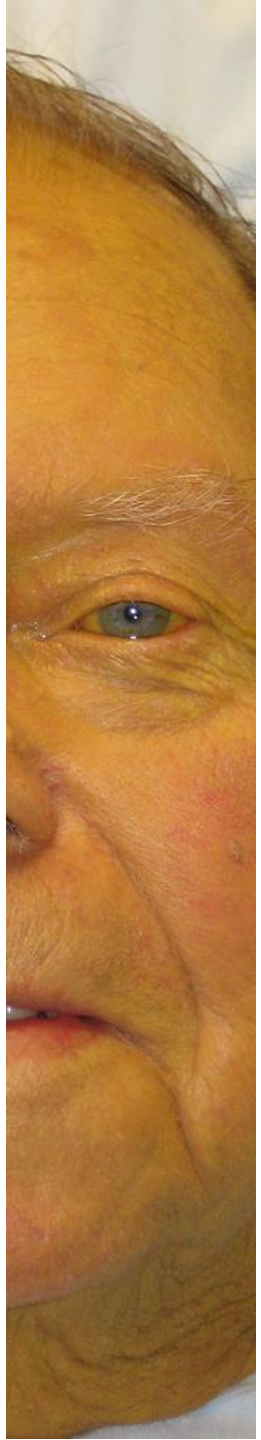
O doente com Hipercolesterolemia Primária

Francisco Araújo
Hospital Beatriz Ângelo



H 69 anos,
icterícia e prurido, associada a colúria e fezes acólicas, c/8 dias de evolução.

Negava: febre, dor abdominal, emagrecimento ou anorexia, história familiar de doenças hepáticas, episódios anteriores de icterícia em momentos de maior stress…

Hábitos etanólicos: 1 copo 150cc vinho tinto diário

Medicação lisinopril desde há cerca de 2 meses

Negava viagens recentes para fora do país, contactos sexuais de risco ou hábitos toxifílicos, contacto habitual c/cães, gatos, ratos.

	AST	ALT	gGT	F Alc	Bil T	Col T	LDL	HDL	TG
25-07-12	**304**	**306**	**667**	**842**	**15,9**	**422**	**387**	-	136

Eco, TC Abdómen fígado e Vb normais

Estudo negativo para hepatites virais (A,B,C,E,EBV,CMV), brucelose, febre escaro-nodular hepatite autoimune, cirrose biliar primária, Dç Wilson, hemocromatose, deficit alfa1-antitripsina e sarcoidose

Biopsia hepática: colangite activa com componente de eosinófilos, padrão sugestivo de acção de drogas. Aspectos morfológicos a serem correlacionados com a clínica.

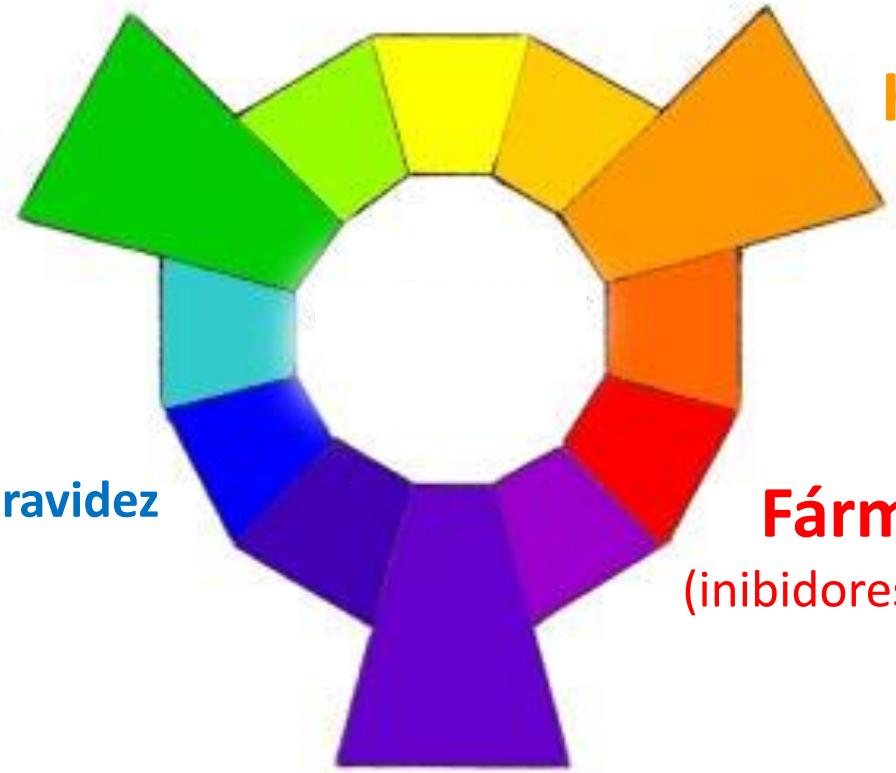
Tx: suspensão lisinopril e melhoria da icterícia

	AST	ALT	gGT	F Alc	Bil T	Col T	LDL	HDL	TG
25-07-12	304	306	667	842	**15,9**	**422**	**387**	-	136
01-04-13	18	36	50	98	**0,77**	**203**	**128**	49	129

Causas secundárias de Hipercolesterolemia

Porfíria

Colestase



Hipotiroidismo

Gravidez

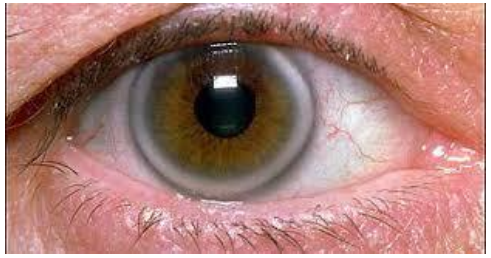
Fármacos
(inibidores protease)

Síndrome Nefrótico

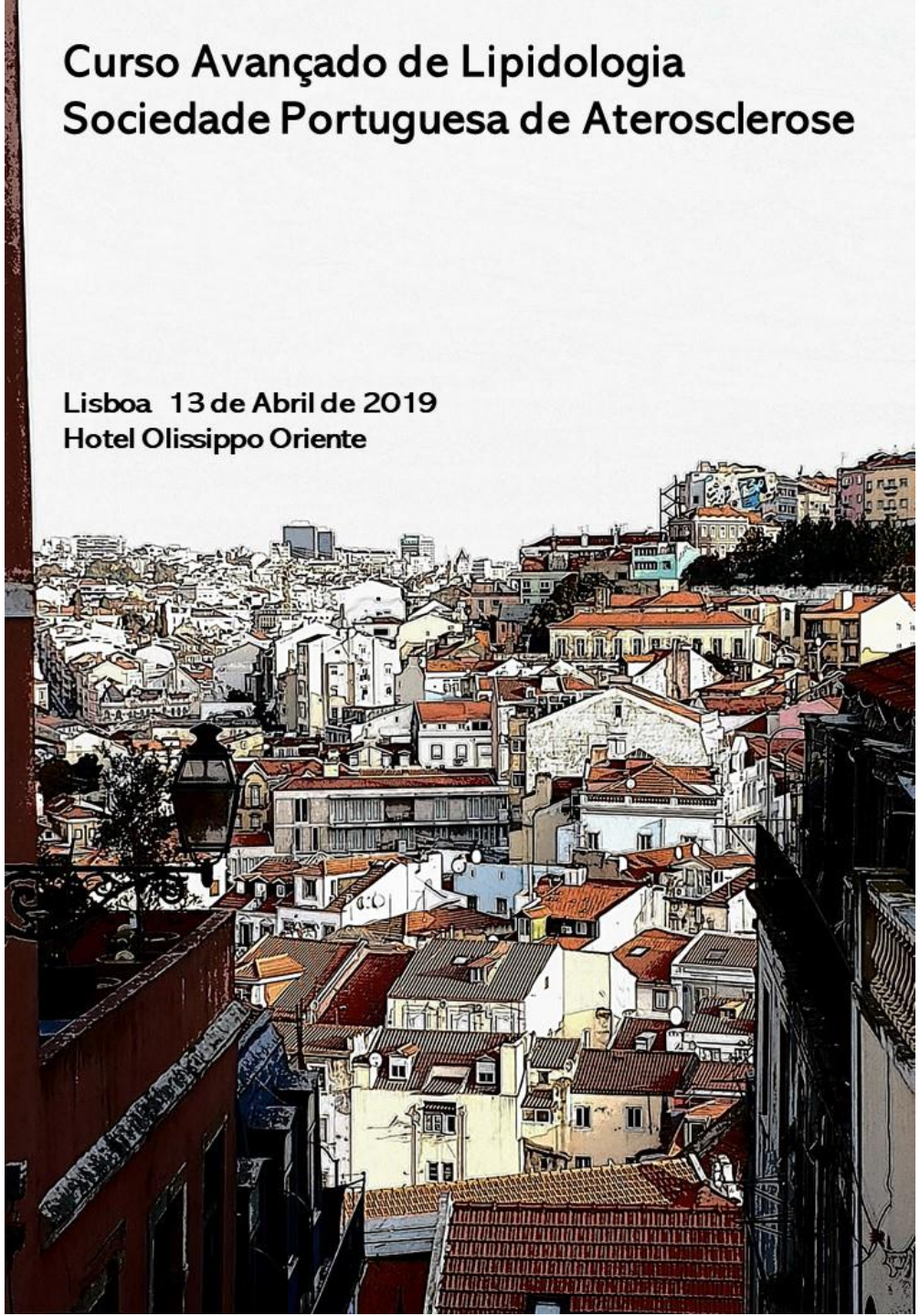
- Homem de 43 anos, recorre à consulta pós análises na medicina do trabalho.
- Engenheiro informático, não fuma, joga Padel. Pai EAM aos 60, dois filhos saudáveis

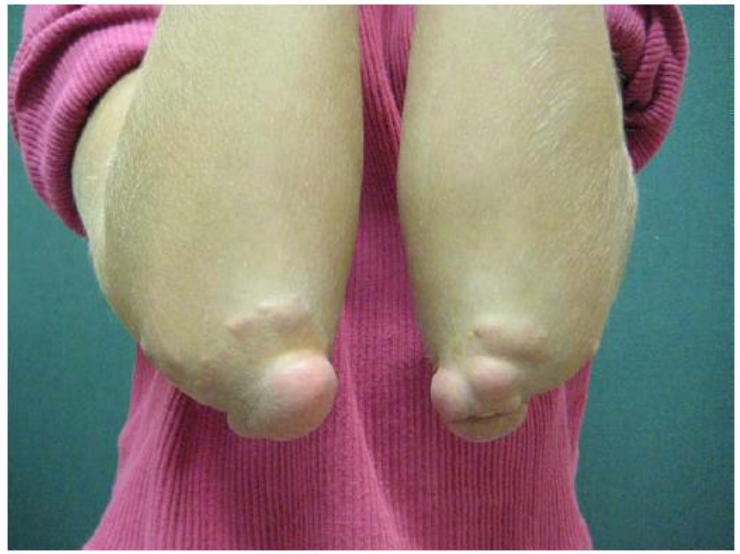
	Col T	LDL	HDL	TG
20-03-18	**370**	**250**	88	160

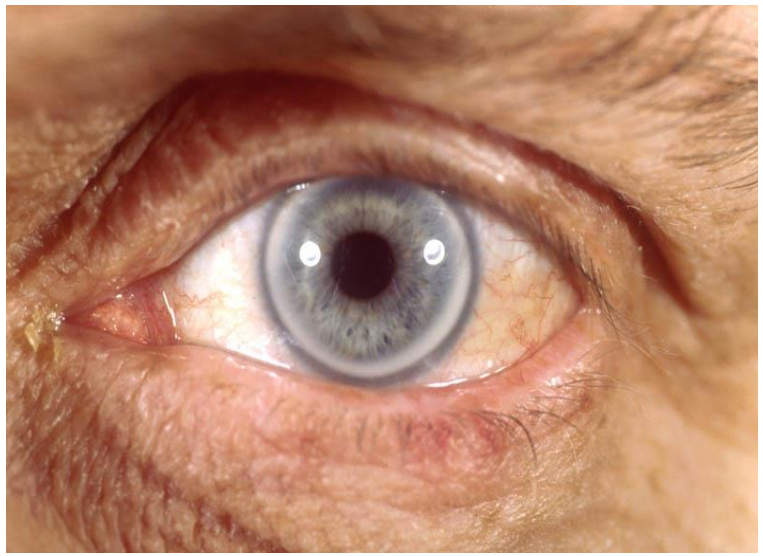
- Já sabia destas análises há mais tempo. Sempre lhe disseram que o colesterol bom, anulava o mau .
- Não faz terapêutica. Cuidado com dieta..

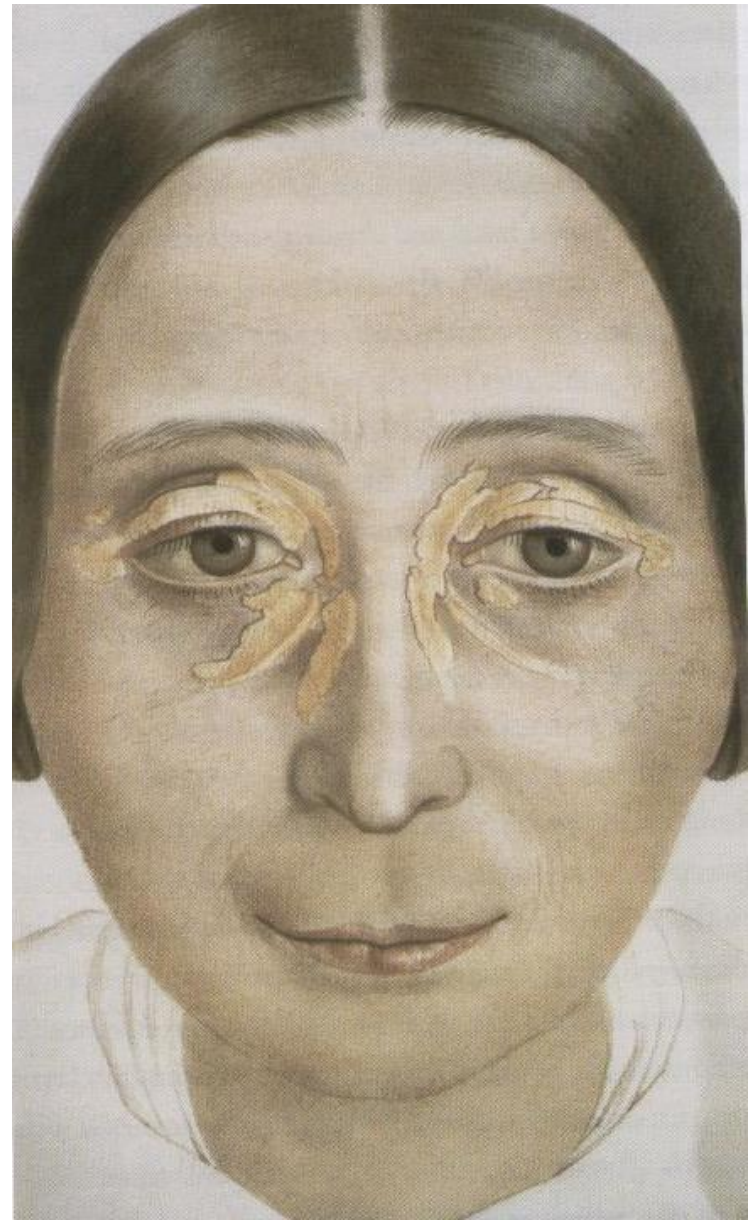


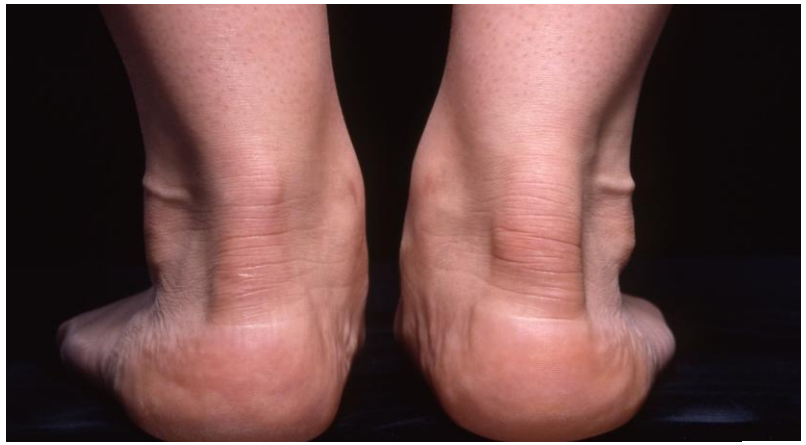
Que procurar no exame objectivo ?







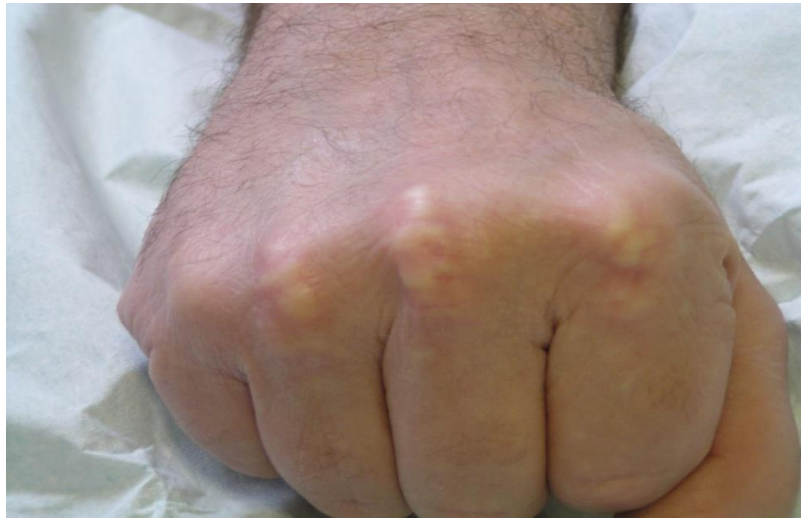




Xantomas Tendinosos

10-25% não têm HF

xantomatose cérebro-tendinosa
sitosterolemia



apenas 33% mutação LDL-R

e 19% mutação apoB

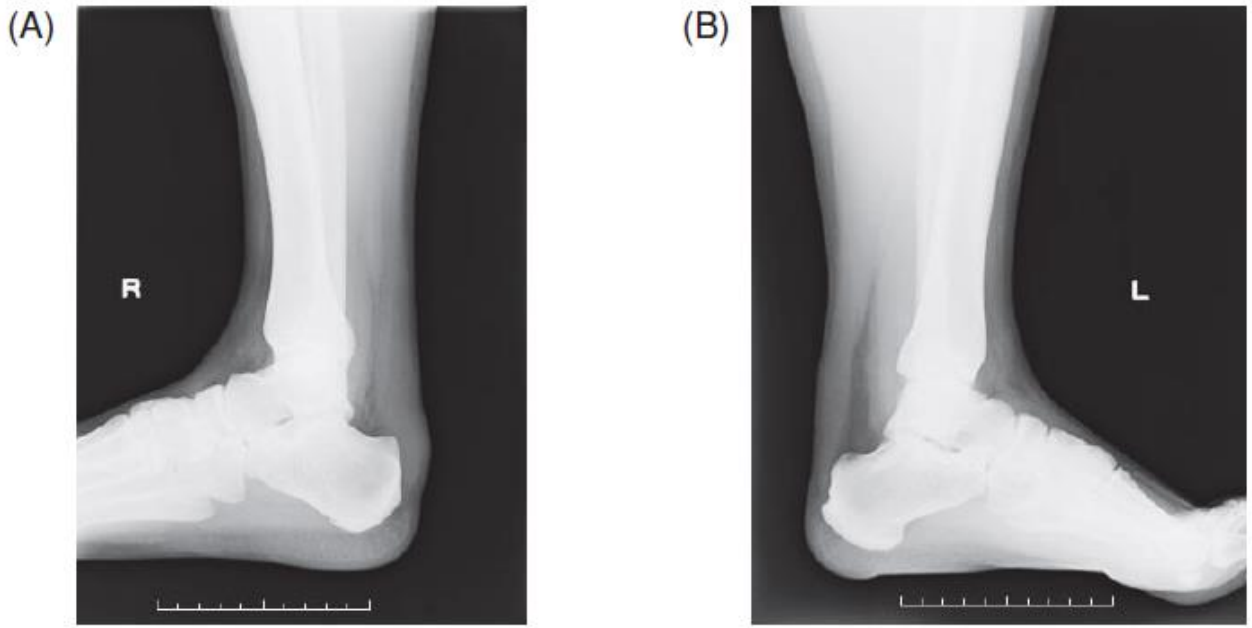
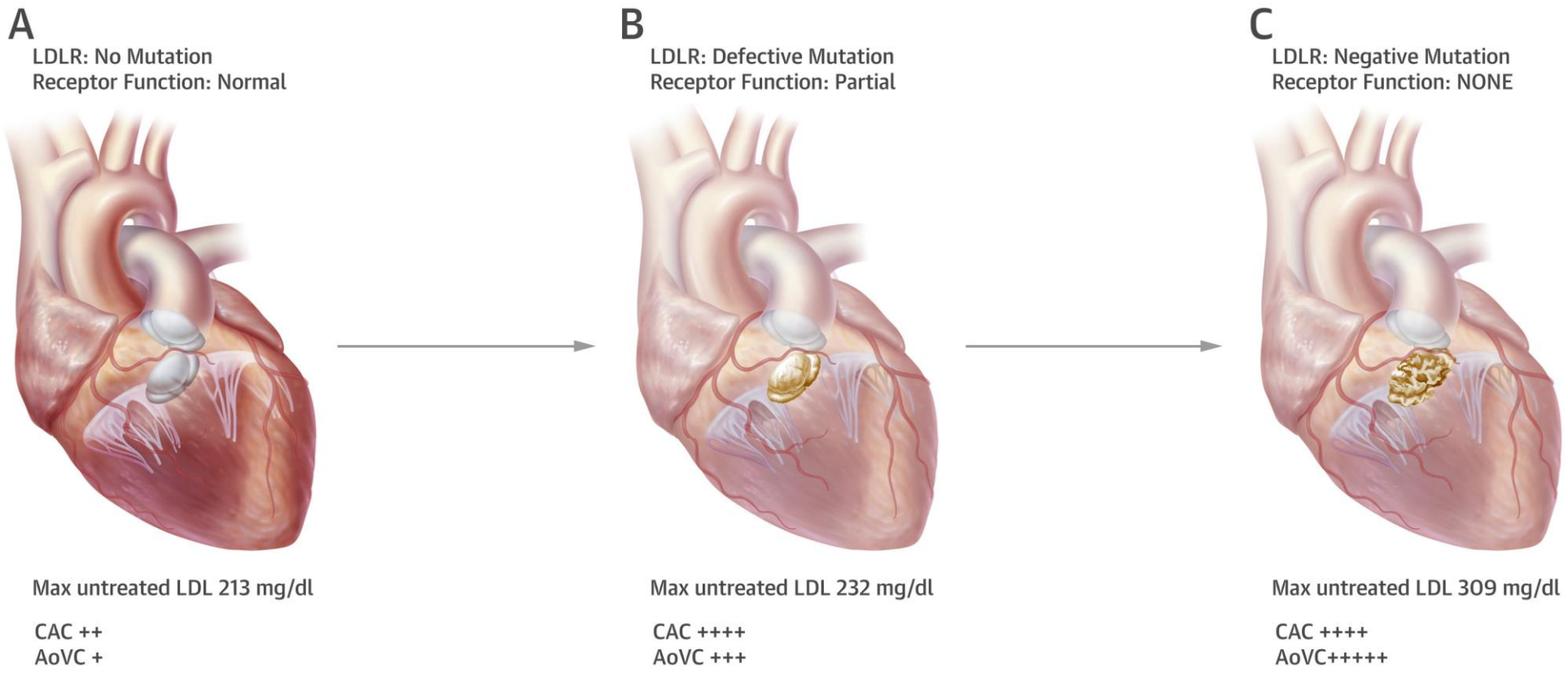


Fig. 7. Radiograms of the Achilles tendon in FH patients. (A) Achilles tendon in a 40-year-old man (maximun thickness: 22 mm), (B) Achilles tendon in a 29-year-old man (maximum thickness: 19 mm).

9 mm

Estenose aórtica

Em pessoas entre os 50-60 anos
EA 30-40 % HF
EA 0,2% pop geral



FH DUTCH CLINIC CRITERIA

Group 1 Family history	Points
First degree relative with Known premature CHD (<55 y in men, <60 years in women)	1
•Known LDL cholesterol >95th percentile by age and gender for country •Tendon xanthoma and/or corneal arcus •Children <18 years with LDL chol >95th percentile by age and gender for country	1 2 2
Group 2 Clinical history	
•Premature CHD (<55 years, men; <60 years, women*) •Premature cerebral or peripheral vascular disease (*)	2 1
Group 3 Clinical examination	
•Tendon xanthoma •Corneal arcus in a person <45 years	6 4
Group 4 Biochemistry (LDL cholesterol)	
• >325 mg/dL • 251-325 mg/dL • 191-250 mg/dL • 155-190 mg/dL	8 5 3 1
Group 5 Molecular genetic testing	
Causative mutation in the LDLR, APOB, or PCSK9 genes	8

The highest single score in each group is considered.
Score >8 definite FH; 6-8 probable FH; 3-5 possible FH; 0-2 unlikely FH

Management of Familial Hypercholesterolemia: A Review of the Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

- The likelihood of FH is higher in individuals with a positive family history of hypercholesterolemia or of premature CHD (onset in men aged < 55 years and women aged < 65 years).

MEDPED – make early diagnosis to prevent early deaths

Níveis de CT e de LDL sugestivos de HF em doentes não tratados

Ages	First-Degree Relative	Second-Degree Relative	Third-Degree Relative	General Population
< 18 years	220 (155) CT (LDL)	230 (165)	240 (170)	270 (200)
20-29 years	240 (170)	250 (180)	260 (185)	290 (220)
30-39 years	270 (190)	280 (200)	290 (210)	340 (240)
≥ 40 years	290 (205)	300 (215)	310 (225)	360 (260)

- Cholesterol screening should be considered beginning at age 2 for children with a family history of premature CVD or elevated cholesterol levels. All individuals should be screened by age 20.

J Manag Care Pharm. 2013;19(2):139-49

Simon Broome Criteria Diagnosis of FH

“DEFINITIVE” FH

TC greater than 290 mg/dL or LDL-C greater than 190 mg/dL in adults TC greater than 260 mg/dL or LDL-C greater than 155 mg/dL in children aged less than 16 years AND Tendon Xanthoma in patient or a first degree relative
OR
DNA based evidence of mutation in LDLR, APOB, or PCSK9

“PROBABLE” FH

TC greater than 290 mg/dL or LDL-C greater than 190 mg/dL in adults TC greater than 260 mg/dL or LDL-C greater than 155 mg/dL in children aged less than 16 years AND Family history of MI under 50 years of age in a second degree relative or under 60 years of age in a first degree relative
OR
TC greater than 290 mg/dL or LDL-C greater than 190 mg/dL in adults TC greater than 260 mg/dL or LDL-C greater than 155 mg/dL in children aged less than 16 years AND Family history of TC greater than 290 mg/dL in a first or second degree relative

The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Correspondence

J Atheroscler Thromb, 2018; 25: 751-770. http://doi.org/10.5551/jat.CR003

Guidelines for Diagnosis and Treatment of Familial Hypercholesterolemia 2017

Table 1. Diagnostic criteria for heterozygous FH in Adults (15 years of age or older)

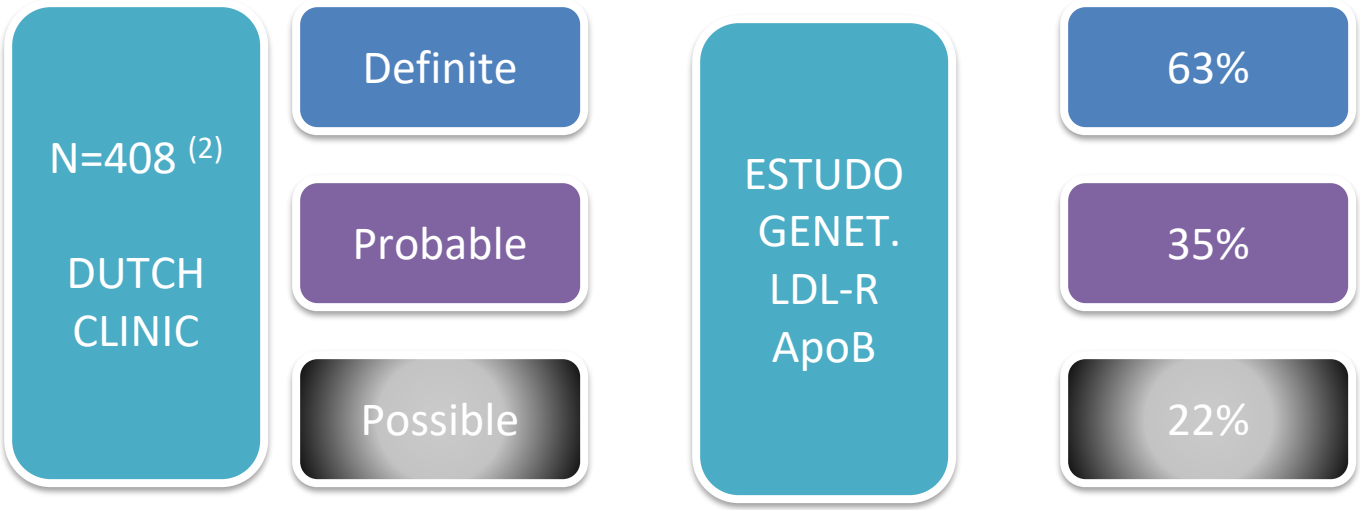
- Hyper-LDL-cholesterolemia (an untreated LDL-C level ≥ 180 mg/dL)
- Tendon xanthomas (thickening of tendons on dorsal side of the hands, elbows, knees or Achilles tendon hypertrophy) or xanthoma tuberosum
- Family history of FH or premature CAD (within the patient's second-degree relatives)

- The diagnosis should be made after excluding secondary dyslipidemia.
- If a patient meets two or more of the above-mentioned criteria, the condition should be diagnosed as FH. In case of suspected heterozygous FH, making a diagnosis using genetic testing is desirable.
- Xanthelasma is not included in xanthoma tuberosum.
- Achilles tendon hypertrophy is diagnosed if the Achilles tendon thickness is ≥ 9 mm on X-ray imaging. (See Appendix)
- An LDL-C level of ≥ 250 mg/dL strongly suggests FH.
- If a patient is already receiving drug therapy, the lipid level before treatment should be used as the reference for diagnosis.
- Premature CAD is defined as the occurrence of CAD in men <55 years of age or women <65 years of age, respectively.
- If FH is diagnosed, it is preferable to also examine the patient's family members.
- These diagnostic criteria also apply to HoFH.

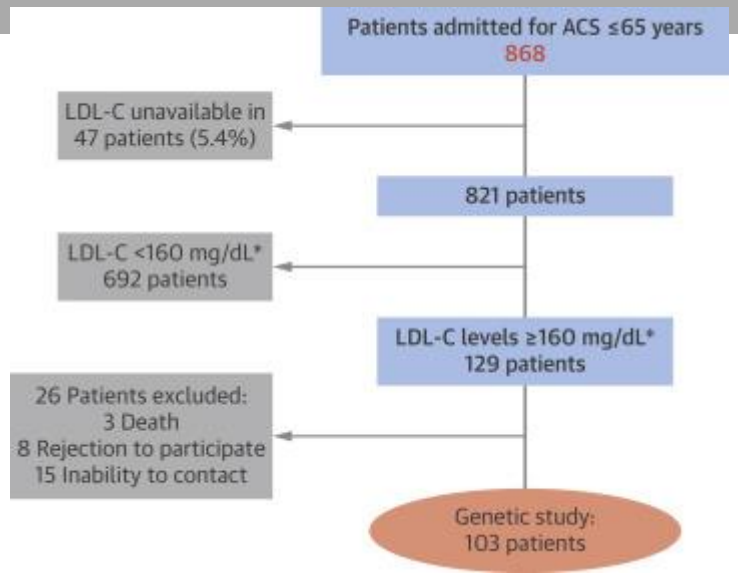
Failure to identify a distinct variant in LDLR, APOB or PCSK9 in a patient with a presentation suggestive of FH does not exclude the diagnosis

Molecular genetic analysis can be expanded to encompass LDLRAP1 and APOE.

With advances in next-generation sequencing additional novel genes for FH are likely to be discovered (1)



(1) Maya S. Safarova, Iftikhar J. Kullo, My Approach to the Patient With FamilialHypercholesterolemia Mayo Clin Proc. 2016;91(6):770-786
(2) Damgaard D, Larsen ML, Nissen PH, et al. The relationship of molecular genetic to clinical diagnosis of familial hypercholesterolemia in a Danish population. Atherosclerosis. 2005;180(1): 155-160.



Genetically Confirmed Familial Hypercholesterolemia in Patients With Acute Coronary Syndrome

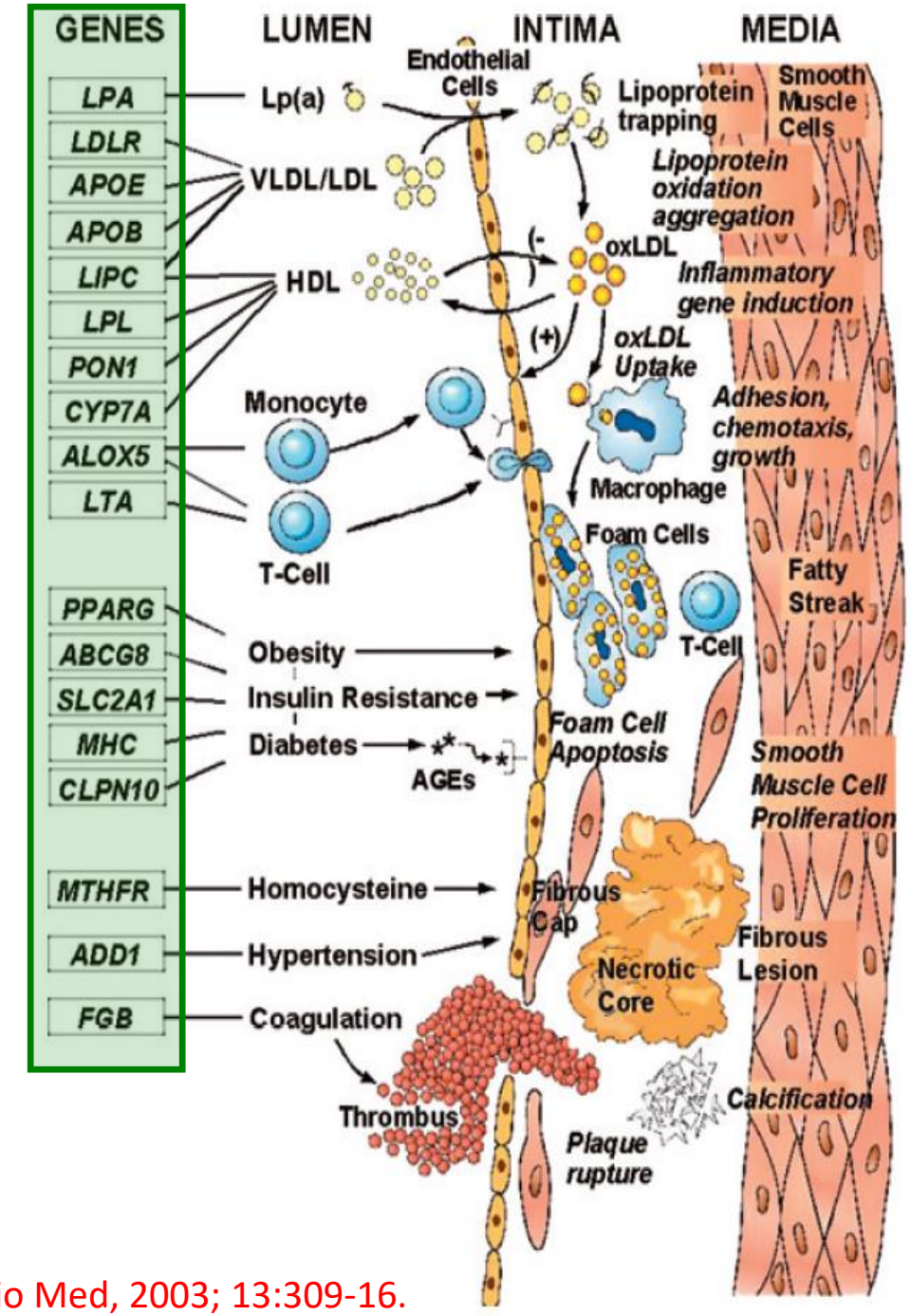
Amor-Salamanca, A. et al. J Am Coll Cardiol. 2017;70(14):1732-40.

Dutch Lipid Clinic Criteria	Simon Broome Criteria	Genetic Study
Unlikely FH: 23 (22.3)	Unlikely FH: 75 (72.8)	Negative: 62 (60.2)
Possible FH: 52 (50.4)	Possible FH: 26 (25.2)	VUS: 32 (31.1)
Probable FH: 16 (15.5)	Definite FH: 2 (1.9)	Pathogenic: 9 (8.7)
Definite FH: 12 (11.7)		

- DLC and SB algorithms failed to diagnose 4 (44%) and 3 (33%) patients with genetically confirmed FH, respectively.

- Cascade genetic testing in first-degree relatives identified 6 additional individuals with FH

Genes contributing to CAD susceptibility

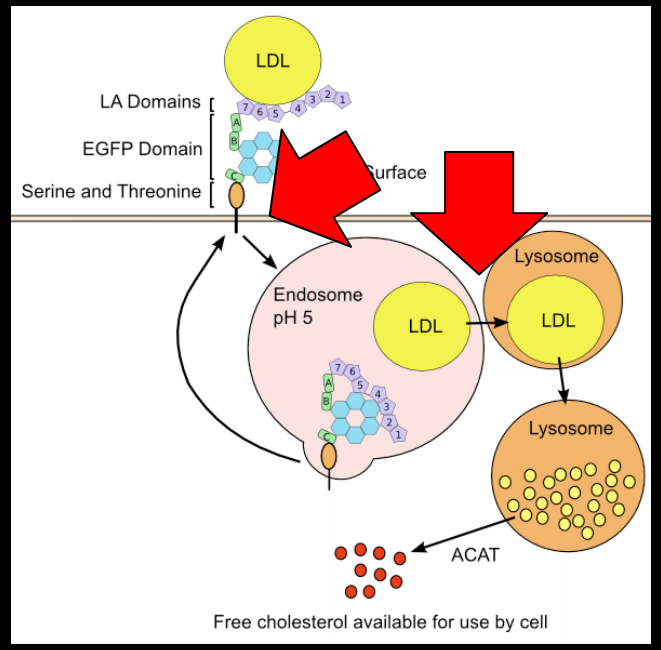


Lusis A, Trends Cardio Med, 2003; 13:309-16.

HF Autossomica Recessiva

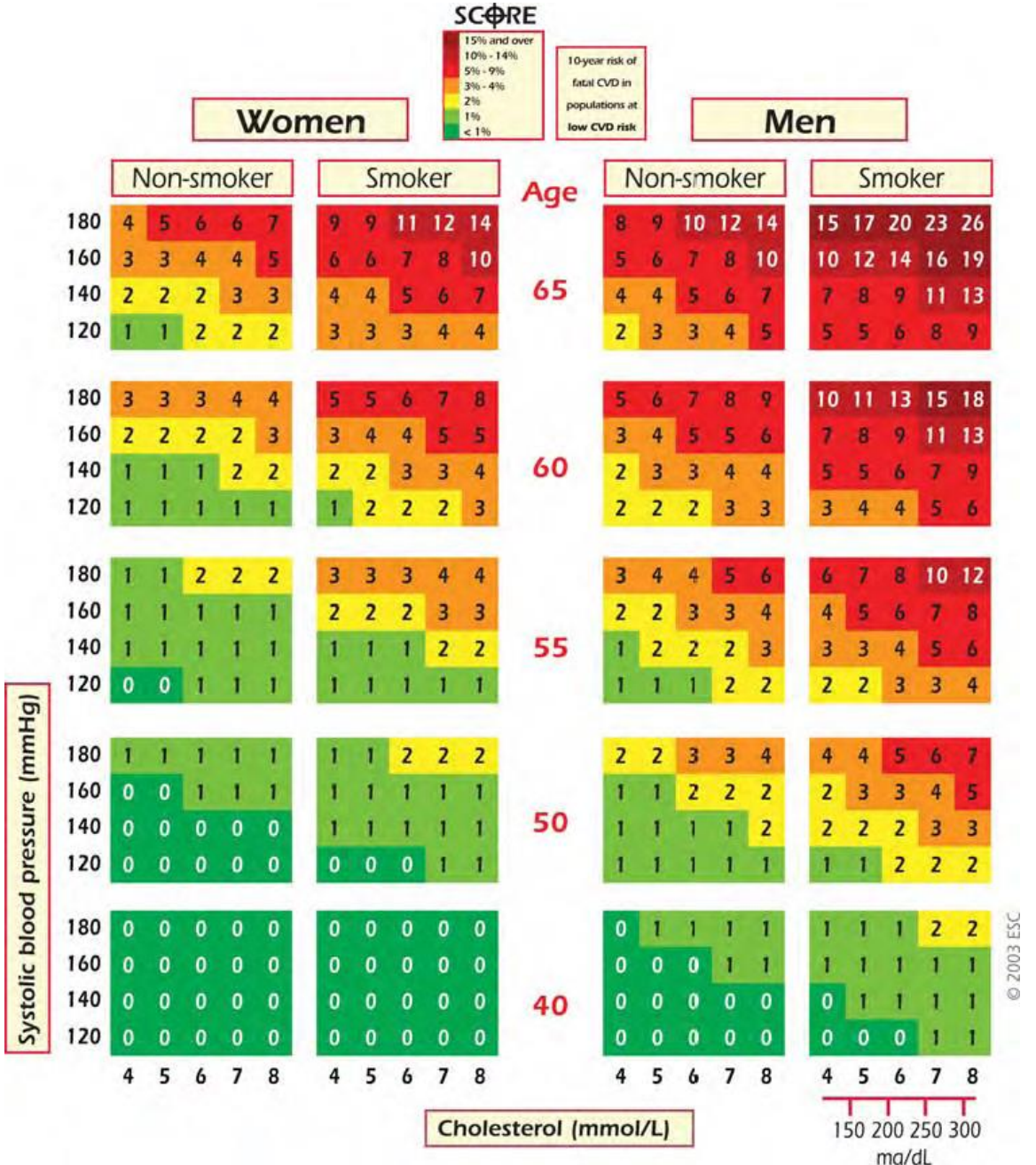
Chave x: crianças com níveis CT 350-500, pais com CT N

Associada a mutação cromossoma 1



- N função do LDL R em cultura de fibroblastos (D Dif com HF)
- Normal Ligação LDL com LDL R
- Defeito na internalização e degradação de LDL no lisossoma

tabela SCORE de cálculo de risco a 10 anos para indivíduos provenientes de áreas de BAIXO RISCO entre os quais se encontra Portugal



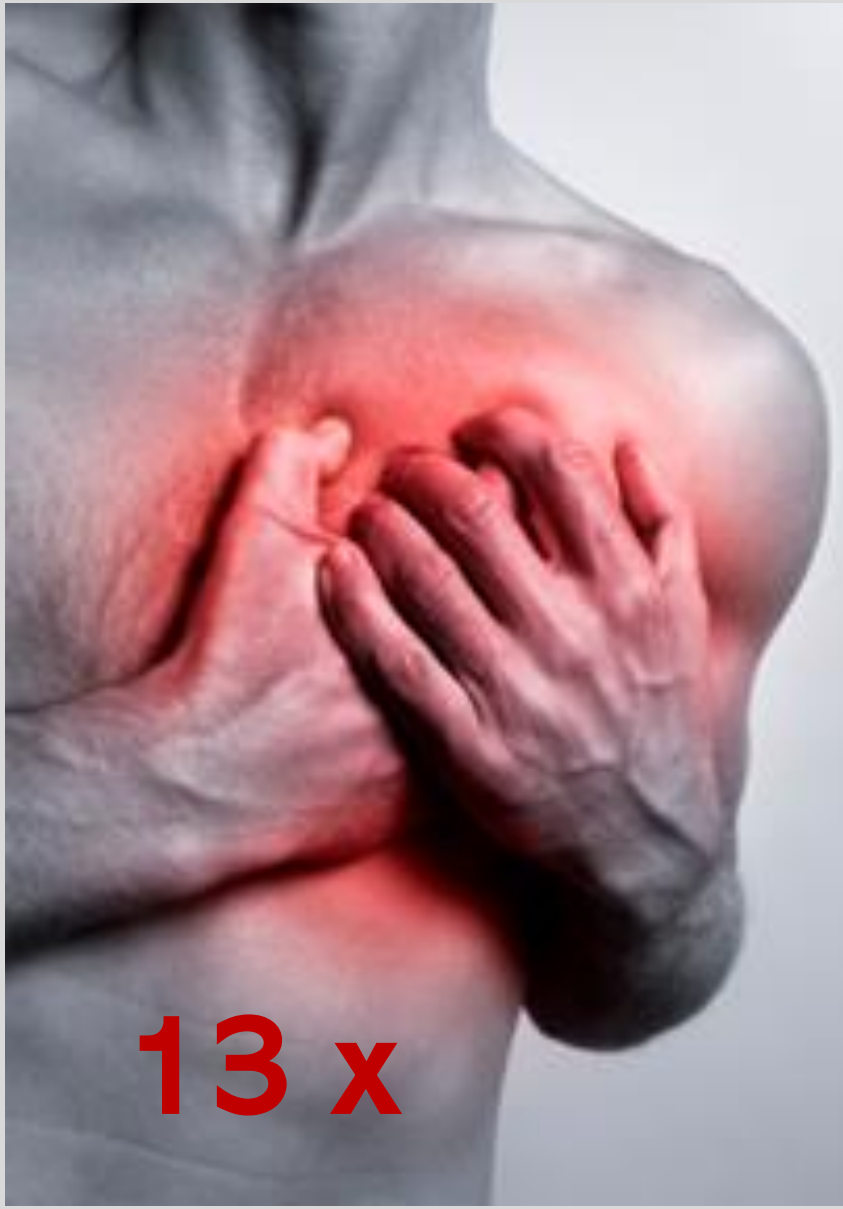
Other risk markers / factors

Recommendations	Class	Level
Assessment of family history of premature CVD (55M/65F)	I	C
Generalized use of DNA-based tests	III	B
Coronary artery calcium scoring	II b	B
Ankle–brachial index	II b	B
Atherosclerotic plaque detection by carotid artery scanning	II b	B
Carotid ultrasound IMT screening	III	A

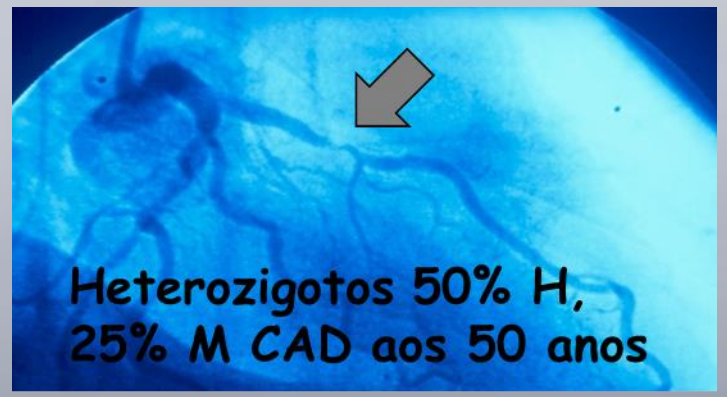
2016 ESC/EAS Guidelines
for the Management of Dyslipidaemias

Nível de Colesterol Total > 310 mg/dL

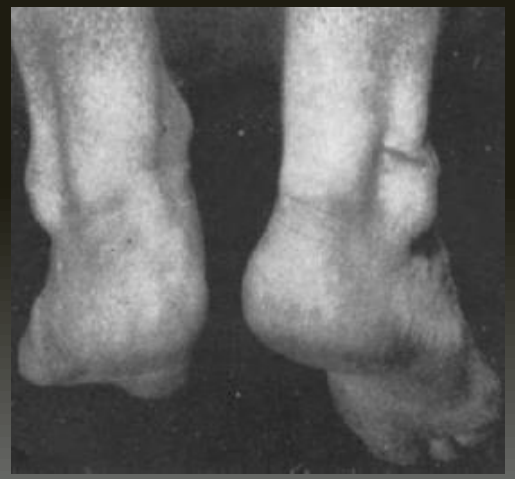
VERY HIGH RISK	• Documented clinical CVD: previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. . Documented clinical CVD: plaque on coronary angiography or carotid ultrasound. It does NOT include intima–media thickness 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 m2). • A calculated SCORE ≥10%.
HIGH RISK	• Markedly elevated single risk factors. Ex: cholesterol >310 mg/dL, or BP ≥180/110 mmHg. • Most other people with DM • Moderate CKD (GFR 30–59 mL/min/1.73 m2). • A calculated SCORE ≥5% and <10%.
Moderate R.	SCORE is ≥1% and <5% at 10 years.
Low Risk	SCORE <1%

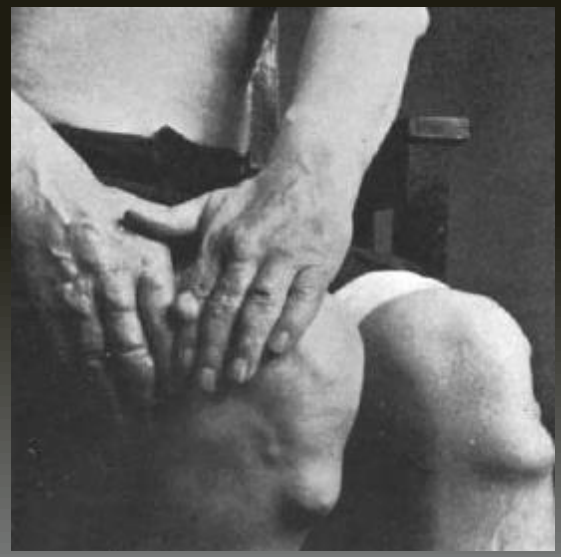


15% doentes com EAM e < 60 anos têm HF



Carl Müller,
Angina pectoris in hereditary xanthomatosis.
Arch. Intern. Med.1939; **64:**675–700.



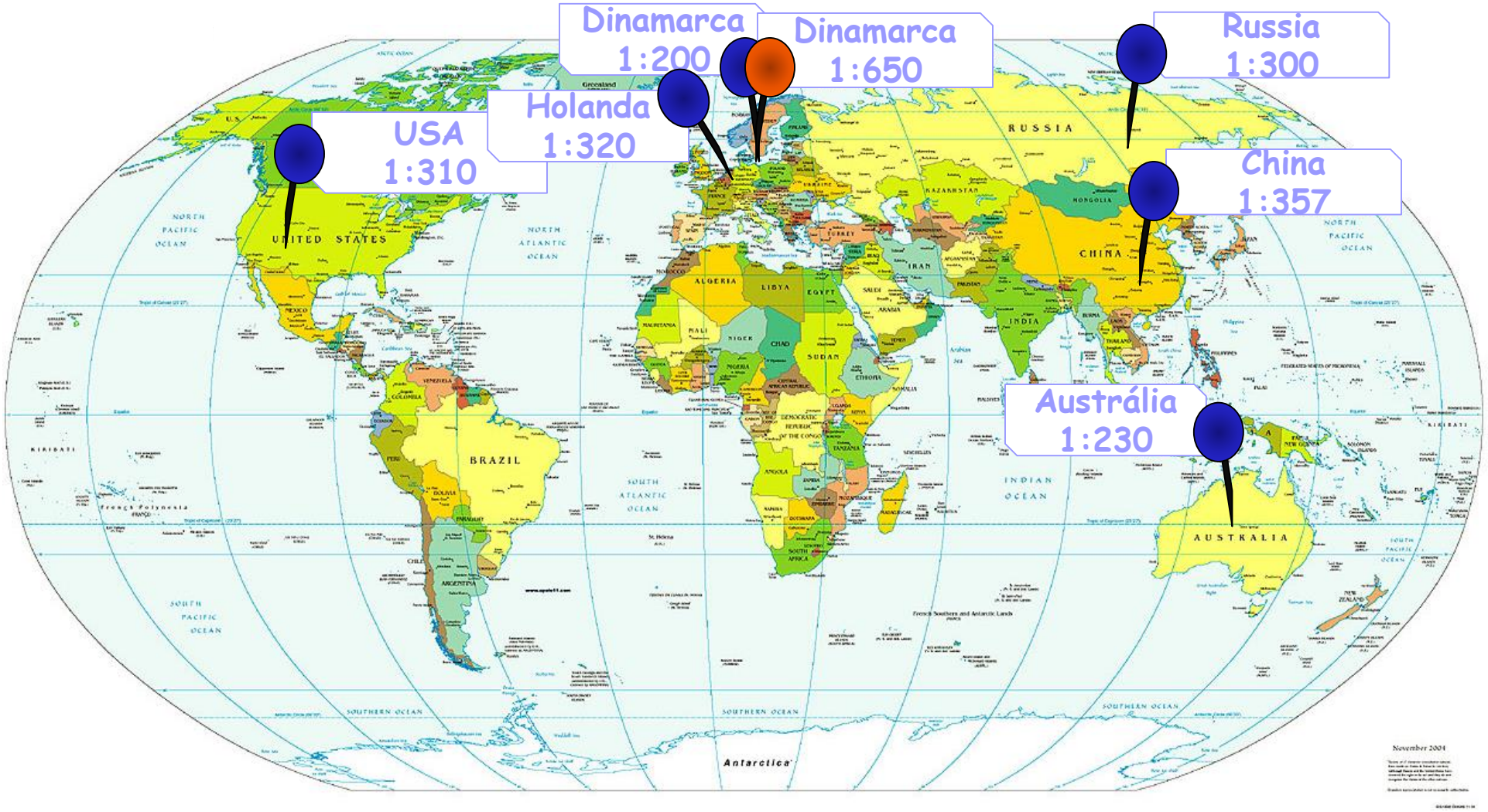


The reports I have presented confirm the previous observations on xanthomatosis as a cause of hereditary heart disease.
They reveal further that the syndrome of cutaneous xanthomatosis, hypercholesterolemia and angina pectoris presents itself as a well defined clinical entity .

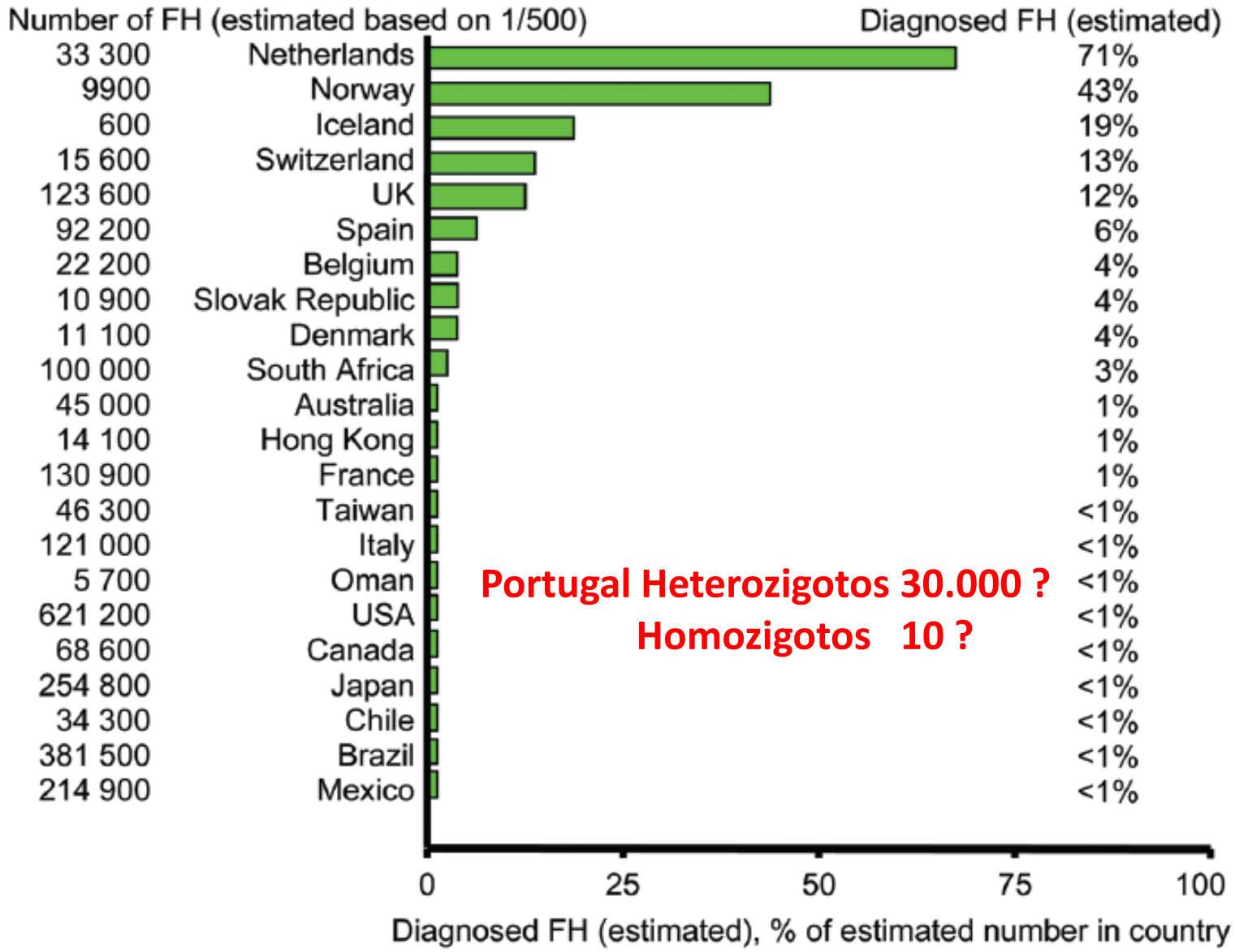
Prevalência da FH heterozigota

Clinica vs Genética

Geral 1:200-500



Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population



European Heart Journal doi:10.1093/eurheartj/eht273

Mutational analysis of a cohort with clinical diagnosis of familial hypercholesterolemia: considerations for genetic diagnosis improvement.

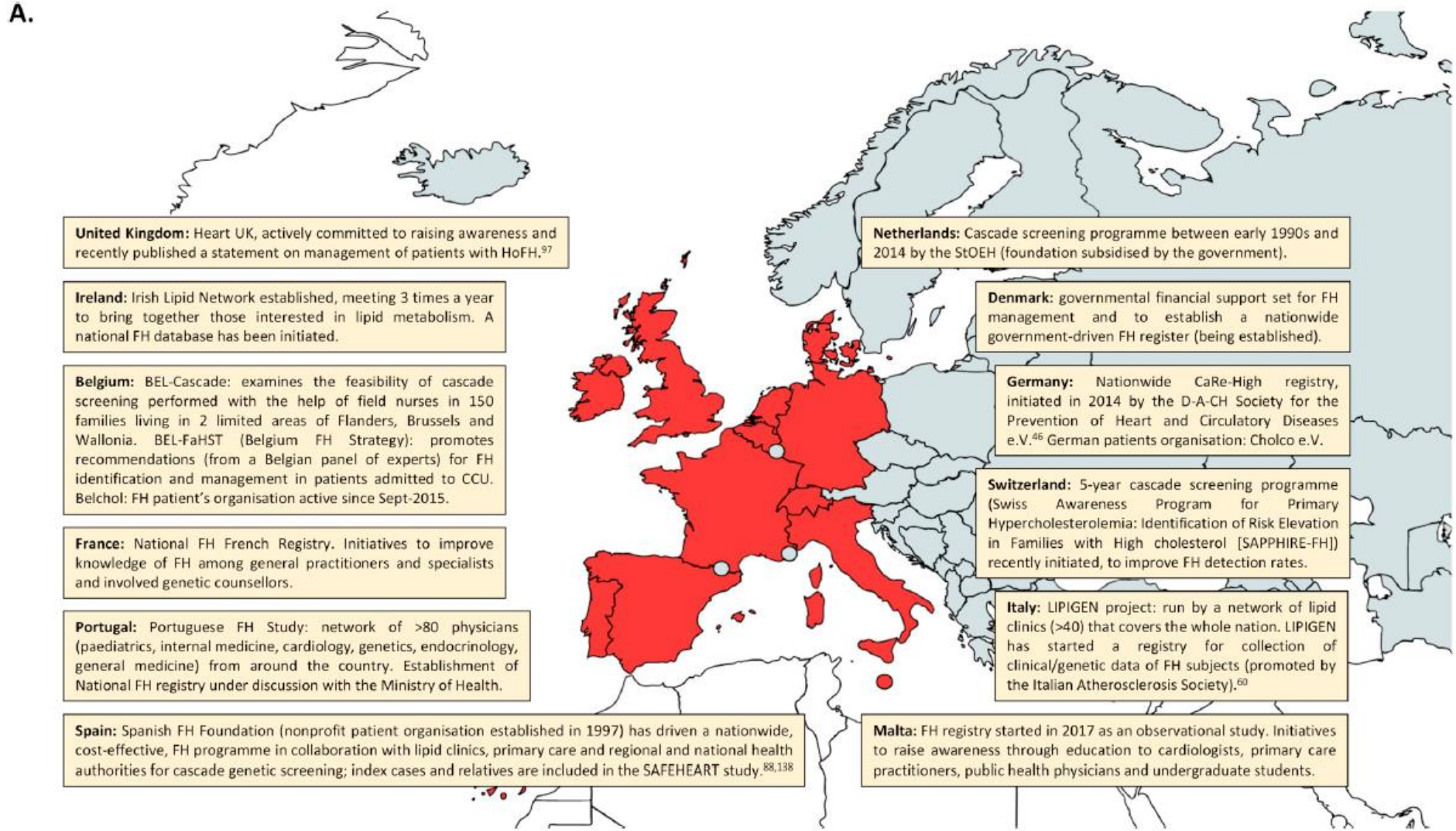
Medeiros AM, Alves AC, Bourbon M

- A total of 2,122 individuals were enrolled.
- identified 660 heterozygous pts: LDLR (623), APOB (33), and PCSK9 (4)
- 8 patients presented with homozygous FH.
- A detection rate of 41.5% was observed.
- Overall, we have identified 3.4% and 80% of all heterozygous and homozygous patients, respectively, estimated to exist in our country

Genetics in Medicine (2016) 18, 316–324

EAS Familial Hypercholesterolaemia Studies Collaboration

A.



United Kingdom: Heart UK, actively committed to raising awareness and recently published a statement on management of patients with HoFH.[97]

Ireland: Irish Lipid Network established, meeting 3 times a year to bring together those interested in lipid metabolism. A national FH database has been initiated.

Belgium: BEL-Cascade: examines the feasibility of cascade screening performed with the help of field nurses in 150 families living in 2 limited areas of Flanders, Brussels and Wallonia. BEL-FaHST (Belgium FH Strategy): promotes recommendations (from a Belgian panel of experts) for FH identification and management in patients admitted to CCU. Belchol: FH patient's organisation active since Sept-2015.

France: National FH French Registry. Initiatives to improve knowledge of FH among general practitioners and specialists and involved genetic counsellors.

Portugal: Portuguese FH Study: network of >80 physicians (paediatrics, internal medicine, cardiology, genetics, endocrinology, general medicine) from around the country. Establishment of National FH registry under discussion with the Ministry of Health.

Spain: Spanish FH Foundation (nonprofit patient organisation established in 1997) has driven a nationwide, cost-effective, FH programme in collaboration with lipid clinics, primary care and regional and national health authorities for cascade genetic screening; index cases and relatives are included in the SAFEHEART study.[88,138]

Netherlands: Cascade screening programme between early 1990s and 2014 by the StOEH (foundation subsidised by the government).

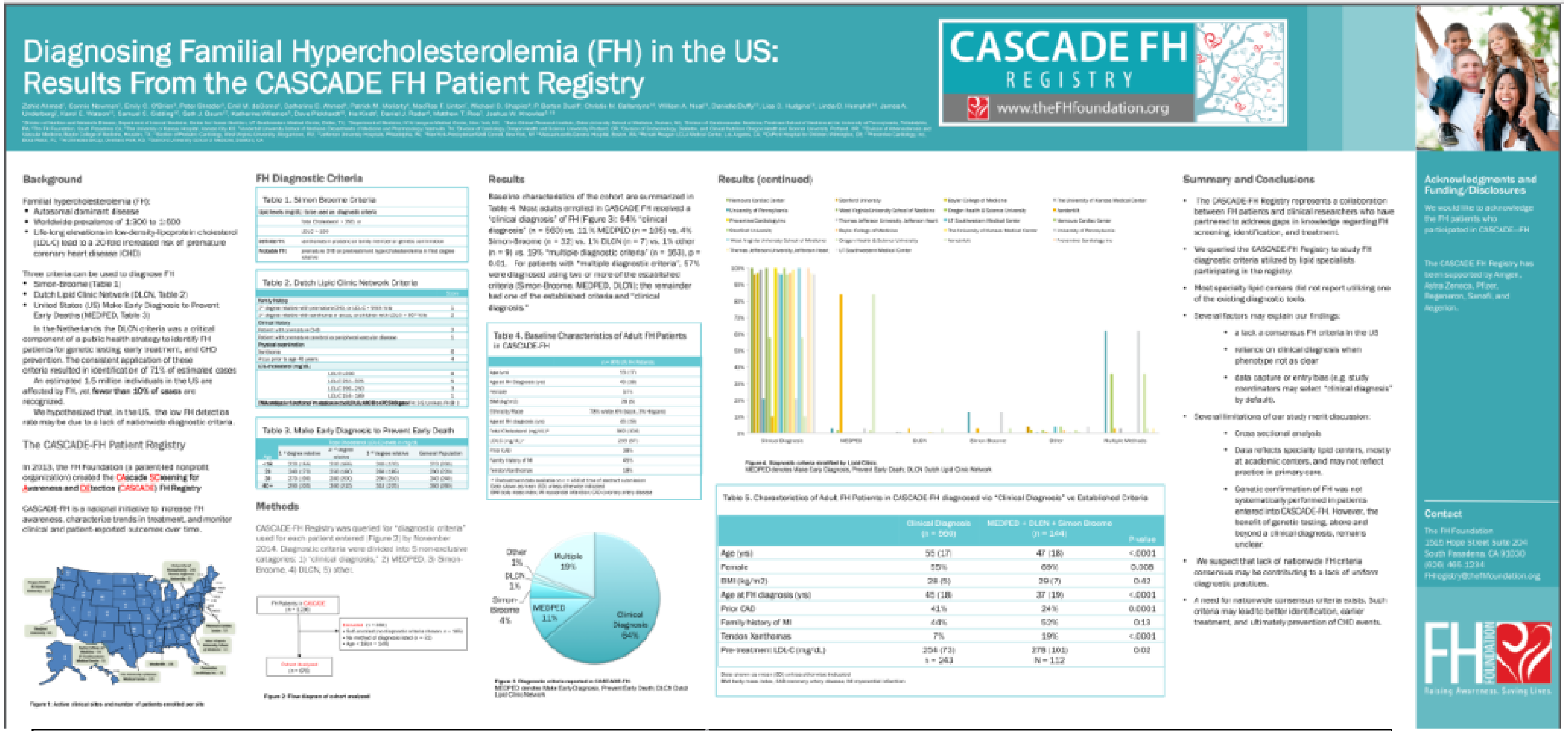
Denmark: governmental financial support set for FH management and to establish a nationwide government-driven FH register (being established).

Germany: Nationwide CaRe-High registry, initiated in 2014 by the D-A-CH Society for the Prevention of Heart and Circulatory Diseases e.V.[46] German patients organisation: Cholco e.V.

Switzerland: 5-year cascade screening programme (Swiss Awareness Program for Primary Hypercholesterolemia: Identification of Risk Elevation in Families with High cholesterol [SAPPHIRE-FH]) recently initiated, to improve FH detection rates.

Italy: LIPIGEN project: run by a network of lipid clinics (>40) that covers the whole nation. LIPIGEN has started a registry for collection of clinical/genetic data of FH subjects (promoted by the Italian Atherosclerosis Society).[60]

Malta: FH registry started in 2017 as an observational study. Initiatives to raise awareness through education to cardiologists, primary care practitioners, public health physicians and undergraduate students.



29%
Family member with FH

54
Average Age of Participants

3030

41%
Male

59%
Female

fh portugal

associação portuguesa
de hipercolesterolemia familiar

Membro de:
fh International foundation

NOTICIAS

1 FEVEREIRO, 2016

NOVO VIDEO DA FH PORTUGAL

Veja aqui o novo video da FH Portugal sobre Hipercolesterolémia Familiar.

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27 OUTUBRO, 2015

[VIDEO] 'FROM THE HEART': STORIES OF PEOPLE ACROSS EUROPE LIVING WITH FH

Histórias de pessoas que vivem pela europa com FH.

NOTÍCIAS RECENTES

Atherosclerosis Supplements
Volume 36, March 2019, Pages 28-30

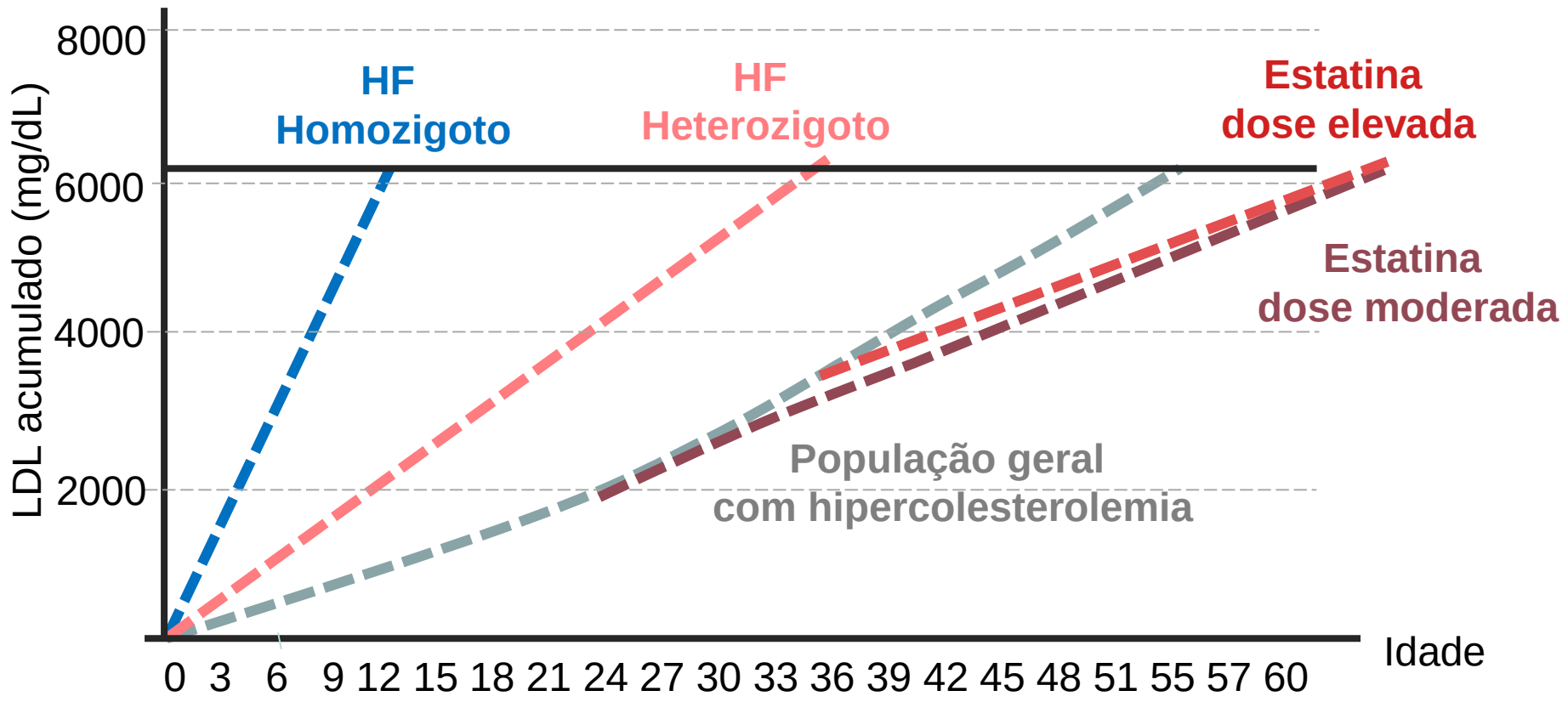
Variable expression and penetrance in Portuguese families with Familial Hypercholesterolemia with mild phenotype

I.M. Gaspar [a, b, c], A. Gaspar [c]

A negative blood genetic test result does not exclude FH, because the pathogenic LDLR mutation can be expressed only in the liver (a mutation in somatic tissue) or occasionally there is a vertical transmission from partner to future child by a mutation on germinal line - germinal mosaicism.

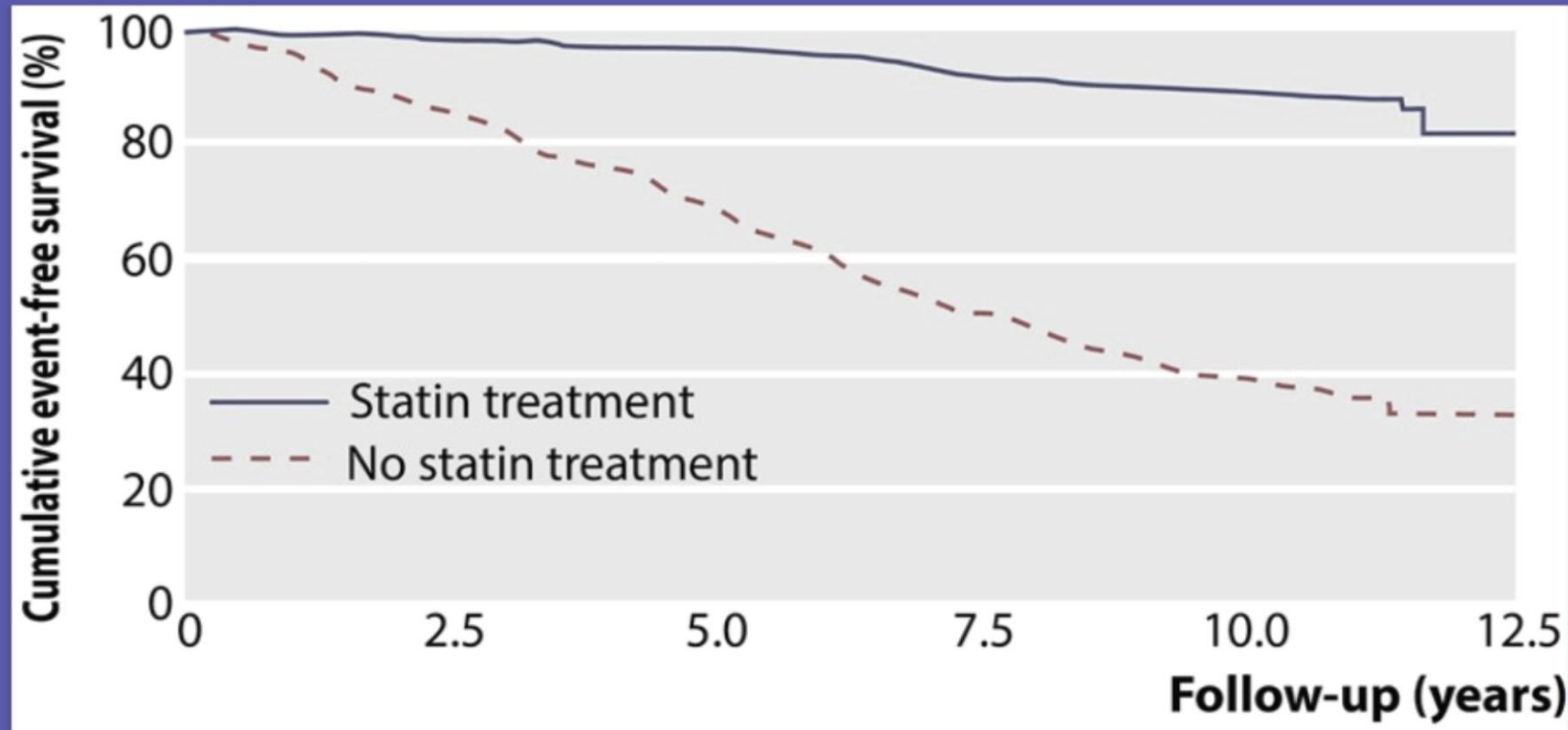
Unlike north European countries, the most FH carriers and patients had less severe phenotypes, for example with have children and young adult carriers with LDL-R mutation had normal TC and LDL-C, old women had a milder phenotype without ASCVD events, tendon xanthomas are seen in <1% patients, and most homozygous FH patients are under combined therapy.

LDL cholesterol burden – A carga de colesterol



Adaptado de European Heart Journal doi:10.1093/eurheartj/eht273

Observational Epidemiologic Cohort Study of 2146 Patients with FH and no CHD at Baseline

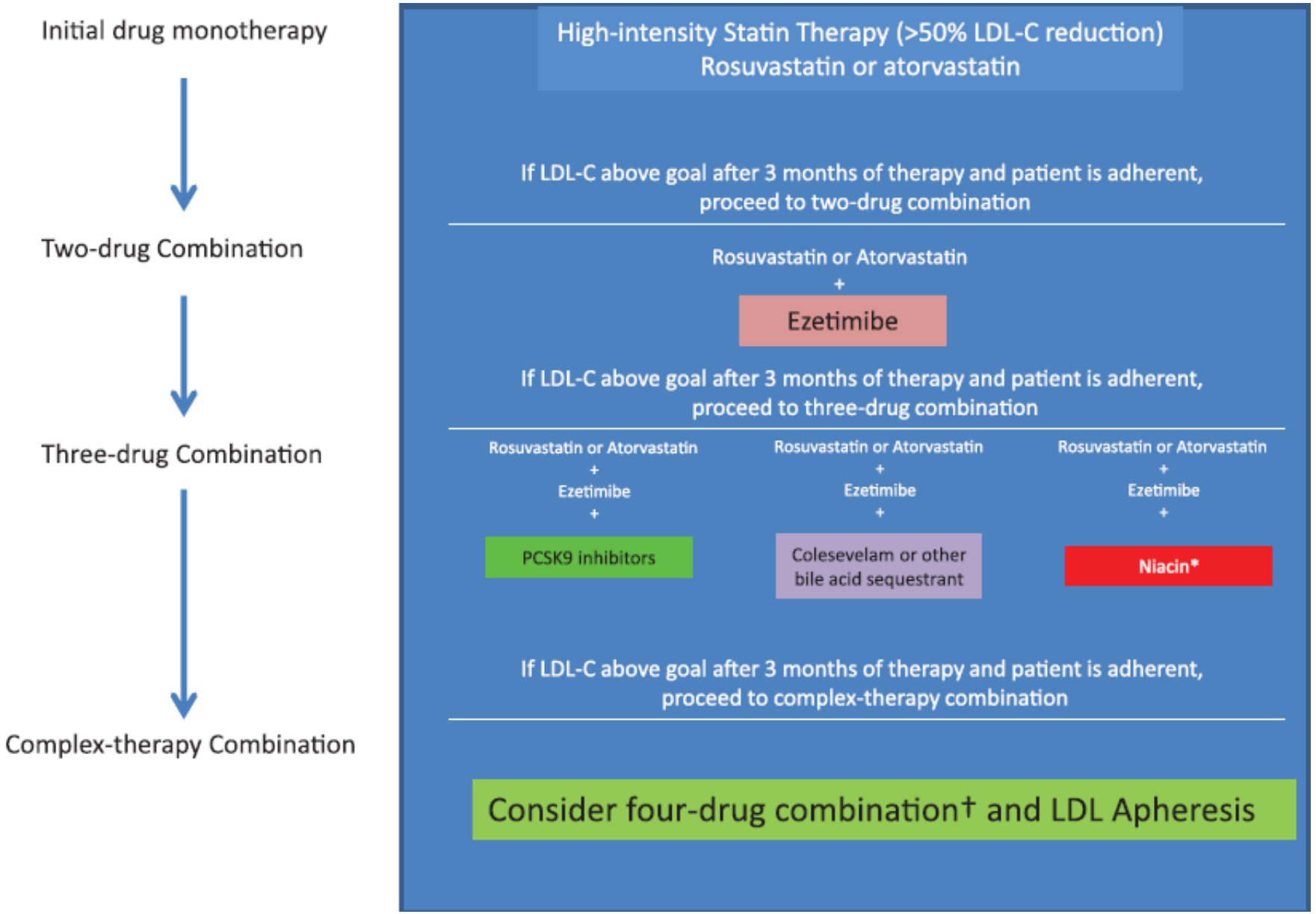


Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with Familial hypercholesterolemia according to statin treatment (P<0.001 for difference)

Versmissen J, et al. BMJ 2008;337:a2423.

2016 ESC/EAS Guidelines
for the Management of Dyslipidaemias

Os objetivos terapêuticos mantêm-se



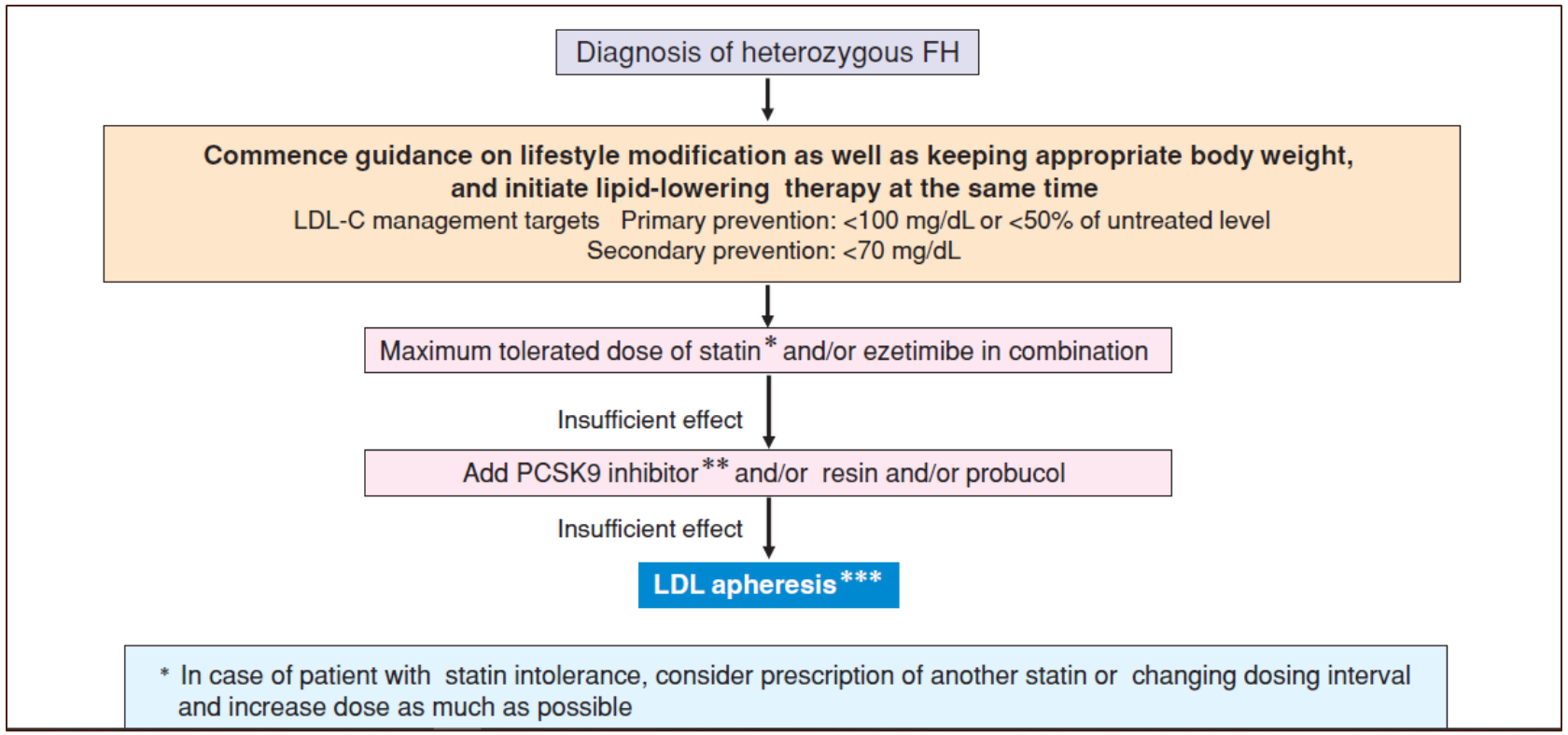
The Agenda for Familial Hypercholesterolemia A Scientific Statement From the American Heart Association Circulation. 2015;132:00-00. DOI: 10.1161

The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Correspondence

J Atheroscler Thromb, 2018; 25: 751-770. http://doi.org/10.5551/jat.CR003

Guidelines for Diagnosis and Treatment of Familial Hypercholesterolemia 2017



Inibidores da PCSK9

Intervention	Study, n Sample Size Endpoint	Concomitant Lipid Therapy (% High-Dose) Baseline LDL-C	PCSK9 Inhibitor Dose	Difference in LDL-C Change
Heterozygous familial hypercholesterolemia versus placebo				
Alirocumab	2 RCTs[38,39] N=99 12 weeks	High-dose statin (51.0%-77.0%)+ ezetimibe. 151-170 mg/dL	150 mg, 200 mg, or 300 mg every 4 weeks or 150 mg every 2 weeks	-8.0% to -57.4% ★★
Evolocumab	2 RCTs[32,34] N=499 12 weeks	High-intensity statin (89.7%)+ ezetimibe. 150-155 mg/dL	140 mg every 2 weeks to 420 mg every 4 weeks	-44.1% to -61.3% ★★★★
Homozygous familial hypercholesterolemia versus placebo				EVOLUCUMAB
1 RCT[33] N=50 12 weeks	High-dose statin (94.0%)+ezetimibe. 348 mg/dL	420 mg every 4 weeks		-32.1% (95% CI= -45.1 to -19.2) ★★

Guia Prático para a Utilização dos Inibidores da PCSK9 em Portugal

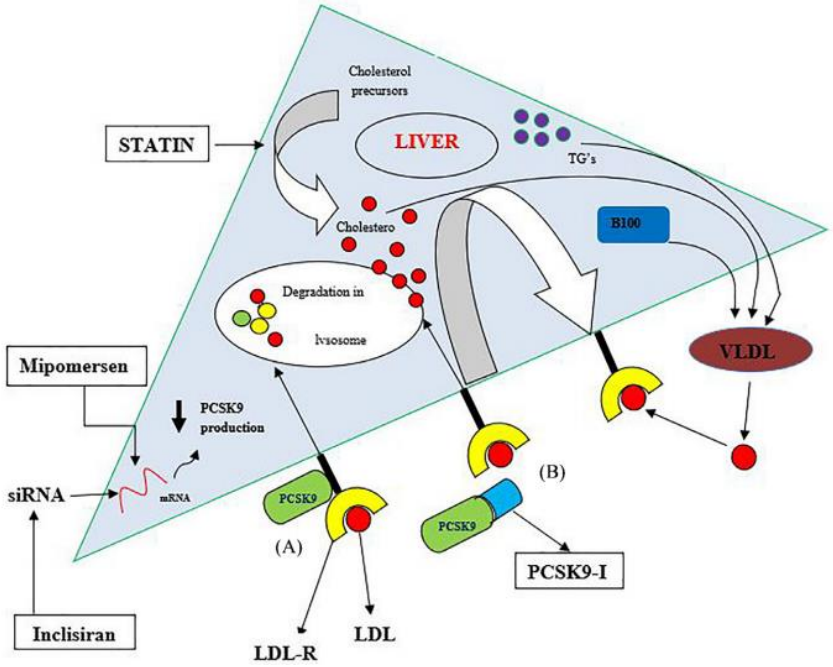
Com o apoio da Sociedade Portuguesa de Cardiologia; Sociedade Portuguesa de Aterosclerose; Sociedade Portuguesa de Endocrinologia; Núcleo de Estudos de Prevenção e Risco Vascular da Sociedade Portuguesa da Medicina Interna

UTILIZAÇÃO DOS IPCSK9 NA HIPERCOLESTEROLEMIA FAMILIAR

Em doentes com diagnóstico comprovado de hipercolesterolemia familiar (sem evento aterotrombótico prévio) a prescrição de iPCSK9 está recomendada naqueles que, após terapêutica hipolipemiante otimizada, mantenham:

1. **c-LDL ≥ 180 mg/dl**
2. **c-LDL ≥ 140 mg/dl**
   e um dos seguintes fatores:

- **Diabetes com lesão de órgão-alvo (ex. proteinúria) ou 1 fator de risco maior**
- **Lipoproteína (a) > 50 mg/dL**
- **Fatores de risco *major*: exemplo, hipertensão arterial estadio 2 e 3 (PA > 160/100 mmHg) não controlada**
- **Doença cardiovascular prematura em familiar 1º grau (homem < 55 anos; mulher < 60 anos)**
- **Doença aterosclerótica subclínica significativa**



Inclisiran

small interfering ribonucleic acid molecule inhibitor pf PCSK9 synthesis

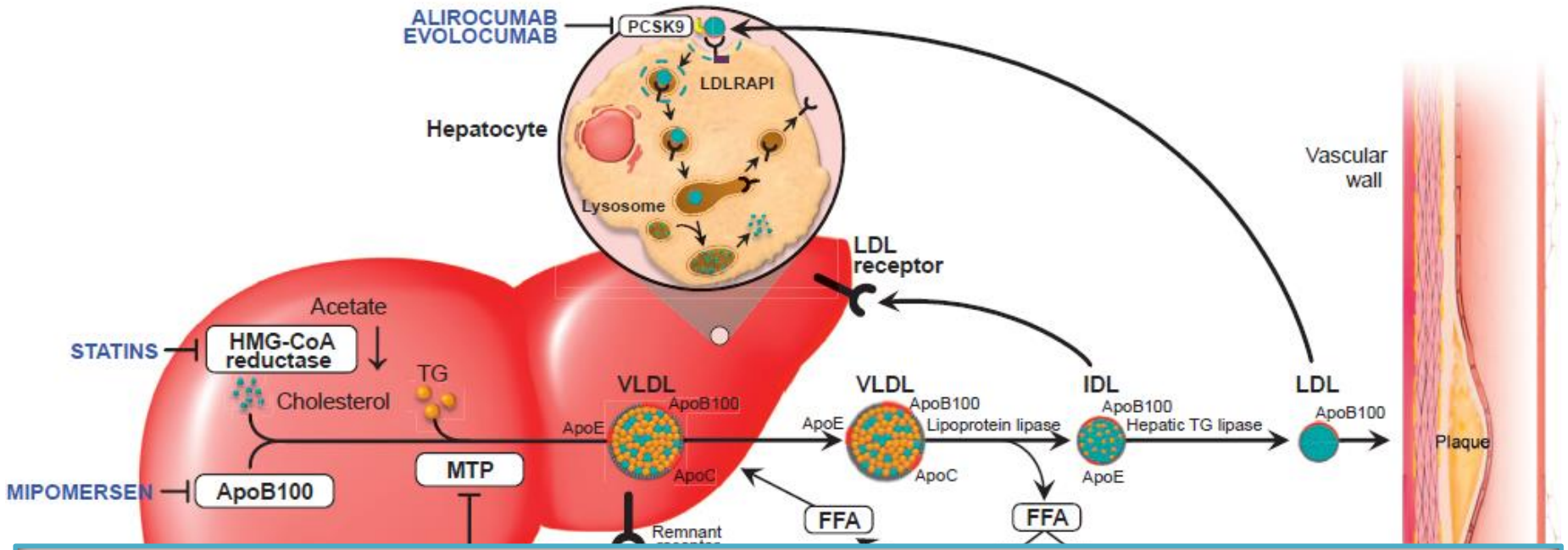
A single dose can decrease LDL-C for around 6 months

Clinical trials on inclisiran

Phase of trial	Title	Outcome	Study subjects	Results
Phase 1	–	Safety, side effects & pharmacodynamics	Healthy subjects	Safe & significant reduction in LDL-C
Phase 2	ORION-1	% change in LDL-C	Pts with ASCVD	Upto 35.5–52.6% at 180 days
Phase 2	ORION-2	% change in LDL-C	Pts with HFH	Not yet published
Phase 2	ORION-3	% change in LDL-C	Pts with high CV risks	Not yet published
Phase 1	ORION-7	Safety, side effects Kinetics and dynamics	Pts with renal impairments	Not yet published

Note: ASCVD = atherosclerotic cardiovascular disease; HFH = Homozygous familial hypercholesterolemia; Pts = patients.

Am J Cardiol 2018;122:12721277



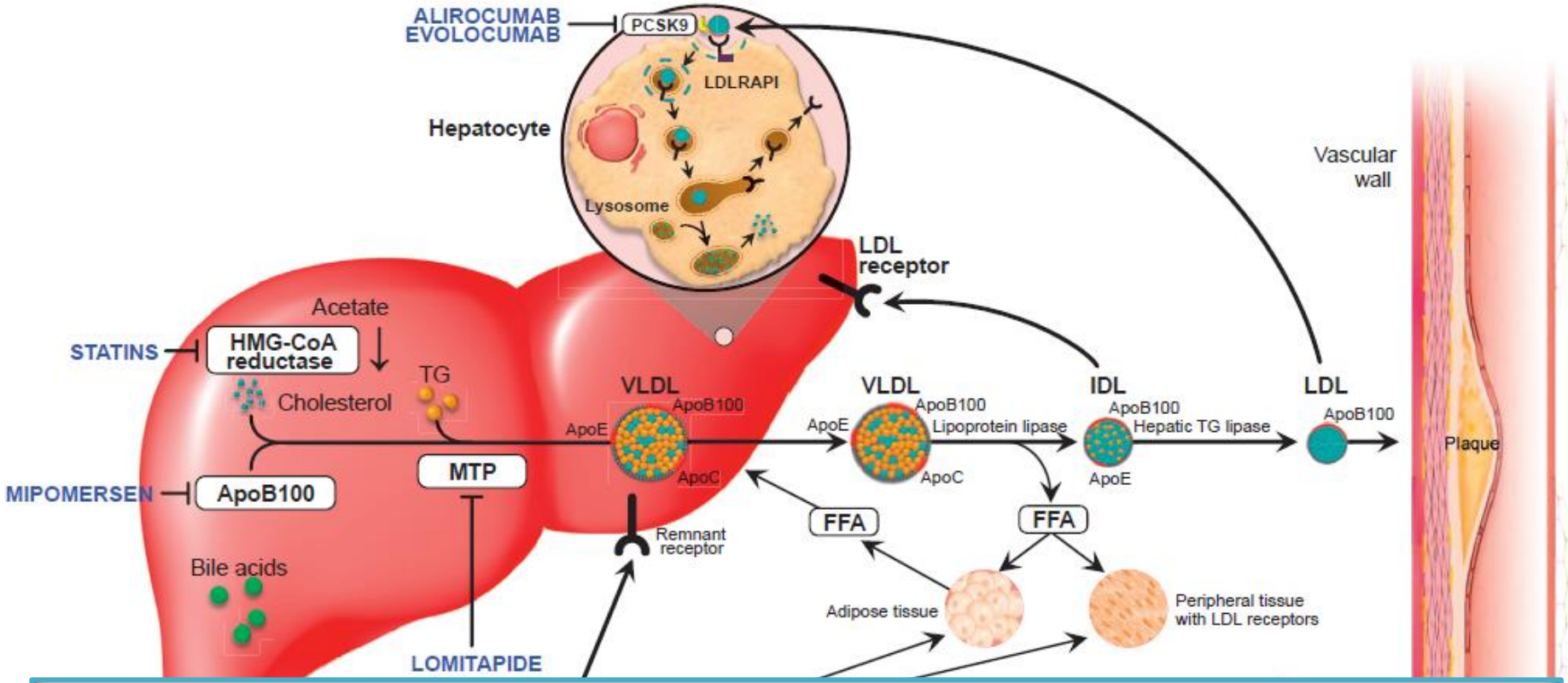
Mipomersen

ApoB antisense oligonucleotide drug class

binds to APOB mRNA and inhibits subsequent synthesis of ApoB

FDA: hoFH receiving maximally tolerated therapy, but not lipoprotein apheresis

LDL - 36 to 18%, Lp(a) - 39 to 21, HDL + 3 to 27; TG - 36 to 4



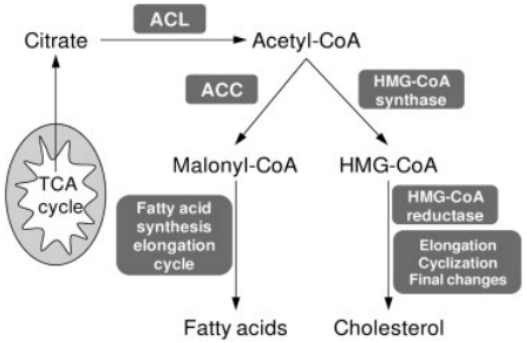
Lomitapide

Inhibits MTP microsomal triglyceride transfer protein
MTP participates in assembly of chylomicrons in enterocytes and very low-density lipoprotein particles in the hepatocytes - reduces the rate of secretion of apoB containing lipoproteins

FDA: hoFH receiving maximally tolerated therapy
LDL - 52 to - 24%, Lp(a) - 17 to + 1%, HDL - 13 to + 3%; TG - 54 to – 8%

Inibidores da ATP-citrato Liase

Crucial role of ACL as a precursor supplier for both fatty acid and cholesterol synthesis

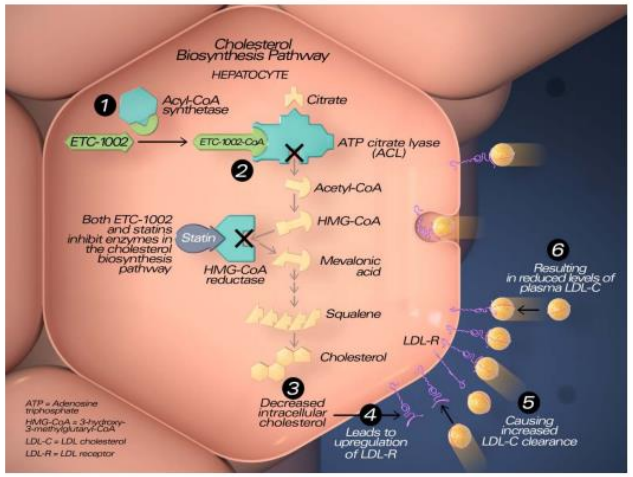


ACC, acetyl-CoA carboxylase; ACL, ATP citrate lyase; ATP, adenosine triphosphate; CoA, coenzyme A; HMG, hydroxymethylglutaryl; TCA, tricarboxylic acid

Mendivil CO et al. *J Clin Lipidol* 2015;9:384–389.

MECHANISM OF ACTION

ETC-1002 Reduces LDL-C via Inhibition of ATP-Citrate Lyase (ACL)



ETC-1002 is converted to ETC-1002-CoA in the liver which directly inhibits ACL, reduces cholesterol synthesis, and up-regulates LDL receptor activity

Mendelian Randomization Study of *ACLY* and Cardiovascular Disease

Brian A. Ference, M.D., Kausik K. Ray, M.D., Alberico L. Catapano, Ph.D., Thatcher B. Ference, Stephen Burgess, Ph.D., David R. Neff, D.O., Clare Oliver-Williams, Ph.D., Angela M. Wood, Ph.D., Adam S. Butterworth, Ph.D., Emanuele Di Angelantonio, M.D., John Danesh, D.Phil., John J.P. Kastelein, M.D., Ph.D., and Stephen J. Nicholls, M.B., B.S., Ph.D.

Genetic variants that mimic the effect of ATP citrate lyase inhibitors and statins appeared to lower plasma LDL cholesterol levels by the same mechanism of action and were associated with similar effects on the risk of cardiovascular disease per unit decrease in the LDL cholesterol level.

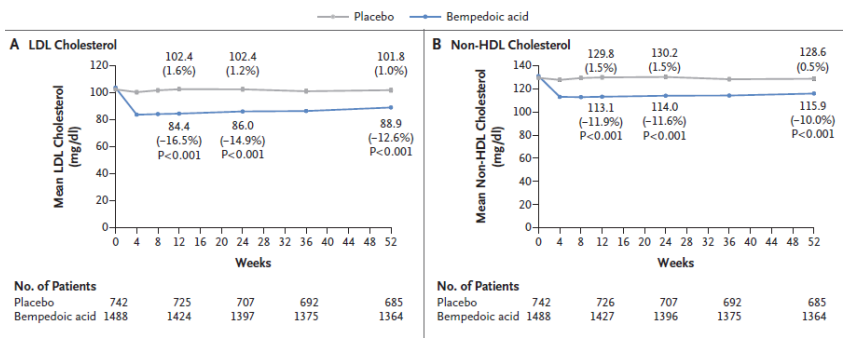
N Engl J Med 2019;380:1033-42.

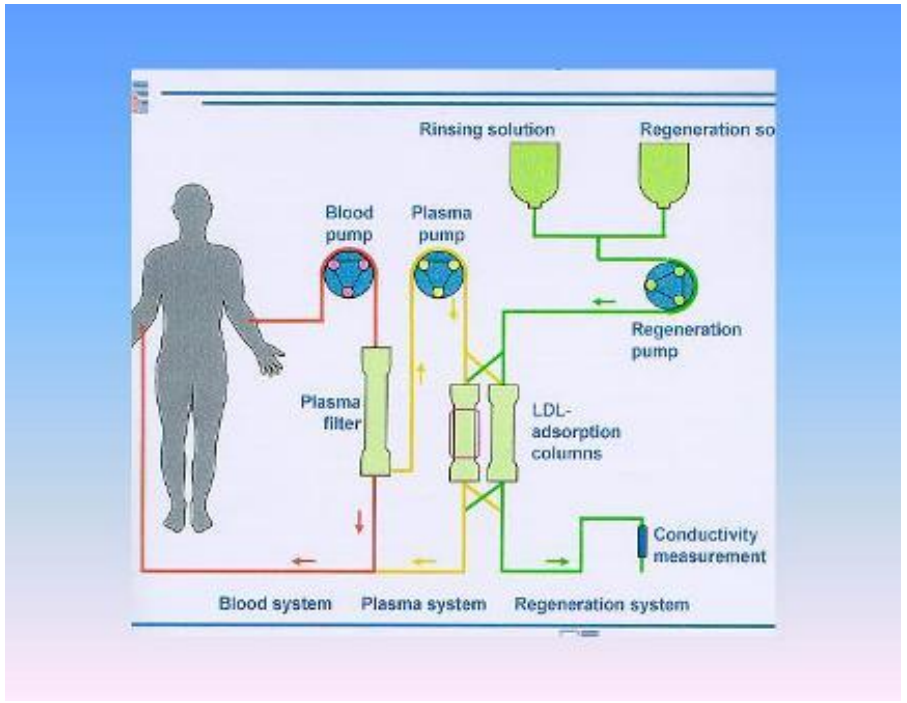
Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., Harold E. Bays, M.D., Alberico L. Catapano, Ph.D., Narendra D. Lalwani, Ph.D., M.B.A., LeAnne T. Bloedon, M.S., R.D., Lulu R. Sterling, Ph.D., Paula L. Robinson, M.S., and Christie M. Ballantyne, M.D., for the CLEAR Harmony Trial*

In this 52-week trial, bempedoic acid added to maximally tolerated statin therapy did not lead to a higher incidence of overall adverse events than placebo and led to significantly lower LDL cholesterol levels.

N Engl J Med 2019;380:1022-32.





LDL Aferese

Children:
Lipoprotein apheresis in homozygotes.

Adults:
Lipoprotein apheresis in homozygotes and in resistant heterozygotes with CHD.

LDL - 82 to - 52%,
Lp(a) - 72 to – 51 %
HDL - 27 to -7%
TG - 34 to – 49%