

M E D P **A** C E

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Cincinnati, OH USA



West Virginia ACC
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Familial Hypercholesterolemia
Epidemiology, Diagnosis and Treatment

Disclosures

- *My institution, Medpace Metabolic and Atherosclerosis Research Center, has received research site clinical trial funds from Amgen, Arisaph, Astra-Zeneca, Bristol Myers Squibb, Catabasis, Elcelyx, Eli-Lilly, Esperion, Gemphire, GlaxoSmithKline, Ionis-Akcea, The Medicines Company, Pfizer, Pronova, Regeneron, Roche-Genentech, Sanofi, and Zydus*

Objectives

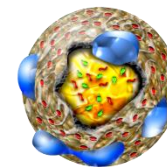
- Epidemiology of Familial Hypercholesterolemia (FH)
 - Definition and Prevalence
 - Pathophysiology
 - Diagnosis
 - Clinical Criteria and Genetic Analysis
- Disease Risk and Recent Evidence
- Treatment
 - Lifestyle
 - Pharmacotherapy – New Options



Familial Hypercholesterolemia

Epidemiology

Prevalence, Pathophysiology, and Diagnosis



Familial Hypercholesterolemia

Epidemiology

- Familial hypercholesterolemia (FH) is a group of genetic defects resulting in severely elevated cholesterol inherited in an autosomal dominant or co-dominant pattern with $\geq 90\%$ penetrance
 - Prevalence of heterozygous FH (heFH) is reported to be 1 in 300 to 500 in many populations, and 1 in one million is homozygous (or compound heterozygous)
 - There are a ~620,000 FH patients in the US and ~10 million worldwide
 - Higher prevalence of 1 in 50 to 100 is seen in communities with a “founder effect”
 - Dutch Afrikaners, Christian Lebanese, French-Canadians
- Affected patients are at increased risk for all forms of atherosclerotic disease and premature death secondary to lifelong elevations in LDL cholesterol (LDL-C)
 - ~5% of heart attacks under age 60 and up 20% under age 45 are due to FH
 - The risk of premature CHD is elevated ~20-fold in untreated FH patients
 - Untreated FH is associated with a ~90-fold increase in ASCVD mortality in young adults
- Known causes of FH include mutations in the LDL receptor, apolipoprotein B, and PCSK9 genes
 - 85-90% of FH cases are due to mutations in the LDL receptor gene, with >1600 documented mutations
 - 5 to 10% are due to mutations in the Apo B gene
 - <5% are due to gain-of-function mutations of the PCSK9 gene

Cooper, et al. Eur Heart J. 2008;29:2625–2633

Hopkins, et al. Journal of Clinical Lipidology (2011) 5, S9–S17

FH Prevalence in the US

NHANES data 1999-2012 using Dutch Lipid Clinic Network criteria

- Current estimates of heFH prevalence range widely from 1 in 500 to 1 in 137
 - Variables include the population studied and diagnostic criteria used
- 36,949 adults ≥ 20 and 13,343 adolescents 12 to 19 years of age
 - Prevalence of FH found to be 0.4%, or 1 in 250 adults (95% confidence interval, 1 in 311 to 209), and adolescents 0.42%, or 1 in 237
 - suggests 834,500 US adults have FH
 - FH prevalence was similar in men and women but varied by race and ethnicity, with whites and blacks affected most frequently
 - FH prevalence was higher in older ages and in the presence of obesity
- All DLCN criteria was not collected in NHANES, and not included in the analysis
 - Genetic testing, family history of hypercholesterolemia, personal history of PAD, and relevant physical exam findings, were **not** collected in NHANES and were not considered in this analysis
 - Genetic testing in a nationally representative sample would improve the accuracy of the FH prevalence estimates
- The results of a Copenhagen population study demonstrate that when the DLCN criteria are used, the combination of phenotype and genotype leads to a higher prevalence of FH than either alone
 - Absence of genetic criteria implies the true prevalence of FH in the US population is likely ~ 1 in 200

Ferranti, et al. Circulation. 2016;133:1067-1072.

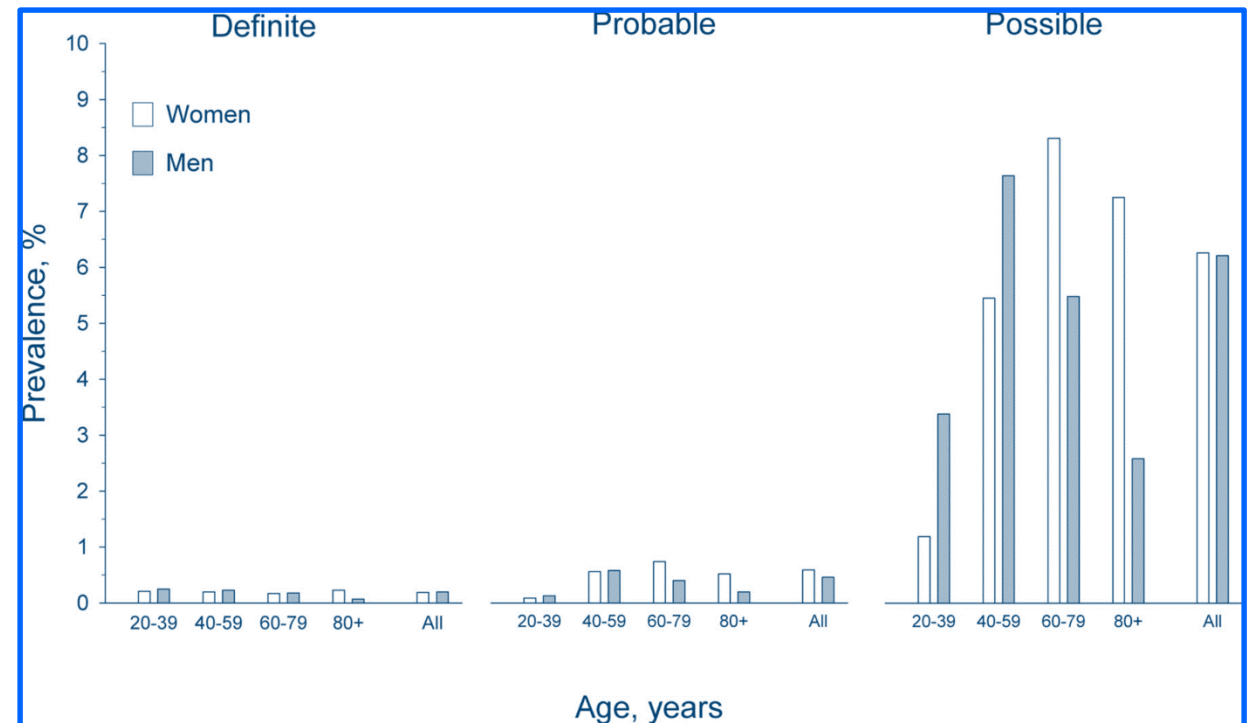
Benn, et al. J Clin Endocrinol Metab. 2012;91(11):3956-3964

Copenhagen General Population Study

Prevalence according to DCLN criteria

- Study of an adult community based Danish population initiated in 2003
- Prevalence of definite, probable, or possible FH by 20-yr age groups and gender, based on 69,016 individuals
- *LDLR* W23X, W66G, and W556S and *APOB* R3500Q mutations were genotyped in 60,710 individuals
- In those meeting criteria for definite/probable FH
 - 20% carried one of the tested mutations
 - 53% had LDL-C of 250 to 329 mg/dL
- Suggested prevalence of FH **one in 137**, more frequent than the commonly reported prevalence of one in 500 for heFH

	Diagnostic probability of FH				All
	Definite	Probable	Possible	Unlikely	
Number	137	365	4,295	64,219	69,016
Prevalence (%)*	0.20	0.53	6.3	93	100
	1 in 504	1 in 189	1 in 16		
*definite or probable FH combined (>5 points) 0.73% (1 in 137)					



Benn, et al. J Clin Endocrinol Metab. 2012;91(11):3956-3964

FH Genetic Prevalence and Mutation Distribution

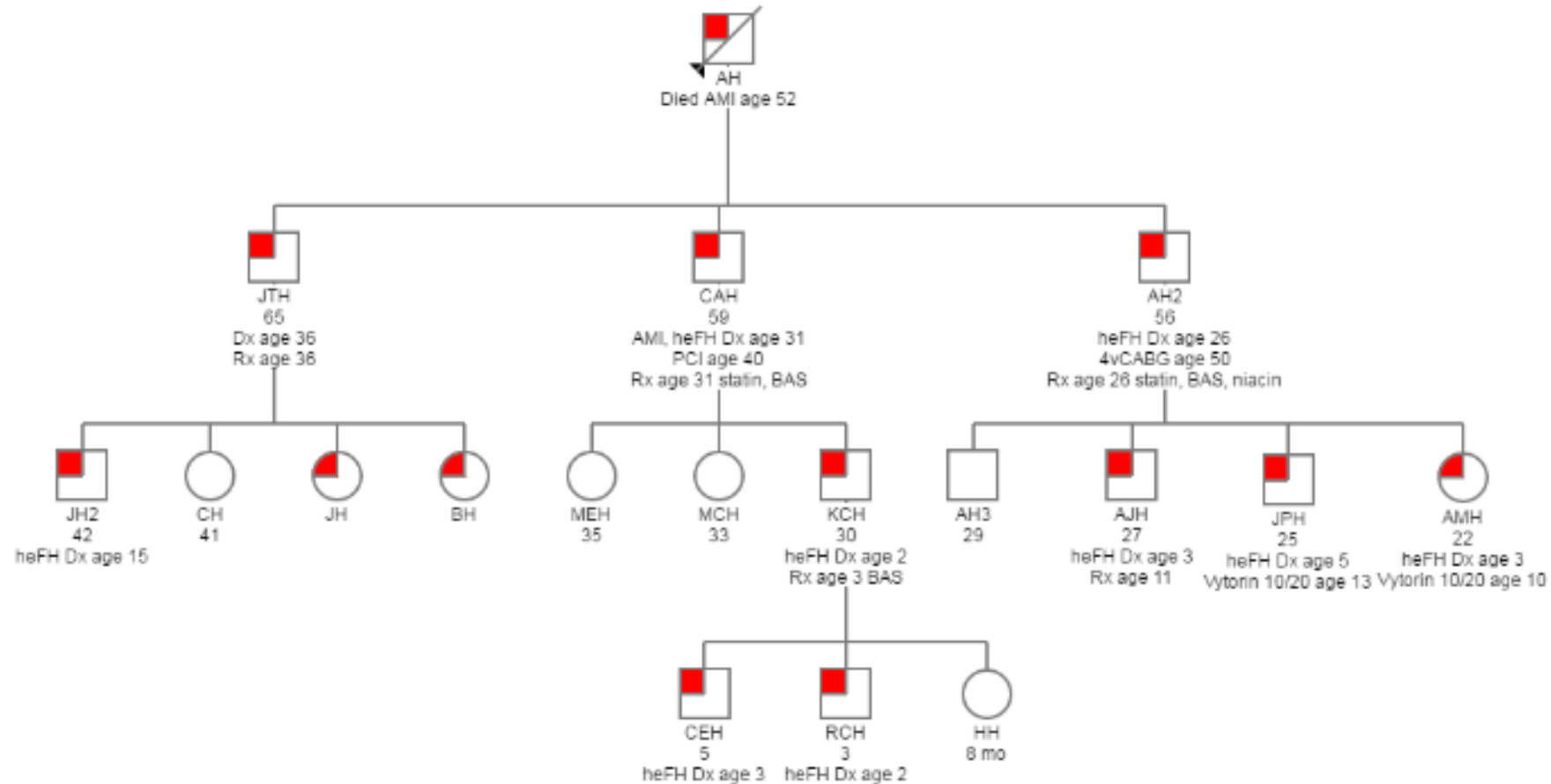
Population	Prevalence
General population	1:250
French Canadian	1:270
Old Order Amish	1:10
Christian Lebanese	1:85
Tunisia	1:165
South African Afrikaners	1:72 to 1:100
South African Ashkenazi Jews	1:67

Gene	Proportion of FH Attributed to Pathogenic Variants in This Gene	Proportion of Pathogenic Variants Detectable by This Method	
		Sequence analysis	Gene-targeted deletion/duplication analysis
<i>APOB</i>	1%-5%	>99%	1 individual
<i>LDLR</i>	60%-80%	>90%	~2.5%-10%
<i>PCSK9</i>	0%-3%	~100%	None reported
Unknown	20%-40%	NA	

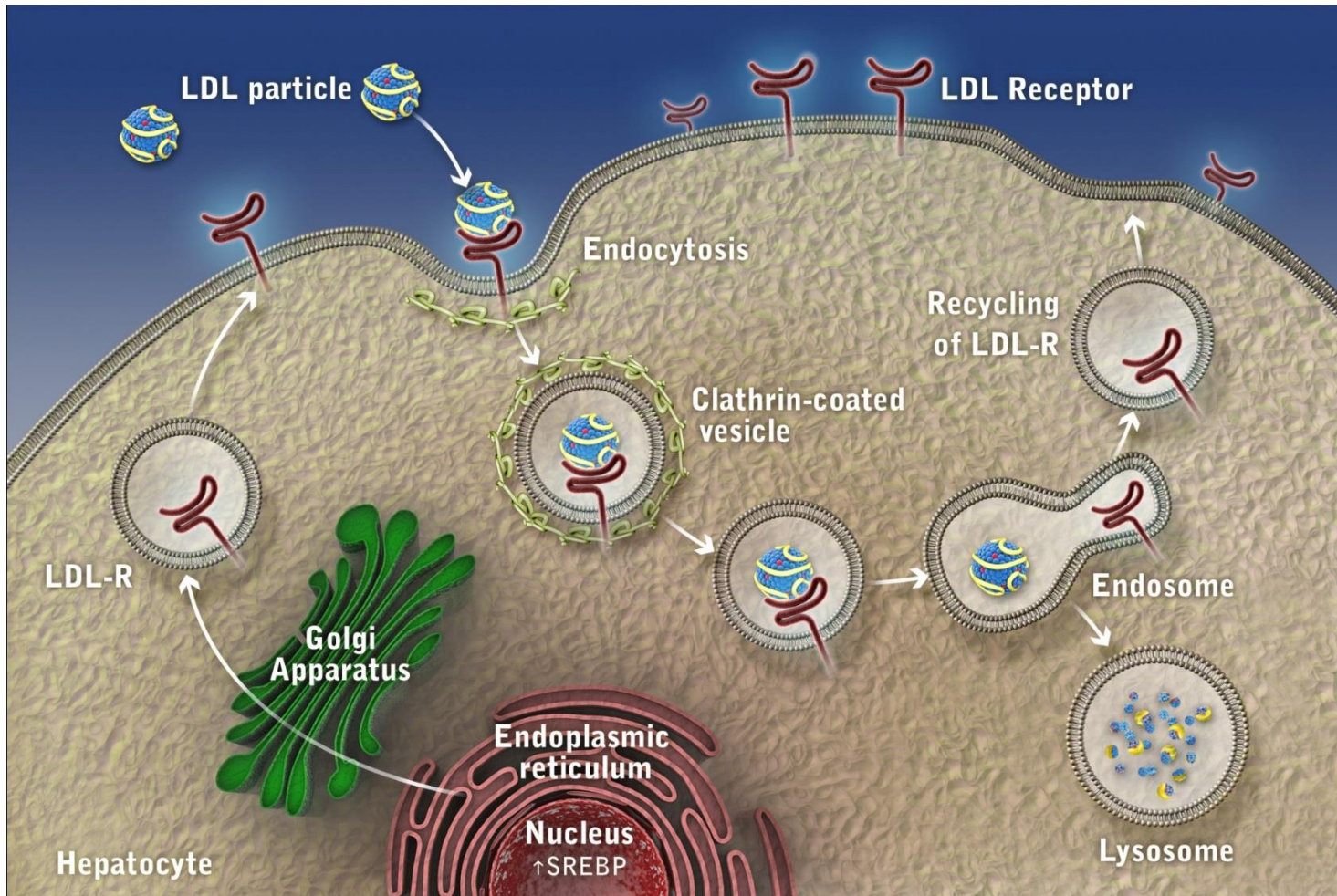
Youngblom, et al. 2014 Jan 2 [Updated 2016 Dec 8]. GeneReviews® <https://www.ncbi.nlm.nih.gov/books/NBK174884/>

Familial Hypercholesterolemia: A Family Disease

Case Study: 4 generations



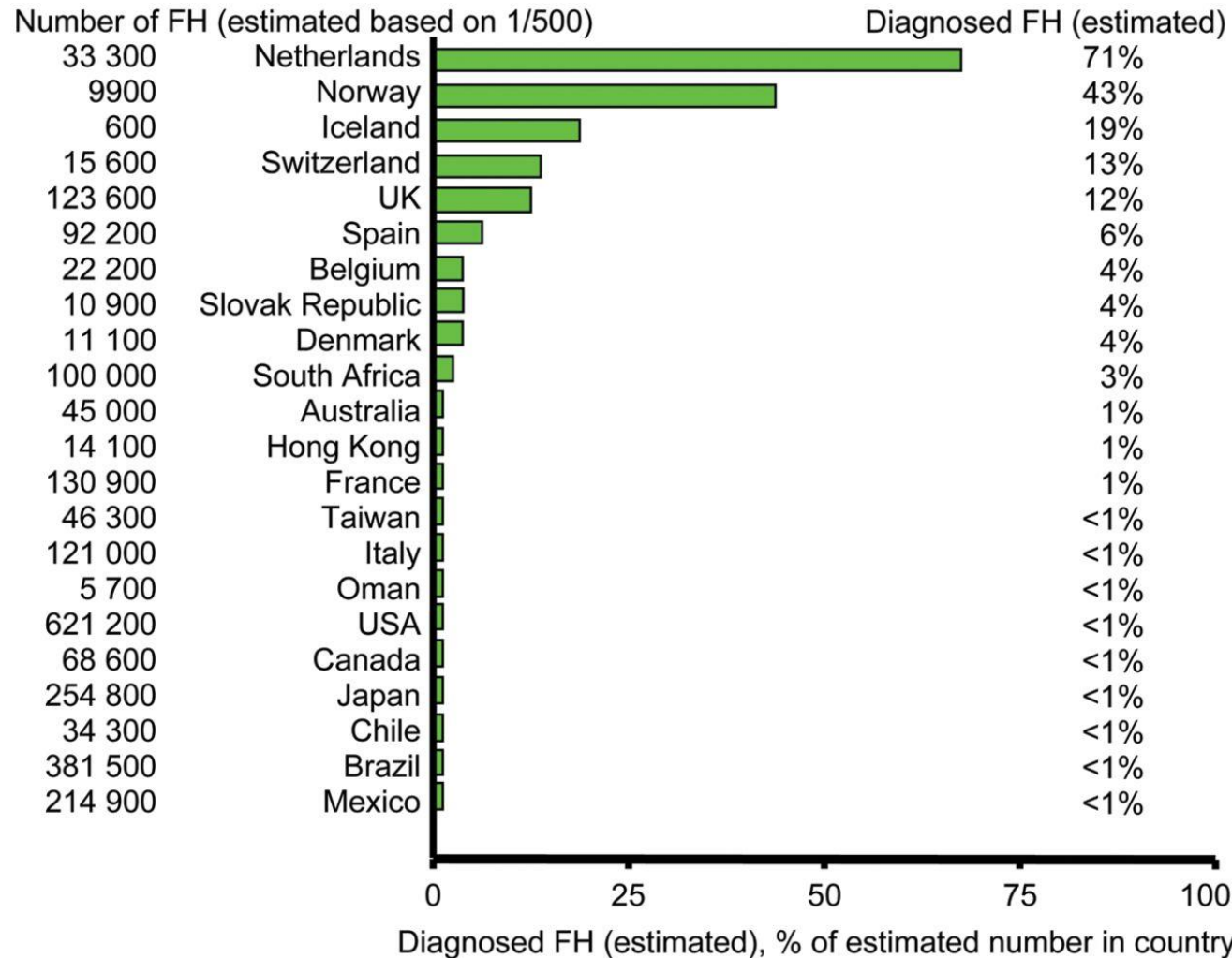
LDL Receptor Function and Life Cycle



- <10% of FH patients are formally diagnosed in the US, and many are not adequately treated
- heFH *LDLR* mutations result in 1/2 the normal number of LDL receptors, with hepatocyte uptake up LDL-C at ~1/2 the normal rate
- In heFH, untreated LDL-C levels are about 220 mg/dL

Adapted from Lambert G, et al. J Lipid Res. 2012;53(12):2515-24.
O'Brien, et al. Am Heart J 2014;167:342-349.e317

Estimated percent of individuals diagnosed with FH as a fraction of those theoretically predicted based on a frequency of 1/500 in the general population



Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490

FH Diagnostic Criteria

Dutch Lipid Clinic Network (DLCN)

Table 1 | DLCN diagnostic criteria for FH¹¹¹

Criteria	Points
Family history	
First-degree relative with known premature (men: <55 years; women: <60 years) coronary and vascular disease, or first-degree relative with known LDL-C level above the 95th percentile by age, gender for country	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, or children aged less than 18 years with LDL-C level above the 95th percentile by age, gender for country	2
Clinical history	
Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
Patient with premature (men: <55 years; women: <60 years) cerebrovascular or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
LDL-C levels	
LDL-C ≥ 8.5 mmol/l (~330 mg/dl)	8
LDL-C 6.5–8.4 mmol/l (~250–329 mg/dl)	5
LDL-C 5.0–6.4 mmol/l (~190–249 mg/dl)	3
LDL-C 4.0–4.9 mmol/l (~155–189 mg/dl)	1
DNA analysis	
Causative mutation in the LDLR, ApoB or PCSK9 gene	8

- Based on LDL-C levels, physical exam findings, genetic testing, and personal and family history of premature ASCVD
- Stratification of FH, as determined by total score
 - Definite FH total score >8
 - Probable FH score between 6 and 8
 - Possible FH score between 3 and 5
 - Unlikely FH score <3

World Health Organization. Familial Hypercholesterolaemia (FH): Geneva; 1999.
Haase et al. Current Opinion in Lipidology. 2012;23:282-289.

FH Diagnostic Criteria – Simon Broome Register Group

- (A) *TC* > 7.5 mmol/L in adults or *TC* > 6.7 mmol/L in children <16 years, or *LDL-c* > 4.9 mmol/L in adults or > 4.0 mmol/L in children
- (B) **Tendon xanthomas** in the patient, or a first-degree or second-degree relative
- (C) **DNA-based evidence of mutation** in the *LDLR*, or *apo-B100* or *PCSK9* gene
- (D) **Family history of premature CHD** (age <50 years in a second-degree relative or <60 years in a first-degree relative)
- (E) **Family history of raised TC** >7.5 mmol/L in a first- or second-degree relative, or >6.7mmol/L in child, brother or sister <16yrs of age

Diagnosis

- Definite FH diagnosis requires either A + B or A + C
- Possible FH diagnosis requires either A +D or A + E

- Research register established in 1980 of individuals with FH, based in Oxford, describing the natural history of FH in the UK
- Simon Broome Criteria for diagnosis were based on study of this group of individuals with FH
- criteria include cholesterol levels, physical exam findings, molecular diagnosis, and family history

FH Diagnostic Criteria: MEDPED

Make Early Diagnosis to Prevent Early Deaths

- Humanitarian program to identify persons with inherited high cholesterol, founded in 1989 in Utah, now with 38 participating countries
- Specify cut-points for total cholesterol concentrations specific to an individual's age and family history
 - validation study of these criteria using 5 large Utah pedigrees with DNA-verified mutations
 - A priori probabilities applied to develop 2 sets of screening criteria: one for general population screening and another for relatives of known FH cases
 - Cut-points are different for individuals who are the first-, second- or third-degree relatives of a patient with FH, and for the general population, as individuals with a relative with FH have a higher likelihood of having FH
- At a cholesterol level of 310 mg/dl, only 4% of persons in the general population would have FH but 95% of persons who were first-degree relatives of known cases would have FH
- Using predefined criteria, FH diagnosed with 98% specificity and 87% sensitivity, confirmed by genetic testing

Total cholesterol cut-points in mg/dL (mmol/L)				
Age (years)	First Degree relative with FH	Second Degree relative with FH	Third Degree relative with FH	General Population
<20	220 (5.7)	230 (5.9)	240 (6.2)	270 (7)
20-29	240 (6.2)	250 (6.5)	260 (6.7)	290 (7.5)
30-39	270 (7)	280 (7.2)	290 (7.5)	340 (8.8)
≥40	290 (7.5)	300 (7.8)	310 (8)	360 (9.3)

Williams et al. Am J Cardiol.1993 Jul 15;72(2):171-6.

World Health Organization. Familial Hypercholesterolaemia (FH): Geneva; 1999.

FH Diagnosis

Relationship of genetic testing to clinical Dx of FH in a Danish population

The ability of the Simon Broome Register Group, MEDPED and Dutch Lipid Clinic Network criteria to predict the results of the molecular genetic analysis of the LDL receptor gene and of the apoB R3500 Q mutation

Clinical criteria	Sensitivity (%)	Mutation detection rate (%)	Specificity (%)*	1-Specificity (%)* = false positive rate
Simon Broome Register	34.1 (26.1–42.7) 35.9	61.3 (49.4–72.4) 59.2	89.4 (85.1–92.8)	10.6 (7.2–14.9)
	Definite or possible FH	38.5 (33.1–44.1) 35.4	28.6 (23.3–34.3)	71.4 (65.7–76.7)
MEDPED	Total cholesterol	63.4 (54.5–71.6) 69.0	73.4 (67.8–78.6)	26.6 (21.4–32.2)
	LDL-cholesterol	70.3 (61.2–78.4) 75.5	69.8 (63.8–75.3)	30.2 (24.7–36.2)
Dutch Lipid Clinic Network	Definite FH	41.5 (33.1–50.3) 42.7	87.9 (83.4–91.5)	12.1 (8.5–16.6)
	Definite or probable FH	66.7 (58.0–74.5) 68.3	64.5 (58.5–70.1)	35.5 (29.9–41.5)
	Definite, probable or possible FH	99.3 (95.9–100.0) 99.1	5.9 (3.4–9.3)	94.1 (90.7–96.6)

- 408 index patients referred to a lipid clinic and 385 relatives were included
- index patients were categorized retrospectively, based on clinical criteria, before genetic testing
- the relationship of the FH genotype to the FH phenotype is not straightforward
 - mutation detection rate, even in patients with a clinical diagnosis of definite FH, was as low as 61.3%, it as low as 32% in other studies
- % of index patients/mutation carriers with LDL-C levels above the age- and sex-specific 90th or 95th percentile were 94.7% and 99.2%, respectively

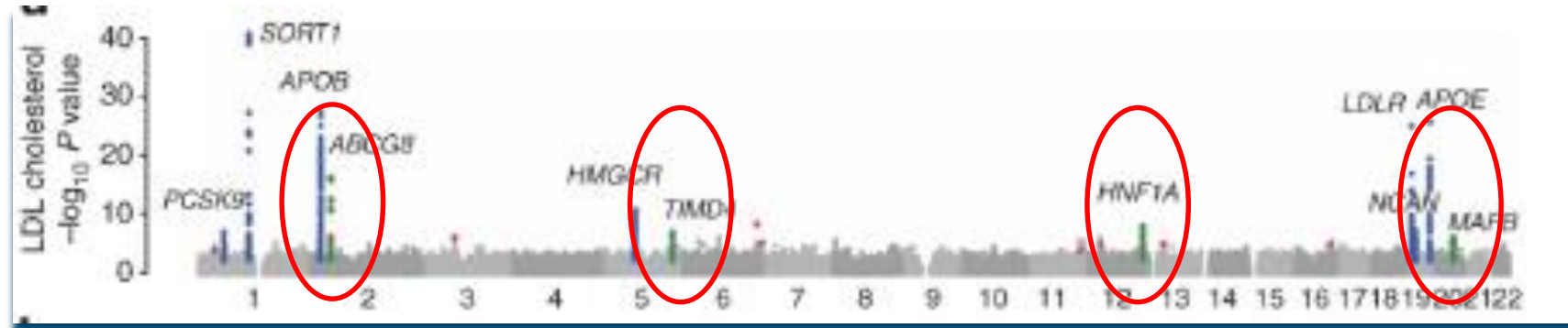
Genetic Diagnosis

Recent genetic analyses

- FH cannot be ruled out in the absence of a known mutation
 - A monogenic defect cannot be identified in a substantial number of cases, mutation rates range from 20 to 40% of patients who meet clinical criteria for probable or definite heFH
 - The FH phenotype may also be due to a large number of relatively benign variations in many genes, termed “polygenic FH”
 - Polygenic risk scores for high LDL-C levels are determined by evaluating in aggregate the patient’s burden of common alleles that cause LDL-C elevations
 - identified by single nucleotide polymorphisms (SNPs) recorded in genome-wide association studies (GWAS)

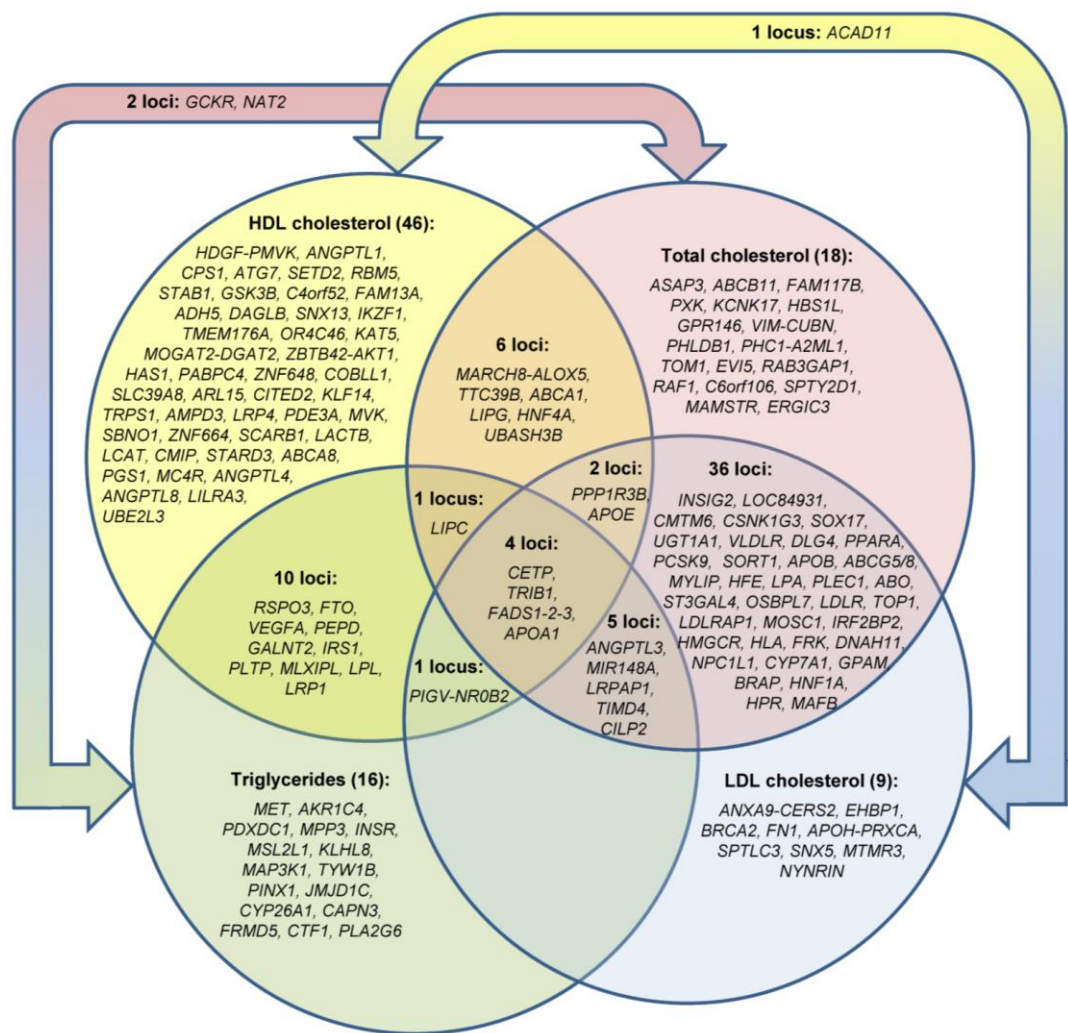
Santos, et al. www.thelancet.com/diabetes-endocrinology. Published online May 27, 2016
[http://dx.doi.org/10.1016/S2213-8587\(16\)30041-9](http://dx.doi.org/10.1016/S2213-8587(16)30041-9)
Hartgers, et al. *Curr Cardiol Rep* (2015) 17:109

Common variants at 30 loci contribute to polygenic dyslipidemia



- GWAS screens in 19,840 individuals identified 30 distinct loci associated with lipoprotein concentrations
- 11 loci that reached genome-wide significance for the first time
- Newly defined loci include common variants associated with LDL cholesterol near *ABCG8*, *MAFB*, *HNF1A* and *TIMD4*

Overlap between loci associated with different lipid traits



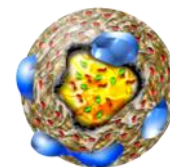
- Lipid-associated loci were strongly associated with CAD, T2D, BMI, SBP, and DBP
- Impact on LDL and TG levels all predicted association with CAD, but HDL did not
- 188,578 European-ancestry individuals and 7,898 non-European ancestry individuals
- 157 loci associated with lipid levels, including 62 new loci

Teslovich et al. Nature. 2010 August 5; 466(7307): 707–713
 Willer et al. Nat Genet. 2013 November ; 45(11)



Familial Hypercholesterolemia

Disease Risk and Recent Evidence
Treatment and New Pharmacotherapies



Why do we still need new LDL-C lowering therapies?

- Despite advances in treatment, CVD remains the leading cause of morbidity and mortality worldwide and is projected to cause >22 million deaths over the next 15 years¹
- CVD end point trials with statins, and evolocumab or ezetimibe added to statins, show greater LDL-C reduction results in additional CVD reduction
 - For every 40 mg/dL reduction in LDL-C there is a 20% reduction in CVD events in 2-3 years
- Most guidelines still continue to set LDL-C goals in very high and high risk patients
- Growing number of statin adverse patients with limited alternatives
- Special populations (e.g. FH and severe hypercholesterolemia) do not achieve current LDL-C goals

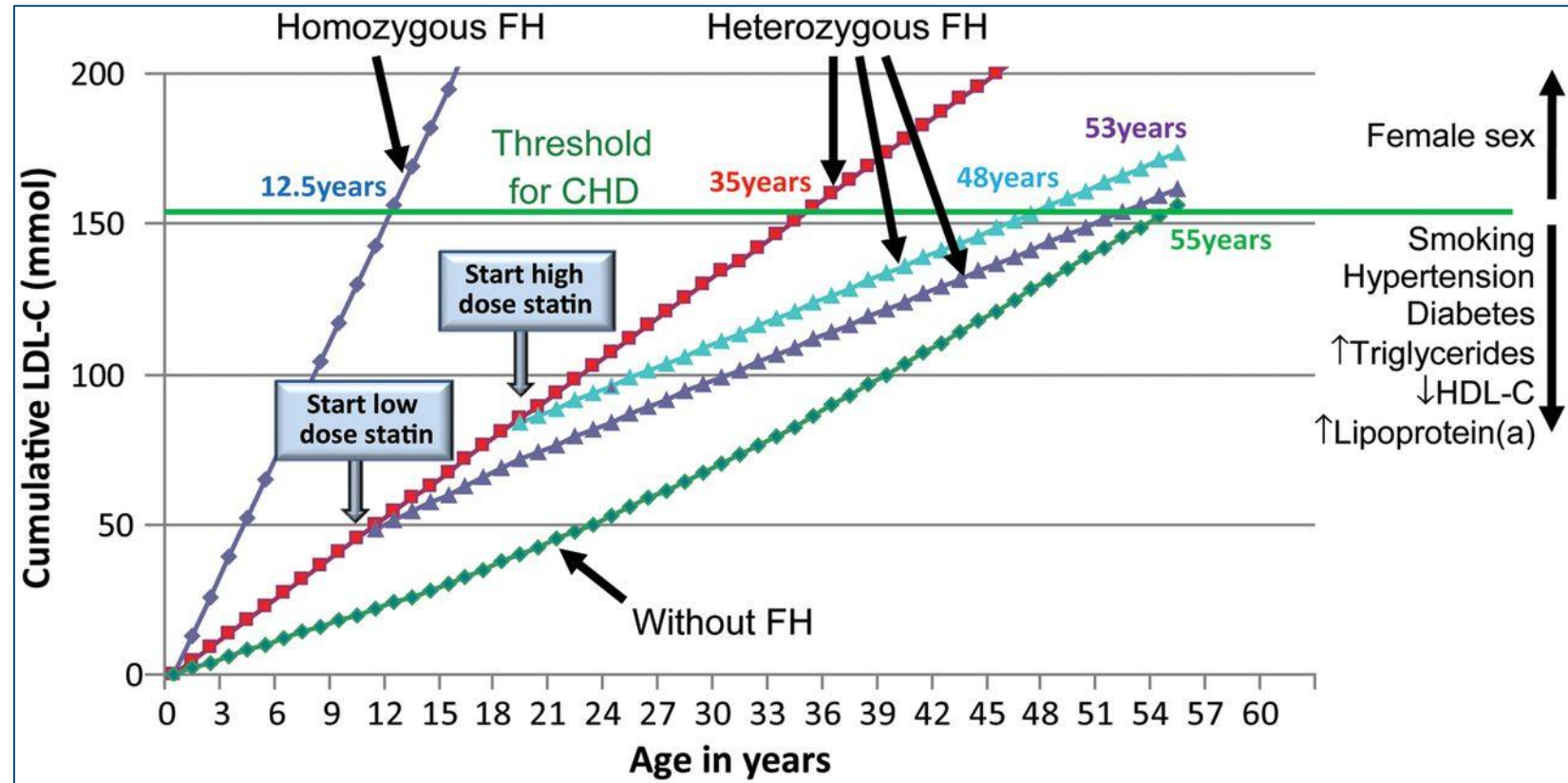
¹Organization WH. World health statistics 2015. 2015

²Cholesterol Treatment Trialists Lancet. 2010;376:1670-1681

Slide courtesy of Evan Stein

Cumulative LDL-C burden in individuals with or without FH as a function of the age of initiation of statin therapy

- Cumulative LDL-C burden of a 55-year-old person without FH is ~160 mmol, sufficient for CHD to develop
- For an individual with heFH, this LDL-C burden is reached by
 - Age 35 if untreated
 - Age 48 if treated since age 18
 - Age 53 if treated since age 10
- An untreated subject with hoFH will reach this level at age 12.5



Nordestgaard et al. Eur Heart J. 2013;34:3478-3490.

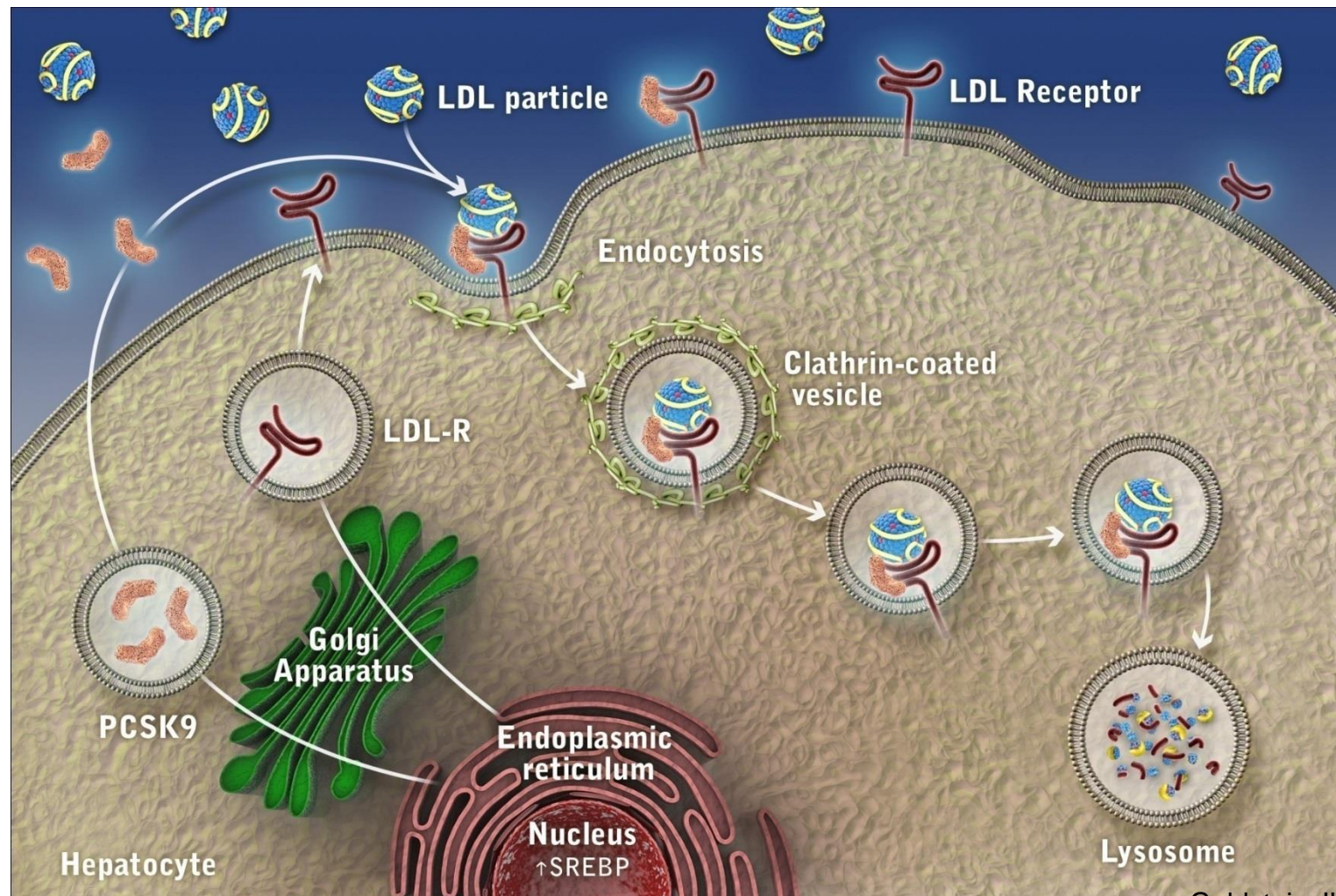
PCSK9 revolution

What we know and what remains to be known?

- PCSK9 in plasma has unique role in regulating the activity of the LDL receptor, with no other known role
- Genetics of loss-of-function mutations are very supportive of reduced CAD and human 'knockout' or double LOF associated with no safety signals
- Extensive clinical trials with two mAbs have shown maximal and stable 60% reductions in LDL-C once all PCSK9 is bound (140 to 150 mg Q2W or 420 mg Q4W) and less reduction and more variability with incomplete suppression at lower doses (75 mg Q2W)
- Same reduction when added to diet alone, low and maximal dose statin or statin plus ezetimibe; in patients with HeFH and nonFH; pts with adverse rxn to statins
- Homozygous FH patients respond about half as well, with mean reductions in LDL-C of 31% to high doses, 420 mg Q4W, of evolocumab
- In addition to LDL-C reductions there is a robust 25-30% decrease in Lp(a)
- No significant safety signals have been identified, even when LDL-C is very low

Slide courtesy of Evan Stein

The Role of PCSK9 in the Regulation of LDL Receptor Expression

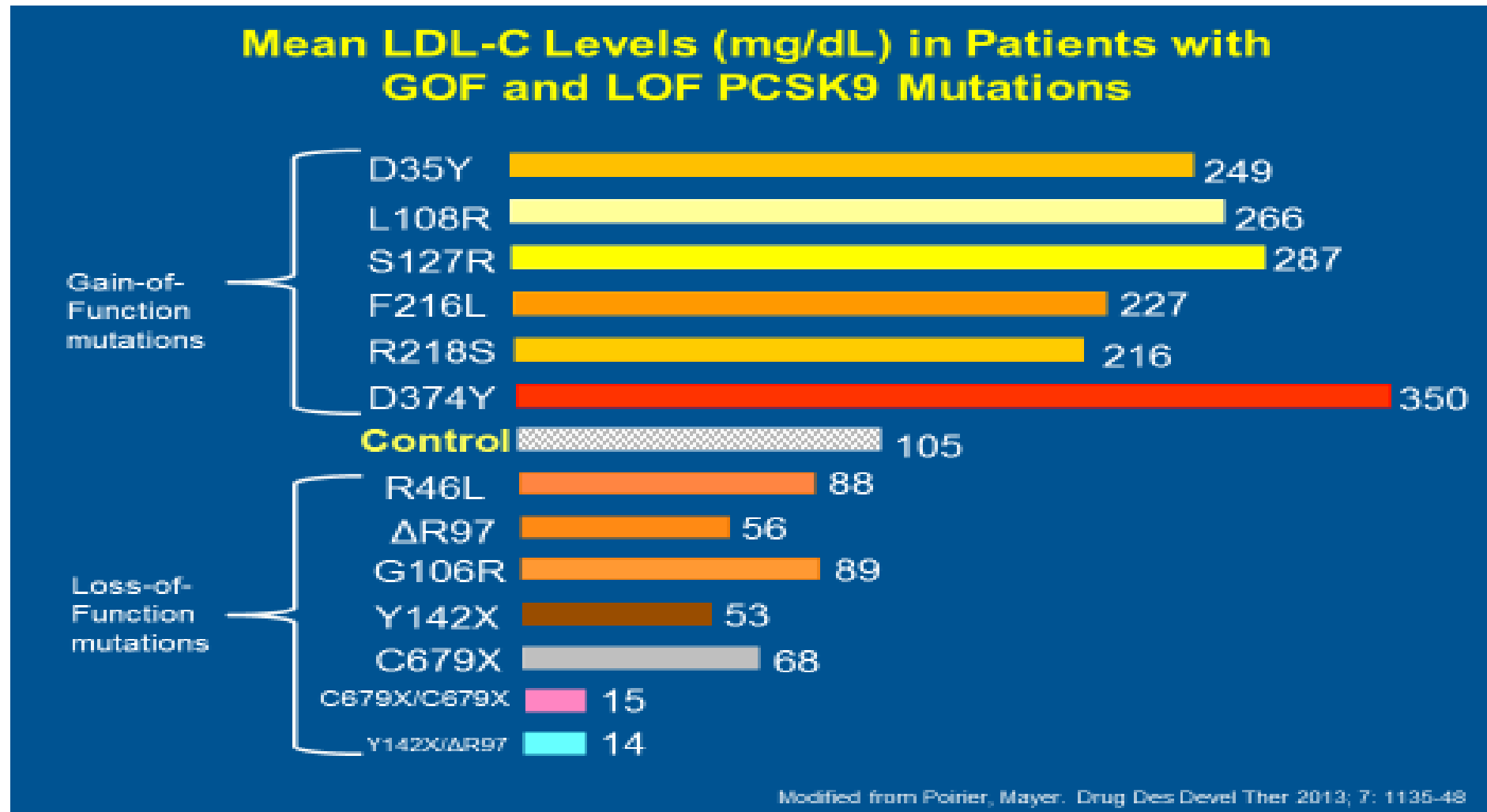


- The LDLR recycles, or makes one “round trip”, into and out of the cell every 10 min for a total of several hundred trips in its 20-hour lifespan
- PCSK9 acts by reducing the amount of LDLR at the cell surface of hepatocytes
- PCSK9 is secreted from liver cells, circulates in the plasma, binds to LDLR, and is internalized together with the LDLR
- PCSK9 binding to the LDLR prevents recycling to the cell membrane and targets the LDLR for lysosomal degradation, promoting the cellular degradation of the LDLR

Adapted from Lambert G, et al. *J Lipid Res.* 2012;53(12):2515-24
Goldstein JL, Brown MS. *Arterioscler Thromb Vasc Biol.* 2009 April ; 29(4): 431–438

Patients with GOF and LOF PCSK9 Mutations

Mean LDL-C Levels (mg/dL)



Slide courtesy of Evan Stein

Loss-of-Function Mutations in PCSK9 Are Associated With Decreased LDL-C and CHD Risk

- Heterozygous LOF mutations found in 1% to 3% of population¹
- Associated with
 - Lower serum LDL-C¹
 - Lower incidence of coronary heart disease¹

PCSK9 Variant	Population	LDL-C	CHD Risk
R46L	ARIC, DHS	↓ 15% ¹	↓ 47% ¹
Y142X or C679X	ARIC, DHS	↓ 28%-40% ^{1,2}	↓ 88% ¹
R46L	CGPS	↓ 11% ³	↓ 46% ³

1. Cohen JC, et al. *N Engl J Med*. 2006;354:1264-1272.

2. Cohen J, et al. *Nat Genet*. 2005;37:161-165.

3. Benn M, et al. *J Am Coll Cardiol*. 2010;55:2833-2842.

4. Zhao et al. *Am Journal of Hum Gen*. 2006;79:514-534.

5. Steinberg D, et al. *Proc Natl Acad Sci U S A*. 2009;106:9546-9547.

Natural Genetic Experiments

Patients with Double Loss-of-Function PCSK9 Mutations

32 yr old woman, fertile, college educated, fitness instructor
Compound heterozygote for 2 loss of function alleles in *PCSK9*
LDL-C 14 mg/dL
No measurable PCSK9

Am J Hum Genet. 2006;79:514-523



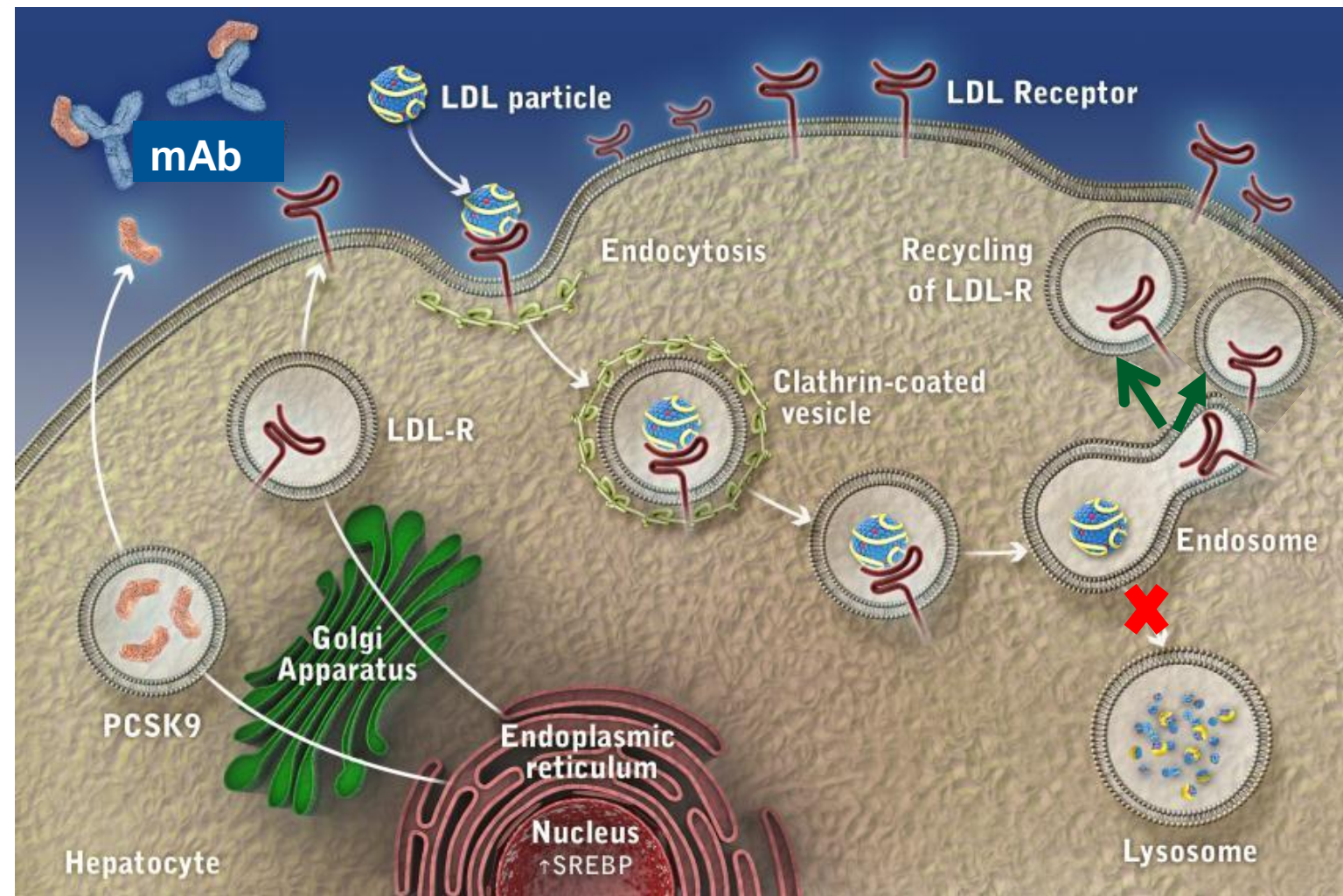
Zimbabwean woman healthy with children
Homozygous C679X
LDL-C 15 mg/dL
No measurable PCSK9
Atherosclerosis 2007;193:445-8

49 year-old French male had no detectable PCSK9 levels
LDL-C of 16 mg/dL

Arterioscler Thromb Vasc Biol. 2009;29:2192-7

Slide courtesy of Evan Stein

Impact of a PCSK9 mAb on LDL Receptor Expression

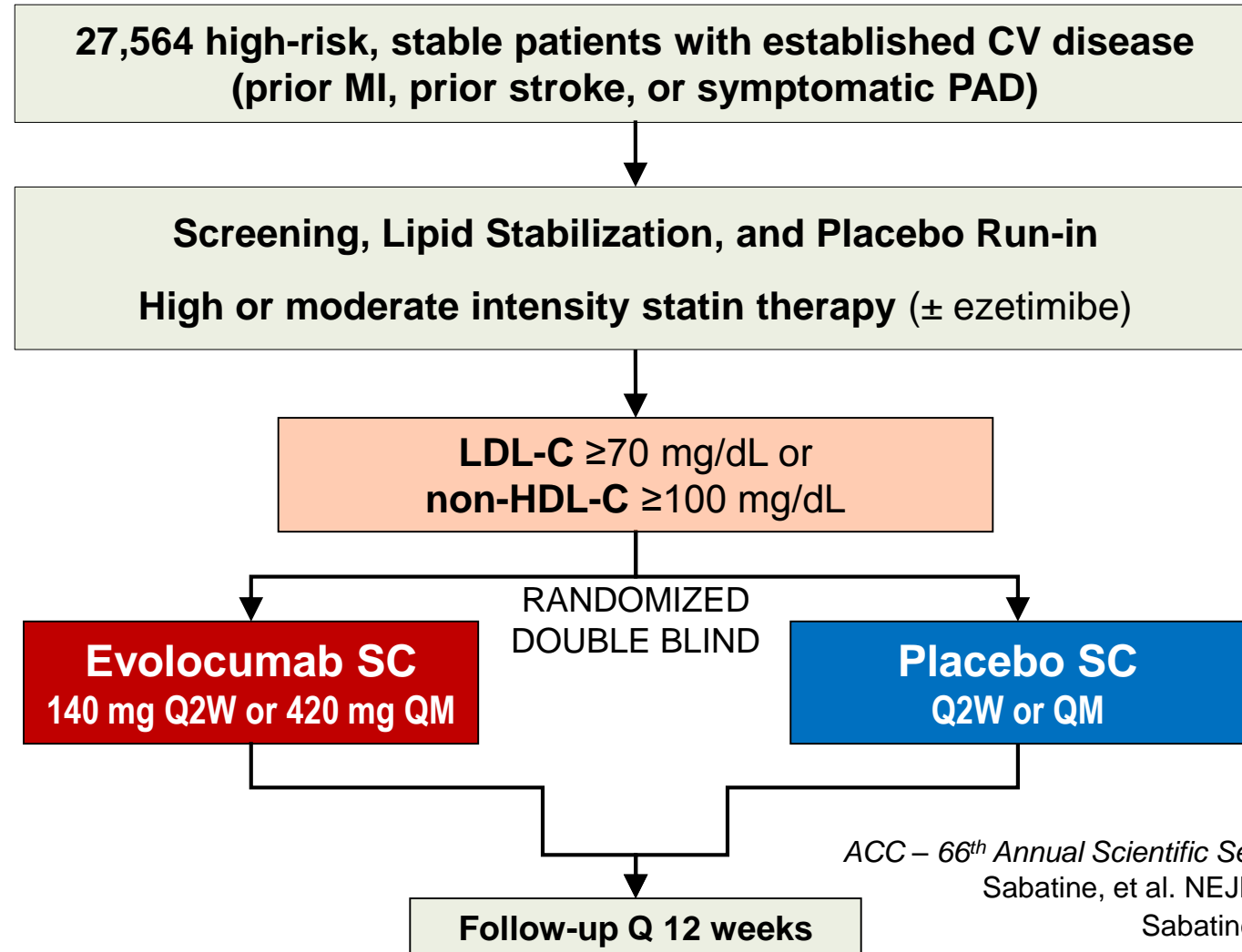


- PCSK9 inhibition
- Monoclonal antibodies bound to PCSK9 prevent the association between PCSK9 and the LDLR
- The LDLR binds the LDL particle and is internalized
- The LDL particle is degraded in the lysosome
- The LDLR is recycled back to the plasma membrane

Adapted from Lambert G, et al. *J Lipid Res.* 2012;53(12):2515-24

FOURIER

Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

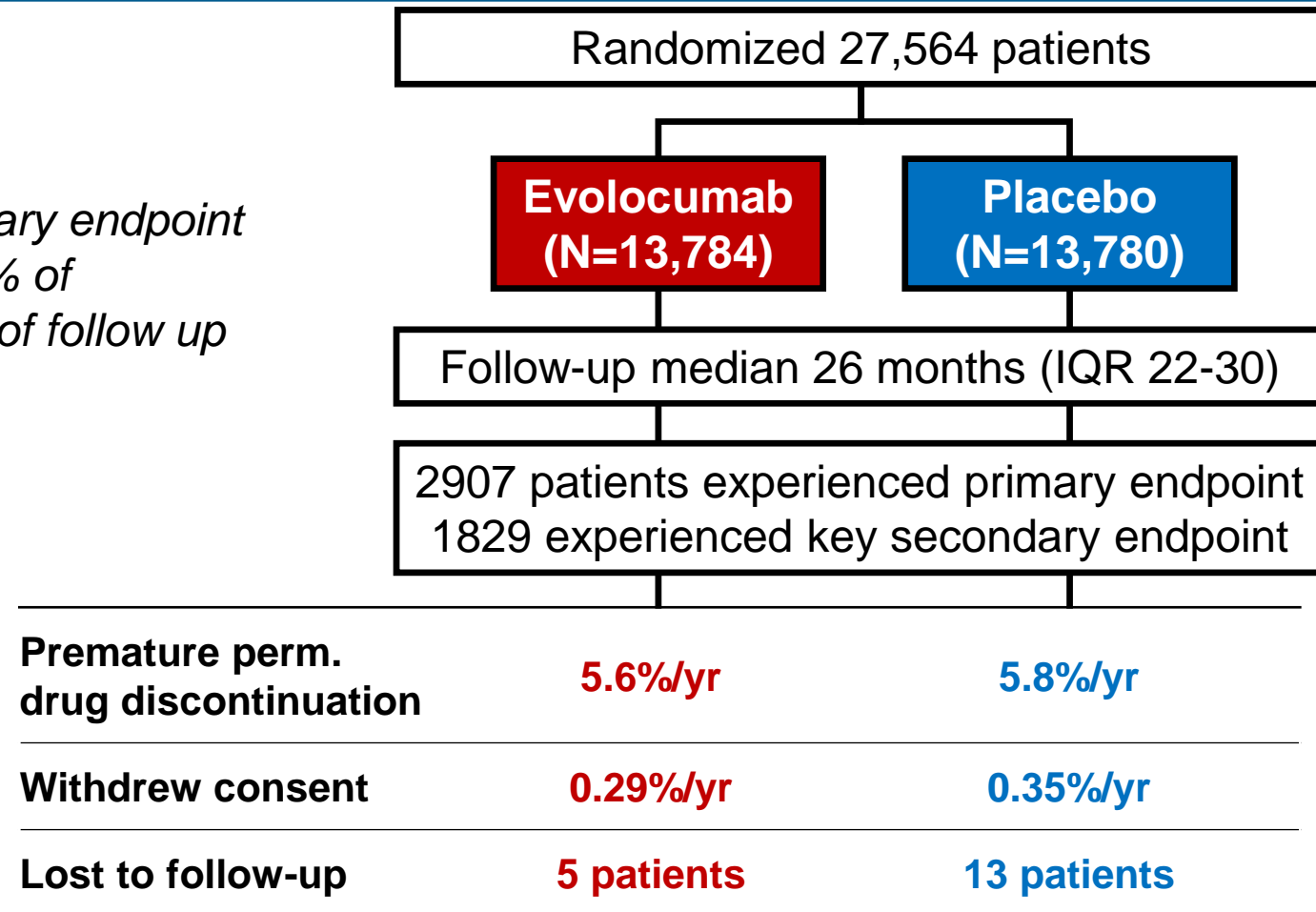


ACC – 66th Annual Scientific Sessions Late-Breaking Clinical Trial 2017
Sabatine, et al. NEJM 2017; DOI: 10.1056/NEJMoa1615664
Sabatine MS et al. *Am Heart J* 2016;173:94-101

FOURIER

Follow-up

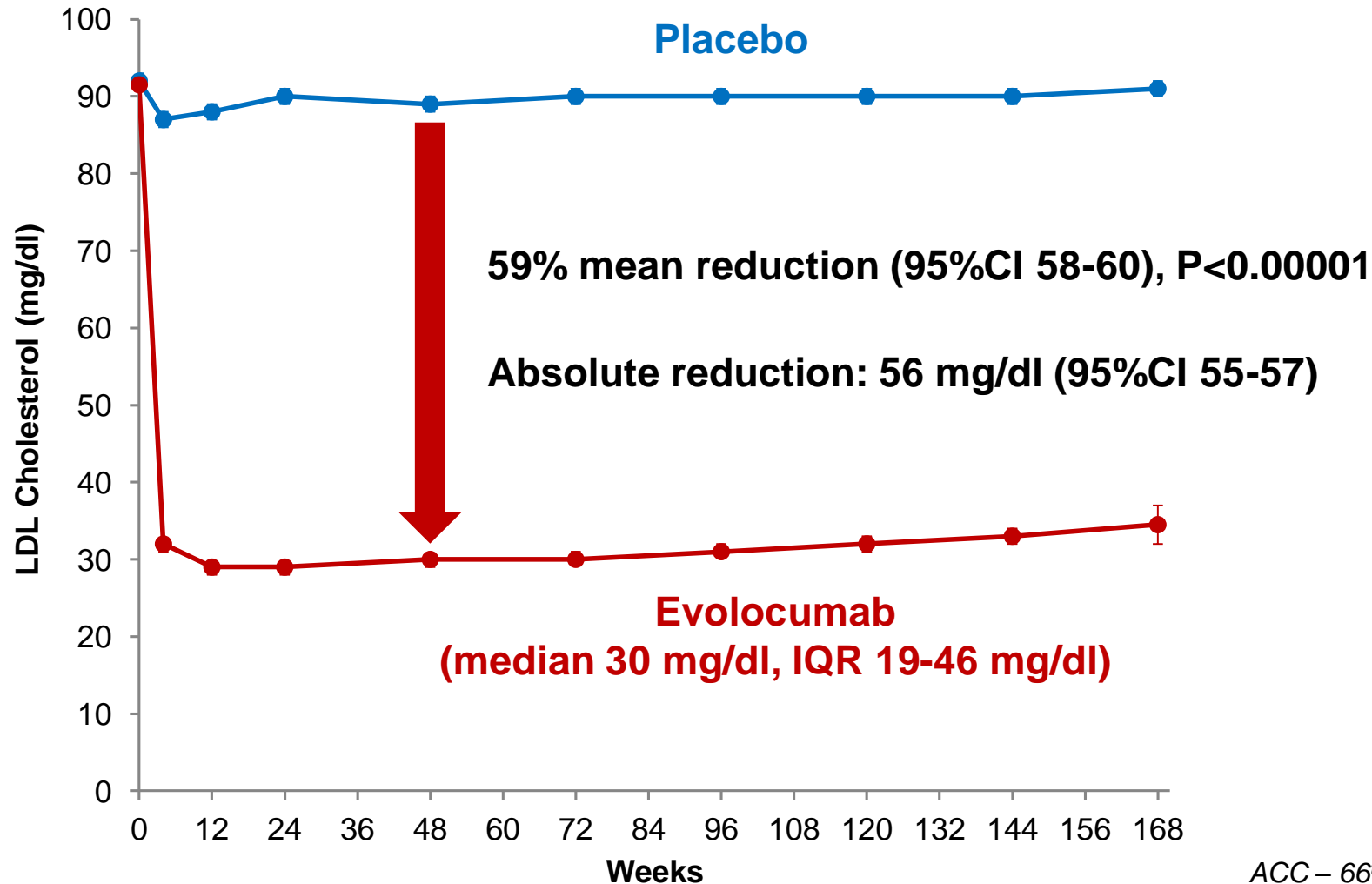
Ascertainment for primary endpoint was complete for 99.5% of potential patient-years of follow up



ACC – 66th Annual Scientific Sessions Late-Breaking Clinical Trial 2017
Sabatine, et al. NEJM 2017; DOI: 10.1056/NEJMoa1615664

FOURIER

LDL Cholesterol reductions with evolocumab over time



LDL-C at 48 weeks

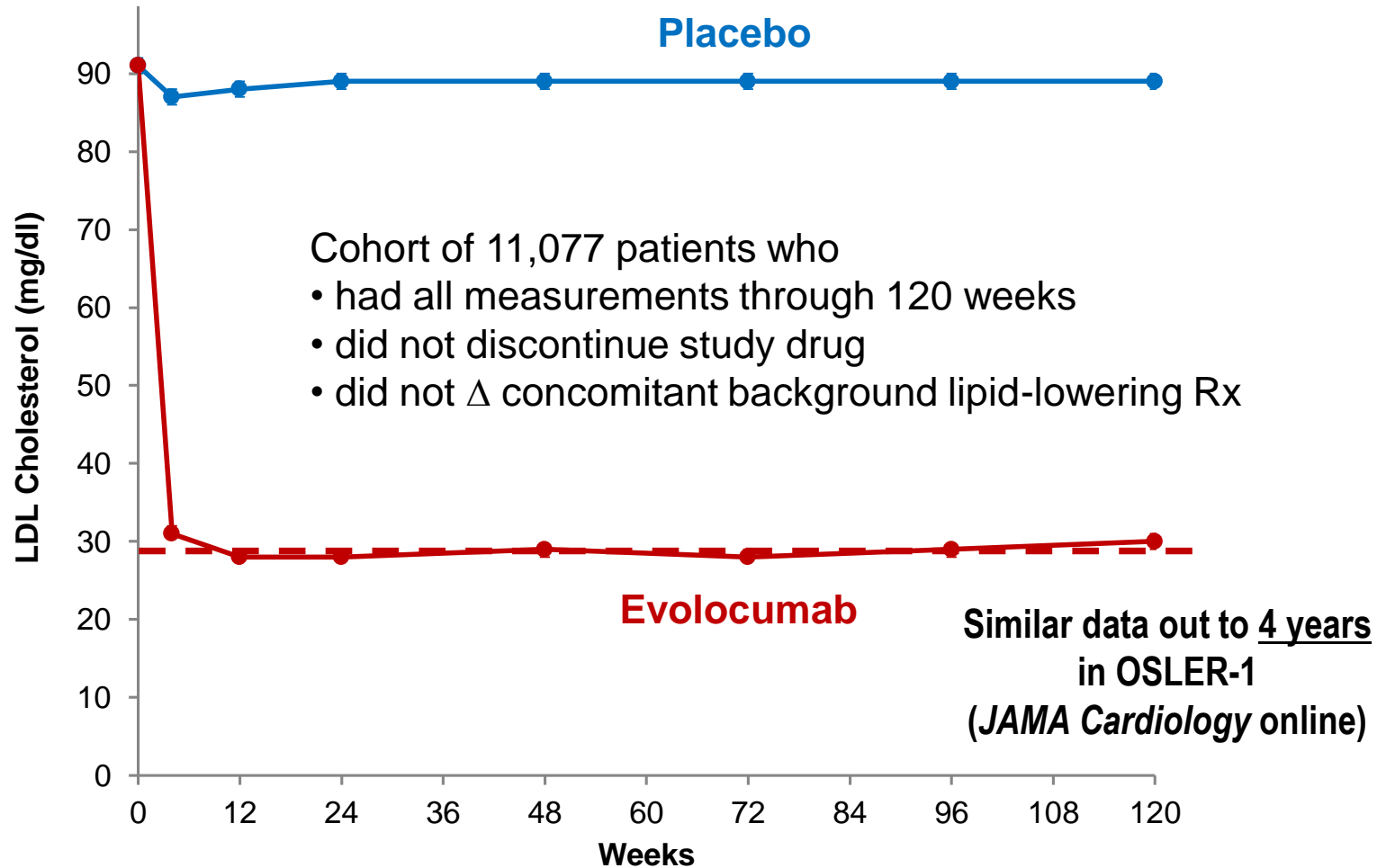
LDL-C	evolocumab	Placebo
Median (IQR)	30 (19,46)	85
≤70 mg/dL	87%	18%
≤40 mg/dL [‡]	67%	0.5%
≤25 mg/dL [‡]	42%	<0.1%

P<0.001 for all treatment comparisons

[‡]LDL-C calculated using the Friedewald equation, except if <40 mg/dL or if TG >400 mg/dL; then LDL-C measured by preparative ultracentrifugation

FOURIER LDL-C Reductions

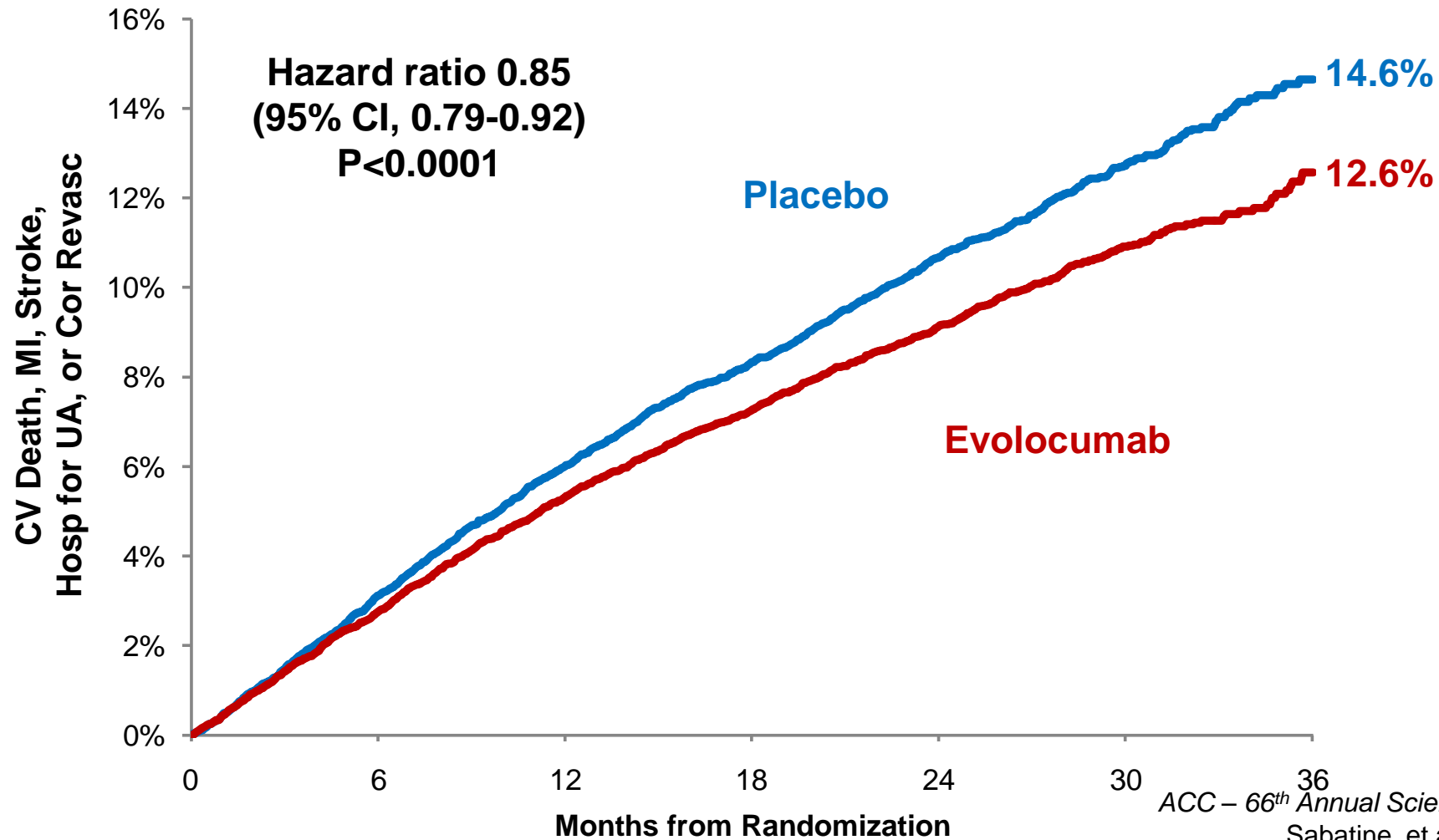
Cohort completing 120 weeks stable LMTs and 100% compliance with evolocumab



ACC – 66th Annual Scientific Sessions Late-Breaking Clinical Trial 2017
Sabatine, et al. NEJM 2017; DOI: 10.1056/NEJMoa1615664

FOURIER: Primary Endpoint

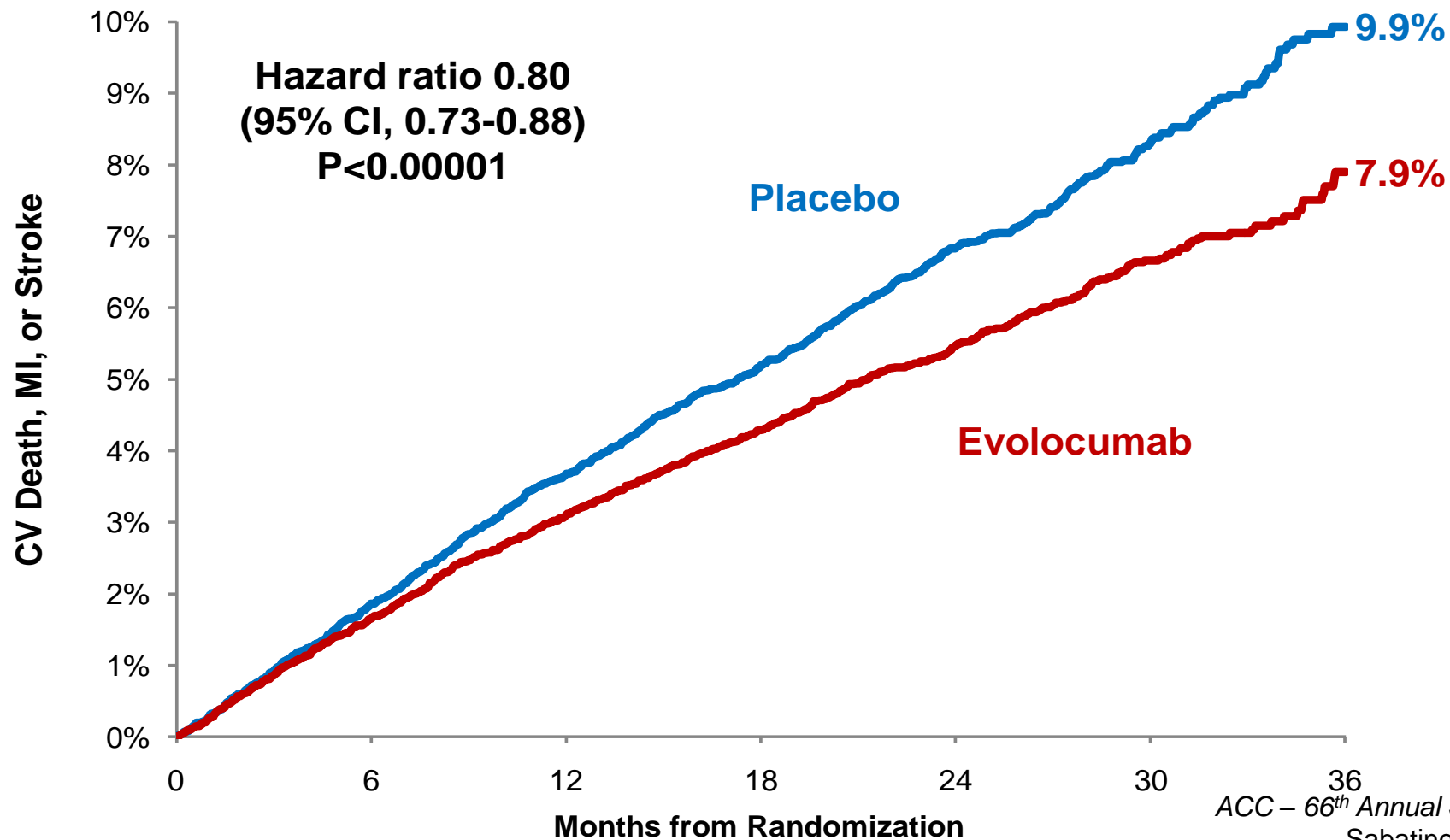
CV MI, Stroke, Hospitalization for UA, or Coronary Revascularization



ACC – 66th Annual Scientific Sessions Late-Breaking Clinical Trial 2017
Sabatine, et al. NEJM 2017; DOI: 10.1056/NEJMoa1615664

FOUTIER: Key Secondary Endpoint

CV Death, MI, or Stroke



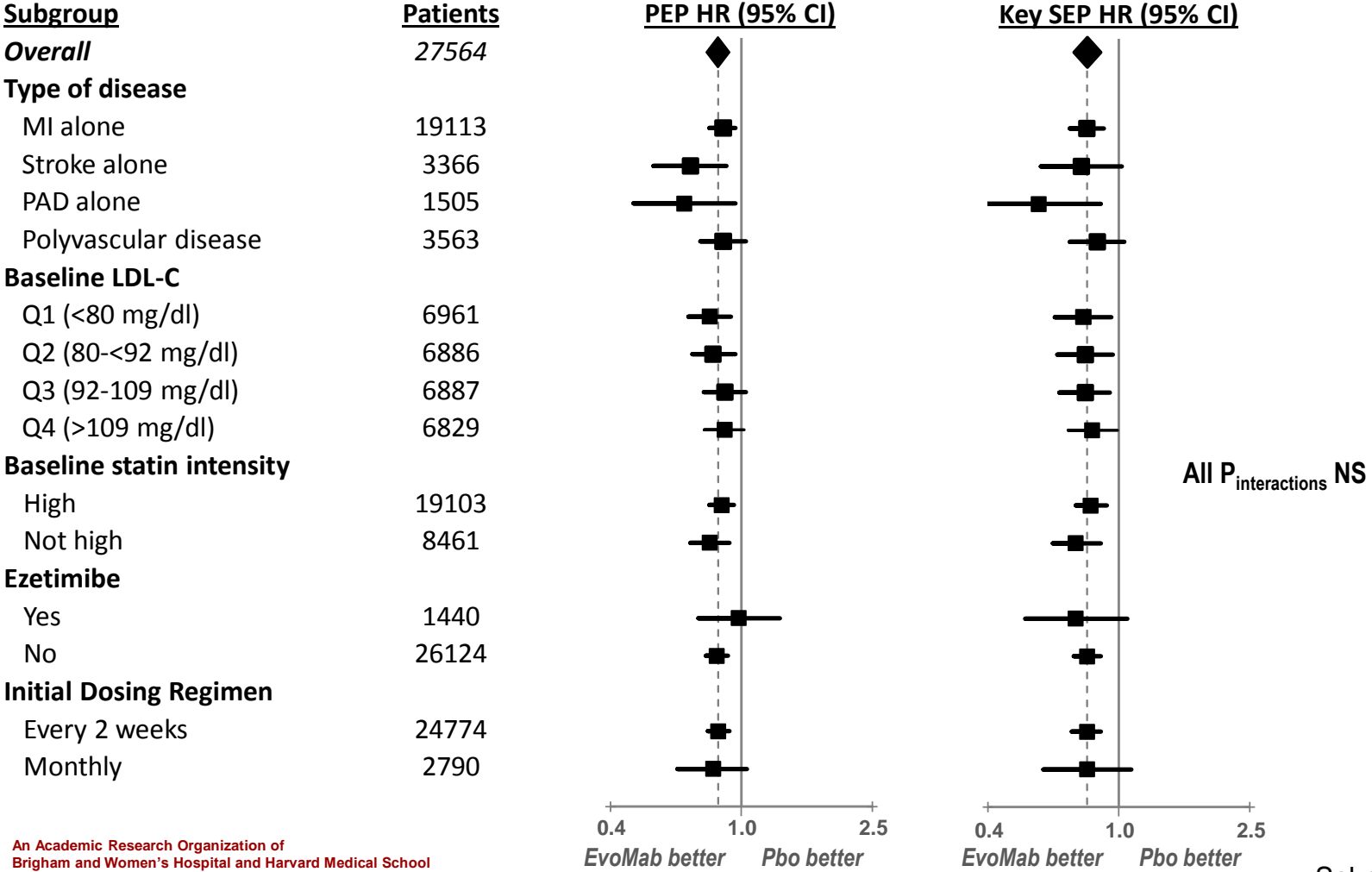
ACC – 66th Annual Scientific Sessions Late-Breaking Clinical Trial 2017
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FOURIER: Types of CV Outcomes

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CVD, MI, stroke, UA, or revasc	12.6	14.6	0.85 (0.79-0.92)
CV death, MI, or stroke	7.9	9.9	0.80 (0.73-0.88)
Cardiovascular death	2.5	2.4	1.05 (0.88-1.25)
MI	4.4	6.3	0.73 (0.65-0.82)
Stroke	2.2	2.6	0.79 (0.66-0.95)
Hosp for unstable angina	2.2	2.3	0.99 (0.82-1.18)
Coronary revasc	7.0	9.2	0.78 (0.71-0.86)
Urgent	3.7	5.4	0.73 (0.64-0.83)
Elective	3.9	4.6	0.83 (0.73-0.95)
Death from any cause	4.8	4.3	1.04 (0.91-1.19)

ACC – 66th Annual Scientific Sessions Late-Breaking Clinical Trial 2017
 Sabatine, et al. NEJM 2017; DOI: 10.1056/NEJMoa1615664

FOURIER: Key Subgroups

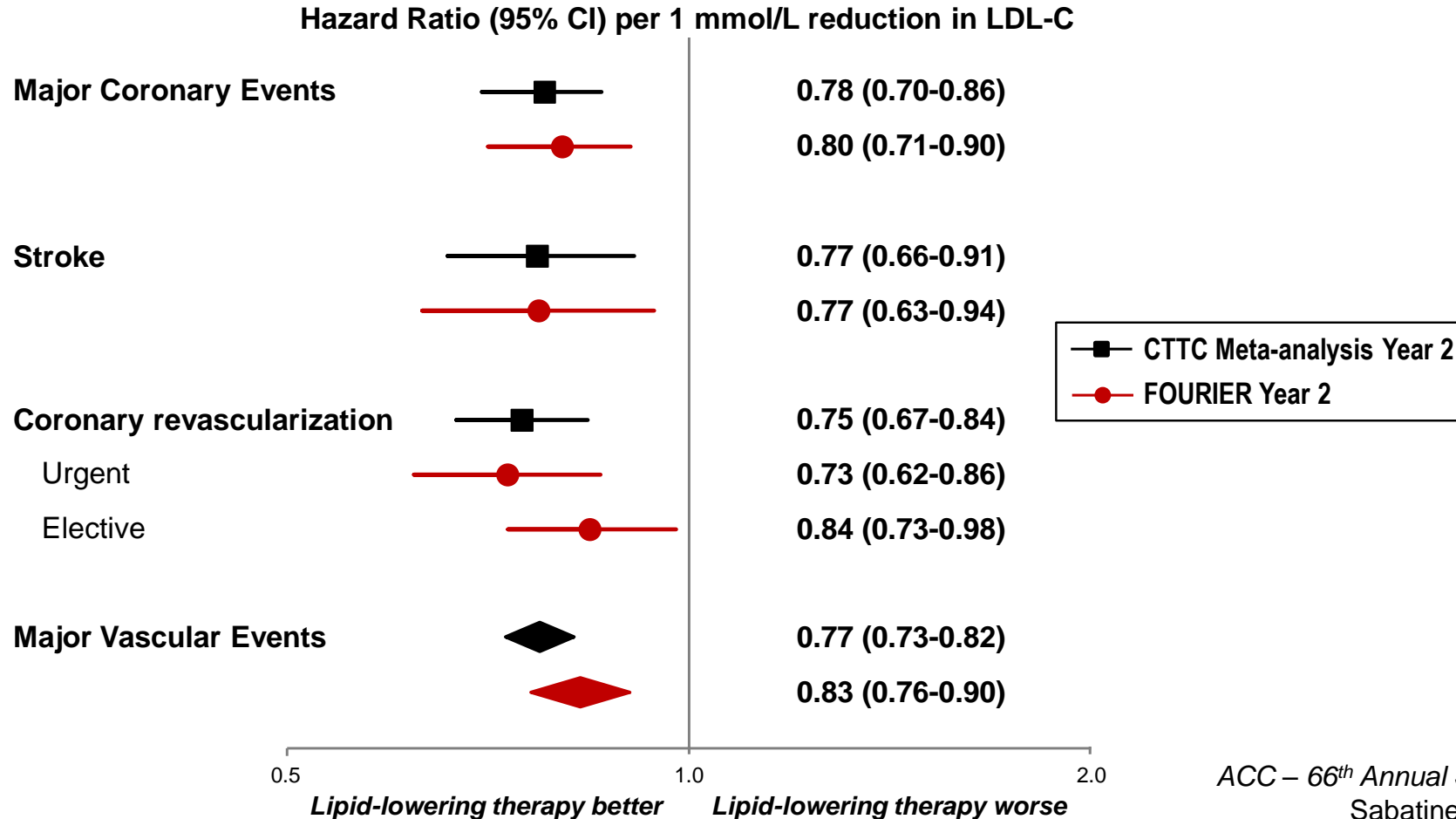


An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

ACC – 66th Annual Scientific Sessions LBCTs 2017
Sabatine, et al. NEJM 2017; DOI: 10.1056/NEJMoa1615664

FOURIER

Comparison to Cholesterol Treatment Trialists Collaboration



ACC – 66th Annual Scientific Sessions Late-Breaking Clinical Trial 2017
Sabatine, et al. NEJM 2017; DOI: 10.1056/NEJMoa1615664
CTTC data from lancet 2010;376:1670-81

FOURIER

Summary for Evolocumab

○ ↓ LDL-C by 59%

- Consistent throughout duration of trial
- Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)

○ ↓ CV outcomes in patients already on statin therapy

- 15% ↓ broad primary endpoint; 20% ↓ CV death, MI, or stroke
- Consistent benefit, incl. in those on high-intensity statin, low LDL-C
- 25% reduction in CV death, MI, or stroke after 1st year
- Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C

○ Safe and well-tolerated

- Similar rates of AEs, including DM & neurocognitive events w/ evolocumab and placebo
- Rates of evolocumab discontinuation low and no greater than placebo
- No neutralizing antibodies developed

○ Conclusions

- In patients with known cardiovascular disease:
- PCSK9 inhibition with evolocumab significantly & safely ↓ major CV events when added to statin therapy
- Benefit was achieved with lowering LDL-C below current targets

ACC – 66th Annual Scientific Sessions LBCTs 2017
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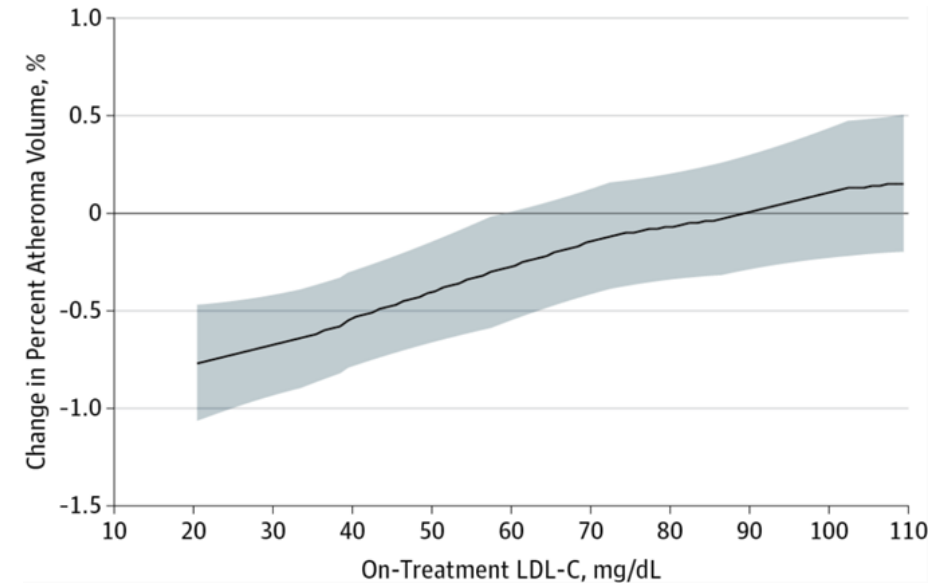
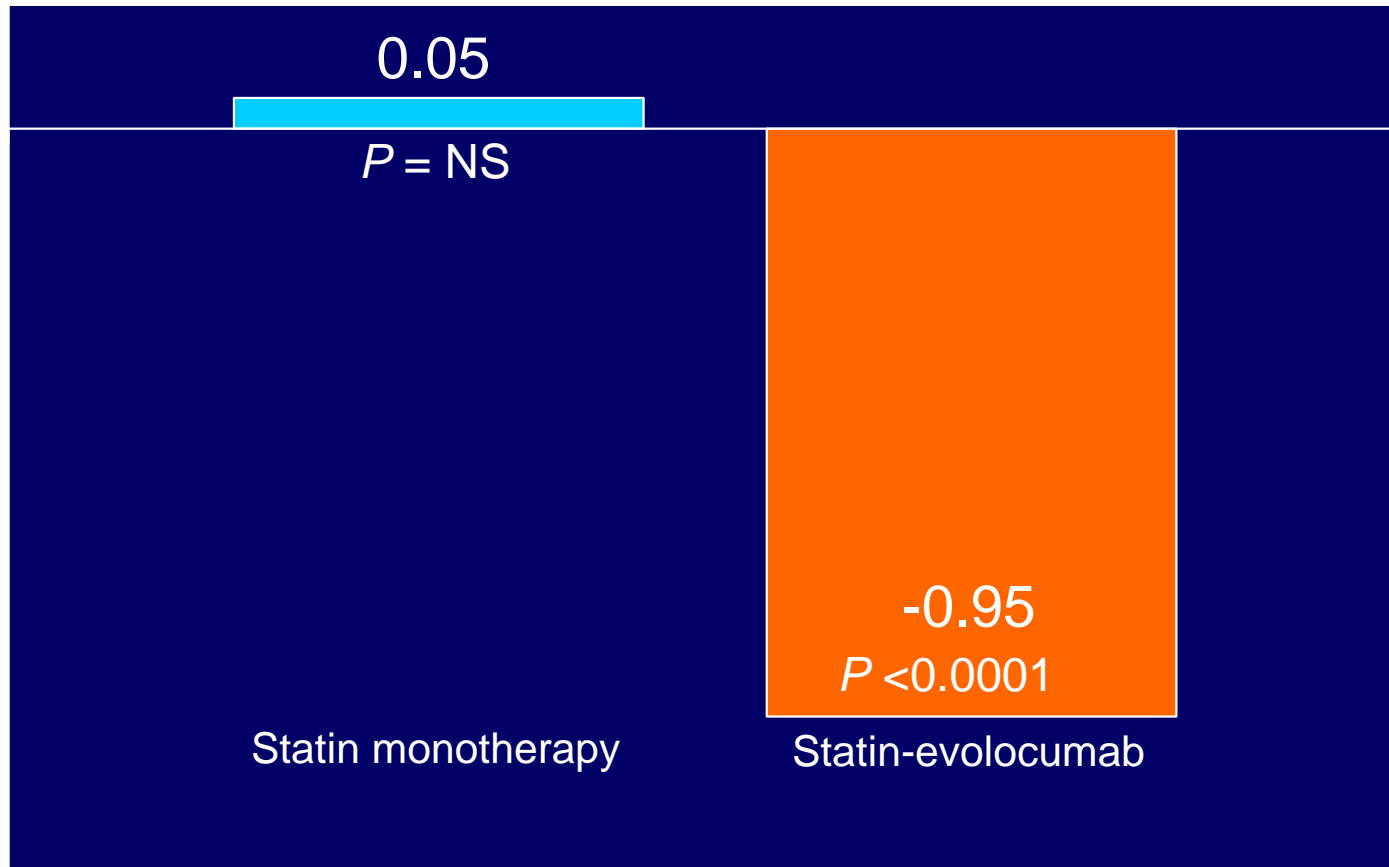
Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients

GLAGOV: Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound

Objective: The GLAGOV trial was designed to assess whether PCSK9 inhibition with evolocumab reduces progression of atherosclerosis as measured by IVUS

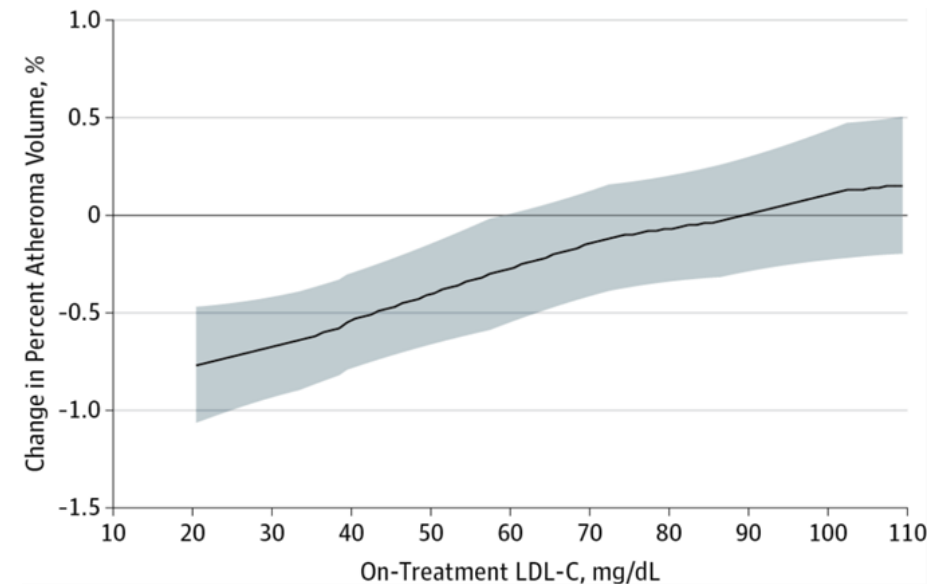
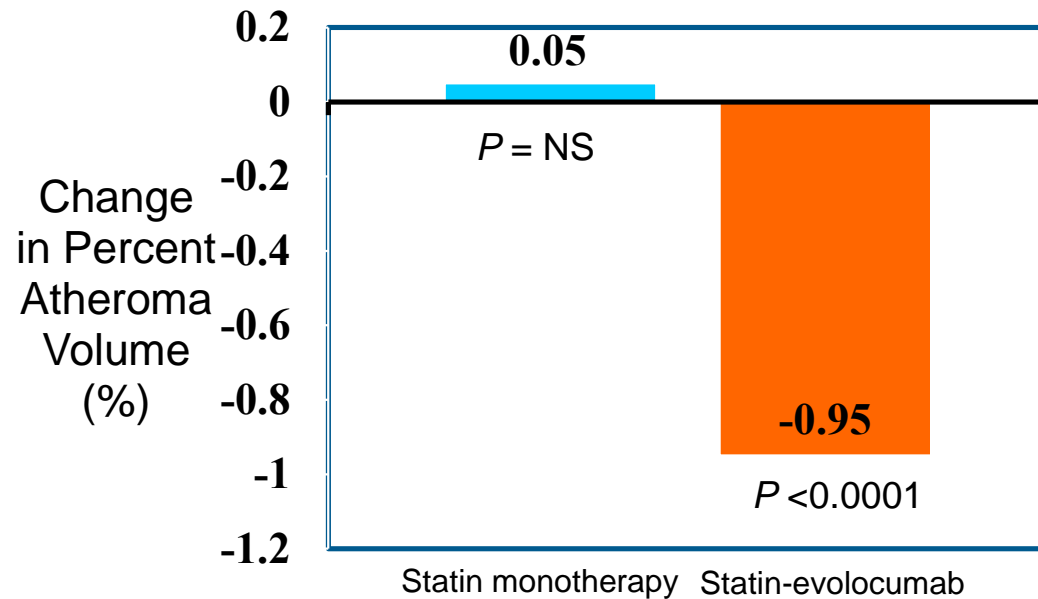
- Prior IVUS trials have shown that statins slow progression or induce regression of CAD in proportion to the magnitude of LDL-C reduction
- No other LDL-lowering therapy has shown regression in an IVUS trial
- The lowest LDL-C achieved in prior trials was approximately 60 mg/dL. Effects of lower levels remain unknown.
- PCSK9 inhibitors incrementally lower LDL-C when added to statins, allowing achievement of very low LDL-C levels, however, no data exist describing effects on progression

GLAGOV Primary Endpoint: Percent Atheroma Volume



Post Hoc Relationship Between LDL-C Level and Change in % Atheroma Volume

GLAGOV Primary Endpoint: Percent Atheroma Volume



Post Hoc Relationship Between LDL-C Level and Change in % Atheroma Volume

EBBINGHAUS

A Cognitive Study of Patients Enrolled in the FOURIER Trial

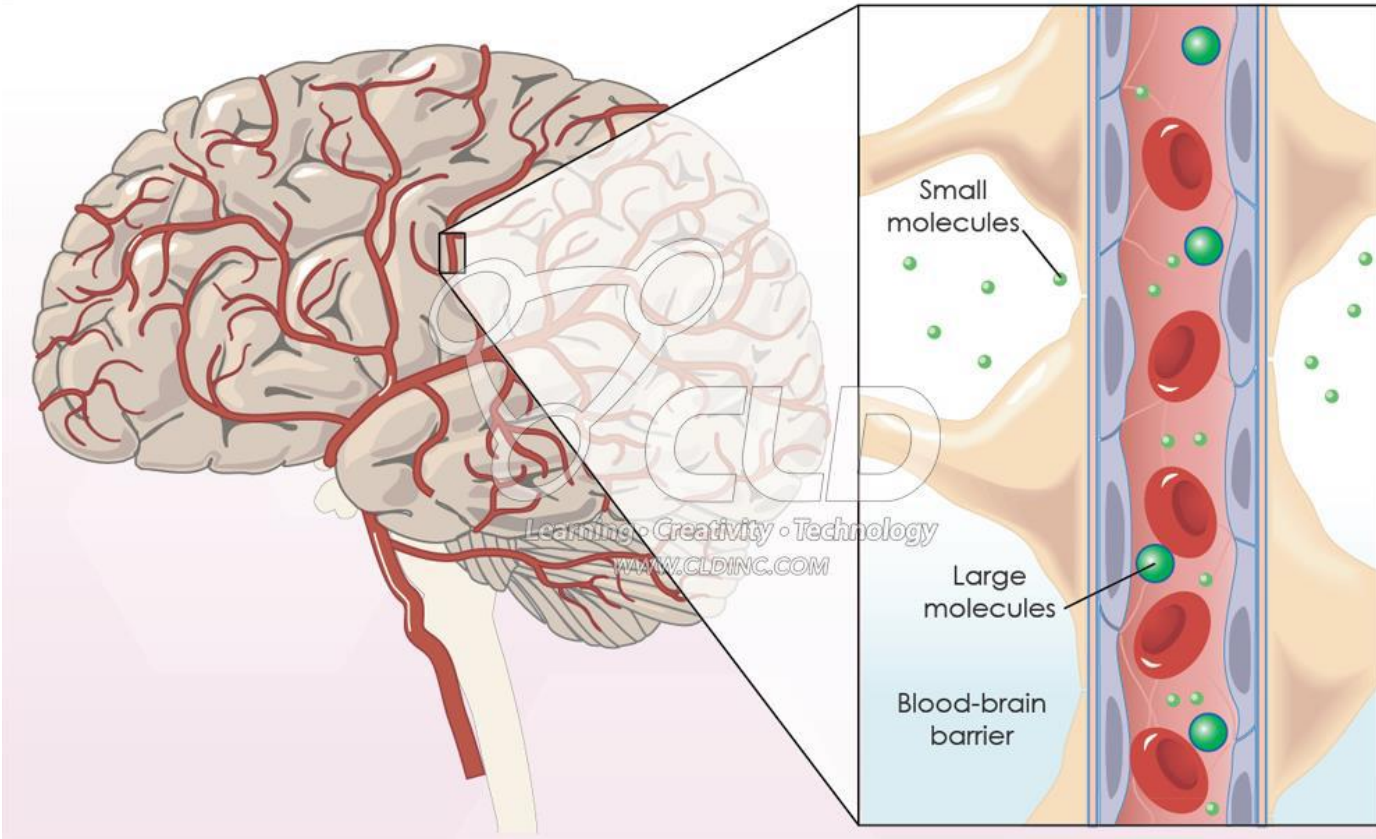
- Case series and 2 small, 6-month RCTs with statins raised concern regarding cognitive deficits
- In 2012 FDA added risk of adverse cognitive effects to label of all statins
- However analyses from large scale RCTs do not support these findings and 2014 Statin Cognitive Safety Task Force* concluded that statins are not associated with cognitive side effects
- In FOURIER parent trial neurocognitive events did not differ between evolocumab 1.6% and placebo 1.5%
 - Randomized 1974 patients to EBBINGHAUS sub-study

Giugliano RP ACC March 18, 2017; <http://www.ajmc.com/conferences/acc-2017/dr-robert-p-giugliano-on-the-results-of-the-ebbinghaus-evolocumab-cognitive-study#sthash.x7y5ECCL.dpuf>,

*The National Lipid Association

Rojas-Fernandez CH, et al. *J Clin.Lipidol.* 2014;8(3 Suppl):S5-16.

Cognition and PCSK9 Inhibitors



- Brain synthesizes cholesterol locally
- mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier
- Meta-analysis* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]
 - Event rates low (<1%)
 - Unadjudicated, diverse AE terms reported
 - Not correlated with LDL-C achieved

Giugliano RP ACC March 18, 2017; <http://www.ajmc.com/conferences/acc-2017/dr-robert-p-giugliano-on-the-results-of-the-ebbinghaus-evolocumab-cognitive-study#sthash.x7y5ECCl.dpuf>,

*Lipinski MJ, et al. Eur Heart J. 2016;37(6):536-545

EBBINGHAUS

A Cognitive Study of Patients Enrolled in the FOURIER Trial

- In patients with known cardiovascular disease on background statin followed for 20 months:
 - No differences between evolocumab vs placebo, assessed at baseline and end of study
 - A battery of cognitive tests
 - Patient-reported everyday cognition
 - Adverse cognitive events reported by MD
- No evidence of differences in cognitive tests by achieved nadir LDL-cholesterol, even <25 mg/dL
 - Compared results of those with LDL-C <25, 25 to 40, >40 mg/dL

Giugliano RP ACC March 18, 2017; <http://www.ajmc.com/conferences/acc-2017/dr-robert-p-giugliano-on-the-results-of-the-ebbinghaus-evolocumab-cognitive-study#sthash.x7y5ECCl.dpuf>,

ORION-1: Primary efficacy & safety outcomes

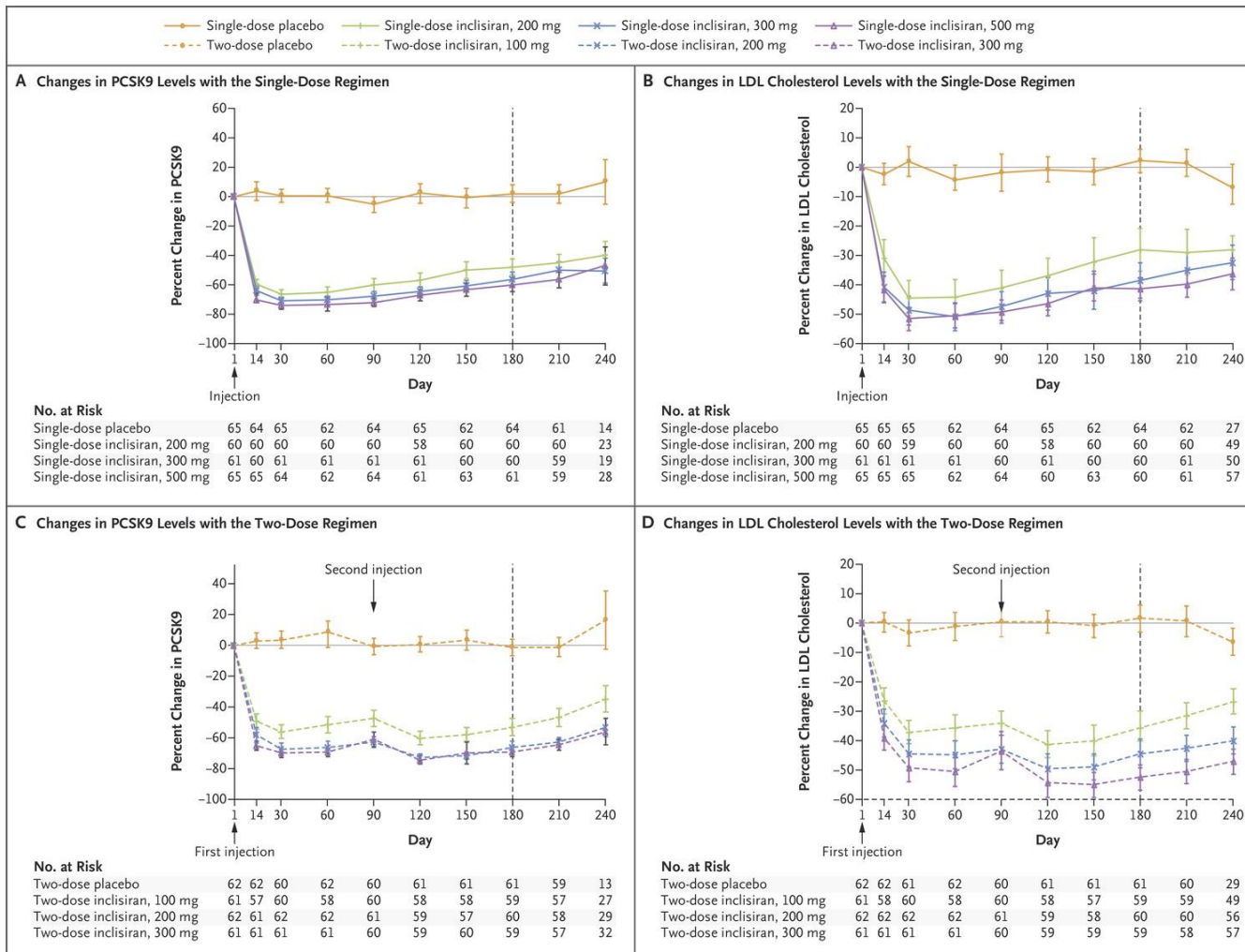
LDL-C reduction from 6 to 9 months following single or second injections of inclisiran, a novel siRNA compound

- Harnessing RNAi offers an alternative treatment for PCSK9 and LDL-C
- Inclisiran, a synthetic siRNA molecule, inhibits PCSK9 synthesis in the liver
- In Phase I, 300 mg inclisiran lowered LDL-C 50-60% for 84 days (n=69)
- Objective of ORION-1: Evaluate optimal dosing regimens in patients with elevated LDL-C and high CV risk

ACC – 66th Annual Scientific Sessions, March, 2017.
Ray, et al. NEJM. March 17, 2017 DOI: 10.1056/NEJMoa1615758
Wittrup A & Lieberman J Nature Rev Gen 2015;16: 543-52
Fitzgerald K et al. Lancet 2013;9911:60-8
Fitzgerald K et al. N Engl J Med 2017;376 (1):41-51

ORION-1: Primary efficacy & safety outcomes

LDL-C reduction from 6 to 9 months following single or second injections of inclisiran, a novel siRNA compound



- Greatest reduction (52.6%) in LDL-C levels observed with the two-dose 300-mg regimen of inclisiran
- In the two-dose 300-mg inclisiran group, every patient had a reduction in LDL-C, with a mean reduction of 64.2 mg/dL at 180 days
- At day 240, PCSK9 levels were 56.1% lower and LDL-C levels 47.2% lower than at baseline, with a mean absolute reduction in LDL cholesterol level of 58.9 mg/dL
- These data suggest that inhibiting the translation of PCSK9 mRNA in the liver represents an alternative to targeting circulating PCSK9

ACC – 66th Annual Scientific Sessions, March, 2017.

Ray, et al. NEJM. March 17, 2017 DOI: 10.1056/NEJMoa1615758

ORION-1: Primary efficacy & safety outcomes

LDL-C reduction from 6 to 9 months following single or second injections of inclisiran, a novel siRNA compound

- Optimal dosage 300 mg given twice as starting regimen then Q6 monthly
 - All patients responded with significant LDL-C lowering
 - At 6 months, mean LDL-C decrease of 52.6% (64 mg/dL), and up to 81% (122 mg/dL)
- No safety concerns: Adverse events similar to placebo
 - No LFT elevations related to drug
 - No difference in incidence of myalgias or CPK enzyme elevation
 - No deaths related to drug administration
 - No thrombocytopenia, neuropathy, or immunogenicity (no ADAs)
 - No pro-inflammatory symptoms or elevated markers
- ORION-4 will study CV outcomes with inclisiran in high risk primary and
- secondary prevention patients with average LDL-C ~130 mg/dL

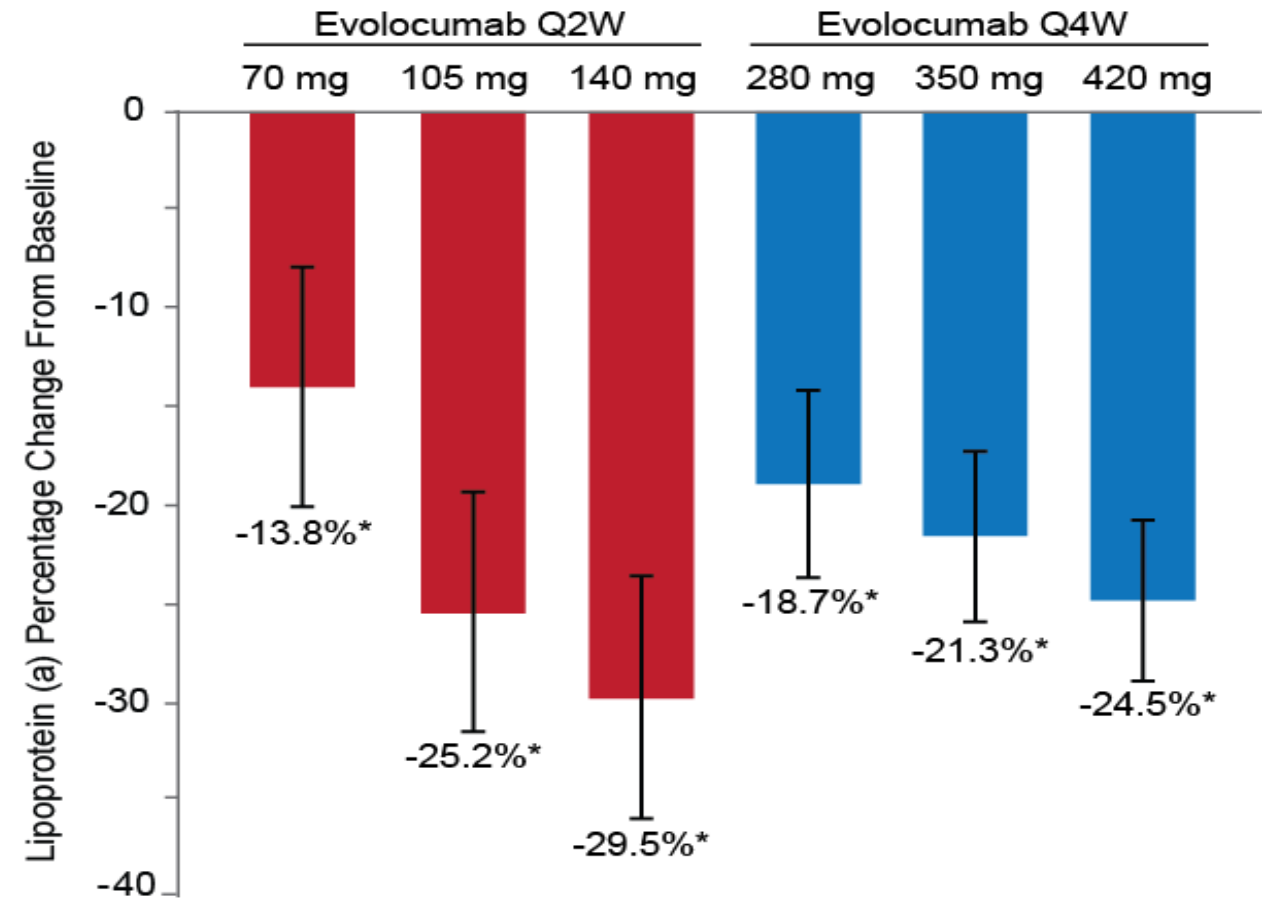
ACC – 66th Annual Scientific Sessions, March, 2017.

Ray, et al. NEJM. March 17, 2017 DOI: 10.1056/NEJMoa1615758

Reduction in Lipoprotein(a) With Evolocumab

Pooled Analysis of More Than 1,300 Patients in 4 Phase II Trials

- Lp(a) is recognized as an independent risk factor for MI, stroke, and PAD and is believed to increase the risk for CVD via its atherogenic LDL moiety and its prothrombotic, proinflammatory apolipoprotein(a) moiety
- Levels of Lp(a) >125 nmol/l (approximately 50 mg/dl), the 80th percentile for most populations, have shown a consistent and independent positive association with CVD risk in epidemiological studies
- A large Mendelian randomization study demonstrated that a genetically determined doubling of Lp(a) was associated with a 22% increase in CVD risk, suggesting a causal link
- elevated Lp(a) is an independent CVD risk factor in patients with FH



Error bars represent standard error.

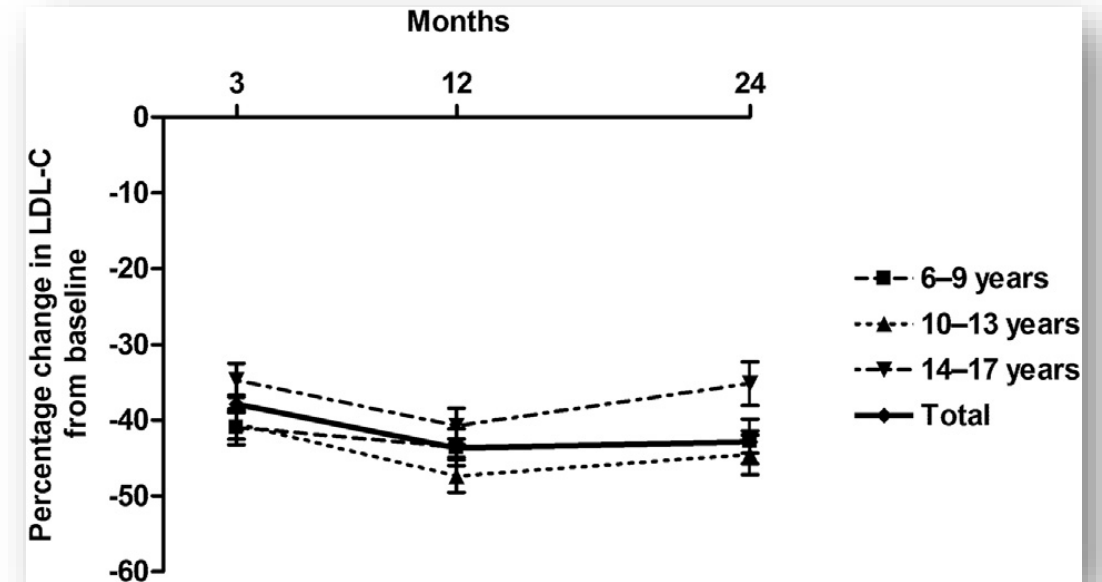
* P < 0.001

Raal et al JACC 2014;doi:10.1016/j.jacc.2014.01.006

Pediatric Treatment Considerations

CHARON: hyperCholesterolaemia in cHildren and Adolescents taking Rosuvastatin OpeN label

- Investigated the efficacy, PK, tolerability, and safety of rosuvastatin over **2 yrs** in heFH patients ages 6 to 17
- 198 randomized with LDL-C >190 mg/dL or >158 mg/dL with other CV risk factors received rosuvastatin 5 mg daily
- Children aged 6 to 9 yrs were statin naive
- Mean age of patients at baseline was 11.6 yrs, 44% were boys, mean LDL-C level was 236 mg/dL, 77% had a family history of premature CVD in 1st- or 2nd-degree relatives
- Rosuvastatin 5 mg was titrated at 3 month intervals to 10 mg (6- to 9-year olds) or 20 mg (10- to 17-year olds) to achieve an LDL-C goal of <110 mg/dL
- Primary efficacy variable was % change from baseline in LDL-C after 3, 12, and 24 months with rosuvastatin 5, 10, or 20 mg



- % change from baseline in LDL-C at 3, 12, and 24 months ranged from 35 to 45% p <0.001
- 58% overall achieved an LDL-C goal <130 mg/dL and 38% reached an LDL-C goal of <110 mg/dL
- Primary safety outcomes were growth and sexual maturation at baseline, 12, and 24 months

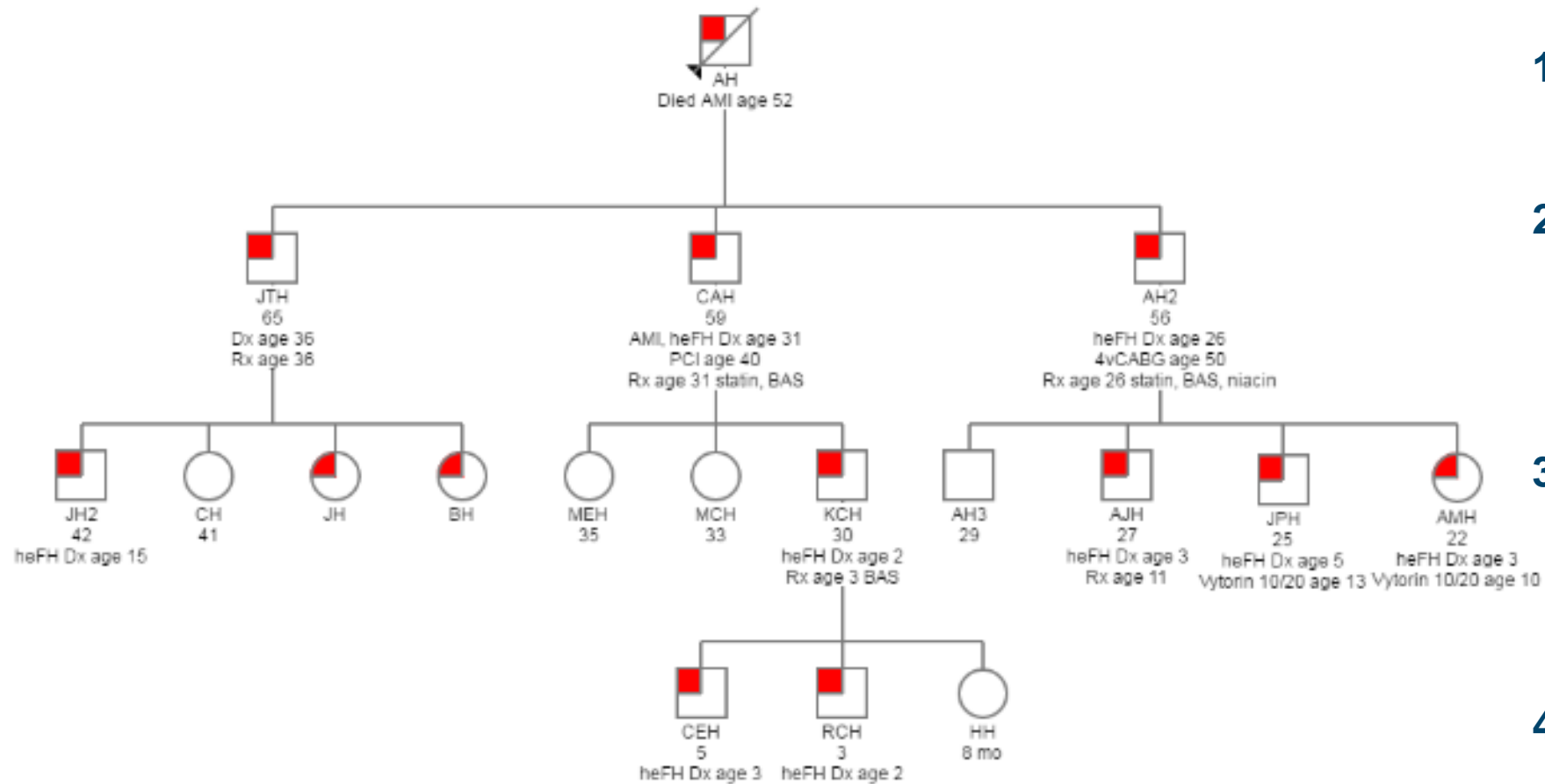
FH: A Family Disease

Pediatric trials currently underway with PCSK9 inhibitors

- HAUSER: Evolocumab for LDL-C Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects From 10 to 17 with heFH or hoFH
 - *(ClinicalTrials.gov Identifier: NCT02624869)*
- To evaluate the effect of alirocumab on low-density lipoprotein cholesterol (LDL-C) levels after 8 weeks of treatment in heFH patients age of 8 to 17 years, with LDL-C ≥ 130 mg/dL on optimal stable daily dose of statin therapy +/- other LMTs or a stable dose of non-statin LMTs in case of intolerance to statins
 - *(ClinicalTrials.gov Identifier: NCT02890992)*

FH: A Family Disease

Case Study: 4 generations



1st Generation

- Early CV death at age 52
- Never on LMT

2nd Generation

- LMT started ages 26 to 36
- Current ages of those affected 56 to 65
- Early CVD in 2/3

3rd Generation

- LMT started ages 3 to 13
- Current ages of those affected 22 to 42
- No CVD to date

4th Generation

- heFH Dx ages 2 to 3



Thank you

MEDPACE