¿HASTA DÓNDE BAJAR EL LDL?

¿SON IMPORTANTES LOS TRIGLICÉRIDOS?

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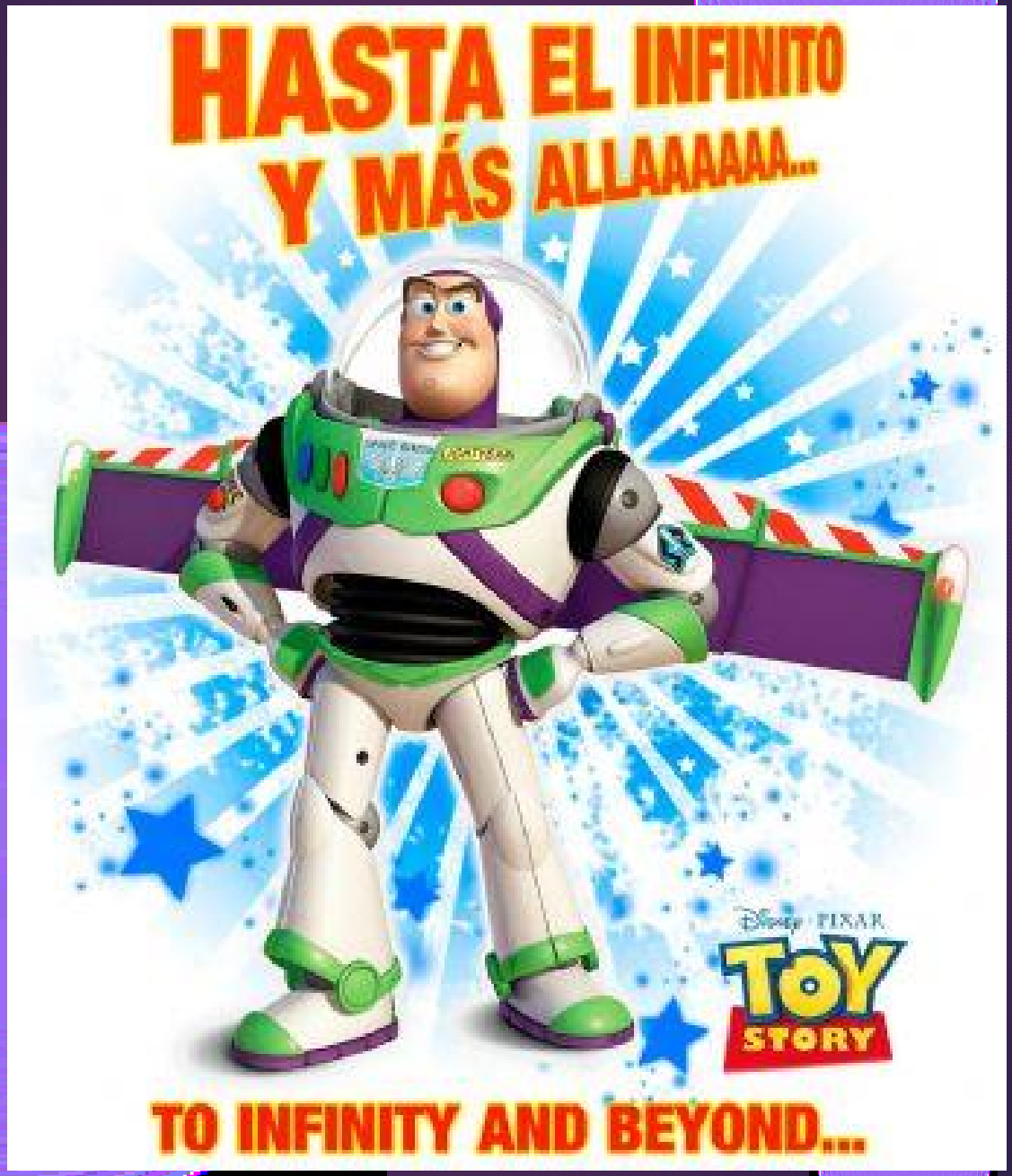
Donostia 18.05.2017

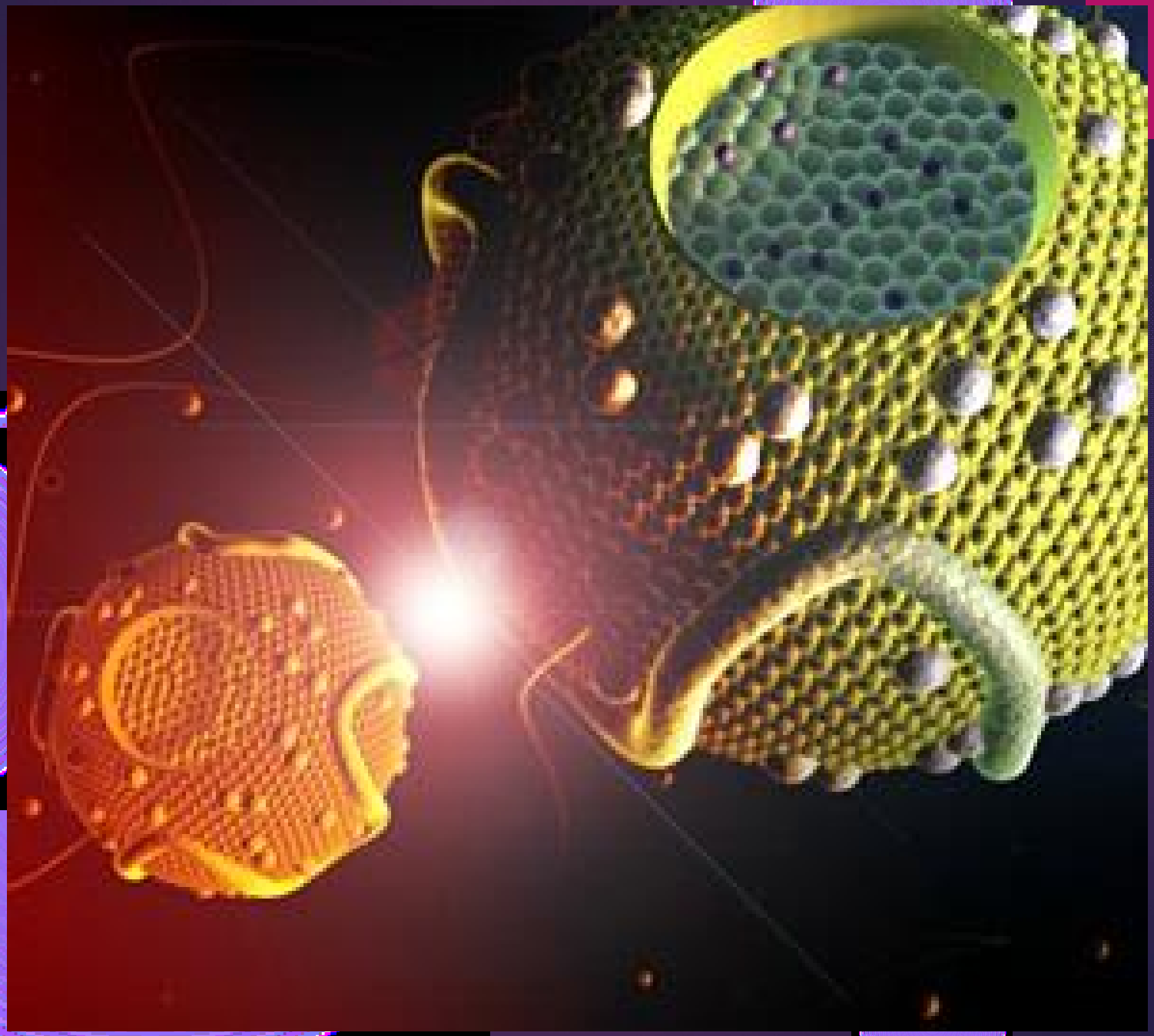
https://www.dropbox.com/sh/5j0lkwv3tkprj92/AABtVTppaPkVu80iE59ROXHwa?dl=0

¿HASTA DÓNDE BAJAR EL LDL?

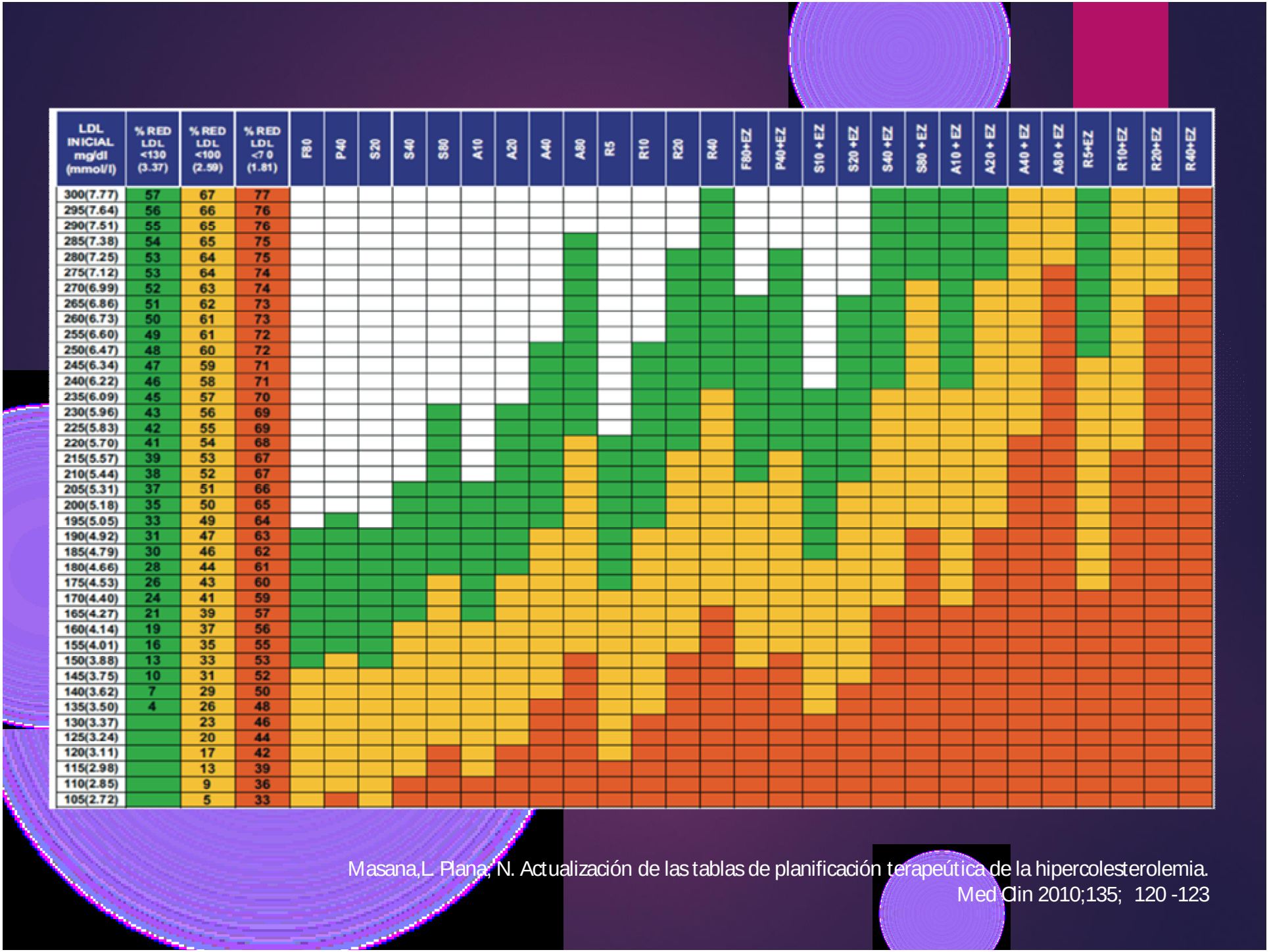

HASTA EL INFINITO
Y MÁS ALLAAAAAA...
TOY STORY
TO INFINITY AND BEYOND...

¿SON IMPORTANTES LOS TRIGLICÉRIDOS?


CLARO QUE SÍ
GUAPI

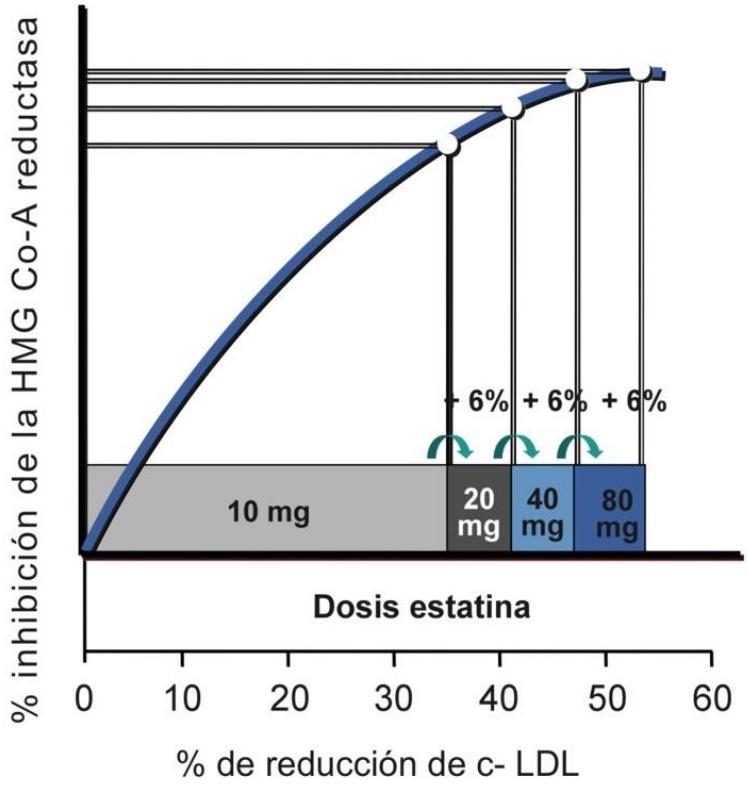


	LDL	HDL	Triglicéridos
Estatinas	↓↓↓	↑ / ↔	↓
Ezetimibe	↓	↓ / ↔	↓ / ↔
Omega 3	↓	↑	↓↓↓
Fibratos	↓	↑	↓↓↓
Resinas	↓	↔	↔
Nicotínico	↓	↑	↓↓



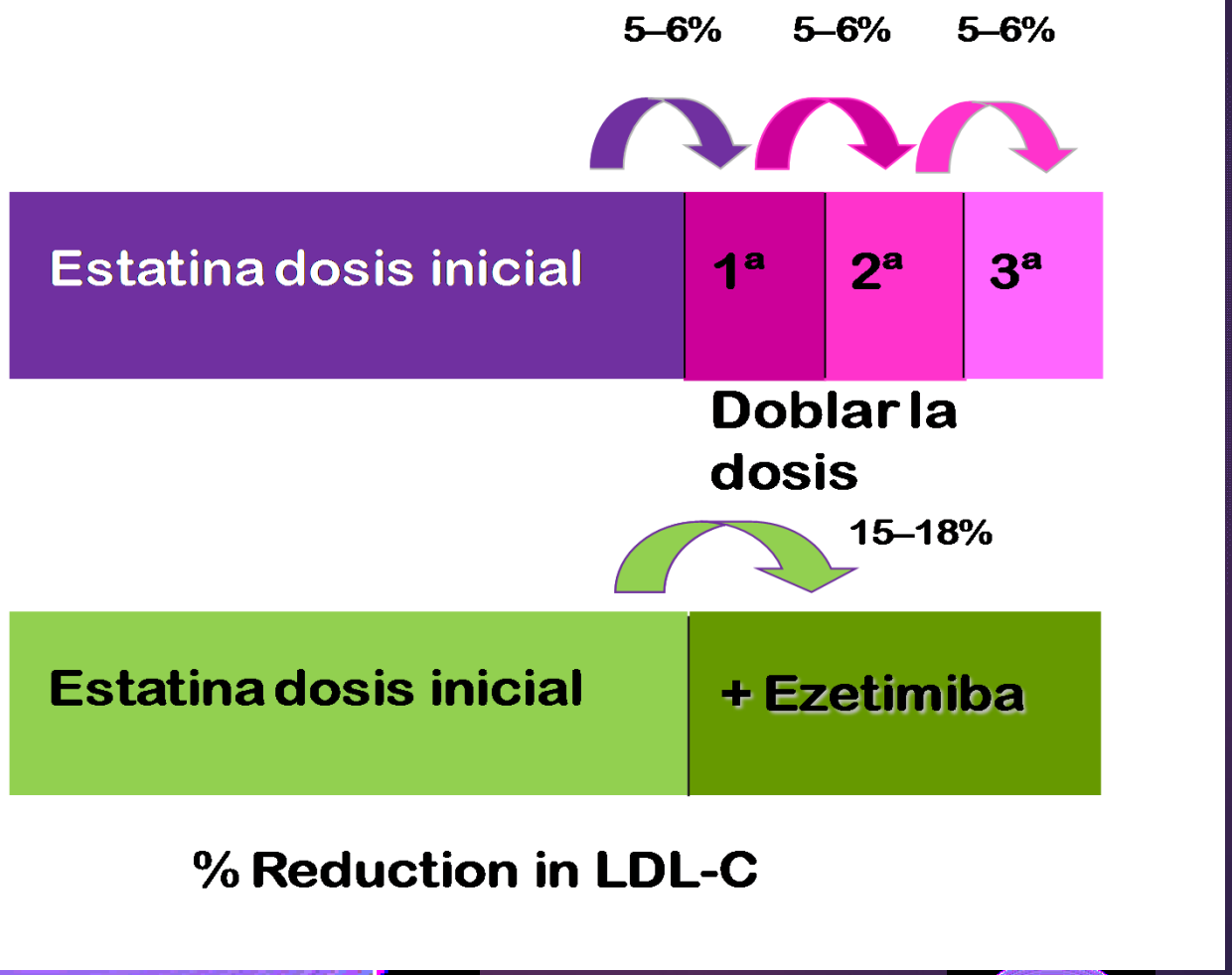
Masana,L. Plana, N. Actualización de las tablas de planificación terapeútica de la hipercolesterolemia. Med Clin 2010;135; 120 -123

DOSIS INICIAL Y POSTERIORES DE ESTATINAS

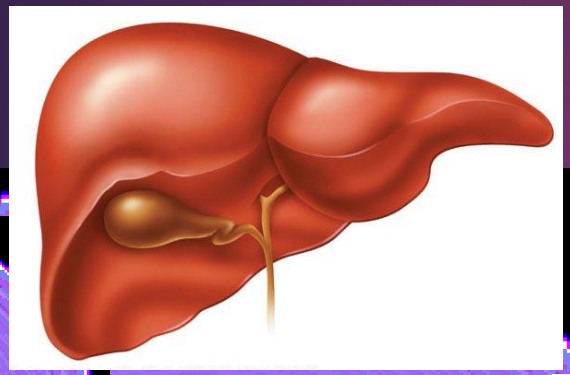


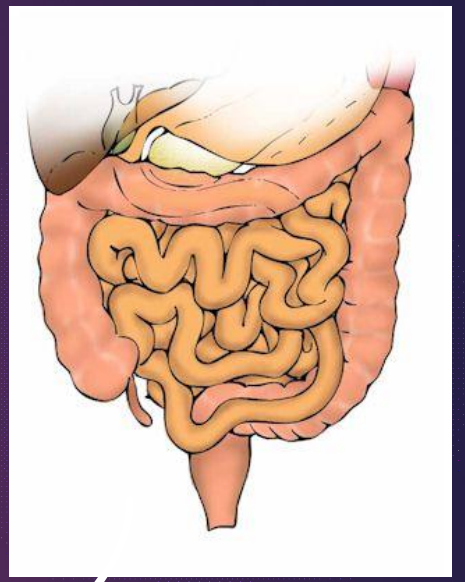
Elaboración propia del Dr. FJ García-Norro Herreros.

Acción porcentual sobre la reducción de LDL-C al aumentar la dosis de estatinas o asociar con ezetimiba



FUENTES DE COLESTEROL





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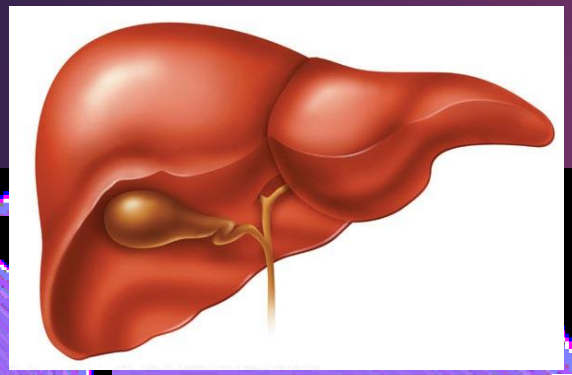
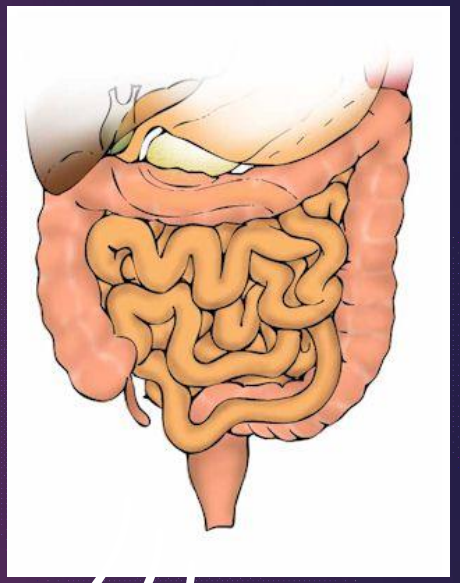
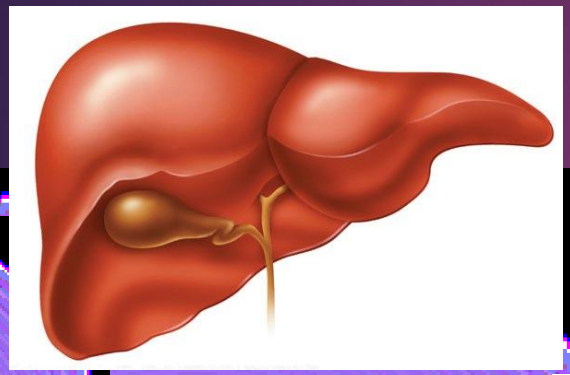
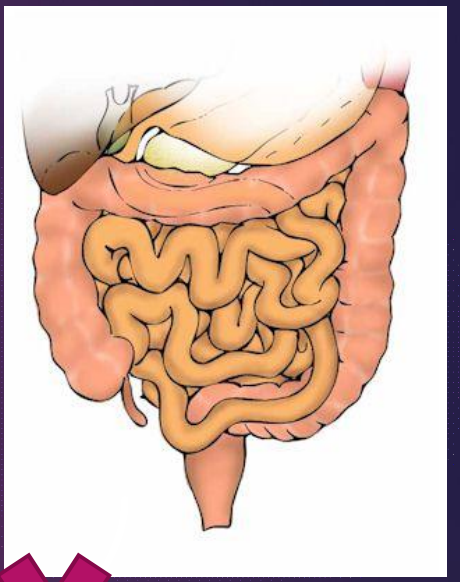


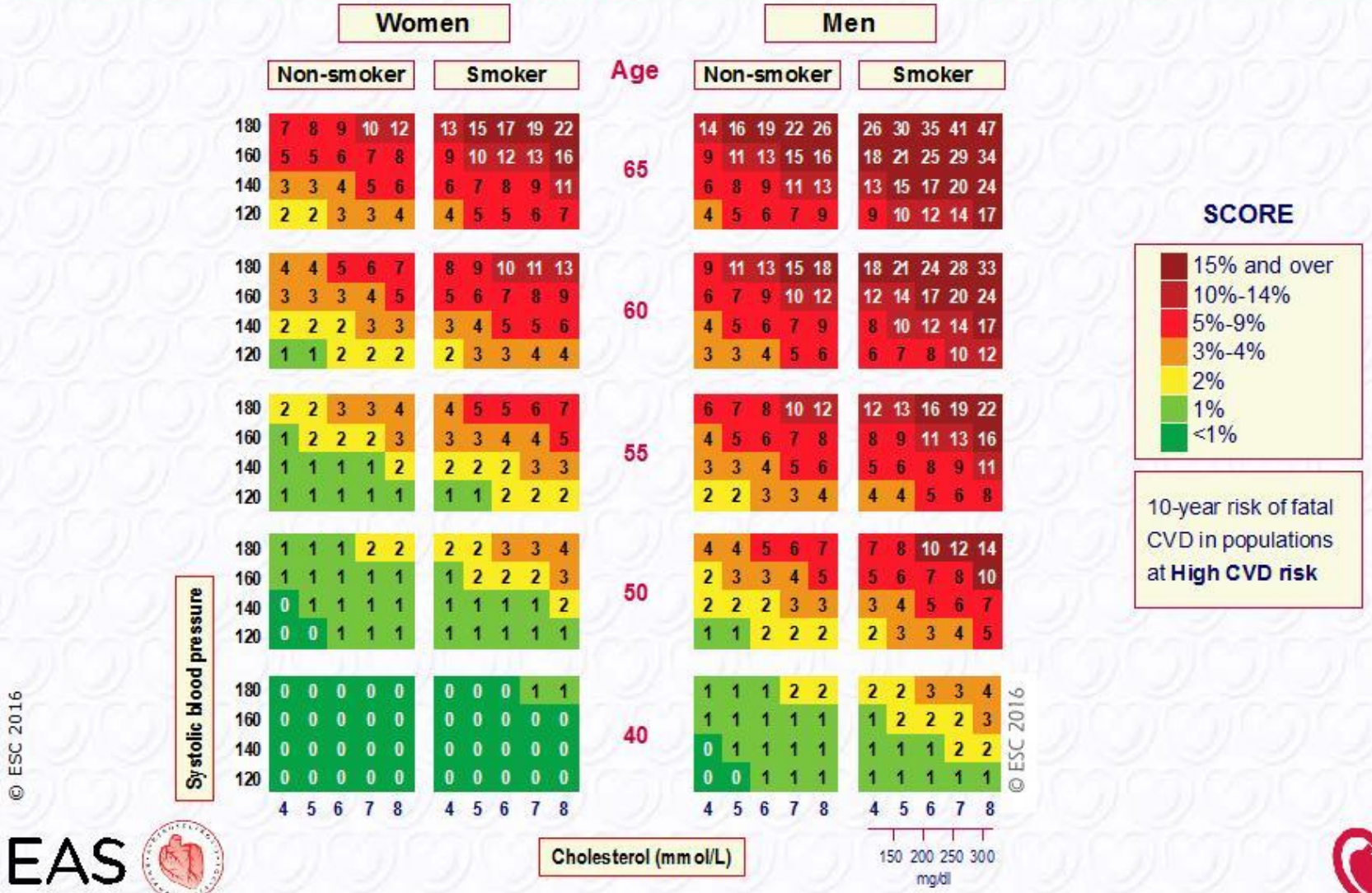


FUENTES DE COLESTEROL





SCORE chart: 10-year risk fatal cardiovascular disease (CVD) in population at high CVD risk



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European Heart Journal 2016; 37:2999–3058 - doi:10.1093/eurheartj/ehv272
Atherosclerosis 253 (2016) 281-344-d oi:10.1016/j.atherosderosis.2016.08.018

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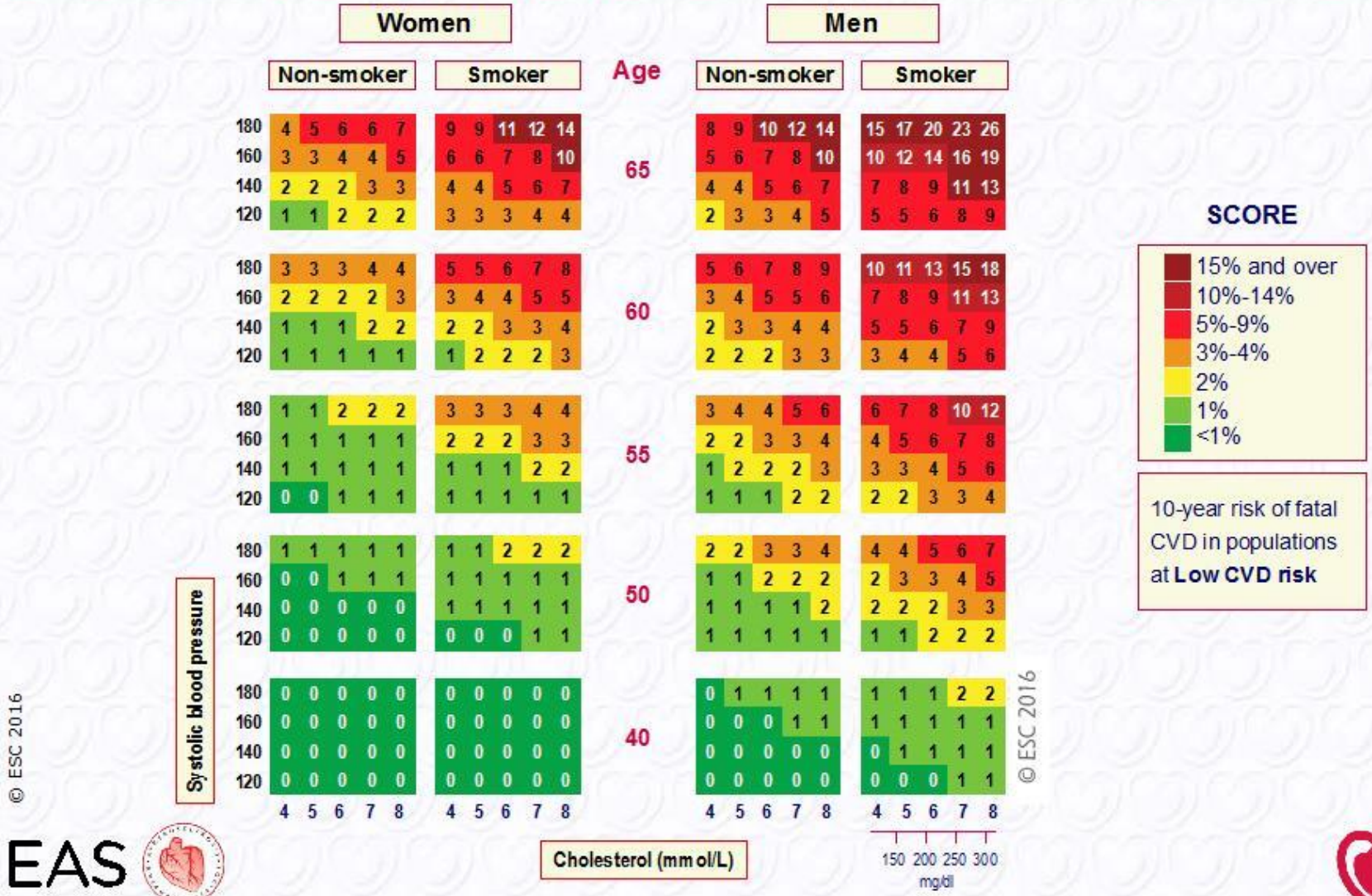
SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in population at low CVD risk



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Factors modifying SCORE risks

Social deprivation–the origin of many of the causes of CVD.
Obesity and central obesity as measured by the body mass index and waist circumference respectively.
Physical inactivity.
Psychosocial stress including vital exhaustion.
Family history of premature CVD (men: <55 years; women: <60 years).
Autoimmune and other inflammatory disorders.
Major psychiatric disorders.
Treatment for human immunodeficiency virus (HIV) infection.
Atrial fibrillation.
Left ventricular hypertrophy.
Chronic kidney disease.
Obstructive sleep apnoea syndrome.

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Risk categories (1)

Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE ≤10%.

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Risk categories (2)

High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10%.
Moderate-risk	SCORE is ≥1% and <5% at 10 years. Many middleaged subjects belong to this category.
Low-risk	SCORE <1%.

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Treatment targets and goals for cardiovascular disease prevention (1)

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish.
Physical activity	2.5–5 h moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m^2, waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg.

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Treatment targets and goals for cardiovascular disease prevention (2)

Lipid LDL-C is the primary target	**Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
	High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
	Low to moderate risk: LDL-C <3 mmol/L (115 mg/dL).
	Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively.
	HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk.
	TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<8.6 mmol/L).

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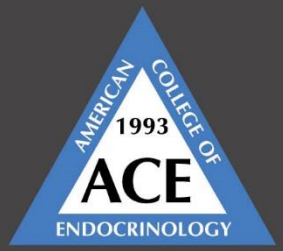
RIESGO	DEFINICION	FRCV	LDL
EXTREMO	- ECV documentada - DM2 con lesión OD - ERC con FG <30 - SCORE	- Stop tabaco - Dieta - Ejercicio (2,5 5 h/sem) - BMI 20 25 - P cintura H: 94 cm M: 80 cm - TA 140/90 - HbA1c < 7% - HDL > 40/48 mg/dl - Tg < 150 mg/dl	70 mg/dl
ALTO	- Un FRCV especialmente alto (CT>310 / HFH) - DM - ERC con FG 30 -59 - SCORE		100 mg/dl
MODERADO	- SCORE		115 mg/dl
BAJO	- SCORE < 1		115 mg/dl



AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2017

TASK FORCE

Alan J. Garber, MD, PhD, FACE, *Chair*

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 DOI 10.4158/EP161682.CS

RIESGO	DEFINICION	FRCV	LDL
EXTREMO	- ECV documentada - DM2 con lesión OD - ERC con FG <30 - SCORE	- Stop tabaco - Dieta - Ejercicio (2,5 5 h/sem) - BMI 20 25 - P cintura H: 94 cm M: 80 cm - TA 140/90 - HbA1c < 7% - HDL > 40/48 mg/dl - Tg < 150 mg/dl	70 mg/dl 55
ALTO	- Un FRCV especialmente alto (CT>310 / HFH) - DM - ERC con FG 30 -59 - SCORE		100 mg/dl 70
MODERADO	- SCORE		115 mg/dl 100
BAJO	- SCORE < 1		115 mg/dl

¡¡¡¡¡ IMPORTANTE !!!!!

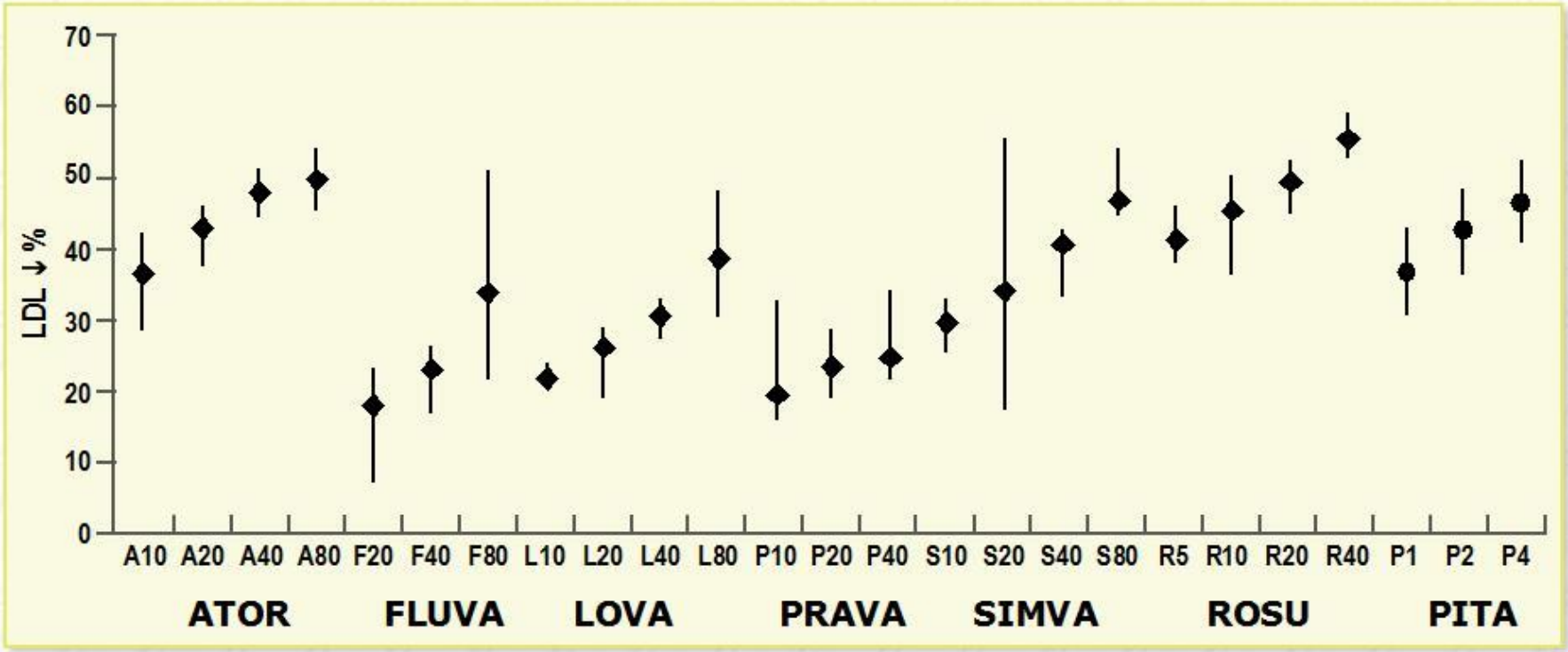
Realizar al menos dos determinaciones de perfil lipídico
- > 1 semana
- < 3 meses

Realizar incluso una tercera determinación si hay variaciones
- > 25% para colesterol total
- > 65% para triglicéridos

DESCARTAR UNA DISLIPEMIA SECUNDARIA

- Diabetes mellitus
- Obesidad
- Hipotiroidismo
- Alcohol
- Anticonceptivos orales
- Fármacos: tiazidas, betabloqueantes, corticoides,..
- Insuficiencia renal crónica
- Insuficiencia hepática
- Enfermedades sistémicas (conectivopatías, LES,

A systematic review and meta-analysis of the therapeutic equivalence of statins



Weng TC, et al. *J Clin Pharm Ther.* 2010;35;139-151
Mukhtar RY, et al. *Int J Clin Pract.* 2005;59(2):239-252

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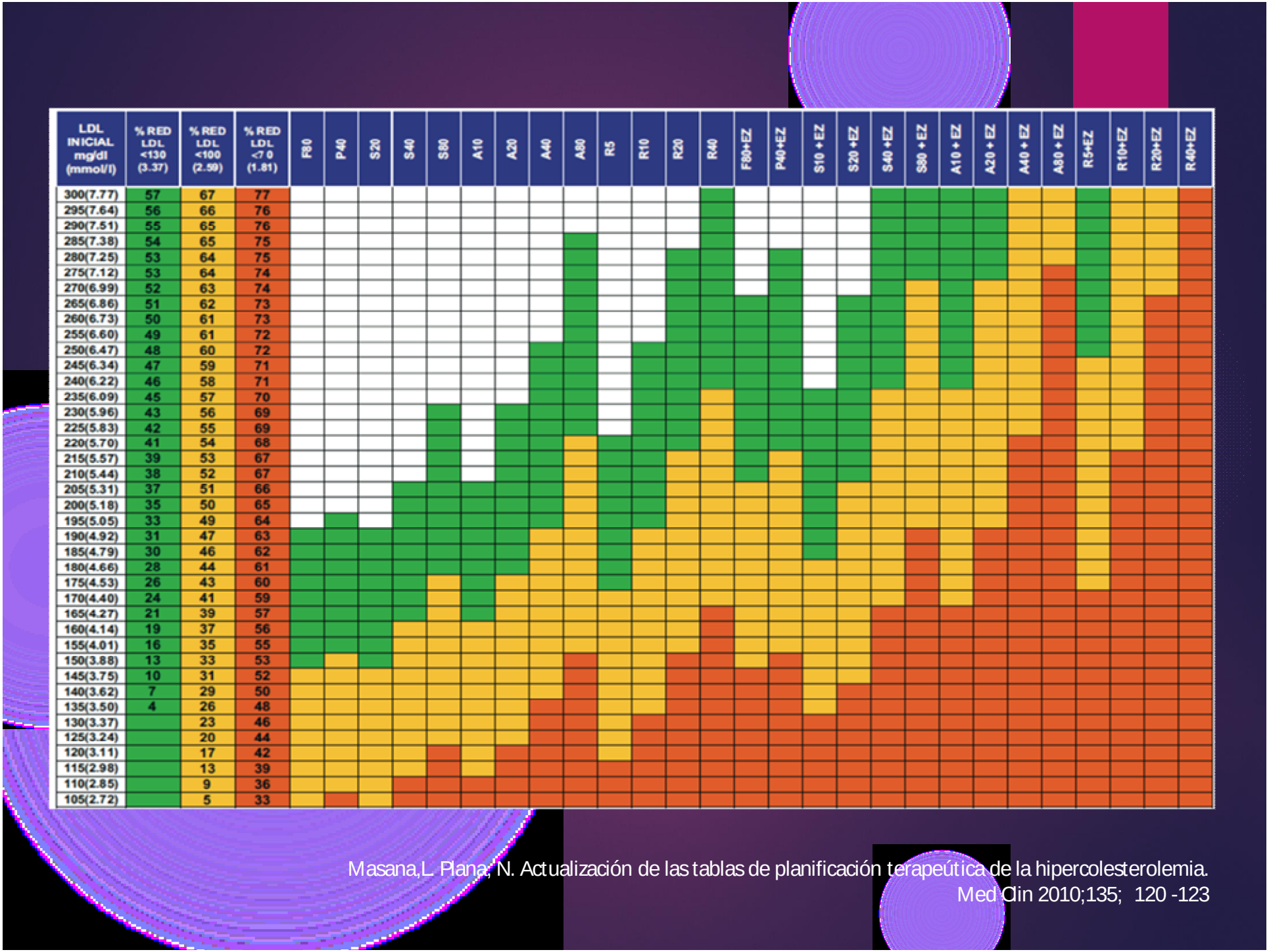
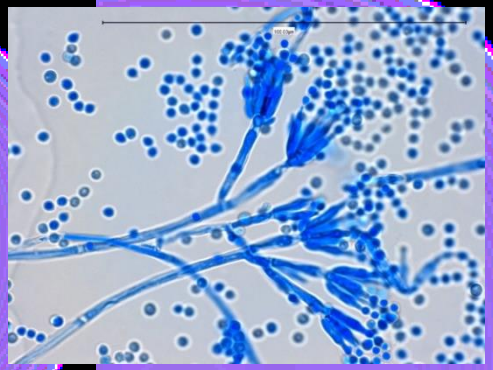
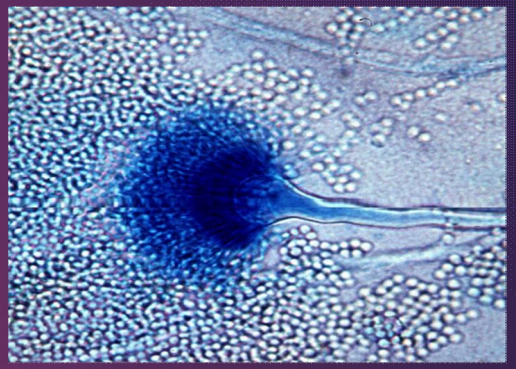


Masana,L. Plana, N. Actualización de las tablas de planificación terapeútica de la hipercolesterolemia. Med Clin 2010;135; 120 -123

1971



Penicillium citrinum
Mevastatina



Aspergillus terreus
Lovastatina

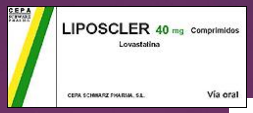

MSD
Tredaptive


Simvastatina CUVE
20 mg comprimidos recubiertos EFG
VÍA ORAL
28 comprimidos recubiertos
pérezgiménez


Lovastatina MYLAN 20 mg
comprimidos EFG
Mylan


Mevacor® 10 mg
Mevacor® 20 mg


Pritadol
(Pravastatina)
10 mg
Comprimidos
Vía oral


LIPOSCLER 40 mg Comprimidos
Lovastatina
Vía oral


ZARATOR 10 mg


Gemfibrozilo
600 mg


Zocor 10 mg


secalip 145mg


LOPID® 600 mg
Comprimidos recubiertos


Prareduct® 20 mg


Alipza 1mg
Alipza 2mg
Alipza 4mg


digaril prolib


NOVARTIS
LESCOL
Fluvastatin
40 mg


Resincolestiramina


EZETROL
10mg Comprimidos


Praluent
alirocumab
75 mg/mL


CRESTOR
10 mg
Tablets
rosuvastatin


CARDYL® 10 mg
ATORVASTINA
Comprimidos
Vía oral


INEGY


OMACOR


Cholestagel


Vaditon Prolib


PRAVAFENIX

ADVANCE

Action to Control Cardiovascular Risk in Diabetes

ACCORD

VADT

PRINCIPALES ESTUDIOS DE ESTATINAS EN CARDIOPATIA ISQUÉMICA

PREV. PRIMARIA
- WOSCOPS
- AFCAPS/Tex CAPS
- ASCOT-LLA
- ALLHAT LLT
- CARDS
- ASPEN
- MEGA
- JUPITER

PREV. SECUNDARIA
- 4S
- CARE
- LIPID
- GREACE
- TNT
- AVERT
- IDEAL

SÍNDROME CORONARIO AGUDO
- MIRACL
- PROVE IT-TIMI 22
- A to Z (2004)
- STATIN STEMI
- ARMYDA-ACS
- ARMYDA-RECAPTURE

Goals

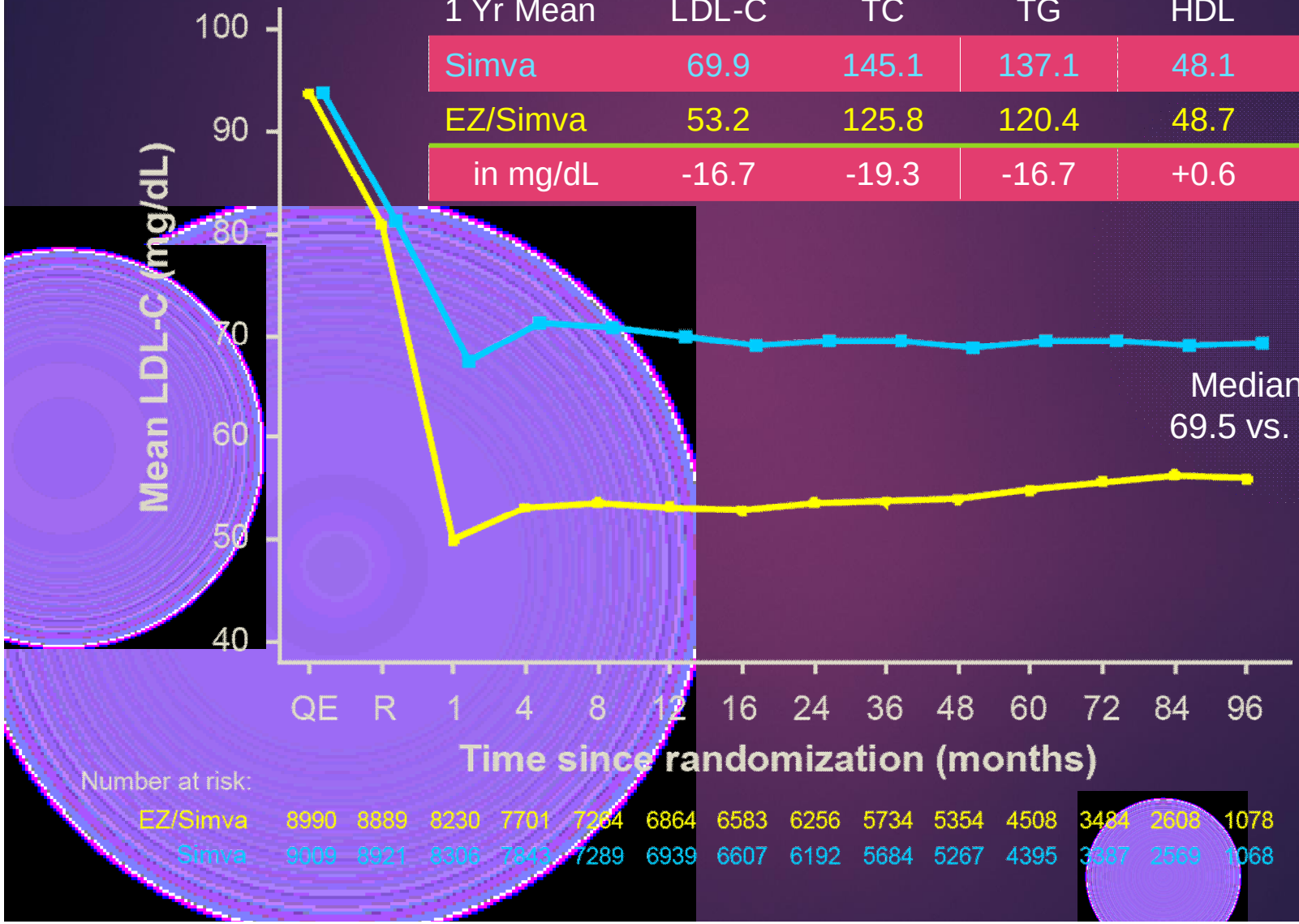
- IMPROVE-IT: First large trial evaluating clinical efficacy of combination EZ/Simva vs. simvastatin (i.e., the addition of ezetimibe to statin therapy):
  - Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?
  - "Is (Even) Lower (Even) Better?" (estimated mean LDL-C ~50 vs. 65mg/dL)
  - Safety of ezetimibe

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

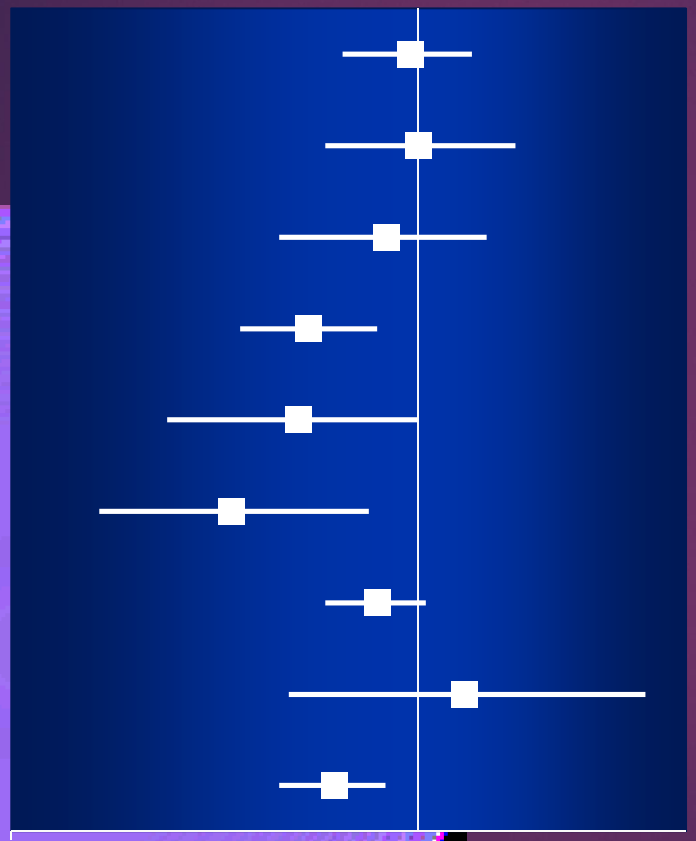
LDL-C and Lipid Changes

IMPROVE-IT

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



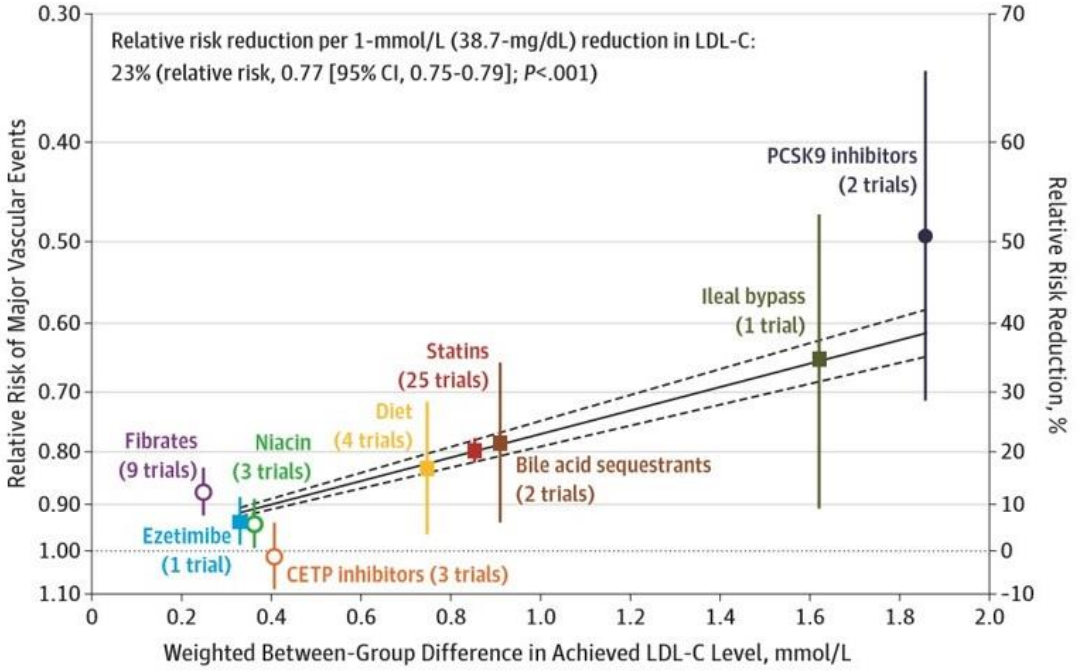
Individual Cardiovascular Endpoints and CVD/MI/Stroke



	HR	Simva*	EZ/Simva*	p-value
All-cause death	0.99	15.3	15.4	0.782
CVD	1.00	6.8	6.9	0.997
CHD	0.96	5.8	5.7	0.499
MI	0.87	14.8	13.1	0.002
Stroke	0.86	4.8	4.2	0.052
Ischemic stroke	0.79	4.1	3.4	0.008
Cor revasc	0.95	23.4	21.8	0.107
UA	1.06	1.9	2.1	0.618
CVD/MI/stroke	0.90	22.2	20.4	0.003

*7-year event rates (%)

Figure 3. Weighted Between-Group Difference in Achieved Low-Density Lipoprotein Cholesterol (LDL-C) Level and Relative Risk for Major Vascular Events for Each Class of Intervention



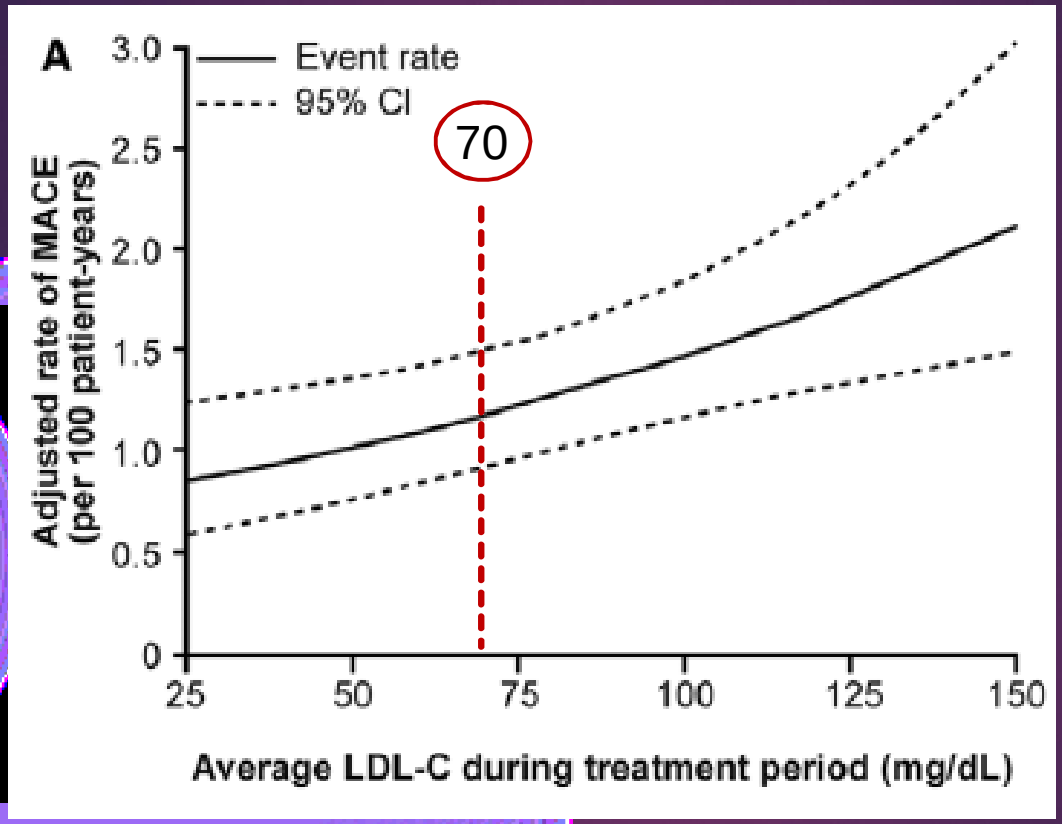
LDLc 38,7mg/dL

RRR 23%

La combinación de los datos de los 33 ensayos generó la línea de metarregresión (RR previsto de acontecimientos vasculares mayores para diferentes niveles de reducción del cLDL), en la cual cada reducción de 1 mmol/L en el cLDL se asoció a un RR de 0,77 (IC 95%, 0,75-0,79) de acontecimientos vasculares mayores

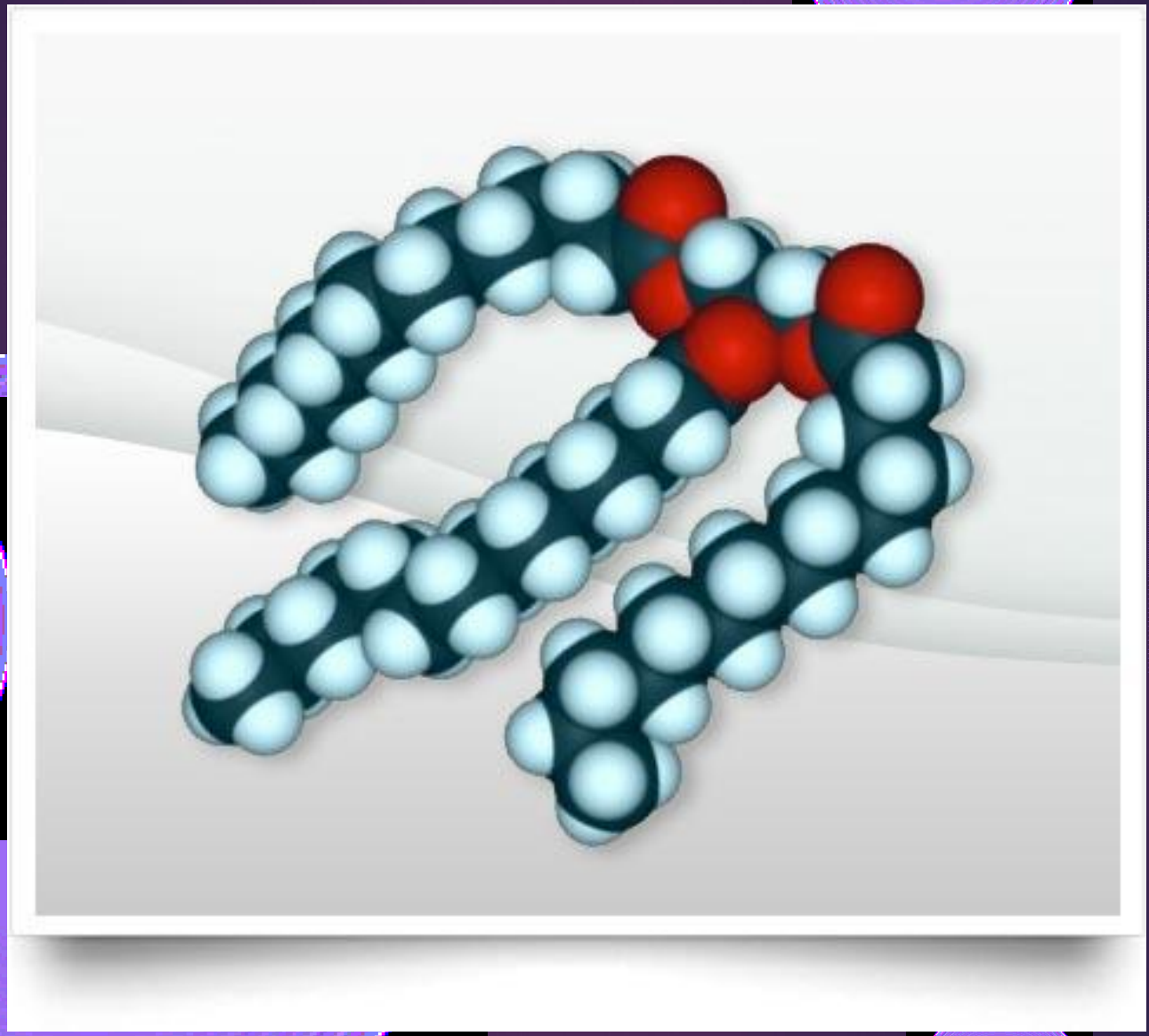
Tasas de MACE ajustadas según los niveles alcanzados de LDLc

Multivariate Analysis Adjusted on Baseline Characteristics; Pool of Phase 3 Trials



39 mg/dL lower LDL-C
MACE 24% lower
(HR 0.76, 95% CI: 0.63
0.91)

- For every additional 39 mg/dL lower LDL-C achieved with either alirocumab or ezetimibe (on top of maximally tolerated statins in most patients), there was a further 24% lower risk of MACE (HR 0.76, 95% CI: 0.63 0.91).




blah, bla, blah,
bla, blah, bla,
blah, bla, blah,
bla, blah, bla,

¿Triglicéridos?

Possible causes of hypertriglyceridaemia (1)

Genetic predisposition.
Obesity.
Type 2 diabetes.
Alcohol consumption.
Diet high in simple carbohydrates.
Renal disease.
Hypothyroidism.
Pregnancy (physiological triglyceride concentrations double during the third trimester).

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Possible causes of hypertriglyceridaemia (2)

Paraproteinaemia and auto-immune disorders such as systemic lupus erythematosus.

Multiple medications including:

- Corticosteroids.
- Oestrogens, especially those taken orally.
- Tamoxifen.
- Antihypertensives: adrenergic beta-blocking agents (to a different degree), thiazides.
- Isotretinoin.
- Bile acid-binding resins.
- Ciclosporin.
- Antiretroviral regimens (protease inhibitors).
- Psychotropic medications: phenothiazines, second generation antipsychotics.

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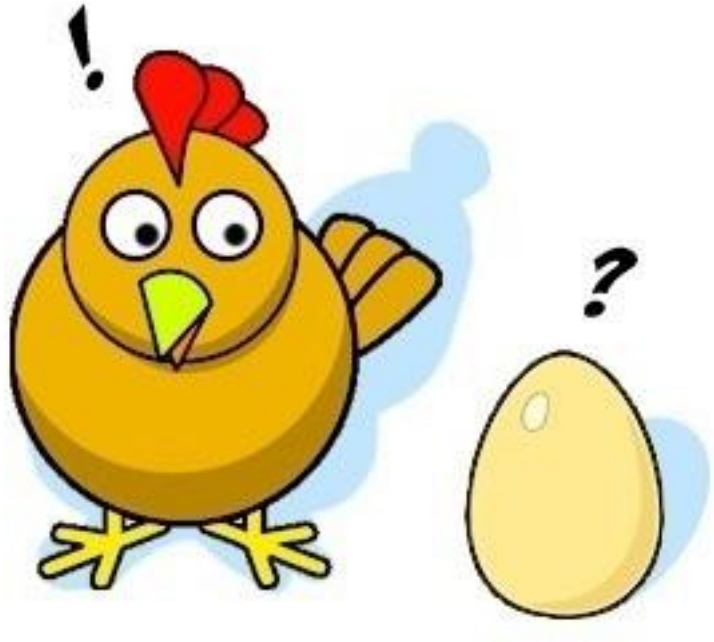
Drug treatments of hypertriglyceridaemia

Recommendations	Class	Level
Drug treatment should be considered in high-risk patients with TG >2.3 mmol/L (200 mg/dL).	IIa	B
Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia.	IIb	B
In high-risk patients with TG >2.3 mmol/L (200 mg/dL) despite statin treatment, fenofibrate may be considered in combination with statins.	IIb	C

European Heart Journal 2016; 37:2999–3058 - doi:10.1093/eurheartj/ehv272
Atherosclerosis 253 (2016) 281-344-d oi:10.1016/j.atherosderosis.2016.08.018

WHO CAME FIRST?



ARCHIVES OF
INTERNAL MEDICINE

Serum Triglycerides in Coronary Artery Disease

MARGARET J. ALBRINK, M.D., and EVELYN B. MAN, Ph.D., New Haven, Conn.

The identification of cholesterol as a constituent of atheromatous plaques has aroused recurrent waves of suspicion that lipid metabolism is in some way responsible for the development of atherosclerosis and coronary artery disease. Lipids are transported in serum as constituents of three major classes of compounds: cholesterol and its esters, phospholipids, and triglycerides or neutral fat. Most investigations in recent years have centered about the notion that serum cholesterol plays a causative role in the development of coronary artery disease in spite of numerous studies focusing attention on triglycerides. Included in these studies are reports of increased turbidity, increased and prolonged chylomicronemia, and increased ratio of β- to α-lipoproteins. Although triglycerides rather than cholesterol are chiefly responsible for turbidity of serum and constitute an important fraction of β-lipoproteins, the quantitative estimation of triglycerides has been largely neglected in studies of serum lipids in coronary artery disease.

The present research was undertaken to observe the interrelations of the three major serum lipid fractions [1-4]; their interrelations had been studied in certain metabolic disorders in 1943.[5,6] The neglected fraction, triglycerides, appeared to be most frequently elevated in coronary artery disease.[7]

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Presented at the 71st annual meeting of the Association of American Physicians, Atlantic City, N. J., May 6, 1958.

From the Department of Internal Medicine, Yale University School of Medicine, and the Medical Service, the Grace-New Haven Community Hospital.

This investigation was supported (in part) by research Grant H-3498 from the National Heart Institute and research Grant A-392 from the Institute of Arthritis and Metabolic Diseases, Public Health Service.

Materials and Methods

The subjects were 100 patients with a history of a documented myocardial infarction 1 day to 12 years previously, confirmed by electrocardiographic studies and laboratory and clinical findings. The patients were obtained during the past five years from the clinics and inpatient services of the Grace-New Haven Hospital, and we include all patients meeting the above requirements whose physicians requested lipid determinations. The 100 patients, 82 men and 18 women, ranged from 21 to 78 years of age, the greatest number being in the 50's. Eleven were diabetics.

Control subjects consisted of a heterogeneous group of healthy medical school students and personnel, healthy industrial workers, and hospital patients without evidence of focal vascular disease and without known metabolic disorders. Ages ranged from 20 to 78.

Blood was drawn before breakfast, and the serum was analyzed for total fatty acids after hydrolysis, for total cholesterol, and for lipid phosphorus.[8] Triglyceride fatty acids were estimated by subtracting the fatty acids attributed to cholesterol esters and phospholipids from the total fatty acids. Cholesterol-phospholipid ratios were not remarkable.

Normal ranges for cholesterol and triglycerides were established as two standard deviations above

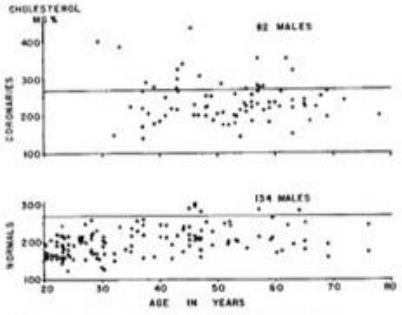

Fig. 1.—Concentration of cholesterol by age in the sera of 82 men, including 9 diabetics, with a history of myocardial infarction (upper graph) and of 134 normal men (lower graph). In each a horizontal line indicates the upper limit of normal, 269 mg. %.

1959

The NEW ENGLAND JOURNAL of MEDICINE

ASSOCIATION BETWEEN MULTIPLE CARDIOVASCULAR RISK FACTORS AND ATHEROSCLEROSIS IN CHILDREN AND YOUNG ADULTS

GERALD S. BERENSON, M.D., SATHANUR R. SRINIVASAN, PH.D., WEIHANG BAO, PH.D., WILLIAM P. NEWMAN III, M.D., RICHARD E. TRACY, M.D., PH.D., AND WENDY A. WATTIGNEY, M.S., FOR THE BOGALUSA HEART STUDY

ABSTRACT

Background In adults, cardiovascular risk factors reinforce each other in their effect on cardiovascular events. However, information is scant on the relation of multiple risk factors to the extent of asymptomatic atherosclerosis in young people.

Methods We performed autopsies on 204 young persons 2 to 39 years of age, who had died from various causes, principally trauma. Data on antemortem risk factors were available for 93 of these persons, who were the focus of this study. We correlated risk factors with the extent of atherosclerosis in the aorta and coronary arteries.

Results The extent of fatty streaks and fibrous plaques in the aorta and coronary arteries increased with age. The association between fatty streaks and fibrous plaques was much stronger in the coronary arteries ($r=0.60$, $P<0.001$) than in the aorta ($r=0.23$, $P=0.03$). Among the cardiovascular risk factors, body-mass index, systolic and diastolic blood pressure, and serum concentrations of total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, as a group, were strongly associated with the extent of lesions in the aorta and coronary arteries (canonical correlation [a measure of the association between groups of variables]: $r=0.70$; $P<0.001$). In addition, cigarette smoking increased the percentage of the intimal surface involved with fibrous plaques in the aorta (1.22 percent in smokers vs. 0.12 percent in nonsmokers, $P=0.02$) and fatty streaks in the coronary vessels (8.27 percent vs. 2.89 percent, $P=0.04$). The effect of multiple risk factors on the extent of atherosclerosis was quite evident. Subjects with 0, 1, 2, and 3 or 4 risk factors had, respectively, 19.1 percent, 30.3 percent, 37.9 percent, and 35.0 percent of the intimal surface covered with fatty streaks in the aorta (P for trend $=0.01$). The comparable figures for the coronary arteries were 1.3 percent, 2.5 percent, 7.9 percent, and 11.0 percent, respectively, for fatty streaks (P for trend $=0.01$) and 0.6 percent, 0.7 percent, 2.4 percent, and 7.2 percent for collagenous fibrous plaques (P for trend $=0.003$).

Conclusions These findings indicate that as the number of cardiovascular risk factors increases, so does the severity of asymptomatic coronary and aortic atherosclerosis in young people. (N Engl J Med 1998;338:1650-6.)

ATHEROSCLEROSIS leading to coronary heart disease is complex in origin. Involved in the pathogenesis of atherosclerosis are hemodynamic, thrombotic, and carbohydrate–lipid metabolic variables, along with intrinsic characteristics of the arterial wall.[1] These physiologic and biochemical factors underlie the clinical events that may eventually occur. Environmental factors such as smoking or a sedentary lifestyle also contribute to this process. The progression of atherosclerotic disease and the increasing severity of atherosclerosis relate not only to the presence and extent of cardiovascular risk factors but also to the persistence of risk factors over time.[2,3] Sudden death may occur in a young person with only a single lesion complicated by a coronary thrombus, without extensive vessel disease. Consequently, the extent of vascular lesions may not be directly related to the occurrence of clinical events, such as myocardial infarction. Morbidity due to coronary artery disease, however, is generally related to the extent of vascular lesions.[4] In this regard, clinical risk factors are considered to be useful in predicting the severity of atherosclerosis.[5]

Epidemiologic studies have established that multiple risk factors increase the probability of cardiovascular events, since cardiovascular risk factors tend to reinforce each other in their influence on morbidity and mortality.[6] Although a specific risk factor influences the risk that a person will have cardiovascular disease, risk factors tend to aggregate and usually appear in combination. Furthermore, since clustering of risk factors is evident in childhood and persists into young adulthood,[7-10] the presence of multiple risk factors could indicate the acceleration of atherosclerosis in young people.

Coronary arteriography has contributed considerably to elucidating the relation of the severity of coronary artery disease to cardiovascular risk factors. Unfortunately, assessing the extent of atherosclerotic coronary lesions by this invasive method in asymptomatic young people is not practical, and its

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Clinical Investigation and Reports

Triglyceride Concentration and Ischemic Heart Disease

An Eight-Year Follow-up in the Copenhagen Male Study

Jørgen Jeppesen, MD; Hans Ole Hein, MD; Poul Suadicani, DD; Finn Gyntelberg, MD

Background—The role of triglycerides as a risk factor of ischemic heart disease (IHD) remains controversial. For the present study, we examined the relation between fasting triglycerides and risk of IHD in the Copenhagen Male Study.

Methods and Results—Baseline measurements of fasting lipids and other IHD risk factors were obtained for 2906 white men (age range, 53 to 74 years) who were initially free of overt cardiovascular disease. During an 8-year follow-up period, 229 men had a first IHD event. Crude cumulative incidence rates of IHD were 4.6% for the lowest, 7.7% for the middle, and 11.5% for the highest third of triglyceride levels (P for trend <.001). Compared with the lowest third level and adjusted for age, body mass index, alcohol, smoking, physical activity, hypertension, non–insulin-dependent diabetes mellitus, social class, and LDL and HDL cholesterol, relative risks of IHD (95% confidence interval) were 1.5 (1.0 to 2.3; P=.05) and 2.2 (1.4 to 3.4; P<.001) for the middle and highest third of triglyceride levels, respectively. When triglyceride levels were stratified by HDL cholesterol levels (triglyceride third multiplied by HDL cholesterol third), a clear gradient of risk of IHD was found with increasing triglyceride levels within each level of HDL cholesterol, including high HDL cholesterol level, which are thought to provide protection against IHD.

Conclusions—In middle-aged and elderly white men, a high level of fasting triglycerides is a strong risk factor of IHD independent of other major risk factors, including HDL cholesterol. **(*Circulation*. 1998;97:1029-1036.)**

Key Words: coronary disease ■ lipids ■ lipoproteins ■ risk factors

The role of serum TG as a screening test and a risk factor of IHD remains controversial.[1-3] Although in most epidemiological studies a positive relationship has been found between TG level and the risk of IHD, the usefulness of measuring TG in general screening strategies has been questioned because multivariate analysis control for HDL-C usually eliminates or substantially diminishes the role of TG as a predictor of IHD.[1-3] However, the interpretation of multivariate models that include TG and HDL-C is complex and associated with several problems.[1-3] TG and HDL-C are closely associated both

See p 1027

distinct roles of TG and HDL-C in IHD in standard multivariate analysis.[1-3] In addition, in comparison with HDL-C, the distribution of TG levels is markedly skewed, requiring logarithmic transformation for distribution-dependent analyses such as standard regression analysis, a statistical maneuver that may not provide an appropriate representation of underlying biological processes.[1] Finally, adding to the complexity, some individuals with very high TG levels, such as those with lipoprotein phenotype I or V, appear to have no increased risk of IHD.[4] With these problems kept in mind, the purpose of the present study was to present an analysis of data from the CMS to determine the effect of TG versus that of HDL-C on the risk of IHD.

Methods

Participants

The CMS was started in 1970 as a prospective cardiovascular study.[5,6] The prospective male participants were derived from 14 workplaces in Copenhagen: the air force, army, navy, emergency management agency, postal service, customs service, a railroad company, national bank, a telephone company, three municipal service centers (for electricity and engineering and a fire brigade), a pharmaceutical company, and a building contractor company. All eligible 6125 men were employed and aged 40 to 59 years (mean age, 48 years); a total of 5249 men (87%) participated.

In 1985 through 1986, a new baseline was established, which was used for the present prospective study. All survivors from the 1970 study were traced by means of the Danish Central Population Register. Between June 1985 and June 1986, all survivors (4505 except 34 emigrants) from the original cohort were invited to take part in this study. Three thousand three hundred eighty-seven men (75%) agreed and gave informed consent. Their mean age was 63 years (age range, 53 to 74 years). The study took place at The Glostrup Population Study, Glostrup Hospital, University of Copenhagen (Denmark). Each subject was interviewed by a physician (H.O.H.) regarding a previously completed questionnaire and examined, with height, weight, and blood pressure measurements taken. A venous blood sample was taken after the subjects had fasted for ≥12 hours for the measurement of serum concentrations of lipids.

Criteria of Exclusion

Men who at baseline had a history of acute myocardial infarction, angina pectoris, stroke, or intermittent claudication were excluded

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Correspondence to Dr Jørgen Jeppesen, The Copenhagen Male Study, Epidemiological Research Unit, Copenhagen University Hospital, Bispebjerg, Bispebjerg Bakke 23, DK-2400 Copenhagen NV, Denmark.

The NEW ENGLAND JOURNAL of MEDICINE

PLASMA TRIGLYCERIDE LEVEL AND MORTALITY FROM CORONARY HEART DISEASE

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Abstract *Background.* Whether the plasma triglyceride level is a risk factor for coronary heart disease has been controversial, and evaluation of the triglyceride level as a risk factor is fraught with methodologic difficulties.

Methods. We studied the association between plasma triglyceride levels and the 12-year incidence of death from coronary heart disease in 10 North American populations participating in the Lipid Research Clinics Follow-up Study, while adjusting for the potential confounding effects of other risk factors for cardiovascular disease, including the level of high-density lipoprotein (HDL) cholesterol. All analyses were sex-specific, and separate analyses were performed in high and low strata of HDL cholesterol, low-density lipoprotein (LDL) cholesterol, fasting plasma glucose, and age.

Results. The rates of coronary death in both men and women increased with the triglyceride level. In Cox proportional-hazards models adjusted for age, in which the natural log of the triglyceride levels was used to give a normal distribution, the relative risk per natural-log unit of triglyceride (e.g., a triglyceride level of 150 mg per deciliter vs. a level of 55 mg per deciliter) was 1.54 (95 percent confidence interval, 1.19 to 1.98; P<0.001) in men and 1.88 (95 percent confidence interval, 1.19 to 2.98; P = 0.007) in women. After an adjustment for potential covariates, however, these relative risks were not statistically significant. Analyses based on lipoprotein cholesterol levels revealed a positive association between the triglyceride level and coronary mortality in the lower stratum of both HDL and LDL cholesterol, but not in the higher stratum. Conversely, the HDL cholesterol level was unrelated to coronary mortality in the lower stratum of LDL cholesterol, but was strongly inversely associated with coronary death in the higher stratum of LDL cholesterol. The relative risk of coronary death associated with triglyceride level was higher at younger ages. The associations between the triglyceride level and coronary mortality in the lower HDL cholesterol, LDL cholesterol, and age strata were small and were further reduced by an adjustment for the fasting plasma glucose level.

Conclusions. Overall, the plasma triglyceride level showed no independent association with coronary mortality. However, in subgroups of subjects with lower HDL and LDL cholesterol levels and in younger subjects, defined a priori, an association between the triglyceride level and coronary mortality was observed, although this association was small and was not statistically significant after an adjustment for the plasma glucose level. (N Engl J Med 1993;328:1220-5.)

DESPITE decades of interest and numerous clinical and epidemiologic investigations, the status of the plasma triglyceride level as a risk factor for coronary heart disease remains unsettled.[1-3] In many prospective studies the triglyceride level has been a strong risk factor for coronary heart disease in univariate analyses, but an adjustment in multivariate analyses for the total or high-density lipoprotein (HDL) cholesterol level often diminished the association.[1,4-7] Nonetheless, the triglyceride level has been reported to be an independent and statistically significant risk factor in multivariate analyses in several studies.[8-15]

The formulation of multivariate models that include the triglyceride level as an independent variable is complex and associated with several problems. First, the conventional adjustment for the total cholesterol level, which is used as a surrogate for the level of low-density lipoprotein (LDL) cholesterol, is inappropriate. In patients with very high triglyceride levels, a large portion of the total cholesterol will consist of very-low-density lipoprotein (VLDL) cholesterol, which is reflected in the total triglyceride level.[3] Thus, in this instance, the total triglyceride level is, in effect, being adjusted for the VLDL triglyceride level.

Second, the distribution of triglyceride levels is markedly skewed.[16] Thus, only categorical or normalizing transformations are appropriate for distribution-dependent analyses, such as standard regression techniques.

Third, there is considerable individual variation in triglyceride levels, and this variability increases with the level of triglyceride.[17] Thus, when a covariate such as HDL cholesterol appears to explain the effect of triglyceride in multivariate analysis, this could be because of true confounding or because HDL cholesterol is simply measured more precisely.

Fourth, the levels of HDL cholesterol and apolipoprotein A-I are strongly and inversely correlated with triglyceride levels,[18] as is consistent with the active metabolic link between triglyceride-rich lipoproteins and the lipoprotein particles in the high-density range. The levels of HDL cholesterol (or apolipoprotein A-I) may be indicators of efficient metabolism of triglycer-

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JAMA The Journal of the American Medical Association

September 18, 1996

A Prospective Study of Triglyceride Level, Low-Density Lipoprotein Particle Diameter, and Risk of Myocardial Infarction

Meir J. Stampfer, MD; Ronald M. Krauss, MD; Jing Ma, MD; et al

≫ Author Affiliations

JAMA. 1996;276(11):882-888. doi:10.1001/jama.1996.03540110036029

Objective. —To test whether a predominance of small, dense low-density lipoprotein (LDL) particles and elevated triglyceride levels are independent risk factors for myocardial infarction (MI).

Design. —Nested case-control study with prospectively collected samples.

Setting. —Prospective cohort study.

Participants. —Blood samples were collected at baseline (85% nonfasting samples) from 14916 men aged 40 to 84 years in the Physicians' Health Study.

Main Outcome Measurements. —Myocardial infarction diagnosed during 7 years of follow-up.

Results. —Cases (n=266) had a significantly smaller LDL diameter (mean [SD], 25.6 [0.9] nm) than did controls (n=308) matched on age and smoking (mean [SD], 25.9 [8] nm; *P*<.001). Cases also had higher median triglyceride levels (1.90 vs 1.49 mmol/L [168 vs 132 mg/dL]; *P*<.001). The LDL diameter had a high inverse correlation with triglyceride level (*r*=-0.71), and a high direct correlation with high-density lipoprotein cholesterol (HDL-C) level (r=0.60). We observed a significant multiplicative interaction between triglyceride and total cholesterol (TC) levels (*P*=.01). After simultaneous adjustment for lipids and a variety of coronary risk factors, LDL particle diameter was no longer a statistically significant risk indicator, with a relative risk (RR) of 1.09 (95% confidence interval [CI], 0.85-1.40) per 0.8-nm decrease. However, triglyceride level remained significant with an RR of 1.40 (95% CI, 1.10-1.77) per 1.13 mmol/L (100-mg/dl) increase. The association between triglyceride level and MI risk appeared linear across the distribution; men in the highest quintile had a risk about 2.5 times that of those in the lowest quintile. The TC level, but not HDL-C level, also remained significant, with an RR of 1.80 (95% CI, 1.44-2.26) per 1.03-mmol/L (40-mg/dL) increase.

Conclusions. —These findings indicate that nonfasting triglyceride levels appear to be a strong and independent predictor of future risk of MI, particularly when the total cholesterol level is also elevated. In contrast, LDL particle diameter is associated with risk of MI, but not after adjustment for triglyceride level. Increased triglyceride level, small LDL particle diameter, and decreased HDL-C levels appear to reflect underlying metabolic perturbations with adverse consequences for risk of MI; elevated triglyceride levels may help identify high-risk individuals.

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ORIGINAL INVESTIGATION

Do Triglycerides Provide Meaningful Information About Heart Disease Risk?

Andrew L. Avins, MD, MPH; John M. Neuhaus, PhD

Background: Prior research suggests that adding triglyceride determinations to measurements of total cholesterol and cholesterol subfractions may improve the prediction of coronary heart disease (CHD).

Objective: To determine the additional value of measuring triglyceride levels, in addition to cholesterol levels and subfractions, for predicting CHD.

Study Design: A set of secondary analyses of previously reported studies.

Methods: We performed secondary analyses of data from the Multiple Risk Factor Intervention Trial, the Lipid Research Clinics Coronary Primary Prevention Trial, and the Lipid Research Clinics Prevalence and Mortality Follow-Up Study. Predictor variables included the levels of fasting triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and fasting blood glucose; age; blood pressure; cigarette smoking; body mass index; and postmenopausal estrogen use. Analytic methods included Cox proportional hazards models, calculation of stratified crude incidence rates, and measurement of the area under the receiver operating characteristic curve.

Main Outcome Measures: Outcome variables were fatal and nonfatal myocardial infarctions.

Results: With few exceptions, no significant interactions between cholesterol subfractions and triglyceride levels were found and receiver operating characteristic curve analyses revealed that triglyceride measurements did not improve discrimination between those subjects who did and did not suffer CHD events. In men, categorical analyses employing both triglyceride and cholesterol levels were similar to those using cholesterol categories alone. In the one study of women, those subjects with both a high-risk cholesterol profile and high triglyceride levels were more likely to have a CHD event, though this finding was based on fewer subjects and CHD events.

Conclusion: These data suggest that, in men, measurement of serum triglyceride levels does not provide clinically meaningful information about CHD risk beyond that obtainable by measurement of serum cholesterol subfractions alone.

Arch Intern Med. 2000;160:1937-1944

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THE RELATION between serum triglyceride levels and coronary heart disease (CHD) has remained enigmatic despite 40 years of research. Because numerous statistical and biological problems plague the analysis of an independent association between triglyceride levels and CHD, attention has recently focused on the value of triglyceride levels, when combined with the measurement of other lipid levels, in predicting the development of CHD.

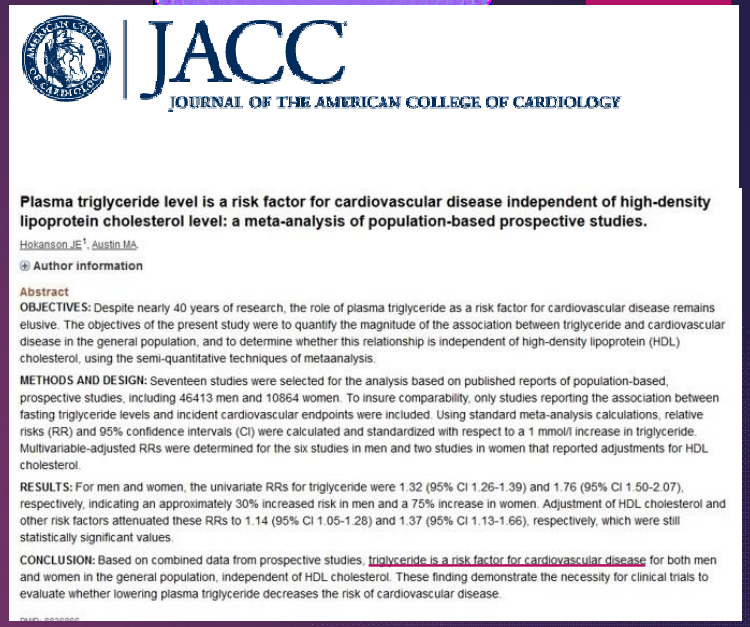
Several studies have suggested interactions between triglyceride and cholesterol levels in the prediction of CHD (ie, the magnitude of the cholesterol-CHD association is dependent on the triglyceride level).[1-3] In the most notable example, an elegant post hoc analysis of the Helsinki Heart Study[3] found that cholesterol levels were not strongly predictive of CHD in the absence of hypertriglyceridemia. Similar interactions were reported for men in the Prospective Cardiovascular

For editorial comment see page 1903

Münster (PROCAM) study.[4] These observations have been widely cited as evidence that triglyceride measurement plays an important role in the clinical assessment of CHD risk.[4-15]

While such observations raise intriguing questions about the clinical use of triglyceride measurement, these analyses also have potentially serious analytic

No. Metaanálisis de 12 años



JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies.

Hokanson JE[1], Austin MA

⊕ Author information

Abstract

OBJECTIVES: Despite nearly 40 years of research, the role of plasma triglyceride as a risk factor for cardiovascular disease remains elusive. The objectives of the present study were to quantify the magnitude of the association between triglyceride and cardiovascular disease in the general population, and to determine whether this relationship is independent of high-density lipoprotein (HDL) cholesterol, using the semi-quantitative techniques of metaanalysis.

METHODS AND DESIGN: Seventeen studies were selected for the analysis based on published reports of population-based, prospective studies, including 46413 men and 10864 women. To insure comparability, only studies reporting the association between fasting triglyceride levels and incident cardiovascular endpoints were included. Using standard meta-analysis calculations, relative risks (RR) and 95% confidence intervals (CI) were calculated and standardized with respect to a 1 mmol/l increase in triglyceride. Multivariable-adjusted RRs were determined for the six studies in men and two studies in women that reported adjustments for HDL cholesterol.

RESULTS: For men and women, the univariate RRs for triglyceride were 1.32 (95% CI 1.26-1.39) and 1.76 (95% CI 1.50-2.07), respectively, indicating an approximately 30% increased risk in men and a 75% increase in women. Adjustment of HDL cholesterol and other risk factors attenuated these RRs to 1.14 (95% CI 1.05-1.28) and 1.37 (95% CI 1.13-1.66), respectively, which were still statistically significant values.

CONCLUSION: Based on combined data from prospective studies, triglyceride is a risk factor for cardiovascular disease for both men and women in the general population, independent of HDL cholesterol. These finding demonstrate the necessity for clinical trials to evaluate whether lowering plasma triglyceride decreases the risk of cardiovascular disease.

Sí. Metanálisis de 7 años


ENTONCES EN QUE QUEDAMOS
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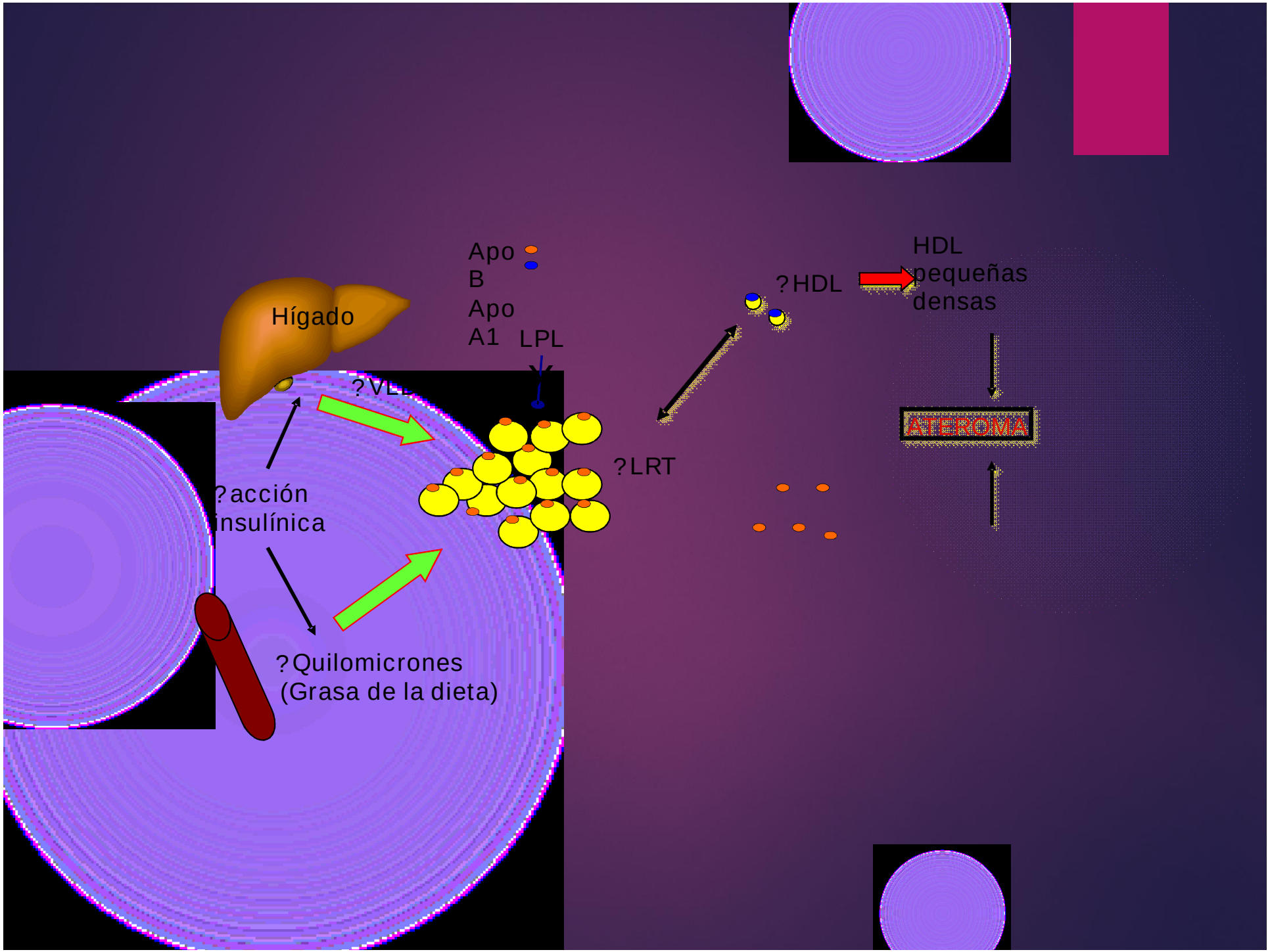
Apo
B
Apo
A1
LPL
Hígado
?HDL
HDL
pequeñas
densas
ATEROMA
?LRT
?acción
insulínica
?Quilomicrones
(Grasa de la dieta)

Tabla 3. Principales mecanismos aterogénicos de los triglicéridos

• Contribuye al depósito lipídico en la íntima arterial
• Las moléculas más pequeñas de lipoproteínas ricas en TG son captadas por los macrófagos
• Hiperlipemia postprandial como factor de riesgo
• Asociación a factores lipídicos: descenso HDL y elevación LDL pequeñas y densas
• Disfunción endotelial
• Estímulo de citoquinas y moléculas proinflamatorias
• Aumento de la actividad monocitaria
• Secreción factor tisular en endotelio y monocitos
• Generación de trombina
• Elevación de factores de coagulación (fibrinógeno, FVII, FXII)
• Deterioro de la fibrinolisis por aumento de PAI-1

Tabla 4. Mecanismos aterogénicos de las partículas LDL pequeñas y densas

• Aumento de su periodo de residencia en el espacio subendotelial.
• Mayor fijación a los proteoglicanos arteriales.
• Mayor susceptibilidad a la agregación subendotelial.
• Mayor susceptibilidad a la oxidación.
• Menor afinidad por el receptor LDL.
• Mayor afinidad por los receptores “barrendero” de los macrófagos vasculares.


Y EL MÉDICO ME DECÍA:
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LAS NUBES... TIENE
EL COLESTEROL POR
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