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XIX JORNADAS DE AVANCES EN HEPATOLOGIA

MÁLAGA 2020
8-9 DE OCTUBRE | AULA MAGNA | FACULTAD DE MEDICINA
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- DPTO. DE MEDICINA Y UNIDAD DE GESTIÓN CLÍNICA DE DIGESTIVO.
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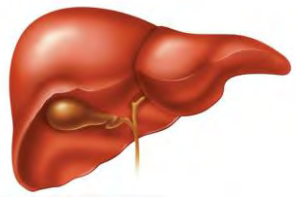
DIRECTOR DE LAS JORNADAS:
RAÚL J. ANDRADE BELLIDO.

Implicaciones del riesgo cardiovascular en el manejo de la esteatosis hepática metabólica



Dr. Javier Ampuero
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Sevilla, España

ESPECTRO E HISTORIA NATURAL

Esteatosis hepática metabólica

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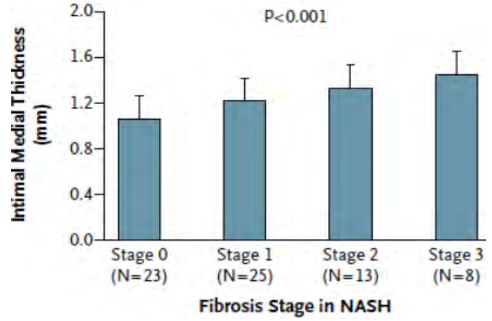
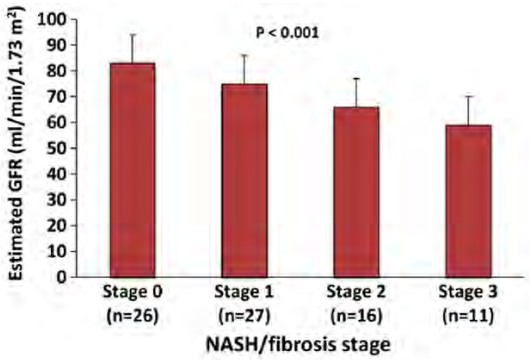
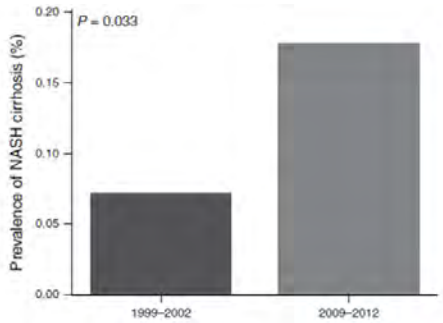
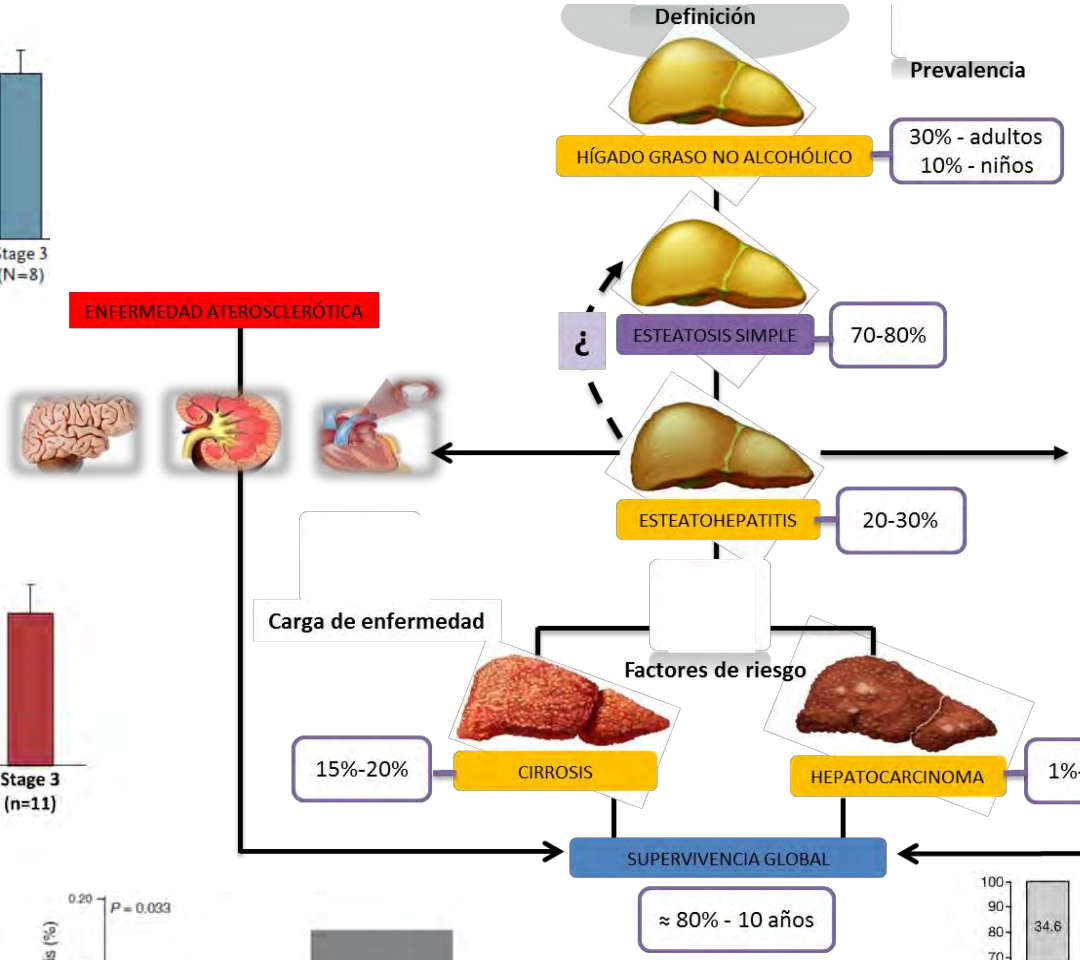
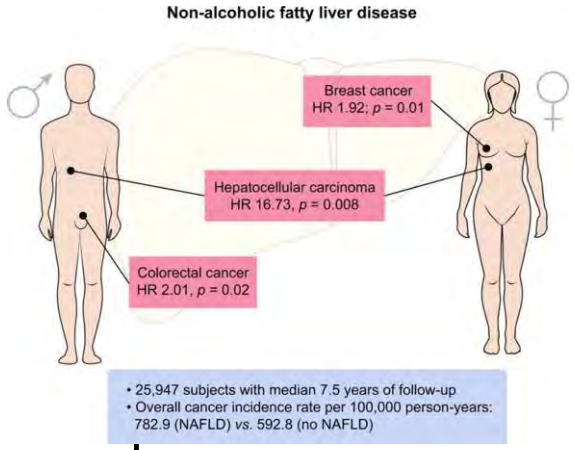










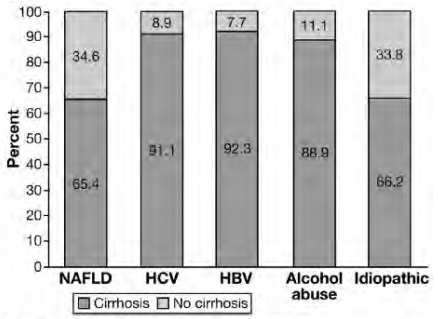
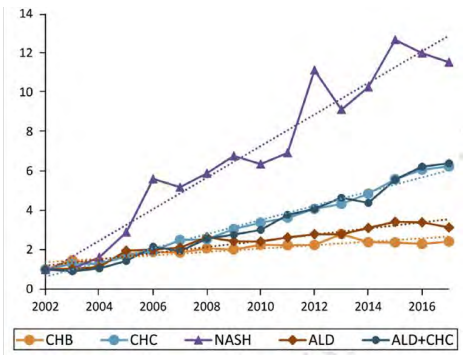


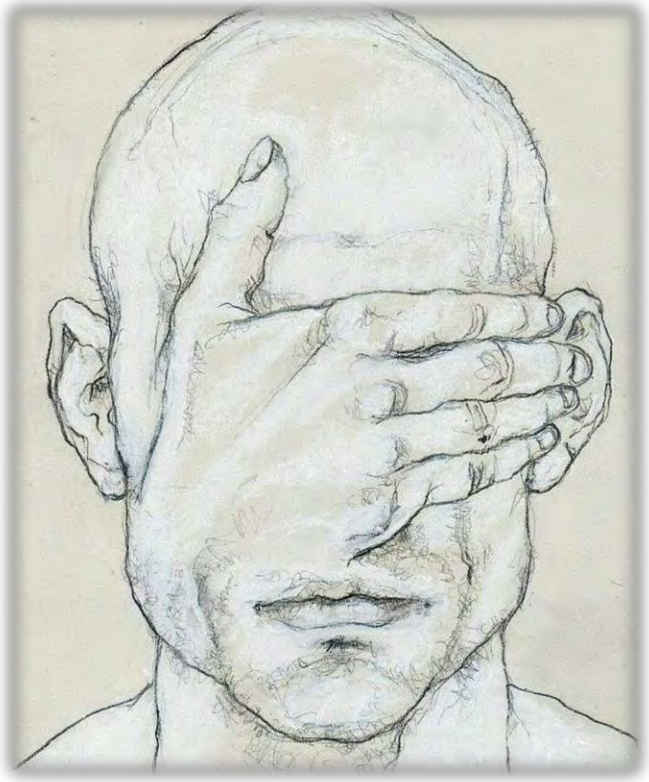
Figure 1. Proportion of HCC patients with or without evidence of cirrhosis by risk factor.



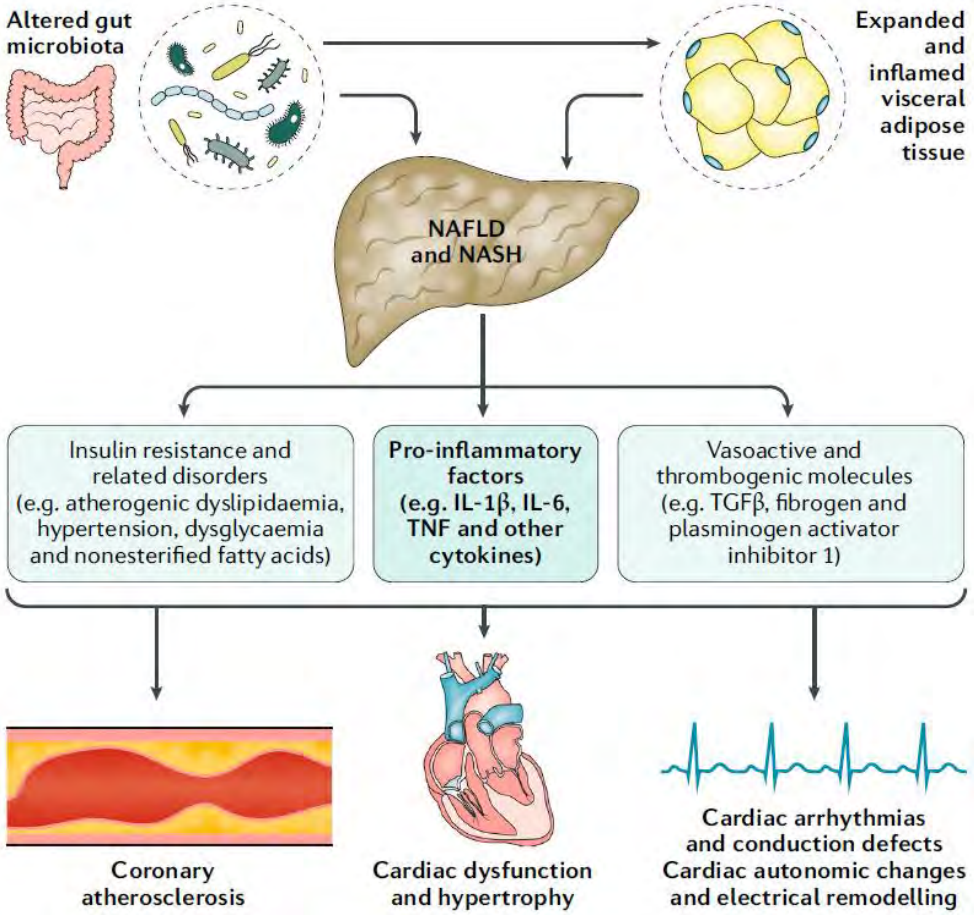
Vilar-Gómez et al, SEPD 2015

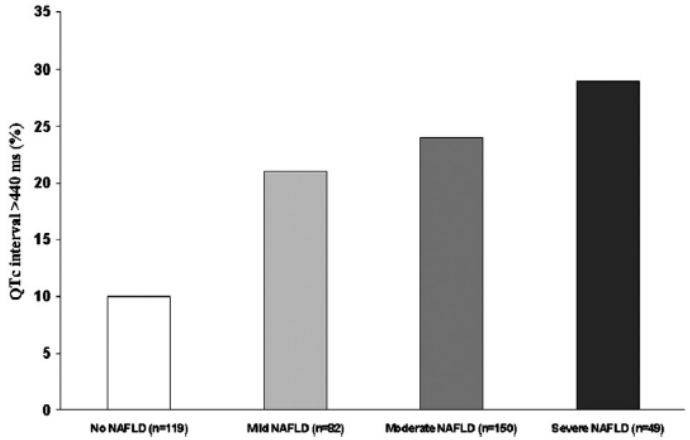
¿Estamos exagerando?

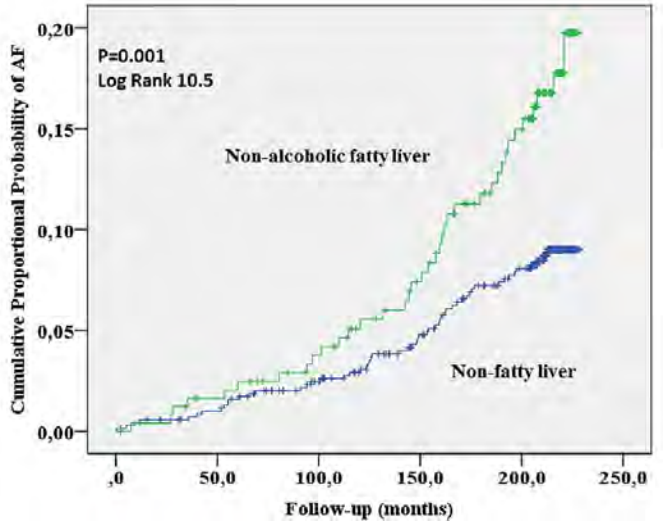
Ver lo que no hay o no ver lo que hay

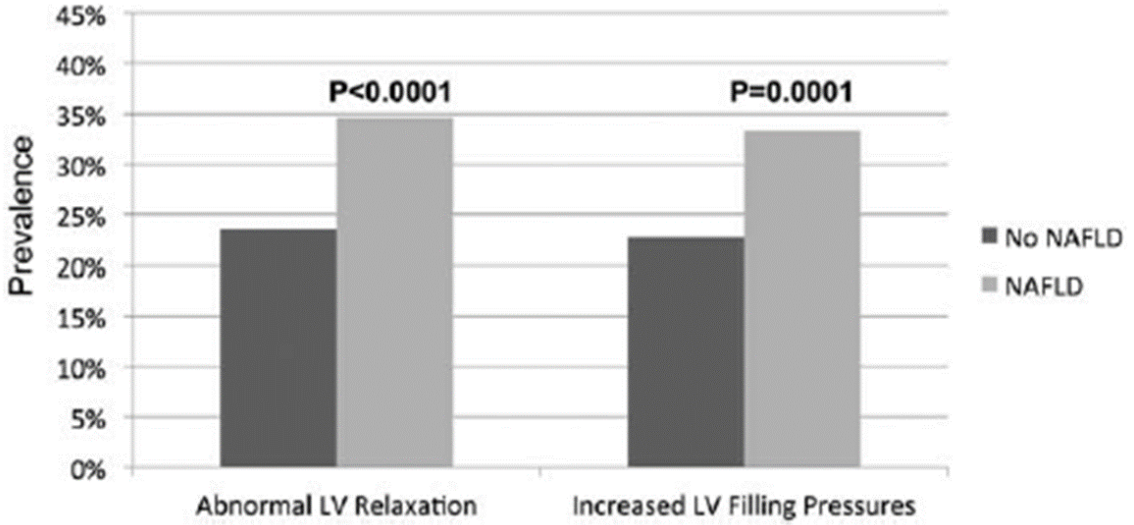


Esteatosis hepática metabólica

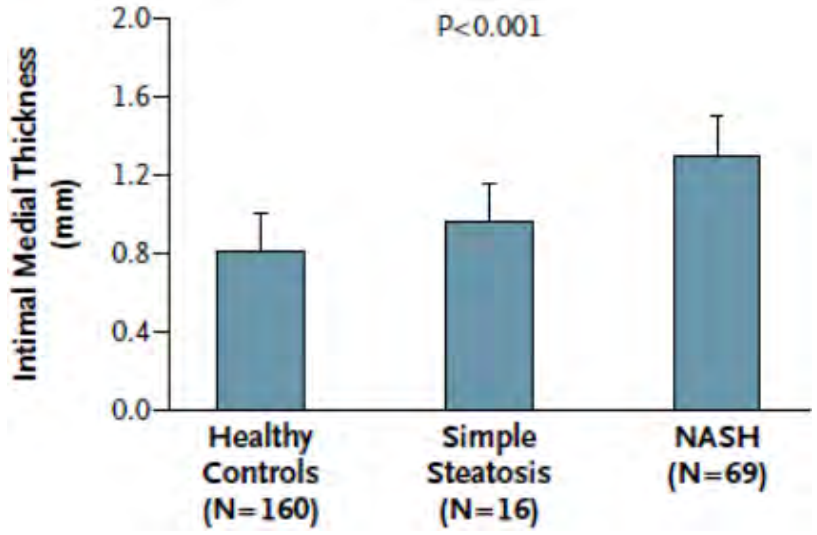


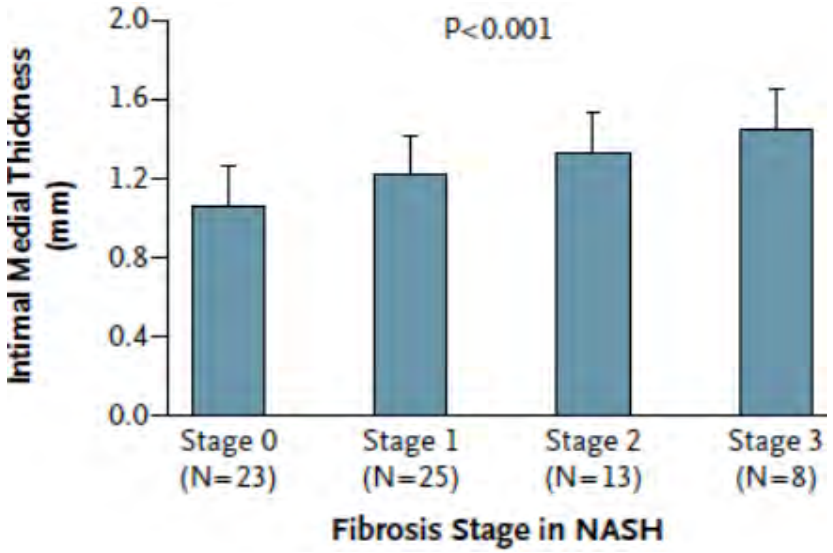






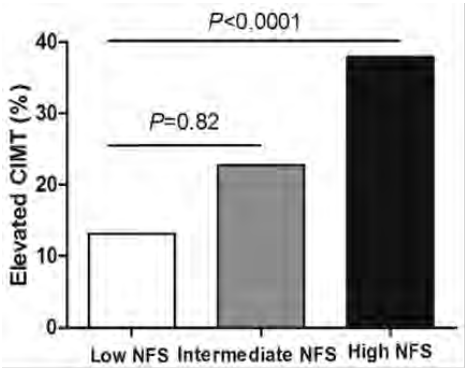
Anstee et al, Nat Rev Gastroenterol Hepatol 2018 Targher et al, Nutr Metab Cardiovasc Dis 2014 Van Wagner et al, Hepatology 2015

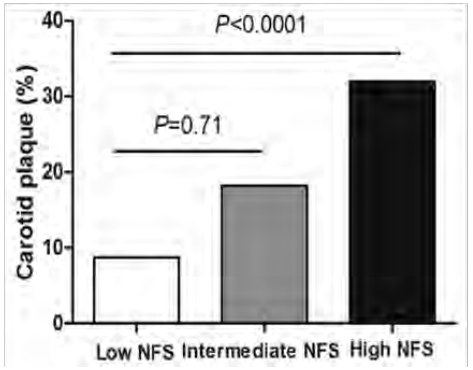


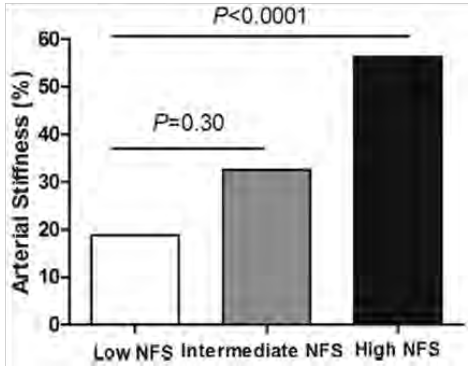


Coronary CT Angiography Characteristics of Patients Stratified according to Presence of NAFLD

Characteristic	Total (*n* = 445)	NAFLD (*n* = 182)	No NAFLD (*n* = 263)	*P* Value
CAD category				
No CAD	197 (44.3)	17 (9.3)	180 (68.4)	<.001
Nonobstructive CAD (1%–49% stenosis)	206 (46.3)	136 (74.7)	70 (26.6)	<.001
Significant CAD (≥50% stenosis)	42 (9.4)	29 (15.9)	13 (4.9)	<.001
Coronary plaque				
Calcified plaque	205 (46.1)	142 (78.0)	63 (24.0)	<.001
Noncalcified plaque	190 (42.7)	125 (68.7)	65 (24.7)	<.001
Any high-risk plaque	158 (35.5)	108 (59.3)	50 (19.0)	<.001
Calcium score				<.001
0	239 (53.7)	46 (25.3)	193 (73.4)	…
1–100	127 (28.5)	73 (40.1)	54 (20.5)	…
101–300	41 (9.2)	32 (17.6)	9 (3.4)	…
>300	38 (8.5)	31 (17.0)	7 (2.7)	…



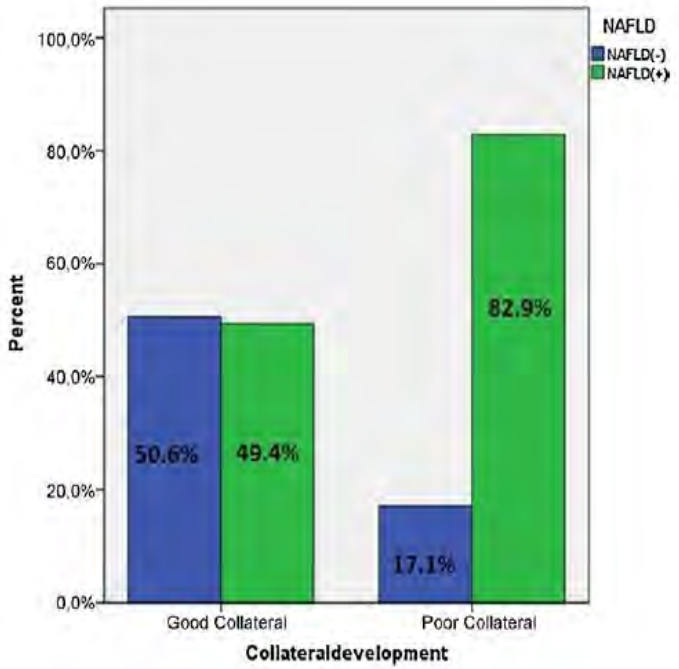


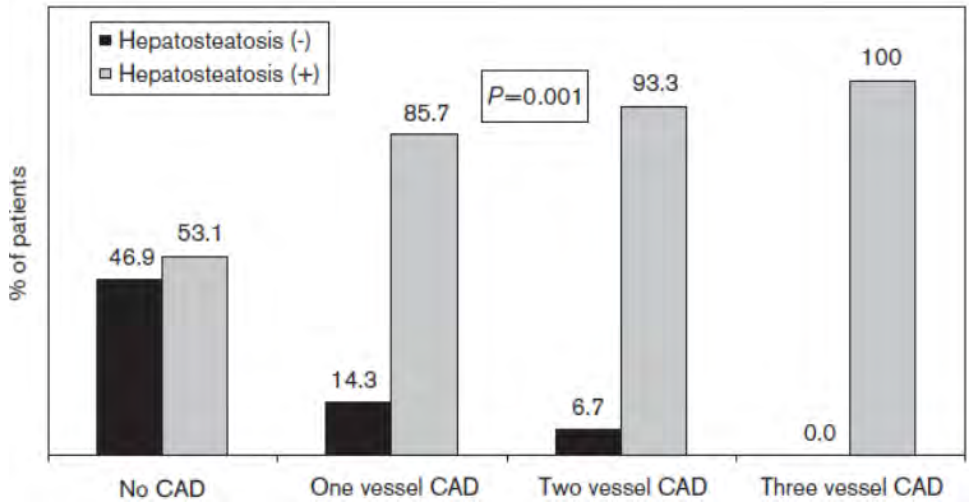


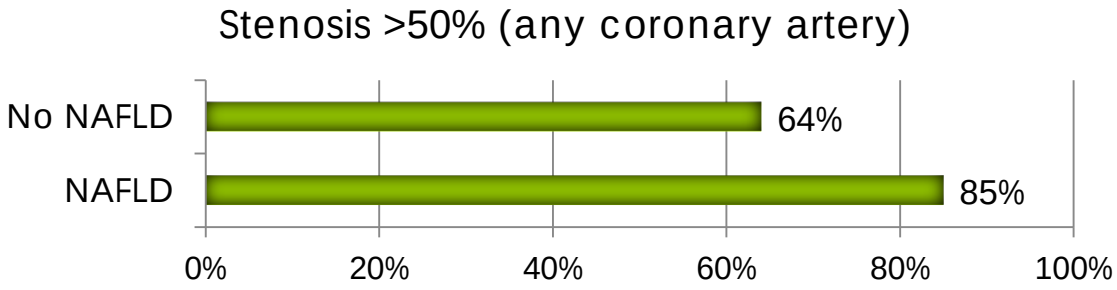
Targher et al, Diabetes Care 2006

Chen et al, Atherosclerosis 2015

Puchner et al, Radiology 2015





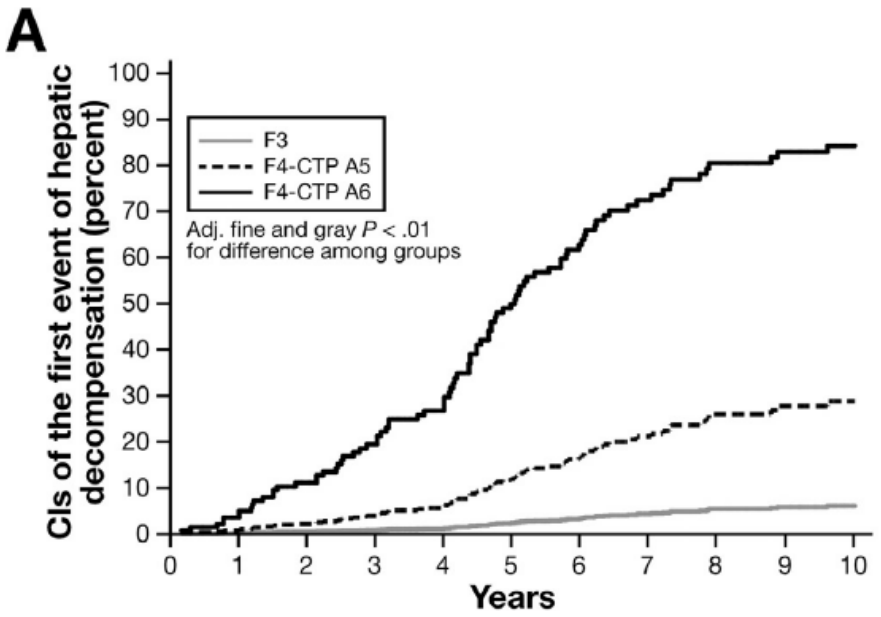


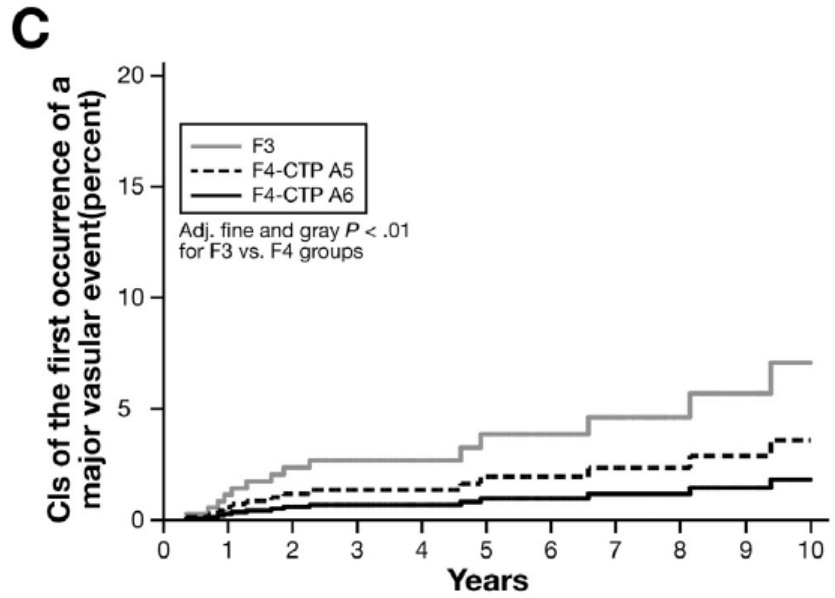
	Multivariate analysis	
Factors	**OR (95% CI)**	**p Value**
Fatty liver	2.31 (1.46 to 3.64)	<0.001
Age (years)	1.05 (1.03 to 1.07)	<0.001
Male gender	2.60 (1.65 to 4.09)	<0.001
Smoking		
Alcohol		
Diabetes	1.45 (0.84 to 2.51)	0.18
Hypertension		
Systolic blood pressure (mm Hg)		
Diastolic blood pressure (mm Hg)		
Body mass index (kg/m^2)		
Waist circumference (cm)	0.99 (0.97 to 1.02)	0.56
Fasting glucose (mmol/l)	1.12 (0.98 to 1.28)	0.092
Total cholesterol (mmol/l)		
HDL-cholesterol (mmol/l)	0.25 (0.13 to 0.48)	<0.001
LDL-cholesterol (mmol/l)		
Triglycerides (mmol/l)		
Creatinine (μmol/l)		
Alanine aminotransferase (IU/l)	1.01 (1.00 to 1.02)	0.044

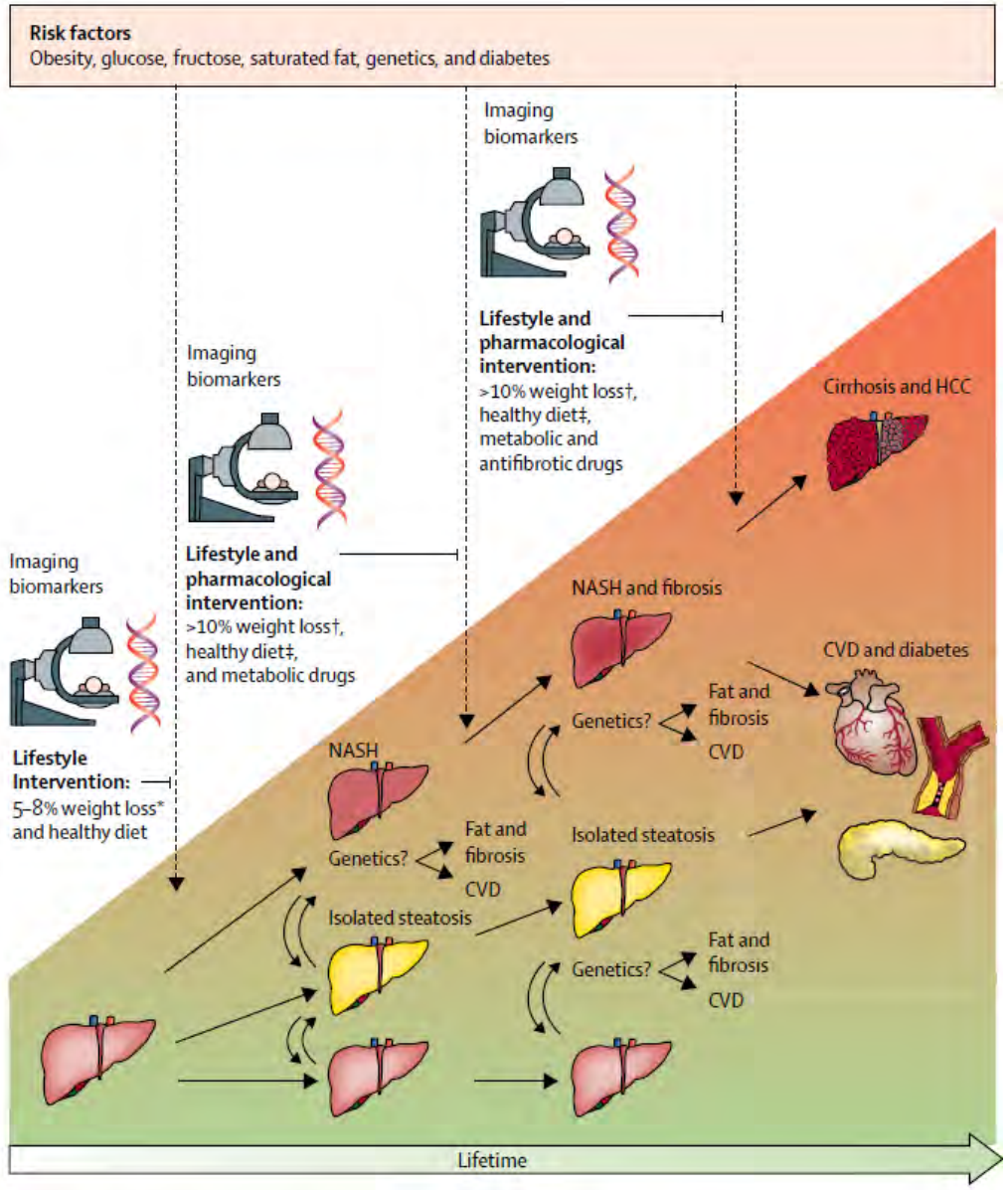
Arslan et al, J Cardiol 2012

Wong et al, Gut 2012

EVENTOS CARDIOVASCULARES







Vilar-Gomez et al, Gastroenterology 2018

Stefan et al, Lancet Diabetes Endocrinol 2018

Table 3. Liver Events and Causes of Death

Outcome	Number
Death or OLT	(n = 193)
Cardiovascular disease	74 (38.3%)
Nonliver cancer	36 (18.7%)
Cirrhosis complications	15 (7.8%)
HCC	2 (1%)
Liver transplantation	1 (0.5%)
Infections	15 (7.8)
Other	35 (18.1%)
Pulmonary	5
Autoimmune disease	4
Renal failure	4
Accidents/trauma	10
Pancreatitis	2
Nonvariceal GI bleeding	4
Surgery complications	2
Others	4
Unknown	15 (7.8)
Liver events	(n = 26)[a]
Gastroesophageal varices/bleeding	12 (46%)
Ascites	9 (34.6%)
Portosystemic encephalopathy	6 (23.1%)
Spontaneous bacterial peritonitis	3 (11.5%)
Hepatocellular cancer	3 (11.5%)
Hepatopulmonary syndrome	2 (7.7%)
Hepatorenal syndrome	4 (15.4%)

Angulo et al, Gastroenterology 2015

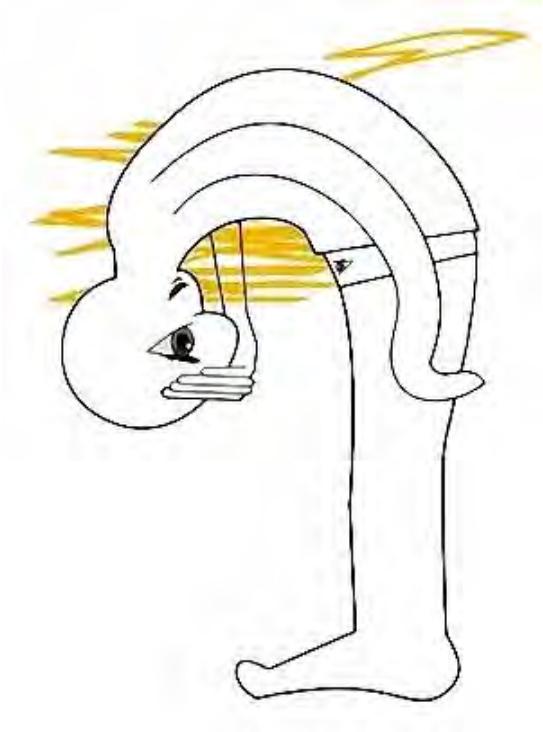
Cause of Death	Number of Patients (n = 96)
Cardiovascular disease	41 (43%)
Non-gastrointestinal malignancy	18 (19%)
Hepatocellular carcinoma	5 (5%)
Infection	5 (5%)
Gastrointestinal malignancy	4 (4%)
Cirrhosis	4 (4%)
Endocrine	3 (3%)*
Respiratory	3 (3%)
Other	7 (7%)
Missing	6 (6%)

	Stage of Fibrosis					
Cause of Death	1	2	3	4	0	Missing
Cirrhosis			2	1		1
Perforation of intestine	1					
Liver cancer	1		1	3		
Extrahepatic cancer	2	6	1	2	1	
Diabetes		2			1	
Cardiovascular	4	6	3	1	1	
Alcohol abuse	1					
Poisoning/accident	1			1	1	

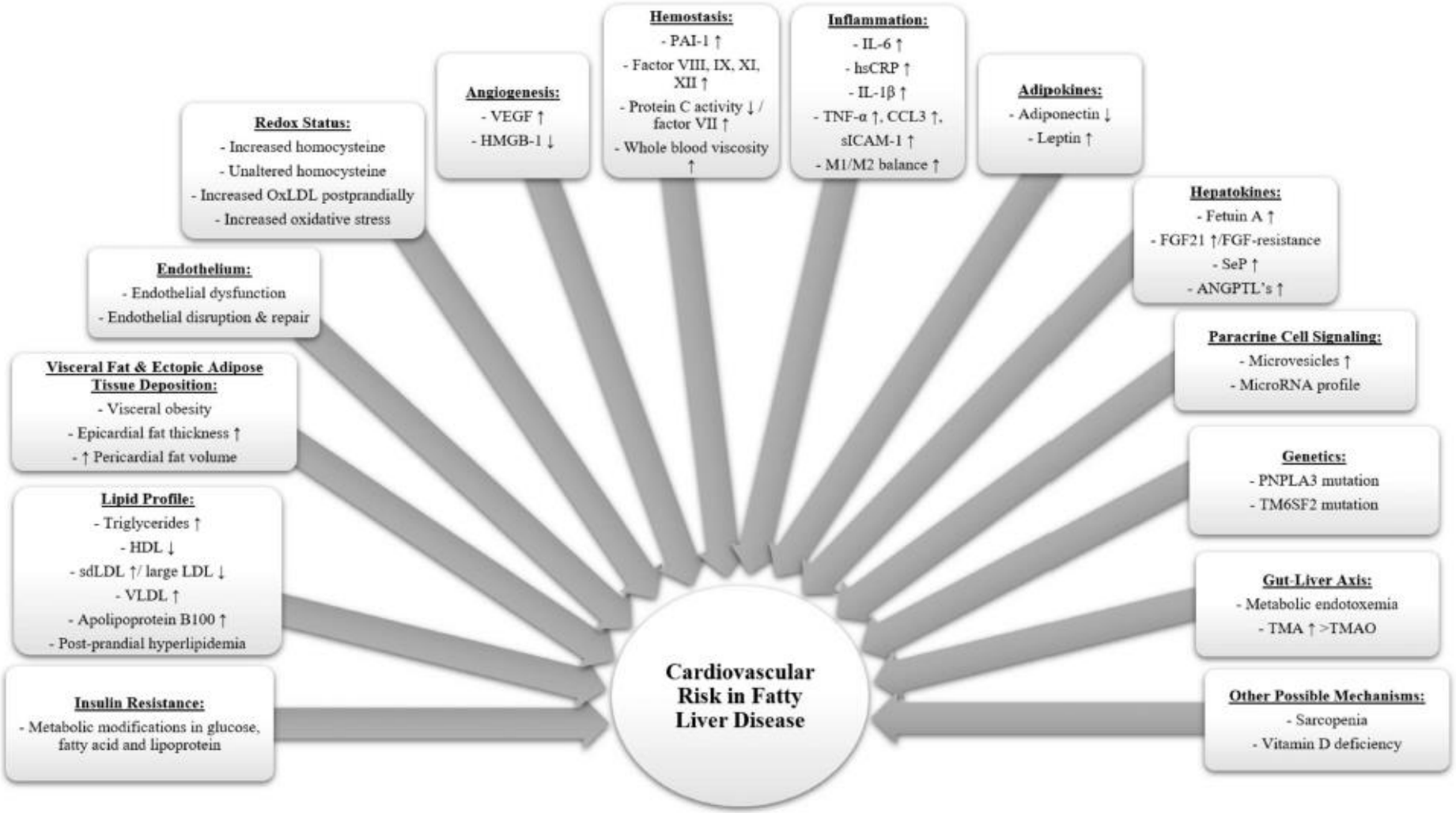
Ekstedt et al, Hepatology 2015

¿Cuáles son los mecanismos implicados?

Hay que mirarlos de frente



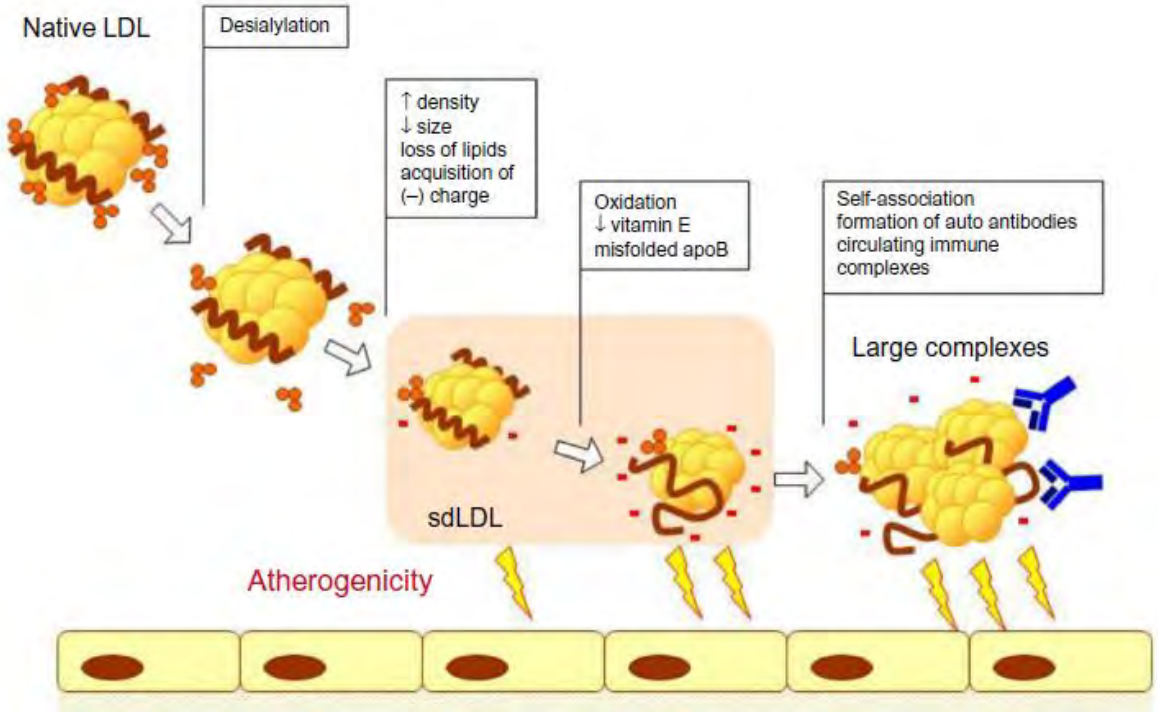
MECANISMOS ASOCIADOS AL RIESGO CV



Ismaiel et al, Front Med 2019

	ALD (Refs. [12–36,40,41, 45–48])	NAFLD (Refs. [10,52–54,65–68,72–74])	Chronic HBV (Refs. [88–94,97])	Chronic HCV (Refs. [11,105–107,111, 116,119–124])	PBC (Refs. [160,164–179, 182–184])	Cirrhosis – HCC (Refs. 158–163,190,191,198
Tot-CH	≈ ↑	≈ ↑	↓	↓↓	↑↑	↓
LDL	≈ ↓	↑	↓	↓	↑↑	≈ ↓
HDL	↑	↓↓	↓	↓	↑↑	↓
TG	↑ ≈	↑	↓	≈ ↓	↑↑	↓
IR/T2DM	↑[a]	↑	↓	↑	↓	↑
Steatosis	↑	↑	↓[c]	↑[b,c]	↓	↑[d]
CVR	↑[a]	↑	↓	↑	↓	?, ↑[d]

Lipid marker	Physiopathological effect
LDL modified particles (oxidized LDL, electronegative LDL, and glycosylated LDL)	Stimulation of the immunological system (increased number of mononuclear cells and antibodies)
Lipoprotein-associated phospholipase A_2	Hydrolysis of oxidized phospholipids minimizing oxidative components associated with the LDL particle, but with the generation of pro-inflammatory lisophospholipids
Apolipoprotein AI	HDL component, reflecting the number of anti-atherogenic particles found in the bloodstream
Apolipoprotein B	Component of atherogenic lipoproteins (VLDL, IDL and LDL), reflecting the number of atherogenic particles found in the bloodstream
Lipoprotein(a)	Atherogenic and thrombogenic potential due to the biding of Apo (a) to Apo B
Cholesteryl ester transfer protein	Transfer of cholesteryl esters from HDL to lipoproteins containing Apo B (VLDL, IDL, LDL), which, in their turn, transfer TG to HDL
LDL size and density	Small and dense LDL (phenotype B): greater susceptibility to oxidation and lower affinity to B/E receptor Larger and less dense LDL (phenotype A): opposite characteristics
HDL size and density	Small and dense fractions; probable greater atheroprotective properties (antioxidant, anti-inflammatory, cholesterol efflux, antithrombotic capacity) compared with the larger and less dense fraction



PERFIL LIPÍDICO: PARTICULARIDADES

	LEAN (N=81)	OBESE (N=81)	NAFLD (N=81)
TRADITIONAL PARAMETERS			
Cholesterol-Total (mg/dL)	198±38	185±42***	203±49
HDL-C (mg/dL)	63±16	53±18‡	55±15*
LDL-C (mg/dL)	105±29	98±31	118±41**
Triglycerides (mg/dL)	104±53	113±58	154±87**
LOW DENSITY LIPOPROTEIN			
LDL-P (nmol/L)	1432±456	1447±469	1717±684**
Small-density LDL-C (mg/dL)	25.1±9.5	24.1±9.6	36.8±17.3**
% Small-density LDL	24.1±9.6	24.8±7,5	32.6±15.7**
Small density LDL-P (nmol/L)	591±388	652±355	870±654**
VERY LOW DENSITY LIPOPROTEIN	89±22	87±23	101±31**
Apolipoprotein-B (mg/dL)	1.4±1.5	2.1±2.3	3.2±3.1**
VLDL-P (nmol/L)	43.4±4.9	45.1±5.5‡	47.1±5.2*
VLDL size (nm)			
HIGH DENSITY LIPOPROTEIN			
Apolipoprotein-A1 (mg/dL)	168±32	154±34‡	148±30*
HDL-2 (mg/dL)	15.4±6.7	13.3±6.8	12.7±6*
HDL-P (nmol/L)	36.7±6.2	33.8±7.5‡	33.0±5.7

	Simple Steatosis (N=32)	Steatohepatitis (N=35)	Cirrhosis (N=14)
DEMOGRAPHICS			
Age (years)	53±13	56±13	61±8
BMI (kg/m^2)	32.6±6.0	33.2±6.2	34.7±6.0
ALT (IU/mL)	61±42	51±37	41±17
AST (IU/mL)	49±38	42±25	48±21
Gender (%M)	13 (40.6%)	11 (31.4)	3 (21.4)
TRADITIONAL PARAMETERS			
Cholesterol-Total (mg/dL)	202±40	204±56	171±30**
HDL-C (mg/dL)	58±22	49±13	49±11
LDL-C (mg/dL)	120±36	118±46	92±28**
Triglycerides (mg/dL)	147±73	160±98	109±39**
LOW DENSITY LIPOPROTEIN			
LDL-P (nmol/L)	1619±570	1784±753	1327±601**
Small-density LDL-C (mg/dL)	36.8±17.3	36.7±17.5	23.0±12.1**
% Small-density LDL	31.8±13.5	33.1±17.3	24.1±6.4**
Small density LDL-P (nmol/L)	710±497	935±708	736±361
VERY LOW DENSITY LIPOPROTEIN			
Apolipoprotein-B (mg/dL)	97±26	103±34	81±25**
VLDL-P (nmol/L)	3.3±3.7	3.1±2.9	1.9±1.3
VLDL size (nm)	46.3±7.8	47.5±3.2	45.8±3.8
HIGH DENSITY LIPOPROTEIN			
Apolipoprotein-A1 (mg/dL)	154±26	144±31	136±49
HDL-2 (mg/dL)	12.5±5.3	12.8±6.1	15.1±9.4

Siddiqui et al, Clin Gastroenterol Hepatol 2015

GENÉTICA Y RIESGO CARDIOVASCULAR

Esteatosis hepática metabólica

Gene	Variant	Impact on protein	Effect of the variant	Allelic frequency Europeans	Hispanics	Asians	Africans	Effect size	Effect of the variant	Direction of association (Ancestral allele)	Fat	NASH	Fibrosis	HCC	Mortality	Response to therapies
PNPLA3	rs738409 C>G	I148M	Complex: loss- plus gain-of-function	0.23	0.57	0.38	0.14	+++	Complex: loss plus gain of function	↑	+	+	+	+	+	+
TM6SF2	rs58542926 C>T	E167K	Loss-of-function	0.08	0.03	0.07	0.04	+++	Loss-of-function	↑	+	+	+	+		+
GCKR	rs1260326 T>C	P446L	Loss-of-function	0.60	0.67	0.50	0.86	+	Loss-of-function	↑	+	+	+			
MBOAT7	rs641738 C>T	Linked to 3'-UTR	Reduced expression	0.42	0.33	0.24	0.34	+	Reduced expression	↑	+	+	+	+		
HSD17B13	rs72613567 T>TA rs62305723 G>A	Alternate splicing P260S	Loss-of-function	0.27 0.07	0.09 0.02	0.34	0.06 0.01	++	Loss-of-function	↓		+	+	+		
IL28B (IFNL3/4)	rs368234815 TT>δG	Alternate protein translation site	Alternative protein	0.27	0.09	0.34	0.06	+	Alternative protein	↓		+	+			
MERTK	rs4374383 G>A	Noncoding variant	Reduced expression	0.37	0.37	0.73	0.47	+	Reduced expression	↓			+			

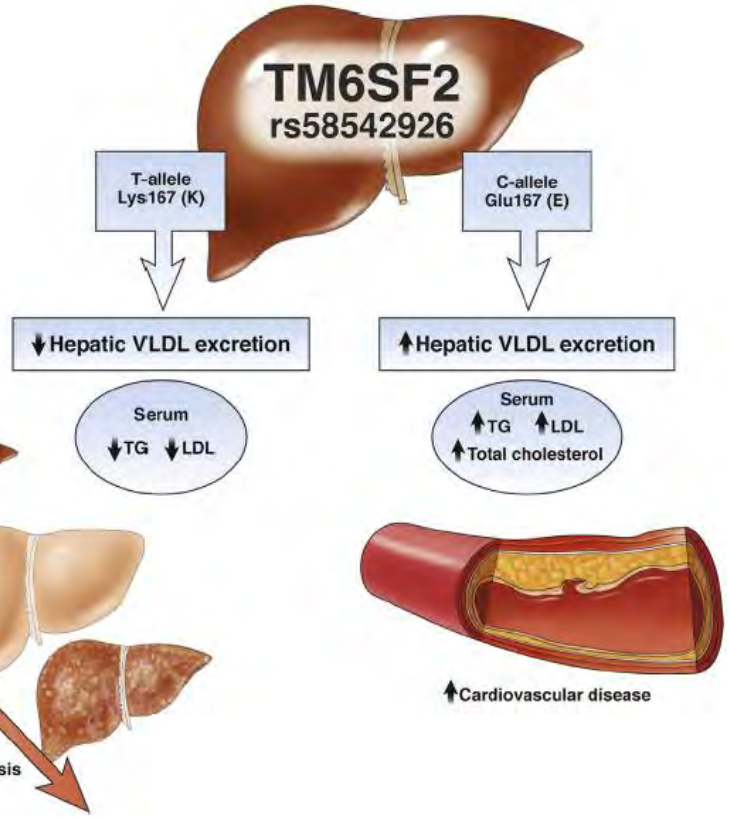
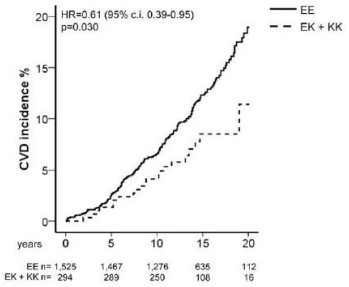


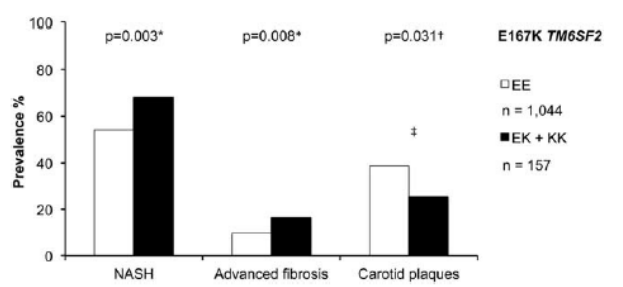
TABLE 3. LOGISTIC REGRESSION ANALYSES OF CHD

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age [years]	1.02 (0.99-1.05)	0.14	1.03 (1.00-1.06)	0.09
Male sex	0.31 (0.15-0.66)	0.002	0.41 (0.18-0.98)	0.04
Waist circumference [cm]	1.03 (1.00-1.06)	0.08		
Nicotine consumption [py]	1.01 (1.00-1.02)	0.2		
Presence of diabetes mellitus	1.22 (0.79-1.87)	0.4		
Use of statins	2.96 (1.46-6.00)	0.003	2.85 (1.34-6.06)	0.006
LDL [mg/dL]	1.00 (0.99-1.01)	0.4		
HDL [mg/dL]	0.98 (0.96-0.99)	0.006	0.98 (0.96-1.00)	0.04
FibroScan [kPa]	1.03 (0.97-1.09)	0.4		
CAP [dB/m]	1.00 (0.99-1.01)	0.2		
PNPLA3 rs738409 G allele	0.34 (0.09-1.23)	0.10	0.21 (0.05-0.88)	0.03

Table 1. *PNPLA3, TM6SF2* and *MBOAT7* in Association With Coronary Artery Disease

					Association Model					
					Additive			Recessive		
Variant	Locus name	Chr.	A1/A2	Effect allele (A1) Frequency	No. of Studies	Odds Ratio (95% CI)	*P*	No. of Studies	OR (95% CI)	*P*
rs738409	*PNPLA3*	22	G/C	0.24	48	0.98 (0.96-1.00)	.08	43	0.92 (0.87-0.97)	.002
rs5854292	*TM6SF2*	19	T/C	0.07	46	0.95 (0.92-0.98)	.005	37	0.78 (0.65-0.93)	.005
rs641738	*MBOAT7*	19	T/C	0.43	42	1.02 (0.76-1.04)	.15	37	1.01 (0.37-1.05)	.51





Trepo et al, J Hepatol 2020

Ruschenbaum et al, Hepatol Commun 2018

Kahali et al, Gastroenterology 2015

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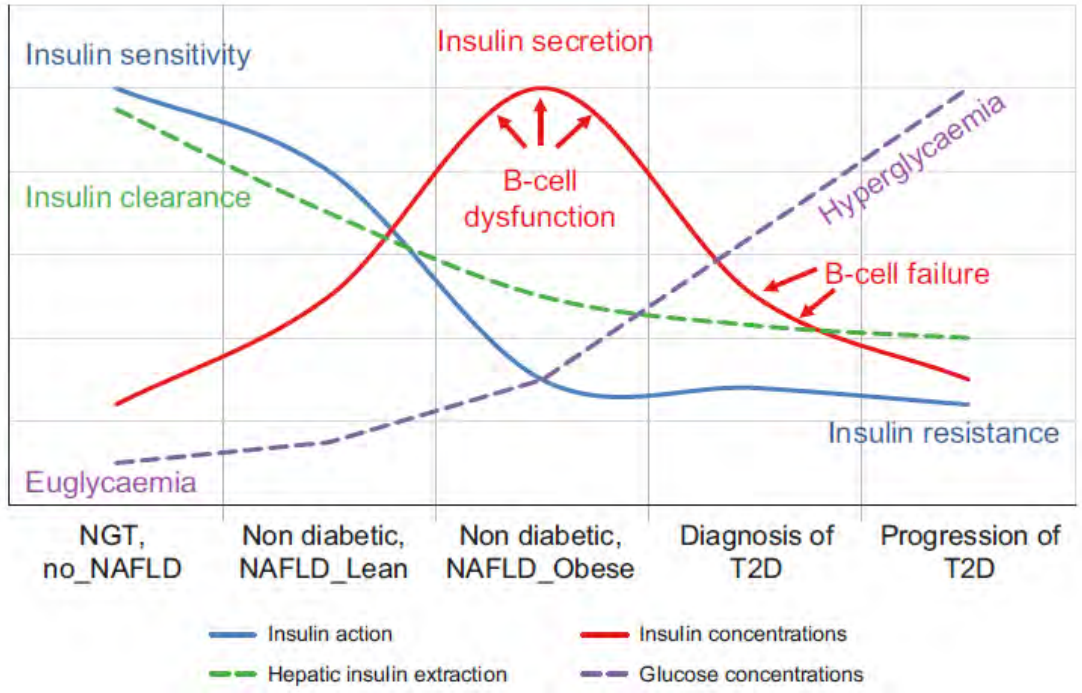
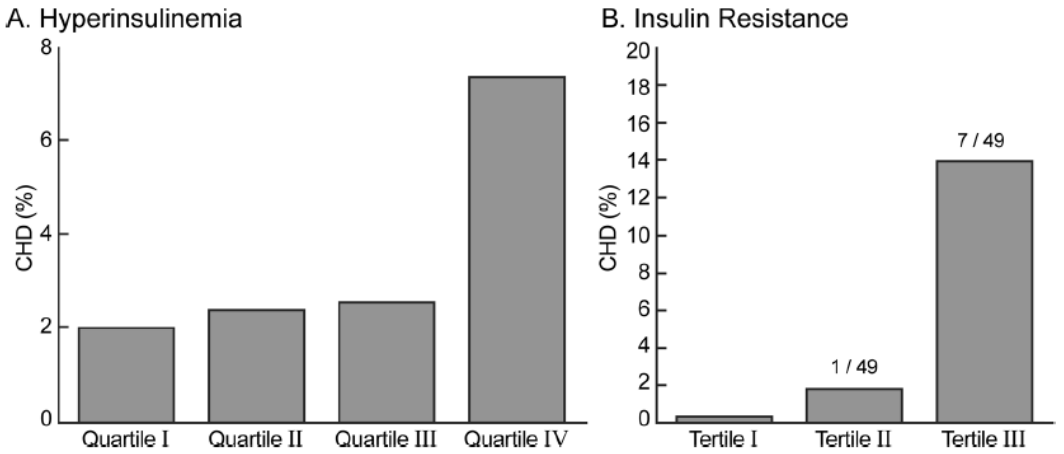


			Number of Studies	Participants	Pooled relative risk per 1 SD (95% CI)	I^2
CHD	Glucose		23	140,721	1.21 (1.13, 1.30)	64.9%
	Insulin		9	32, 104	1.04 (0.96, 1.12)	43.0%
	HOMA-IR		7	17,452	1.46 (1.26, 1.69)	0.0%
CVD	Glucose		44	450, 487	1.19 (1.14, 1.23)	66.8%
	Insulin		16	46,236	1.13 (1.05, 1.22)	58.3%
	HOMA-IR		17	51,161	1.25 (1.16, 1.35)	52.4%
CVD	Glucose	men	22	183,802	1.13 (1.08, 1.18)	29.3%
		women	14	51,527	1.25 (1.11, 1.41)	65.0%
	Insulin	men	10	18,411[a]	1.06 (0.97, 1.16)	60.4%
		women	4	5,082[a]	1.24 (1.08, 1.44)	18.5%
	HOMA-IR	men	6	9,768	1.41 (1.12, 1.77)	66.5%
		women	3	5,049	1.37 (1.05, 1.80)	33.6%



Gastaldelli et al, JHEP Rep 2019

Reaven et al, Arterioscler Thromb Vasc Biol 2012

Gast et al, PLOS ONE 2012

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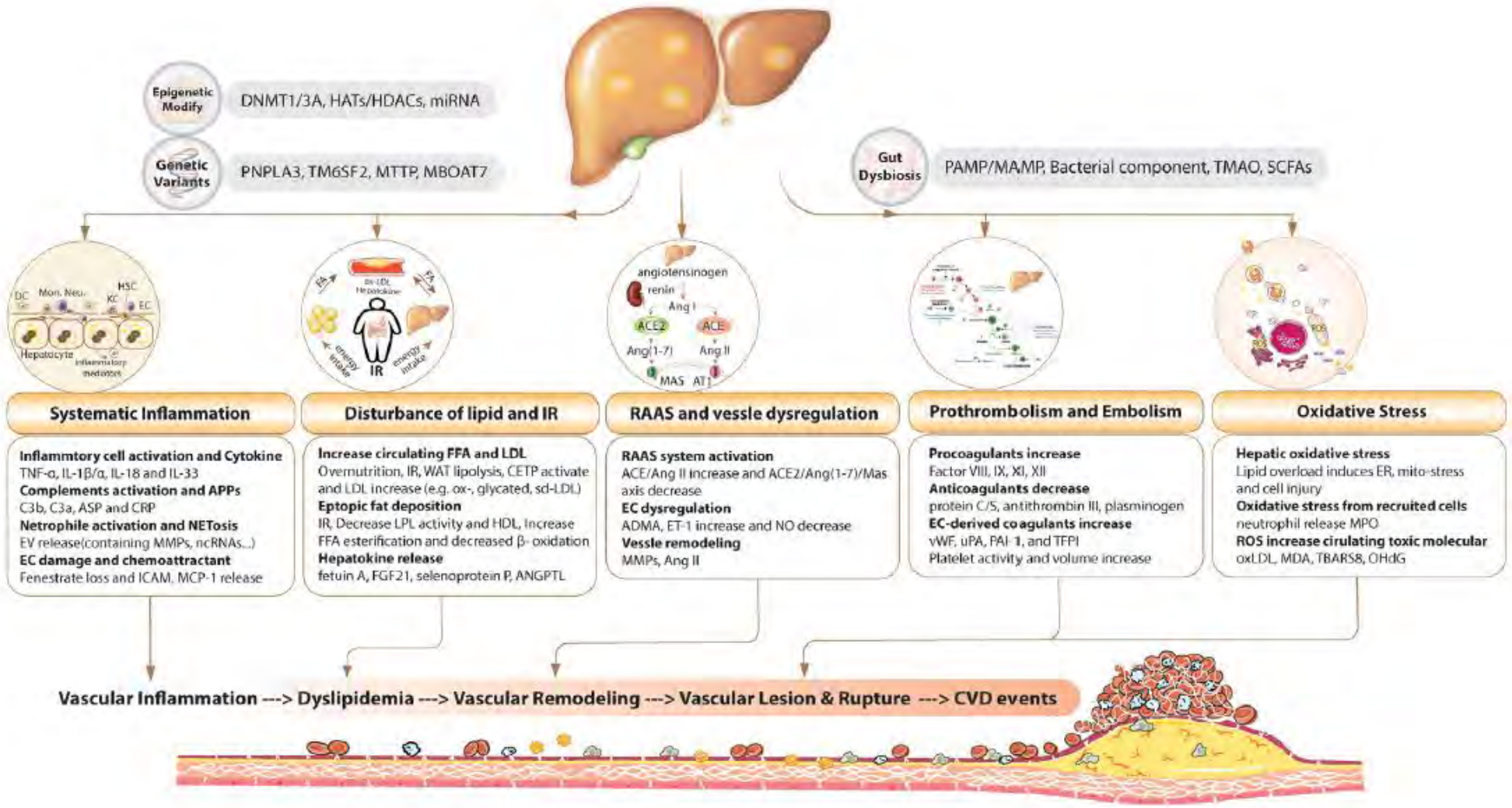


Cai et al, Circ Res 2020

¿Qué tiene que saber (y hacer) un hepatólogo del riesgo cardiovascular?

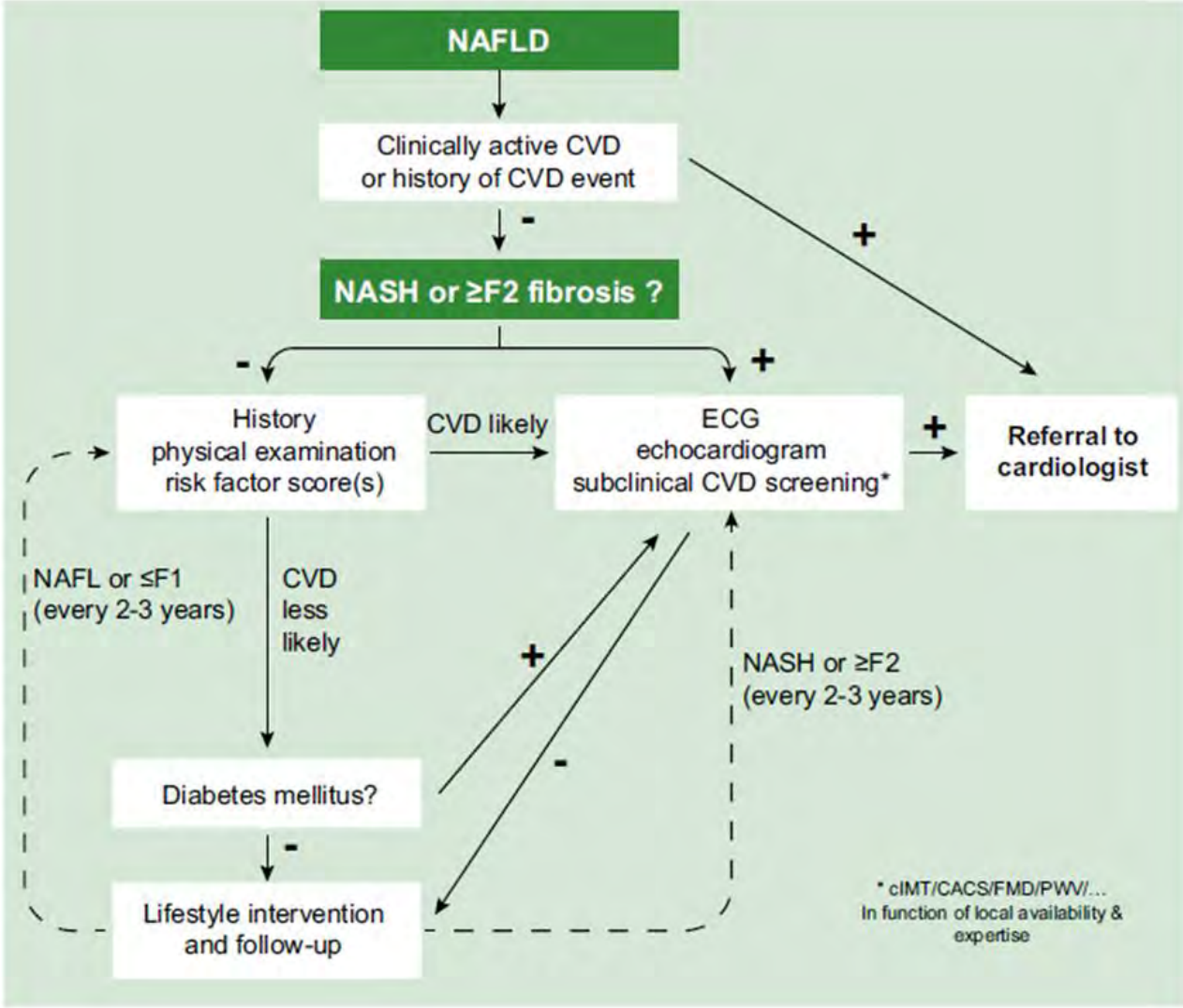
Esa es la cuestión

CVR assessment to include **in NAFLD patient's history**

Modifiable Risk Factors
*Smoking status
*Alcohol intake
*Physical activity
*Waist circumference
*Body Mass Index
*Blood pressure
*Serum lipids
*Nutrition

Non-modifiable Risk Factors
*Age and sex
*Family history of premature CV

Related conditions
*Diabetes (fasting glucose, Hb1ac)
*CKD (albuminuria, GFR<60)
*Family hypercholesterolemia
*Atrial fibrillation



Franqce et al, J Hepatol 2016

Table 2 Ten-year CHD risk by absence or presence of subclinical atherosclerosis in asymptomatic people

Type of test	Test result	Sex, age (years)	CHD risk (%)
Positive			
Carotid IMT	Overall mean ≥1.13 mm (>95th percentile)	Men, 45–65	14
Carotid IMT	Overall mean ≥0.97 mm (>95th percentile)	Women, 45–65	11
Carotid IMT	Maximal common ≥1.18 mm (>5th quintile)	Men/women, ≥65	15
Aortic PWV	>14.6 m/s, males;14.2 m/s, females (>3rd tertile for age and sex)	Men/women, ≥55	13
Ankle arm index	<0.90	Men/women, ≥65	15
Carotid plaque	Focal protrusion >1.5 mm or mineralization	Men, 42–60	25
Coronary calcium	Total calcium score ≥301	90% men, >45	20
Coronary calcium	Total calcium score ≥400	Men/women, 50–70	28

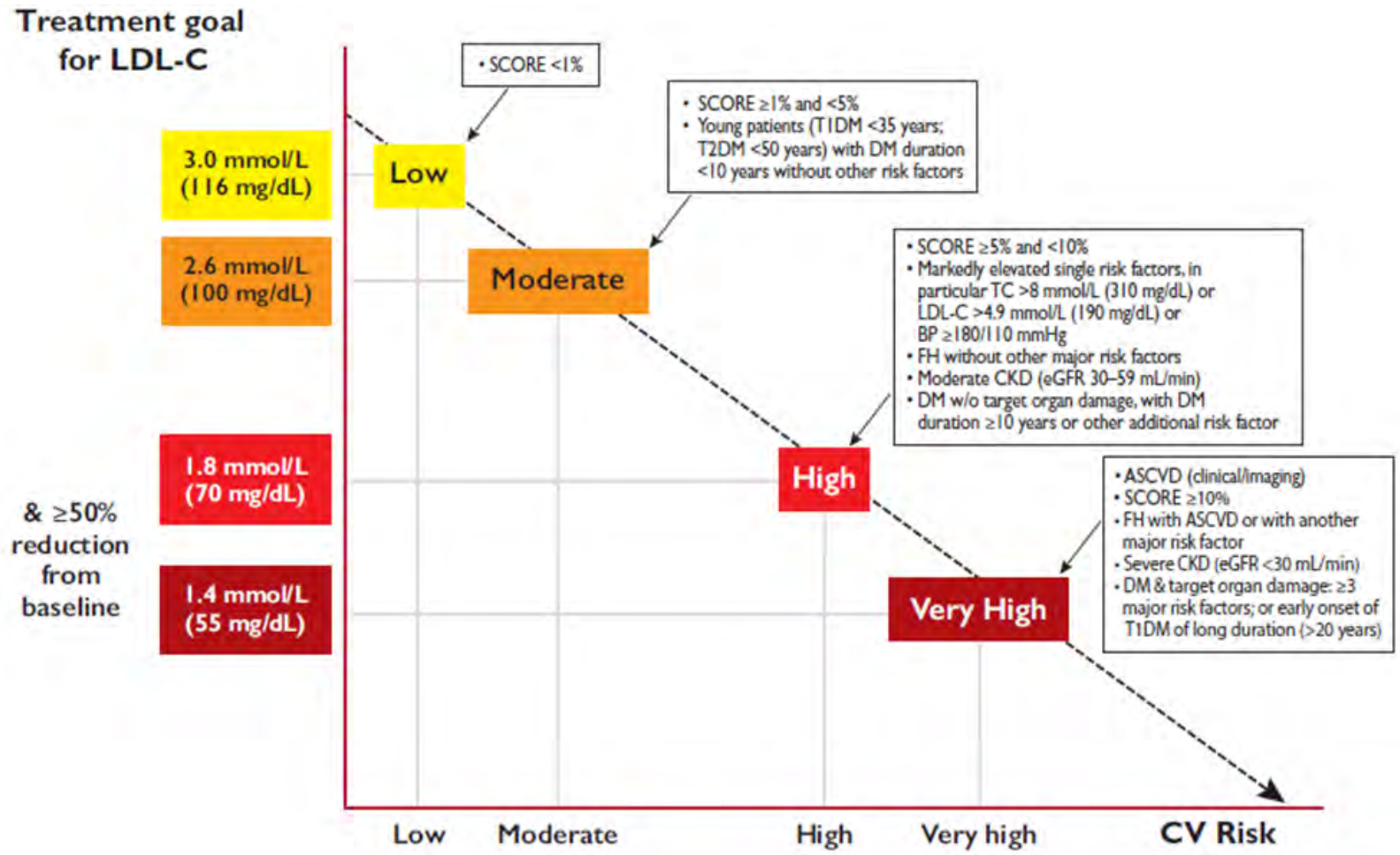
Table 3 Criteria for choosing subclinical atherosclerosis test

Test criteria	Carotid IMT	Ankle–arm index	Aortic PWV	Carotid plaque	Coronary calcium
Predictive value	Fair	Fair	Fair	Excellent	Excellent
Simplicity	Good	Excellent	Good	Good	Fair
Reproducibility	Excellent	Fair	Fair	Good	Fair
Safety	Excellent	Excellent	Excellent	Excellent	Fair (radiation)
Low cost	Good	Excellent	Excellent	Good	Poor

Cardiovascular complications in fatty liver disease	Common methods of assessment
Coronary artery disease	Increased coronary artery calcium score—Multiple detector computed tomography
Carotid disease	Increased carotid intima media thickness and presence of carotid plaques—Carotid ultrasound
Structural alterations	Increased left ventricular mass index, interatrial thickness, left atrial stiffness—Transthoracic echocardiography
Epicardial Fat	Increased epicardial fat thickness measurements—Transthoracic echocardiography
Valvular calcifications	Aortic-valve sclerosis and mitral annular calcification—Transthoracic echocardiography
Functional alterations	Diastolic dysfunction—Transthoracic echocardiography
Arrythmias	Atrial fibrillation, ventricular arrhythmias—Electrocardiogram
Conduction alterations	Atrioventricular blocks, bundle branch blocks—Electrocardiogram
QTc interval	Prolonged QTc interval—Electrocardiogram

Simon et al, Eur Heart J 2007

Ismaiel et al, Front Med 2019



Mach et al, Eur Heart J 2020

Recommendations

6.6 An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) is appropriate. A

6.7 On the basis of provider judgement and patient preference, achievement of lower A1C levels (such as <6.5%) may be acceptable if this can be achieved safely without significant hypoglycemia or other adverse effects of treatment. C

6.8 Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.

Table 1. Screening for and diagnosis of prediabetes and type 2 diabetes, according to American Diabetes Association guidelines 2018.[16]

	Fasting plasma glucose*	Glucose tolerance (2-hour PG)#	Haemoglobin A1C§
Normal (NGT#)	FPG <100 mg/dl (5.6 mmol/L)	2-hour PG <140 mg/dl (7.8 mmol/L) during 75 g OGTT	<5.7% (39 mmol/mol)
Prediabetes (IFG and/or IGT#)	FPG from 100 mg/dl (5.6 mmol/L) to 125 mg/dl (6.9 mmol/L) (IFG)	2-hour PG from 140 mg/dl (7.8 mmol/L) to 199 mg/dl (11.0 mmol/L) (IGT#)	5.7 to 6.4% (39–47 mmol/mol)
Type 2 diabetes	FPG ≥126 mg/dl (7.0 mmol/L).	2-hour PG ≥200 mg/dl (11.1 mmol/L) during OGTT	≥6.5% (48 mmol/mol)

Approach to Individualization of Glycemic Targets

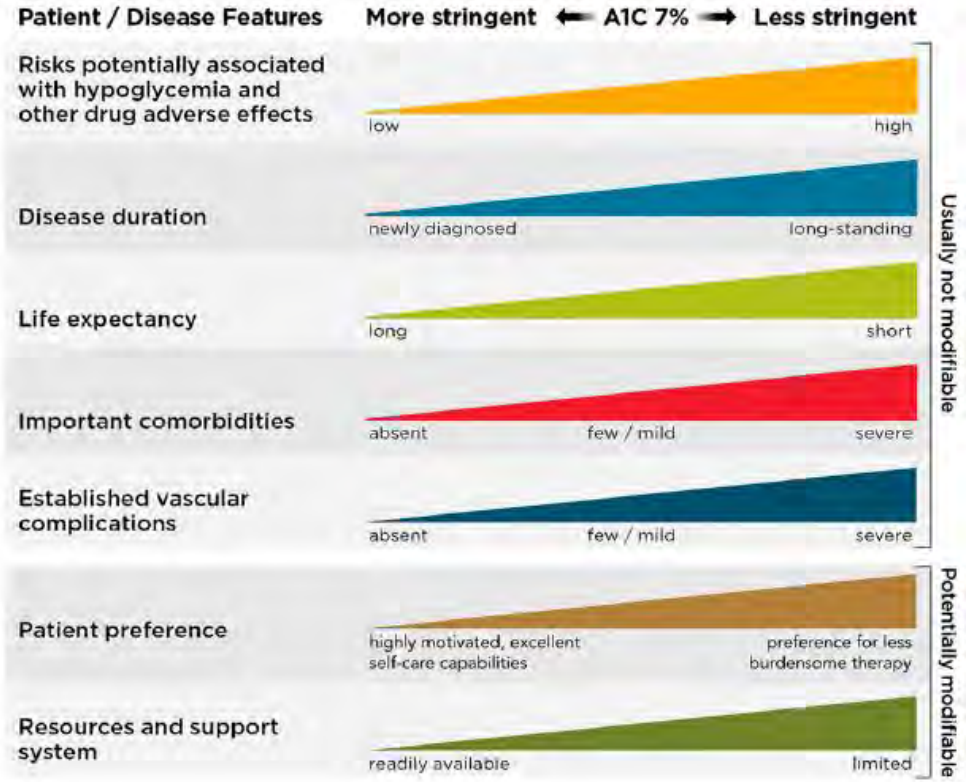


Table 6.1—Estimated average glucose (eAG)

A1C (%)	mg/dL*
5	97 (76–120)
6	126 (100–152)
7	154 (123–185)
8	183 (147–217)
9	212 (170–249)
10	240 (193–282)
11	269 (217–314)
12	298 (240–347)

Diabetes Care 2020

JOURNAL OF HEPATOLOGY

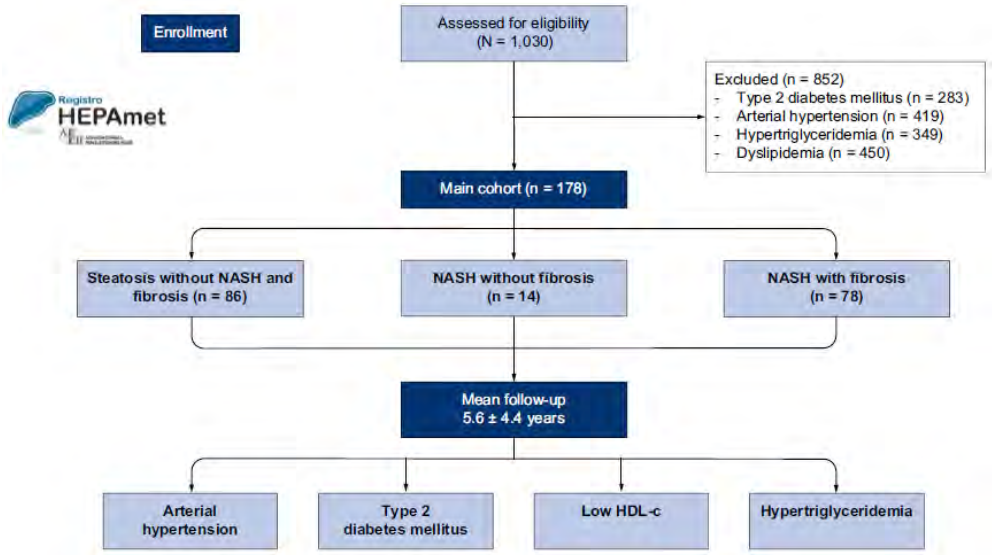
Research Article
NAFLD and Alcohol-Related Liver Diseases

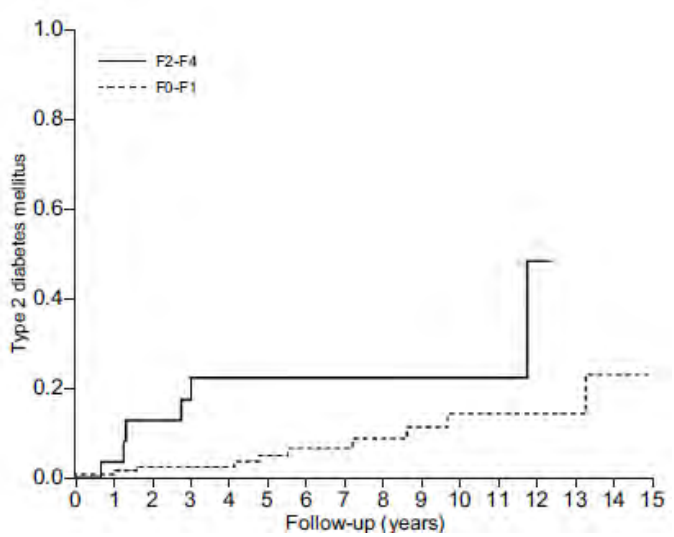
Significant fibrosis predicts new-onset diabetes mellitus and arterial hypertension in patients with NASH

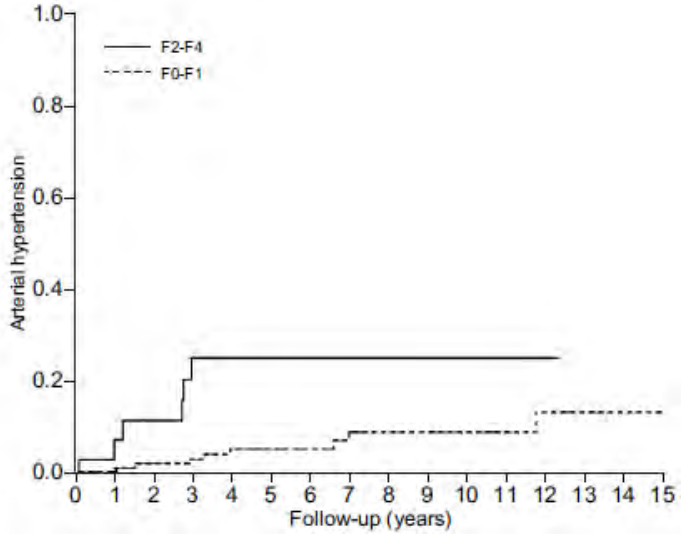
Table 4. Incidence rates of metabolic comorbidities in patients with NAFLD showing a metabolically healthy status.

A	F0–F1	F2–F4	F0–F1 and BMI <30 kg/m²	F0–F1 and BMI ≥30 kg/m²	F2–F4 and BMI <30 kg/m²	F2–F4 and BMI ≥30 kg/m²
T2DM	1.2	4.4	1.0	2.2	1.6	7.0
AHT	1.1	4.6	1.1	1.5	1.8	6.7
T2DM or AHT	2.4	6.6	2.3	2.9	1.8	10.6

B	Type 2 diabetes mellitus		Arterial hypertension	
Cumulative Incidence	F2–F4	F0–F1	F2–F4	F0–F1
1-year	2.9% (1/35)	0.7% (1/143)	2.9% (1/35)	0.7% (1/143)
3-year	11.4% (4/35)	2.1% (3/143)	14.3% (5/35)	2.8% (4/143)
5-year	14.3% (5/35)	3.5% (5/143)	17.1% (6/35)	4.2% (6/143)
10-year	14.3% (5/35)	6.3% (9/143)	17.1% (6/35)	5.6% (8/143)
15-year	17.1% (6/35)	7% (10/143)	17.1% (6/35)	6.3% (9/143)







Ampuero et al, J Hepatol 2020

Conclusiones

¿Qué nos llevamos a casa?

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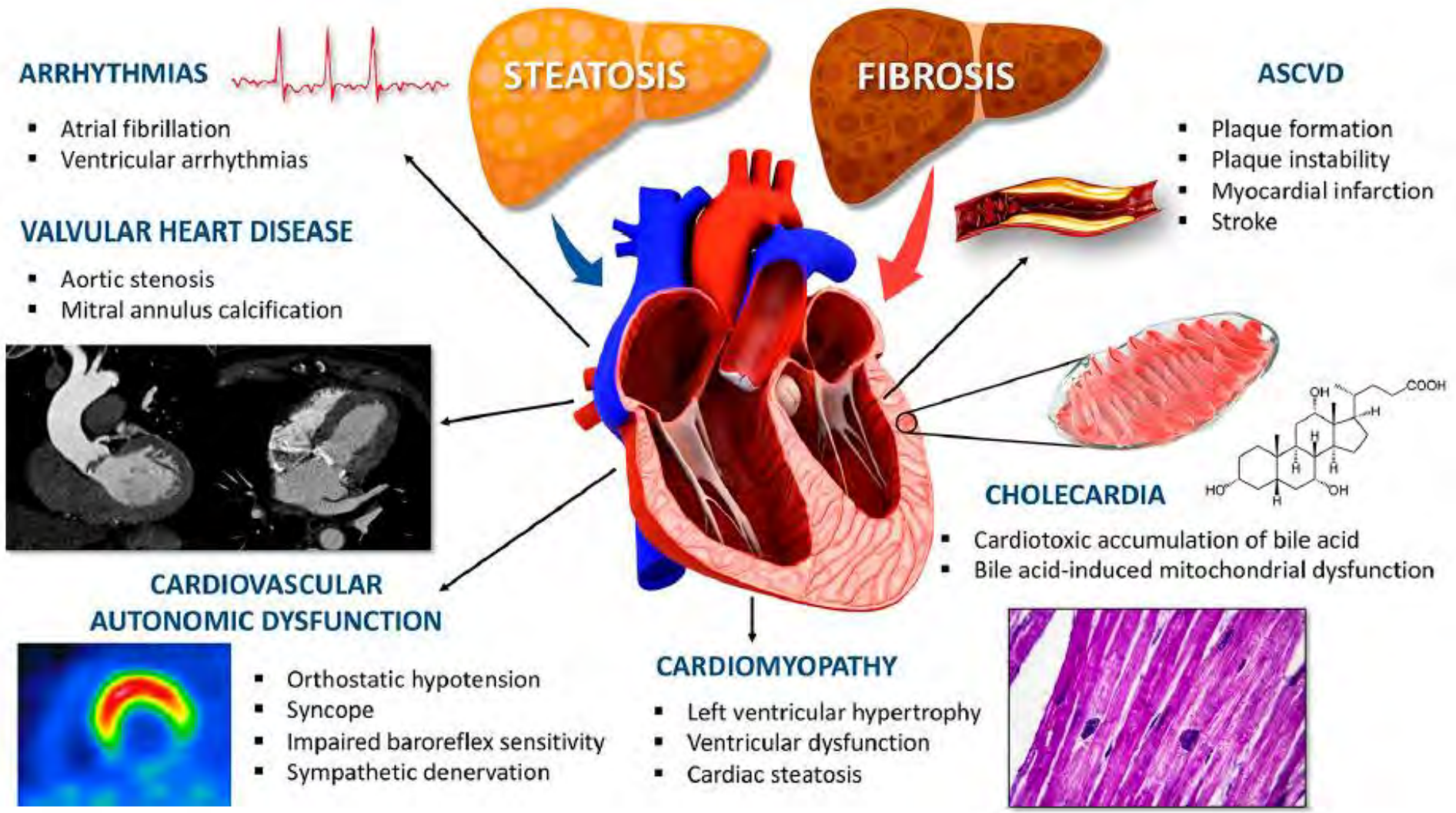

Bisaccia et al, SAGE Open Med 2020

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