

Familial Hypercholesterolemia: A model of Preventive Medicine

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Pedro Mata MD, PhD
Spanish FH Foundation
Iberoamerican FH Network

www.colesterolfamiliar.org



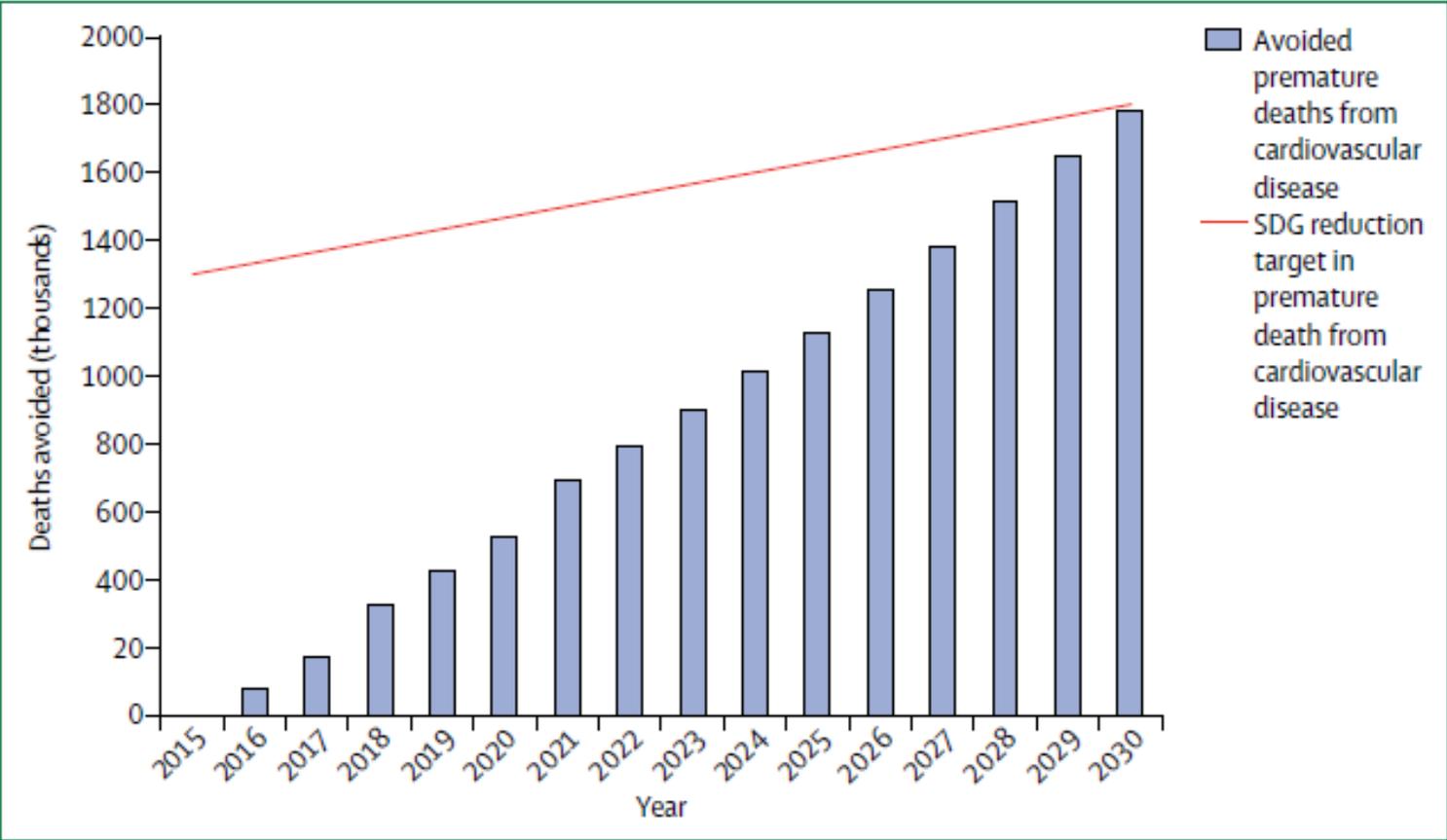
Time to Focus on Non Communicable Diseases (NCDs)

- **NCDs such as CVD and Cancer account for over 70% of all deaths**
- **≈ 50% are in people younger than 60 years**
- **CVD are the leading cause of death worldwide**
- **Over 17 million deaths every year**
- **CVD represent a major public health challenge**
- **NCDs are important causes of health inequalities and inequities**
- **NCDs produce large economic burdens**
- **Acting on NCDs is the best evidence to transform policy**
- **Call for 1/3 reduction in premature mortality from NCDs by 2030**

The Lancet Taskforce on NCDs 2018

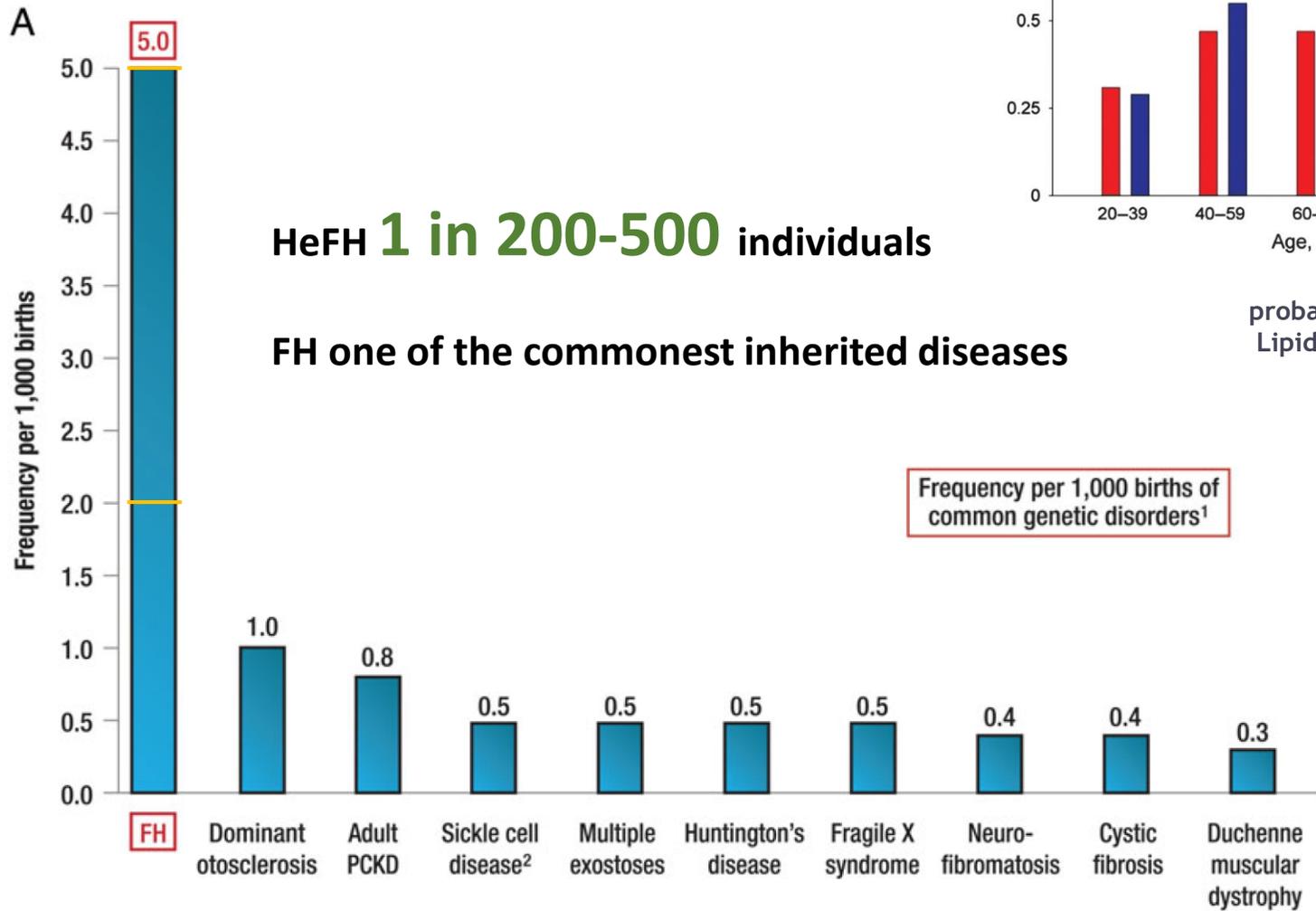
Horton R, Sargent J. Lancet 2018. doi.org/10.1016/S0140-6736(18)30674-3

Number of avoided premature deaths from CVD



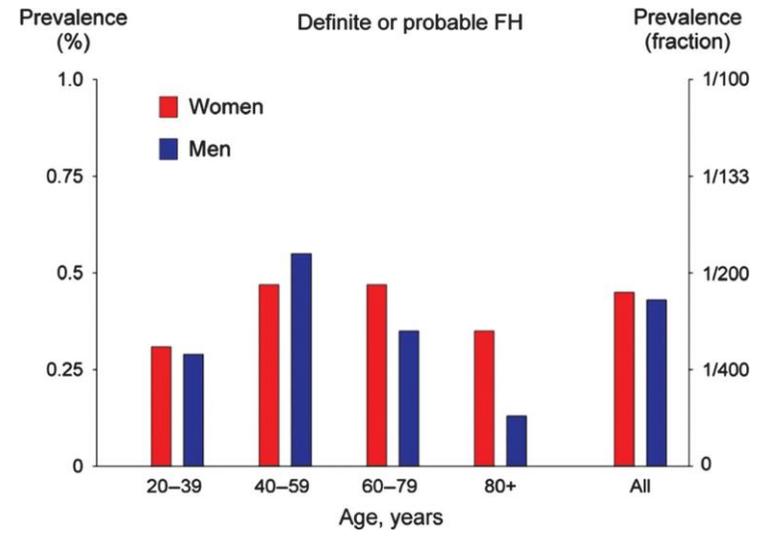
Number of avoided premature deaths from cardiovascular disease in the 20 modelled countries between 2015 and 2030, relative to the Sustainable Development Goal.

FH prevalence



HeFH 1 in 200-500 individuals

FH one of the commonest inherited diseases



Prevalence of definite or probable FH according to Dutch Lipid Clinic Network Criteria in the Copenhagen General Population Study

Wiegman A et al. Eur Heart J 2015;36:2425-2437
 Børge G. Nordestgaard et al. Eur Heart J 2013;34:3478-3490



FH: Figures and Facts

- Prevalence: 1/250 individuals. Affects all race/ethnic groups
- 30 millions of people with FH worldwide
- **2.5 millions in Latam** (625 mill/people)
- **Miocardial infarction between 35 and 50 years**
- 20% MI patients under 50 years age could have FH
- **Decreased life expectancy in 20-40 years**
- FH is underdiagnosed and undertreated
- Public Health challenge. Detection is mandatory

Adapted from Nordestgaard BG et al. Eur Heart J 2013;34:3478-90

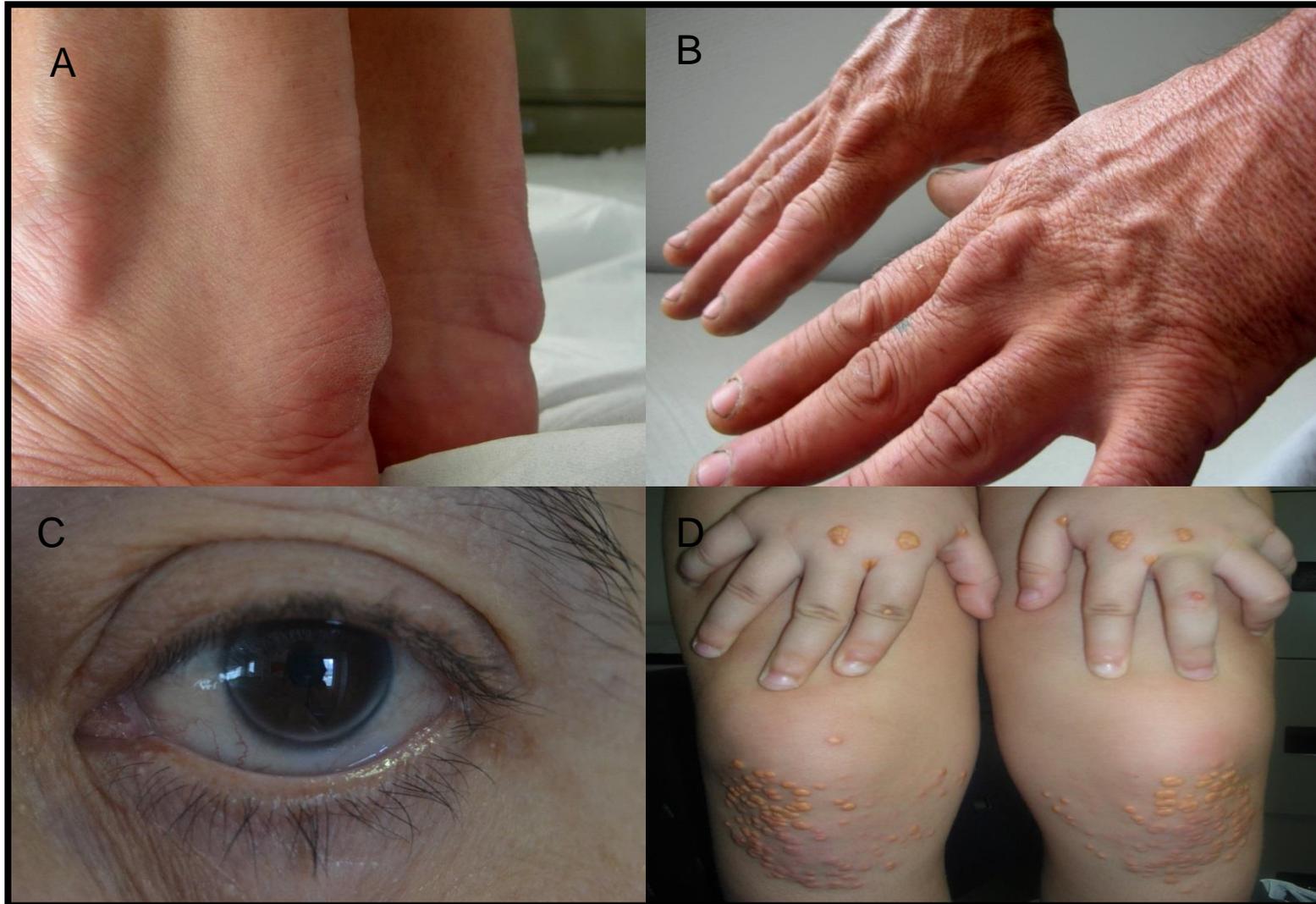


Familial Hipercholesterolemia

- Most common inherited condition (1/250-300)
- Caused by mutations in LDL-R, ApoB, PCSK9 genes
- Affects males and females equally from birth
- Variable Clinical expression:
 - High LDL-C levels (**CT \geq 300 mg/dl**)
 - Family history of high LDL-C levels
 - Tendon Xanthomas
 - Early Cardiovascular Disease
- **FH can be diagnosed based on a combination of lipid levels, family history, physical exam findings and genetic testing**



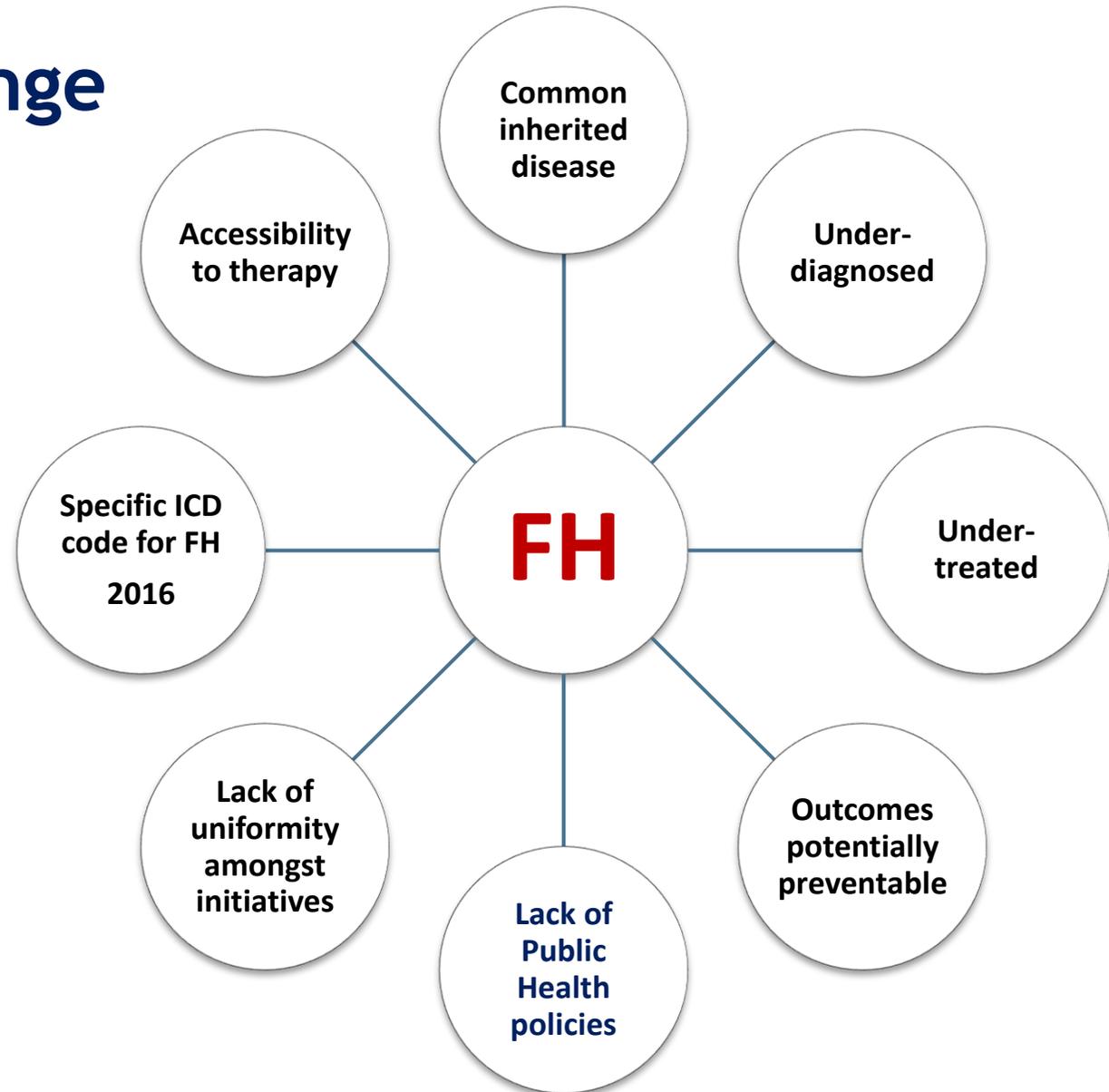
Signs of Familial Hipercholesterolemia



A , B) Xantomas en tendón de Aquiles y extensores de la mano; C) Arco corneal completo en un varón joven (< 45 años); D) Xantomas eruptivos y planos en manos y rodillas de un niño de 5 años con HFHo (Fotos cortesía de la Fundación Hipercolesterolemia Familiar).

Global Public Health challenge

Global FH burden





FH: Barriers to Diagnosis and Treatment

- **Most patients with FH are attended in primary care**
- Most of the severe FH are usually identified in specialist care
- Lack of uniformity among different diagnosis (clinical vs genetic)
- Statin doses and combined treatment are often insufficient
- Treatment is often started in the late stages of disease
- **Health care systems are not sufficiently aware of the problem**
- **There is a lack of screening programs**

- **> 160.000 FH patients in Spain**
- **> 20%** of FH patients have been detected in Spain (\pm 30 % with genetic diagnosis and > 65% with clinical criteria (DLCN))



FH: Clinical Detection Criteria

Index Cases (IC) should be identified if **LDL-C >220 mg/dL (TC ≥300)** and at least one of the following criteria:

- Family member <18 years with **LDL-C >150 mg/dL**
- Family member >18 years with **LDL-C >190 mg/dL**
- Premature CV Disease in the IC and/or in first degree-relatives
- Presence of xanthomas in the IC and/or in first degree-relatives

Nordestgaard BG et al. Eur Heart J 2013;34:3478-90

Mata P et al. Aten Primaria 2015;47:56-65



Why a FH genetic screening program is necessary?

- **Fulfills the WHO criteria for genetic screening**
- Serious consequences to young and middle age people
- Physical signs not always present (xanthomas <20%)
- Provides family cascade screening and avoid “overlap”
- **Cascade genetic testing is a cost-effective method**
- Good available treatment: “Reduction in morbidity and mortality”
- Clinical utility for patients, families and society

Consensus Statement on Clinical Genetic Testing for FH.JAAC 2018 (in press)
Lazaro P, et al. J Clin Lipidol 2017;11:260-71



Role and Aims of Registries in FH

- Identification of unmet clinical needs
- **Prospective observation of natural history**
- Improves cascade screening in families
- Evaluation and effectiveness of current diagnostic–therapeutic processes
- Long-term safety of recommended treatments
- Clinical profiles of low and high-risk patients with and without incident CV events
- **Determinants influencing optimal management on LDL-C goal attainment**
- **Identification of predictors for CV events**
- **Evaluation of CV morbidity and mortality**
- Better elaboration of recommendations in the guidelines
- Systematic information on results and cost
- **Provides data for healthcare planning and economic evaluation**



The Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART)

<https://www.colesterolfamiliar.org/estudio-safeheart>

- **Promote awareness of FH**
 - **Identify and enroll FH patients and their unaffected relatives**
 - **Evaluate patterns of real clinical practice**
 - **Contribute to the state of scientific knowledge of FH**
 - **Improve health outcomes, quality of life and impact policy decisions**
- Nationwide, long-term, prospective cohort in a molecularly defined FH population
 - >12 years to evaluate the principal prognostic factors related to total and CV mortality
 - Collect clinical data (central electronic database) and blood samples (including DNA)
 - Identify IC using clinical criteria and DNA test. Collaboration with Lipid clinics and GP's

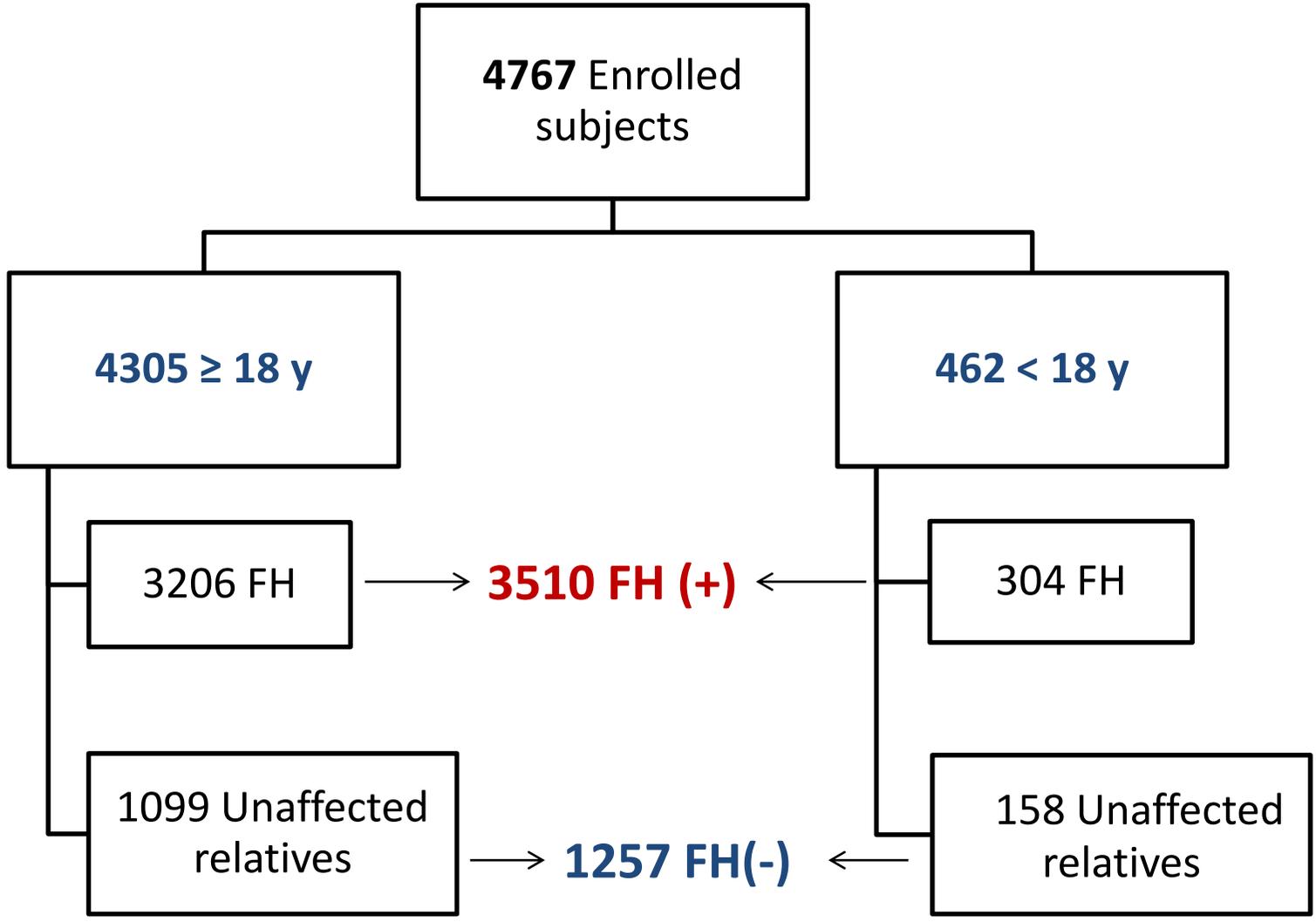
Nat Rev Cardiol 2009;6:23-27. Supported by Fundación HF, ISCIII and CNIC

Clinical Trial Registration: ClinicalTrials.gov number NCT02693548



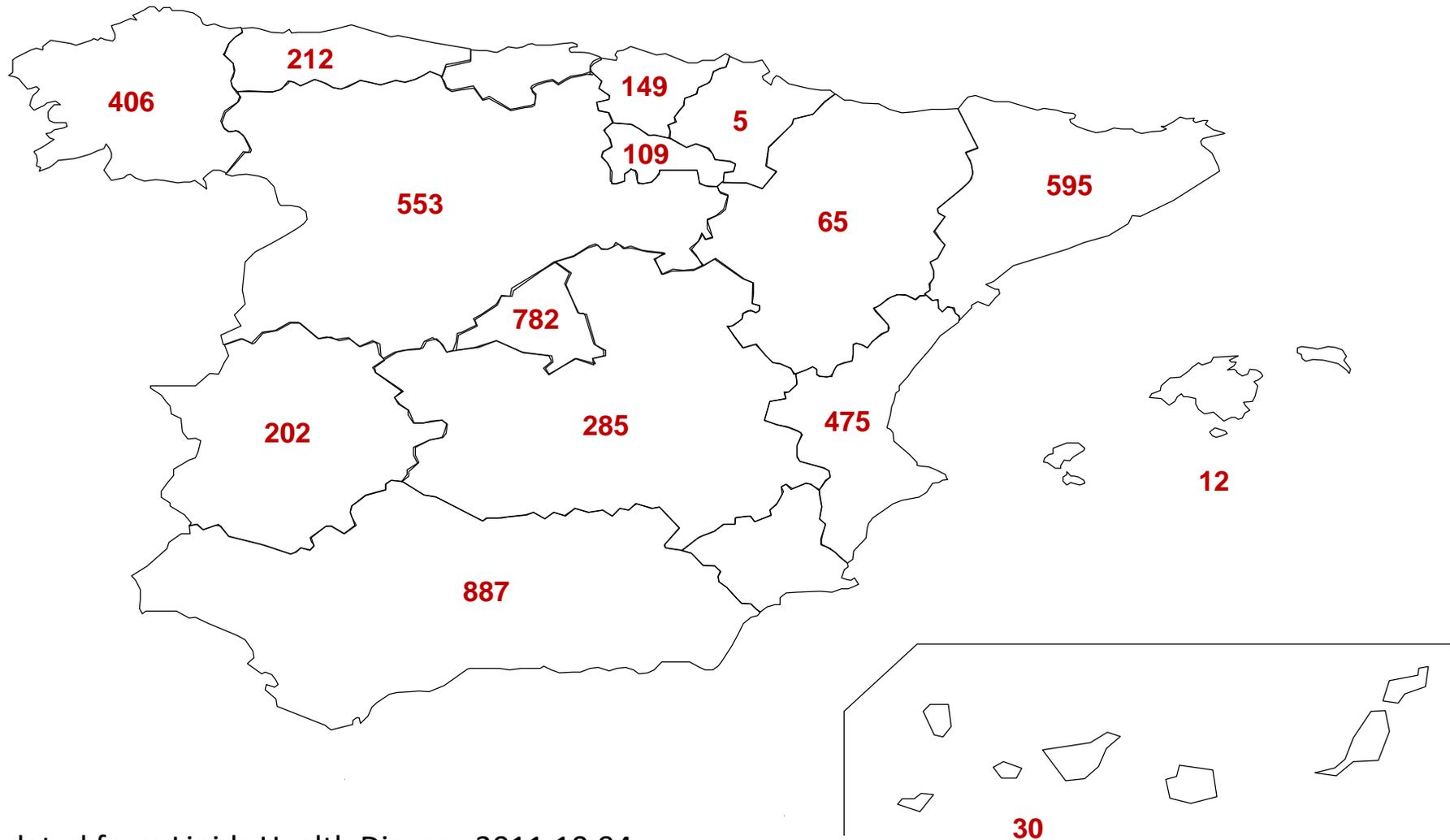
Recruitment of cases in the SAFEHEART Registry

(2004-2016)





The Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART) Years: 2004-2016



Updated from Lipids Health Disease 2011;10:94

Supported by Fundación HF, ISCIII and CNIC



SAFEHEART Registry

A model for the familial cascade screening

- \approx 20% of relatives with molecular diagnosis did not know they have FH
- \approx 50% of relatives are controlled by the GP's
- Subjects recruited: 4767

Index cases/Families = 871

Relatives = 3896. Cases for family = 5.5

Xanthomas 14%. Corneal Arcus 33%

73% with positive genetic diagnosis

Total functional mutations: 194, LDLr (97%) and apoB (3%)

- Mean follow-up time **7 years**
- Follow-up data every year by phone call



FH patients and unaffected relatives baseline main characteristics

	FH cases	Unaffected relatives	P
	Median (Q1-Q3) / n (%)	Median (Q1-Q3) / n (%)	
n	2752	993	
Gender (male)	1264 (45.9%)	463 (46.6%)	0.71
Age at enrolment (years)	44 (34.0 – 57.0)	40 (29.0 - 53.0)	<0.001
Corneal arcus	916 (33.3%)	122 (12.3)%	<0.001
Xanthomas	376 (13.7%)	0	<0.001
T2DM	119 (3.2%)	47 (1.3%)	0.59
High Blood Pressure	397 (14.4%)	143 (14.4%)	0.98
Active Tobacco smoker	725 (26.4%)	336 (33.9%)	<0.001
BMI (Kg/m ²)	25.89 (22.96 – 29.14)	25.34 (22.63 – 28.39)	0.004
LDL-C (mg/dl)	165.0 (138.6 – 207.8)	127.2 (106.4 – 156.0)	<0.001
HDL-C (mg/dl)	49.0 (41.0 – 57.2)	53.0 (45.0 – 62.2)	<0.001
Lp(a) (mg/dl)	22.6 (8.8 – 55.6)	18.8 (7.0 – 45.5)	<0,001



Coronary Disease in FH

- Variable prevalence: **FH have a 3-13-fold** increased risk of CAD compared to general population
- Era pre-statin vs post-statin
- Risk of CAD is increased in FH Patients
- Relative Risk is elevated in young adults
- 9% patients < 65 years with ACS and LDL-C \geq 160 mg/dL have FH
- **At the same level of LDL-C, FH have a 2-4 times higher CAD risk**
- **FH accelerates CV aging, \pm 20 years in Men and 20-30 years in Women**

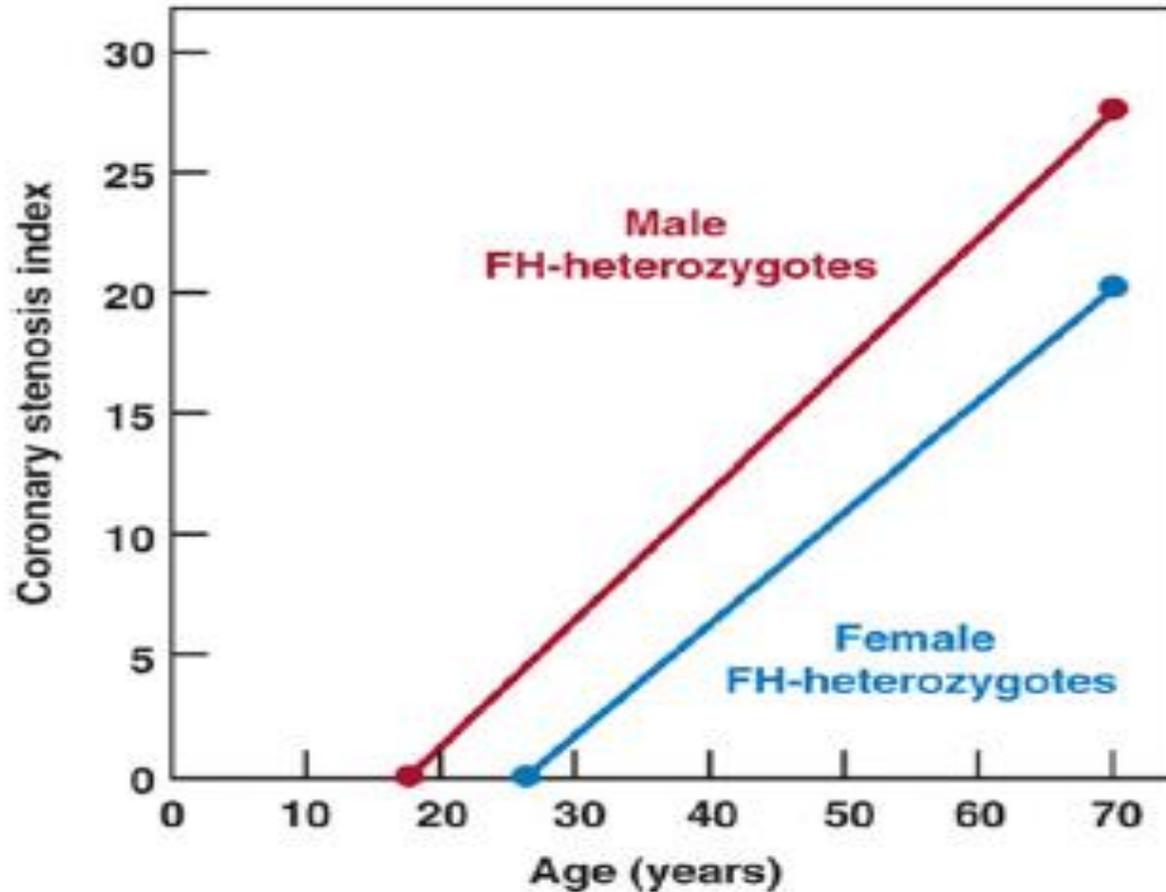
Benn M, et al. J Clin End Metab 2012; 97:3956-64

Khera AV, et al. JACC 2016;67:2578-89

Perez de Isla L, et al. ATVB 2016;36:2004-10

Amor-Salamanca A, et al. JACC. 2017;70:1732-40

Coronary Artery Disease in FH



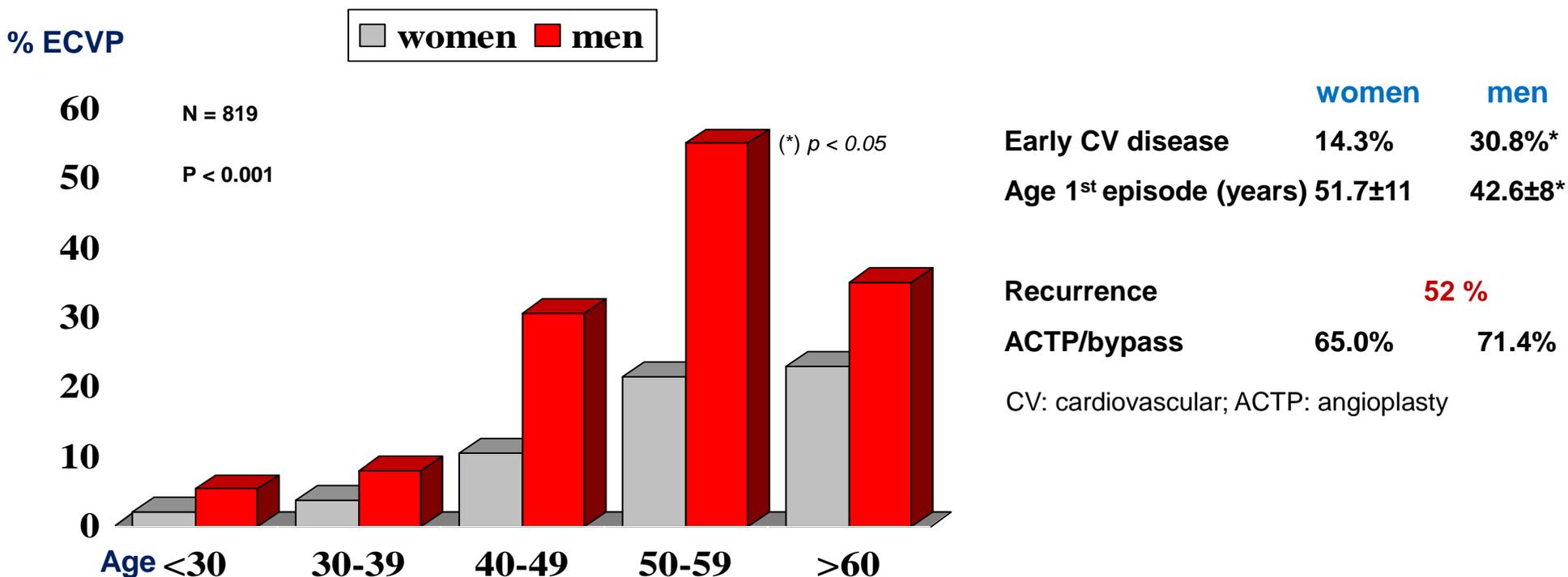
The correlation between age and angiographically determined extent of CAD among 105 males and 56 females FH in the pre-statin era.

Modified from Mabuchi et al. *Circulation* 1989;79:225–32.



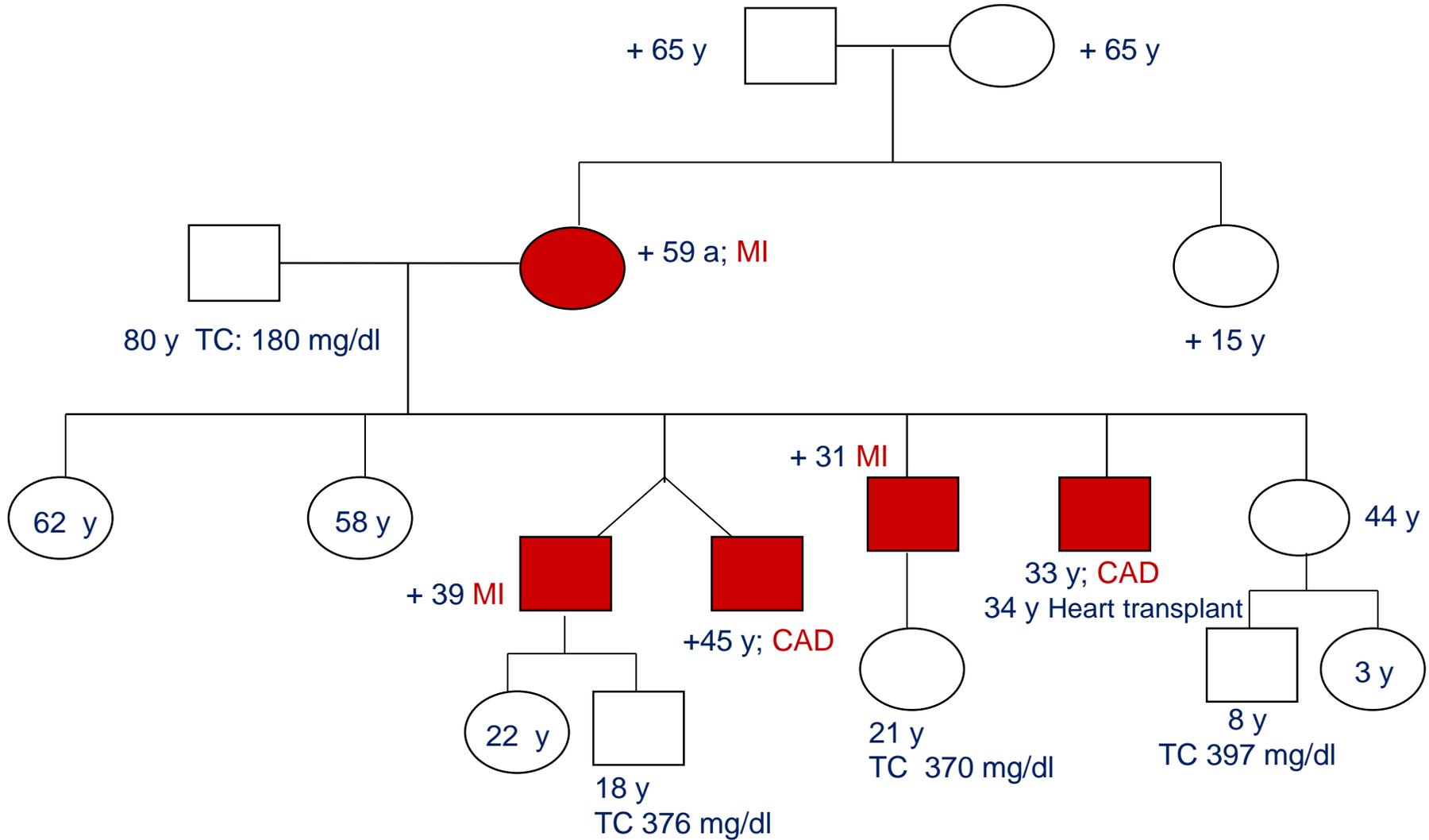
Cardiovascular disease in FH

Spanish Records (n=819)





FH: Importance for the family (Q12X)



Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Coronary Heart Disease, Peripheral Arterial Disease, and Stroke in Familial Hypercholesterolaemia: Insights From the SAFEHEART Registry (Spanish Familial Hypercholesterolaemia Cohort Study)

Leopoldo Pérez de Isla, Rodrigo Alonso, Nelva Mata, Adriana Saltijeral, Ovidio Muñoz, Patricia Rubio-Marin, José L. Diaz-Diaz, Francisco Fuentes, Raimundo de Andrés, Daniel Zambón, Jesús Galiana, Mar Piedecausa, Rocio Aguado, Daniel Mosquera, José I Vidal, Enrique Ruiz, Laura Manjón, Marta Mauri, Teresa Padró, José P. Miramontes, Pedro Mata and for the SAFEHEART Investigators

Arterioscler Thromb Vasc Biol. published online July 21, 2016.

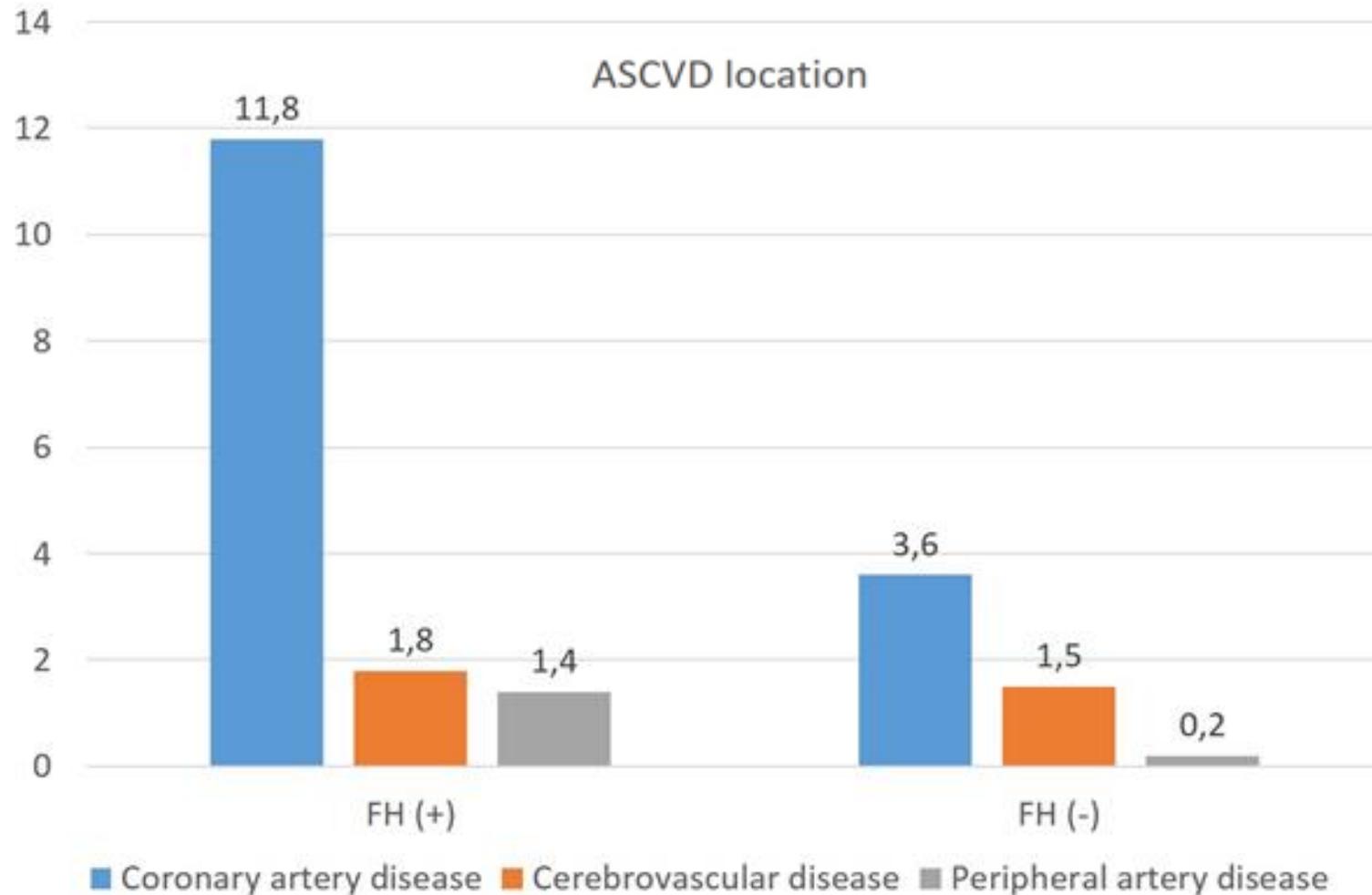
FH patient's characteristics depending on the presence of ASCVD

	FH cases & ASCVD (+)	FH cases & ASCVD (-)	P
	Median (Q1-Q3) / n (%)	Median (Q1-Q3) / n (%)	
n	358	2394	
Gender (male)	242 (67.6%)	1021 (42.7%)	<0.001
Age (years)	59.0 (49.0-70.0)	42.0 (32.0-54.0)	<0.001
Corneal arcus	195 (54.6%)	721 (30.2%)	<0.001
Xanthomas	98 (27.5%)	278 (11.6%)	<0.001
T2DM	47 (13.2%)	72 (3.0%)	<0.001
High Blood Pressure	135 (37.8%)	262 (10.9%)	<0.001
Active Tobacco smoker	47 (13.2%)	678 (28.3%)	<0.001
BMI (Kg/m ²)	28.3 (25.6-31.3)	25.5 (22.6-28.7)	<0.001
LDL-c (mg/dl)	145.7 (120.6-180.0)	170.0 (141.0-212.0)	<0.001
Lp(a) (mg/dl)	39.4 (14.9-82.5)	20.6 (8.2-51.2)	<0.001
Patients on maximum statin dose	248 (69.3%)	797 (33.3%)	<0.001
Patients on maximum LLT	287 (80.2%)	1042 (43.4%)	<0.001



ASCVD manifestations in FH and unaffected relatives

SAFEHEART Registry (91% Coronary, 13% CV, 11% PA)



CME

Lipoprotein(a) Levels in Familial Hypercholesterolemia

An Important Predictor of Cardiovascular Disease Independent
of the Type of LDL Receptor Mutation

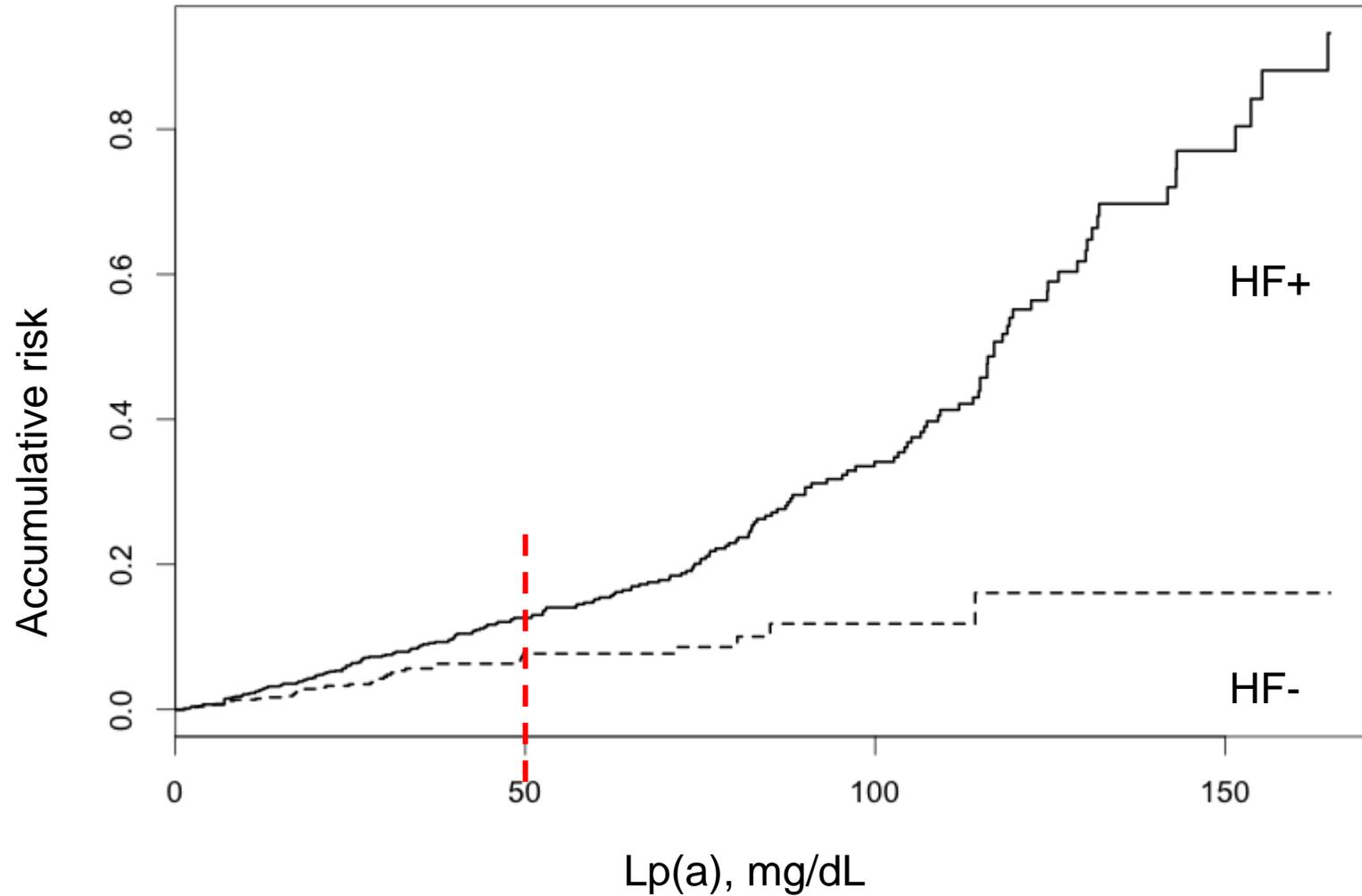


Rodrigo Alonso, MD, PhD,* Eduardo Andres, BSc,† Nelva Mata, MD,‡
Francisco Fuentes-Jiménez, MD, PhD,§ Lina Badimón, PhD,|| José López-Miranda, MD, PhD,§
Teresa Padró, PhD,|| Ovidio Muñiz, MD, PhD,¶ Jose Luis Díaz-Díaz, MD, PhD,#
Marta Mauri, MD,** Jose María Ordovás, PhD,†† Pedro Mata, MD, PhD,‡‡
for the SAFEHEART Investigators

Madrid, Córdoba, Barcelona, Sevilla, A Coruña, and Terrassa, Spain; and Boston, Massachusetts



Cumulative Hazard for CVD and Lp(a) levels





Lp(a) in the Study Group According to the Presence of CVD

(Elevated Lp(a) was detected in >30% of FH)

	(A) FH+ CVD+ (n = 247)	(B) FH+ CVD- (n = 1,713)	(C) FH- CVD+ (n = 41)	(D) FH- CVD- (n = 916)
Total cholesterol, mg/dl	225 ± 54.8	260 ± 67.7*	185 ± 32.2†	208 ± 45.5*†
Triglycerides, mg/dl	97 (70-129)	81 (62-129)*	98 (80-129)	84 (62-129)*‡
HDL-C, mg/dl	46 ± 11.4	51 ± 11.4*	52 ± 15.0‡	55 ± 15.0‡
LDL-C, mg/dl	158 ± 49.2	189 ± 49.2*	109 ± 24.4†	132 ± 24.4*†
Non-HDL-C, mg/dl	179 ± 52.9	209 ± 67.8*	133 ± 29.6†	153 ± 44.2*†
Apo A1, mg/dl	133 ± 25.0	140 ± 27.6*	147 ± 26.6‡	151 ± 58.0†
Apo B, mg/dl	111 ± 30.0	122 ± 37.9*	83 ± 21.0†	91 ± 26.3†§
Lp(a), mg/dl	43.4 (18.2-84.3)	21.3 (8.9-53.9)*	21.5 (8.4-37)‡	20.8 (7-47.3)‡
Lp(a) > 50 mg/dl	114 (46.2)	460 (26.9)*	6 (14.6)†	206 (22.5)

Values are mean ± SD, median (interquartile range), or n (%). *p < 0.0001 and §p < 0.05 between A and B and between C and D; †p < 0.0001; ‡p < 0.005, and ||p < 0.05 between A and C and between B and D.

Attainment of LDL-Cholesterol Treatment Goals in Patients With Familial Hypercholesterolemia

5-Year SAFEHEART Registry Follow-Up

Leopoldo Perez de Isla, MD,^{a,b} Rodrigo Alonso, MD,^{b,c} Gerald F. Watts, MD,^{d,e} Nelva Mata, MD,^{b,f} Adriana Saltijeral Cerezo, MD,^{b,g} Ovidio Muñiz, MD,^h Francisco Fuentes, MD,ⁱ José Luís Diaz-Diaz, MD,^j Raimundo de Andrés, MD,^k Daniel Zambón, MD,^l Patricia Rubio-Marin, MD,^m Miguel A. Barba-Romero, MD,ⁿ Pedro Saenz, MD,^o Juan F. Sanchez Muñoz-Torrero, MD,^p Ceferino Martinez-Faedo, MD,^q José P. Miramontes-Gonzalez, MD,^r Lina Badimón, MD,^s Pedro Mata, MD,^b for the SAFEHEART Investigators

J Am Coll Cardiol 2016;67:1278–85



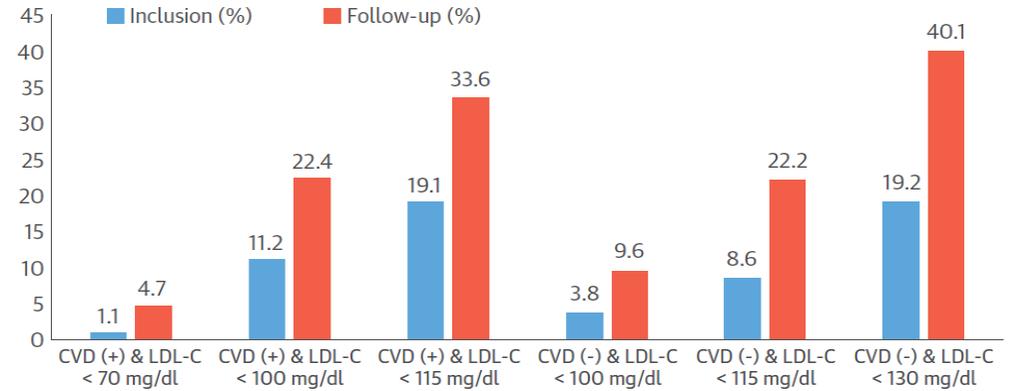
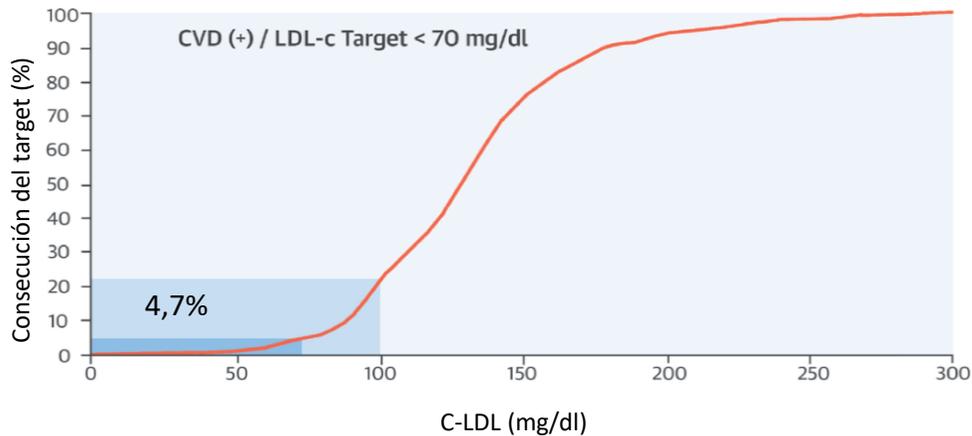


Attainment of LDL-C Treatment Goals in FH Patients

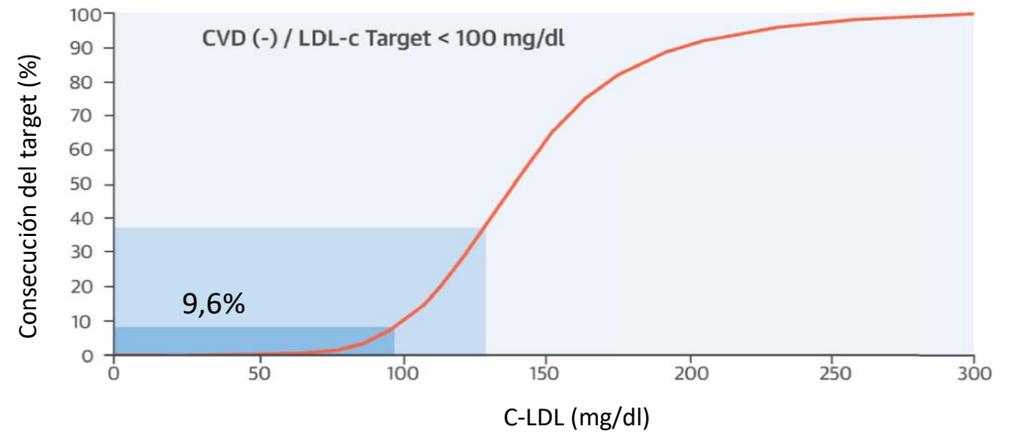
SAFEHEART Registry

- Patients (n): 2.170
- Mean follow-up (years): 5,1 ± 3,1
- Maximal LLT*: **72 %**

LDL-C at entry (mg/dl): 163
LDL-C at follow-up (mg/dl): **137**



% de pacientes que consiguen los objetivos de C-LDL

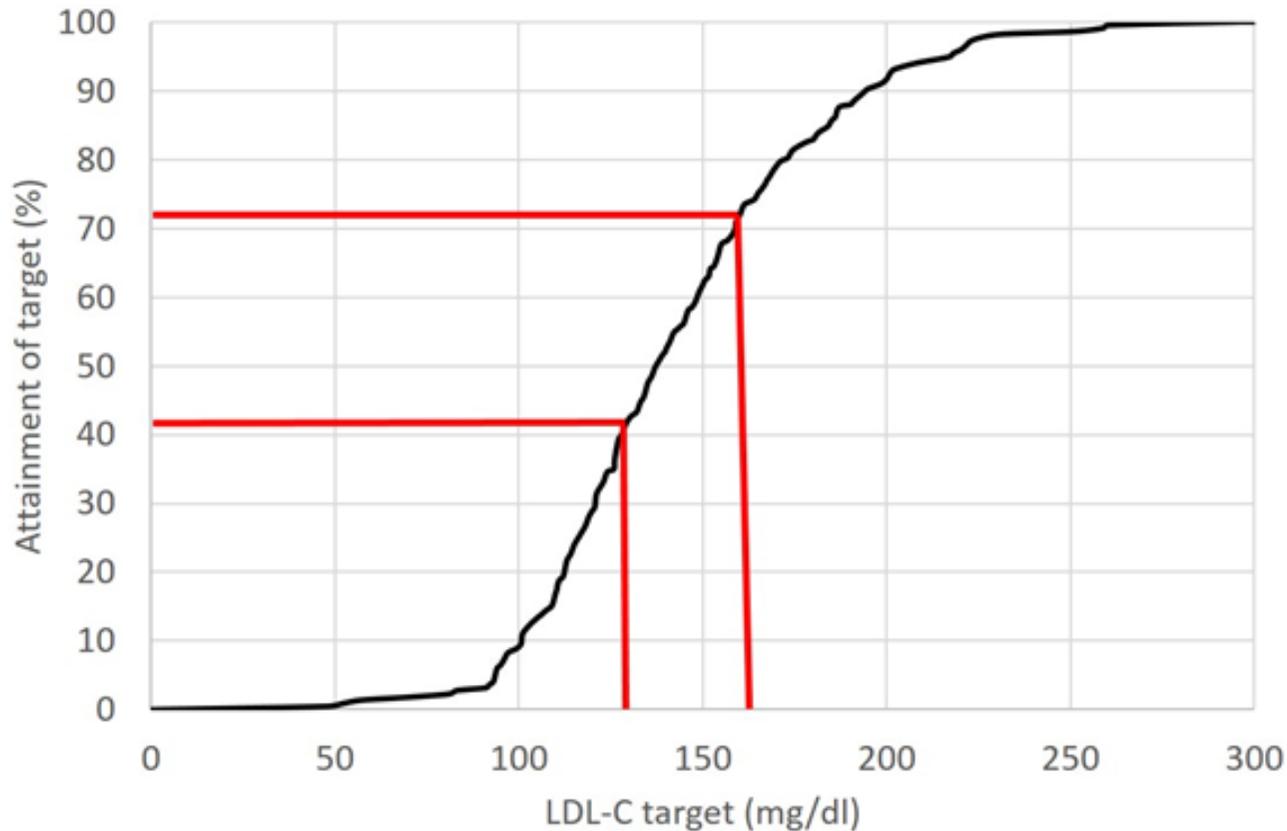


LLT: lipid lowering therapy.

Perez de Isla et al. JACC. 2016;67:1278-85



Attainment of LDL-C Treatment Goals in Children and Adolescents (N= 217; 53 % male; 68% on medication)



LDL-C <130mg/dl, 41.5%

LDL-C <160mg/dl, 71%



Cost-Effectiveness of a FHDP in Spain

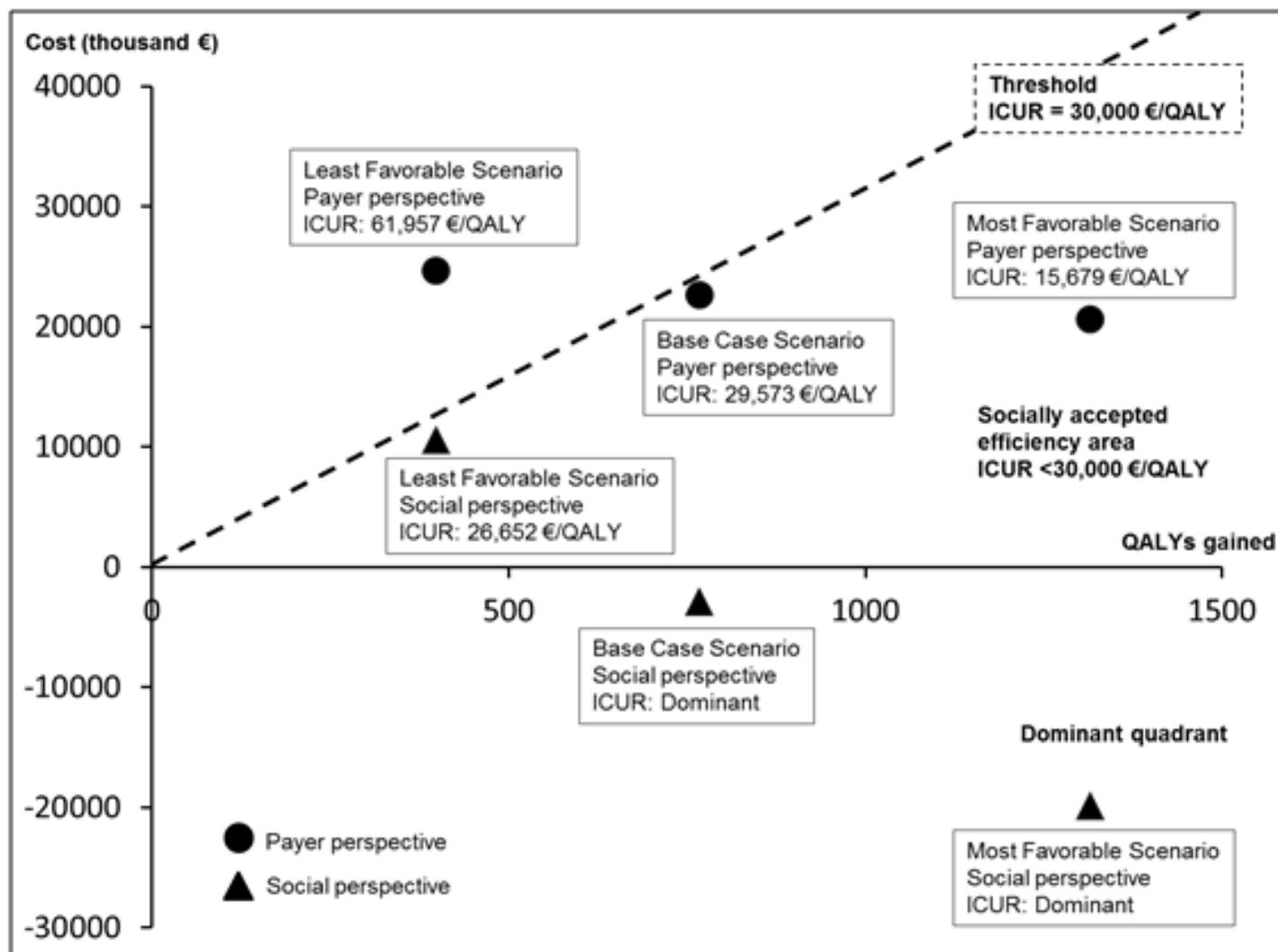
- Horizon 10 years: 2017-2026. **The design simulates a prospective cohort study**
- Genetic detection of 9.000 FH cases/year (2.250 IC and 6.750 relatives), ratio1:3
- Two perspectives were considered: **the payer and the social perspective**
- Participation of GP's is crucial

IF FHDP was applied in Spain, and 9.000 FH cases were detected in a year, within the next ten years, we could avoid:

- 847 Coronary Events (Mis+CPs)
- 203 Coronary Deaths
- > 200.000 days of work productivity lost
- Produce 767 QALYs
- **For each 6 FH (>18 years) detected and treated we avoid 1 fatal or no fatal Coronary Event**



Cost-effectiveness of a FH Detection Program



ICER: incremental cost-effectiveness ratio; ICUR: Incremental cost-utility ratio.



EUROPEAN JOURNAL OF PUBLIC HEALTH

Quality of life in a cohort of familial hypercholesterolemia patients from the south of Europe

Nelva Mata¹, Rodrigo Alonso², Jose R Banegas³, Daniel Zambón⁴, Ángel Brea⁵, Pedro Mata²

- Quality of life (QL) in FH patients is **similar to their unaffected relatives**
- The main factors independently associated with a worse QL in patients with FH are CVD, female gender, older age and depression
- This is the first study that describes the **negative impact of CVD** in QL in FH
- Early detection, adequate management and prevention of CVD may improve QL in this high risk population



The Continuum of FH

Need for Risk Stratification

- High lifelong Cardiovascular Risk
- **Heterogeneity in risk:**
 - LDL-C levels
 - Previous CV Disease
 - Lp(a)
 - Others Risk Factors
 - Susceptibility=Subclinical Atherosclerosis Disease
- Overlapping LDL-C among HeterFH and HoFH forms
- New treatments: PCSK9-I, Lomitapide



Circulation



Predicting Cardiovascular Events in Familial Hypercholesterolemia: The SAFEHEART Registry

Leopoldo Pérez de Isla, Rodrigo Alonso, Nelva Mata, Cristina Fernández-Pérez, Ovidio Muñiz, José Luis Díaz-Díaz, Adriana Saltijeral, Francisco J. Fuentes-Jiménez, Raimundo de Andrés, Daniel Zambón, Mar Piedecausa, José María Cepeda, Marta Mauri, Jesús Galiana, Ángel Brea, Juan F. Sanchez Muñoz-Torrero, Teresa Padró, Rosa Argueso, José Pablo Miramontes-González, Lina Badimón, Raúl D. Santos, Gerald F. Watts and Pedro Mata
For the SAFEHEART investigators

Circulation. published online March 8, 2017;



Predictors of incident ASCVD events in FH SAFEHEART Registry

- Age
- Male Gender
- **History of previous ASCVD**
- Hypertension
- BMI increased
- Active Smoking
- **Treated LDL-C > 100 and especially >160 mg/dL**
- Lp (a) > 50 mg/dL

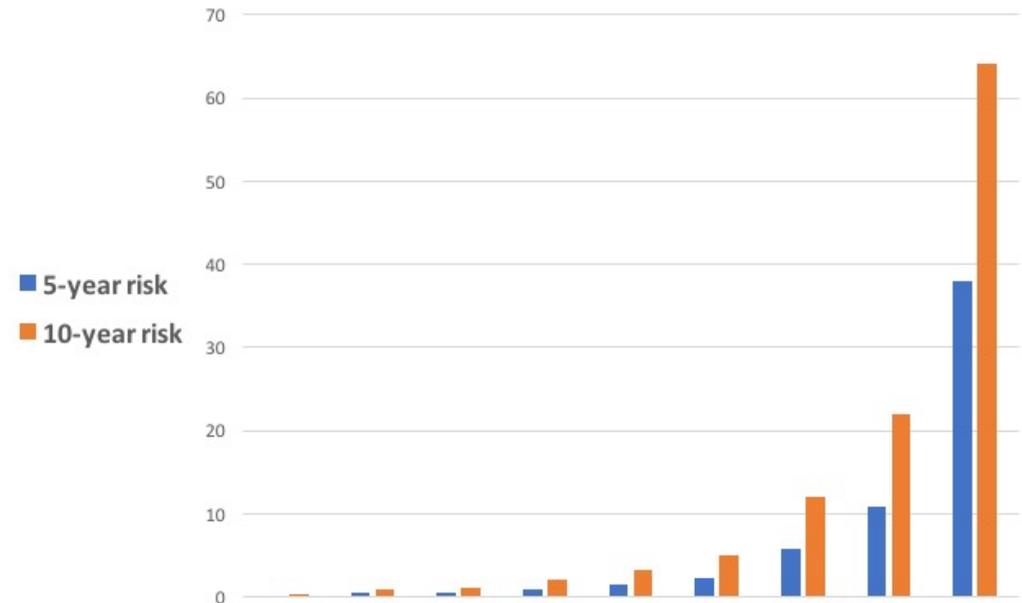
Risk Equation Predictors with a Harrell's C Index of 0.85

The risk calculator is available in (web, iOS and Android) at www.cholesterolfamiliar.org



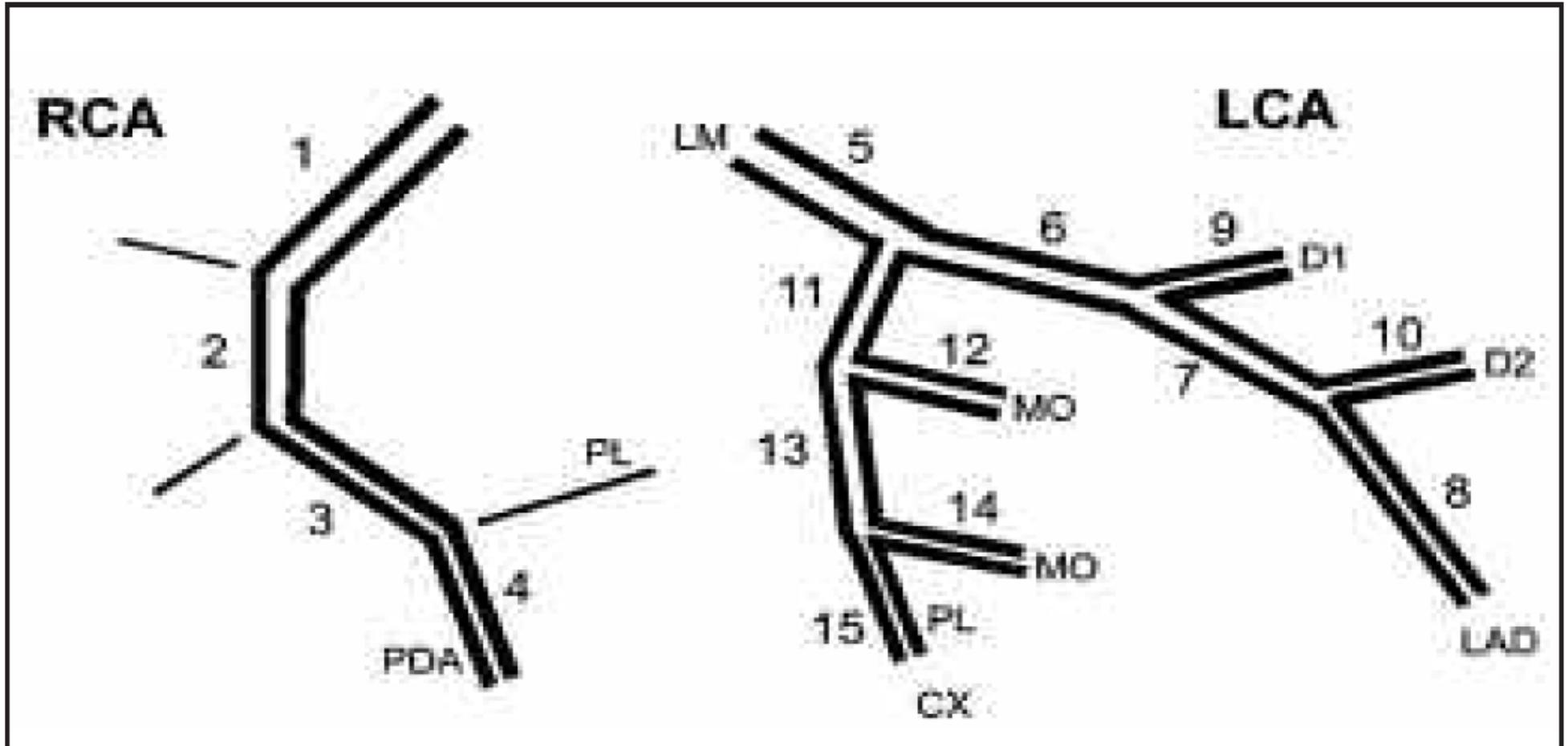
Five vs 10-year risk of developing incident ASCVD for 66-year-old men with FH and LDL-C < 100 mg/dl.

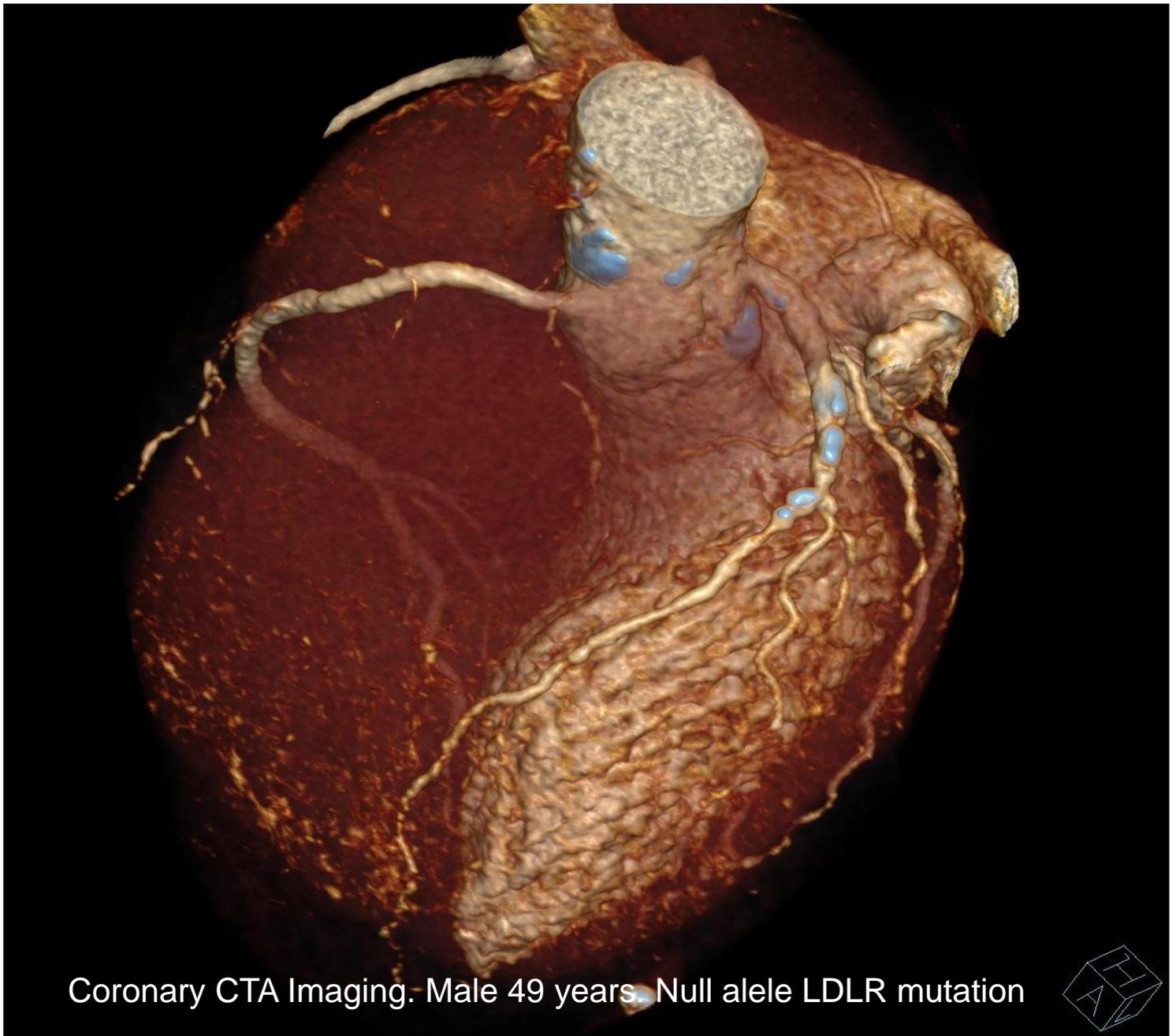
Estimated % risk of developing incident ASCVD



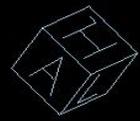
Overweight	-	+	-	-	-	-	-	-	-
Obesity	-	-	+	+	+	+	+	+	+
High blood pressure	-	-	-	+	+	+	+	+	+
Active smoking	-	-	-	-	+	+	+	+	+
Lp(a)>50 mg/dl	-	-	-	-	-	+	+	+	+
LDL-C 100-159 mg/dl	-	-	-	-	-	-	+	-	-
LDL-C ≥ 160 mg/dl	-	-	-	-	-	-	-	+	+
History of ASCVD	-	-	-	-	-	-	-	-	+

Coronary CT Imaging Evaluation of Subclinical Atherosclerosis in FH





Coronary CTA Imaging. Male 49 years. Null allele LDLR mutation

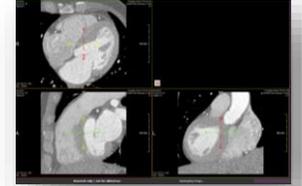




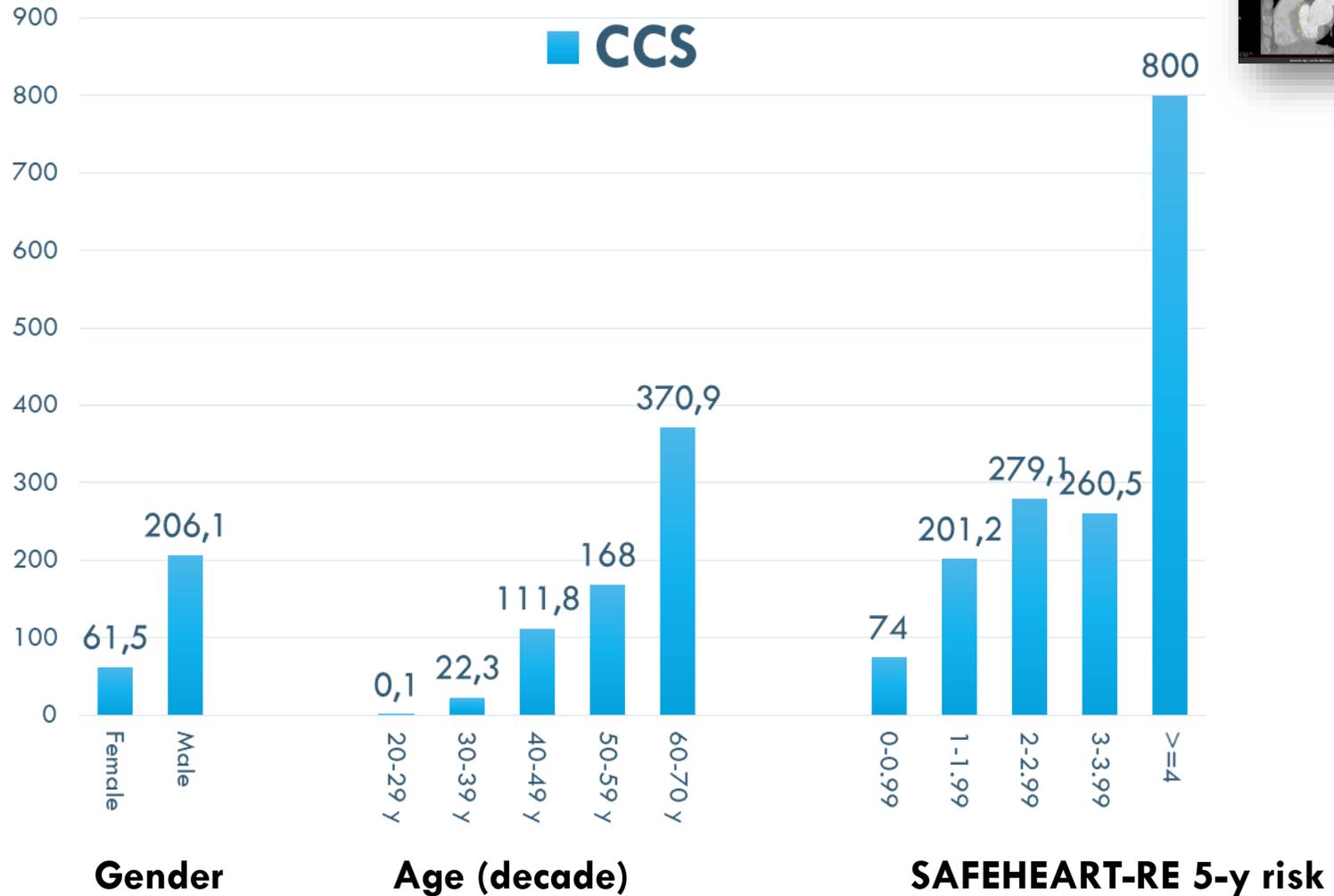
Coronary CT in CVD asymptomatic FH patients SAFEHEART Registry

- We include 440 patients from 6 Centres
- Inclusion Criteria: Men and Women from 20 to 70 years old
- Mean age 46.4 years, 52% females
- Predictors of CCS and plaque characteristics
- Evaluate and Improve Risk Stratification
- **Presence of CCS 56%** (52% women and 70% men)
- **Mean CCS (Agatston score) 130.9**
- **CA Stenosis in 46%** (41% women and 53% men)

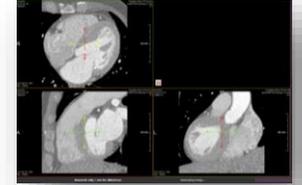
Coronary Calcium Score; n = 440 FH



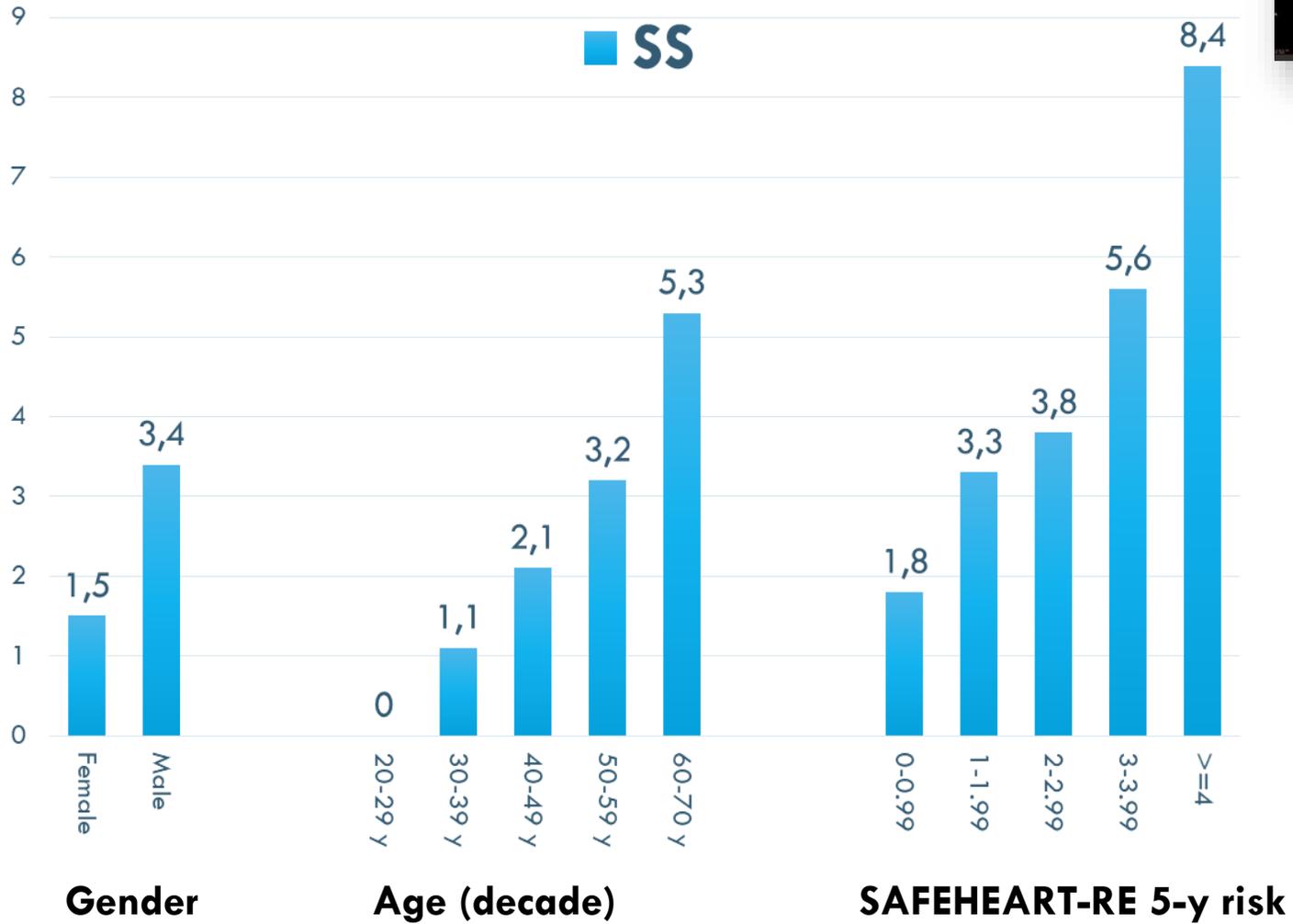
SAFEHEART



Stenosis Sum; n = 440 FH



SAFEHEART



Impact of coronary CTA results in patients' management and care

	Coronary disease (-)*			Coronary disease (+)*			Δ Coronary disease + vs Δ Coronary disease -
	N=174 (39.5%)			N=266 (60.5%)			
	Before	After	p	Before	After	p	p
LDL-C (mg/dl)**	174.3 (59.6)	136.9 (49.3)	<0.001	181.3 (63.1)	123.6 (44.4)	<0.001	0.005
Patients on maximum LLT	80 (46%)	97 (56%)	0.06	165 (62%)	207 (78%)	<0.001	0.01
Patients on PCSK9 inhibitors		2 (1%)			27 (10%)		
Coronary revascularization		0			15 (6%)		
SAFEHEART-RE 5 years (%)	0.7 (0.7)	0.5 (0.5)	<0.001	1.1 (0.9)	0.7 (0.8)	<0.001	<0.001
Use of aspirin	23 (13%)	25 (14%)	0.760	24 (9%)	44 (17%)	0.001	<0.001

New horizons in in the treatment of FH: PCSK9-Inhibitors

LDL-C values < 70 mg/dL in refractory FH patients

- Rutherford-2¹
 - 61-66% treated with evolocumab
- Odyssey FH I and II²
 - 60-68% in those receiving alirocumab

1-Raal et al. Lancet 2015; 385: 331-40.

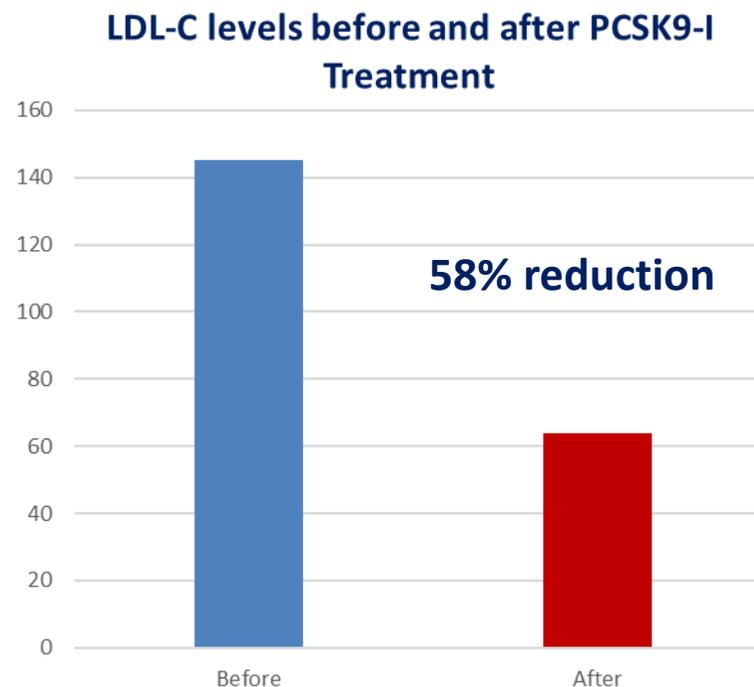
2-Kastelein et al. Eur Heart J 2015; 36:2996-3003.



Patients with PCSK9-I: SAFEHEART Study

(Data 2017)

- **281** subjects >20 years ($\approx 10\%$):
 - Men: 145 (52%)
 - Women: 136 (48%)
- Age Range: 22-82 years
- Mean age: 58 years
- Mean LDL-C (before): **145 mg/dl**
- Mean LDL-C (after): **64 mg/dl**
- 90 patients with CV Disease (**32%**)
- 24 Casos >75 años: 8 V y 16 M
 - 12 CVD (50%)
 - 3 Statin Intolerance





Severe genetic disorder affecting Family

“most vulnerable population in a health system”





Conclusions and messages

- FH is a common hereditary cause of premature CVD
- FH is underdiagnosed and undertreated
- **Fulfills the WHO criteria for detection screening**
- It is necessary to implement a detection cascade screening program (involving GP's, specialists, families..). Patients organizations are essential in FH screening
- **FH detection screening is easy and cost-effective**
- We can treat effectively (statins and PCSK9 Inhibitors)
- **New risk equation for predicting Absolute Risk of CV events**
- High Quality Contemporary Registries improve the care of FH
- Need to Put FH on the Public Health agenda (Future challenge for **PHO**)

any following MI or death caused by FH can be avoided!