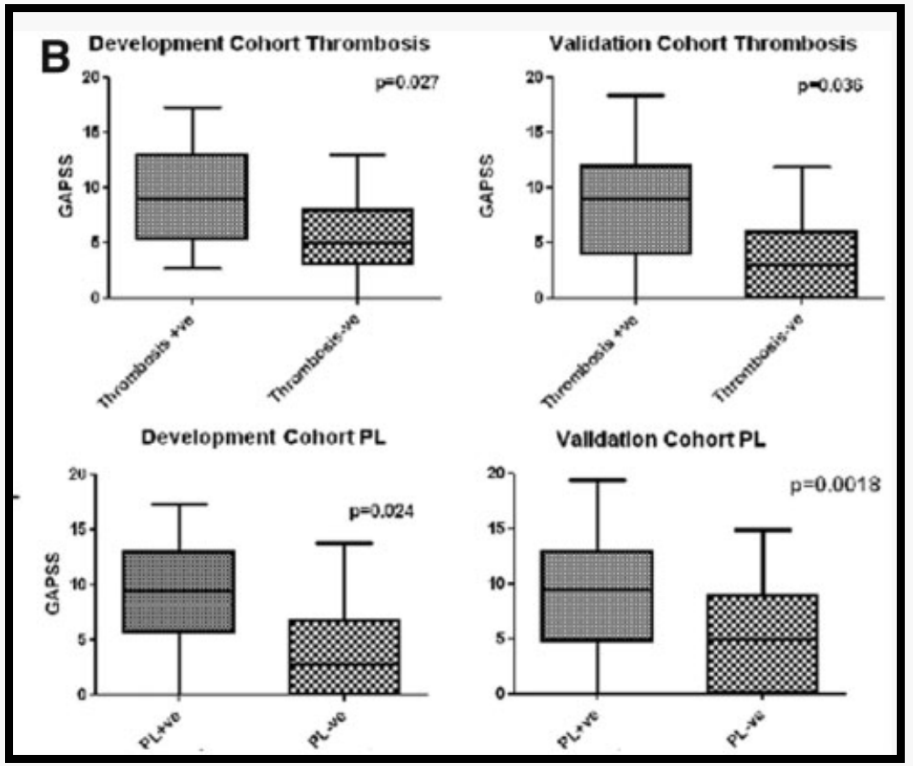


TABLE 4 Diagnostic accuracy including sensitivity, specificity, PPV and NPV for different cut-off values of GAPSS

	AUC	Sensitivity	Specificity	NPV	PPV	*P*-value
GAPSS cut off = 10	0.736	0.709	0.793	0.7705	0.7045	0.000
GAPSS cut off = 12	0.697	0.578	0.817	0.7206	0.7027	0.001
GAPSS cut off = 15	0.664	0.378	0.950	0.6706	0.8500	0.004

Concise report

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The global anti-phospholipid syndrome score in primary APS

Savino Sciascia[1,2], Giovanni Sanna[1,3], Veronica Murru[1], Dario Roccatello[2], Munther A. Khamashta[1,2] and Maria Laura Bertolaccini[1]

- Evaluación de la relevancia clínica del GAPPS en SAF 1º.

- 62 pacientes
- Resultados mas altos en pacientes con trombosis previas respecto a aquellos con solo pérdidas gestacionales
- Resultados mas altos en pacientes con trombosis recurrentes.

- GAPSS mayores de 11 mostraron el mayor riesgo de recurrencia

Herramienta para la cuantificación del riesgo trombótico en LES y SAF

CONCISE REPORT

A prospective open-label pilot study of fluvastatin on proinflammatory and prothrombotic biomarkers in antiphospholipid antibody positive patients

Doruk Erkan,[1] Rohan Willis,[2] Vijaya L Murthy,[2] Gurjot Basra,[2] JoAnn Vega,[1] Patricia Ruiz-Limón,[2] Ana Laura Carrera,[2] Elizabeth Papalardo,[2] Laura Aline Martínez-Martínez,[2] Emilio B González,[2] Silvia S Pierangeli[2]

Objetivo: determinar si los marcadores proinflamatorios y protrombóticos están diferencialmente aumentados en pacientes con AAF positivos persistentemente, y examinar los efectos de fluvastatina en estos biomarcadores.

41 pacientes divididos en 4 grupos: SAF primario, LES con SAF secundario, LES con AAF y AAF sin LES ni SAF.
30 controles sanos

Fluvastatina durante 3 meses+ seguimiento durante 3 meses adicionales.

Ann Rheum Dis 2014;**73**:1176–1180.

Niveles basales de biomarcadores

Table 1 Levels of proinflammatory and prothrombotic biomarkers in antiphospholipid antibody (aPL) positive patients compared with healthy controls: combined and subgroup analysis

Biomarkers Median (IQR)	Controls n: 30	Combined n: 41	PAPS n: 18	SLE/APS n: 7	SLE/aPL n: 7	Primary aPL n: 9
IL6 (pg/mL)	0.7 (0.0)	38.0* (47.3)	31.2* (48.4)	12.2* (103.5)	2.7* (76.8)	0.4 (0.7)
IL1β (pg/mL)	0.3 (0.1)	4.7* (25.1)	3.0* (7.7)	11.4* (20.1)	0.5 (5.1)	0.3 (0.6)
IL8 (pg/mL)	27.4 (30.0)	42.6 (43.9)	24.5** (48.4)	27.4** (53.7)	21.6** (48.9)	7.2 (50.4)
VEGF (pg/mL)	88.3 (85.2)	225.1* (318.4)	242.2*** (399.6)	109.1 (348.4)	67.2 (499.4)	74.6 (158.3)
TNFα (pg/mL)	0.5 (0.0)	29.9* (27.3)	21.5*,** (50.5)	11.6*,** (24.1)	53.9** (62.5)	8.9* (15.7)
IFNα (pg/mL)	0.1 (10.2)	12.9* (115.7)	10.1 (88.4)	0.3 (367.1)	13.2 (558.5)	0.3 (512.2)
IP10 (pg/mL)	96.2 (58.0)	584.4* (551.8)	427.2*,** (569.8)	656.2*,** (454.8)	472.5*,** (690.5)	249.7 (698.9)
sCD40L (pg/mL)	16.4 (14.6)	230.1* (2730.8)	276.5* (676.0)	145.6* (5159.8)	76.9* (970.0)	149.7* (17 035.6)
sTF (pM)	13.0	134.0* (206.0)	153.6* (381.0)	329.2* (447.0)	102.1* (177.0)	190.4* (139.0)
sICAM-1 (ng/mL)	9.5	151.3* (300.2)	281.6*,*** (406.8)	55.1* (70.3)	2.8 (32.9)	163.5 (341.7)
sVCAM-1 (ng/mL)	33.7	41.9 (444.2)	1128.4*,*** (1152.8)	156.4 (19.3)	41.1 (27.2)	321.3 (1015.1)
sE-sel (ng/mL)	10.1	14.1 (27.5)	27.7* (36.7)	14.7 (20.4)	4.1 (21.5)	10.9 (26.4)
# of biomarker elevated*		9/12	9/12	7/12	4/12	3/12

The mean levels of aCL IgG (53.3 GPL), aCL IgM (30.9 MPL), aCL IgA (13.7 APL), antiB2GPI IgG (42.3 SGU), antiB2GPI IgM (44.7 SMU) and antiB2GPI IgA (29.8 SAU) were significantly higher compared to healthy controls ($p<0.05$).

*$p<0.05$ compared with controls, **$p<0.05$ compared with primary aPL patients, ***$p<0.05$ in PAPS versus all other patient groups.

APS, antiphospholipid syndrome; IFNα, interferon α; IL, interleukin; IP10, inducible protein 10; PAPS, primary antiphospholipid syndrome; sCD40L, soluble CD 40 ligand; sEsel, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule; SLE, systemic lupus erythematosus; sTF, soluble tissue factor; sVCAM-1, soluble vascular cell adhesion molecule 1; TNFα, tumour necrosis factor α; VEGF, vascular endothelial growth factor.

Efecto de la fluvastatina sobre los biomarcadores en pacientes con AAF positivos

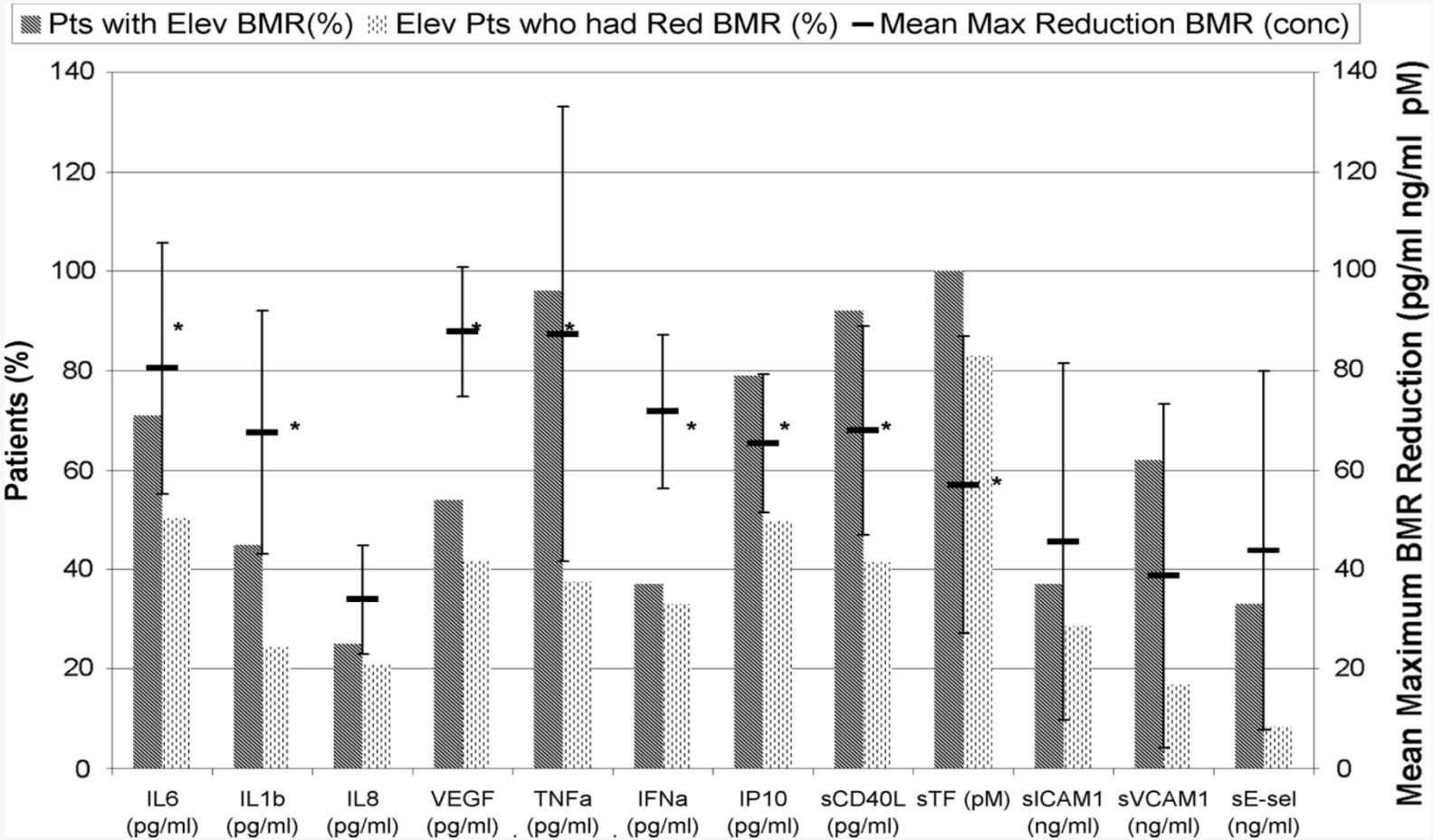


Table 2 Proinflammatory and prothrombotic biomarkers in aPL-positive patients after stopping fluvastatin

Biomarker (BMR)	# of Patients with increased BMR after stopping fluvastatin (%)	Mean±SD maximum BMR increase after stopping fluvastatin	Mean time (days) to maximum BMR increase after stopping fluvastatin
IL6 (pg/mL)	9/12 (75%)	56.7±34.5	35±12
IL1β (pg/mL)	5/6 (83%)	89.0±23.5*	43±15
IL8 (pg/mL)	3/5 (60%)	45.6±34.1	60±10
VEGF (pg/mL)	5/10 (50%)	57.8±28.5*	48±15
TNFα (pg/mL)	6/9 (67%)	90.3±4.5*	58±17
IFNα (pg/mL)	6/8 (75%)	56.7±21.0	60±20
IP10 (pg/mL)	8/12 (67%)	87.5±14.5*	55±15
sCD40L (pg/mL)	9/10 (90%)	90.6±4.3*	45±15
sTF (pM)	13/20 (65)	80.4±10.3*	50±12
sICAM-1 (ng/mL)	1/7 (14)	23.4±12.0	60
sVCAM-1 (ng/mL)	3/4 (75)	47.6±10.4	46±15
sE-sel (ng/mL)	0/2 (0)	N/A	N/A

*$p<0.05$.

IFNα, interferon α; IL, interleukin; IP10, inducible protein 10; N/A, not applicable; sCD40L, soluble CD 40 ligand; sEsel, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule; sTF, soluble tissue factor; sVCAM-1, soluble vascular cell adhesion molecule 1; TNFα, tumour necrosis factor α; VEGF, vascular endothelial growth factor.

- IL6, IL1B, VEGF,TNF alfa, IFN alfa,IP10, sCD40L, sTF e ICAM están aumentados en paciente con AAF positivos con o sin trombosis o con o sin lupus.

- La mayoría de estos biomarcadores pueden ser significativamente y de forma reversible disminuidos por la fluvastatina.

- Los marcadores son sensibles a fluctuaciones en la actividad de la enfermedad a pesar del tto con estatinas

Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial

Marc A Rodger, William M Hague, John Kingdom, Susan R Kahn, Alan Karovitch, Mathew Sermer, Anne Marie Clement, Suzette Coat, Wee Shian Chan, Joanne Said, Evelyne Rey, Sue Robinson, Rshmi Khurana, Christine Demers, Michael J Kovacs, Susan Solymoss, Kim Hinshaw, James Dwyer, Graeme Smith, Sarah McDonald, Jill Newstead-Angel, Anne McLeod, Meena Khandelwal, Robert M Silver, Gregoire Le Gal, Ian A Greer, Erin Keely, Karen Rosene-Montella, Mark Walker, Philip S Wells, for the TIPPS Investigators

36 Hospitales terciarios de 5 paises.

292 pacientes con trombofilia fueron aleatorizadas a dalteparina profilactica anteparto vs no dalteparina

End point primario: aparición de cualquiera de los siguientes→

- Trombosis venosa sintomática
- PE grave o precoz
- CIR
- Pérdida del embarazo.

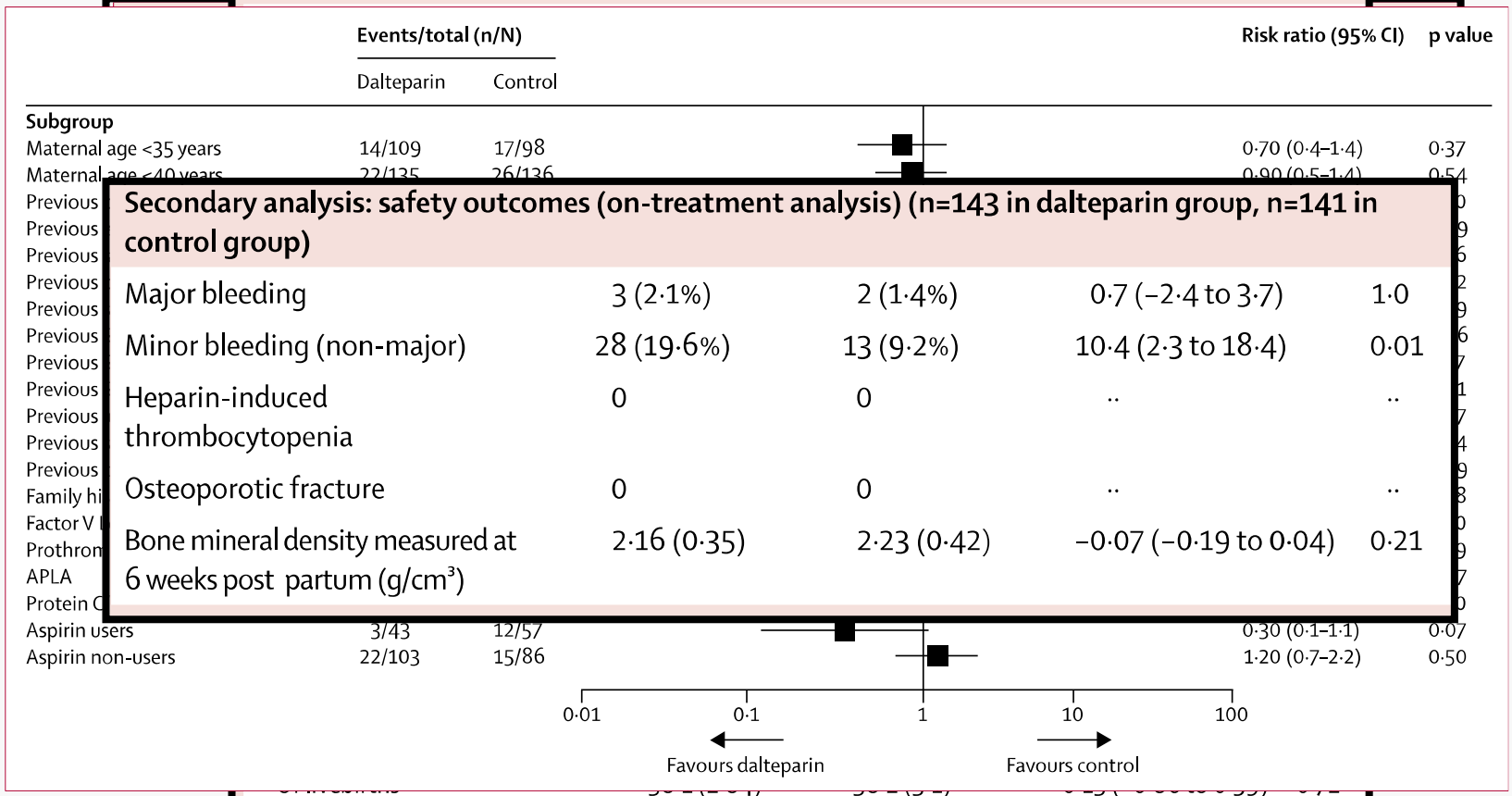
End point secundario:

- Hemorragia
- Parto pretérmino
- Desprendimiento placenta
- Trombocitopenia
- Fractura

Lancet 2014

Resultados

Secondary analysis: efficacy outcomes



Secondary analysis: safety outcomes (on-treatment analysis) (n=143 in dalteparin group, n=141 in control group)

Major bleeding	3 (2·1%)	2 (1·4%)	0·7 (−2·4 to 3·7)	1·0
Minor bleeding (non-major)	28 (19·6%)	13 (9·2%)	10·4 (2·3 to 18·4)	0·01
Heparin-induced thrombocytopenia	0	0	..	..
Osteoporotic fracture	0	0	..	..
Bone mineral density measured at 6 weeks post partum (g/cm³)	2·16 (0·35)	2·23 (0·42)	−0·07 (−0·19 to 0·04)	0·21
Of pregnancy loss	16·8 (8·2)	10·8 (5·3)	6·0 (−0·09 to 12·11)	0·06

- Dalteparina anteparto no redujo el riesgo de pérdida del embarazo, trombosis venosa o complicaciones mediadas por la placenta en pacientes con trombofilia.

- Ninguna de las mujeres con trombofilia sin trombosis previa tuvo un TEV en el grupo control.

- Todas las mujeres que experimentaron un TEV tenían historia de trombosis distal o secundaria. Todas estuvieron bajo dalteparina profiláctica.

Profilaxis mas agresiva?

- En el análisis de subgrupos en mujeres con trombofilia y abortos previos, no se objetivó mejoría en la tasa de recién nacidos vivos con el tto con dalteparina.

Consistente con ensayos previos

- Meta-análisis del mismo grupo: evidencia de mayor calidad sugiere que la administración de LMWH no previene complicaciones no graves medidas por la placenta.