Familial hypercholesterolemia, PCSK9 inhibition, and other lipid biomarkers of cardiovascular risk

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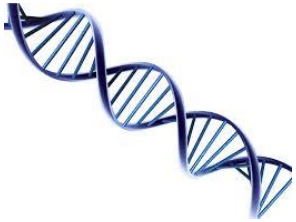
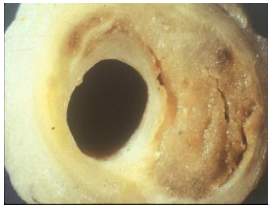
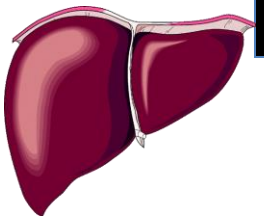
AMERICAN COLLEGE of CARDIOLOGY

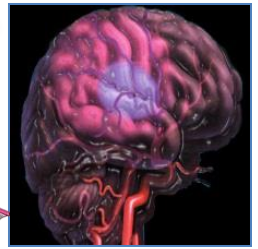
Genomic and Precision Medicine in Prevention



Preventive and therapeutic interventions





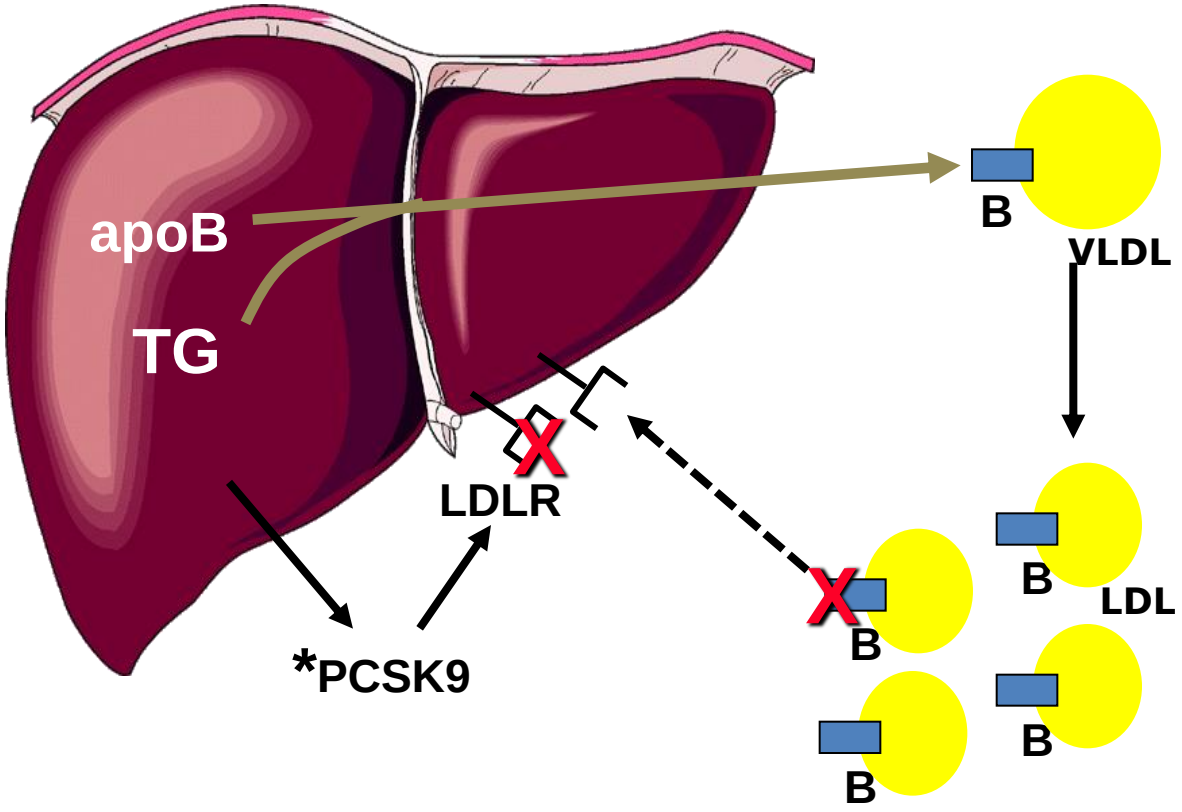


Linking genomic and phenomic data at scale

Genotyping and sequencing

Electronic health records
Deep phenotyping

Familial hypercholesterolemia: mutations in genes that impair LDL receptor function



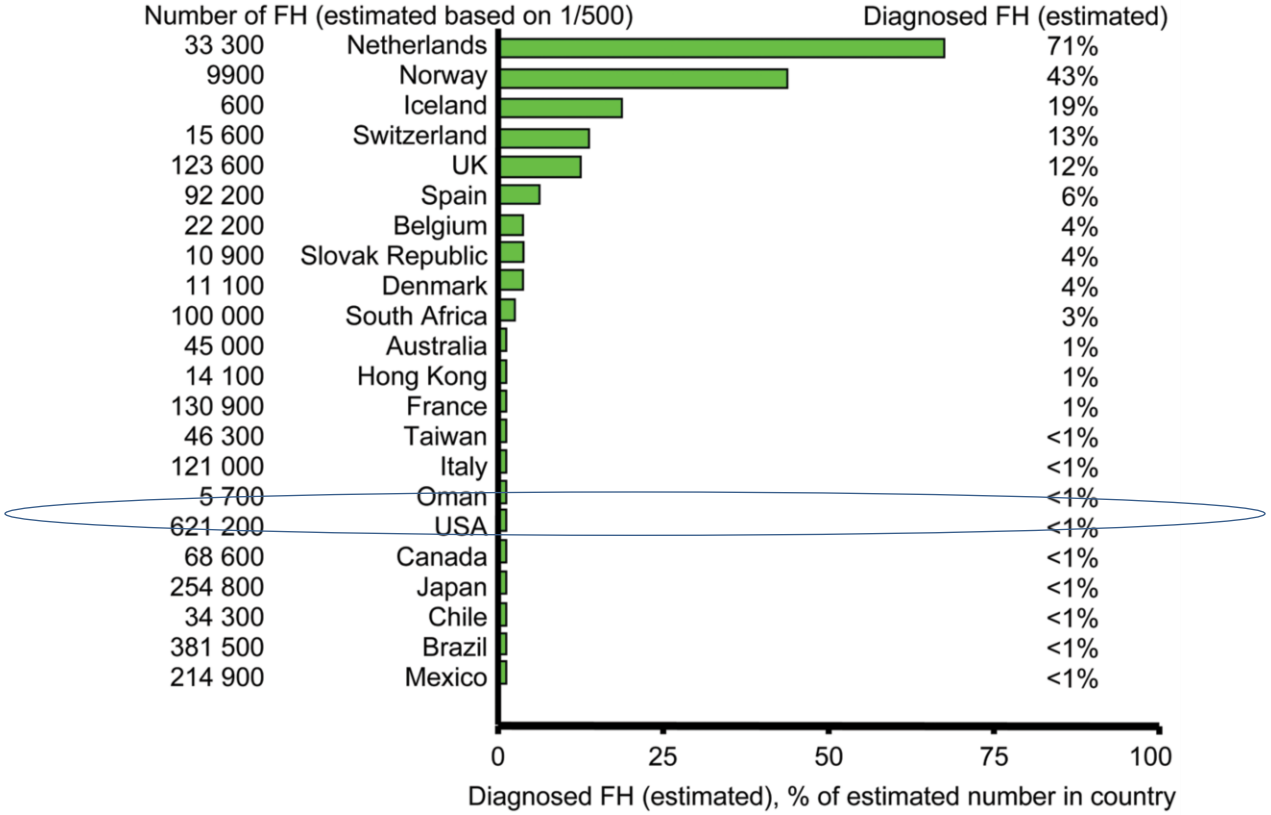
FH Genes

LDLR

APOB

*PCSK9

FH is grossly underdiagnosed in the US and most of the world



Eur Heart J. 2013;34(45):3478-3490. doi:10.1093/eurheartj/eht273

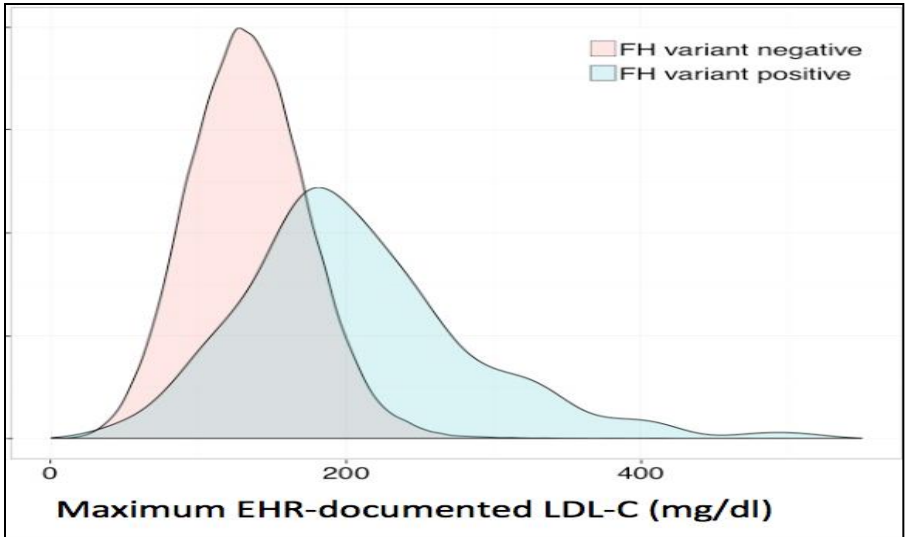
A ‘Genome-first’ approach to finding undiagnosed patients with Familial Hypercholesterolemia

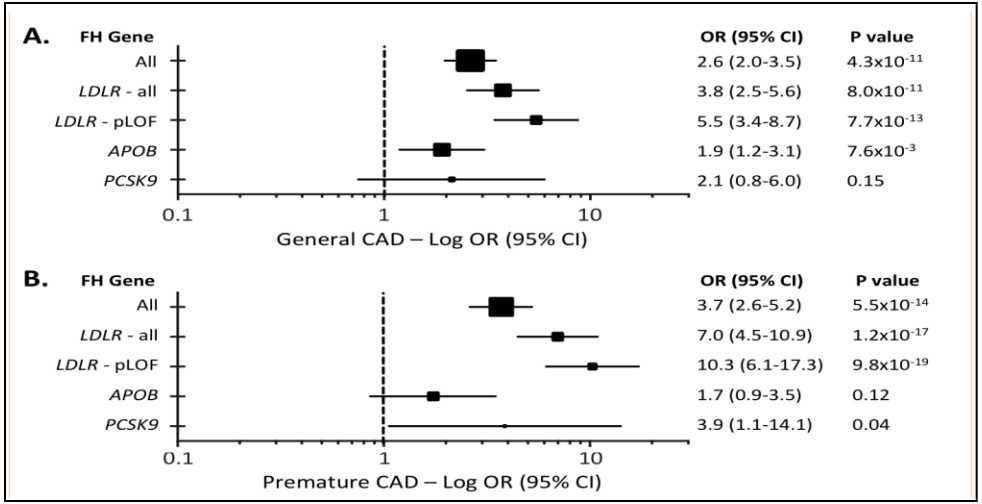
RESEARCH ARTICLE

HUMAN GENETICS

Genetic identification of familial hypercholesterolemia within a single U.S. health care system

FH prevalence:
~ 1 in 250





FH is a CDC-designated ‘Tier 1’ genetic health condition

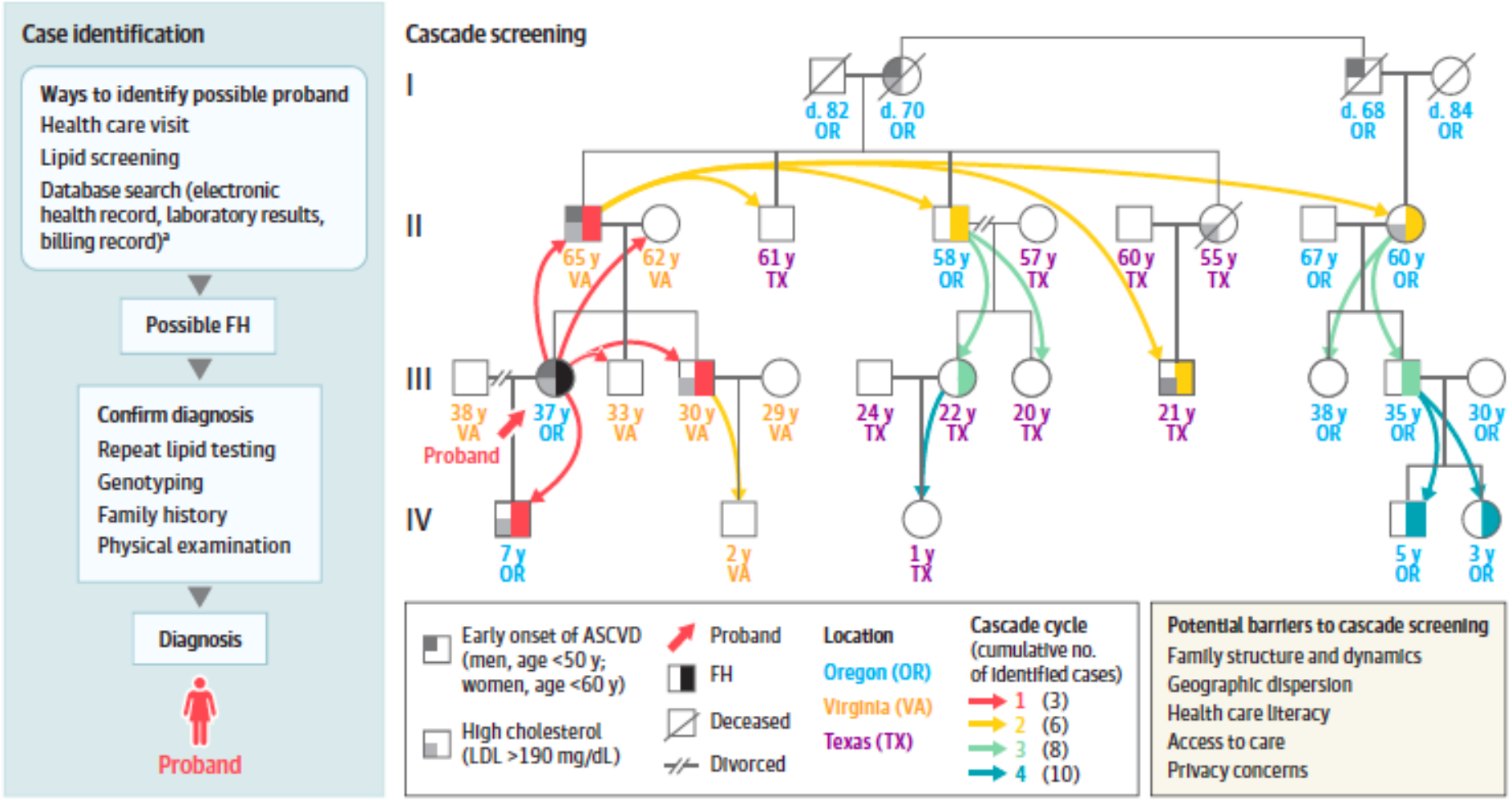
CDC has designated three ‘Tier 1’ genetic health conditions for application of genomic medicine to public health:

1. Hereditary Breast and Ovarian Cancer (HBOC) Syndrome
2. Lynch Syndrome (colon cancer and other cancers)
3. Familial Hypercholesterolemia (FH)

- ➔ Significant public health concerns
- ➔ Effective preventive therapies
- ➔ Autosomal dominant conditions

Family screening for FH saves lives

Figure. Process From Case Identification to Cascade Screening



Addressing barriers to care in FH

- Increase awareness of prevalence and severity
- New ICD10 code **(E78.01)**
- Promote systematic approach to cascade screening and genetic testing
- First FH disease registry
- Find all the undiagnosed cases

JAMA Insights

Cascade Screening for Familial Hypercholesterolemia and the Use of Genetic Testing

Joshua W. Knowles, MD, PhD; Daniel J. Rader, MD; Muin J. Khoury, MD, PhD

CASCADE FH REGISTRY

FH Foundation

Reducing the burden of disease and death from familial hypercholesterolemia: A call to action

Joshua W. Knowles, MD, PhD,[a,b] Emily C. O'Brien, PhD,[c] Karen Greendale, MA, CGC,[b] Katherine Wilemon, BS,[b] Jacques Genest, MD,[d] Laurence S. Sperling, MD,[e] William A. Neal, MD,[f] Daniel J. Rader, MD,[g] and Muin J. Khoury, MD, PhD[b] *Stanford, South Pasadena, CA; Durham, NC; Montreal, Canada; Atlanta, GA; Morgantown, WV; and Philadelphia, PA*

FIND FH Project

Flag, Identify, Network, Deliver

FH: Call to action

Make the diagnosis: FH Diagnosis app, ICD 10 **E78.01**

Educate the patient: thefhfoundation.org

Consider genetic testing

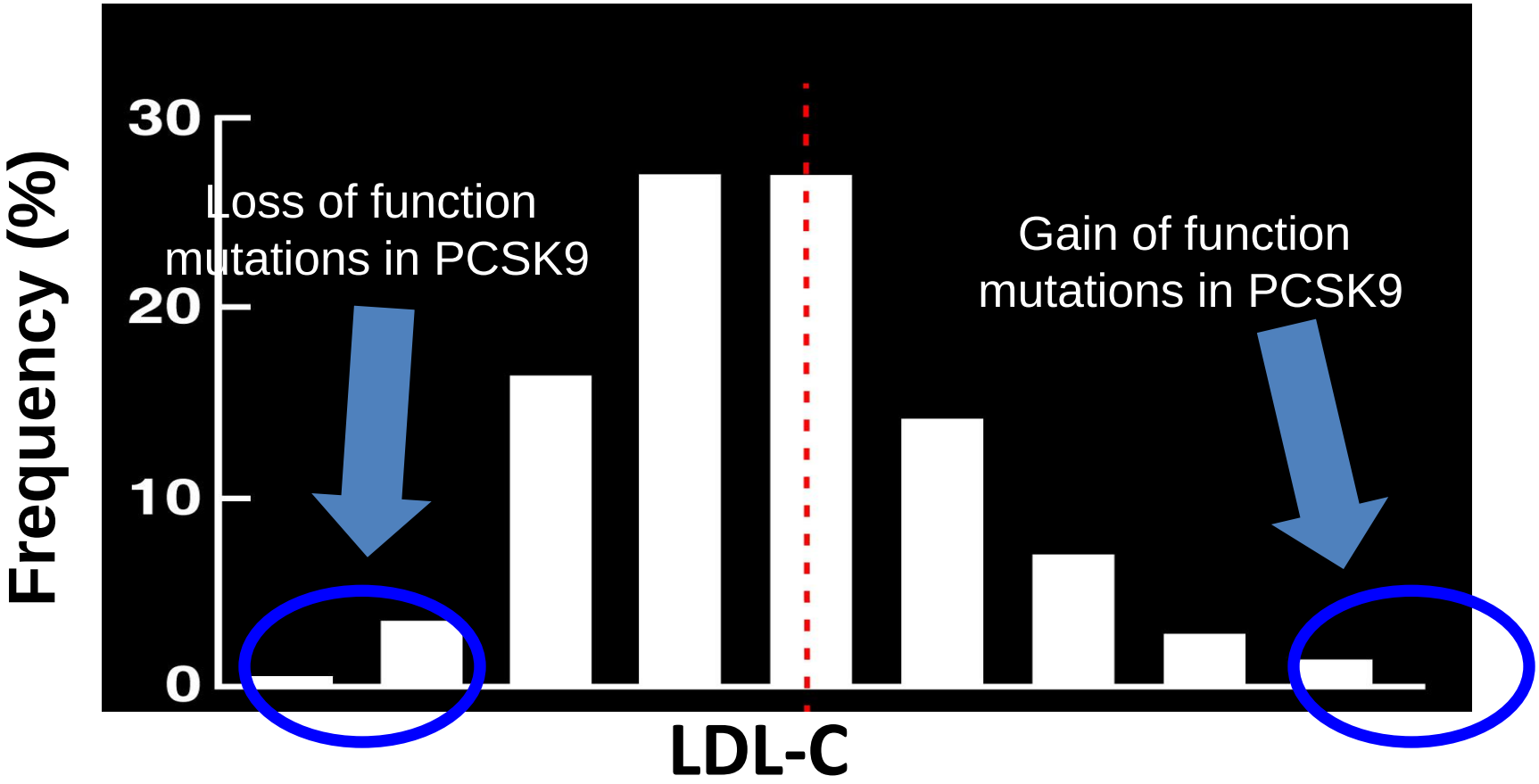
Actively promote family-based cascade screening

Evaluate other risk factors [ie Lp(a)]

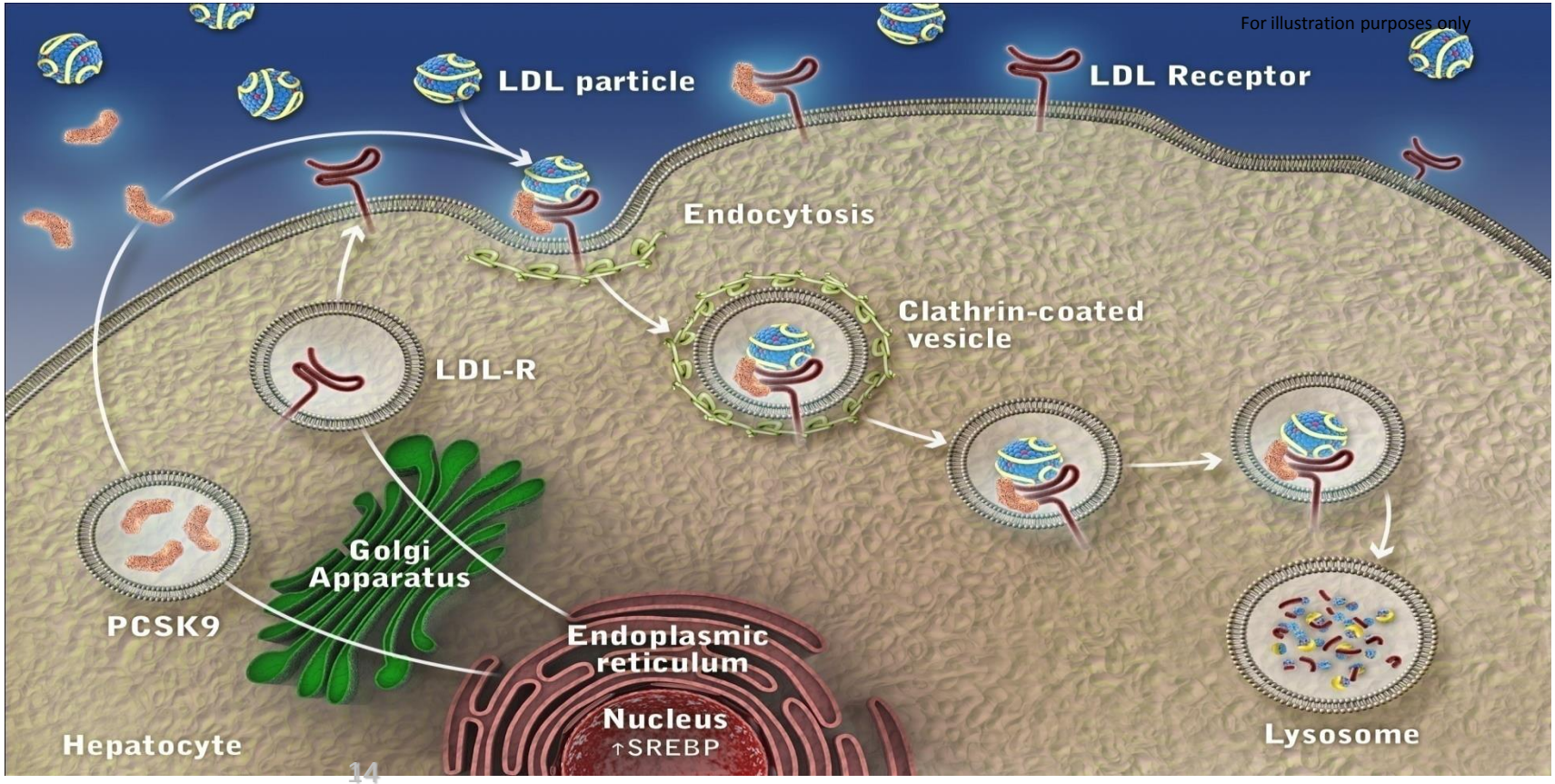
Aggressively treat LDL, including combination therapies

Refer for clinical trials where appropriate

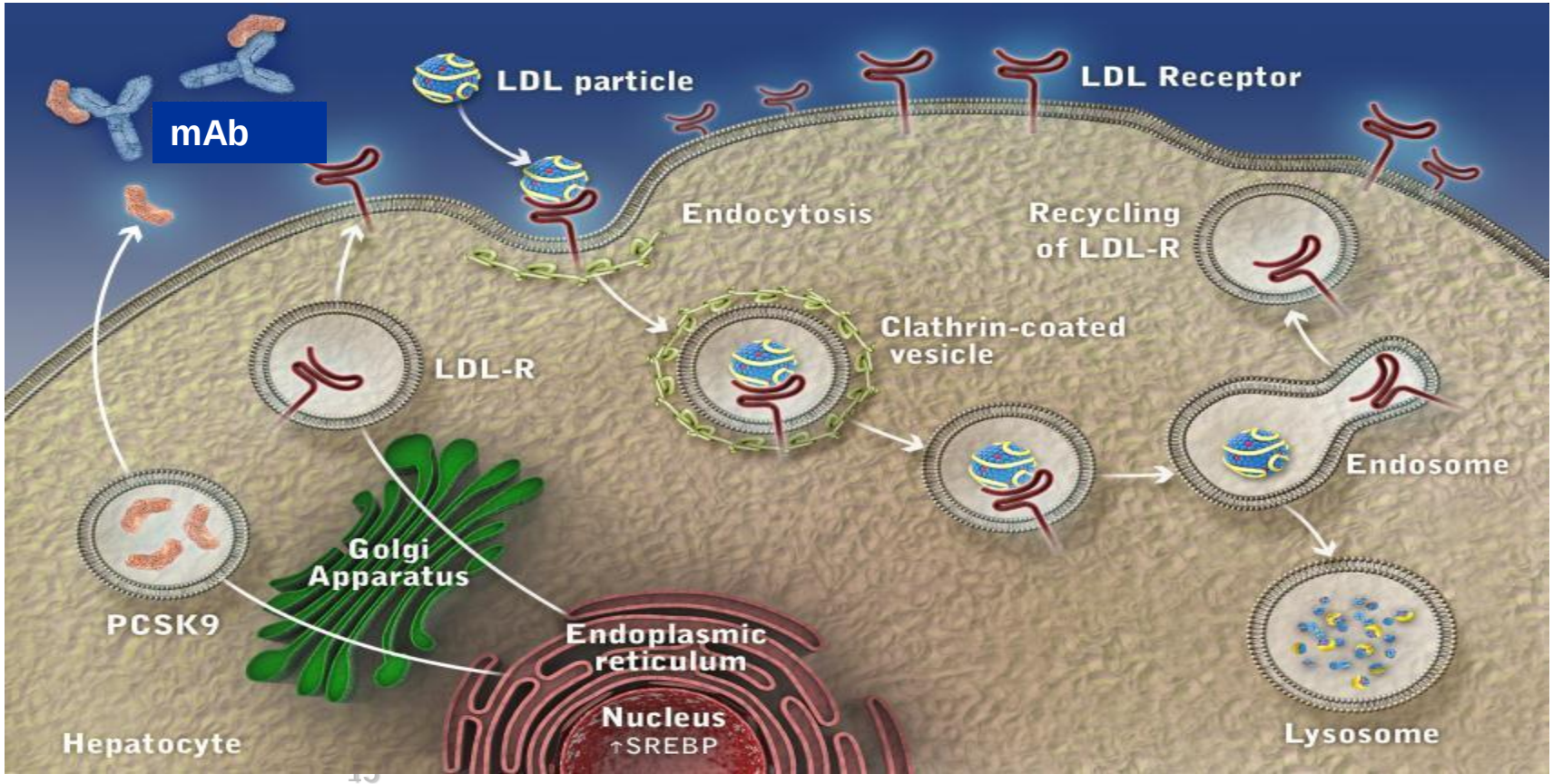
Inherited Syndromes of Extremes of LDL-C: Story of PCSK9



The Role of PCSK9 in the Regulation of LDL Receptor Expression



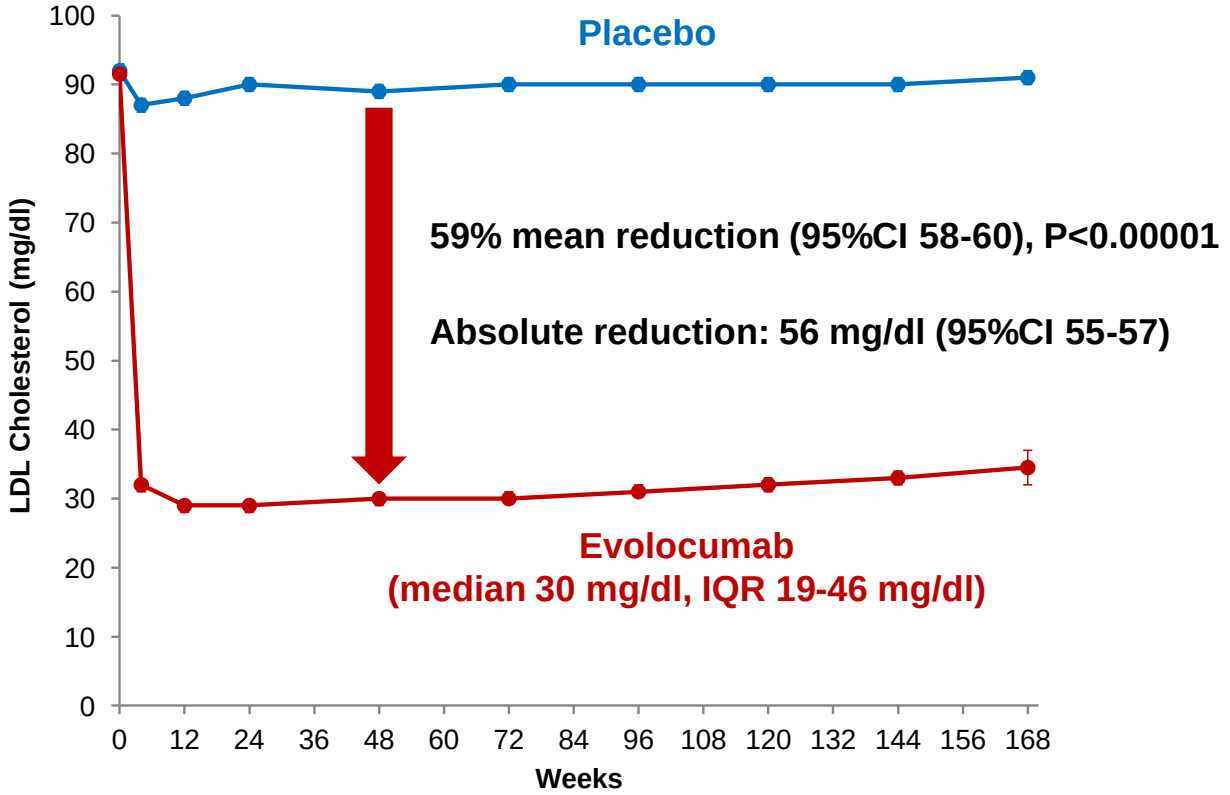
Impact of an PCSK9 mAb on LDL Receptor Expression



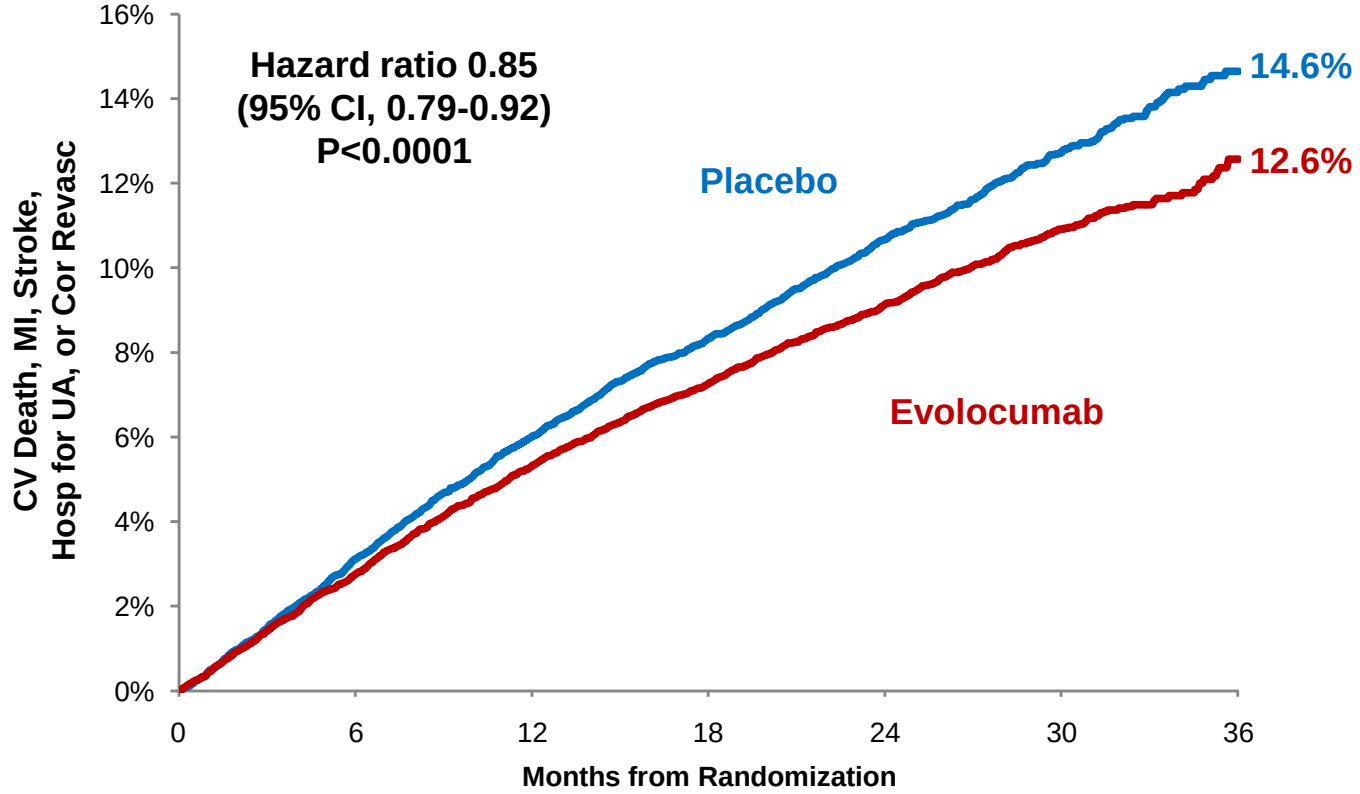
PCSK9 Inhibitors

- Alirocumab and Evolocumab
- SQ injection biweekly or monthly
- Indications:
  - Patients with heterozygous familial hypercholesterolemia on maximally tolerated statin therapy with inadequate plasma LDL levels
  - Patients with a history of CHD with inadequate plasma LDL levels
- Reduce cardiovascular outcomes (FOURIER)

LDL Cholesterol

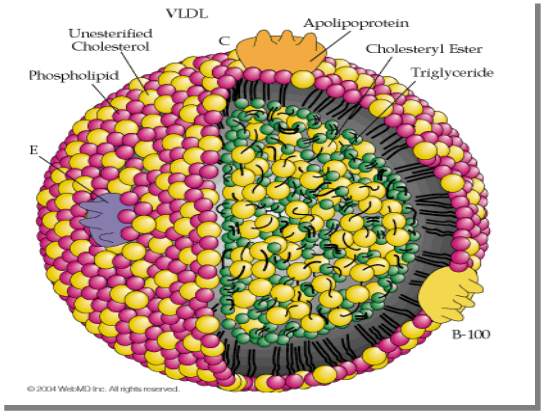


Primary Endpoint



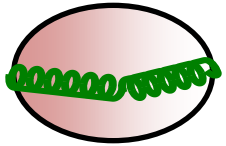
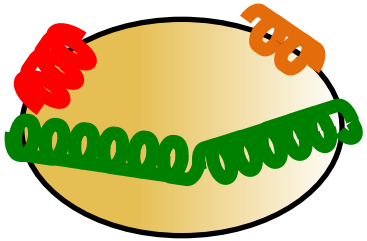
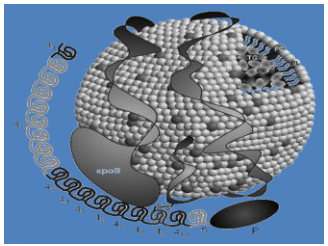
Substantial residual risk of CV events remains even in patients treated to very low levels of LDL-C

Lipoproteins and Coronary Disease

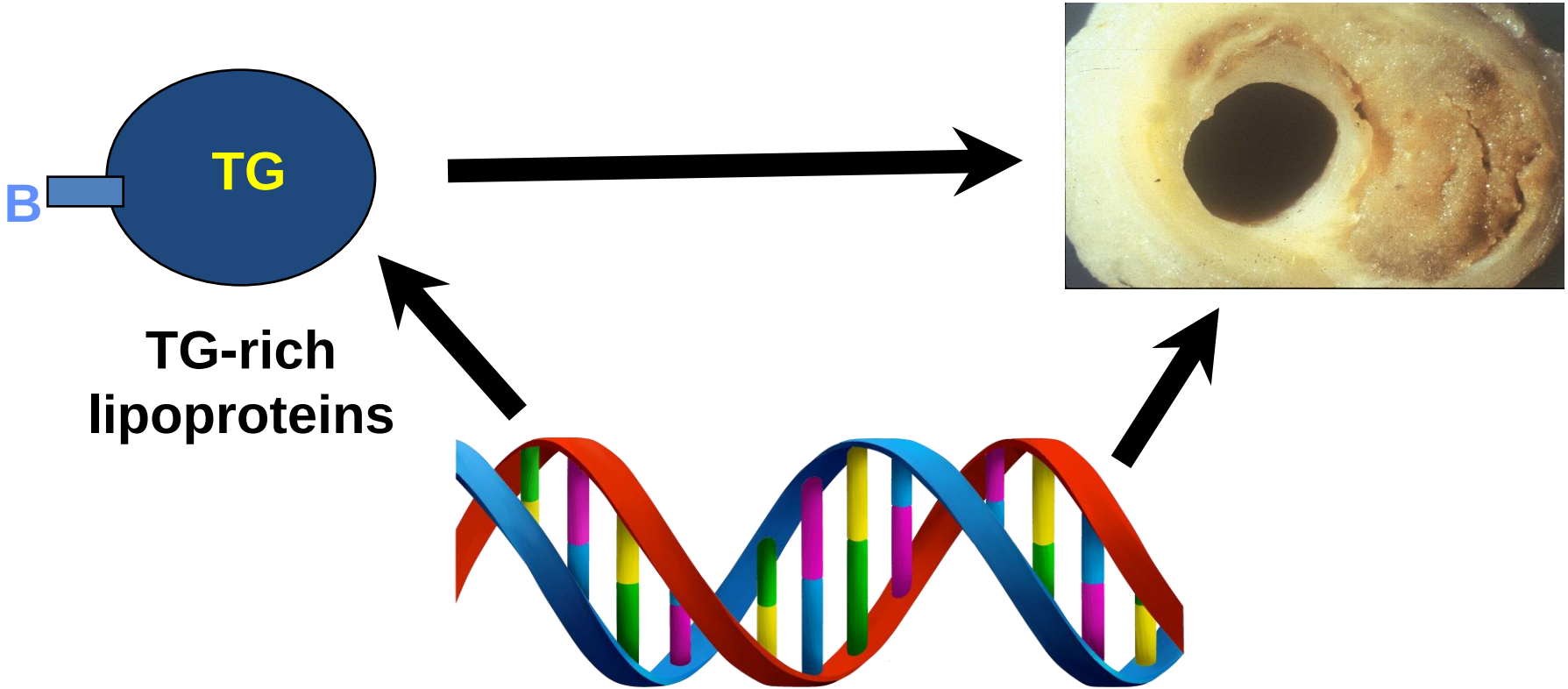


Remaining opportunities for reducing residual risk through lipid modulation

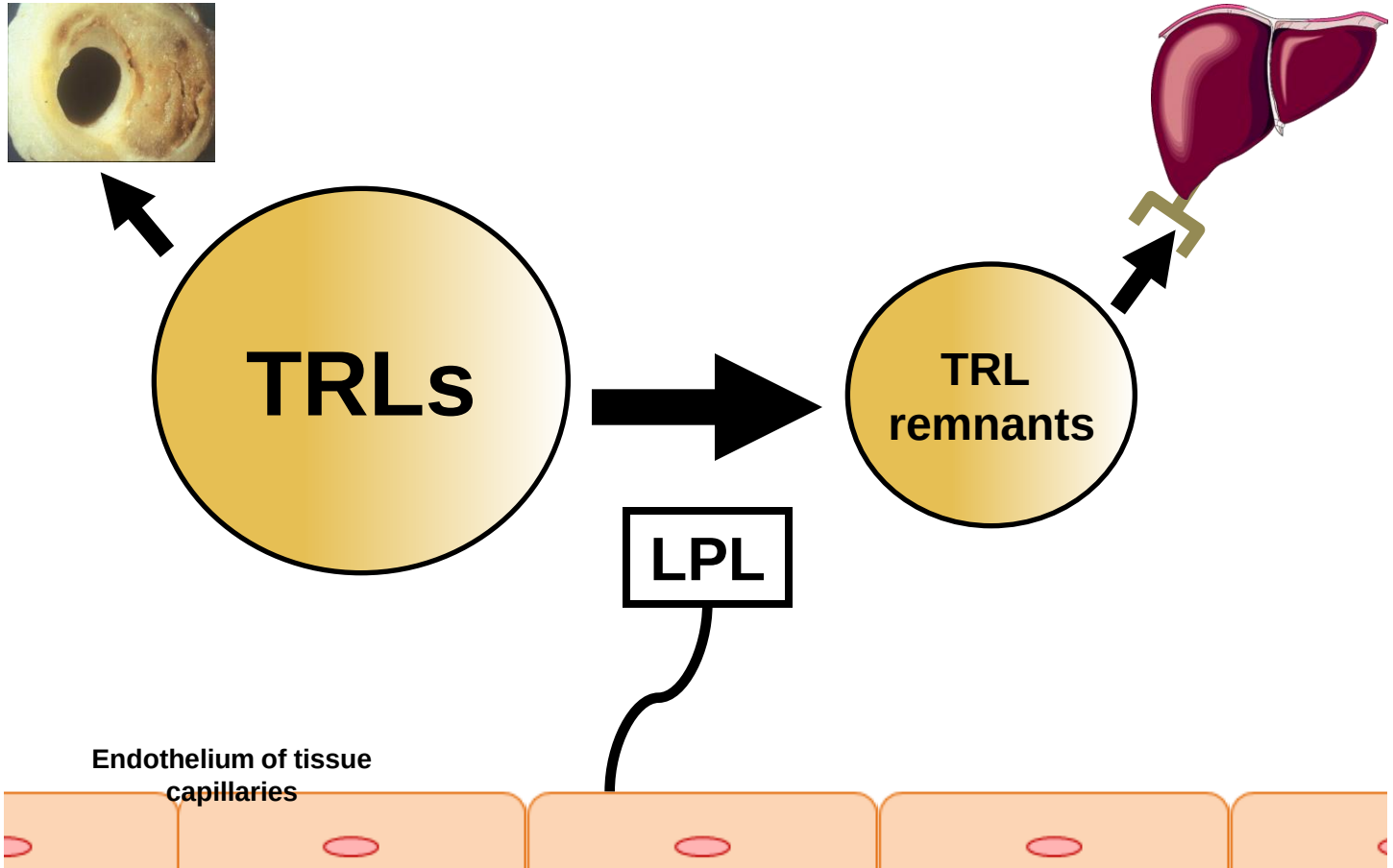
ApoB-lipoproteins are biomarkers of CAD risk

Clinical trait	Association with CAD	Lipoprotein class
LDL cholesterol	↑	
Triglycerides	↑	
Lipoprotein(a)	↑	

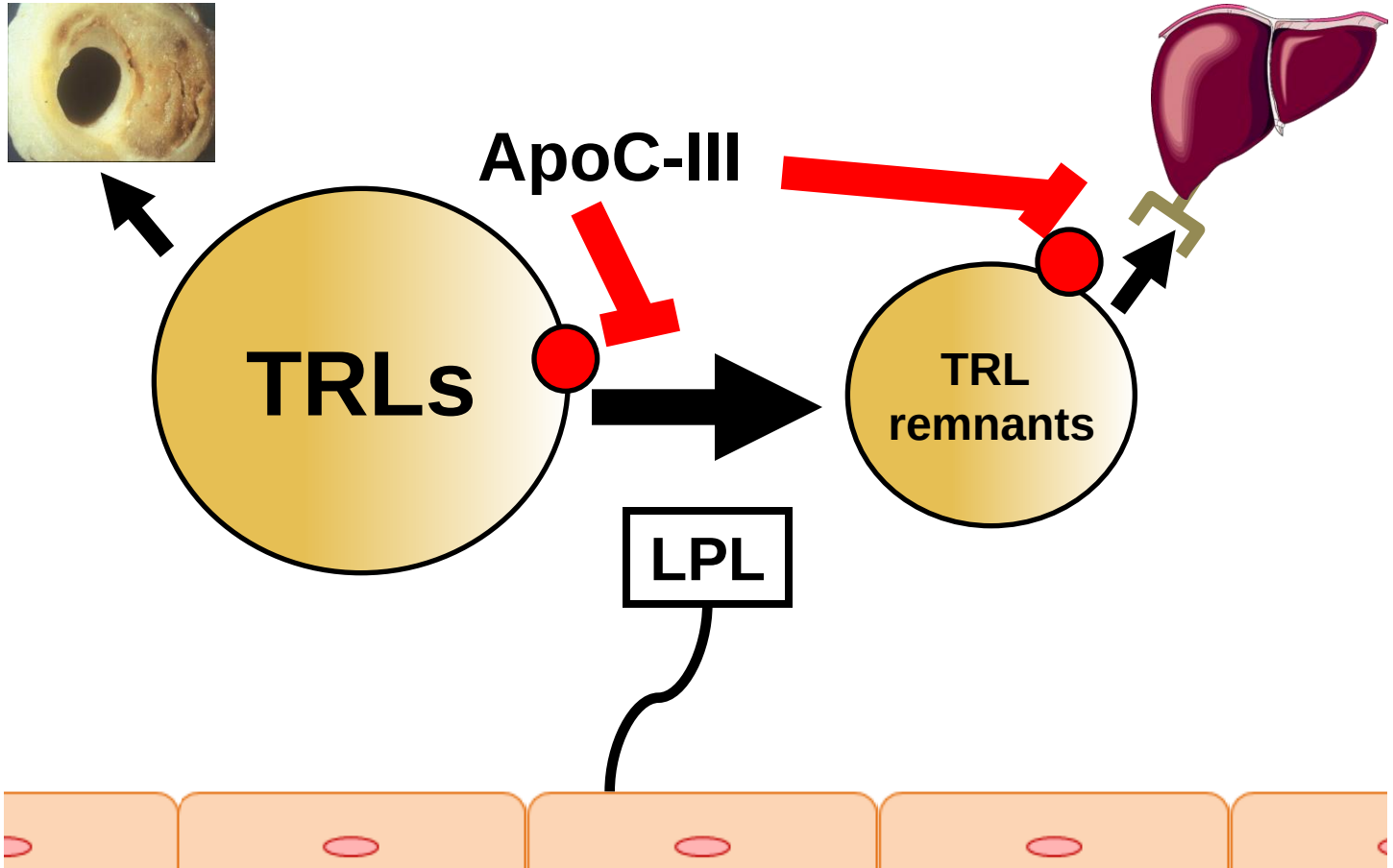
TG-rich lipoproteins are causally related to coronary disease



Lipoprotein lipase is a critical regulator of TG-rich lipoprotein metabolism



ApoC3 inhibits metabolism of TG-rich lipoproteins and is a genetically validated therapeutic target



Volanesorsen (ASO to *APOC3*) reduces apoC-III and TGs

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antisense Inhibition of Apolipoprotein C-III in Patients with Hypertriglyceridemia

Daniel Gaudet, M.D., Ph.D., Veronica J. Alexander, Ph.D., Brenda F. Baker, Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D., Walter Singleton, M.D., Richard S. Geary, Ph.D., Steven G. Hughes, M.B., B.S., Nicholas J. Viney, B.Sc., Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D., Joseph L. Witztum, M.D., John D. Brunzell, M.D.,* and John J.P. Kastelein, M.D., Ph.D.

BRIEF REPORT

Targeting APOC3 in the Familial Chylomicronemia Syndrome

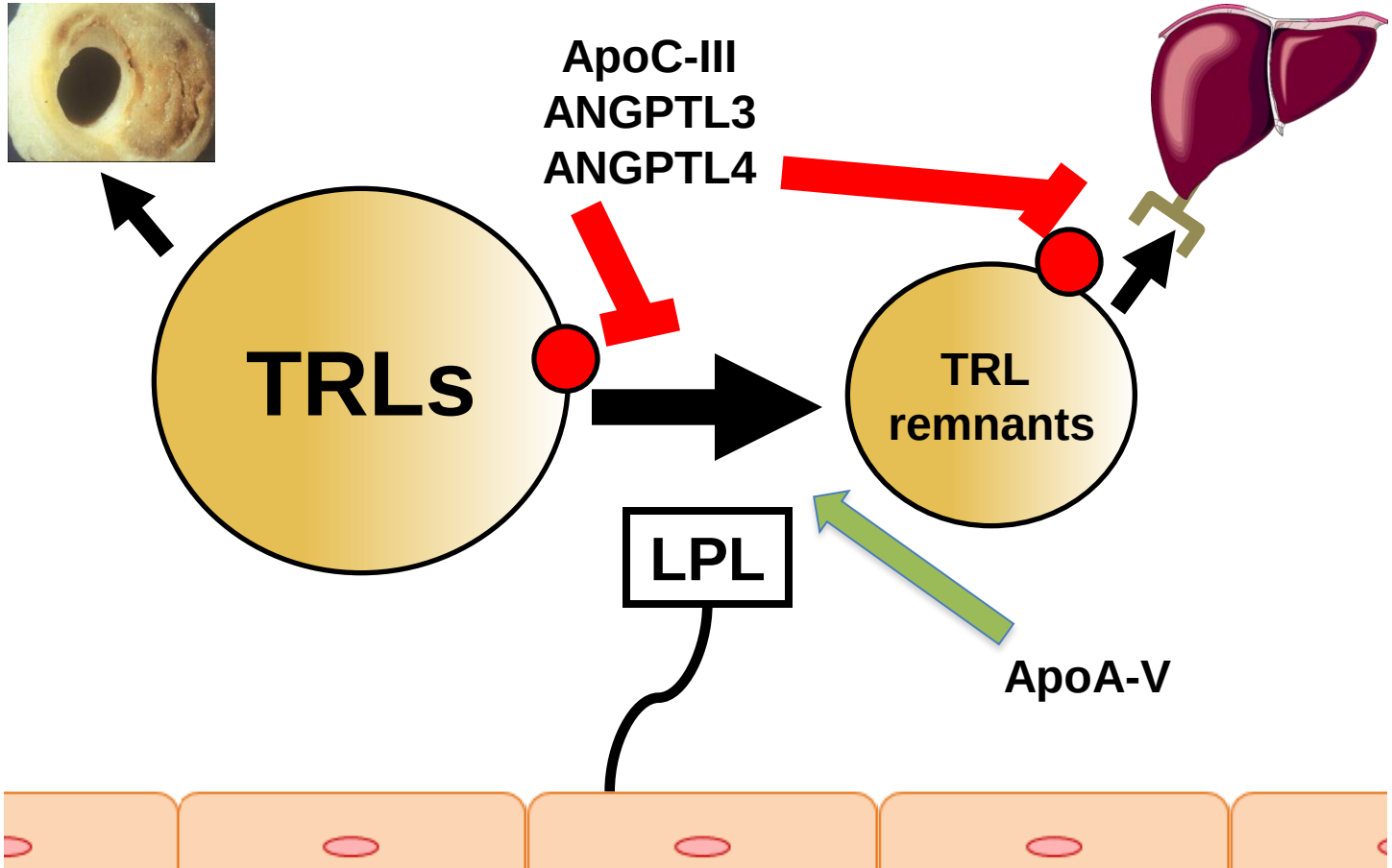
Daniel Gaudet, M.D., Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D., Veronica J. Alexander, Ph.D., Walter Singleton, M.D., Steven G. Hughes, M.B., B.S., Richard S. Geary, Ph.D., Brenda F. Baker, Ph.D., Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D., and Joseph L. Witztum, M.D.

Antisense-Mediated Lowering of Plasma Apolipoprotein C-III by Volanesorsen Improves Dyslipidemia and Insulin Sensitivity in Type 2 Diabetes

Andres Digenio,[1] Richard L. Dunbar,[2] Veronica J. Alexander,[3] Marcus Hompesch,[4] Linda Morrow,[4] Richard G. Lee,[2] Mark J. Graham,[3] Steven G. Hughes,[3] Rosie Yu,[3] Walter Singleton,[3] Brenda F. Baker,[3] Sanjay Bhanot,[3] and Rosanne M. Crooke[3]

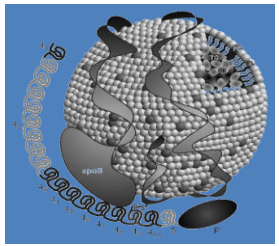
Diabetes Care 2016;39:1408–1415 | DOI: 10.2337/dc16-0126

Other proteins influencing the LPL pathway are genetically validated targets

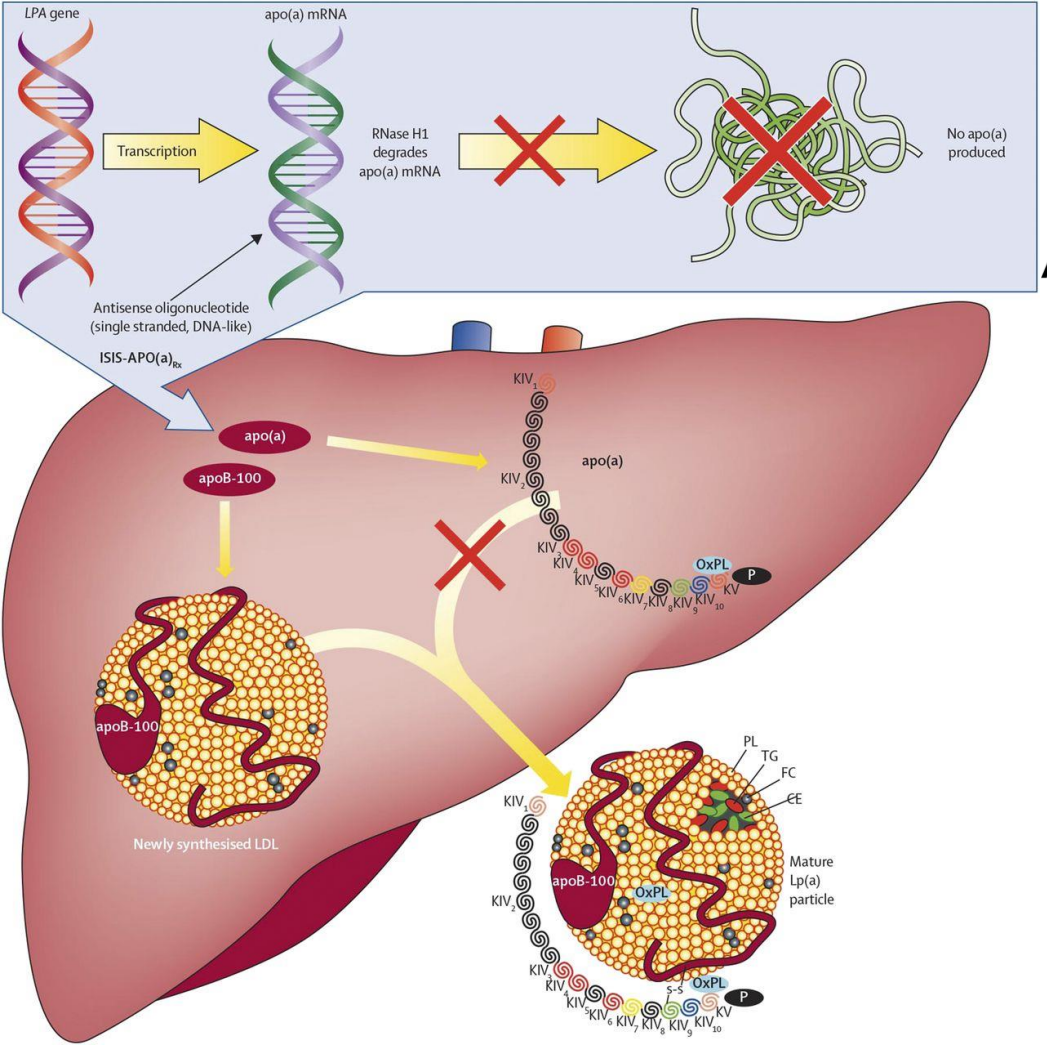


Blood biomarkers that predict risk of and are causal for cardiovascular disease

- Lipoprotein(a) [Lp(a)]



An ASO to APO(a) reduces Lp(a) levels in humans



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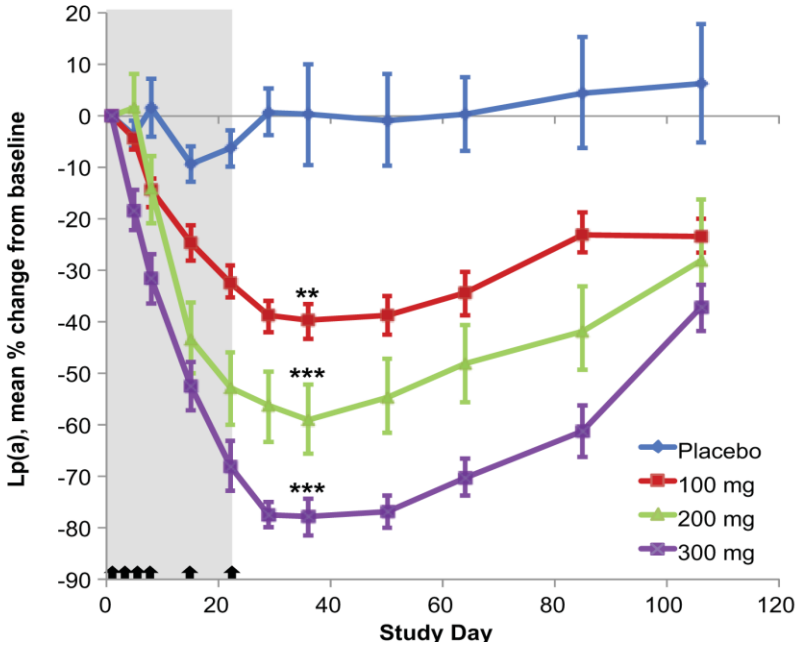
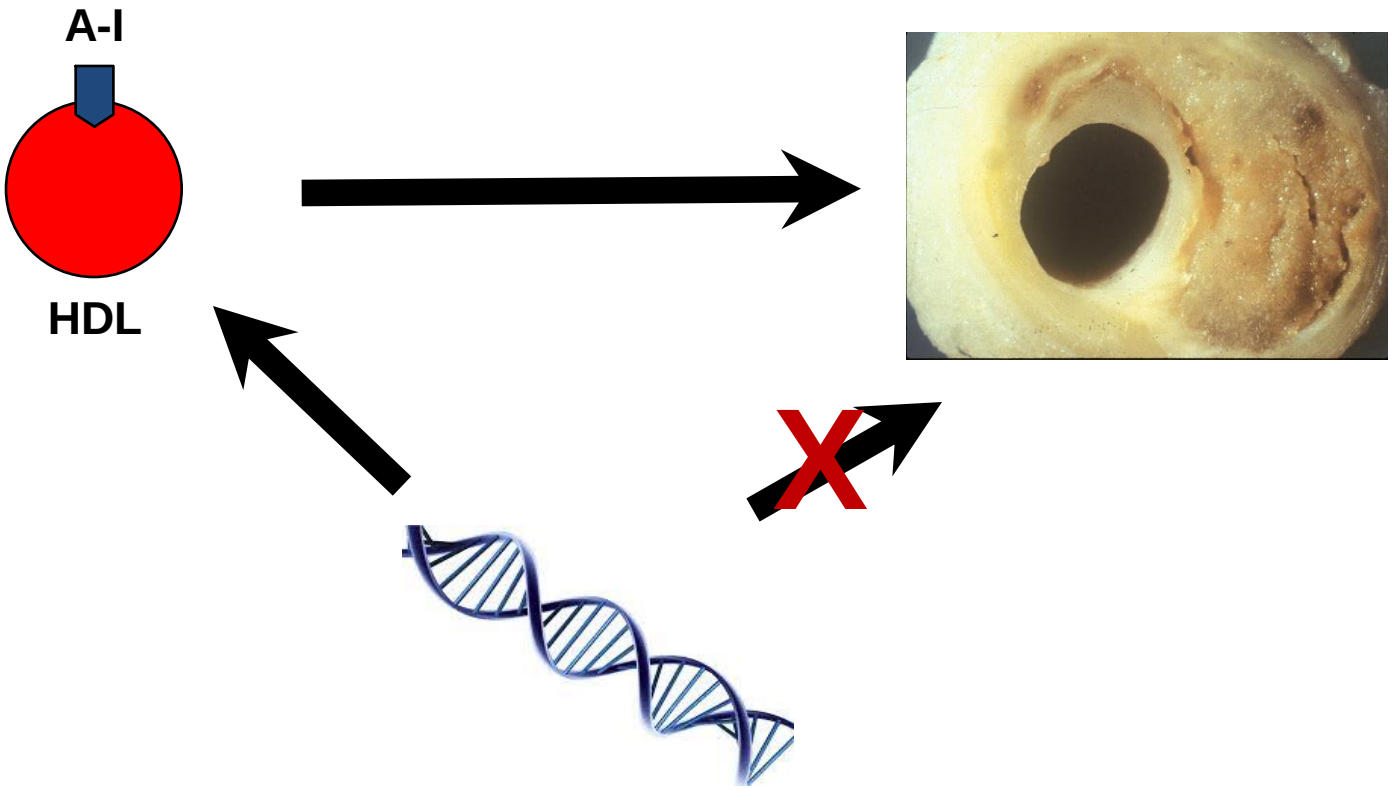
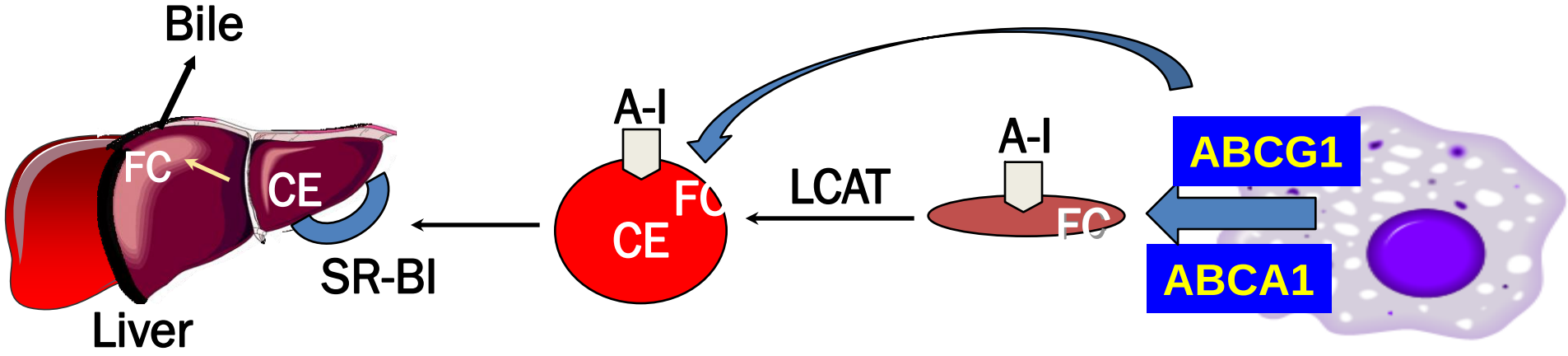


Mark J. Graham et al. J. Lipid Res. 2015;57:340-351; Tsmikas et al, Lancet 2015

HDL-C is a strong inverse predictor of CAD risk but is NOT causally associated with CAD

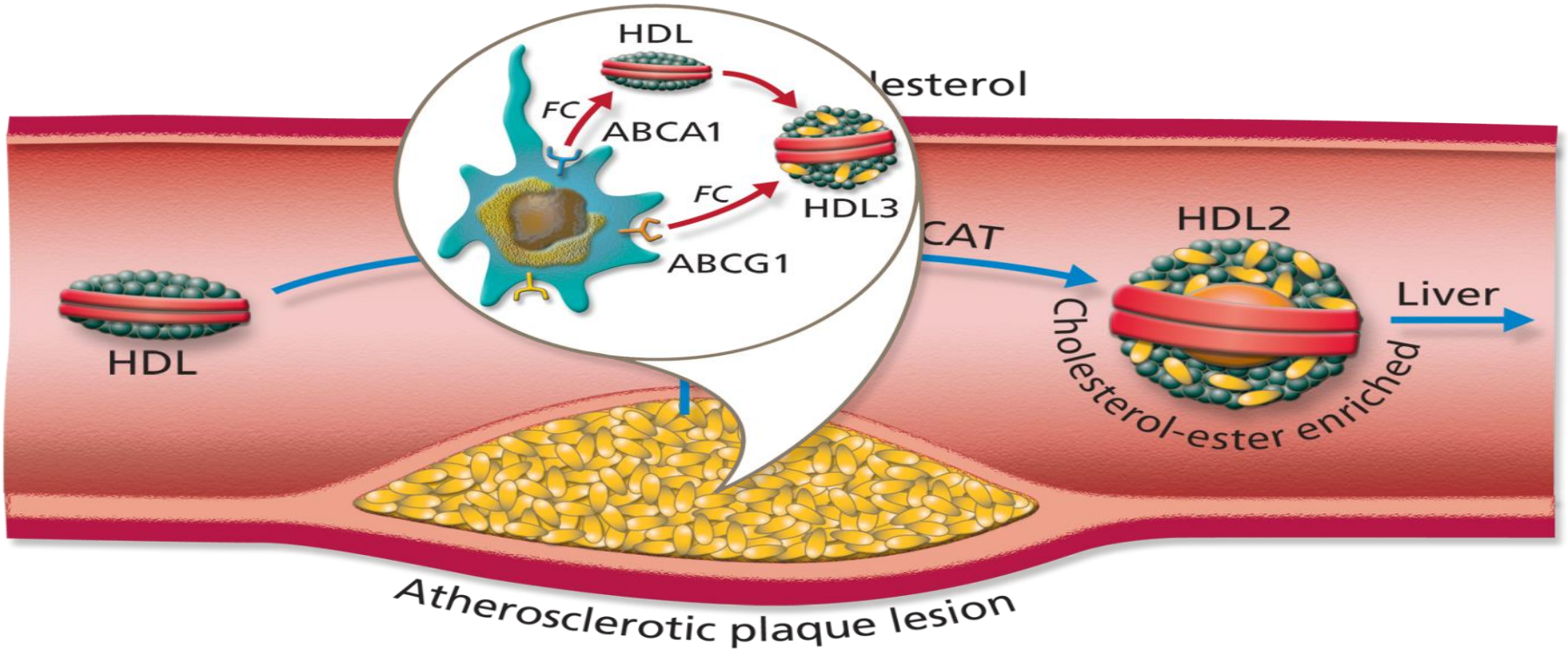


ApoA-I promotes macrophage cholesterol efflux and reverse cholesterol transport

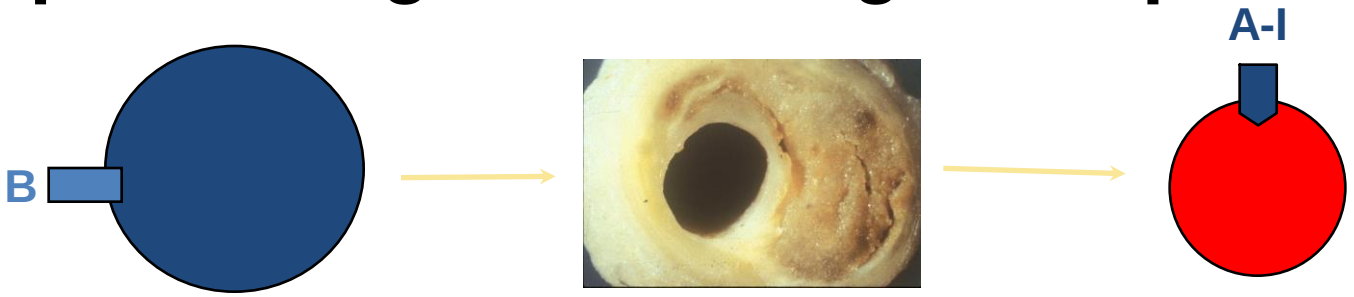


"Cholesterol efflux capacity" of HDL is predictive of cardiovascular events

Will apoA-I/reconstituted HDL remove cholesterol from plaque and reduce CV events after ACS?



Lipid management in high-risk patients



LDL, TG-rich lipoproteins, Lp(a)

HDL

- **High-intensity statin therapy**
- **Target LDL-C aggressively, using combinations as needed**
- **Non-HDL-C and possibly TG-rich lipoproteins as secondary targets**
- **Enroll in clinical trials of new lipid-lowering therapies**

If HDL-C is low:

Lifestyle intervention

High-intensity statin therapy

Consider TG reduction if TGs are elevated