FH: Vision of the International Atherosclerosis Society

Raul D. Santos MD, PhD
Sao Paulo, Brazil

Declaration

- I have received honoraria related to consulting, talks or research from :

- Akcea, Amgen, Astra Zeneca, Biolab, Esperion, Kowa
- Merck, Pfizer, Novo-Nordisk, Sanofi/Regeneron

International Atherosclerosis Society

Mission: promote the scientific understanding of the etiology, prevention, and treatment of atherosclerosis.

- Federation of 64 societies
- Focus on developing regions
- Joint activities with member societies
- Practice documents
- Research and fellowship grants

www.athero.org

Member Societies (updated March, 2018)

- **Argentina –** Argentina Lipid Society
- **Asian Pacific** Society of Atherosclerosis and Vascular Diseases
- **Australia –** Australian Atherosclerosis Society
- **Austria –** Austrian Atherosclerosis Society
- **Belgium –** Belgian Lipid Club
- **Brazil –** Department of Atherosclerosis, Brazilian Society of Cardiology
- **Canada –** Canadian Society of Atherosclerosis, Thrombosis and Vascular Biology (CSATVB)
- **Chile –** Chilean Working Group on Atherosclerosis
- **China –** Chinese Atherosclerosis Society
- **Croatia –** Croatian Atherosclerosis Society
- **Cuba –** Cuban Atherosclerosis Society
- **Czech Republic –** Czech Society for Atherosclerosis
- **Ecuador –** Ecuadorian Society of Atherosclerosis and Endothelium
- **Egypt –** Egyptian Society of Atherosclerosis
- **Egypt –** Egyptian Association of Endocrinology, Diabetes, and Atherosclerosis (EAEDA)
- **Egypt –** Egyptian Association of Vascular Biology and Atherosclerosis (EAVA)
- **Finland –** Finnish Atherosclerosis Society
- **France –** New French Atherosclerosis Society (NFAS)
- **Georgia –** Georgian Atherosclerosis Association
- **Germany –** German Atherosclerosis Society
- **Greece –** Hellenic Atherosclerosis Society
- **Greece –** Hellenic Society of Lipidology, Atherosclerosis and Vascular Disease
- **Hungary –** Hungarian Atherosclerosis Society
- **India –** Diabetes India
- **India –** Indian Society for Atherosclerosis Research
- **India –** Lipid Association of India (LAI)
- **Indonesia –** Indonesian Cardiocerebrovascular Society (ICS), Council on Atherosclerosis
- **Iran –** Iranian Heart Foundation - Council on Atherosclerosis, Nutrition and Lipids
- **Israel –** Israeli Society for Research, Prevention and Treatment of Atherosclerosis
- **Italy –** Italian Society for the Study of Arteriosclerosis (SISA)
- **Japan –** Japan Atherosclerosis Society
- **Korea –** Korean Society of Lipidology and Atherosclerosis
- **Kyrgyzstan –** The Lipid Working Group of the Kyrgyz Society of Cardiology
- **Latin American –** Atherosclerosis Society (SOLAT)
- **Mediterranean –** Society of Atherosclerosis
- **Mexico –** Mexican Association for the Study of Atherosclerosis and Metabolic Syndrome
- **Morocco –** Moroccan Society of Atherosclerosis (SMA)
- **The Netherlands –** Dutch Atherosclerosis Society
- **Oman –** Oman Society of Lipid & Atherosclerosis (OSLA)
- **Philippines –** Diabetes Philippines (formerly Philippine Diabetes Association)
- **Philippines –** Philippine Lipid and Atherosclerosis Society (PLAS)
- **Poland –** Polish Society for Atherosclerosis Research
- **Portugal –** Portuguese Atherosclerosis Society
- **Romania –** Romanian Association for Atherosclerosis and Lipidology (RAAL)
- **Russia –** Russian National Atherosclerosis Society
- **Scandinavian –** Society for Atherosclerosis Research (SSAR)
- **Serbia –** Atherosclerosis Society of Serbia
- **Serbia –** Serbian Association for Arteriosclerosis, Thrombosis and Vascular Biology Research/Serbian ATVB
- **Slovak Republic –** Slovak Association of Atherosclerosis
- **Slovak Republic –** Slovak Section for Atherosclerosis of the Slovak Society of Clinical Biochemistry
- Sociedad **Iberolatinoamericana** de Aterosclerosis (SILAT)
- **South Africa –** Lipid and Atherosclerosis Society of Southern Africa (LASSA)
- **Spain –** Spanish Society of Arteriosclerosis
- **Switzerland –** Swiss Atherosclerosis Association
- **Taiwan R.O.C. –** Taiwan Society of Atherosclerosis & Vascular Diseases
- **Taiwan R.O.C. –** Taiwan Society of Lipids & Atherosclerosis
- **Tunisia –** Tunisian Association of Study and Research on Atherosclerosis (ATERA)
- **Turkey –** Lipid Working Group of the Turkish Society of Cardiology
- **UAE –** Emirates Cardiac Society
- **UK –** British Atherosclerosis Society
- **Ukraine –** Ukrainian Atherosclerosis Society
- **USA –** Arteriosclerosis, Thrombosis, and Vascular Biology Council/American Heart Association (ATVB/AHA)
- **USA –** National Lipid Association (NLA)
- **Venezuela –** Venezuelan Atherosclerosis Association (AVA)

Familial Hypercholesterolemia in a Nutshell

- Severe Dyslipidemia LDL-C usually > 190 mg/dL in adults
  - (> 160 mg/dL in kids)
- Prevalence
  - 1/250-500 heterozygotes
  - $1/10^6$-300.10^3 homozygotes
- Elevated ASCVD risk (10-13X)
  - Early ASCVD
- Cutaneous stigmata
- Family history
  - Early CHD
  - Dyslipidemia in the family
  - Autosomal dominant inheritance
- Hard to normalize LDL-C

Defesche JC et al. Nat Rev Dis Primers. 2017 Dec 7;3:17093. doi: 10.1038/nrdp.2017.93

FH Prevalence and its consequences

Estimated FH Prevalence

Most FH Patients Are in Developing Countries !!!

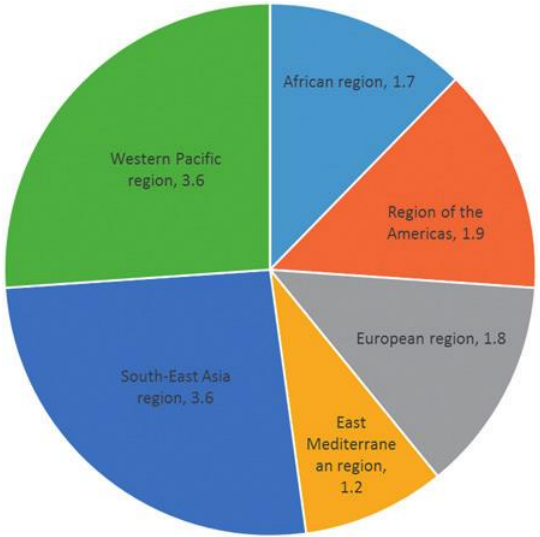


Fig. 1. Estimated number (millions) of individuals with FH in WHO-defined regions based on the theoretical prevalence of 1:500[3] for heterozygous FH (Adapted from Pang *et al*[42]. At least 50% of FH patients in the world are likely to come from Asian countries (included in the Western Pacific region and South-East Asia region).

14-28 million people

Watts G et al. J Atheroscler Thromb. 2016;23:891-900

Original Contribution

Clinical and molecular aspects of familial hypercholesterolemia in Ibero-American countries

Raul D. Santos*, Mafalda Bourbon, Rodrigo Alonso, Ada Cuevas, Alexandra Vásquez-Cárdenas, Alexandre C. Pereira, Alonso Merchan, Ana Catarina Alves, Ana Margarida Medeiros, Cinthia E. Jannes, Jose E. Krieger, Laura Schreier, Leopoldo Perez de Isla, Maria Teresa Magaña-Torres, Mario Stoll, Nelva Mata, Nicolas Dell Oca, Pablo Corral, Sylvia Asenjo, Virginia G. Bañares, Ximena Reyes, Pedro Mata, on behalf of the Ibero-American Familial Hypercholesterolemia Network

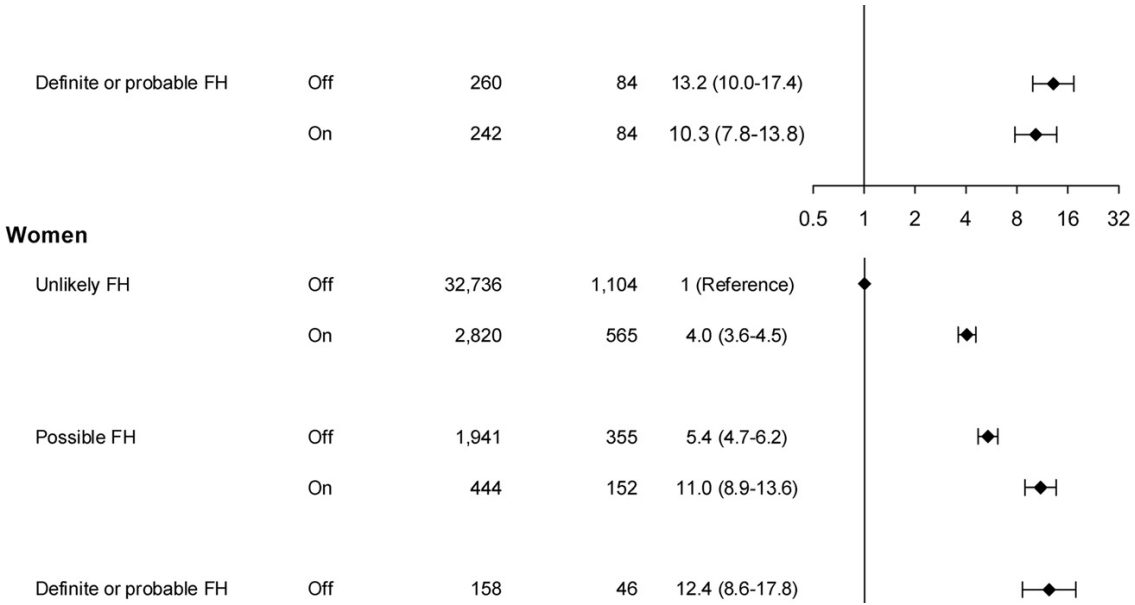
High prevalence of previous CVD in FH Index cases

Country	% With Molecular Diagnosis	% Index Cases CVD
Spain	8.3%	13%
Portugal	3.82%	16.9%
Brazil	0.27%	23%
Uruguay	2.5%	35%
Mexico	0.13%	38%

Santos RD et al. J Clin Lipidol. 2017;11:160-166.

Familial Hypercholesterolemia in the Danish General Population: Prevalence, Coronary Artery Disease, and Cholesterol-Lowering Medication

Marianne Benn, Gerald F. Watts, Anne Tybjaerg-Hansen, and Børge G. Nordestgaard



Benn et al. JCEM 2012, 97:3956–3964

Estimated costs of hospitalization due to coronary artery disease attributable to familial hypercholesterolemia in the Brazilian public health system

Luciana R. Bahia[1], Roger S. Rosa[2], Raul D. Santos[3], Denizar V. Araujo[1]

Table 2. Hospitalizations due to coronary artery disease attributable to familial hypercholesterolemia and distributed by age group. Annual average values for the period of 2012-2014 (Brazilian Unified Health Care System, SUS)

ICD-10: I20 – I25	Age groups (years)				Total
	20-44	45-64	65-74	75+	
Total CAD	18,012	123,306	64,426	40,237	245,981
COSTS (R$/Intl$)*	48,956,113 / 29,742,474	508,160,232 / 308,724,321	286,604,042 / 174,121,532	142,198,678 / 86,390,448	985,919,064 / 598,978,775
Attributable to FH (prevalence 0.4%)	531	3,634	1,899	1,186	7,249
Coef/10,000/year	0.1	0.9	2.1	2.1	0.5
COSTS (R$/Intl$)*	1,442,660 / 876,464	14,974,691 / 9,097,625	8,445,775 / 5,131,091	4,190,374 / 2,545,792	29,053,500 / 17,650,972
Attributable to FH (prevalence 0.73%)	946	6,474	3,383	2,113	12,915
Coef/10,000/year	0.1	1.6	3.7	3.7	1.0
COSTS (R$/Intl$)*	2,570,366 / 1,561,583	26,680,177 / 16,209,099	15,047,708 / 9,141,985	7,465,924 / 4,535,799	51,764,175 / 31,448,466

ICD-10: International Classification of Diseases, Tenth Revision; CAD: Coronary Artery Disease; R$: Brazilian Real; Intl$: International Dollar; FH: Familial Hypercholesterolemia; Coef/10,000/year: coefficient per 10,000 inhabitants per year.

* International dollar: PPP 2013; correction factor 1.646.

Bahia L et al. Arch Endocrinol Metab 2018 e pub

How FH is Diagnosed?

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association

Samuel S. Gidding, Mary Ann Champagne, Sarah D. de Ferranti, Joep Defesche, Matthew K. Ito, Joshua W. Knowles, Brian McCrindle, Frederick Raal, Daniel Rader, Raul D. Santos, Maria Lopes-Virella, Gerald F. Watts and Anthony S. Wierzbicki

Circulation. published online October 28, 2015;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Gidding S et al. Circulation 2015; 132:2167-92

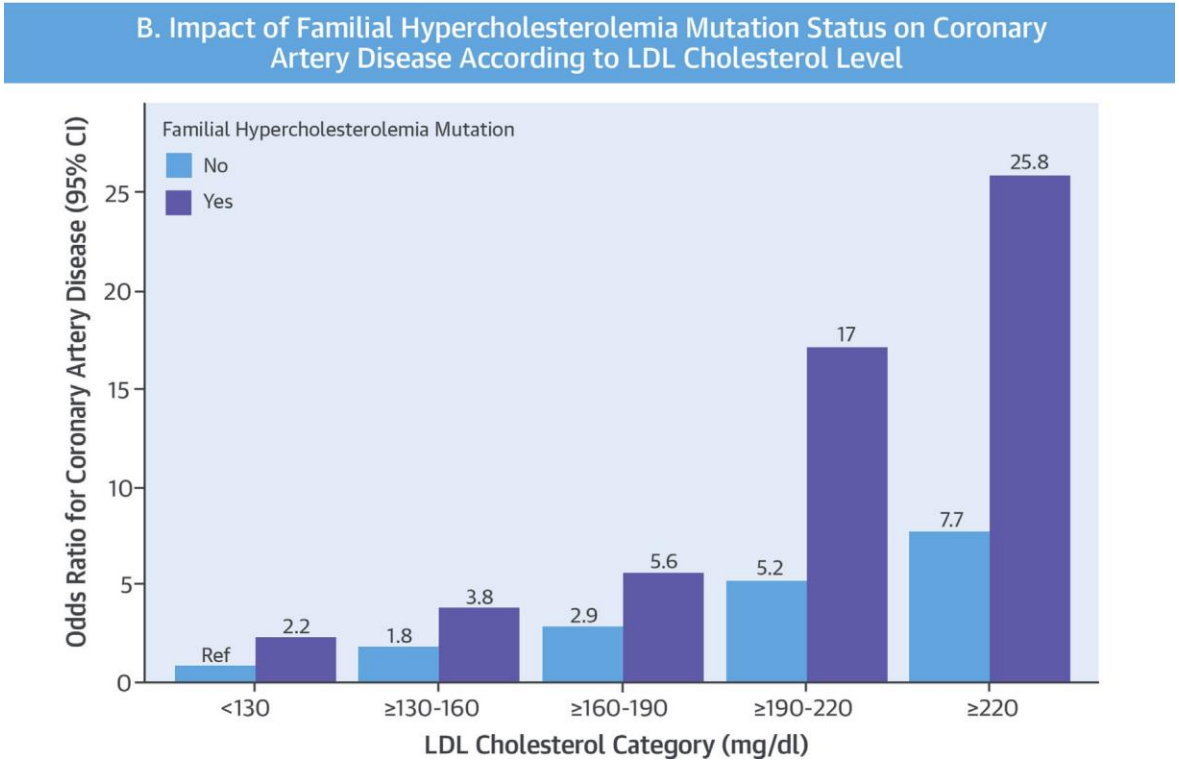
Table 4. FH Diagnostic Categories

ICD-10 Category	Clinical Criteria	With Genetic Testing Performed
Heterozygous FH	LDL-C ≥160 mg/dL (4 mmol/L) for children and ≥190 mg/dL (5 mmol/L) for adults and with 1 first-degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9)	Presence of 1 abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defect
		Diagnosed as heterozygous FH if gene-raising defect positive and LDL-C <160 mg/dL (4 mmol/L)
		Occasionally, heterozygotes will have LDL-C >400 mg/dL (10 mmol/L); they should be treated similarly to homozygotes
		Presence of both abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defect(s) and LDL-C–lowering gene variant(s) with LDL-C <160 mg/dL (4 mmol/L)
Homozygous FH	LDL-C ≥400 mg/dL (10 mmol/L) and 1 or both parents having clinically diagnosed familial hypercholesterolemia, positive genetic testing for an LDL-C–raising (LDL receptor, apoB, or PCSK9) gene defect, or autosomal-recessive FH	Presence of 2 identical (true homozygous FH) or nonidentical (compound heterozygous FH) abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defects; includes the rare autosomal-recessive type
	If LDL-C >560 mg/dL (14 mmol/L) or LDL-C >400 mg/dL (10 mmol/L) with aortic valve disease or xanthomata at <20 y of age, homozygous FH highly likely	Occasionally, homozygotes will have LDL-C <400 mg/dL (10 mmol/L)
Family history of FH	LDL-C level not a criterion; presence of a first-degree relative with confirmed FH	Genetic testing not performed

apoB indicates apolipoprotein B; FH, familial hypercholesterolemia; *ICD-10*, *International Classification of Diseases, 10th Revision*; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtulisin/kexin type 9.

Gidding S et al. Circulation 2015; 132:2167-92

FH Mutation Presence and CAD Risk



Khera, A.V. et al. J Am Coll Cardiol. 2016;67(22):2578-89.

Child–Parent Familial Hypercholesterolemia Screening in Primary Care

David S. Wald, F.R.C.P., Jonathan P. Bestwick, M.Sc., Joan K. Morris, Ph.D.,
Ken Whyte, Lucy Jenkins, F.R.C.Path., and Nicholas J. Wald, F.R.S.

For every 1,000 children 1-2 years of age = 8 FH subjects (4 children and 4 parents) LDL 99% Twice or LDL %95 + mutation

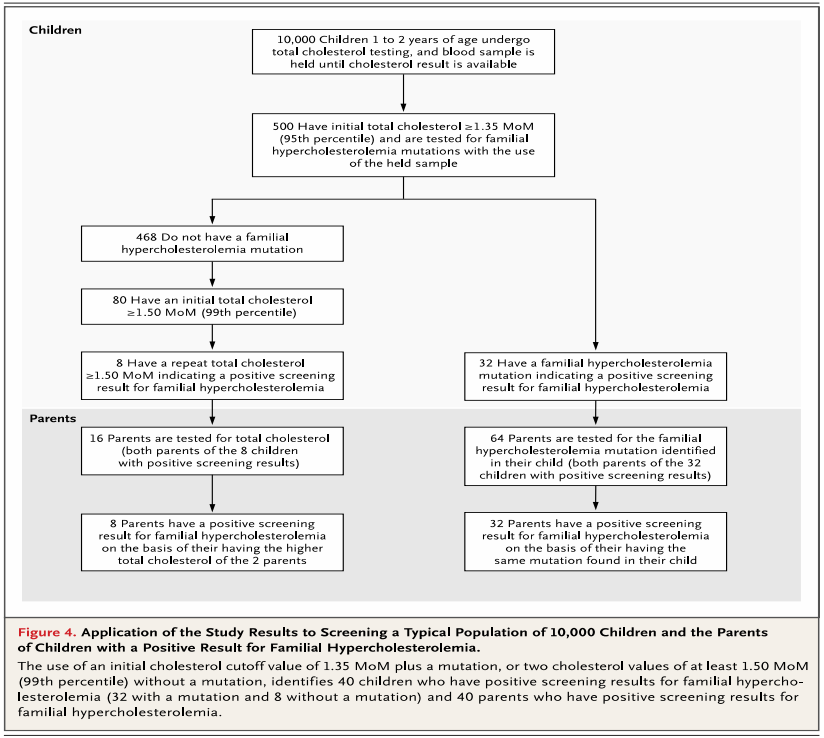
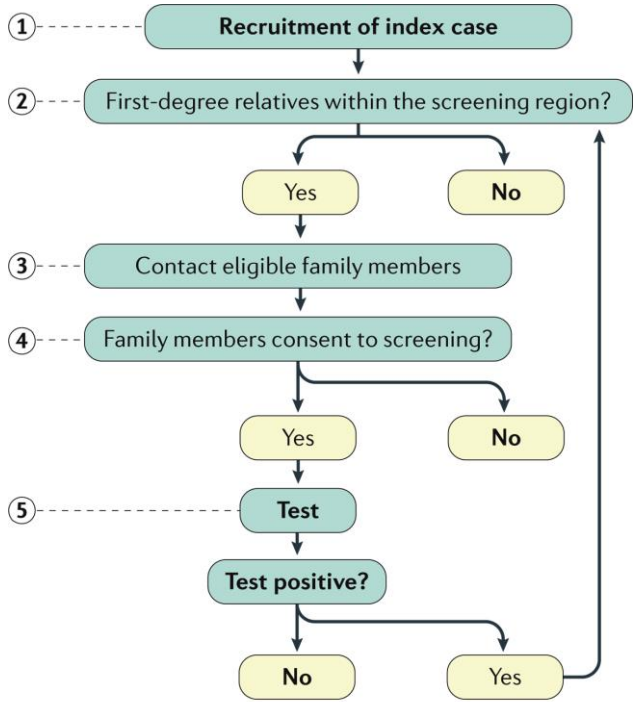


Figure 4. Application of the Study Results to Screening a Typical Population of 10,000 Children and the Parents of Children with a Positive Result for Familial Hypercholesterolemia.

The use of an initial cholesterol cutoff value of 1.35 MoM plus a mutation, or two cholesterol values of at least 1.50 MoM (99th percentile) without a mutation, identifies 40 children who have positive screening results for familial hypercholesterolemia (32 with a mutation and 8 without a mutation) and 40 parents who have positive screening results for familial hypercholesterolemia.

Wald et al. N Engl J Med 2016;375:1628-37.

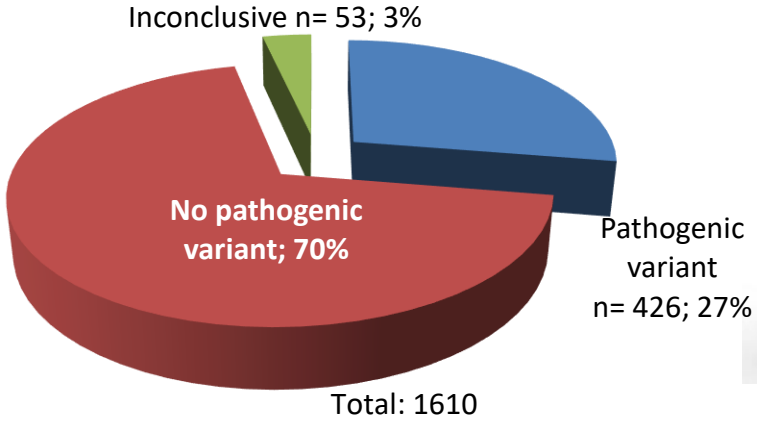
Basic schematic procedure of clinical cascade screening

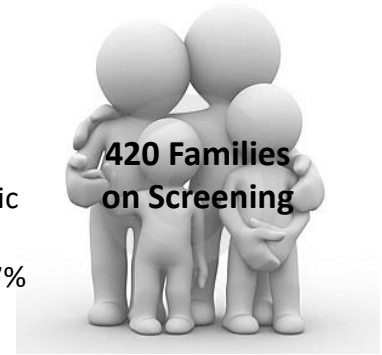


Adapted with permission from Santos, R. D. Cascade screening in familial hypercholesterolemia: advancing forward. *J. Atheroscler. Thromb.* **22**, 869–880 (2015), Japan Atherosclerosis Society

Hipercol Brasil Cascade Screening Program
April 2018

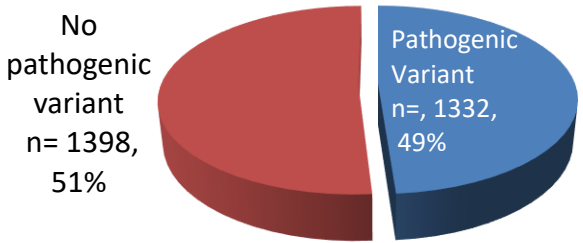
Index Cases





Heterozyotes	1719
Homozygotes	25
Compound Heterozygotes in trans	12
Compound Heterozygotes in cis	4
Double Heterozygotes	1

Relatives



Total:2730

Courtesy Dr. Cinthia E. Jannes

Evaluation of clinical and laboratory parameters used in the identification of index cases for genetic screening of familial hypercholesterolemia in Brazil

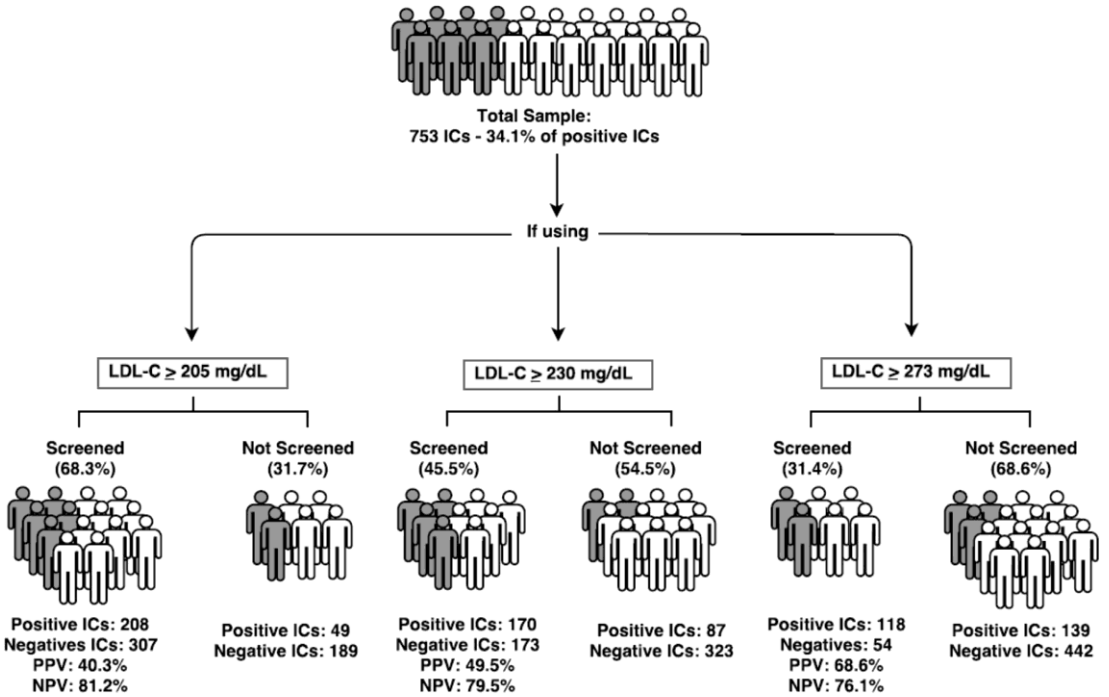


Fig. 1. Proportion of genetic-positive cases based on our population prevalence rate (34.1%) using the three tested cutoff values for LDL-C that correspond to percentiles 25, 50 and 75 for the studied population. Gray shaded individuals represent the percentage of confirmed positive cases while white shaded individuals represent the negative cases.

Silva PRS… Santos RD et al . Atherosclerosis 2017; 263: 257-262

How to face the challenges?

Know Your Enemy!

IAS Sponsored FH 10-Country Study

Fig. 2. Map showing the countries currently participating in the "Ten Countries Study."

Watts G et al. J Atheroscler Thromb. 2016;23:891-900

EAS FH Study Collaboration

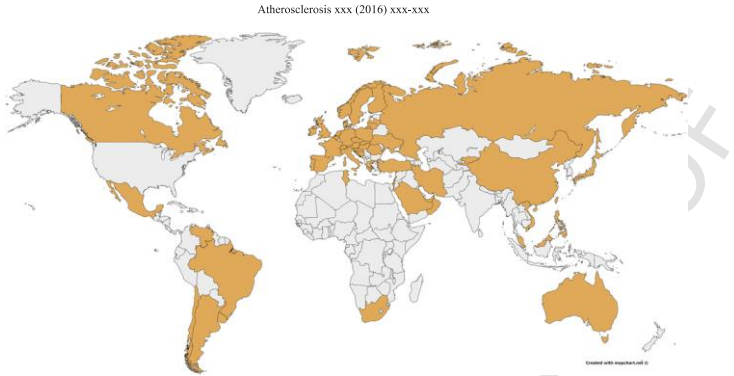
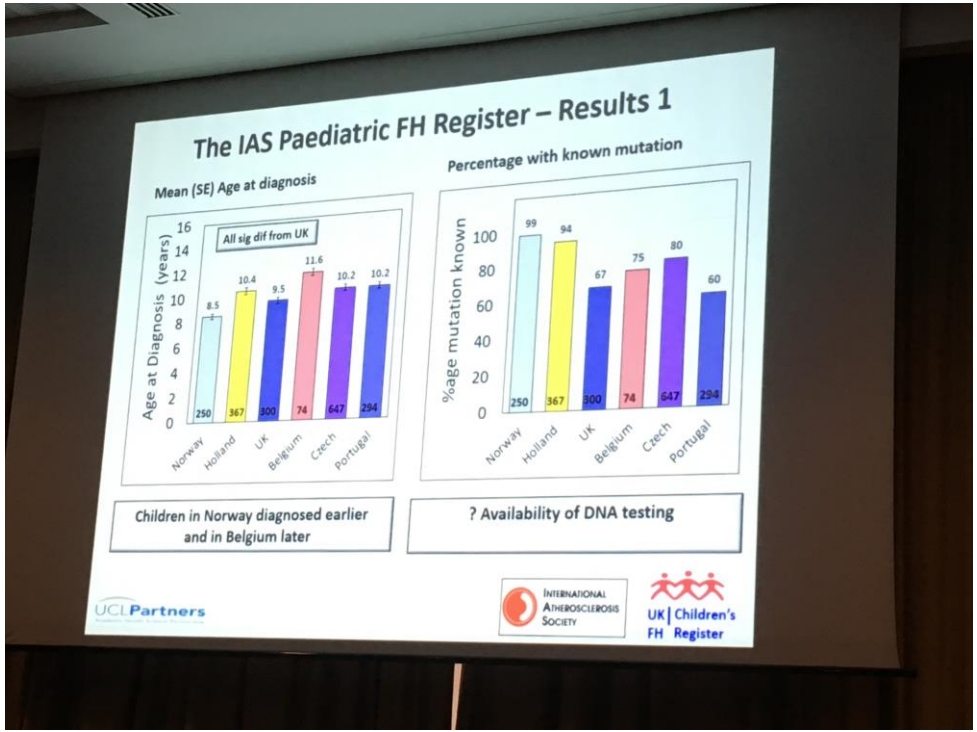


Fig. 2. Countries with investigators formally involved in the EAS FHSC (updated at the time of the present submission). Map created with mapchart.net.

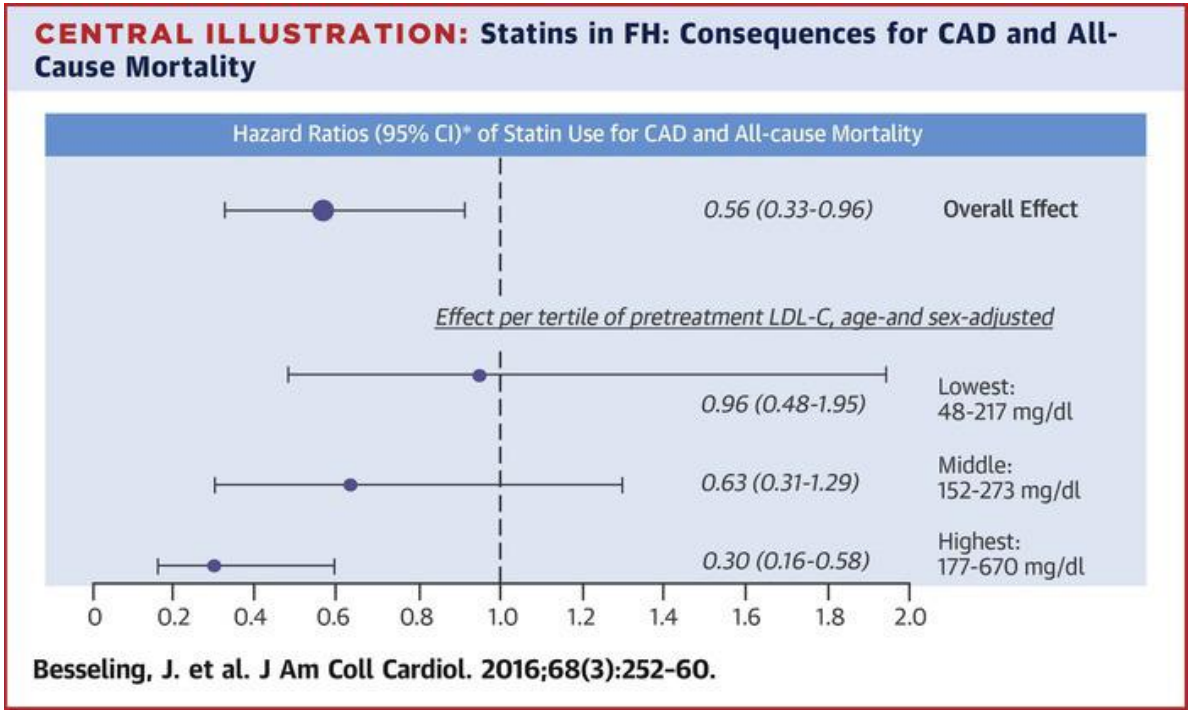
Vallejo-Vaz A. et al. Atheroscler Suppl. 2016 Dec;22:1-32

IAS Sponsored Pediatric FH Registry



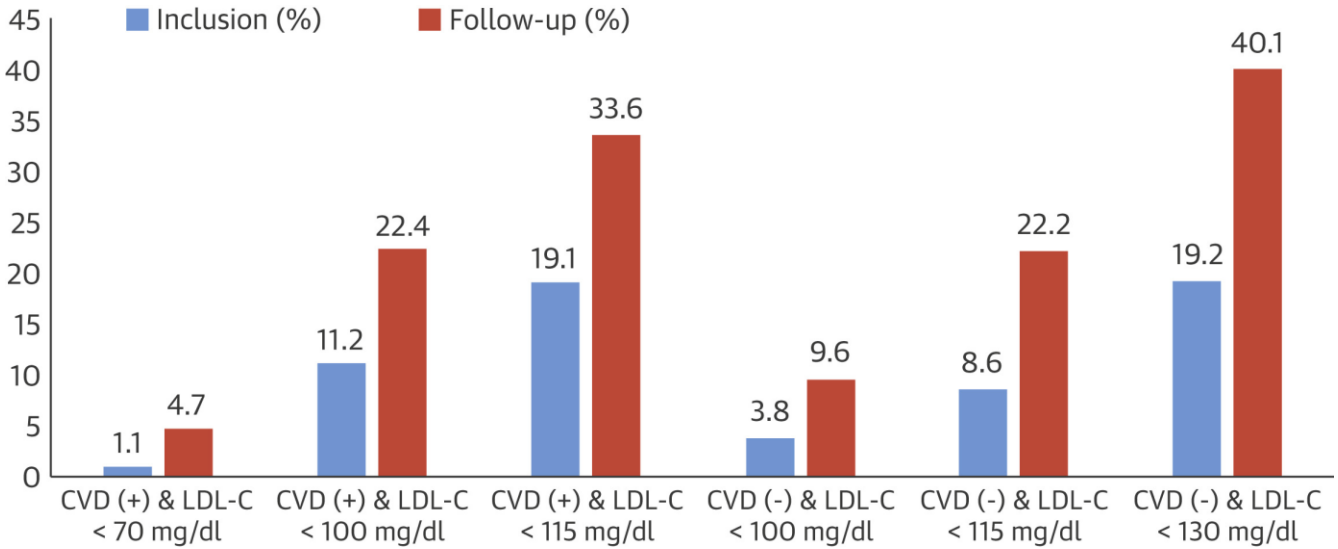
Treatment of FH

Statins Reduce Mortality in FH



LDL-C Control in FH: SAFEHEART Study

N= 2,752 , mean follow-up was 5.1 ± 3.1 years;
71.8% of FH cases were on maximum LLT



Perez de Isla et al J Am Coll Cardiol. 2016;67:1278-85

Heterozygous FH New Horizons: PCSK9 Inhibitors

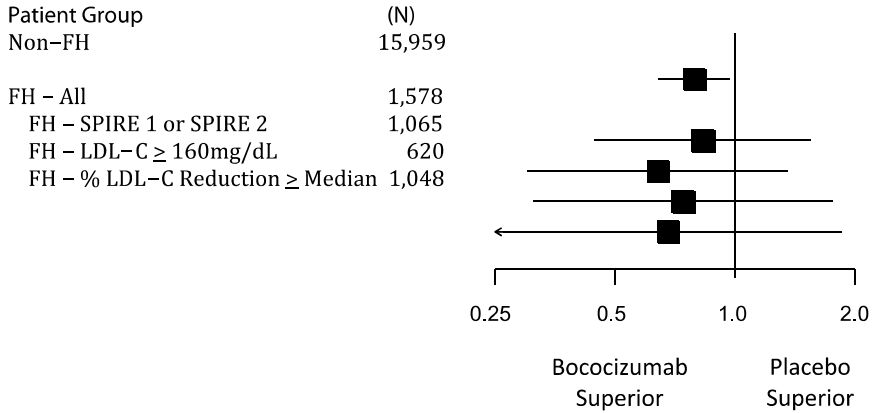
LDL-C values < 1.8 mmol/L (70 mg/dL) in refractory FH patients

- Rutherford-2[1]
  - 61-66% treated with evolocumab
- Odyssey FH I and II[2]
  - 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.

Cardiovascular event reduction with PCSK9 inhibition among 1578 patients with familial hypercholesterolemia: Results from the SPIRE randomized trials of bococizumab

Paul M Ridker, MD*, Lynda M. Rose, MS, John J. P. Kastelein, MD, Raul D. Santos, MD, Caimiao Wei, PhD, James Revkin, MD, Carla Yunis, MD, Jean-Claude Tardif, MD, Charles L. Shear, DrPH, on behalf of the Studies of PCSK9 Inhibition and the Reduction of vascular Events (SPIRE) Investigators



Ridker PM et al J Clin Lipidol 2018 e pub

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel

Raul D Santos, Samuel S Gidding, Robert A Hegele, Marina A Cuchel, Philip J Barter, Gerald F Watts, Seth J Baum, Alberico L Catapano, M John Chapman, Joep C Defesche, Emanuela Folco, Tomas Freiberger, Jacques Genest, G Kees Hovingh, Mariko Harada-Shiba, Steve E Humphries, Ann S Jackson, Pedro Mata, Patrick M Moriarty, Frederick J Raal, Khalid Al-Rasadi, Kausik K Ray, Zelijko Reiner, Eric J G Sijbrands, Shizuya Yamashita, on behalf of the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel

Santos RD et al Lancet Diab Endocrinol 2016;4: 850-61

Severe Familial Hypercholesterolemia: Treating the Continuum

At presentation (untreated LDL-C)	LDL –C >10 mmol/L (400 mg/dL) LDL-C >8.0 mmol/L (310 mg/dL) + one high risk condition LDL-C > 5 mmol/L (190 mg/dL) + two high risk conditions	Realistic goal: reduce ≥ 50% LDL-C Ideal goal: LDL-C < 2.5 mmol/L (100 mg/dL)
With subclinical atherosclerosis assessment	**Advanced subclinical atherosclerosis** *Coronary*: A-Coronary artery calcium (CAC) score > 100 Agatston units, or > 75th percentile for age and gender* B-Computed tomography angiography (CTA) with obstructions > 50% or presence of non-obstructive plaques > one vessel.	Realistic goal: reduce ≥ 50% Ideal goal : LDL-C < 1.8 mmol/L (70 mg/dL)
Presence of clinical atherosclerotic cardiovascular disease		Realistic goal: reduce LDL-C ≥ 50% Ideal goal: LDL-C < 1.8 mmol/L (70 mg/dL)

Santos RD et al Lancet Diab Endocrinol 2016;4: 850-61

Algorithm for Treatment of Severe FH

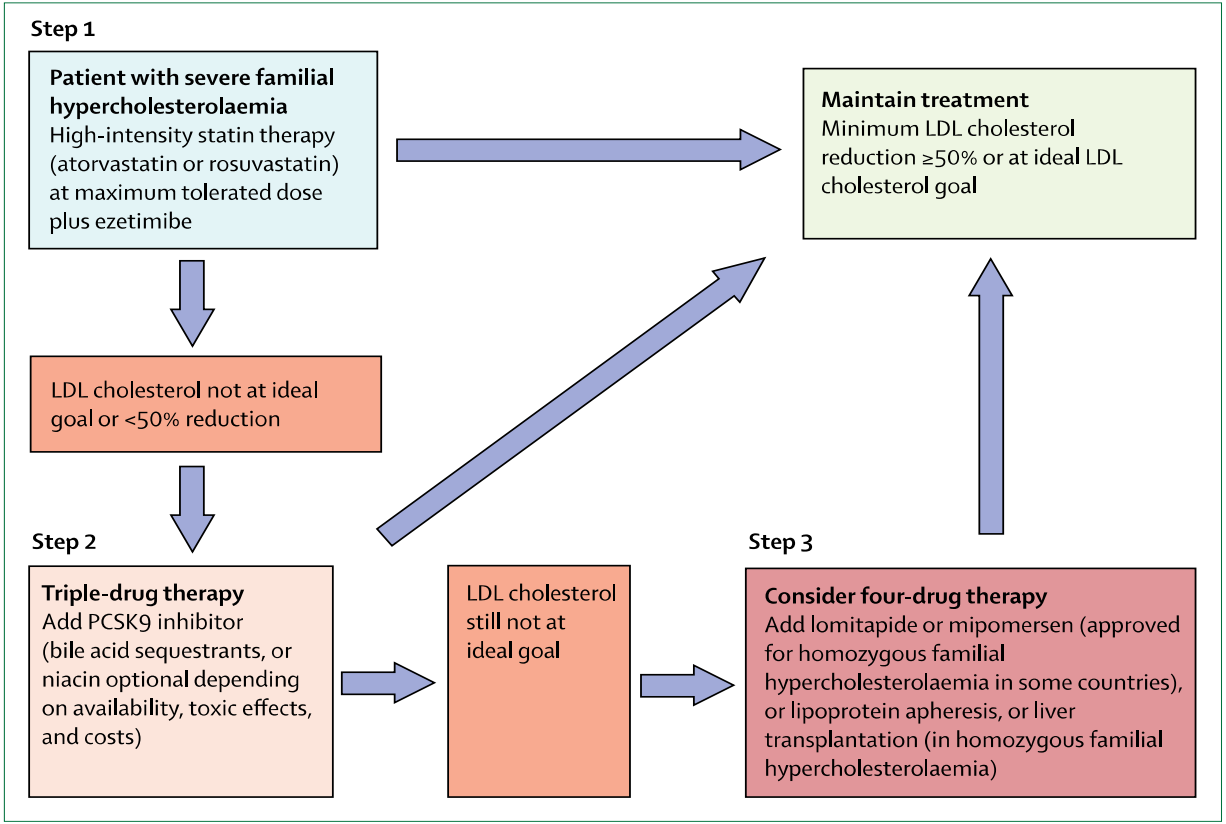


Figure 2: **Treatment algorithm for severe familial hypercholesterolaemia**
The therapeutic strategy is based on refractoriness of treatment, drug or procedure availability, reimbursement, and approval by local regulatory agencies.

Santos RD et al Lancet Diab Endocrinol 2016;4: 850-61

World Heart Federation Cholesterol Roadmap

Adrianna Murphy*, Jose R. Faria-Neto†, Khalid Al-Rasadi‡, Dirk Blom§, Alberico Catapano‖,¶,#, Ada Cuevas**, Francisco Lopez-Jimenez††,‡‡, Pablo Perel§§,‖‖, Raul Santos¶¶,##, Allan Sniderman***, Rody Sy†††,‡‡‡, Gerald F. Watts§§§,‖‖‖, Dong Zhao¶¶¶, Salim Yusuf§§,###,****,††††, David Wood§§,‡‡‡‡,§§§§

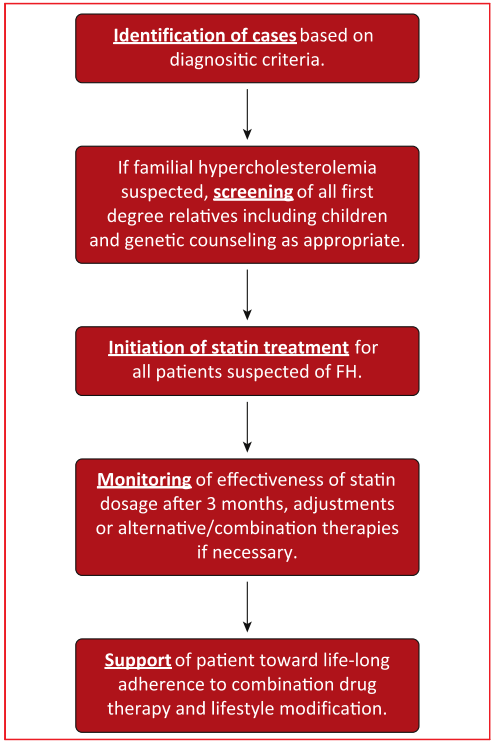


FIGURE 5. Patient pathway of cholesterol treatment for familial hypercholesterolemia (FH).

Challenges to developing countries!

BOX 1. Roadblocks to effective detection, management, and treatment of cholesterol levels for primary and secondary prevention of CVD and patients with FH

Patient-level roadblocks

- **Low access to health facilities among poor or remote populations**
- ***Statins unaffordable for patients***
- ***Lack of awareness among patients regarding importance of adherence to statin treatment***
- ***Undue patient fear of side effects of statin treatment***
- **Infrequent access to follow-up or support for treatment adherence**
- ***Lack of awareness of FH and FH risk factors among general population***

Physician-level roadblocks

- **Lack of awareness among physicians about the importance of CVD risk screening and prevention**
- **Lack of education/training among physicians regarding treatment**
- **Poor capacity among physicians for monitoring treatment, especially with competing disease priorities**
- **Poor patient access to health professionals for follow-up and support toward adherence**
- ***Lack of awareness of FH and FH risk factors among physicians and general population***
- ***Low capacity among physicians for diagnosing and managing statin treatment among FH patients***

Health system-level roadblocks

- **Lack of screening programs or suboptimal screening programs**
- ***Shortage of facilities for large-scale measurement of blood cholesterol levels, especially in rural areas***
- ***Environmental barriers to lifestyle modification (e.g., food insecurity, few options for physical activity, tobacco marketing)***
- **Multiple, complex (and sometimes contradictory) clinical guidelines**

Roadblocks that relate to cholesterol alone are italicized.
CVD, cardiovascular disease; FH, familial hypercholesterolemia.

IAS’ View on FH

Unmet need for FH: IAS' View

- Frequent disease that needs to be recognized
- Early diagnosis = early statin treatment= potential for prevention
  - Universal cholesterol screening and need for family cascade screening
  - Implementation of molecular diagnosis in a more effective way
- Need for education lay people, physicians, authorities
- Need for newer therapies e.g. PCSK9 inhibitors for higher risk patients =risk stratification

ISA 2018 Toronto

XVIIIth INTERNATIONAL SYMPOSIUM ON ATHEROSCLEROSIS

Global Perspectives on Atherosclerosis, Thrombosis and Vascular Biology

Metro Toronto Convention Centre, Toronto, Canada

Connecting Hearts & Minds

5 PROGRAM TRACKS:

- Epidemiology
- Dyslipidemia
- Pathogenesis
- Prevention
- Therapeutics

June 9-12, 2018

www.isa2018.org

#ISA2018_Toronto