RICORS-ICTUS | Instituto de Salud Carlos III

EL EFECTO DE LOS FARMACOS HIPOLIPEMIANTES EN LA ECOGENICIDAD DE LA PLACA DE ATEROMA MEDIDA MEDIANTE ECOGRAFÍA.

MARTA M MARTÍNEZ MARTÍNEZ

Universidad Europea
LAUREATE INTERNATIONAL UNIVERSITIES

frontiers | Frontiers in Cardiovascular Medicine

MINI REVIEW
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Carotid Plaque Composition and the Importance of Non-Invasive in Imaging Stroke Prevention

Martin Andreas Geiger[1], Ronald Luiz Gomes Flumignan[2], Marcone Lima Sobreira[3], Wagner Mauad Avelar[4], Carla Fingerhut[5], Sokrates Stein[1] and Ana Terezinha Guillaumon[1]*

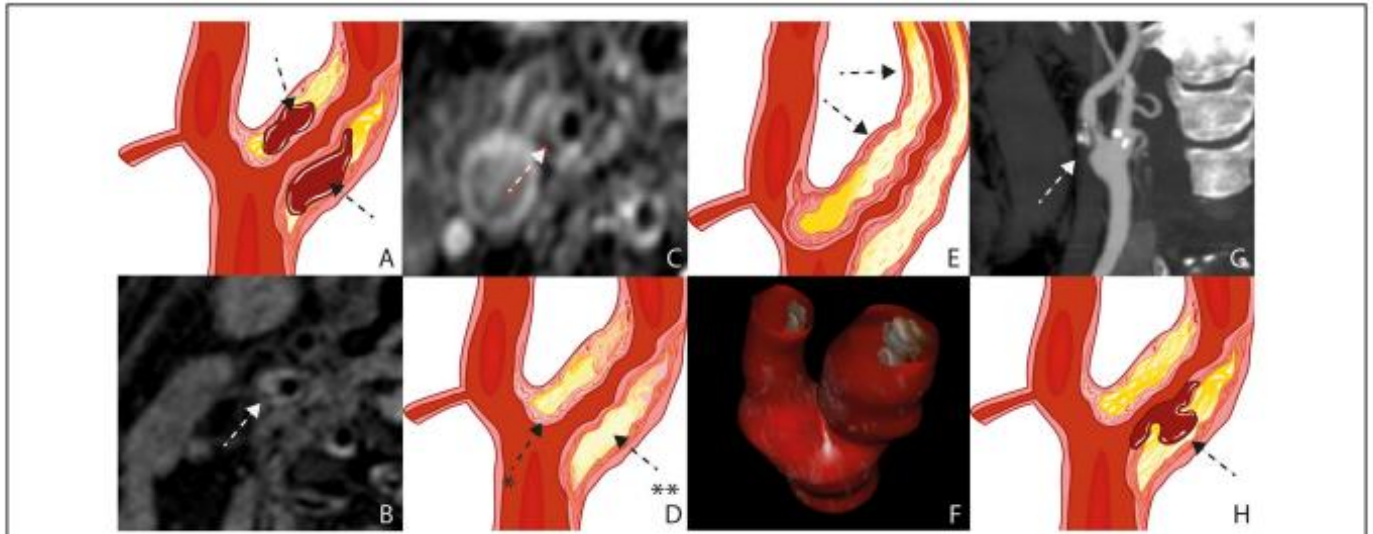


FIGURE 1 | Plaque Characteristics. Schematic figure illustrating intraplaque hemorrhage **(A)**, MRI on a 3 Tesla scanner **(B)**; white arrow), The axial T1 turbo spin-echo with fat saturation image post gadolinium shows a pronounced LRNC covered by an intact fibrous cap **(C)**; white arrow), Schematic figure illustrating a pronounced LRNC (**) covered by an intact fibrous cap (*) **(D)**, Schematic figure illustrating a pronounced bulky plaque **(E)**; black arrows), 3D ultrasound volume analysis **(F)**, surface morphology, image obtained by CT **(G)**, Schematic figure illustrating plaque rupture with an ulceration **(H)**; black arrow). LRNC, lipid-rich necrotic core; MRI, Magnetic Resonance Imaging; CT,Computed Tomography.

Table 1. Overview of the clinical indications, validation status, advantages, and limitations of the discussed noninvasive US methods in the identification and characterization of atherosclerotic plaques and the evaluation of other cardiovascular pathologies.

Noninvasive US Method	Clinical Indications (Validation Status)	Advantages	Limitations
Conventional vascular B-mode US + Doppler mode	• C-IMT measurement (validated) [84] • Direct plaque visualization • Provides GSM values (histopathological validation) [85] • Doppler provides PWV values that estimate atherosclerosis (validated) [86] • Extracranial (direct) and intracranial (indirect) vessel evaluation by Cervical Duplex US (validated) [87,88] • B-flow and B-mode US for carotid fibromuscular dysplasia (unvalidated with catheter angiography) [89] • Large vessel vasculitis diagnosis (unvalidated by histology) [90,91]	• Noninvasive, rapid, widely available • Cost-efficient • Free from ionizing radiation • Provides the possibility for re-examination • Multiple Doppler modes (color, spectral, power) that can visualize and characterize the increased velocity within a stenosis [92] • Doppler US can provide supplementary information through the grayscale median [39]	• Limited depth of examination with the vascular probe • Adequate ultrasound windows must be obtained for a thorough characterization • Limited use for incipient atherosclerosis • Limited use of IMT [19] • Prone to subjectivity and dependent on the examiner
Vascular contrast-enhanced ultrasonography (CEUS)	• Visualization and quantification of plaque neovascularization (histopathological validation) [93] • Better C-IMT index measurement (validated) [94] • Dissecans aneurysm: discernment between the true and the false lumen (validated using computed tomography angiography (CTA) [95] • Abdominal aortic aneurysm: detection of intraluminal thrombus (validated using CTA) [96] • Endovascular aortic aneurysm repair: identification and classification of endoleaks [97] • Myocardial contrast echocardiography: quantification of myocardial perfusion, wall movement, and viability (unvalidated due to increased intra and interobserver variability) [49,98] • Intracardiac thrombus characterization (validated by delayed-enhancement cardiac magnetic resonance) [99,100] • Appraisal of vascularization within the vessel wall in large vessel vasculitis (unvalidated with histology) [101,102] • Intra-cerebral vascular imaging (validated) [101,103]	• Does not use ionizing radiation • Cost-efficient, repeatable • Provides quantifiable data [48] • Provides better image quality and the delineation of the carotid lumen [48] • Provides a better resolution for identifying atherosclerotic plaques and their anatomy—surface, ulceration, and neovascularization [53] • Can provide risk stratification • Can detect slow flow [104] • UCAs are not nephrotoxic [104]	• Uses intravenous contrast agents • Requires specialized training • Time limited (the concentration of UCAs decreases over a period of time—minutes) [104] • Atypical artifacts: pseudo-enhancement artifact that may lead to the misinterpretation of results—non-linear propagation of the US waves [105] • Artifacts: shadows produced by heavily calcified atherosclerotic plaques significantly hamper the examination of entities present within the acoustic shadow
Elastography techniques	• Ultrasound strain imaging (histopathological validation after endarterectomy) [66] (validation using MRI) [106] • Identification of lipid-rich atherosclerotic plaques [66] • (Fibro)atheromatous plaque detection [66] • Myocardial strain imaging: surveillance of adverse effects in cancer therapies (validated) [107,108] • Diastolic wall strain: predictor of CVD [HR = 1.89, 95% CI: 1.04–3.36, $p = 0.04$] [109]	• Adds a new dimension to the examination-the strain of the arterial wall/plaque [59] • May discriminate between the adipose tissue, fibrous tissue, calcifications, hemorrhage and thrombosis [67] • High reproducibility according to several studies [64,67]	• Confounders • SWE values can differ significantly among subjects in relation to patient and plaque characteristics [79] • No standardized cutoff values

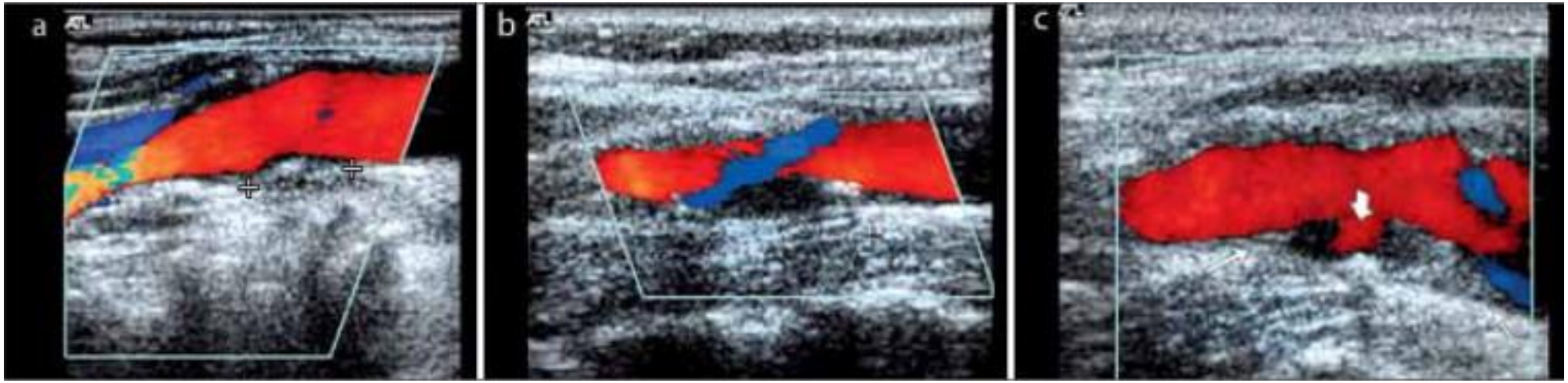
Review

Ultrasound Methods in the Evaluation of Atherosclerosis: From Pathophysiology to Clinic

Gabriel Cismaru [1], Teodora Serban [2] and Alexandru Tirpe [3,*]

Ecografía carotídea

El US es una herramienta útil en la práctica clínica habitual para la valoración de las placas de ateroma y su repercusión dinámica (Doppler)



Grey Scale Median

Cuantifica componentes con diferente grado de ecogenicidad

Placas menos ecogénicas = más riesgo

Postprocesamiento de la imagen.

Adobe Photoshop (Adobe Systems Incorporated)

Se estandariza la imagen a escala 0- 195

Mide GSM automático

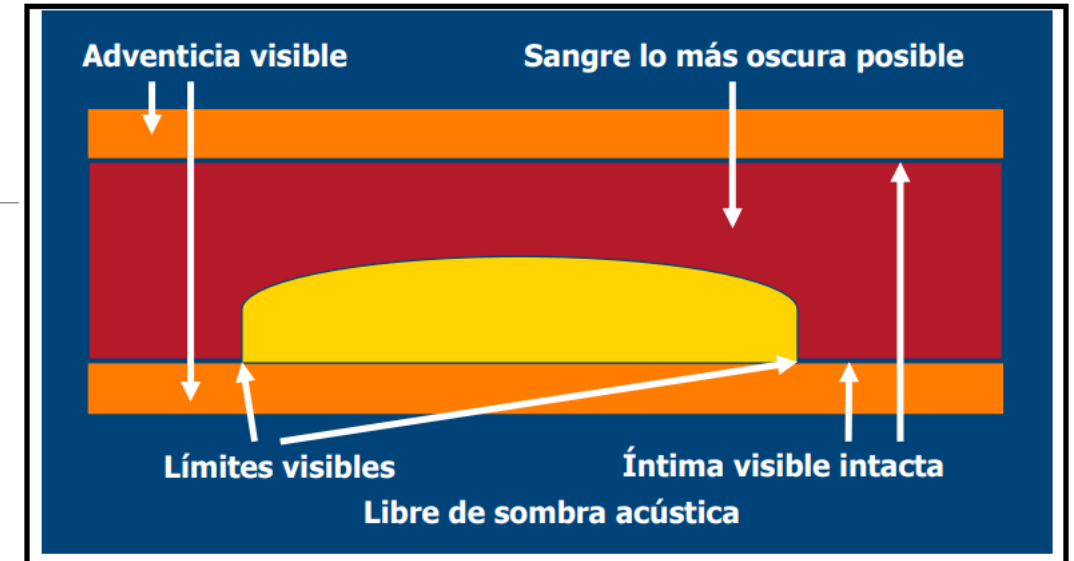
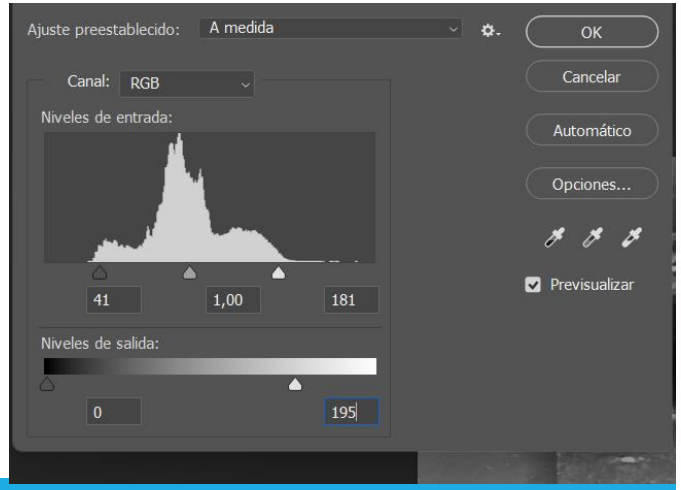
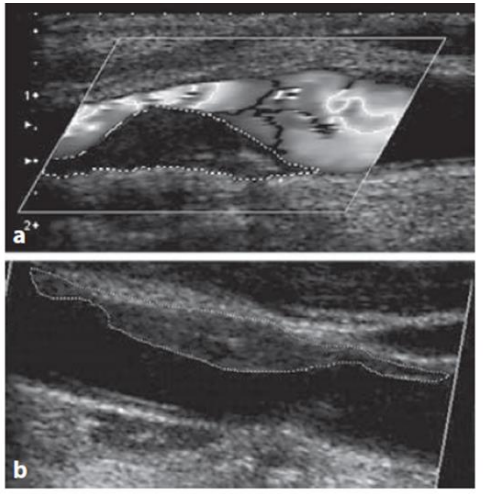


Figura 9: Visión esquemática de los criterios de adquisición de la imagen

Cortesía Dr G Ruiz Ares



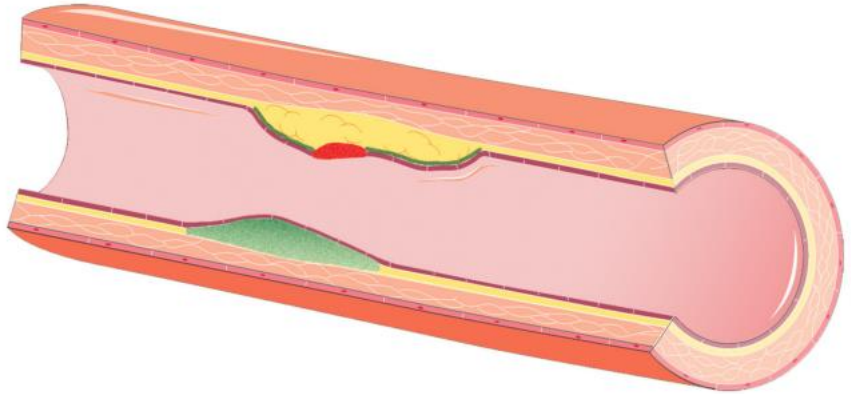


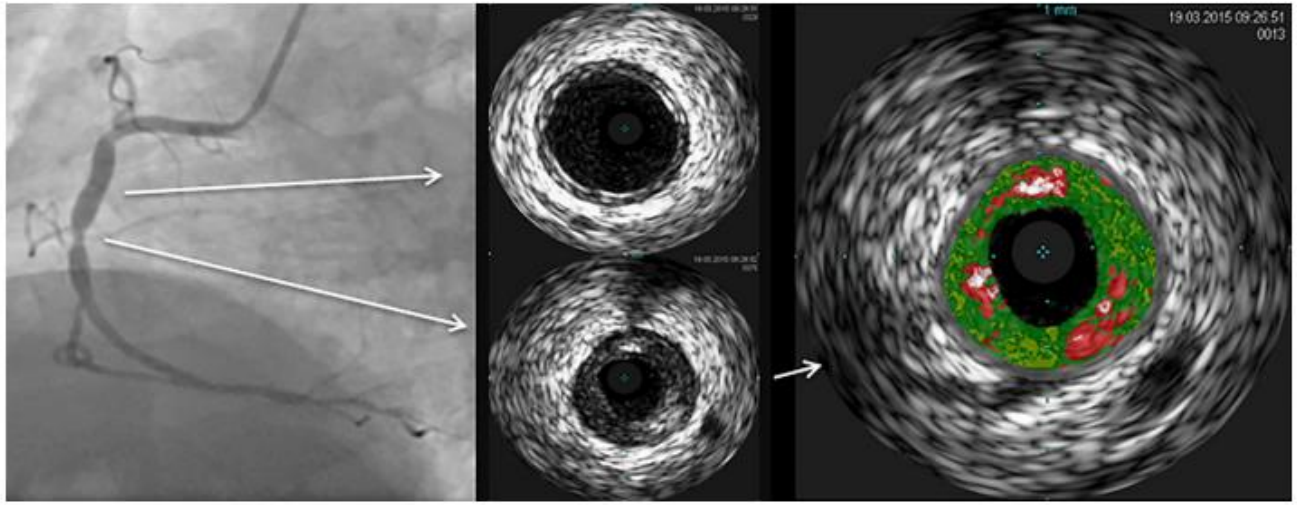
IVUS

Table 3. Virtual histology IVUS (VH-IVUS): histology correlation of atherosclerotic plaques.

Tissue Type	Plaque Histology with Movat Pentachrome Stain	Color on VH-IVUS
Fibrous	Densely packed collagen	Dark green
Fibrofatty	Collagen with significant scattered lipid	Light green
Calcified necrosis	Foam cells, cholesterol clefts and microcalcifications	Red
Dense calcium	Calcium deposits lacking necrosis	White

VIRTUAL HISTOLOGY





Efecto de diferentes fármacos en la aterosclerosis.
Evaluación por US.

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Article

Ultrasound Assessment of Carotid Plaque Echogenicity Response to Statin Therapy: A Systematic Review and Meta-Analysis

Pranvera Ibrahimi, Fisnik Jashari *, Gani Bajraktari, Per Wester and Michael Y. Henein

Department of Public Health and Clinical Medicine, Umeå University, Umeå 901 87, Sweden;
E-Mails: pranvera.ibrahimi@medicin.umu.se (P.I.); ganibajraktari@yahoo.co.uk (G.B.);
per.wester@medicin.umu.se (P.W.); michael.henein@medicin.umu.se (M.Y.H.)

In six studies, other ultrasound-derived measurements were evaluated, including: intima-media thickness [12,16,20], plaque thickness [13,19], plaque volume [16] and degree of stenosis [12]. Except for one study that found a decrease in plaque thickness after statin therapy [13], there was no other change, of the above-mentioned measures, observed after statin therapy.

Author/Year	Study Design	Statin/Dose	Follow-up (Months)	% Change Echogenicity	% Change LDL	% Change HDL
1. Watanabe *et al.*, 2005 [12]	Randomized case-control trial	Pravastatin	6	14.1 ± 3.3	24.5 ± 6.4	10.2 ± 6.0
3. Yamagami *et al.*, 2008 [13]	Randomized case-control trial	Simvastatin 10 mg	1	10.6 ± 4.3	34.2 ± 18.4	0
2. Nakamura *et al.*, 2008 [14]	Randomized case-control trial	Pitavastatin 4 mg	12	32.1 ± 5.9	37.8 ± 12.4	9.3 ± 2.0
4. Kadoglou *et al.*, 2008 [15]	Open-label prospective trial	Atorvastatin	6	36.0 ± 15.2	41.7 ± 19.9	4.5 ± 2.4
5. Yamada *et al.*, 2009 [16]	Randomized case-control trial	Simvastatin	6	17.0 ± 5.9	44.0 ± 23.9	0
6a. Kadoglou *et al.*, 2009 [17]	Open-label prospective trial	Atorvastatin	6	36.8 ± 9.8	38.6 ± 20.0	13.4 ± 6.6
6b. Kadoglou *et al.*, 2009 [17]	Open-label prospective trial	Atorvastatin + CAS	6	48.4 ± 18.6	33.3 ± 15.0	4.4 ± 2.2
7a. Kadoglou *et al.*, 2010 [18]	Randomized case-control trial	Atorvastatin 10–20 mg	12	32.6 ± 11.7	64.5 ± 23.6	5.5 ± 2.6
7b. Kadoglou *et al.*, 2010 [18]	Randomized case-control trial	Atorvastatin 80 mg	12	51.4 ± 18.4	54.2 ± 37.2	10.3 ± 6.0
8. Della-Morte *et al.*, 2011 [19]	Prospective pilot study	NA	1	21.9 ± 4.8	51.4 ± 31.0	2.0 ± 1.1
9. Nohara *et al.*, 2013 [20]	Prospective open label, blinded-endpoint	Rosuvastatin	12	16.9 ± 33.1	50.1 ± 22.9	8.1 ± 3.6

Banach et al. BMC Medicine (2015) 13:229
DOI 10.1186/s12916-015-0459-4

BMC Medicine

Prevention of Cardiovascular Diseases

RESEARCH ARTICLE Open Access

Impact of statin therapy on coronary plaque composition: a systematic review and meta-analysis of virtual histology intravascular ultrasound studies

Maciej Banach[1*†], Corina Serban[2†], Amirhossein Sahebkar[3,4], Dimitri P. Mikhailidis[5], Sorin Ursoniu[6], Kausik K. Ray[7], Jacek Rysz[8], Peter P. Toth[9,10], Paul Muntner[11], Svetlana Mosteoru[12], Hector M. García-García[13,14], G. Kees Hovingh[15], John JP Kastelein[15], Patrick W. Serruys[13,16] and Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group

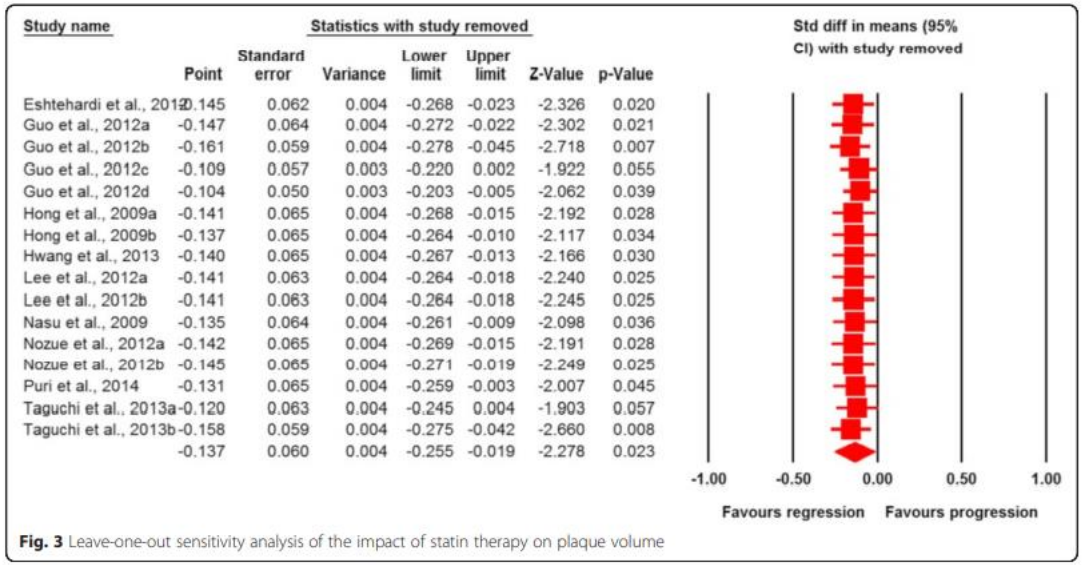

Fig. 3 Leave-one-out sensitivity analysis of the impact of statin therapy on plaque volume

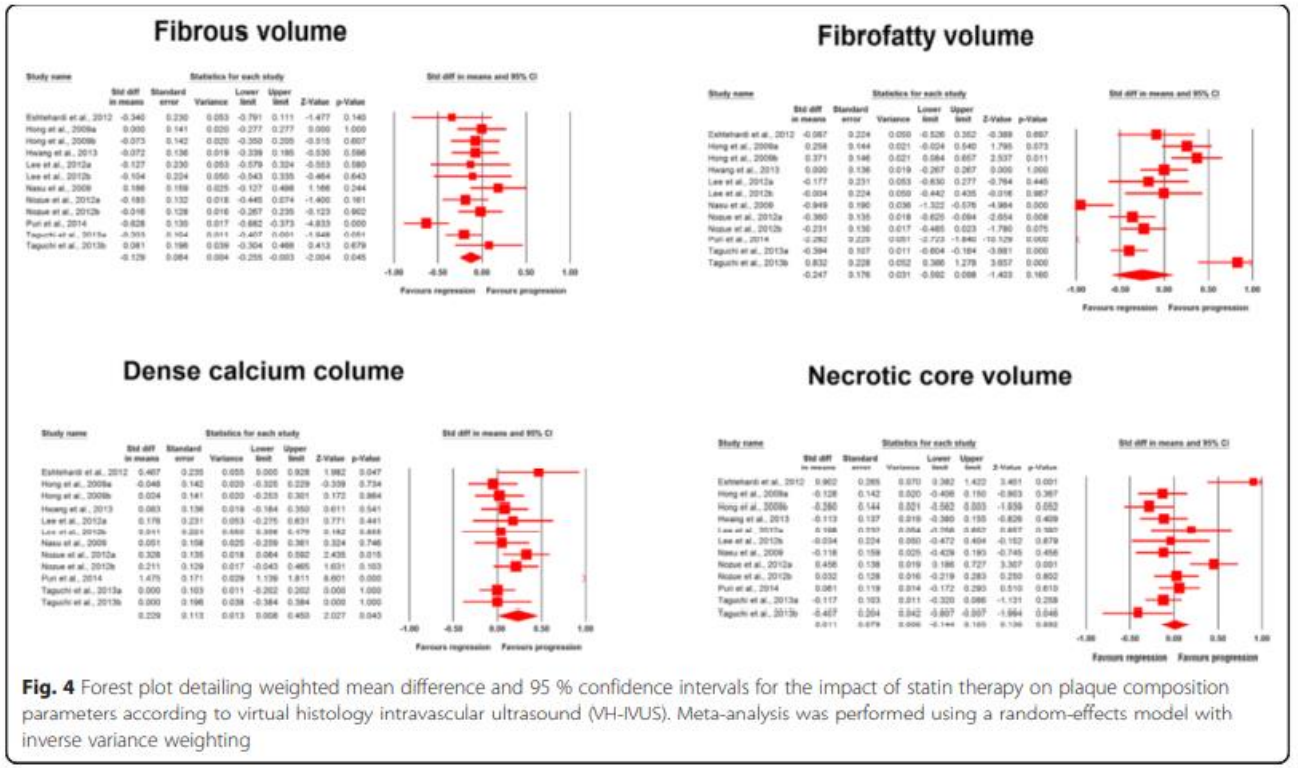

Fig. 4 Forest plot detailing weighted mean difference and 95 % confidence intervals for the impact of statin therapy on plaque composition parameters according to virtual histology intravascular ultrasound (VH-IVUS). Meta-analysis was performed using a random-effects model with inverse variance weighting

Masson et al. Lipids in Health and Disease (2020) 19:111
https://doi.org/10.1186/s12944-020-01297-5

Lipids in Health and Disease

REVIEW Open Access

Role of non-statin lipid-lowering therapy in coronary atherosclerosis regression: a meta-analysis and meta-regression

Walter Masson[1,2], Martin Lobo[1], Daniel Siniawski[1,2], Graciela Molinero[1], Gerardo Masson[1], Melina Huerín[1] and Juan Patricio Nogueira[2,3*]

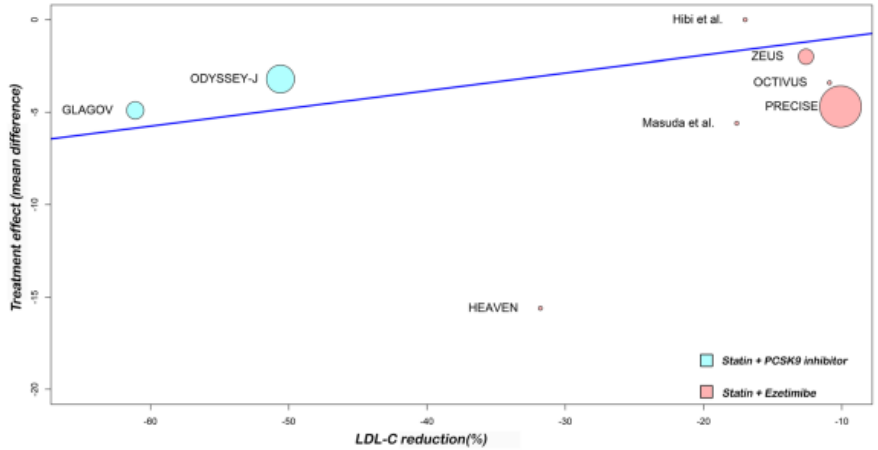

Fig. 4 Random-effects meta-regression analyses: Association between the difference in percentage LDL-C reduction among treatment arms and treatment effect (total atheroma volume regression)

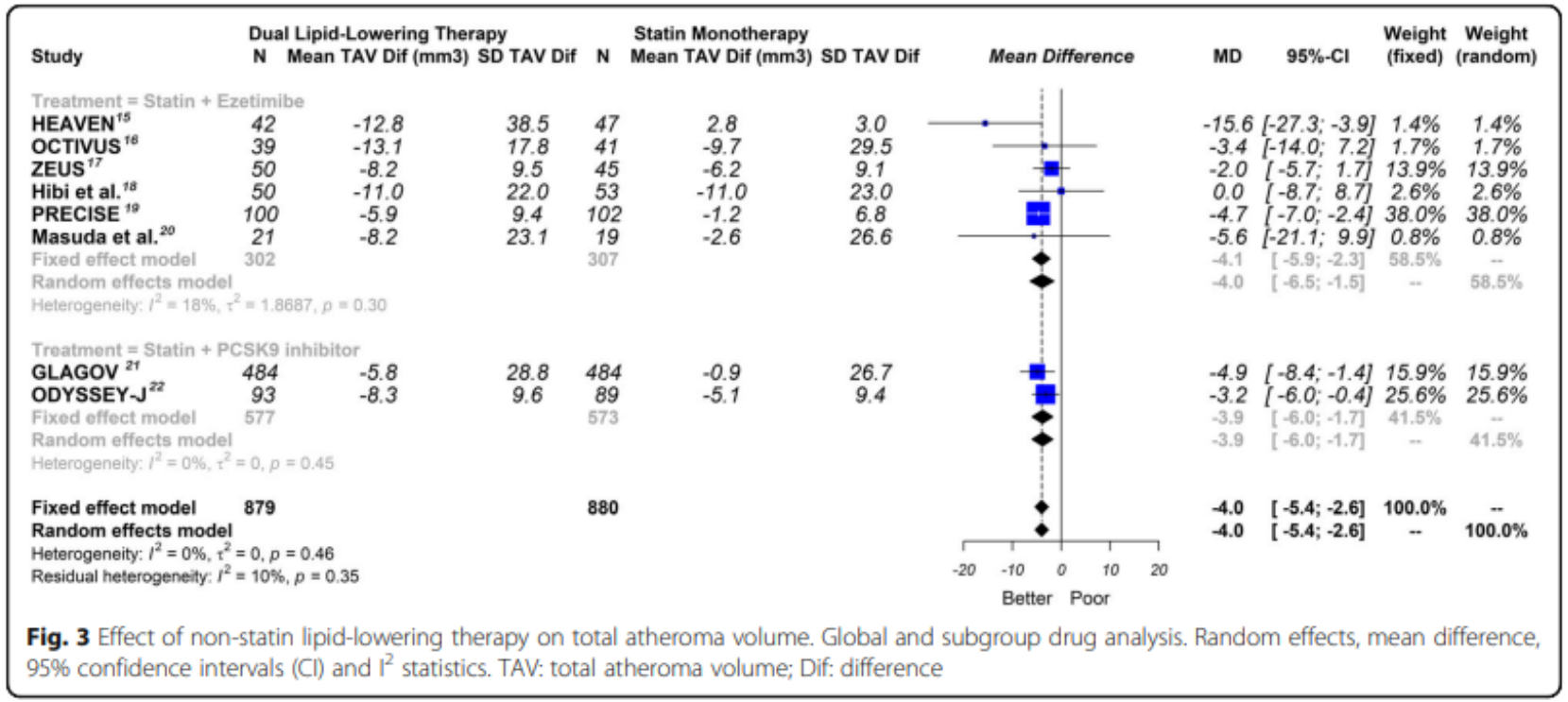

Fig. 3 Effect of non-statin lipid-lowering therapy on total atheroma volume. Global and subgroup drug analysis. Random effects, mean difference, 95% confidence intervals (CI) and I^2 statistics. TAV: total atheroma volume; Dif: difference

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GLAGOV STUDY

Effect of Evolocumab on Coronary Plaque Composition

Stephen J. Nicholls, MBBS, PhD,[a,b] Rishi Puri, MBBS, PhD,[b] Todd Anderson, MD,[c] Christie M. Ballantyne, MD,[d] Leslie Cho, MD,[b] John J.P. Kastelein, MD, PhD,[e] Wolfgang Koenig, MD,[f] Ransi Somaratne, MD,[g] Helina Kassahun, MD,[g] Jingyuan Yang, PhD,[g] Scott M. Wasserman, MD,[g] Satoshi Honda, MD,[a] Daisuke Shishikura, MD, PhD,[a] Daniel J. Scherer, MBBS,[a] Marilyn Borgman, RN, BSN,[b] Danielle M. Brennan, MS,[b] Kathy Wolski, MPH,[b] Steven E. Nissen, MD[b]

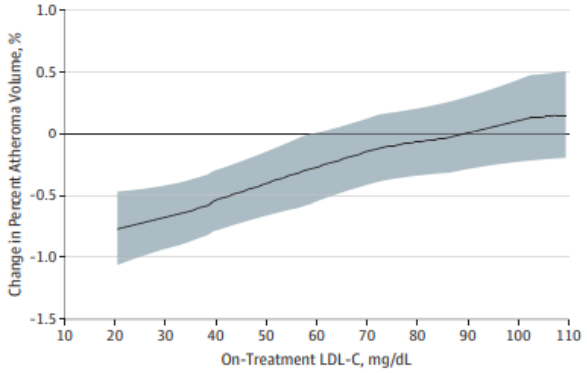
331 pacientes aleatorizados EVOLOCUMAB 420 mg/mes /PLACEBO

Estudio IVUS (y VH-IVUS) basal y a las 76 semanas de tto

LDL 33,5mg/dl vs 89,9mg/dl p<0,0001

TABLE 3 Plaque Burden

	Placebo (n = 167)	Evolocumab (n = 164)	p Value Between Groups
% atheroma volume			
Baseline	36.3 (30.6 to 42.9)	37.2 (30.0 to 43.7)	0.86
Follow-up	35.9 (30.7 to 43.0)	35.9 (29.0 to 42.5)	0.34
Nominal change	0.17 (−1.41 to 1.35)	−1.20 (−2.62 to 0.53)	<0.0001
p value from baseline	0.60	<0.0001	
Total atheroma volume, mm^3			
Baseline	164.0 (118.1 to 232.9)	174.7 (130.5 to 239.2)	0.58
Follow-up	163.7 (120.9 to 222.1)	170.7 (125.9 to 230.2)	0.86
Nominal change	−0.8 (−11.9 to 8.4)	−3.6 (−12.1 to 4.3)	0.04
p value from baseline	0.15	<0.0001	



Correlación inversa entre cambio de LDL colesterol y calcificación

TABLE 4 Plaque Composition

	Placebo (n = 167)	Evolocumab (n = 164)	p Value Between Groups
Normalized volume measures			
Necrotic core, mm^3			
Baseline	8.9 (4.3 to 15.0)	9.1 (4.0 to 17.3)	0.84
Follow-up	8.8 (4.0 to 15.1)	7.5 (3.1 to 15.7)	0.37
Nominal change	−0.1 ± 0.5	−0.6 ± 0.5	0.49†
p value*	0.77	0.21	
Fibrofatty, mm^3			
Baseline	20.4 (7.9 to 44.0)	21.1 (9.4 to 42.6)	0.91
Follow-up	16.6 (7.3 to 38.4)	15.7 (5.4 to 33.2)	0.41
Nominal change	−3.0 ± 1.0	−5.0 ± 1.0	0.49†
p value*	0.002	<0.001	
Fibrous, mm^3			
Baseline	19.0 (10.5 to 33.2)	21.0 (9.9 to 33.7)	0.79
Follow-up	17.5 (9.7 to 30.0)	16.7 (7.1 to 30.0)	0.44
Nominal change	−2.4 ± 0.6	−3.0 ± 0.6	0.49†
p value*	<0.001	<0.001	
Dense calcium, mm^3			
Baseline	2.3 (0.7 to 5.5)	2.1 (0.5 to 6.2)	0.82
Follow-up	2.8 (0.9 to 6.6)	2.3 (0.5 to 7.2)	0.85
Nominal change	0.6 ± 0.3	1.0 ± 0.3	0.49†
p value*	0.03	<0.001	
Percent plaque			
Necrotic core, %			
Baseline	16.0 (11.6 to 21.6)	16.5 (11.9 to 21.8)	0.83
Follow-up	17.1 (11.4 to 21.9)	17.5 (11.2 to 23.0)	0.66
Nominal change	0.4 ± 0.5	0.9 ± 0.6	0.67†
p value*	0.46	0.13	
Fibrofatty, %			
Baseline	40.7 (29.3 to 53.9)	38.5 (28.1 to 49.8)	0.34
Follow-up	38.6 (26.0 to 50.3)	37.2 (24.0 to 48.8)	0.38
Nominal change	−0.9 ± 1.1	−1.6 ± 1.1	0.67†
p value*	0.39	0.15	
Fibrous, %			
Baseline	36.2 (28.3 to 44.5)	36.9 (29.0 to 45.2)	0.32
Follow-up	34.2 (27.8 to 44.0)	35.7 (29.8 to 42.7)	0.54
Nominal change	−0.6 ± 0.8	−1.4 ± 0.8	0.67†
p value*	0.45	0.10	
Dense calcium, %			
Baseline	3.8 (1.6 to 7.7)	4.4 (1.6 to 8.5)	0.65
Follow-up	5.0 (2.1 to 9.9)	6.1 (2.0 to 11.6)	0.26
Nominal change	1.0 ± 0.4	2.2 ± 0.4	0.10†
p value*	0.004	<0.001	

Research

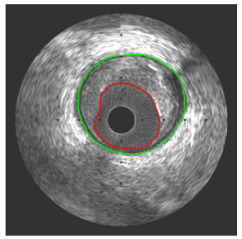
JAMA | Original Investigation

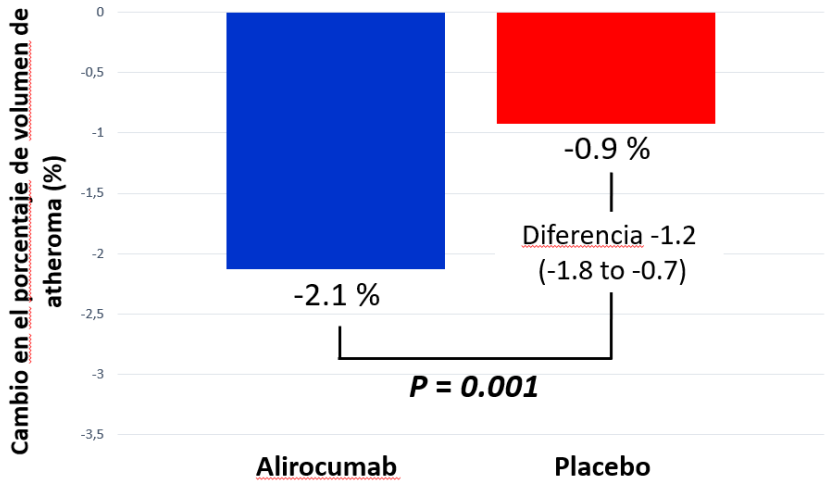
Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction
The PACMAN-AMI Randomized Clinical Trial

Lorenz Räber, MD, PhD; Yasushi Ueki, MD, PhD; Tatsuhiko Otsuka, MD; Sylvain Losdat, PhD; Jonas D. Häner, MD; Jacob Lonborg, MD; Gregor Fahrni, MD; Juan F. Iglesias, MD; Robert-Jan van Geuns, MD, PhD; Anna S. Ondracek, MSc; Maria D. Radu Juul Jensen, MD, PhD; Christian Zanchin, MD, PhD; Stefan Stortecky, MD; David Spirk, MD; George C. M. Siontis, MD, PhD; Lanja Saleh, PhD; Christian M. Matter, MD; Joost Daemen, MD, PhD; François Mach, MD; Dik Heg, PhD; Stephan Windecker, MD; Thomas Engstrøm, MD, PhD; Irene M. Lang, MD; Konstantinos C. Koskinas, MD, MSc; for the PACMAN-AMI collaborators

- 300 pacientes aleatorizados
- ROSUVASTATINA 20mg + ALIROCUMAB 150mg/15d / ROSUVASTATINA 20mg
- 50 semanas de seguimiento
- LDL 23,6mg/dl / 74,6mg/dl, p<0,0001

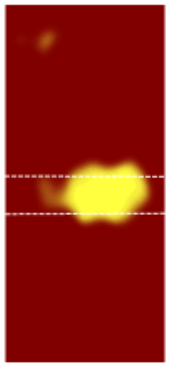
Variable principal:
Cambio en % de volumen de ateroma (IVUS)

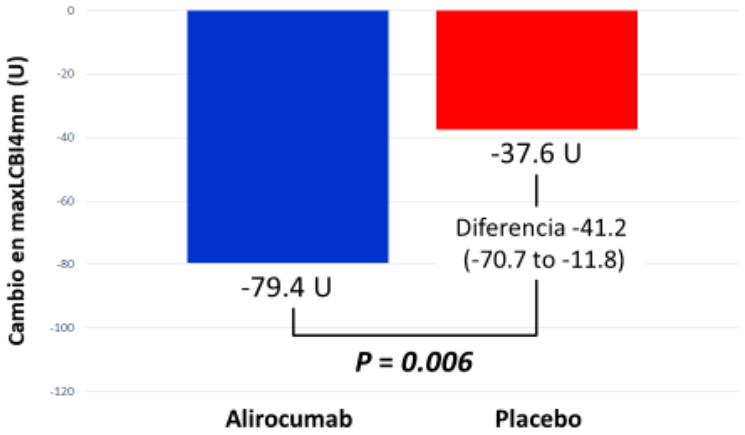




Räber, L et al. *JAMA*. Published online April 3, 2022. doi:10.1001/jama.2022.5218

Variables secundarias potenciadas:
Cambio en maxLCBI$_{4mm}$ (NIRS)





U: unidades

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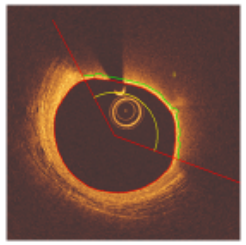
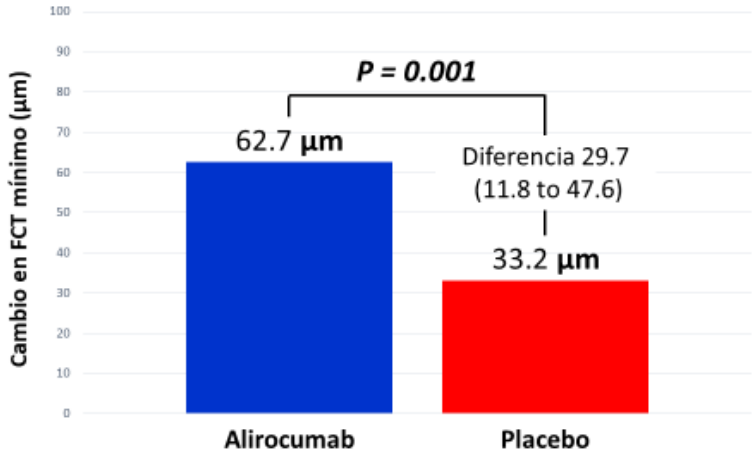
Variables secundarias potenciadas:
Cambio en FCT mínimo (OCT)





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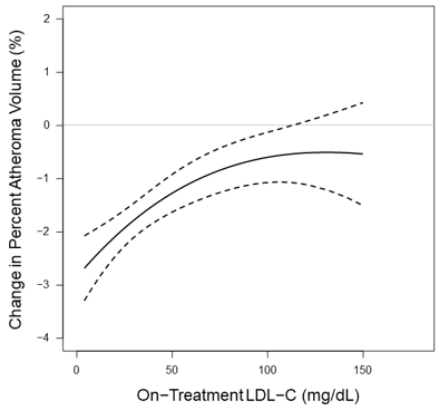
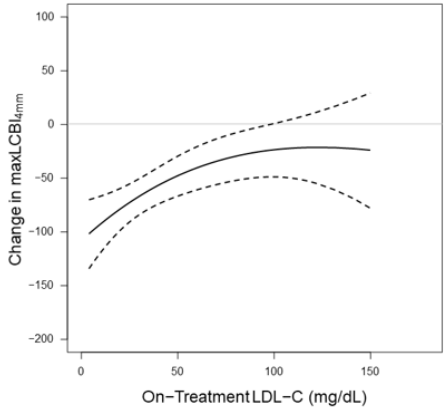
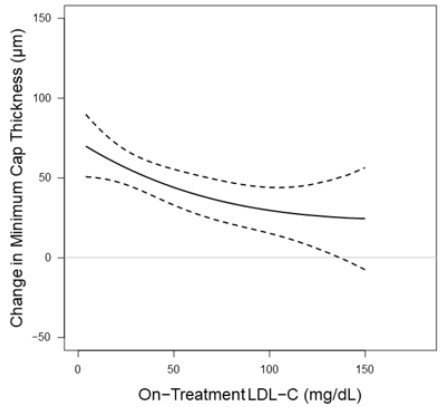
PAV



maxLCBI$_{4mm}$



FCT$_{min}$



Research

JAMA | Original Investigation

Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction
The PACMAN-AMI Randomized Clinical Trial

Lorenz Räber, MD, PhD; Yasushi Ueki, MD, PhD; Tatsuhiko Otsuka, MD; Sylvain Losdat, PhD; Jonas D. Häner, MD; Jacob Lonborg, MD; Gregor Fahrni, MD; Juan F. Iglesias, MD; Robert-Jan van Geuns, MD, PhD; Anna S. Ondracek, MSc; Maria D. Radu Juul Jensen, MD, PhD; Christian Zanchin, MD, PhD; Stefan Stortecky, MD; David Spirk, MD; George C. M. Siontis, MD, PhD; Lanja Saleh, PhD; Christian M. Matter, MD; Joost Daemen, MD, PhD; François Mach, MD; Dik Heg, PhD; Stephan Windecker, MD; Thomas Engstrøm, MD, PhD; Irene M. Lang, MD; Konstantinos C. Koskinas, MD, MSc; for the PACMAN-AMI collaborators

Atherosclerosis 327 (2021) 31–38

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journal homepage: www.elsevier.com/locate/atherosclerosis

Regression in carotid plaque lipid content and neovasculature with PCSK9 inhibition: A time course study

Norman E. Lepor [a,b,1], Jie Sun [c,*,1], Gador Canton [c], Laurn Contreras [a], Daniel S. Hippe [c], Daniel A. Isquith [c], Niranjan Balu [c], Ilan Kedan [b], Americo A. Simonini [b], Chun Yuan [c], Thomas S. Hatsukami [c], Xue-Qiao Zhao [c]

[a] Westside Medical Associates of Los Angeles, Beverly Hills, CA, USA
[b] Smidt Cedars-Sinai Heart Institute, Los Angeles, CA, USA
[c] University of Washington, Seattle, WA, USA

- 27 pacientes con intolerancia a estatinas.
- Alirocumab 150mg/15 d
- Control RM con Gd 0-3-6-12 meses

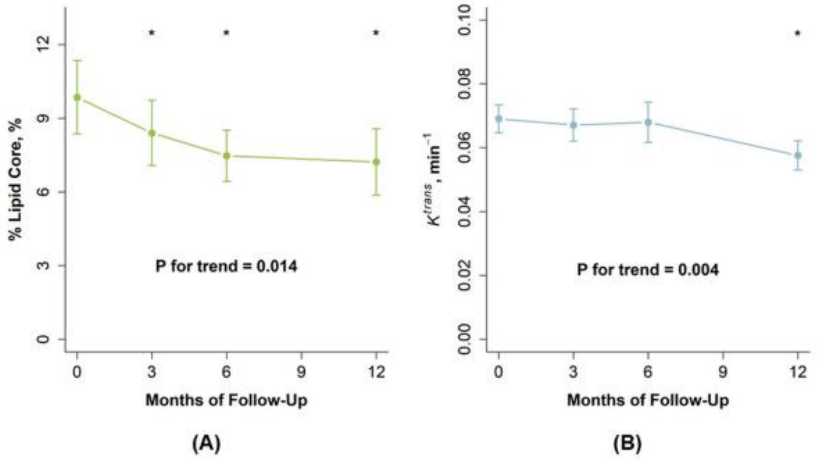
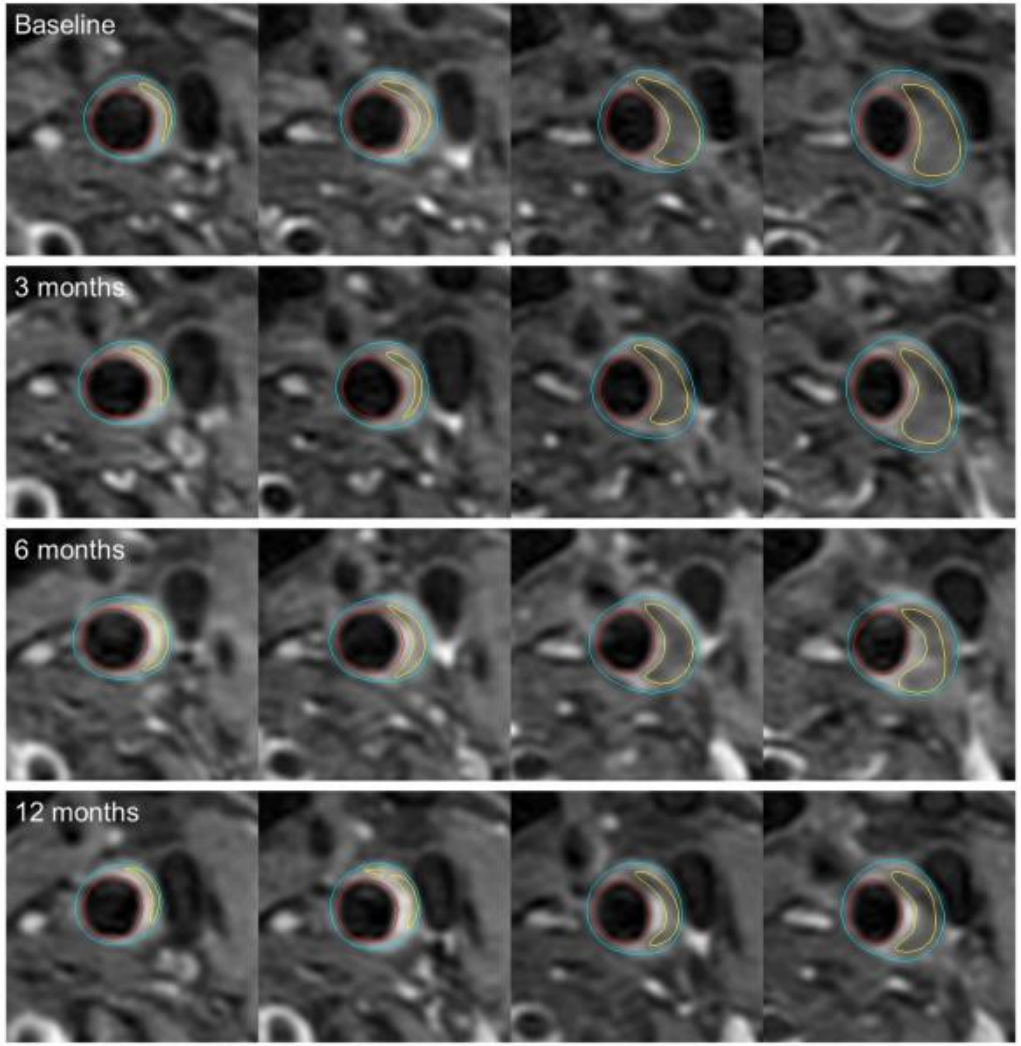


Fig. 3. Time course of reductions in % lipid core and K^{trans}.
(A) % lipid core is summarized using the median (points) and standard error (error bars) at each timepoint. (B) Adventitial K^{trans} is summarized using the mean (points) and standard error (error bars) at each timepoint. In both panels, the star (*) indicates statistically significant decreases relative to baseline ($p < 0.05$).



Effects of PCSK-9 inhibitors on carotid atherosclerosis
Elena De Angelis et al. University of Salerno

46 patients with familial hypercholesterolemia. 12 months follow up.
This is the first study showing that the inhibitors of PCSK9, can decrease or even reverse the progression of carotid atherosclerosis, reducing the intima-media thickness, the lipid content of atheromatous plaques leading to a
reduction of clinical adverse events.

European Heart Journal Supplements (2019) 21 (Supplement J), J112–J114
doi:10.1093/eurheartj/suz256

Received: 9 July 2020 | Accepted: 28 July 2020
DOI: 10.1002/ccd.29231

PERIPHERAL VASCULAR DISEASE
Case Report

WILEY

Morphological stabilization and regression of carotid plaque following therapy with evolocumab in a high-risk patient

Tiziana Claudia Aranzulla MD, MS | Giuseppe Musumeci MD

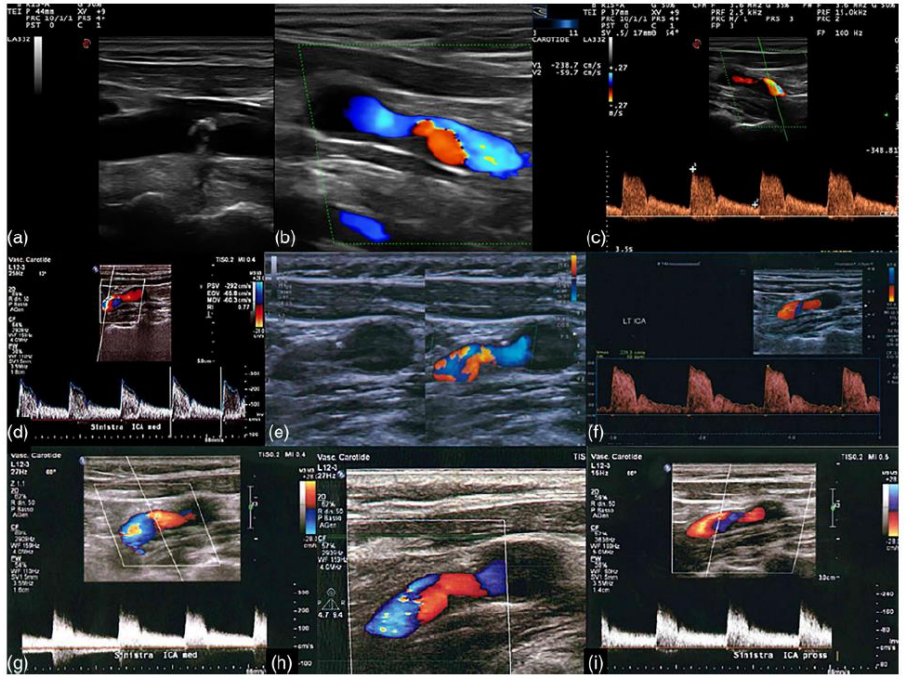


FIGURE 3 Serial carotid Doppler ultraSonographies (DUS). (a–c) First DUS, May 2016:80% hypoechogenic stenosis of the ostial left internal carotid artery (LICA) with irregular morphology and "fluffy" components. Peak systolic velocity (PSV) 238.7 cm/s. (d) DUS November 2016: fibrotic atheroma with 40% ostial LICA and 85% mid LICA stenosis, absence of fluffy components; PSV 292 cm/s. (e, f) DUS April 2017:70% mid LICA fibrocalcific stenosis; PSV 229 cm/s. (g) DUS December 2017: <70% mid LICA fibrocalcific stenosis; PSV 200 cm/s. (h,i). DUS November 2019:60% mid LICA fibrocalcific stenosis; PSV 180 cm/s

Received: 21 March 2021 | Revised: 6 April 2021 | Accepted: 16 April 2021
DOI: 10.1002/ccd.29743

ORIGINAL STUDIES

WILEY

CARotid plaqUe StabilizatiOn and regression with evolocumab: Rationale and design of the CARUSO study

Tiziana Claudia Aranzulla MD, MSc[1] | Salvatore Piazza MD[2] |
Andrea Ricotti PhD, PharmD[3] | Giuseppe Musumeci MD[4] | Andrea Gaggiano MD[2]

The CARUSO Study
CARotid plaqUe StabilizatiOn and regression with evolocumab

Asymptomatic patients (n=100) with ≥50% carotid stenosis (DUS and/or MRI or CT)
± cardiovascular risk factors

↓

Baseline LDL-C ≥ 100 mg/dL (despite ongoing lipid lowering therapy)

↙ ↘

Evolocumab 140 mg sc every 2 weeks (n=50) | No additional treatment (n=50)

↓

At 6 and 12 month-follow-up:
Clinical visit
DUS ± MRI or CT
LDL-C

Primary end-point:
Morphological stabilization of the carotid plaque(s) at 6 months
and/or
Carotid plaque(s) regression at 12 months

Puntos clave

- La caracterización de la placa de ateroma más allá del grado de estenosis ayuda a definir el riesgo de nuestros pacientes.
- Las técnicas ecográficas son útiles en el análisis cualitativo y cuantitativo de la placa de ateroma.
- Diferentes fármacos, en especial los hipolipemiantes, son capaces de modificar y estabilizar las placas de ateroma.
- Los datos en patología carotídea son escasos aún para algunos de los grupos terapéuticos.

We aim to evaluate plaque composition on patients with previous vascular disease under PCSK9i treatment.

Hypothesis: greater LDL control with PCSK9i may lead to more stable plaques and high GSM.

METHODS

Cohorts study

Patients on secondary prevention for vascular events.

Group 1: Statin treatment for at least 6 months

Group 2: PCSK9-i for at least 6 months +/- statins

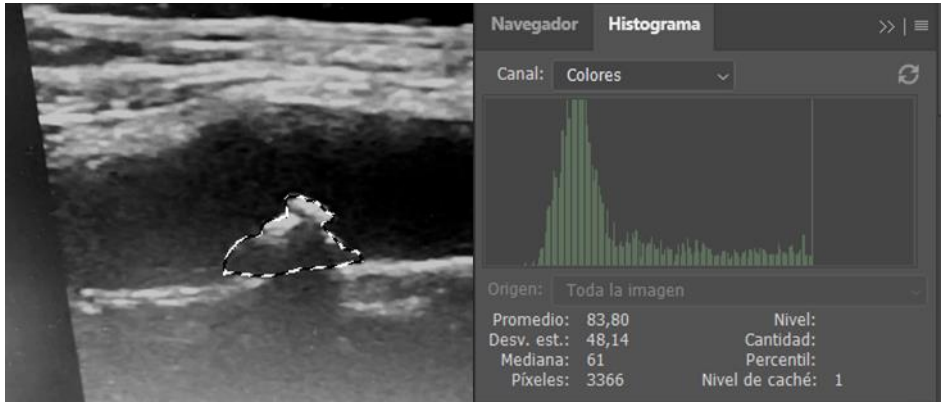
Demographic, clinic, imaging characteristics and LDL values were compared between groups.

US protocol.

- GE Logic Q6. 7Hz linear probe. B-mode imaging
- Color-coded image to avoid underevaluation of hipoechoic plaques.
- Velocimetry to evaluate stenosis.

Image postprocesing for GSM measure.

- Adobe Photoshop
- Standarization of imagen to 0-195 grey scale
- Automatic GSM calculation



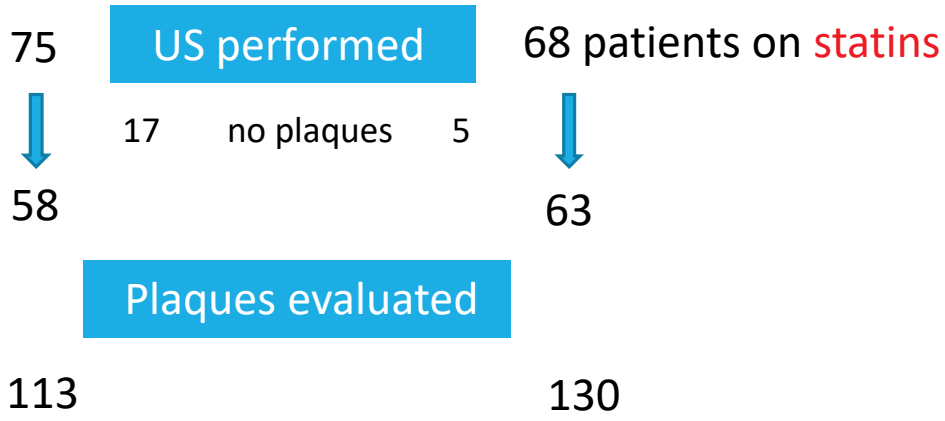
RESULTS.

Sample, clinical profile and demographics

116 Patients on iPCSK9

23 excluded
- 15 primary prevention
- 2 lost to follow up
- 4 discontinued treatment
- 2 death

93 eligible patients



	PCSK9i (75)	Statins (68)	p
Age (media, SD)	64,87 (8,38)	72,99 (10,57)	**0,000**
Sex (male, %)	56 (74,7)	49 (72,1)	0,724
Hypertension, n (%)	60 (80)	53 (77.9)	0,763
DM, n (%)	21 (28)	31 (45.6)	**0,029**
Current smoker, n (%)	38 (50,7)	19 (27,9)	**0,006**
Ischemic cardiopathy, n (%)	66 (88)	33 (48,5)	**0,000**
Ischemic stroke, n (%)	14 (18,7)	32 (47,1)	**0,000**
Peripheral Arteriopathy, n (%)	6 (8)	11 (16,2)	0,131

Treatment

	iPCSK9 (75)	Statin (68)	p
PCSK9i, n (%)	Alirocumab 38 (50,7) Evolocumab 37 (49,3)	-	
Statin, n (%)	No statin, 33 (44) Atorvastatin, 33 (44) Rosuvastatin, 9 (12)	Atorvastatin, 42 (61,7) Rosuvastatin, 17 (25) Simvastatin, 6 (8,8) Other, 3 (4,4)	
Intensive statin dose	32 (42,6)	35 (51.4)	0,428
Ezetimibe, n (%)	44 (58,7)	28 (41,2)	0,037

	iPCSK9	Statins	p
LDL (mg/dl) Media, SD	45,74 (22,2)	82 (41,3)	<0,001

Ecographic results

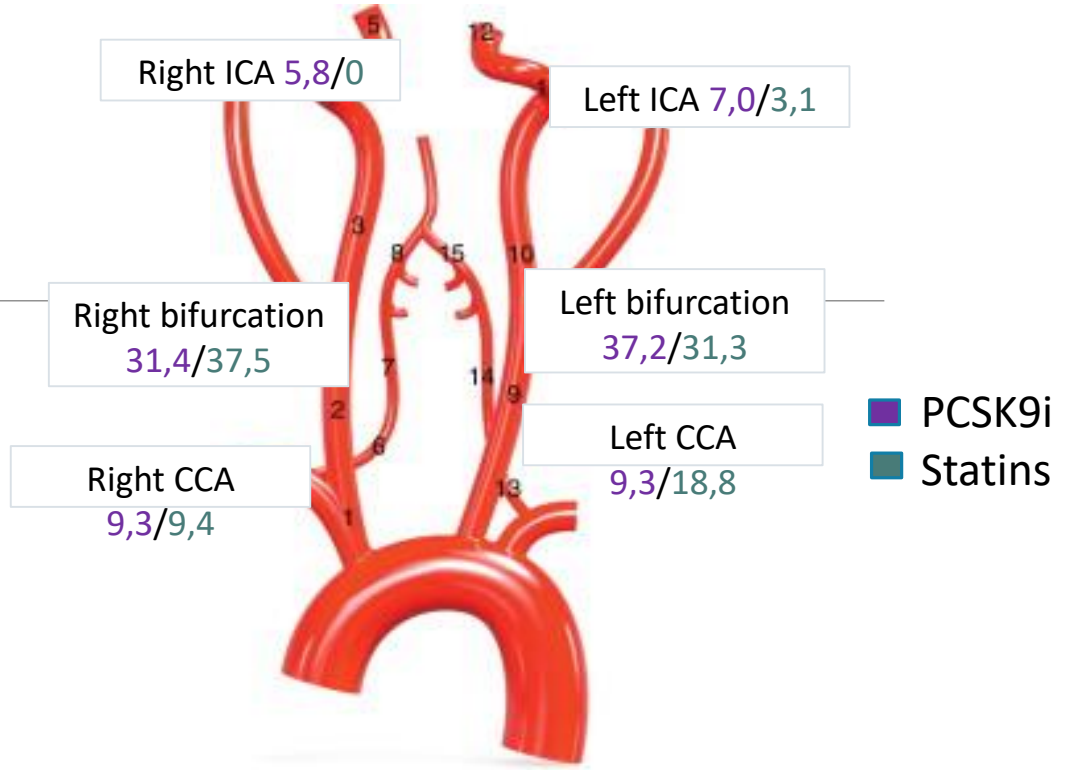
243 plaques evaluated

- 113 PCSK9i
- 130 Statin

Mean number of plaques per patient 1,95 (0,98) vs 2,08 (0,98), p 0,461

Stenosis 50-69 % 2,3% PCSK9i vs 9,4% statins, p 0,122

	PCSK9i (113)	Statin (130)	p
Irregular surface, %	22,1	19,2	ns
Heterogeneus texture, %	28,3	20,8	ns
>50% stenosis, %	1,8	8,3	**0,022**



Localization of plaques evaluated for both groups (%)

	PCSK9i (113)	Statin (130)	p
GSM, media (SD)	72,78 (36,87)	75 (35,17)	0,645
	PCSK9i monotherapy (64)	**PCSK9i plus statin (39)**	
GSM, media (SD)	64,87 (35.41)	**85,76 (35.95)**	**0,005**
	Statin monotherapy (130)	**PCSK9i plus statin (39)**	
GSM, media (SD)	75,31 (35.35)	85,76 (35.95)	0,112

CONCLUSIONS

- This is the first US study to quantify carotid plaque stability for patients on PCSK9i.
- PCSK9i patients had greater lipid control.
- Both groups had mainly stable plaques, according to qualitative evaluation, with no significant differences on GSM values.
- We found higher GSM values for those patients on double therapy.

Larger samples are needed and may reproduce our results and even achieve statistical power.

We aim to perform prospective multicentric analysis. SCODCAiPCSK9.

Estudio colaborativo multicéntrico. Efecto de los iPCSK9 en la ateromatosis carotidea.

Nuestra hipótesis incluye que existirían cambios en la composición de la placa de ateroma valorables mediante estudio ecográfico en los pacientes con patología vascular en los que se administra durante al menos 6 meses tratamiento con iPCSK9.

OBJETIVOS:

Evaluar los cambios de las placas de ateroma carotídea medido por GSM en pacientes con alto riesgo vascular en tratamiento hipolipemiante con i PCSK9 tras seis meses de tratamiento.

Secundarios:

- Correlacionar valores de GSM con LDL colesterol en sangre.
- Valorar si pacientes con GSM mayor (placas más estables) tiene menor incidencia de eventos vasculares durante el tiempo en tratamiento.

Pacientes y métodos:

Tamaño muestral: teniendo en cuenta cambios de GSM de 34 de media (DE 5,29) en pacientes en tto con atorvastatina 80 mg a los seis meses, el número para una potencia del 90% sería sólo de 3 pacientes. Valorando cambio de GSM de 7 puntos en nuestro estudio previo, entre fármacos, precisaríamos un mínimo de 15 pacientes.

Hemos decidido incluir **25 pacientes consecutivos o los posibles en un año, el número mayor.**

Pacientes en los que se decide por evaluación del clínico responsable inicio de iPCSK9.

Dos visitas: basal y a los seis meses

- DTSA: GIM, velocimetría, características cualitativas de las placas
- LDL colesterol
- Eventos vasculares en los seis meses de seguimiento

- Postprocesamiento de las placas con cálculo de GSM (HU Infanta Sofia)

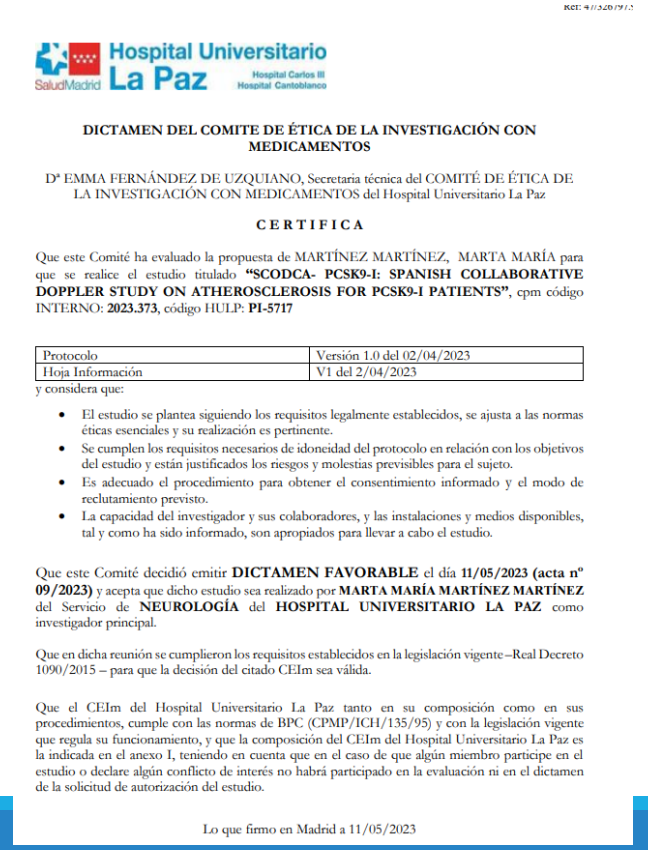
Estudio colaborativo multicéntrico. Efecto de los iPCSK9 en la ateromatosis carotidea.

Contacto: Marta M Martinez Martinez, IP.

mmmartinez.hulp@salud.madrid.org

Hospital Universitario Infanta Sofía

Protocolo de investigación validado CEIM IdiPaz



Hospital Universitario La Paz
Hospital Carlos III
Hospital Cantoblanco

DICTAMEN DEL COMITE DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS

Dª EMMA FERNÁNDEZ DE UZQUIANO, Secretaria técnica del COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS del Hospital Universitario La Paz

C E R T I F I C A

Que este Comité ha evaluado la propuesta de MARTÍNEZ MARTÍNEZ, MARTA MARÍA para que se realice el estudio titulado **"SCODCA- PCSK9-I: SPANISH COLLABORATIVE DOPPLER STUDY ON ATHEROSCLEROSIS FOR PCSK9-I PATIENTS"**, cpm código INTERNO: **2023.373**, código HULP: **PI-5717**

Protocolo	Versión 1.0 del 02/04/2023
Hoja Información	V1 del 2/04/2023

y considera que:

- El estudio se plantea siguiendo los requisitos legalmente establecidos, se ajusta a las normas éticas esenciales y su realización es pertinente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- Es adecuado el procedimiento para obtener el consentimiento informado y el modo de reclutamiento previsto.
- La capacidad del investigador y sus colaboradores, y las instalaciones y medios disponibles, tal y como ha sido informado, son apropiados para llevar a cabo el estudio.

Que este Comité decidió emitir **DICTAMEN FAVORABLE** el día **11/05/2023 (acta nº 09/2023)** y acepta que dicho estudio sea realizado por **MARTA MARÍA MARTÍNEZ MARTÍNEZ** del Servicio de **NEUROLOGÍA** del **HOSPITAL UNIVERSITARIO LA PAZ** como investigador principal.

Que en dicha reunión se cumplieron los requisitos establecidos en la legislación vigente –Real Decreto 1090/2015 – para que la decisión del citado CEIm sea válida.

Que el CEIm del Hospital Universitario La Paz tanto en su composición como en sus procedimientos, cumple con las normas de BPC (CPMP/ICH/135/95) y con la legislación vigente que regula su funcionamiento, y que la composición del CEIm del Hospital Universitario La Paz es la indicada en el anexo I, teniendo en cuenta que en el caso de que algún miembro participe en el estudio o declare algún conflicto de interés no habrá participado en la evaluación ni en el dictamen de la solicitud de autorización del estudio.

Lo que firmo en Madrid a 11/05/2023