REFERCHOL, la cohorte Française de l'Hypercholestérolémie Familiale

Congrès de la SFH, Lyon 2026

SOPHIE BÉLIARD-LASSERRE

Statement of Financial Interest

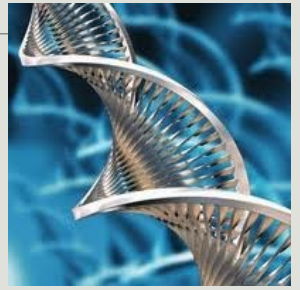
I currently have, or have had over the last two years, an affiliation or financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company :

Speaker's name : Sophie Béliard

☑ I have the following potential conflicts of interest to report

Consulting fees - Novartis
Consulting fees - Viatris
Consulting fees - ULTRAGENYX
Consulting fees - CHIESI
Consulting fees - Amgen

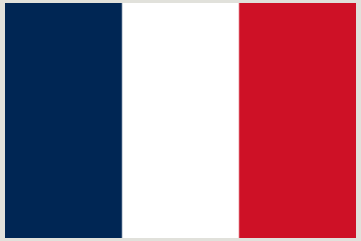
Heterozygous Familial Hypercholesterolemia



- Genetic autosomic dominant disease
- One of the most prevalent genetic disease: 1/311 *(Hu, Circulation, 2020)*
- High cholesterol levels since birth
- High risk of premature coronary heart disease

- It is recommended to screen heFH during childhood from 5 years, to start a heart-healthy diet and statins at 8-10 years old (*Wiegman, Europ Heart Jour, 2015)*

National and international registries are crucial tools for promoting the long time follow up and evaluation



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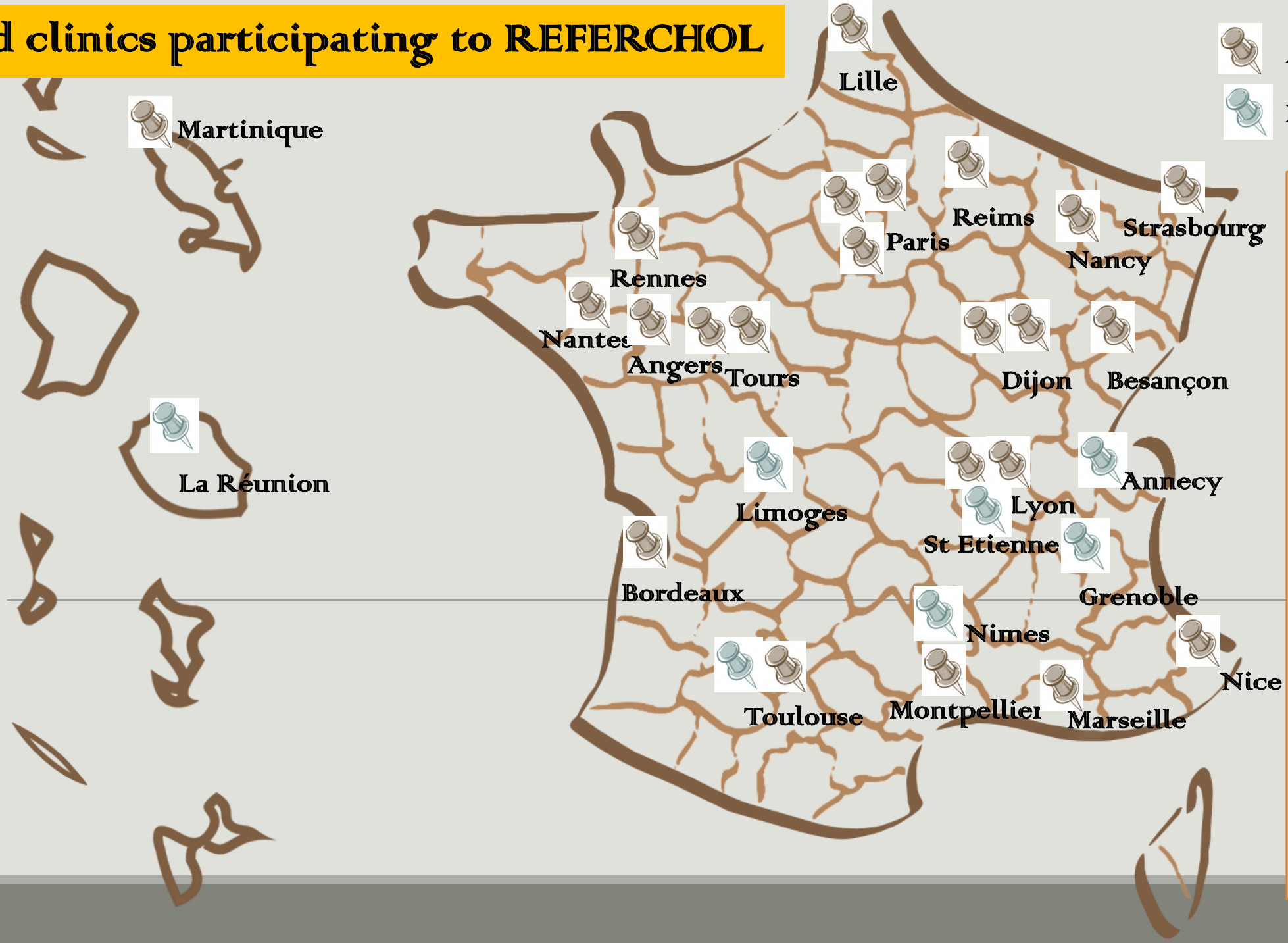
french REgistry of Familial hypERCHOLesterolemia

- Since 2015
- Sponsored by

NSFA

La Santé au Cœur de nos Artères

Lipid clinics participating to REFERCHOL



23 CENTERS

Angers
Besançon
Bordeaux
Dijon 2 centres
Lille
Lyon 2 centres
Marseille
Martinique
Montpellier
Nancy
Nantes
Nice
Paris La Pitié
Paris St Antoine
Paris Trousseau
Rennes
Reims
Toulouse
Tours 2 centres
Strasbourg

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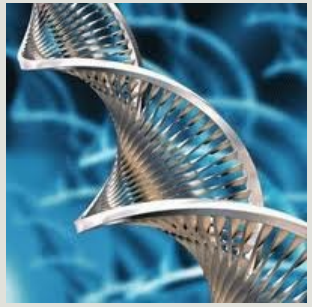
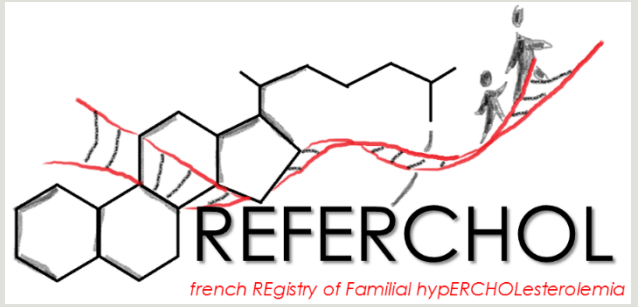
Janvier 2026:

- ❑12 398 patients
- ❑ ≈ + 1 000 patients per year
- ❑ ≈ 600 children

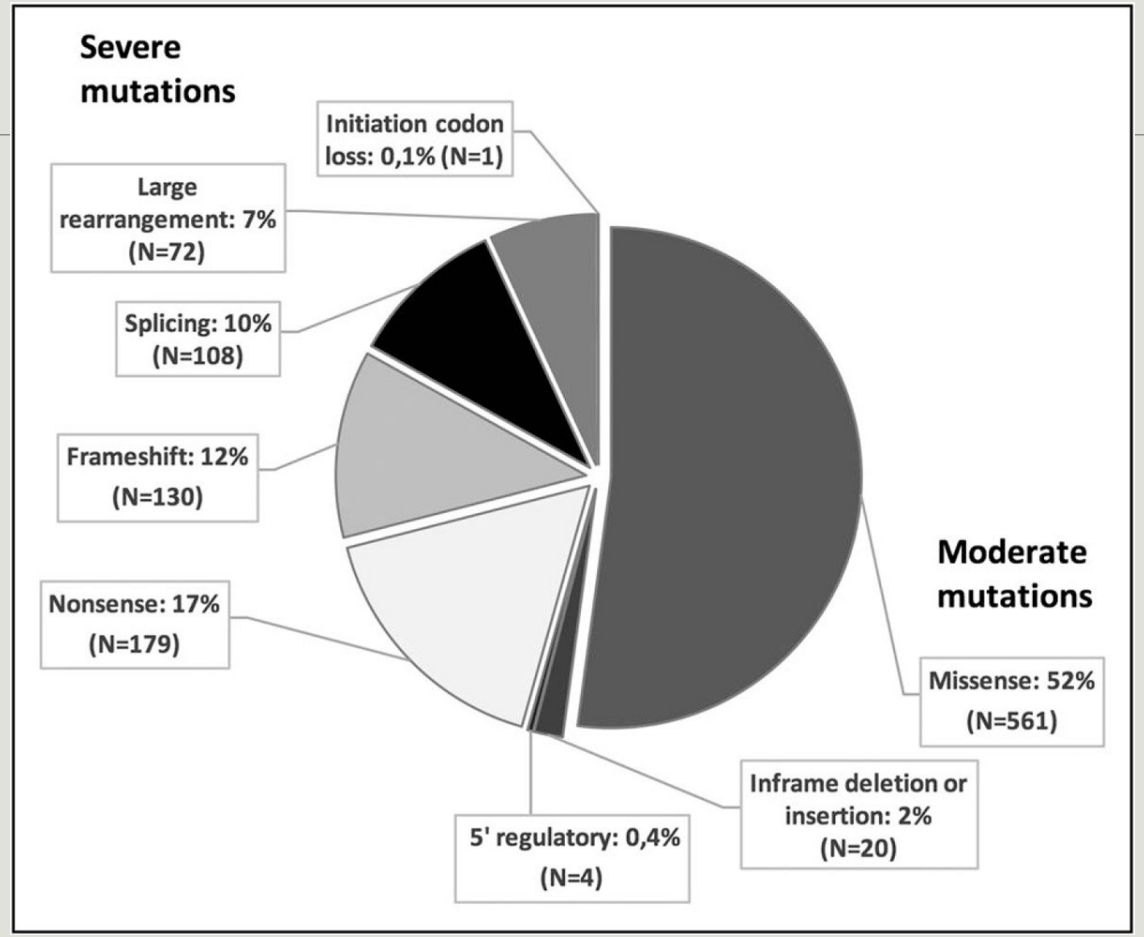
- ❑Genetic confirmed: 6 149 heFH and 191 hoFh

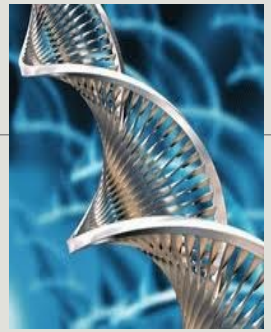


OVERVIEW OF SOME REFERCHOL STUDIES IN heFH ADULTS PATIENTS



Broad spectrum of *LDLR* gene mutations in France





416 pathogenic variants for 1150 mutations

Rabès, Béliard, Carrié, Current Opinion in Lipidology, 2018

Cardiovascular risk in familial Hypercholesterolemia

- High to very high
- But heterogenous
- CHOPIN: **SAFIR**: Study of cardiovAscular contrasted phenotypes in patients with FamIliaI hypercholesteRolemia

PI=Bertrand CARIOU

- Other studies…

The add-on of cardiovascular risk factors

The very high cardiovascular risk in heterozygous familial hypercholesterolemia: Analysis of 734 French patients

Sophie Béliard, MD, PhD*, Aurélie Millier, PhD, Valérie Carreau, MD, Alain Carrié, MD, PhD, Philippe Moulin, MD, PhD, Alexandre Fredenrich, MD, PhD, Michel Farnier, MD, PhD, Gérald Luc, MD, PhD, David Rosenbaum, MD, Mondher Toumi, MD, PhD, Eric Bruckert, MD, PhD, French FH Registry group[1]

Journal of Clinical Lipidology, 2016

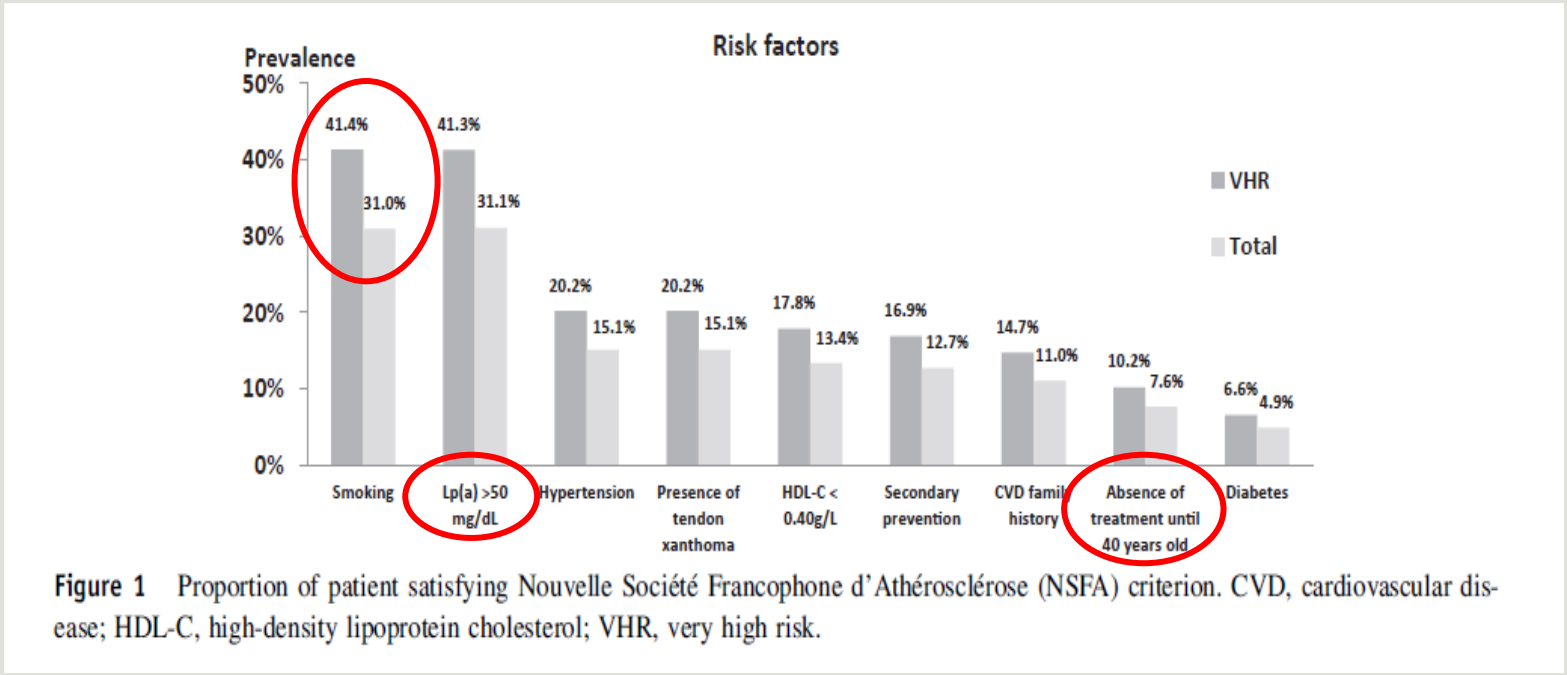


Figure 1 Proportion of patient satisfying Nouvelle Société Francophone d'Athérosclérose (NSFA) criterion. CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; VHR, very high risk.

1/3 heFH are active smokers

¾ heFh patients cumulate several CV risk factors

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EAS FHSC

Pr K Ray
Dr A Vallejo-Vaz

Articles

Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)

EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)*

The Lancet, sept 2021

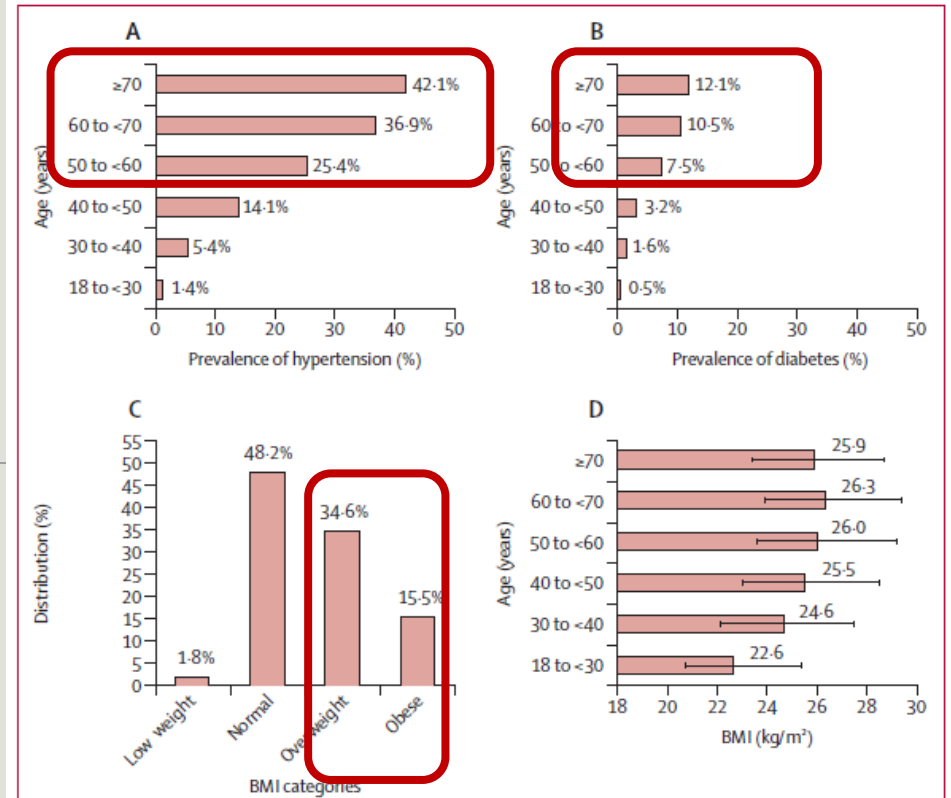
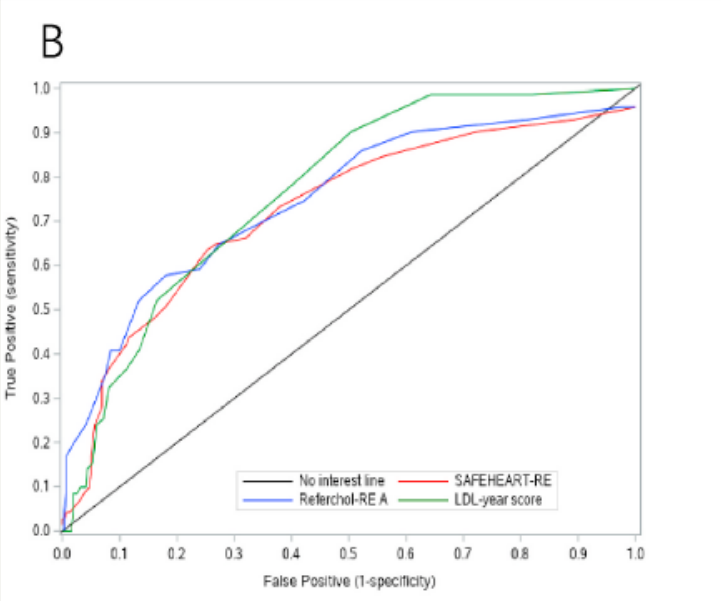


***Figure 2*: Prevalence of hypertension (A) and diabetes (B) by age and distribution of BMI overall (C) and by age (D)**
(C) Low weight indicates BMI lower than 18·5 kg/m², normal weight indicates BMI from 18·5 to lower than 25 kg/m², overweight indicates BMI from 25 to lower than 30 kg/m², and obesity indicates BMI of 30 kg/m² or higher. (D) Data are median and error bars represent the IQR. BMI=body-mass index.

42 000 adults heFH
66 countries

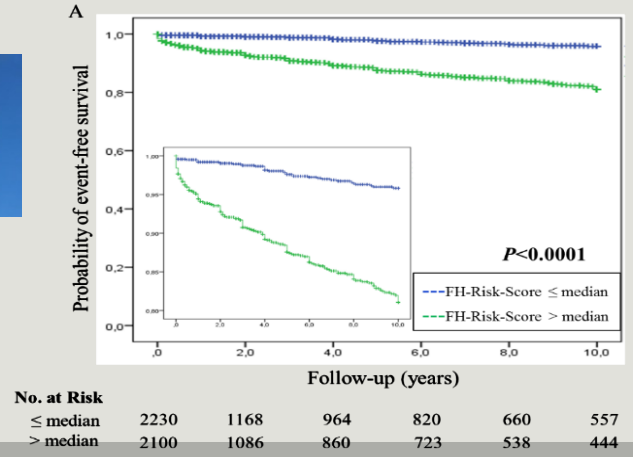
CV risk evaluation in FH is a challenge



Perez de Isla, Circulation, 2017

- 1473 heFH patients, mean follow-up 3.9 y, 103 events

→ **SAFEHEART-RE** and chol-year-score are good predictors of CV events in primary prevention heFH patients (C-index 0,78) *Gallo et al., Atherosclerosis, 2020*



- 3918 primary prevention heFH patients from 5 registries (3097 from REFERCHOL)

→ **MONTREAL-risk score** is a good predictor of MACE and mortality in primary prevention heFH patients *Paquette et al., ATVB, 2021*

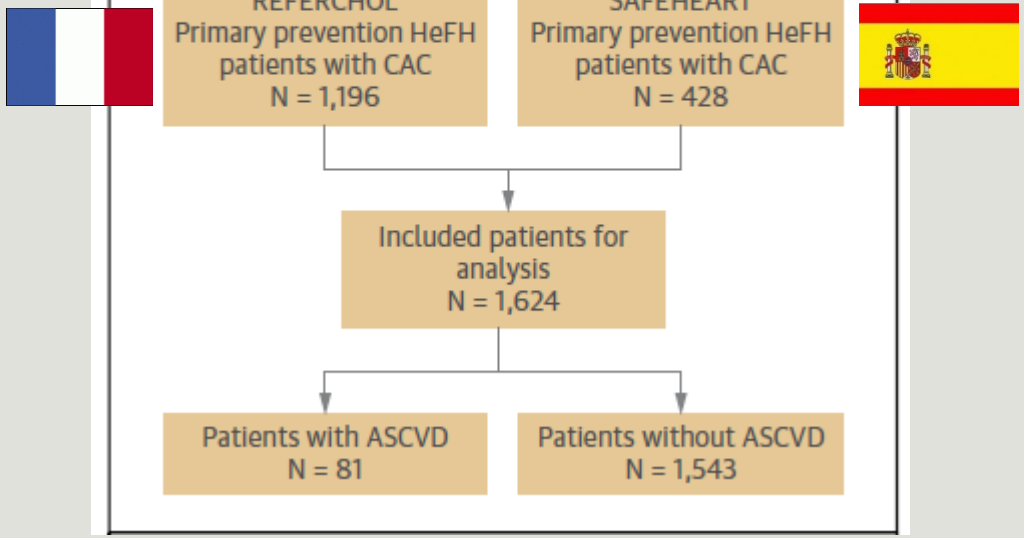
JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2021

PUBLISHED BY ELSEVIER

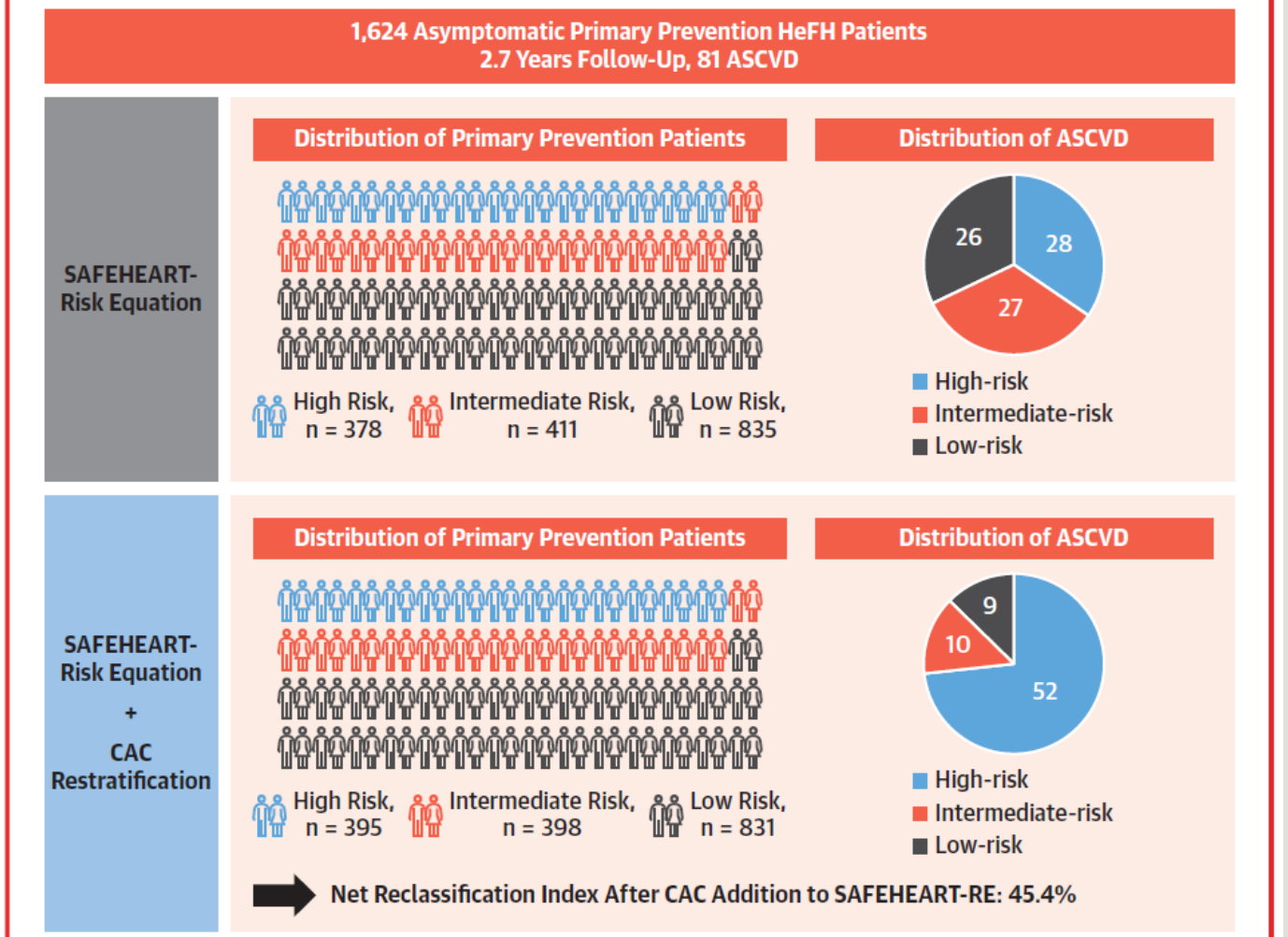
The Added Value of Coronary Calcium Score in Predicting Cardiovascular Events in Familial Hypercholesterolemia

Antonio Gallo, MD, PhD,[a,b,*] Leopoldo Pérez de Isla, MD, PhD,[c,d,*] Sybil Charrière, MD, PhD,[e] Alexandre Vimont,[f] Rodrigo Alonso, MD, PhD,[d,g] Ovidio Muñiz-Grijalvo, MD, PhD,[h] José L. Díaz-Díaz, MD, PhD,[i] Daniel Zambón, MD, PhD,[j] Philippe Moulin, MD, PhD,[e] Eric Bruckert, MD,[a] Pedro Mata, MD,[d] Sophie Béliard, MD, PhD,[k,l] on behalf of the REFERCHOL and SAFEHEART investigators

FIGURE 1 Patient Flowchart Showing the Recruitment of Patients in the REFERCHOL and SAFEHEART Registries



CENTRAL ILLUSTRATION The Added Value of Coronary Artery Calcium Score on Top of SAFEHEART Risk Equation for Atherosclerotic Cardiovascular Disease Prediction in Asymptomatic Heterozygous Familial Hypercholesterolemia



Gallo, A. et al. J Am Coll Cardiol Img. 2021;■(■):■-■.

The high burden of recurrent CV events in heFH

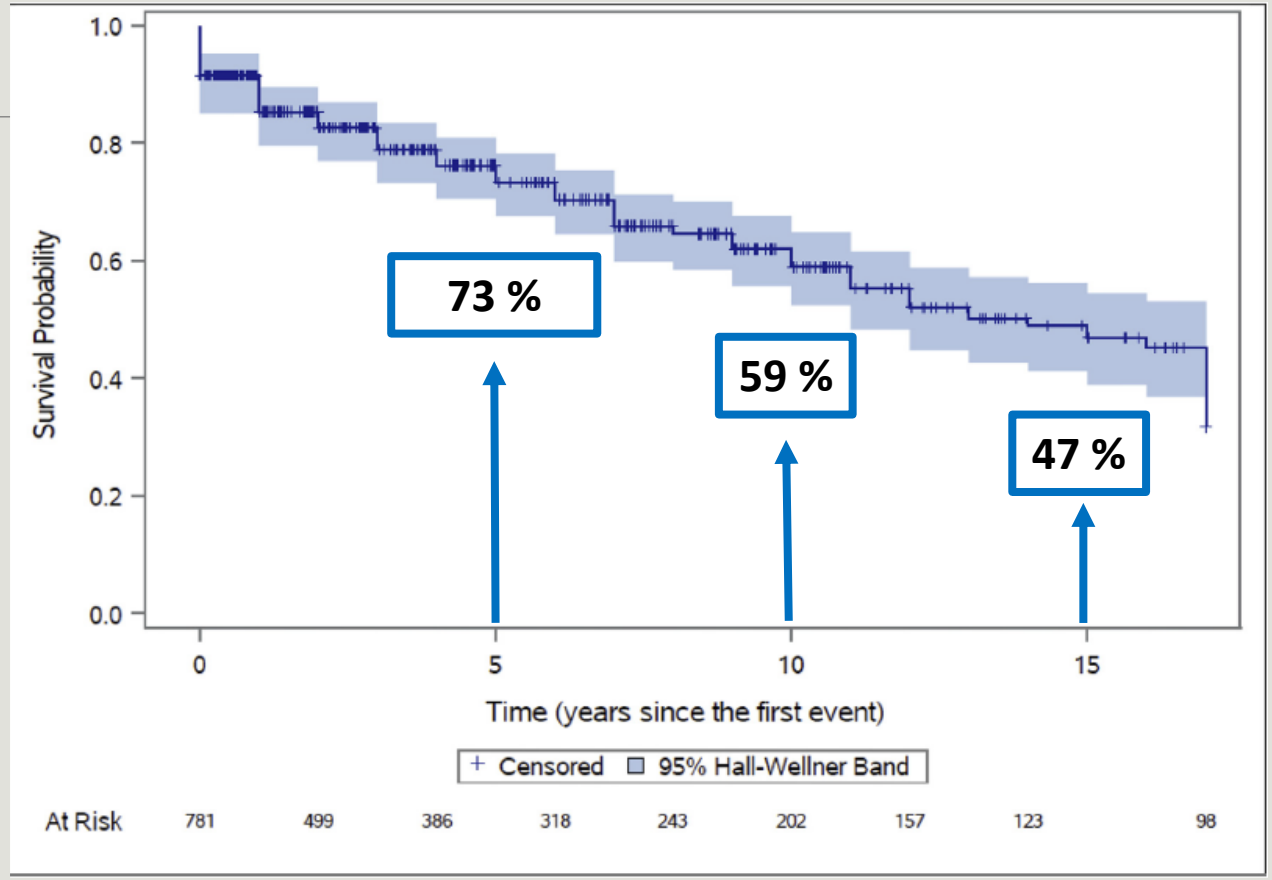
781 secondary prevention heFH
Age at the first event: 47 y

Recurrence of CV events:

37% patients(X2 to 6/G^{ale}pop)

9 for 100 patients/years

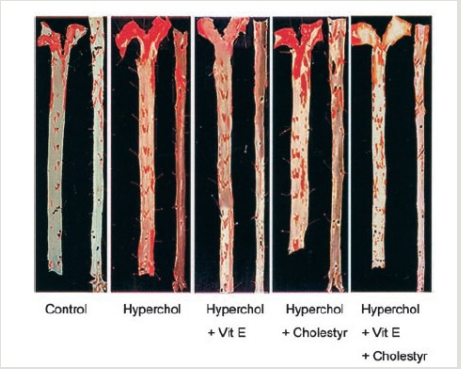
1,8 event/patient



Béliard, Boccara et al,Atherosclerosis, 2018

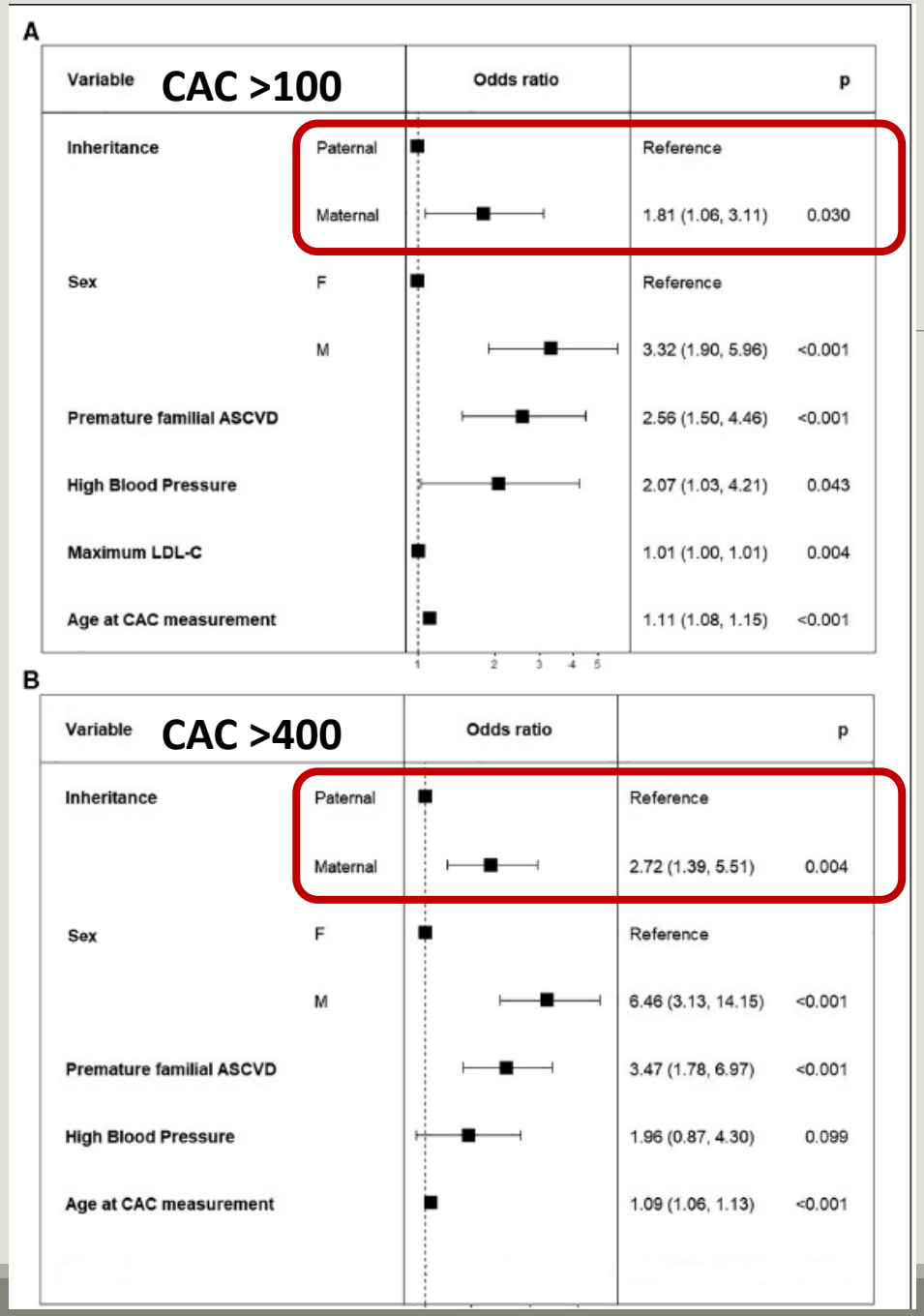
Effect of the maternal inheritance of FH gene mutation on the CV risk in heFH patients

- Animal studies have demonstrated that fetal exposure to high maternal cholesterol levels during pregnancy predisposes to aortic atheroma in the offspring



Palinski, Circulation 2002
Napoli, Circulation 2002

- FH is a unique model disease in which children from FH women are exposed to very high cholesterol levels during pregnancy



Arteriosclerosis, Thrombosis, and Vascular Biology

2023

ORIGINAL RESEARCH

Maternal Inheritance of Familial Hypercholesterolemia Gene Mutation Predisposes to Coronary Atherosclerosis as Assessed by Calcium Score in Adulthood

Florian Mourre, Roch Giorgi, Antonio Gallo, Franck Boccara, Eric Bruckert, Alain Carrié, Regis Hankard, Jocelyn Inamo, Sandrine Laboureau, Philippe Moulin, René Valéro, Sophie Béliard, on behalf of the REFERCHOL Investigators*

In 556 age- and sex-matched pair of patients based on the sex of the parents who transmitted the FH gene mutation

Patients with a maternal inheritance of the mutation have:

- ❑ **1.8 risk of having a CAC >100**
- ❑ **2,72 risk of having a CAC >400**

Effect of FH screening strategy on CV risk ?

3232 adults
heFH patients with a genetic diagnosis
Followed in a lipid clinic (23)

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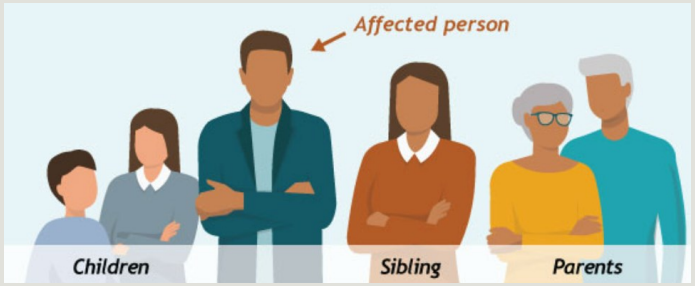
2106
index cases

1126
Non index-cases

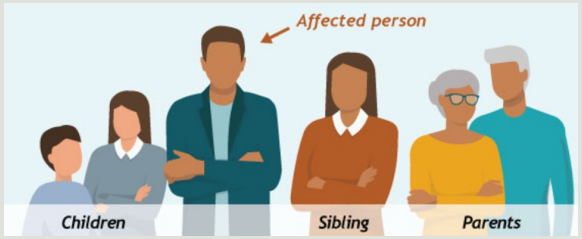


Comparaison of both groups at the first visit, and during the follow-up

Mean follow-up : 2.2 years (2015-2022)

Uni and multivariate analysis with RStudio version 4.1.3 software

Effect of cascade screening on CV events



igure3
A

		Odds ratio	p
Diagnostic modality	Index case		Reference
	Non−index case		0.50 (0.33, 0.76) 0.001
Age at statin initiation	< 18 years old		Reference
	18−30 years old		1.38 (0.70, 2.82) 0.363
	30−40 years old		2.60 (1.29, 5.48) 0.009
	> 40 years old		3.18 (1.48, 7.12) 0.004
Sex	Female		Reference
	Male		4.29 (2.95, 6.33) <0.001
Tobacco user	No		Reference
	Yes		1.54 (1.10, 2.18) 0.013
Hypertension	No		Reference
	Yes		2.67 (1.76, 4.08) <0.001
Premature familial ASCVD	No		Reference
	Yes		2.24 (1.59, 3.15) <0.001
BMI	< 25 kg/m²		Reference
	25−30 kg/m²		2.31 (1.59, 3.36) <0.001
	> 30 kg/m²		2.57 (1.57, 4.20) <0.001
Age at last visit			1.04 (1.02, 1.06) <0.001

0.5 1 2 5

Cascade screening= 50 % lower risk of cardiovascular event

Age of statin initiation is the most powerful predictor of having a CV event

Etat des lieux des aphérèses dans REFERCHOL en 2025

Centres	Nombre de patients dans le registre	Nombre total (historique)	Patients sous aphérèse en 2025	Nombre de HeFH	Nombre de d'arrêts chez patient actif en 2023
LA PITIE	2550	93	43	13	6
MARSEILLE	1062	36	18	8	9
LYON	1225	20	4	1	3
NANTES	1237	10	2	0	8
STRASBOURG	103	11	3	1	1
LILLE	602	28	22	13	0
DIJON	169	2	2	0	0
Total	**12,272**	**>200**	**86**	**36**	**27**

7 centres, 86 patients 2025

Etat des lieux des aphérèses dans REFERCHOL en 2025

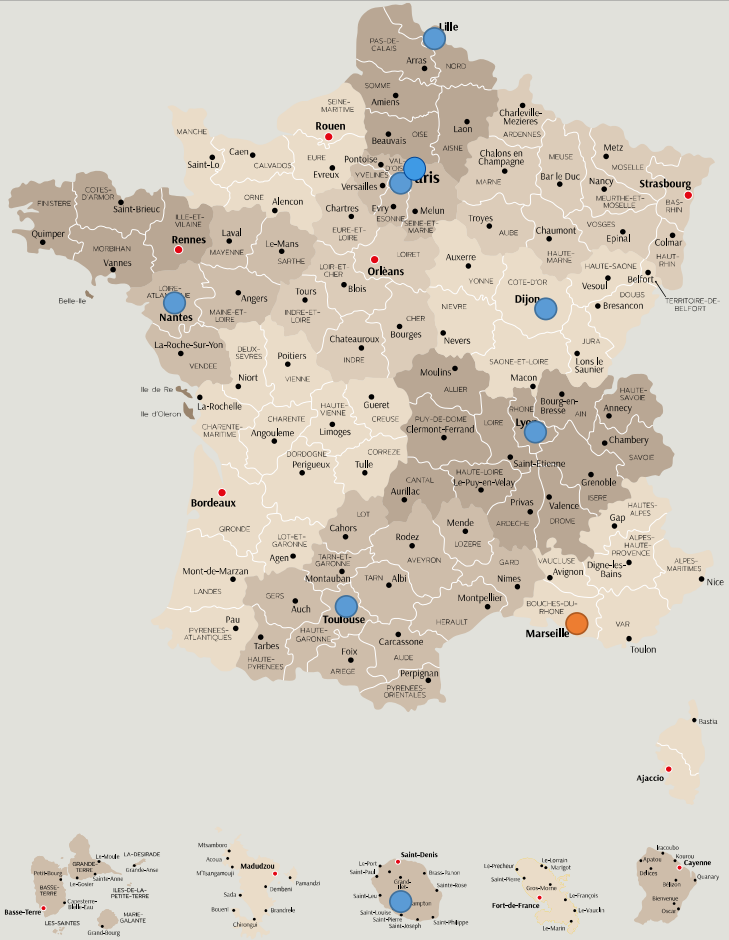
- **> 200 patients** en LDL aphérèses saisis dans REFERCHOL
- *2016*: essais thérapeutiques puis AMM des AC antiPCSK9: sortie d'une majorité des heFH de LA; **en 2018**: **121 patients en LA**
- *2023*: AMM des nouvelles thérapies pour les hoFH: quelques sorties de LDL-aphérèses
- ***2025***: **86 patients en LA, 42% hetFH**

CEDRA: expert center for rare dyslipidemias diseases

CEDRA
CENTRES D'EXPERTISE DES DYSLIPIDEMIES RARES

centre de référence
maladies rares

FIRENDO
FILIÈRE MALADIES RARES ENDOCRINIENNES



Hôpitaux Universitaires de Marseille | ap hm

PNDS de l'Hypercholestérolémie Familiale homozygote

Disponible bientôt sur le site de l'HAS

Disponible sur le site de la NSFA

https://www.nsfa.asso.fr/wp-content/uploads/2026/01/PNDS-Hypercholesterolemie-familiale-homozygote.pdf

Disponible sur le site internet CEDRA:

https://fr.ap-hm.fr/service/centre-expertise-dyslipidemies-genetiques-rares-cedra

Conclusions

- REFERCHOL est une cohorte de patients suivis sur du long terme, enfants comme adultes
- REFERCHOL est un outil précieux pour avancer sur les questions de recherche
- **LDL-aphérèses: stoppées pour de nombreux patients he et hoFH grâce aux nouvelles thérapies (PCSK9i ou thérapies des hoFH)**
- **Mais avec l'amélioration du dépistage, arrivée de nouveaux patients dans les centres experts**

THANK YOU

REFERCHOL INVESTIGATORS: DENIS ANGOULVANT, KARINE AOUCHICHE, SOPHIE BELIARD, ANNIE BERARD, FRANCK BOCCARA, ERIC BRUCKERT, BERTRAND CARIOU, ALAIN CARRIE, SYBIL CHARRIERES, YVES COTTIN, THIERRY COUFFINHAL, MATHILDE DI-FILLIPO, CAROLINE DOURMAP, PIERRE HENRI DUCLUZEAU, VINCENT DURLACH, MICHEL FARNIER, EMILE FERRARI, DOROTA FERRIERES, JEAN FERRIERES, ANTONIO GALLO, REGIS HANKARD, PIERRE JEANTET, JOCELYNE INAMO, SANDRINE LABOUREAU, JULIE LEMALE, PHILIPPE MOULIN, FLORIAN MOURRE, FRANÇOIS PAILLARD, NOEL PERETTI, ALAIN PRADIGNAC, YANN PUCHEU, JEAN PIERRE RABES, RACHEL REYNAUD, VINCENT RIGALLEAU, FRANÇOIS SCHIELE, ARIANE SULTAN, PATRICK TOUNIAN, RENÉ VALERO, BRUNO VERGES, CECILE YELNIK

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