

Familial Hypercholesterolemia: New Insights and Treatment Options

Milan Gupta, MD

**Department of Medicine, University of Toronto
Department of Medicine, McMaster University**

Canadian Collaborative Research Network – www.ccrnmd.com

Overview

- **What is familial hypercholesterolemia?**
- **How have we historically treated it?**
- **Can we do better?**

What is cardiovascular disease (CVD)?



Heart attack / coronary disease



Stroke

Cardiovascular disease is the 2nd highest cause of death among Canadians 45+ years

Every 7 minutes

A Canadian dies of a heart disease or stroke

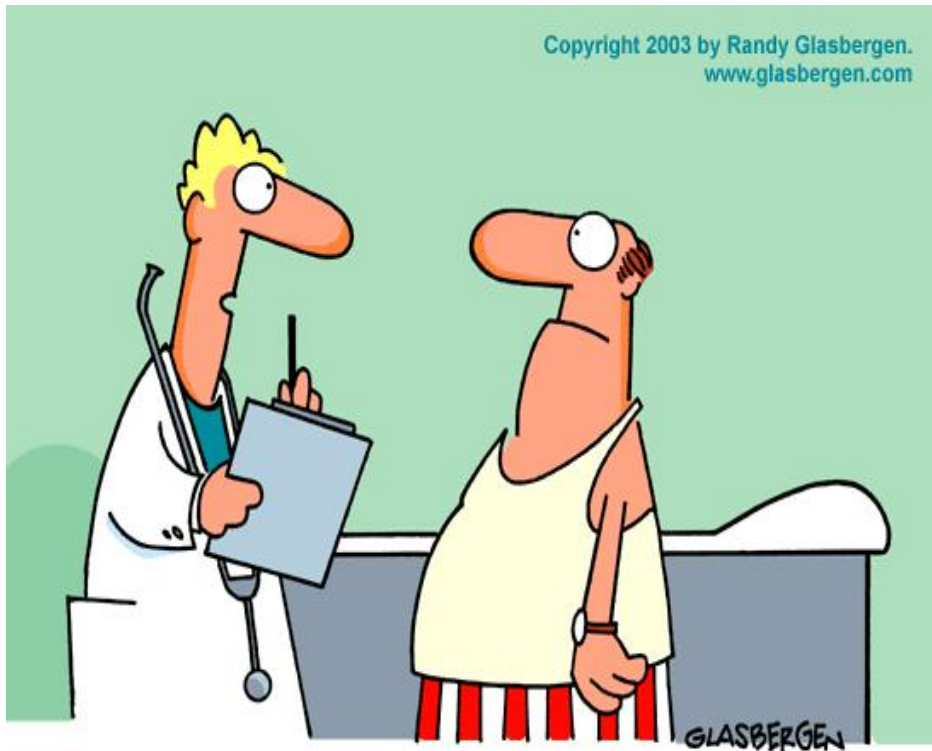
Risk factor control is critical for CVD prevention

80%
OF PREMATURE
HEART DISEASE
AND STROKE IS
PREVENTABLE

Risk factors for CVD

- High cholesterol
- High blood pressure
- Diabetes
- Tobacco use
- Unhealthy diet
- Obesity
- Physical inactivity

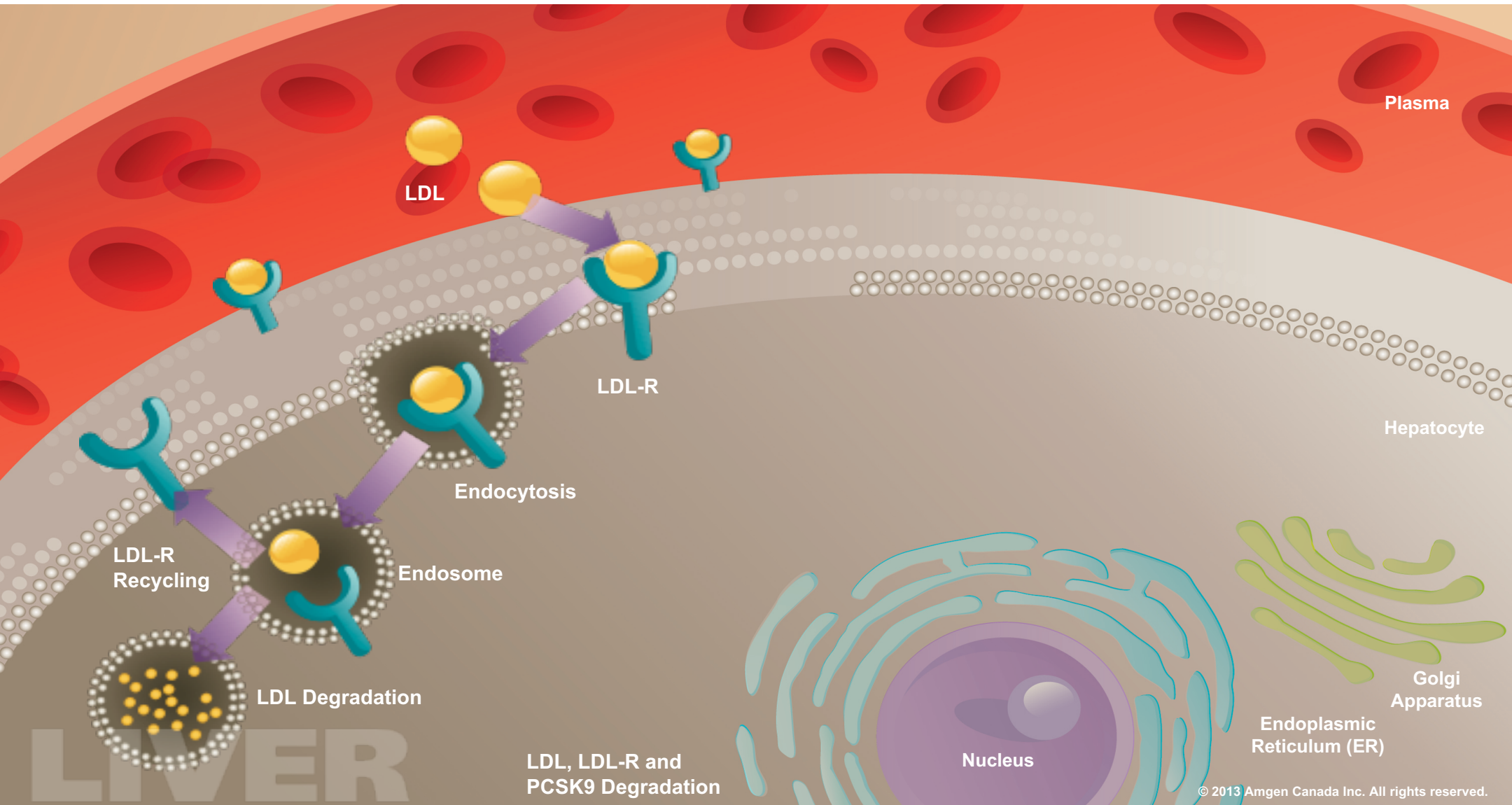
Prevention is not easy...



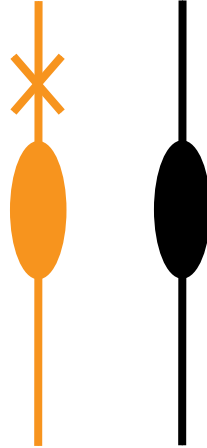
“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”



LDL Cholesterol Levels Are Regulated By LDL Receptors



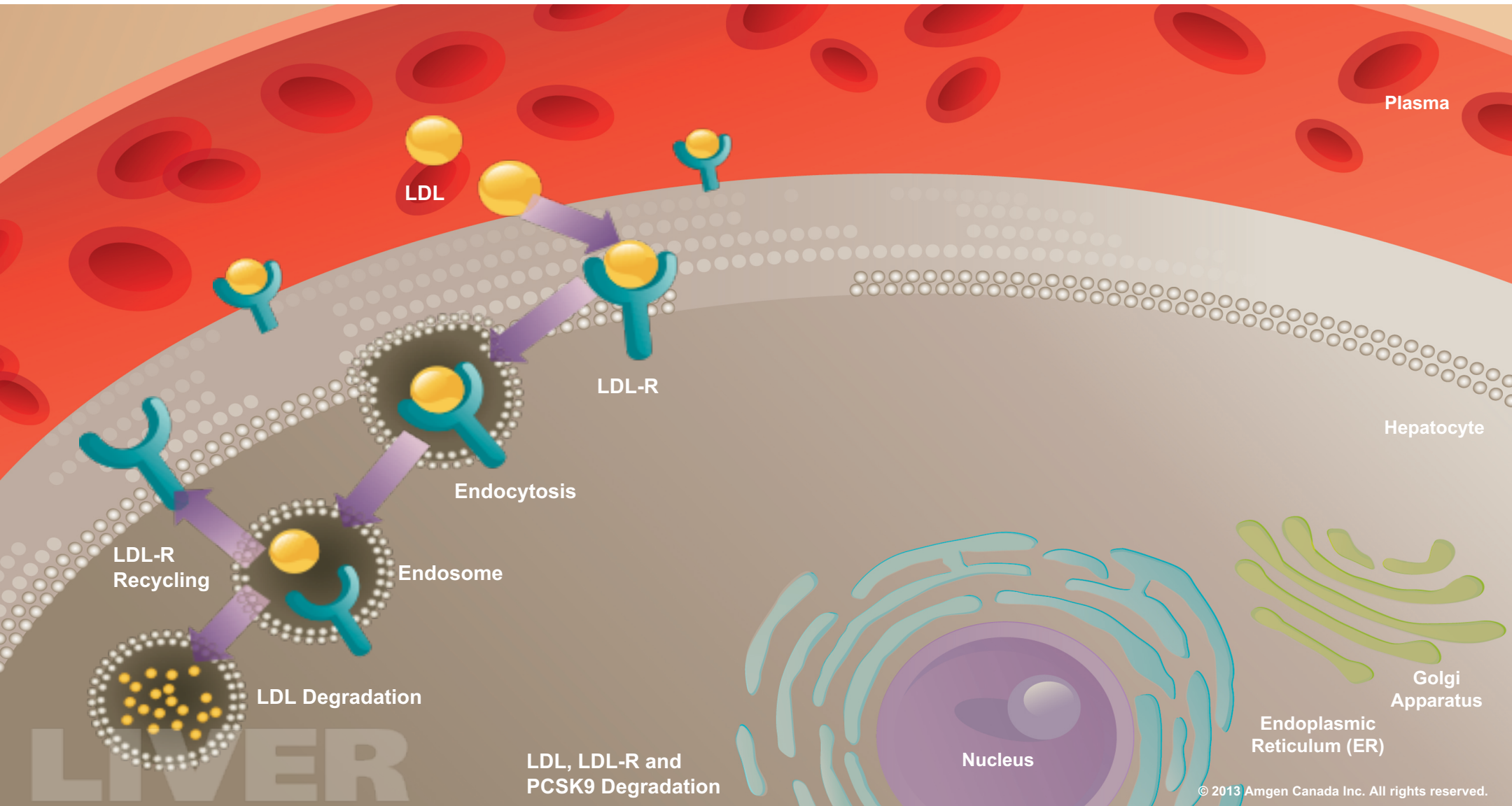
Familial Hypercholesterolemia: Autosomal Dominant Genetic Disease



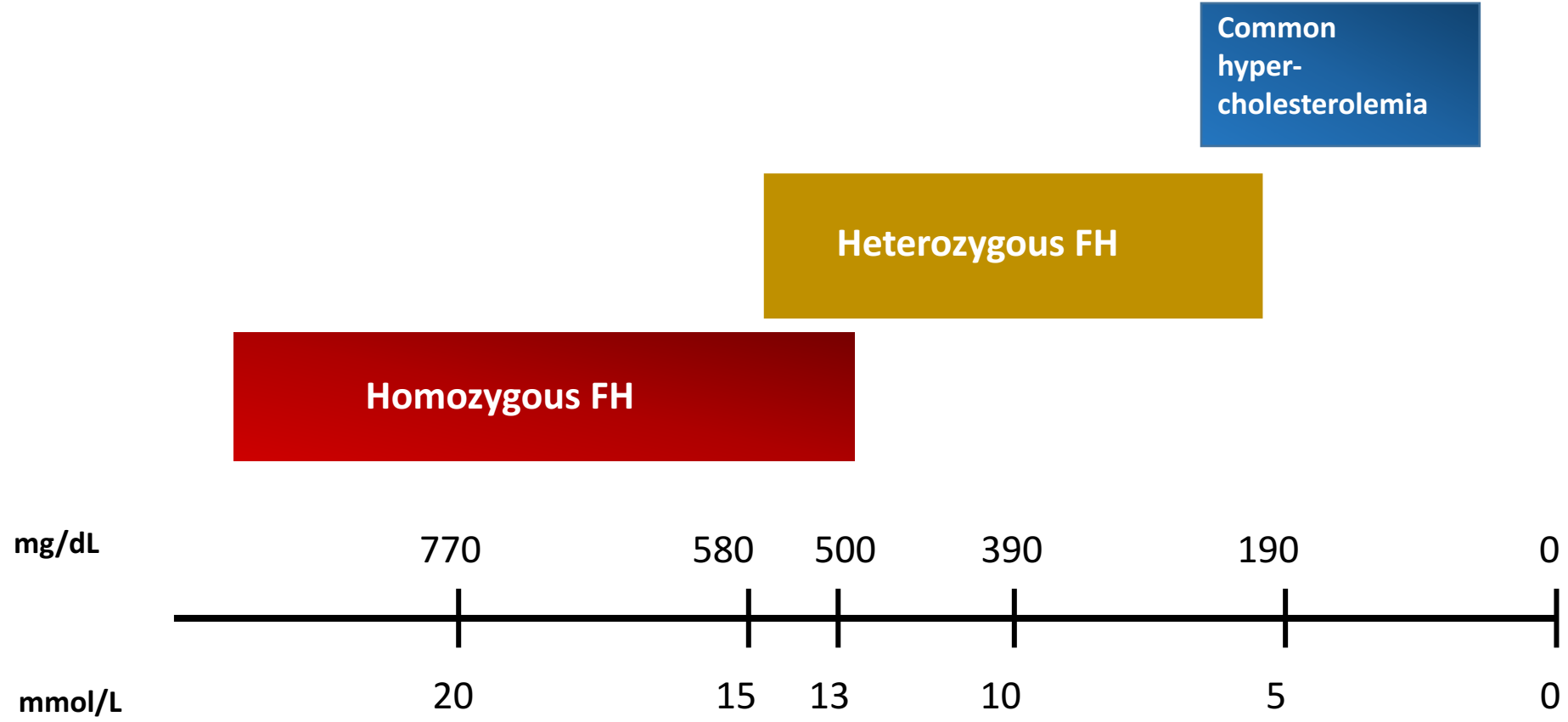
FH Heterozygotes (HeFH)

- One major genetic defect in LDL metabolism
- $\frac{1}{2}$ number of LDL receptors
- 2-fold increase in plasma LDL
- ~20-fold increase risk of CHD in untreated patients
- 5% of all heart attacks under age 60
- Reasonable response to drugs

LDL Cholesterol Levels Are Regulated By LDL Receptors



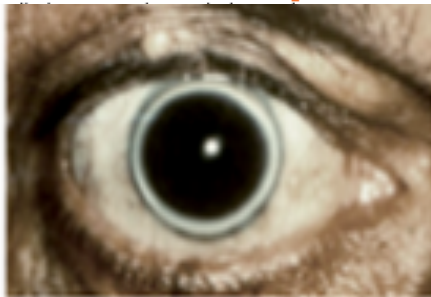
Clinical Features of FH Patients



HeFH Clinical Features



Xanthelasmata



Arcus Corneus



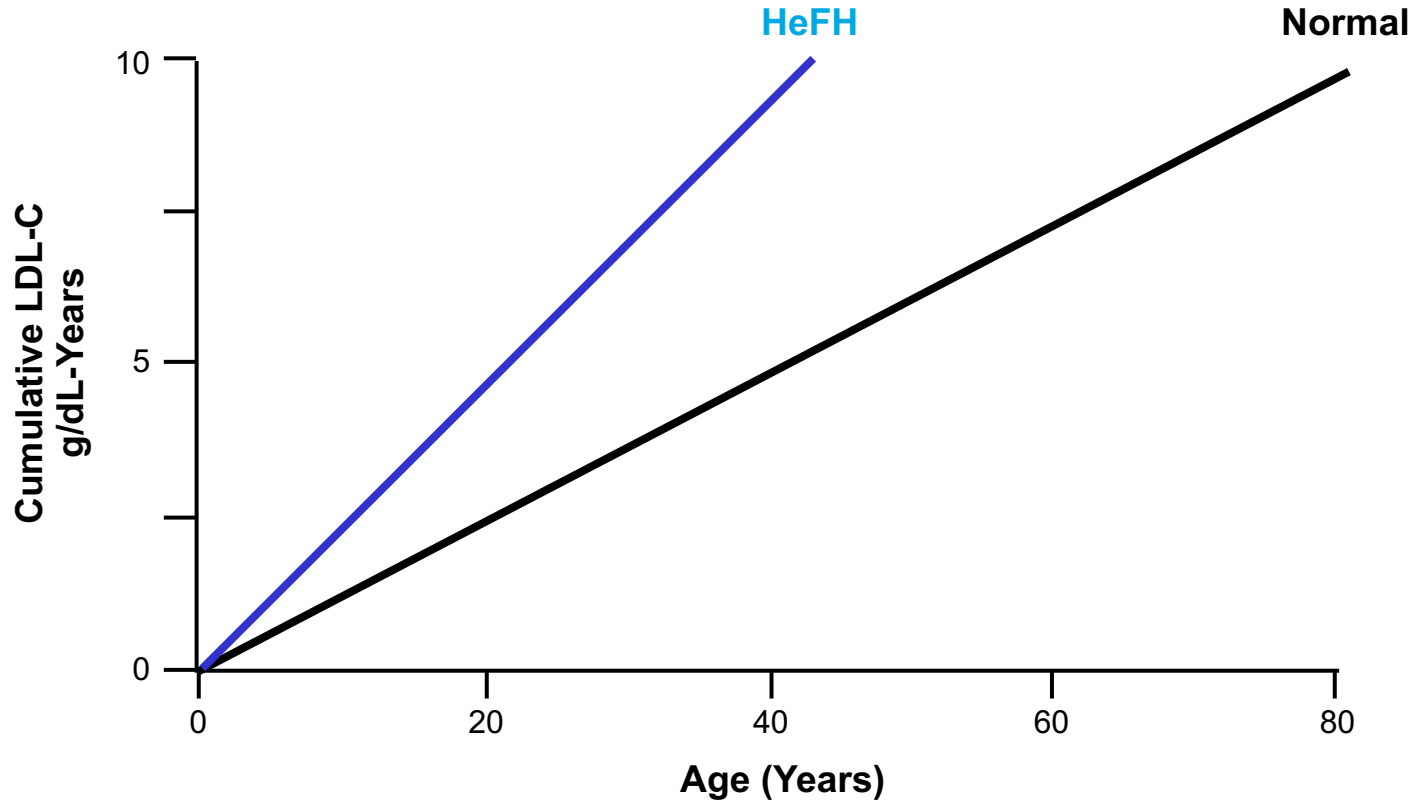
Xanthomas



Xanthomas

These clinical features are not common in clinical practice since patients are on statin

Theoretical relationship between cumulative cholesterol years and development of severe atherosclerosis

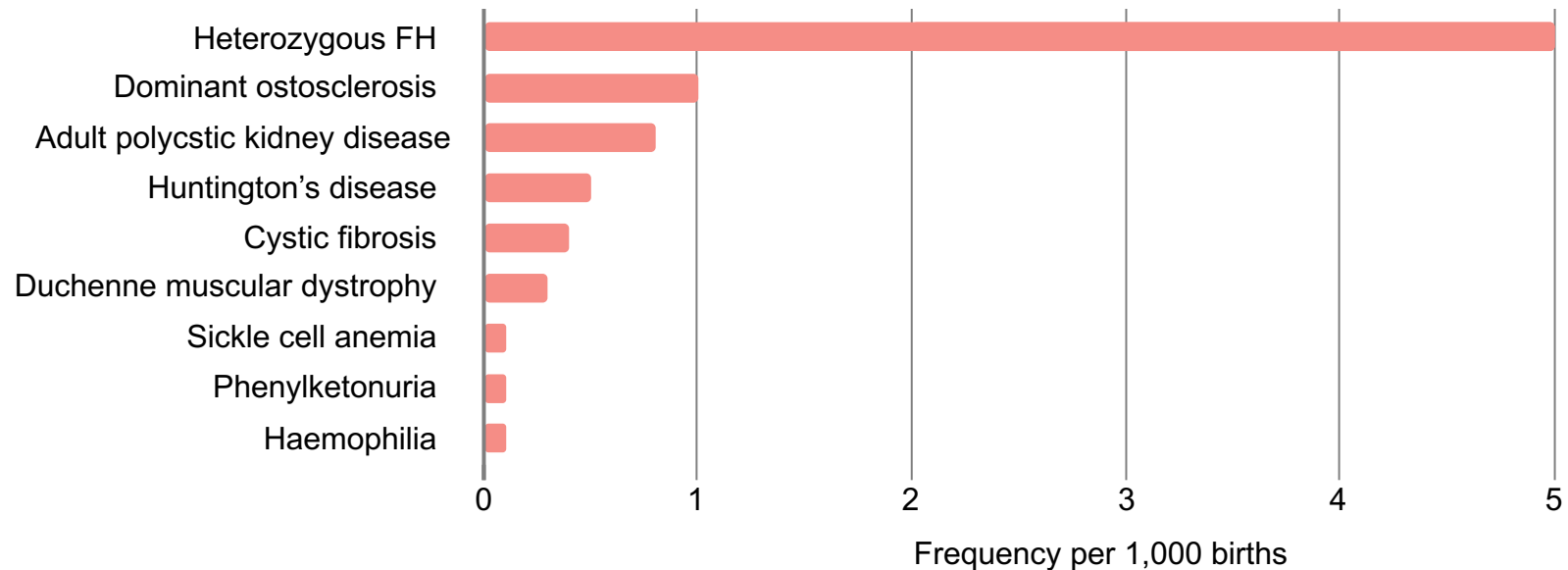


FH More Common than Previously Thought

FH Heterozygote

- **1 in 200 to 500**
- May be as high as 1 in 80 in some populations (e.g. French Canadians) due to founder effect

FH is One of the Most Common Inherited Diseases



Proposed Canadian Cardiovascular Society Definition of FH

Major criterion	LDL-C Low density lipoprotein-cholesterol *	Adult: LDL-C >5.0 Pediatric > 4.0
	DNA Mutation	Definite (2 Major criteria)
Minor criteria		
	Affected First degree relative with Major criterion	Probable (1 Major + 1 Minor criteria)
	Presence of xanthomas in proband	Probable
	First degree relative with early onset CAD	Probable

* secondary causes ruled out ([nephrotic syndrome](#), [obstructive jaundice](#), [hypothyroidism](#))

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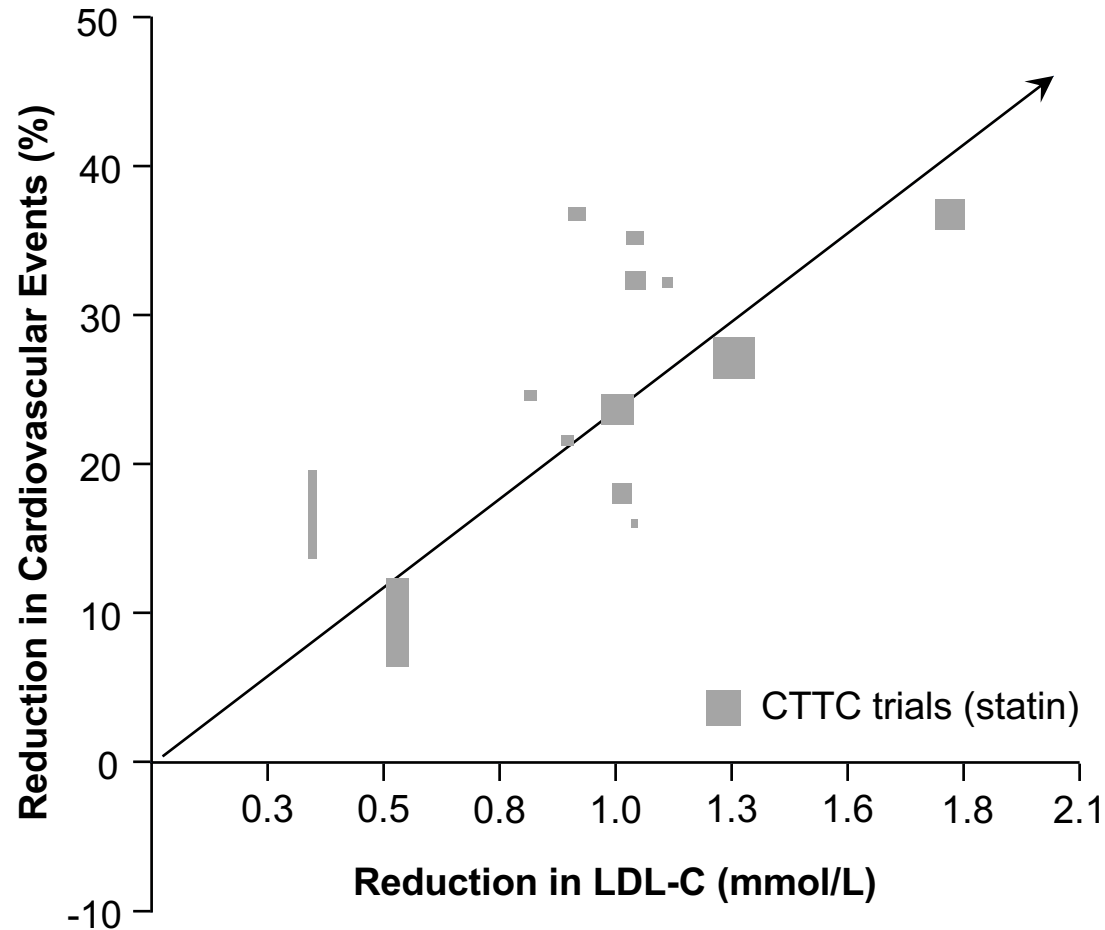
The age of statins

Statins:

- Among the best studied and most successful medications in history
- Have contributed to large declines in CV mortality
- Work by increasing the liver's ability to clear LDL from the circulation
- Safer than aspirin
- Can cause benign muscle aches

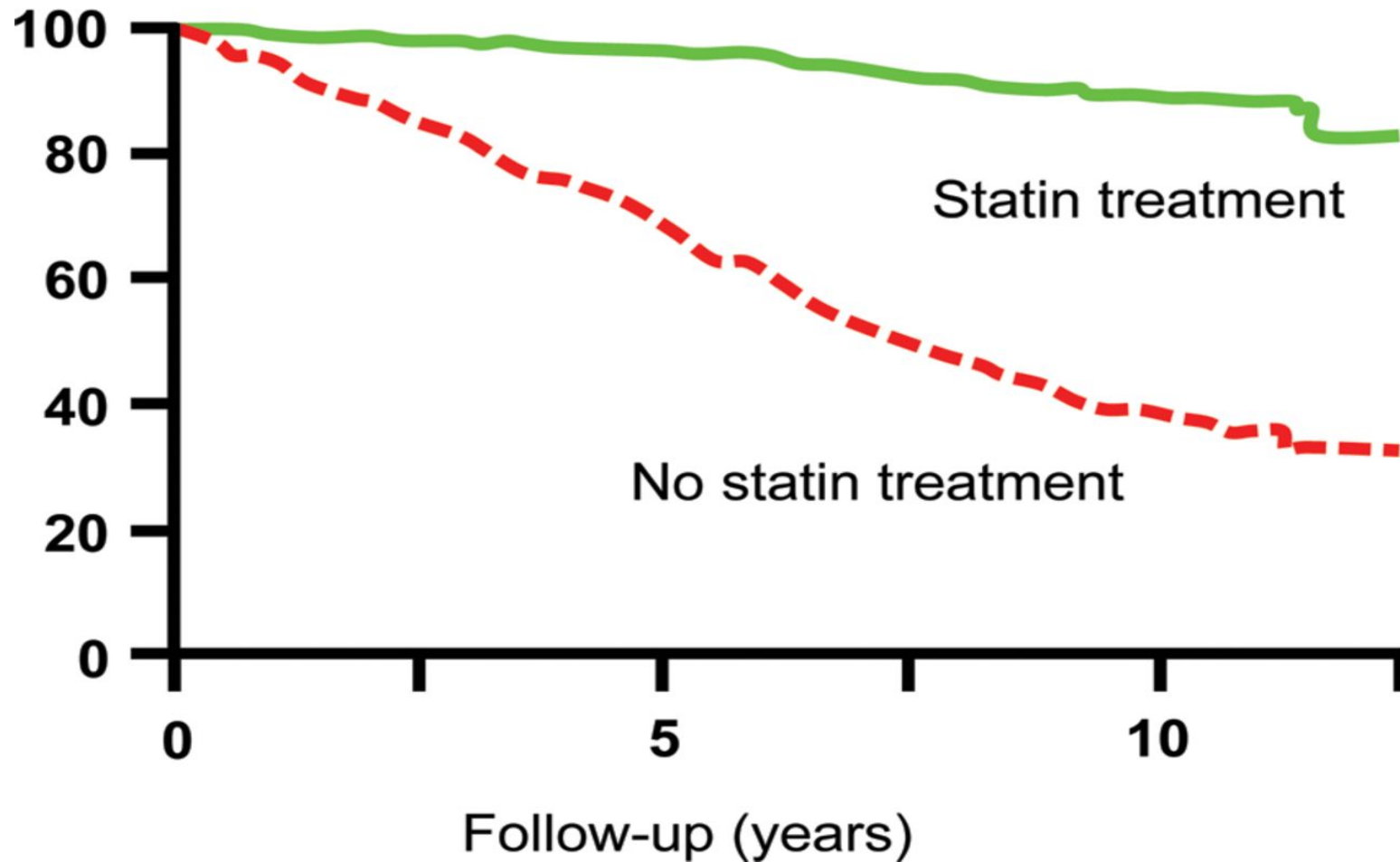


Lowering LDL cholesterol reduces the risk of heart disease and stroke

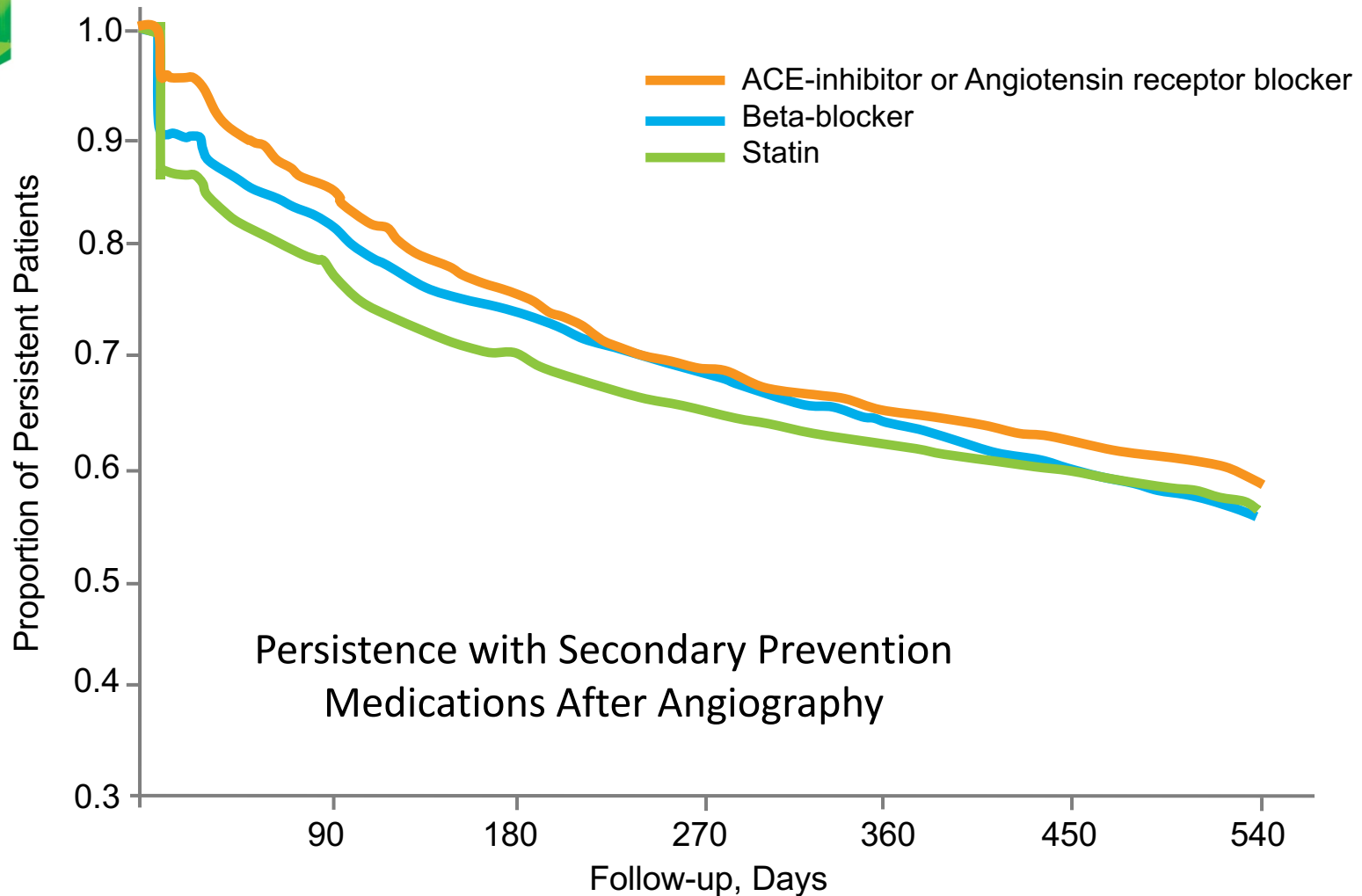


CHD-free survival in HeFH according to statin Rx

($P < 0.001$ for difference)

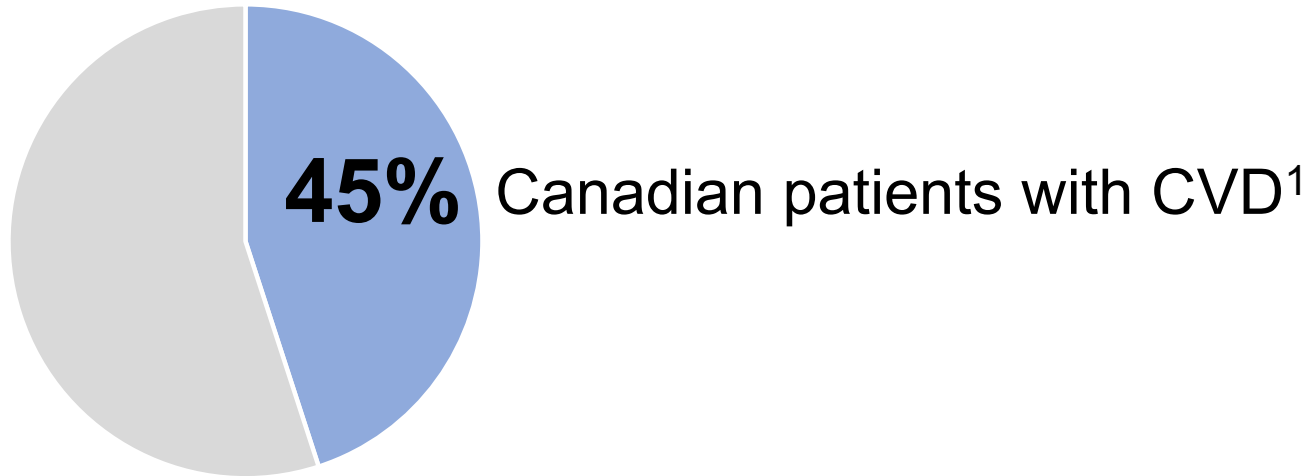


Patient adherence to statins declines over time



Persistence with Secondary Prevention Medications After Angiography

Up to 45% of high-risk Canadians are not achieving recommended LDL target levels



1. Goodman SG, et al. on behalf of the DYSIS Canadian Investigators. Can J Cardiol. 2010;26(9):e330-e335.

2. Leiter LD, et al. Can J Diabetes. 2013;37:82-89.

Overview

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Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease

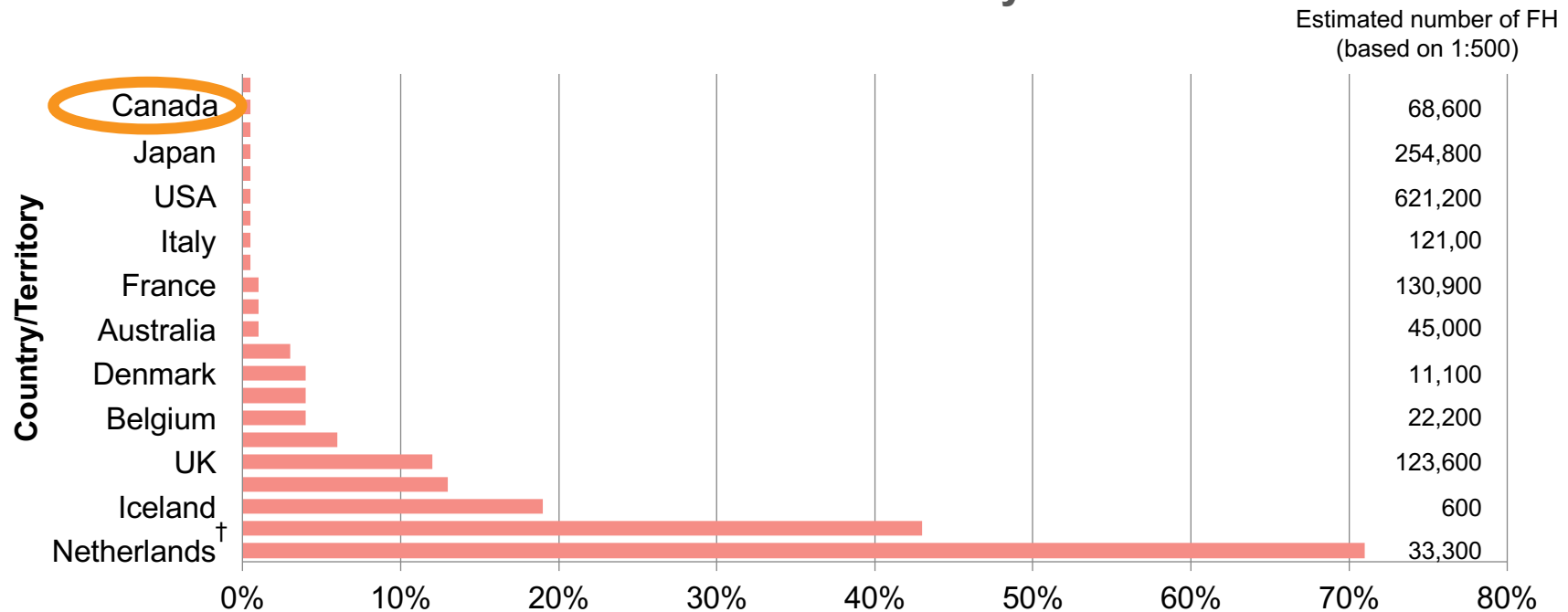
Consensus Statement of the European Atherosclerosis Society

Børge G. Nordestgaard^{1*}, M. John Chapman^{2*†}, Steve E. Humphries^{3†}, Henry N. Ginsberg⁴, Luis Masana⁵, Olivier S. Descamps⁶, Olov Wiklund⁷, Robert A. Hegele⁸, Frederick J. Raal⁹, Joep C. Defesche¹⁰, Albert Wiegman¹⁰, Raul D. Santos¹¹, Gerald F. Watts¹², Klaus G. Parhofer¹³, G. Kees Hovingh¹⁰, Petri T. Kovanen¹⁴, Catherine Boileau¹⁵, Maurizio Averna¹⁶, Jan Borén¹⁷, Eric Bruckert¹⁸, Alberico L. Catapano¹⁹, Jan Albert Kuivenhoven²⁰, Päivi Pajukanta²¹, Kausik Ray²², Anton F. H. Stalenhoef²³, Erik Stroes¹⁰, Marja-Riitta Taskinen²⁴, and Anne Tybjærg-Hansen²⁵, for the European Atherosclerosis Society Consensus Panel

Familial Hypercholesterolemia Remains Largely Underdiagnosed

Estimates of diagnosed FH patients in Canada range from <1% to 15%

Diagnosed FH (Estimated), Percent of estimate in Country*



*Percentage derived from diagnoses values from expert clinician/scientists in local areas, as well as prevalence of 1 in 500 in the general population are FH heterozygotes. [†]Includes Dutch FH registry data

1. Goldberg AC, et al. Journal of Clinical Lipidology. 2011;5:S1-S8.
2. Adapted from: Nordestgaard BG, et al. Eur Heart J. 2013;34:3478-3490.

PCSK9 inhibitors

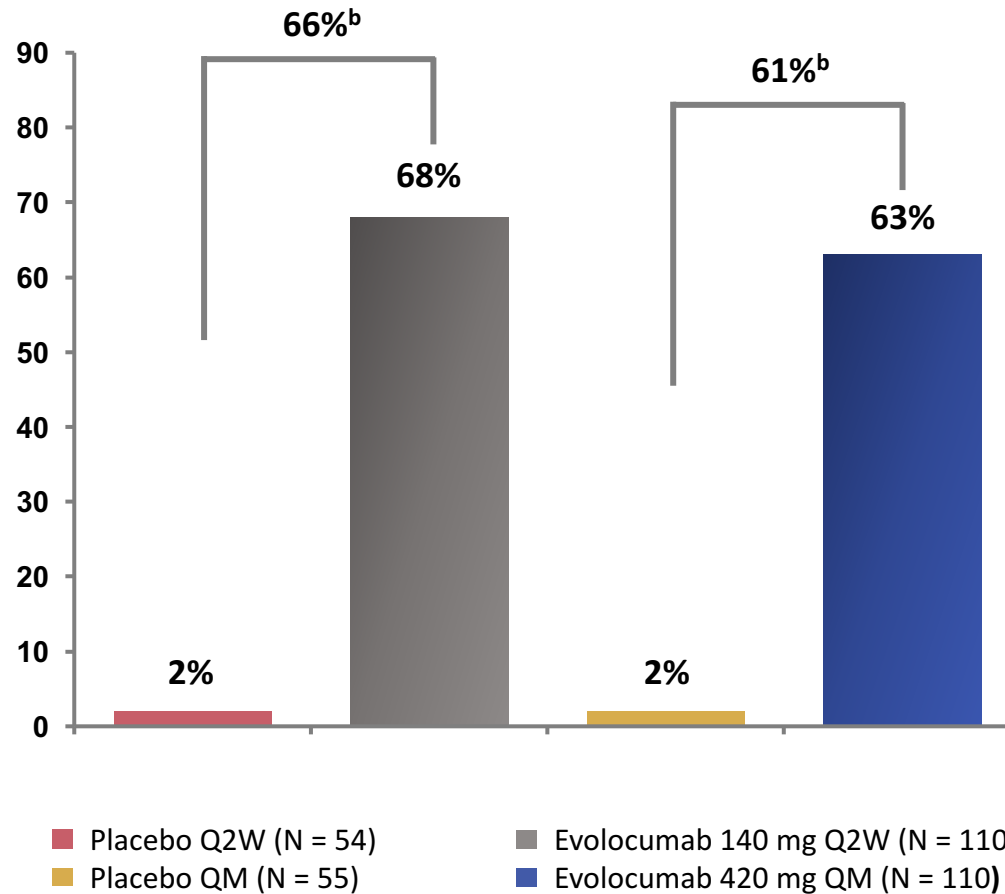
- **A new class of cholesterol-lowering drugs**
- **Evolocumab (Repatha) and Alirocumab (Praluent)**
- **Self-injectable, given every 2 weeks**
- **Work through a statin-like mechanism to lower LDL-C**
- **Lower LDL-C levels by 40-70% on top of statins**
- **No statin-like side effects**



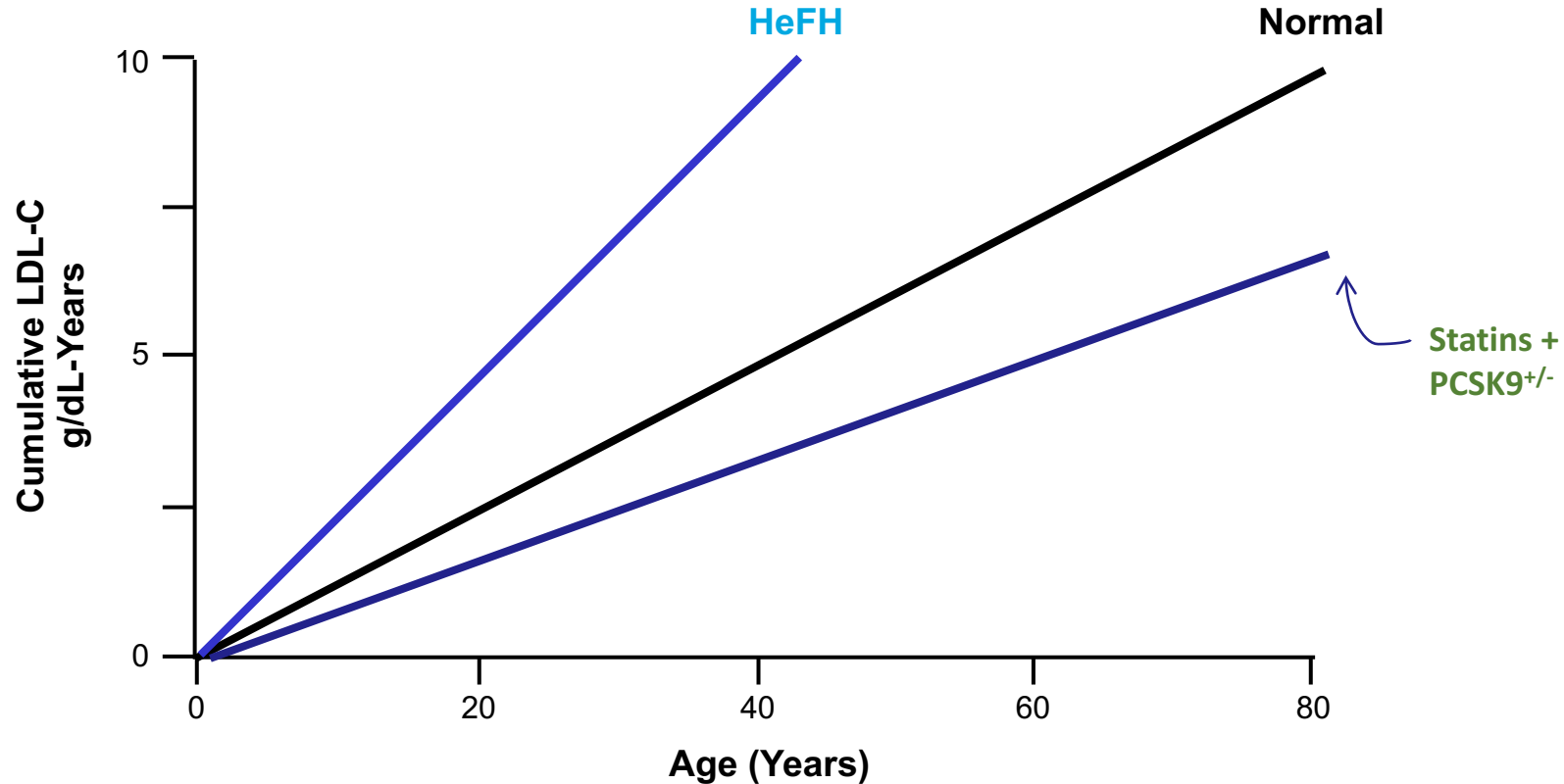
Evolocumab: RUTHERFORD-2

LDL-C Goal Achievement < 1.8 mmol/L

Week 12

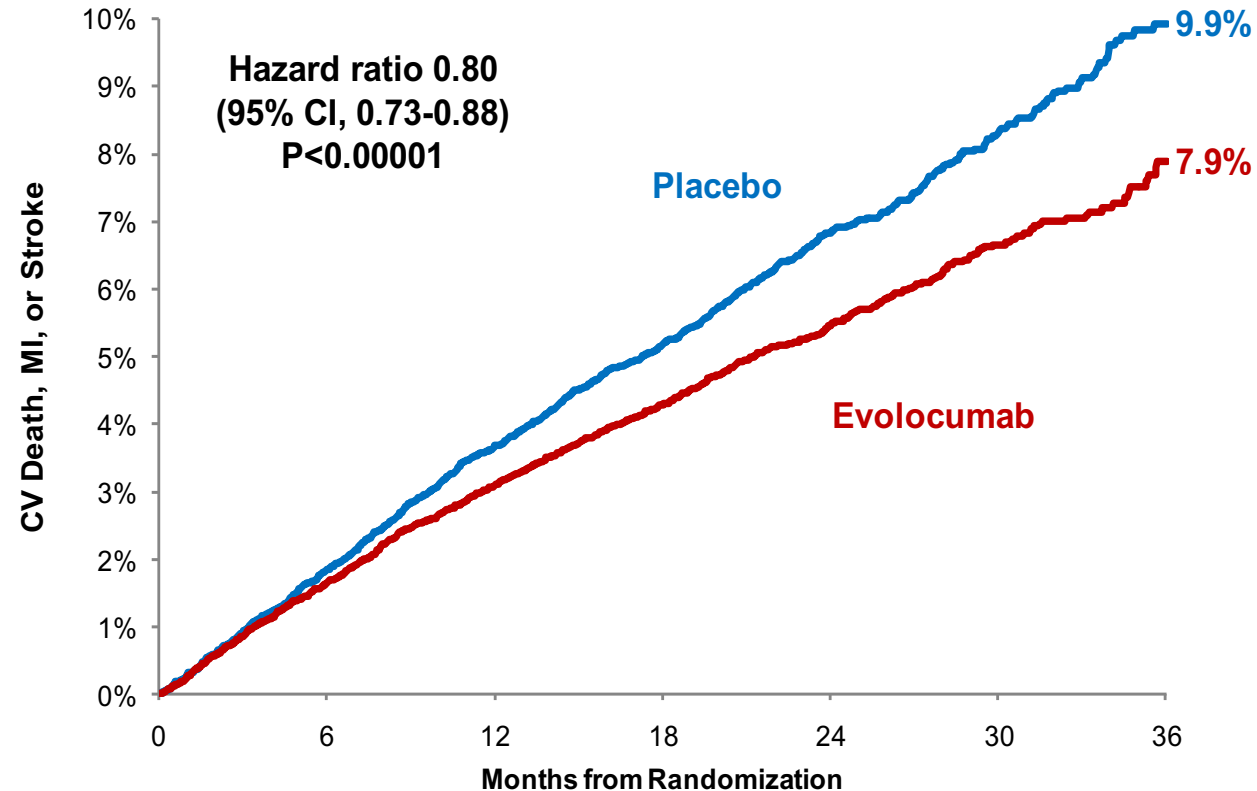


Theoretical relationship between cumulative cholesterol years and development of severe atherosclerosis

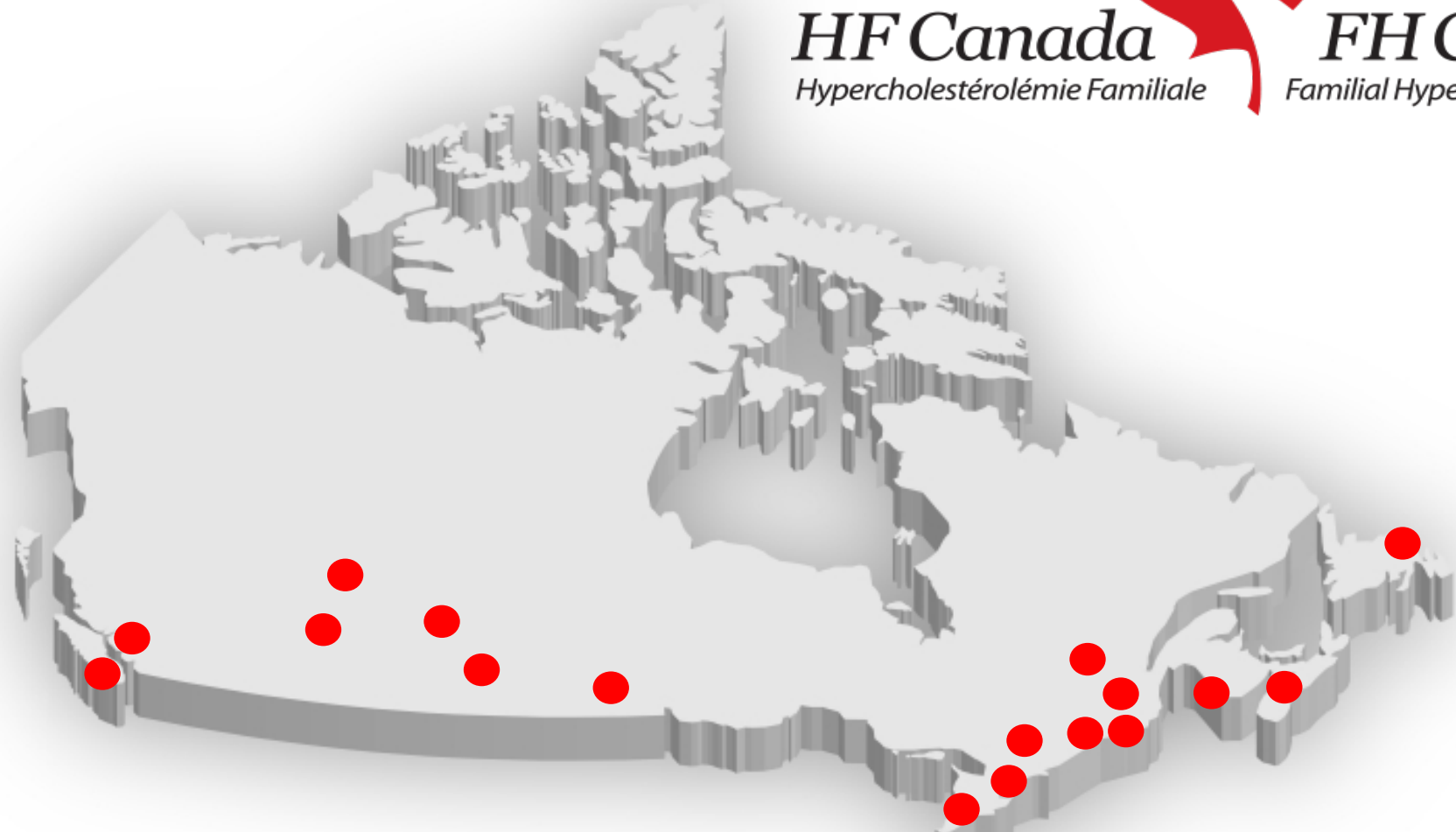


Do PCSK9 inhibitors actually prevent CV events?

- The FOURIER trial studied 27,500 patients with CVD, all of whom had LDL levels above target despite statin therapy.
- Compared to placebo, evolocumab lowered the risk of CV death, heart attack or stroke by 20% within 2.5 years.
- This effect was already apparent by one year after starting treatment.
- No safety signals were noted.



www.FHCanada.net



Canadian Familial Hypercholesterolemia Registry
Régistre Canadien d'hypercholestérolémie familiale

SUMMARY

- 1. FH is a common genetic disorder leading to premature CVD.**
- 2. Lowering LDL-cholesterol early and aggressively with statins prevents heart attack, stroke and death in patients with FH. However, achieving LDL-C targets can be difficult.**
- 1. PCSK9 inhibitors are a promising new option for patients with FH when statins are not enough.**