Framework for Defining Evidentiary Standards for Biomarker Qualification:

LDL-C and HDL-C as Surrogate Endpoints
"The Good, the Bad, and the Ugly"

James Revkin, Pfizer

LDL-C / HDL-C Team

Framework for Defining Evidentiary Standards for Surrogate Endpoints

Biomarker Evidentiary Framework

In Drug Development

Factor likelihood and magnitude

What is the acceptable level of uncertainty?

Informs Required Stringency of EC

Need Statement → **COU** → **Benefit** — **Risk** → **Evidentiary Criteria**

CVD pre-eminent cause of global morbidity and mortality

Hard Endpoints [CV death, non-fatal myocardial infarction, and non-fatal stroke (MACE)] requires:
- Large numbers of subjects
- BMx that predicts a treatment effect
- Need to ID CV therapeutic agents for primary and secondary prevention

- *Level and Δ in serum LDL-C concentration as a predictive biomarker of CV risk long-term (5 year) rate of major coronary event outcomes*
- *Predict risk in 6 month trial with #subject related to event rate, and trial arm(s).*
- *All races, M/F, age 40-70*

Primary prevention
- < deaths, stokes & acute MI
- Early ID of CV risk and initiation of therapeutic interventions

Secondary
- Drive more aggressive therapeutics, address systemic vascular comorbidities
- ID other mechanisms for reducing the risk of CV events

Cholesterol level is only one of several CV risk factors
- May not account for a Δ in risk for these other factors

A therapeutic that acts on one of the other factors will not be recognized as beneficial to CV event reduction

General
- Cumulative LDL arterial burden is central determinant for initiation & progression of atherosclerotic CVD
- Lower LDL-C level = > clinical benefit

Surrogate Endpoint
- Over decades of research has shown that multiple approaches to reducing LDL-C results in a reduction in CV events
- Proportional (relative) risk reduction & absolute risk reduction relate to the magnitude of LDL-C reduction
- Subsequently randomized clinical trials confirmed that the modification of levels of LDL-C could reduce the occurrence rate of major cardiovascular events.

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Need Statement

Cardiovascular Risk Biomarker

- **Epidemiology:**
  - Since the mid-20th century, cardiovascular disease has been and remains the pre-eminent cause of global morbidity and mortality

- **Gold standard:**
 - Hard clinical endpoints: CV death, non-fatal myocardial infarction, and non-fatal stroke (MACE)

- **Challenge:**
  - Given that the ability to detect a treatment effect, i.e., the accrual of hard clinical endpoints, requires the recruitment of large numbers of subjects, the identification of a biomarker (circulating, imaging, or other) that predicts a treatment effect reliably, would enable a more rapid identification of new CV therapeutic agents for primary and secondary prevention

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BIOMARKERS CONSORTIUM **FNIH**
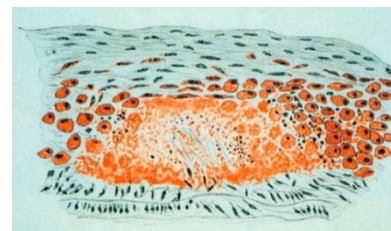
Historical Role of Cholesterol

Atheroma
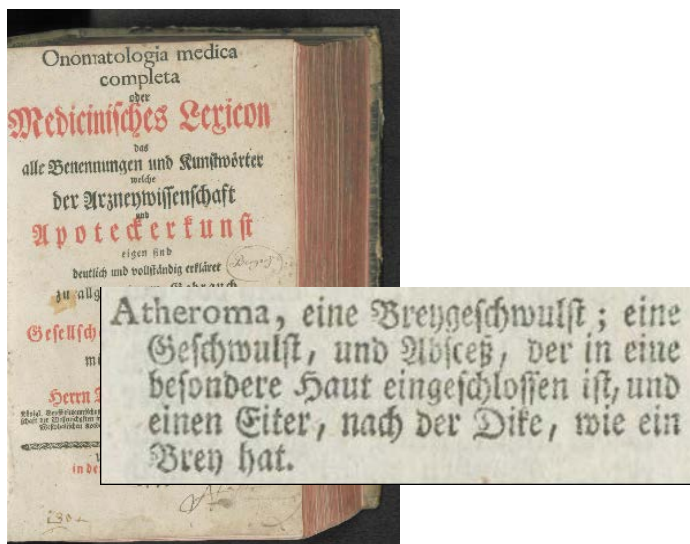
Described by Albrecht Von Haller in 1755 as "a spongy tumor, a tumor and abscess enclosed in a thick membrane, with the consistency of pus."

http://digital.ub.uni-duesseldorf.de/id/1886202

Dietary cholesterol responsible for atheromata
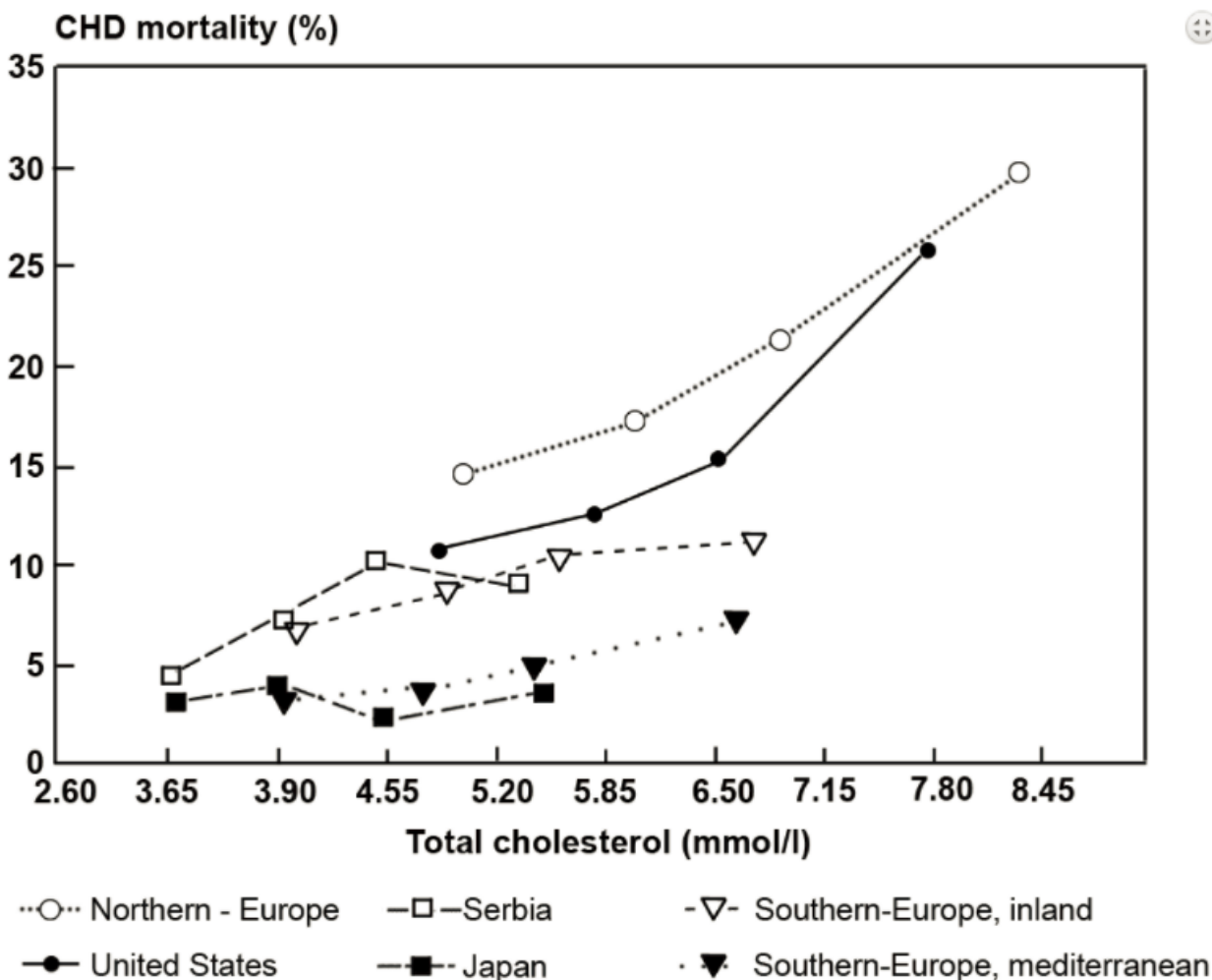

Rabbit aorta 124 days post cholesterol diet

Rabbit aorta 106 days post cholesterol diet followed by 785 days after reversion to normal chow diet

Demonstrated by Nikolai Anitschkow, 1913 Feeding rabbits cholesterol in suflower oil vs. Cholesterol alone.

Anitschkow, N. 1913. Ueber die Veranderungen der Kaninchenaorta bei experimenteller Cholesterinsteatose. Beitr. Pathol. Anat. 56:379–404

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Influences of lifestyle, genetics, diet on cholesterol levels and CV events

Key A. A. (1980) Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease (Cambridge, Massachusetts: Harvard University Press), pp. 1–381.
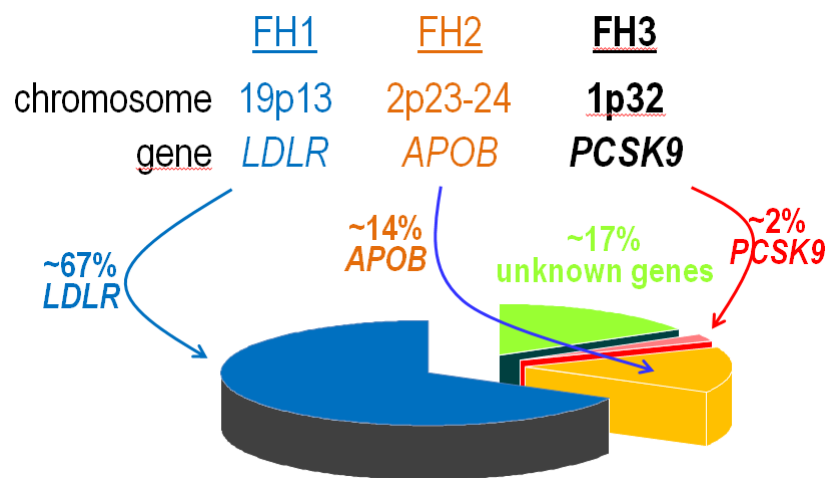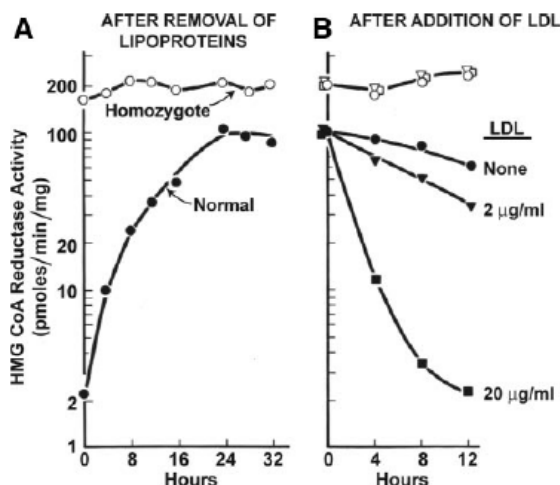
Studies initiated in 1953
- Conducted in 16 cohorts

- Cholesterol rose in proportion to the total fat intake (r = 0.67) and intake of saturated fatty acids (r = 0.87).

- Fatal coronary events rose in proportion to the serum cholesterol level (r = 0.80)

- In an evaluation of Japanese who moved eastward, there was a rise in cholesterol and an increase in mortality.

A. AFTER REMOVAL OF LIPOPROTEINS
B. AFTER ADDITION OF LDL

Homozygote / Normal

HMG CoA Reductase Activity (pmoles / min /mg)

LDL: None, 2 µg/ml, 20 µg/ml

	FH1	FH2	FH3
chromosome	19p13	2p23-24	1p32
gene	LDLR	APOB	PCSK9

~67% LDLR
~14% APOB
~17% unknown genes
~2% PCSK9

Genetics and disorders of lipid metabolism

- 1938 C Müller described **familial hypercholesterolemia** as an "inborn error of metabolism" resulting in CV death

- 1964 Khachadurian decribed two forms of FH, hetero and homo-zygous

- 1974 Brown and Goldstein, by studying fibroblasts of FH subjects, revealed the role of **HMG-Co-A reductase** and **LDL receptors** in the regulation of cholesterol metabolism.

- 1987 Innerarity et al. described a mutation in **Apo B-100** which had a low affinity for the LDL receptor, leading to hypercholesterolemia

- 1999 Varret et al described a distinct third genetic cause for autosomal dominant hypercholesterolemia, which was later attributed to a gain of function **PCSK9** mutation

Goldstein JL and Brown MS. Arterioscler Thromb Vasc Biol. 2009;29:431-438
Innerarity T, et al. Proc Nat Acad Sci USA 84:6919–6923
Varret M, Rabes J-P, et al. Am J. Hum Genet. 1999;64:1378-1387
Abifadel M, et al. Nature Genetics 2003;34:154-156

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LDL- Cholesterol: History of Development

- Atherothrombotic disease is a cause of irreversible end organ injury

- Atheroma and the identification of cholesterol as a agent of atheroma burden

- Understanding the relationship between circulating cholesterol, lipoproteins, and atheroma burden

- The epidemiology revealing the relationship between cholesterol levels and cardiovascular (CV) events

- Discovery of modulators of levels of circulating cholesterol and different lipoproteins
  - LDL-receptor, SR-BI, and PCSK9

- The conduct of CV outcome studies showing that modulating levels of LDL-C impacts CV risk

Context of Use

- **Historical Assumptions**

  - 30 yrs ago, requirement to run 3yr, placebo-controlled trial against major coronary event outcomes (acute MI, stroke, CV death) with ~500+ patients per arm

  - Event rates were much higher

  - Not comparing trial where statin is SOC

- **Use Statement**

  - Level and change in serum LDL-C concentration reflects the long-term (5 year) rate of major coronary event outcomes and can be used to predict this outcome in a 6 month trial with #subject related to event rate, and trial arm(s).

- **Patient Populations**

  - Subjects between the ages of 40 and 70 (women and men, all racial background)

- **Other factors that will define the limits of the decision**

  - Clinical utility, sample size, subtypes, event rate

Benefit Assessment

Cardiovascular Biomarker

- **Primary prevention**
  - Outlier values of the CV biomarker could lead to the early identification of CV risk and the initiation of earlier therapeutic interventions of risk
  - Fewer people die, have a stoke or acute MI
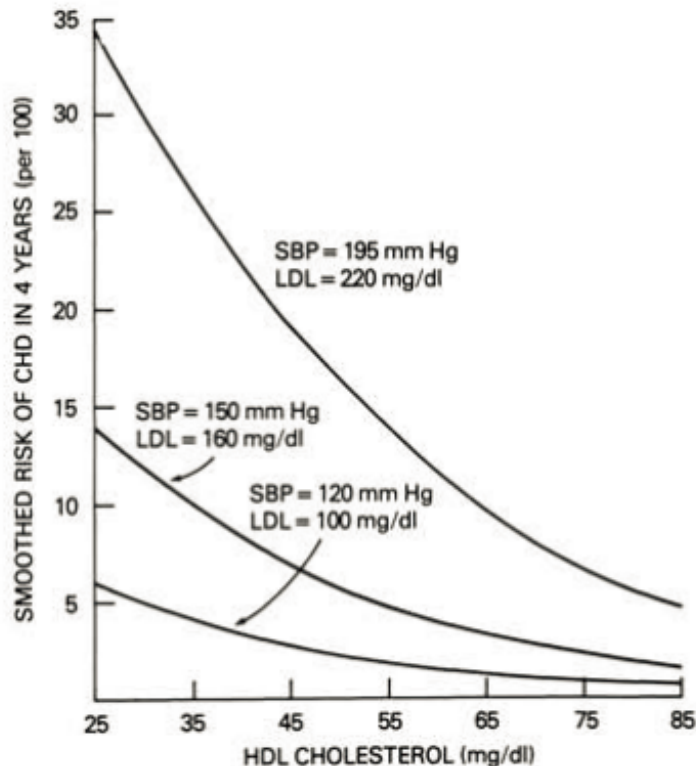
- **Secondary prevention**
  - Given systemic nature of atherosclerosis, outlier values of CV biomarker could drive more aggressive therapeutic interventions to prevent subsequent events in the same or other vascular beds
  - Identification of additional mechanisms for reducing the risk of CV events

Risk Assessment

- Cholesterol level is only one of several CV risk factors and this measurement may not account for a change in risk for these other factors

- A therapeutic that acts on one of the other factors will not be recognized as beneficial to CV event reduction

- Risk Mitigation

- What amount of risk is the patient population willing to take?

LDL-C and HDL-C and CV outcomes:
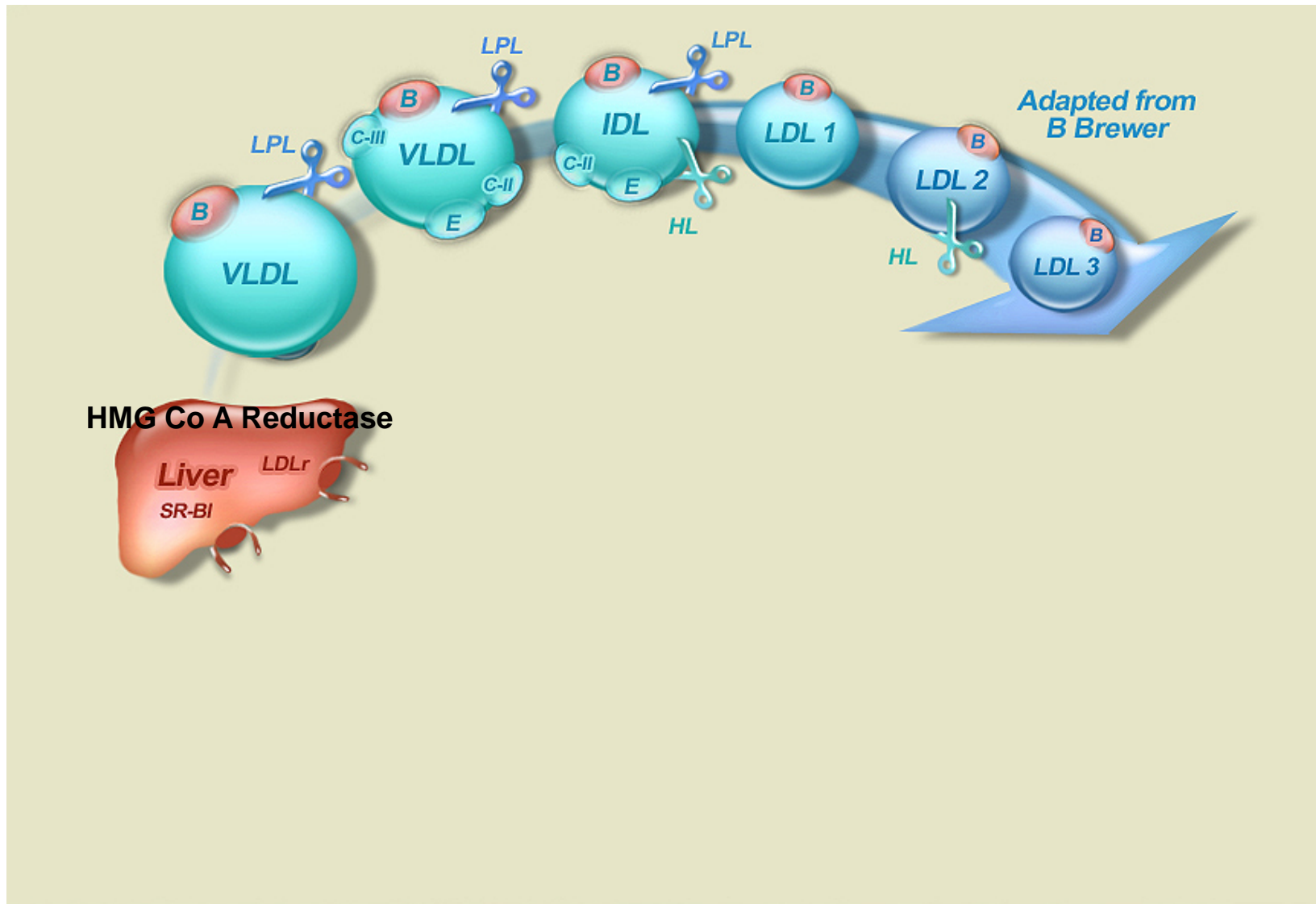## The Framingham Study

Plausibility

Figure 3. Risk of coronary heart disease according to levels of high-density lipoprotein-cholesterol; men aged 55, Framingham Study 24-year follow-up. CHD = coronary heart disease, SBP = systolic blood pressure, LDL = low-density lipoprotein, HDL = high-density lipoprotein.
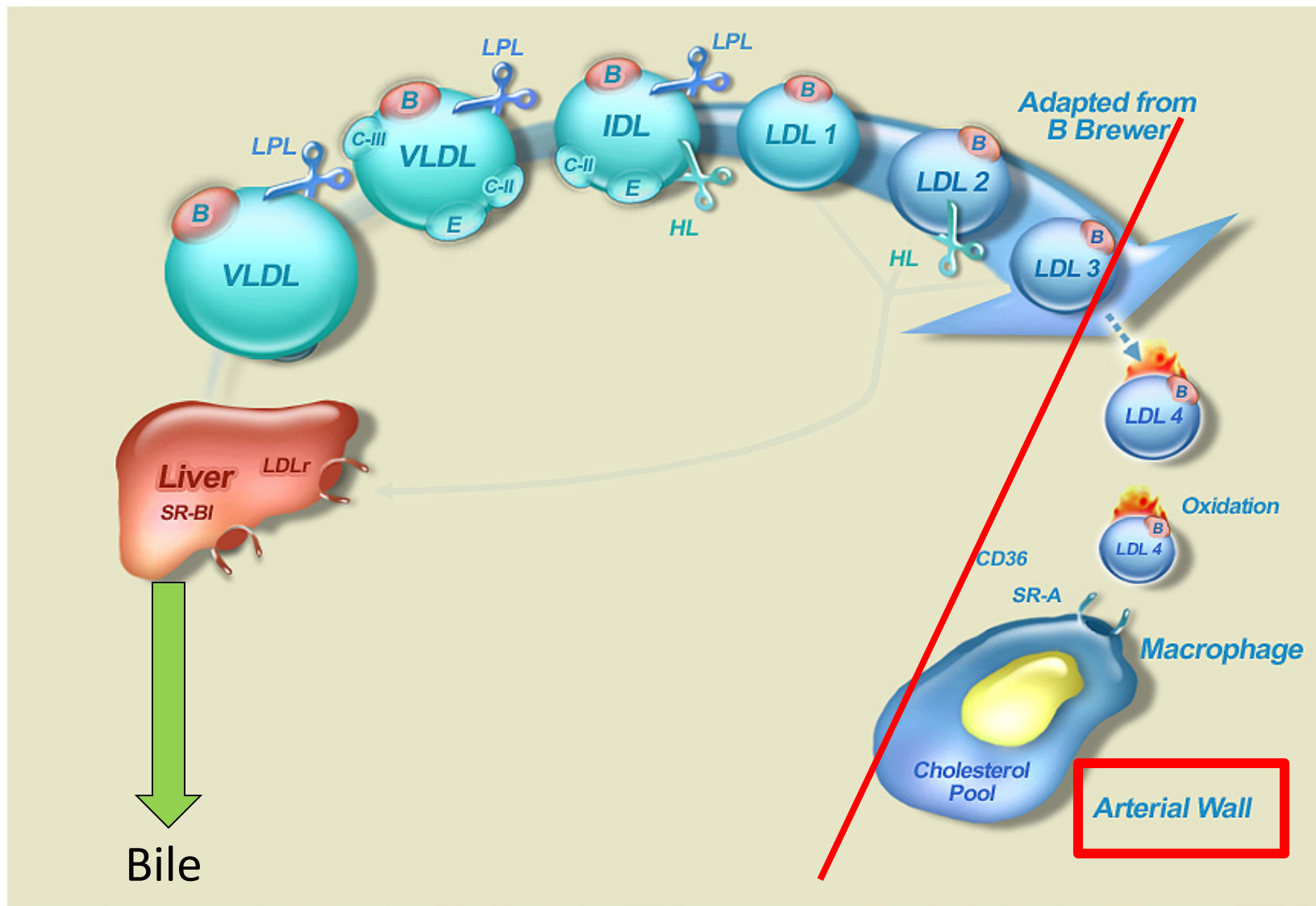
In the search for an optimal therapy for avoiding or correcting atherosclerosis, the ideal lipid response would appear to be the one that raises HD lipoprotein as it lowers LD lipoprotein. Therapeutic maneuvers that affect only one of these lipoprotein particle systems in a favorable way, while adversely affecting the other, may be less promising than those that improve both the HD lipoprotein and LD lipoprotein values.

Kannel WB, Castelli WP, Gordon T. Cholesterol in the prediction of atherosclerotic disease. Ann Intern Med. 1979;90(1):85-91.
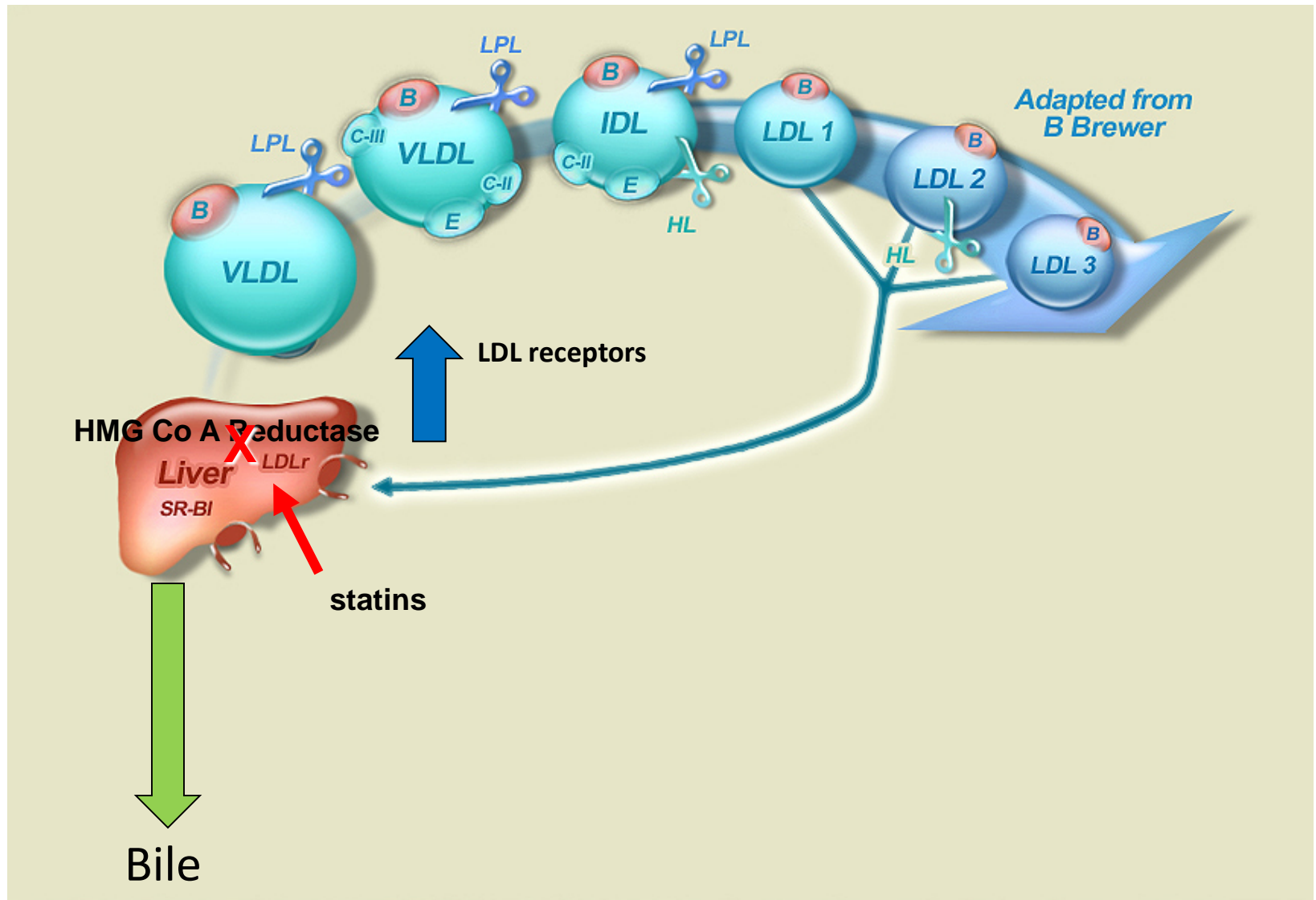
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LDL receptors

PCSK9

PCSK9 expression regulated by sterol regulatory element-binding Protein (SREBP)

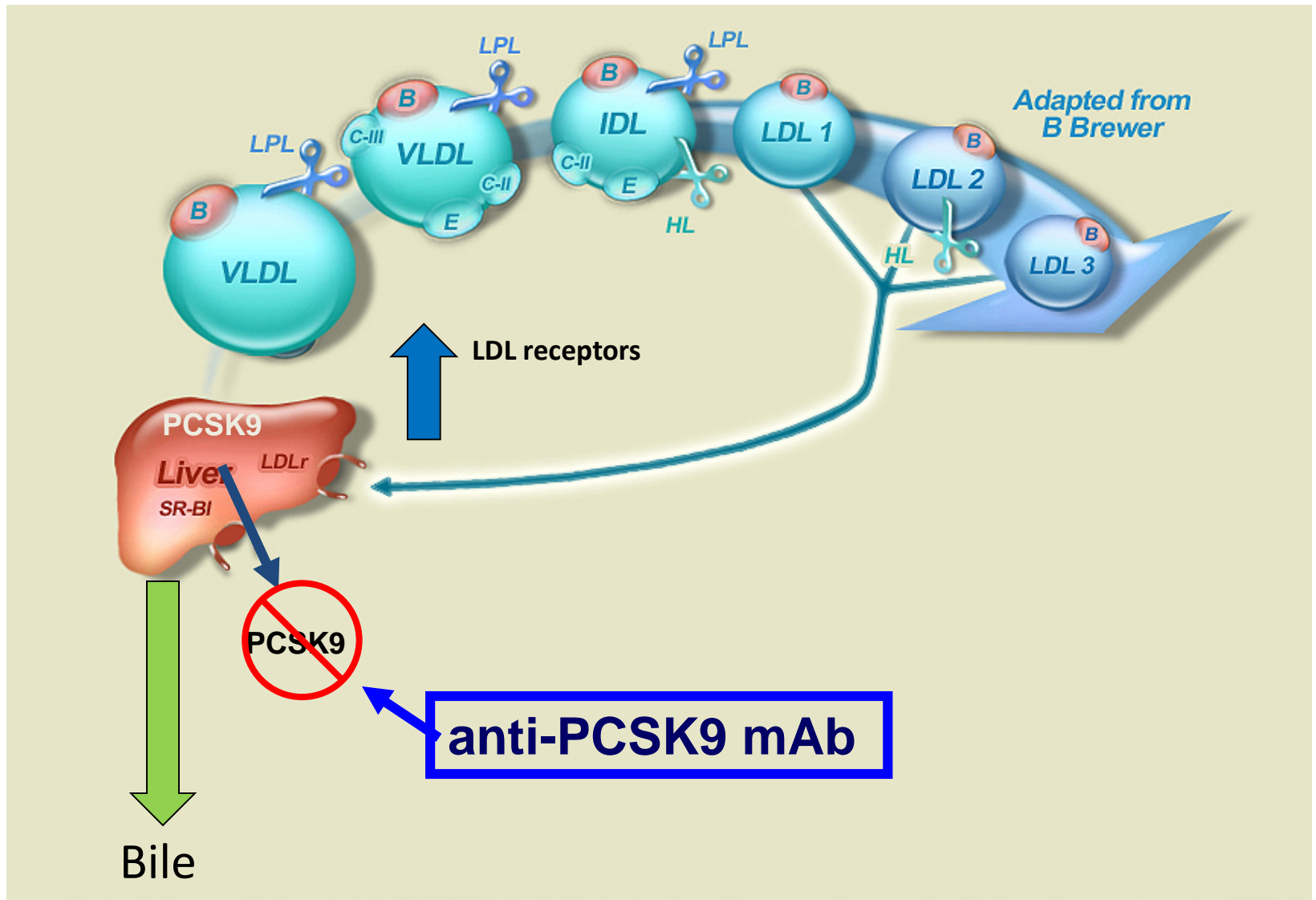Bile

Removal of LDL via LDL-receptor

LDL as a causal factor for atherosclerotic cardiovascular disease: key implications

Causality

- Cumulative LDL arterial burden is a central determinant for the initiation and progression of atherosclerotic cardiovascular disease.

- The lower the LDL cholesterol (LDL-C) level attained by agents that primarily target LDL receptors, the greater the clinical benefit accrued.

- Both proportional (relative) risk reduction and absolute risk reduction relate to the magnitude of LDL-C reduction.

- Lowering LDL-C in individuals at high cardiovascular risk earlier rather than later appears advisable, especially in those with familial hypercholesterolaemia.
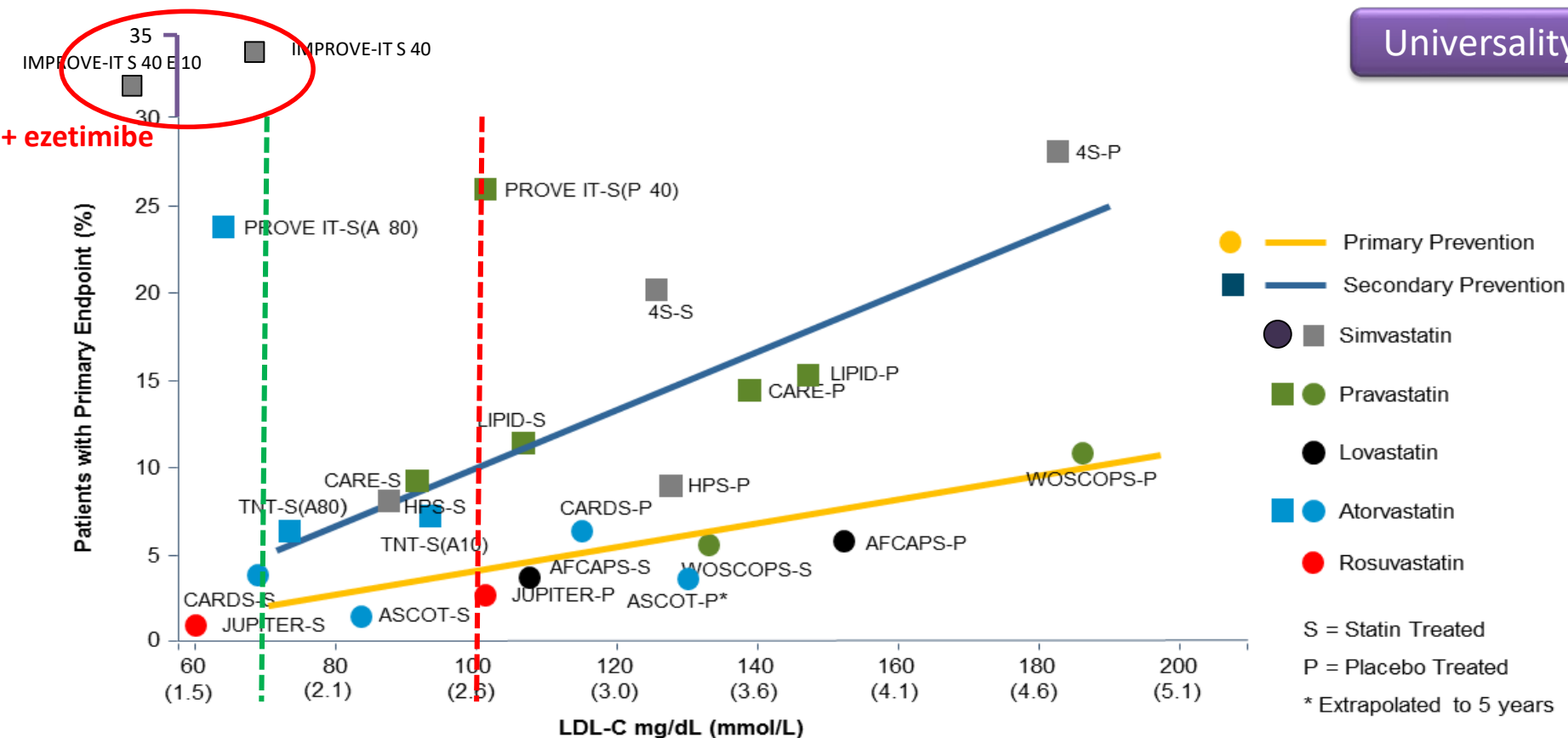
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Relationship between LDL-C and CV Events

Modified from Kastelein JJP. *Atherosclerosis*. 1999; 143 (suppl 1): S17-S21.

Relationship between LDL-C and CV Events

90,056 participants in 14 randomized trials of statins
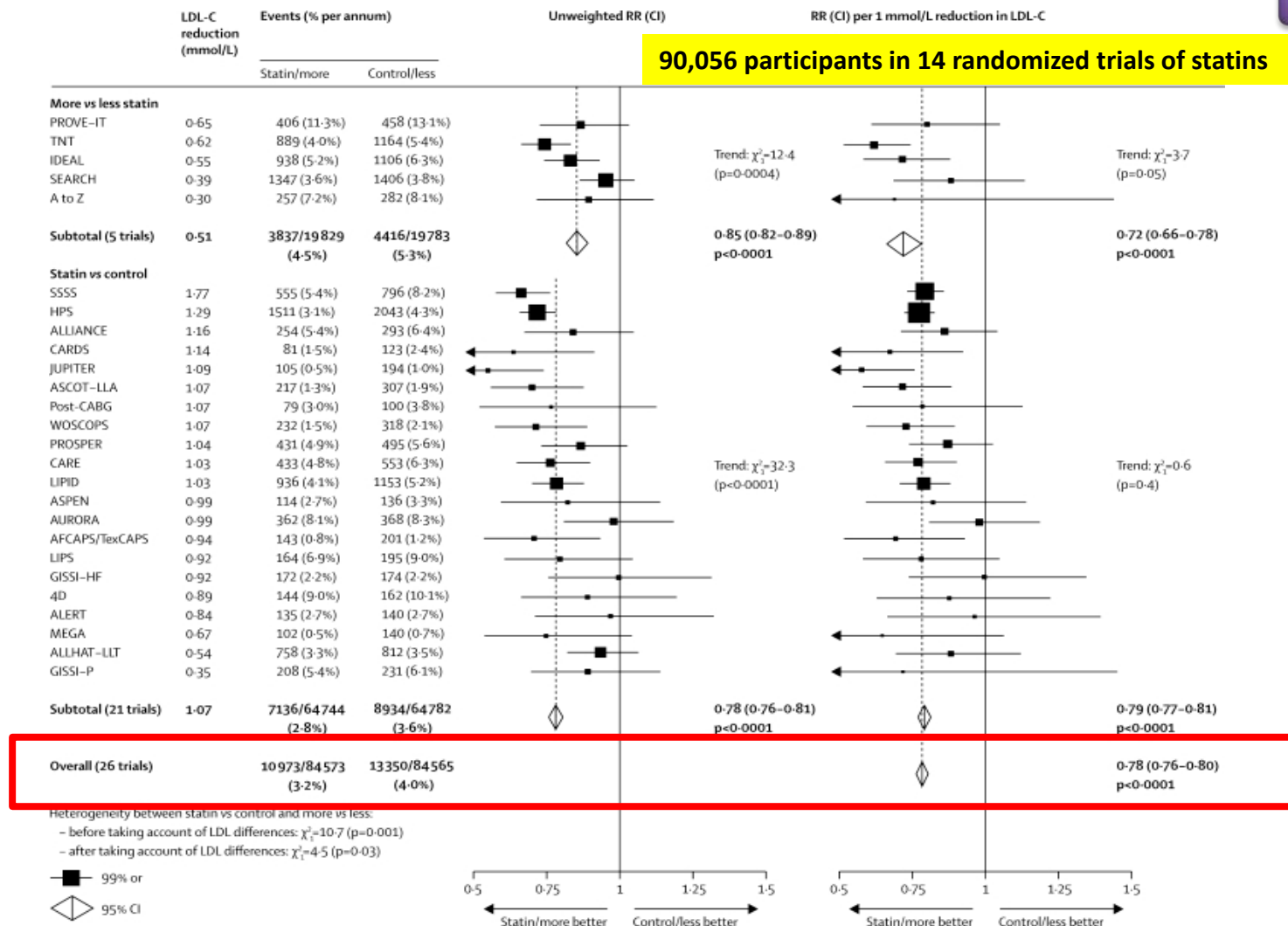
Baigent C, Keech A, Kearney PM, et al. Lancet 2005;366:1267-1278

FDA Acceptance of LDL-C as Surrogate Endpoint

- LDL cholesterol reduction was the basis for FDA approval in 1987 of the first statin (lovastatin)

  - 7 years before the publication of the Scandinavian Simvastatin Survival Trial

  - The first trial to provide definitive evidence of a statin's clinical benefit.

  - Subsequent statin approvals were also based on the LDL cholesterol surrogate, as was approval of the first-in-class drug ezetimibe in 2002.

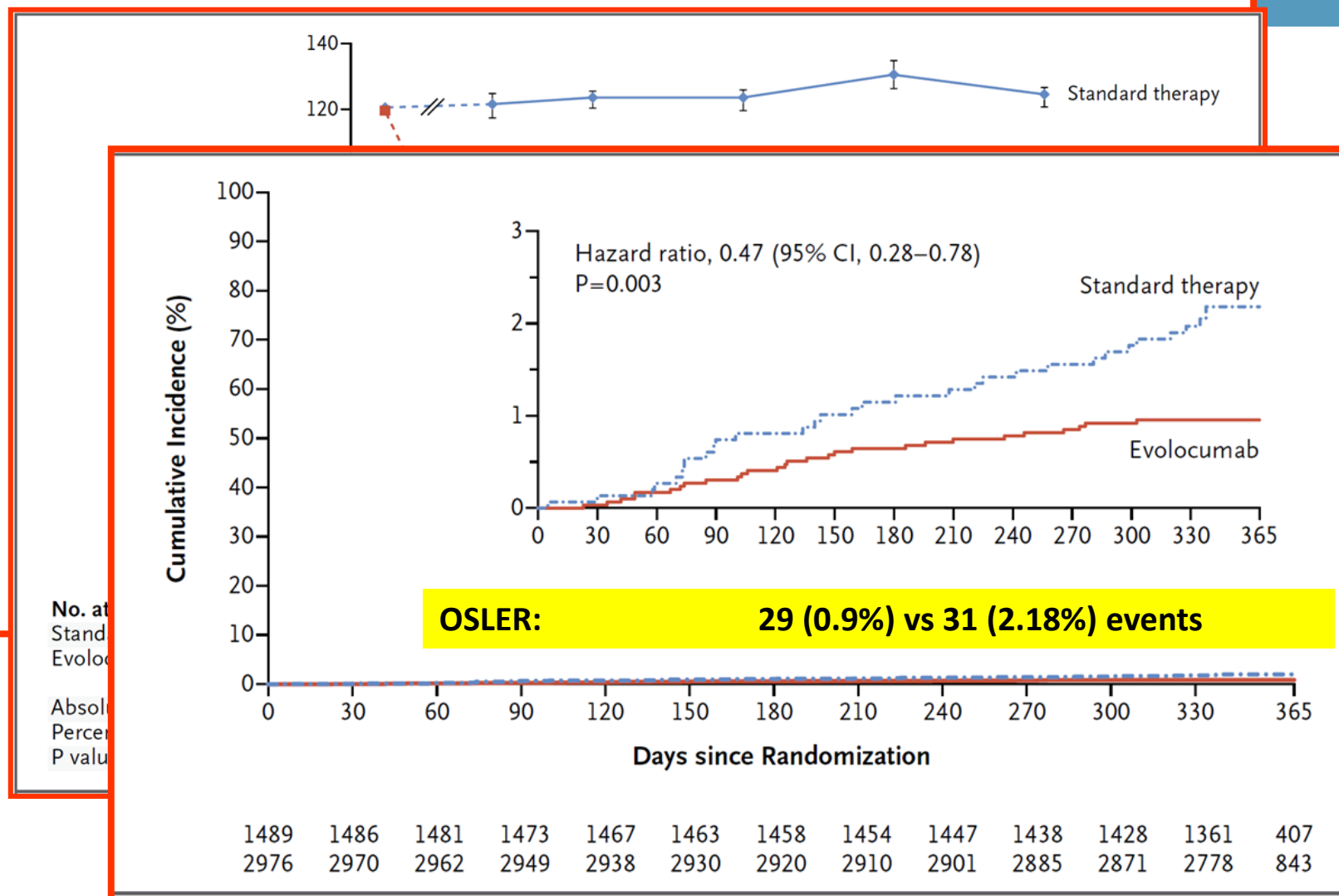|					Cardiovascular Outcome	
Trial	Study Drug	Comparison	Primary End Point	% Difference in LDL Cholesterol Levels†	Hazard Ratio (95% CI)	P Value
HERS	Estrogen (alone or in combination with medroxyprogesterone)	Placebo	Nonfatal myocardial infarction or death due to coronary heart disease	−11	0.99 (0.80–1.22)	0.91
FIELD	Fenofibrate	Placebo	Nonfatal myocardial infarction or death due to coronary heart disease	−12	0.89 (0.75–1.05)	0.16
ILLUMINATE	Torcetrapib–atorvastatin	Placebo plus atorvastatin	Nonfatal myocardial infarction, stroke, hospitalization for unstable angina, or death due to coronary heart disease	−27	1.25 (1.09–1.44)	0.001
HPS-2 THRIVE	Niacin–laropiprant	Placebo	Nonfatal myocardial infarction, death from coronary causes, stroke, or arterial revascularization	−16	0.96 (0.90–1.03)	0.29
IMPROVE-IT	Ezetimibe–simvastatin	Placebo plus simvastatin	Death due to cardiovascular causes, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke	−24	0.94 (0.89–0.99)	0.02

Selected Clinical Trials of Medications for Lowering LDL Cholesterol Levels Other Than Statins Alone and Their Effects on Cardiovascular Events.*

* CI denotes confidence interval, HERS Heart and Estrogen/Progestin Replacement Study,[2] FIELD Fenofibrate Intervention and Event Lowering in Diabetes,[3] ILLUMINATE Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events,[4] HPS-2 THRIVE Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events,[5] and IMPROVE-IT Improved Reduction of Outcomes: Vytorin Efficacy International Trial.[1]
† The percent difference is for the comparison, during treatment, of the study drug with a placebo or another drug.

The NEW ENGLAND JOURNAL of MEDICINE

OSLER: **29 (0.9%) vs 31 (2.18%) events**

Hazard ratio, 0.47 (95% CI, 0.28–0.78)
P=0.003

Sabatine MS, et al. N Engl J Med 2015;372(16):1500-09

PCSK9 inhibitors initially approved solely on the basis of LDL-C lowering

- Humanized MAbs inactivate proprotein convertase subtilisin–kexin type 9 (PCSK9)
  - Inactivation results in decreased LDL-receptor degradation, increased recirculation of the receptor to the surface of hepatocytes, and consequent lowering of LDL cholesterol levels in the bloodstream
  - Statins, by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, similarly act by increasing LDL-receptor expression

- This shared LDL cholesterol–lowering mechanism, combined with data on cardiovascular events from genetic studies of persons with PCSK9 gain- or loss-of-function mutations, provided the optimism of the likely cardiovascular benefits of these agents

- Both drugs were approved by FDA with LDL cholesterol reduction as the surrogate measure of clinical benefit. No efficacy data on cardiovascular outcomes were provided to the advisory committee

- Thus, the principal issue before the advisory committee was whether the observed LDL cholesterol reduction provided sufficient evidence to substitute for demonstration of clinical cardiovascular benefit.

A Primary Efficacy End Point

Hazard ratio, 0.85 (95% CI, 0.79–0.92)
P<0.001

Placebo — 6.0, 10.7, 14.6
Evolocumab — 5.3, 9.1, 12.6
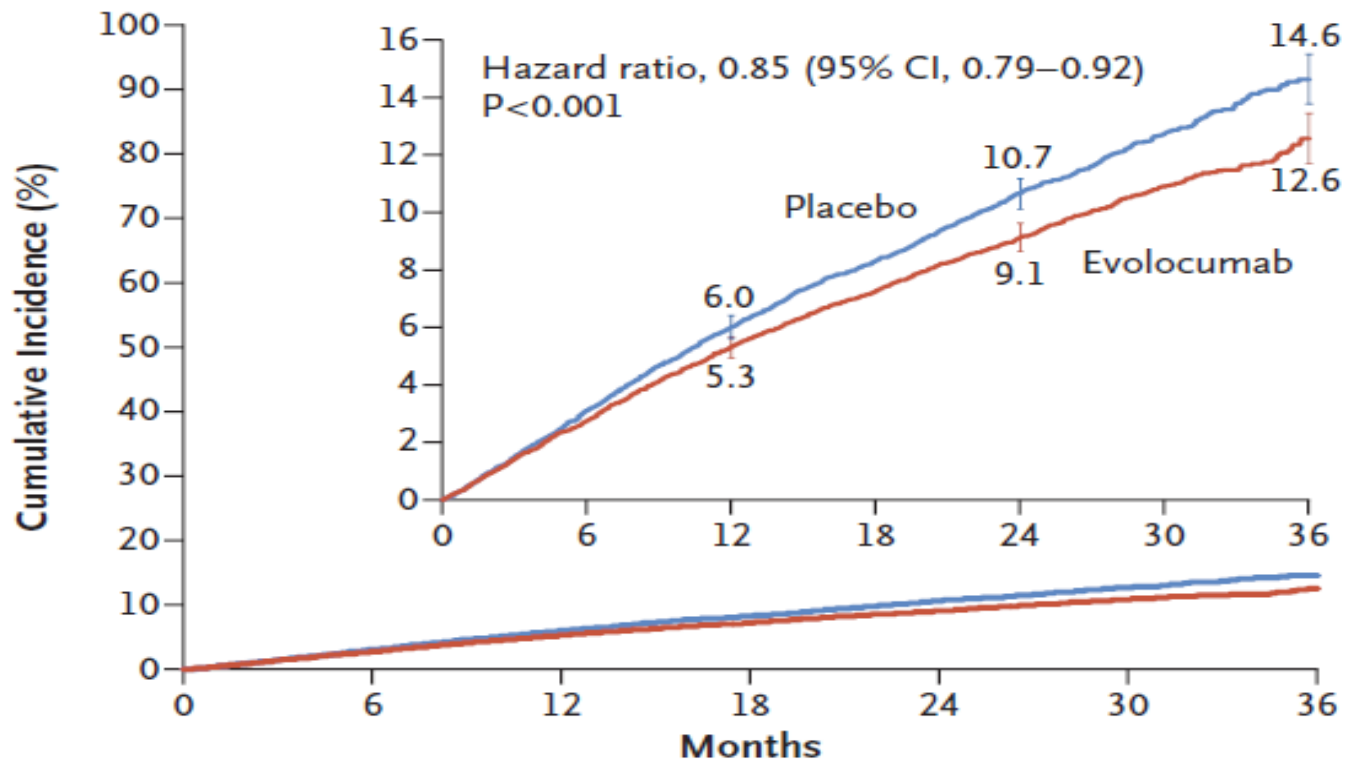
No. at Risk							
Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

OSLER: 29 (0.9%) vs 31 (2.18%) events
FOURIER: 1344 (9.8%) vs 1,563 (11.3%) events

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LDL-C as a Surrogate Endpoint
Summary conclusions

- Links were established between lipids and cardiac end organ injury

  Plausibility

- Over decades of research and innovation, refinements were made in the characterization of which cholesterol carrying lipoproteins were causally related to vascular injury

  Plausibility

- The metabolism of those disease causing lipoproteins was subsequently characterized, permitting the identification of targets which would modify their circulating levels

  Plausibility

- Over decades of research has shown that multiple approaches to reducing LDLc results in a reduction in CV events

  Universality

- Subsequently randomized clinical trials confirmed that the modification of levels of LDL-C could reduce the occurrence rate of major cardiovascular events.

  Proportionality

  - a reduction of 1 mmol per liter (38.7 mg per deciliter) in LDL cholesterol levels yields a consistent 23% reduction in the risk of major coronary events over 5 years
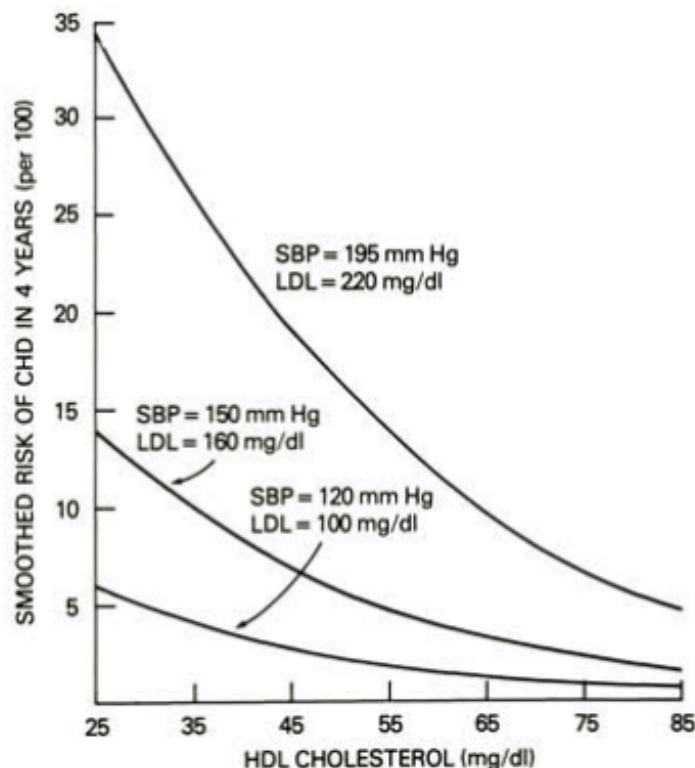
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Plausibility

Figure 3. Risk of coronary heart disease according to levels of high-density lipoprotein-cholesterol; men aged 55, Framingham Study 24-year follow-up. CHD = coronary heart disease, SBP = systolic blood pressure, LDL = low-density lipoprotein, HDL = high-density lipoprotein.

In the search for an optimal therapy for avoiding or correcting atherosclerosis, the ideal lipid response would appear to be the one that raises HD lipoprotein as it lowers LD lipoprotein. Therapeutic maneuvers that affect only one of these lipoprotein particle systems in a favorable way, while adversely affecting the other, may be less promising than those that improve both the HD lipoprotein and LD lipoprotein values.

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Biomarker Evidentiary Framework

In Drug Development

Factor likelihood and magnitude

What is the acceptable level of uncertainty?

Need Statement → **COU** → **Benefit** **Risk** → **Evidentiary Criteria**

Informs Required Stringency of EC

CVD pre-eminent cause of global morbidity and mortality

Can we reduce risk BEYOND what statins have achieved for LDL-C?

Optimal agents with BOTH lower LDL-C and RAISE HDL

- *Level and Δ in serum HDL concentration as a predictive biomarker of CV risk long-term (10 year) rate of major coronary event outcomes*
- *Predict risk in 6 month trial with 1000 subjects - related to event rate, and trial arm(s).*
- *All races, M/F, age 40-70*

Primary prevention
- < deaths, stokes & acute MI
- Early ID of CV risk and initiation of therapeutic interventions

Secondary
- Drive more aggressive therapeutics, address systemic vascular comorbidities
- ID other mechanisms for reducing the risk of CV events

Cholesterol level is only one of several CV risk factors
- May not account for a Δ in risk for these other factors

A therapeutic that acts on one of the other factors will not be recognized as beneficial to CV event reduction

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General
- Multiple LDL-C lowering drugs raise HDL levels
- CEPT deficient patient Subjects Have Increased HDL and Apo A1 Levels

Surrogate Endpoint
- Research has shown that elevating HDL opposes atherothrombosis
- The modification of HDL-C levels by CETP inhibition, in and of itself, does not appear to provide clinical benefit
- Subsequently randomized clinical trials confirmed that the modification of levels of HDL do not provide universal reduction in the occurrence rate of major cardiovascular events

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Basically the same as LDL-C (or for other CVD factors)

Can we reduce risk BEYOND what statins have achieved?

	HPS	WOSCOPS	4S	ASCOT-LLA	CARDS*

Reduction in major coronary events vs. placebo (%)

*Includes stroke
†*P*≤0.0005
**P*≤0.001

Potential for further risk reduction

- HPS: -27†
- WOSCOPS: -31**
- 4S: -34†
- ASCOT-LLA: -36†
- CARDS*: -37**
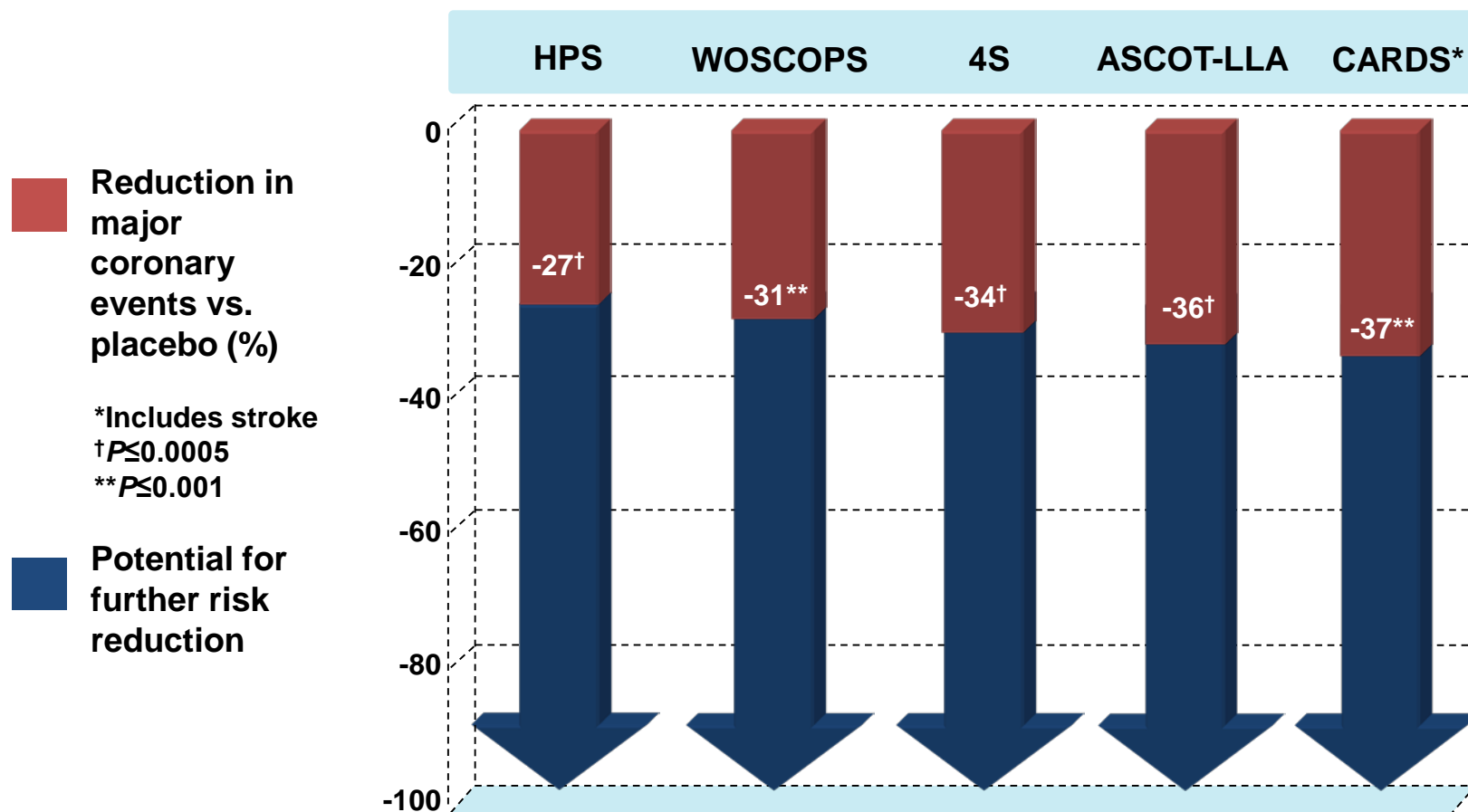
HPS: Heart Protection Study Collaborative Group, *Lancet*. 2002;360:7-22.
WOSCOPS: West of Scotland Coronary Prevention Study. Shepherd J, et al. *New Engl J Med*. 1995;333:1301-1307.
4S: Scandinavian Simvastatin Survival Study Group. *Lancet*. 1994;344:1383-1389.
ASCOT: Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm. Sever P, et al. *Lancet*. 2003;361:1149-1157.
CARDS: Collaborative Atorvastatin Diabetes Study. Colhoun HM, et al. *Lancet*. 2004;364:685-696.

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Context of Use

- **Use Statement**

  - Level and change in serum HDL concentration reflects the long-term (10 year) rate of major coronary event outcomes (acute MI, stroke, CV death) and can be used to predict this outcome in a 6 month trial with 1000 subjects

- **Patient Populations**

  - Subjects between the ages of 40 and 70 (women and men, all racial background)

- **Other factors that will define the limits of the decision**

  - Clinical utility, sample size, subtypes, event rate

Benefit Assessment

Cardiovascular Biomarker

- **Primary prevention**
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  - Fewer people die, have a stoke or acute MI
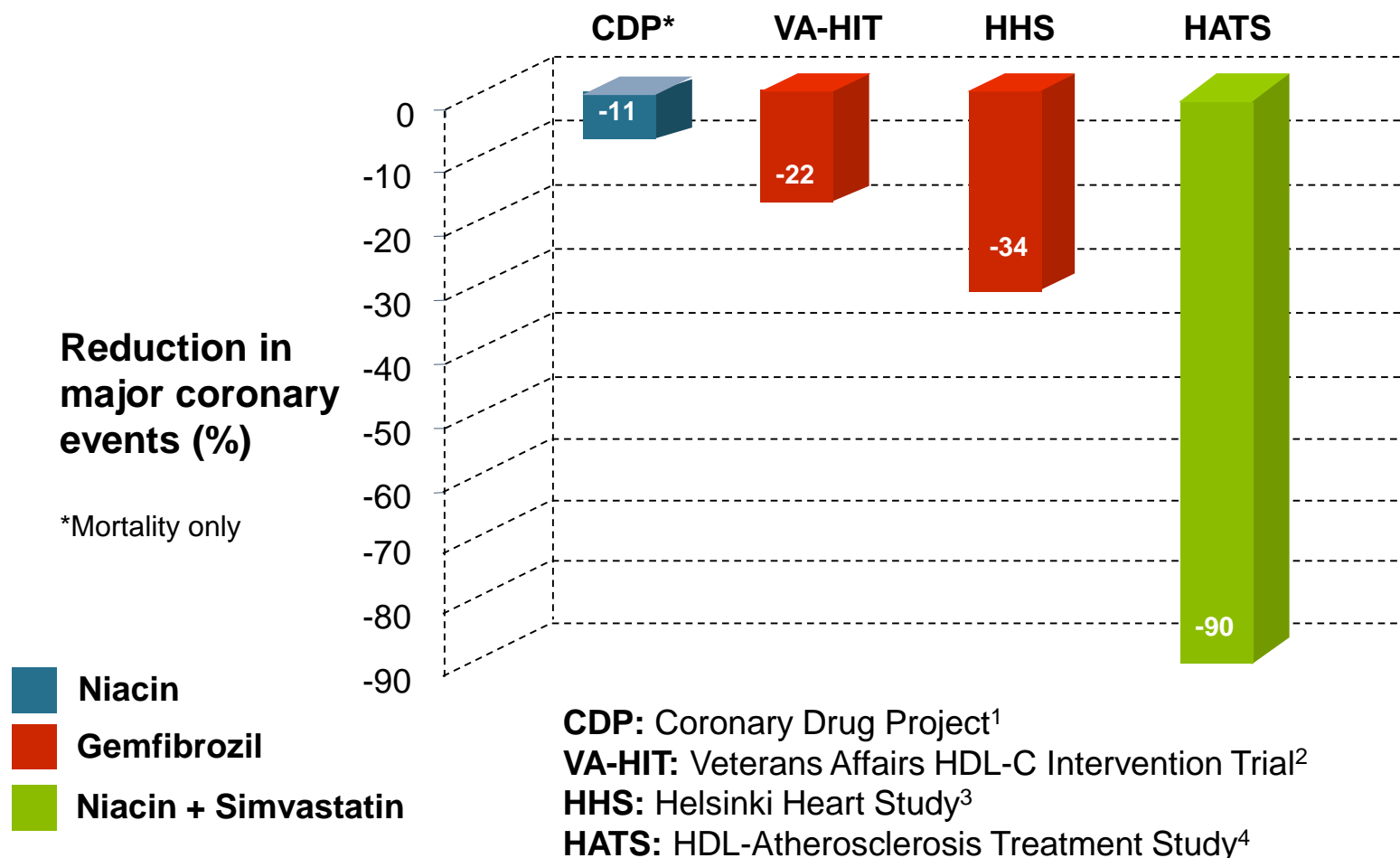
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Risk Assessment

- Cholesterol level is only one of several CV risk factors and this measurement may not account for a change in risk for these other factors

- A therapeutic that acts on one of the other factors will not be recognized as beneficial to CV event reduction

- Risk Mitigation

- What amount of risk is the patient population willing to take?

Reduction in major coronary events (%)

*Mortality only

CDP*   VA-HIT   HHS   HATS

-11
-22
-34
-90

0, -10, -20, -30, -40, -50, -60, -70, -80, -90

- Niacin
- Gemfibrozil
- Niacin + Simvastatin

CDP: Coronary Drug Project[1]
VA-HIT: Veterans Affairs HDL-C Intervention Trial[2]
HHS: Helsinki Heart Study[3]
HATS: HDL-Atherosclerosis Treatment Study[4]

1. Canner PL, Berge KG, Wenger NK, et al. *J Am Coll Cardiol.* 1986;8:1245-55.
2. Rubins HB, Robins SJ, Collins D, et al. *N Engl J Med.* 1999;341:410-418.
3. Frick MH, Elo O, Haapa K, et al. *N Engl J Med.* 1987;317:1237-1245.
4. Brown BG, Zhao XQ, Chait A, et al. *N Engl J Med.* 2001;345:1583-1592.

Lipid and apoprotein levels in CETP-deficient subjects

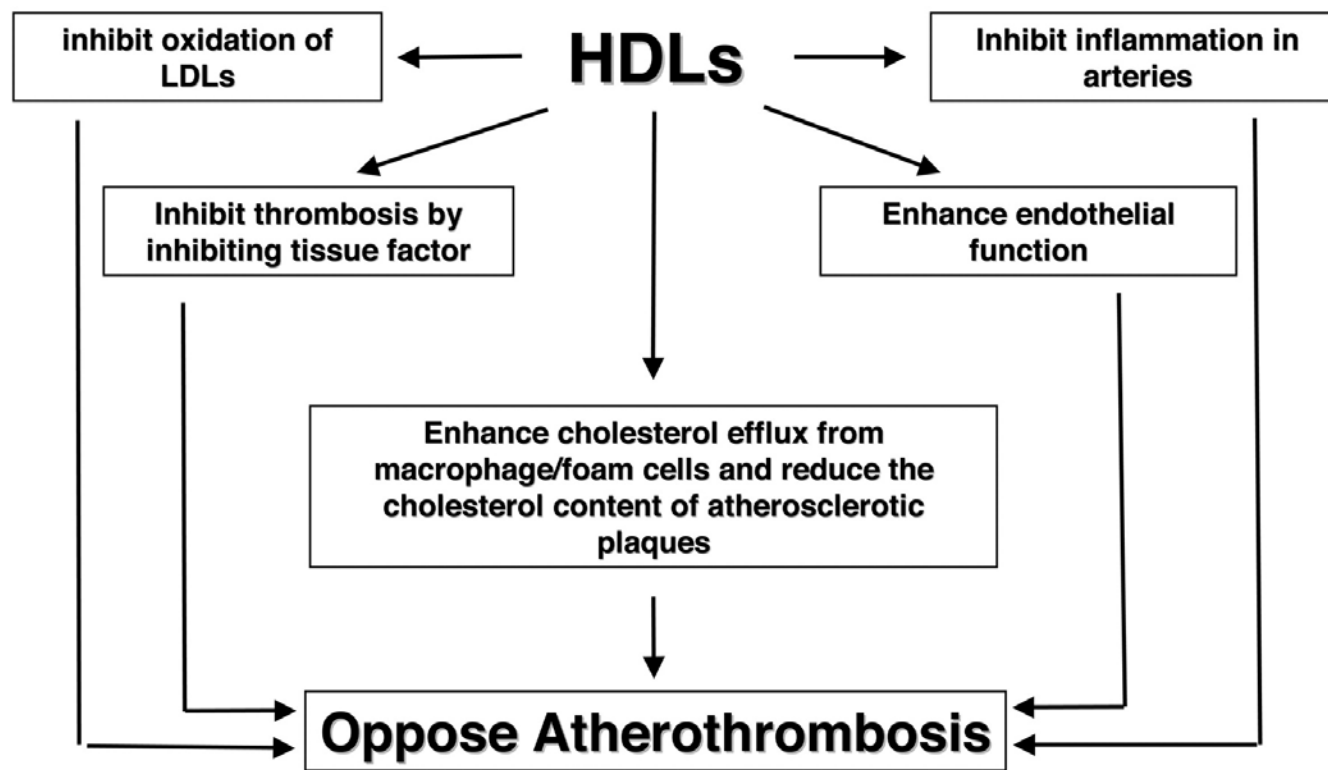| Group	CETP	Cholesterol			Apoproteins	
		Total	HDL	LDL	AI	B
	ug/ml		(mg/dl)		(mg/ml)	
Homozyg. (10)	0*	271*	164* (209%)	77* (-44%)	2.13* (72%)	0.54* (-31%)
Heterozyg. (20)	1.4* (0.3)	195	66 (25%)	111 (-5%)	1.49* (20%)	0.66 (-15%)
Normal (10)	2.3	189	53	117	1.24	0.78

From: Inazu et al. N. Engl. J. Med. 323:1234 (1990)

* Significant difference from Unaffected p<0.05

numbers in parathesis are % change
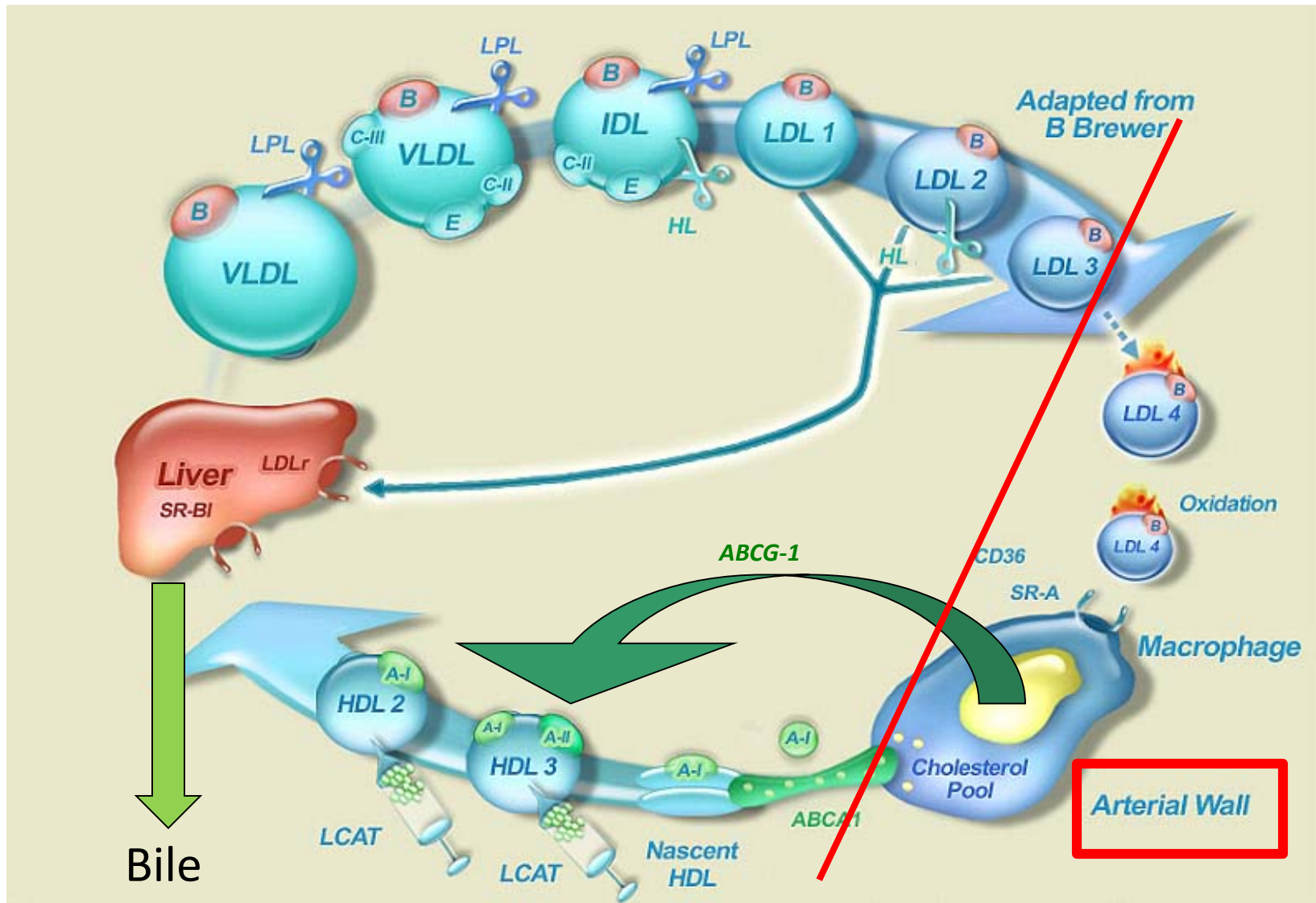
Mechanisms of HDL-C protection

Plausibility

- Reverse cholesterol transport
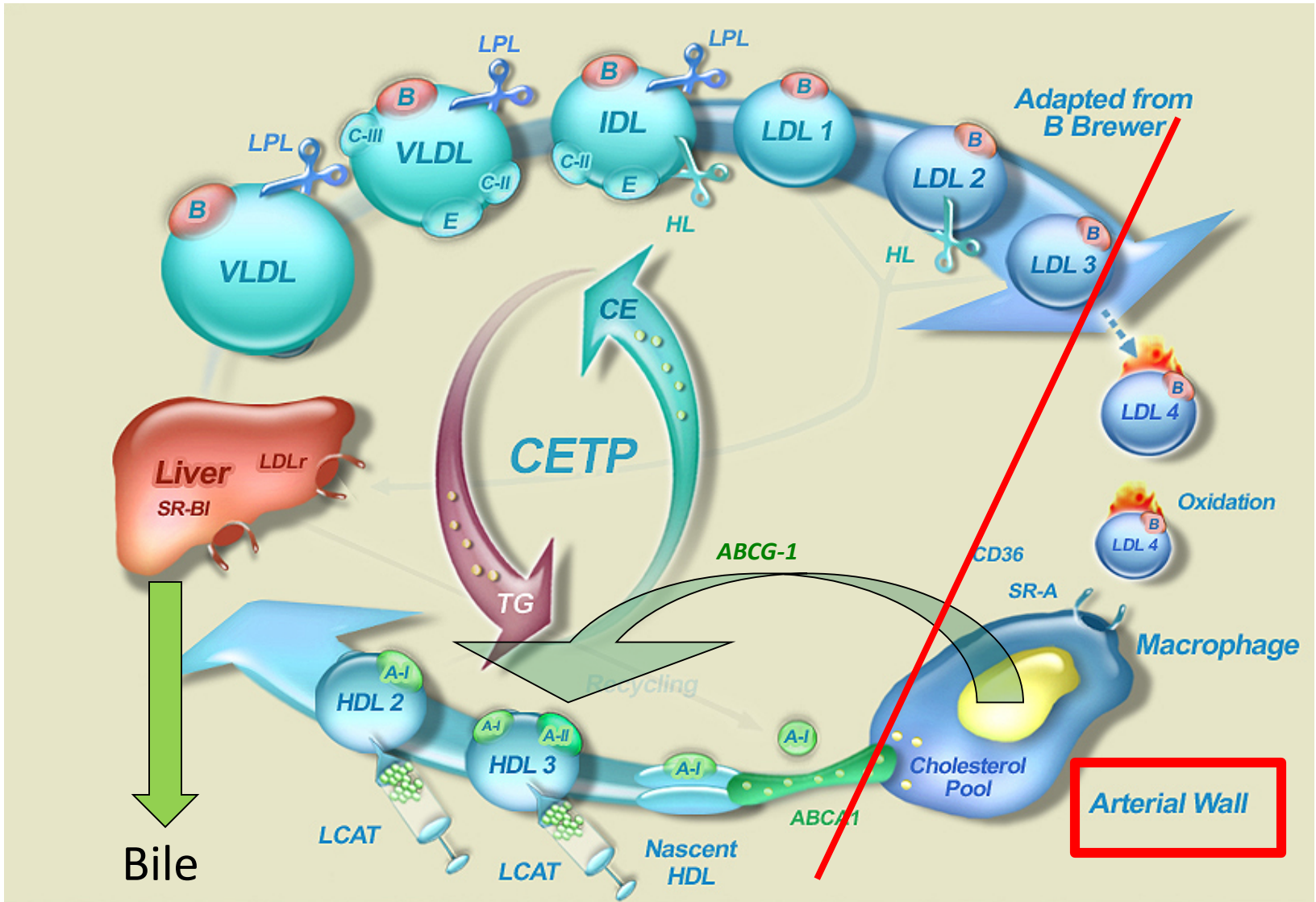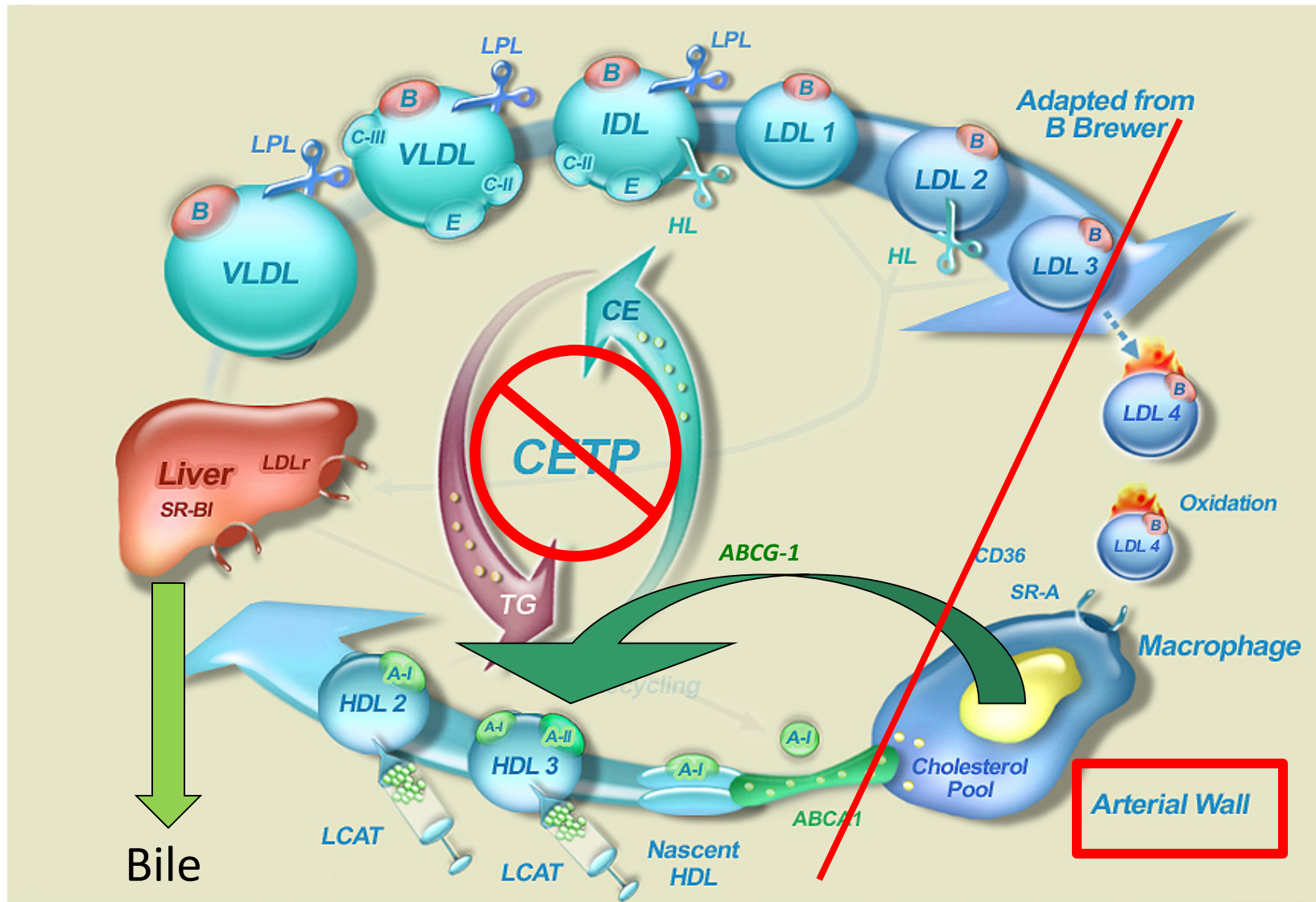- Direct effects on vascular wall

Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events

atorvastatin run-in to LDL <100 mg/dL (2.6 mmol/L) 4-10 weeks	15,067 →	torcetrapib + titrated atorvastatin dose
		Planned 4.5 years of treatment
		titrated atorvastatin dose
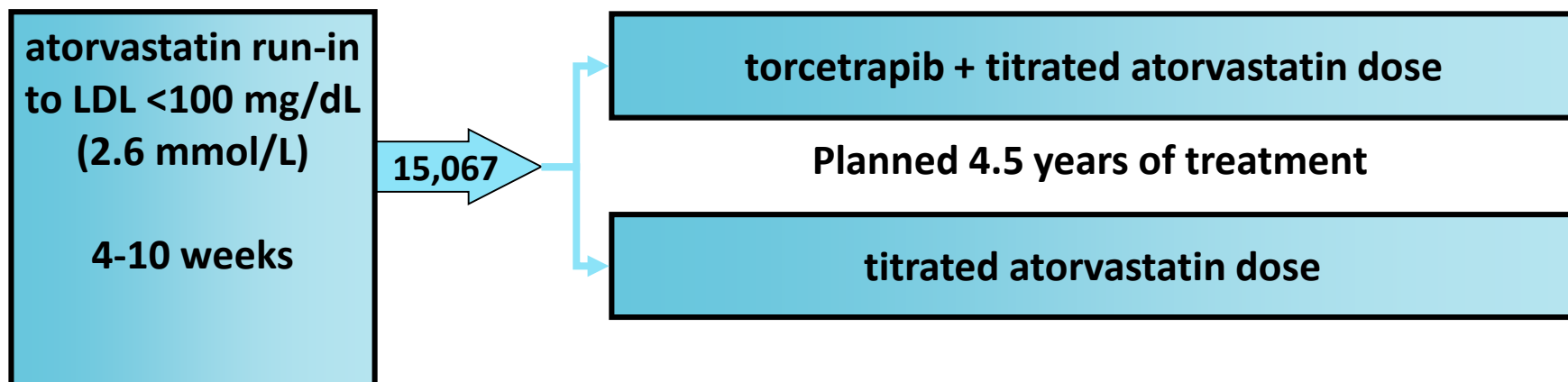
On Dec 2, 2006, after a median follow-up on-treatment of 550 days:
- Prematurely terminated based on the totality of evidence
- Statistically significant excess of deaths (which crossed the pre-defined statistical boundary) and cardiovascular events in the group treated with torcetrapib
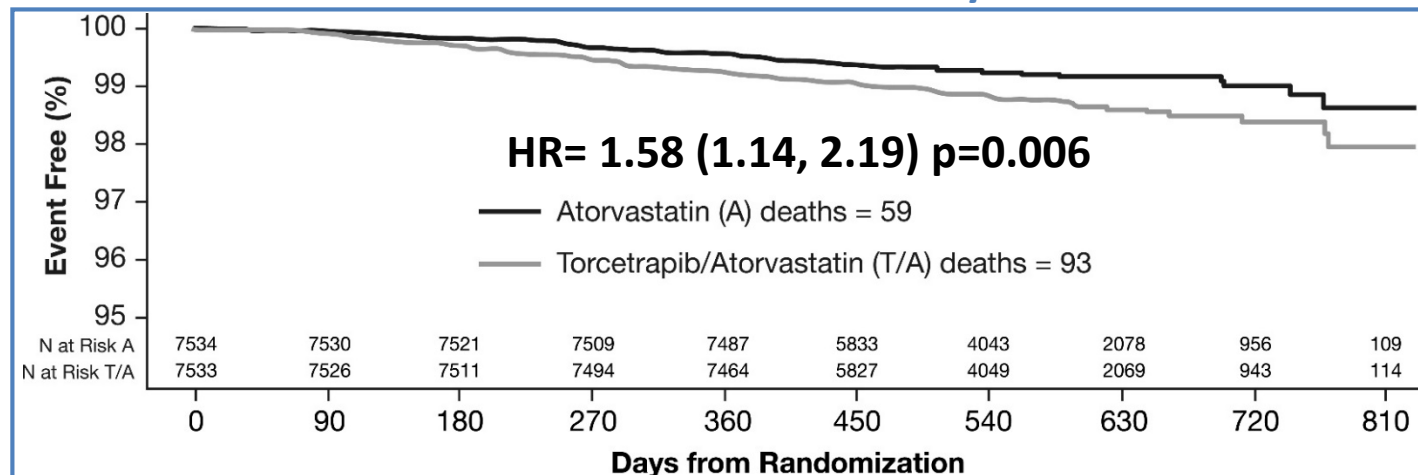
Barter PJ, Caulfield M, Eriksson M, et al. N Engl J. Med 2007;357:2109-22

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All-cause mortality

HR= 1.58 (1.14, 2.19) p=0.006

Atorvastatin (A) deaths = 59
Torcetrapib/Atorvastatin (T/A) deaths = 93

N at Risk A	7534	7530	7521	7509	7487	5833	4043	2078	956	109
N at Risk T/A	7533	7526	7511	7494	7464	5827	4049	2069	943	114

Days from Randomization

Major Cardiovascular Events

HR= 1.25 (1.09, 1.44) p=0.001

Atorvastatin (A) events = 373
Torcetrapib/Atorvastatin (T/A) events = 464

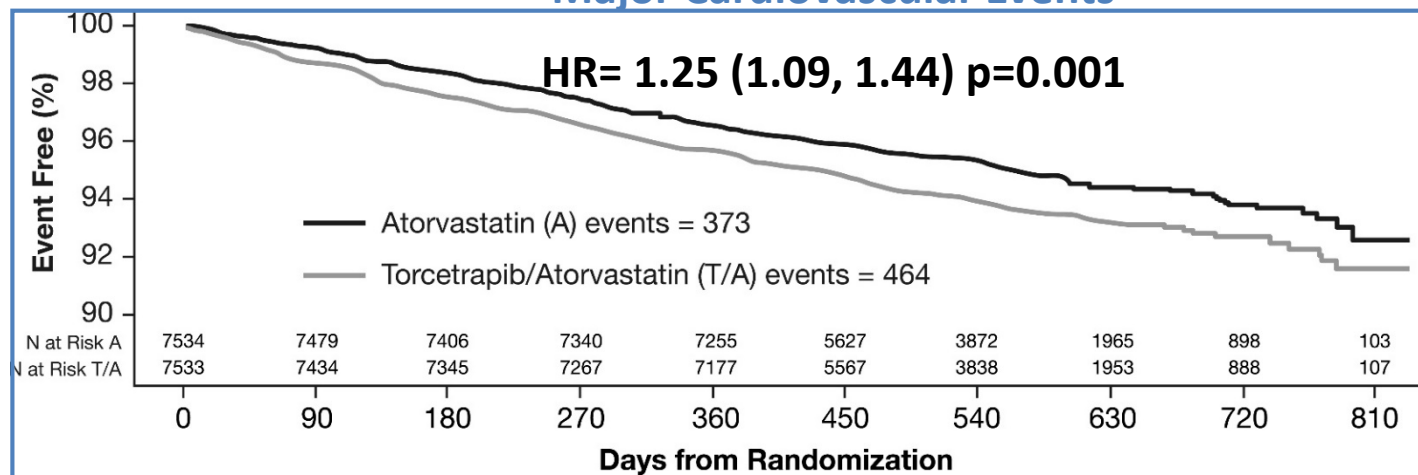|									
N at Risk A	7534	7479	7406	7340	7255	5627	3872	1965	898	103
N at Risk T/A	7533	7434	7345	7267	7177	5567	3838	1953	888	107

Days from Randomization

Lipids
12 months

HDL-C

T/A + 72%
A   + 2%

LDL-C

T/A - 22%
A   + 1%

Barter PJ, Caulfield M, Eriksson M, et al. N Engl J. Med 2007;357:2109-22

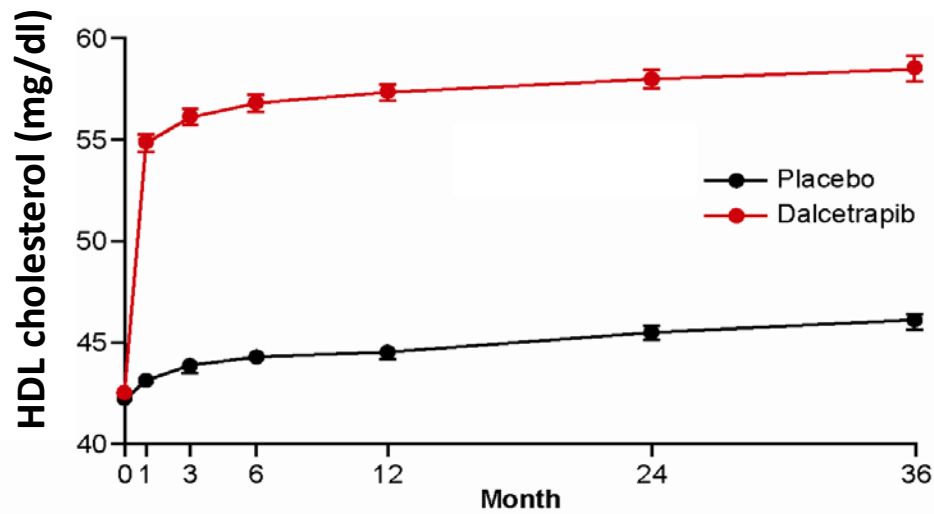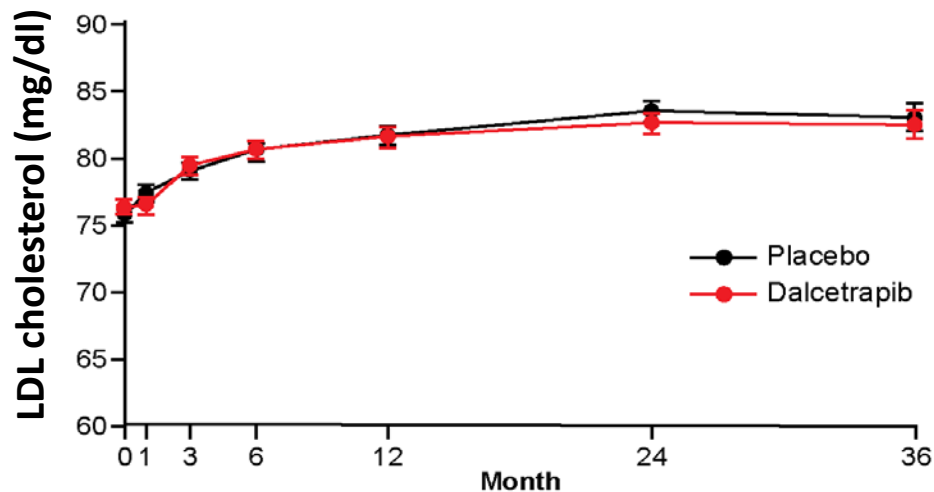|	Torcetrapib 60 mg (12 mo)	Dalcetrapib 900 mg (4 week)	Anacetrapib 150 mg (4 week)
% Δ HDL	+ 72%	~ + 34%	~ + 80%
% Δ LDL	- 25%	~ - 7%	~ - 35%
Δ SBP	**+5.5 mmHg**	**not reported**	**+ 0.6 mmHg**
Aldosterone pre-clinical	+	?	-

Dalcetrapib
HDL-C and LDL-C by treatment group

N=15,871

Data are mean ± 95% CI

Schwartz GG, Olsson AG, Abt M, et al. N Engl J Med. 2012;367(22):2089-99

Legend: Placebo, Dalcetrapib

P = 0.52 by log rank test

Hazard ratio 1.04
(95% CI 0.93-1.16)

Axes: Cumulative % of Patients with Primary Outcome (y-axis), Year (x-axis)
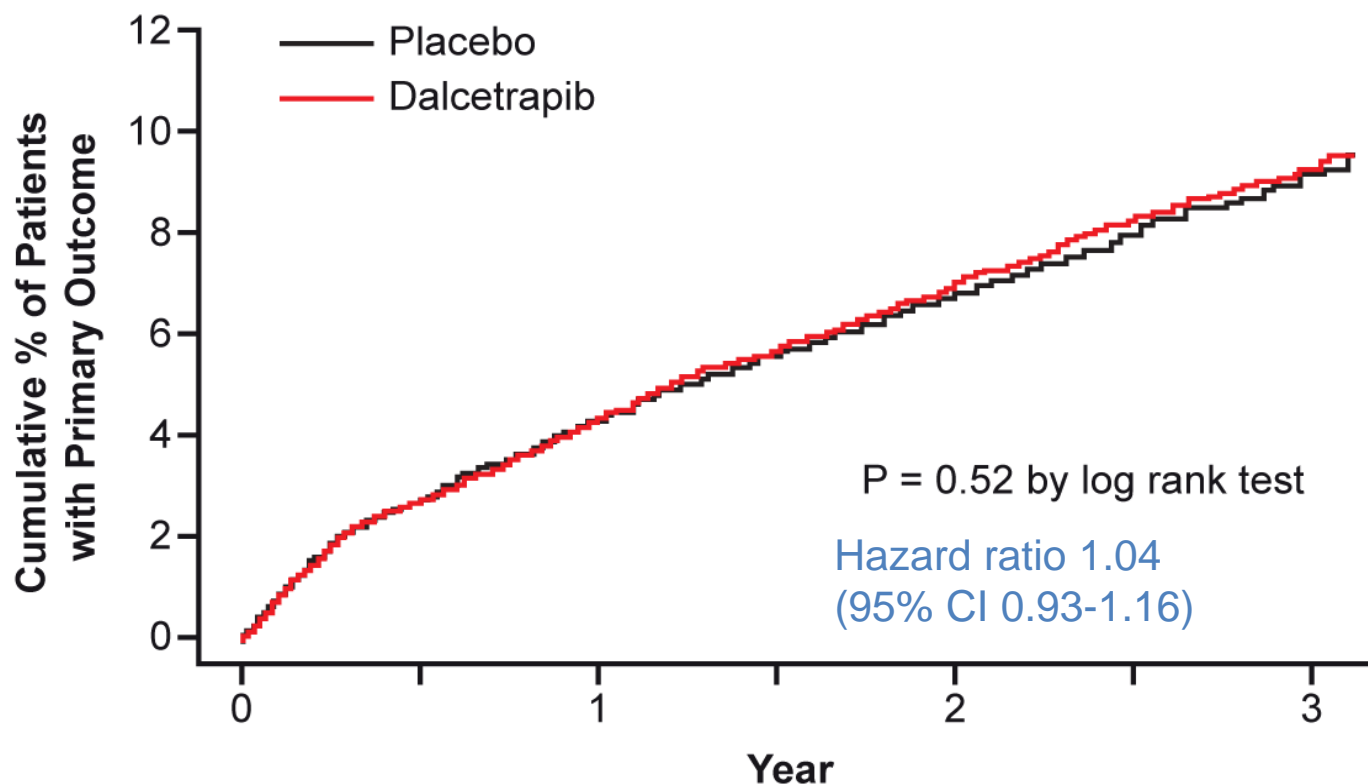
No. at Risk

Placebo	7933	7386	6551	1743
Dalcetrapib	7938	7372	6495	1736

* Coronary heart disease death, non-fatal MI, ischemic stroke, hospitalization for unstable angina, resuscitated cardiac arrest

Schwartz GG, Olsson AG, Abt M, et al. N Engl J Med. 2012;367(22):2089-99

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Anacetrapib
HDL-C and LDL-C by treatment group

Lipid or Lipoprotein	Anacetrapib (N = 15,225)	Placebo (N = 15,224)	Absolute Difference†	Relative Difference
				percent
Mean LDL cholesterol (mg/dl)				
Direct method	38	64	−26	−41
Beta quantification‡	53	63	−11	−17
Mean non-HDL cholesterol (mg/dl)	79	96	−17	−18
Mean HDL cholesterol (mg/dl)	85	42	43	104
Mean apolipoprotein A1 (mg/dl)	160	118	42	36
Mean apolipoprotein B (mg/dl)	54	66	−12	−18
Mean triglycerides (mg/dl)	136	146	−10	−7
Mean lipoprotein(a) (nmol/liter)	43	58	−15	−25

The HPS3/TIMI55–REVEAL Collaborative Group. N Engl J Med. 2017;377:1217-1227

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A First Major Coronary Event

Rate ratio, 0.91 (95% CI, 0.85–0.97)
P=0.004

Placebo

Anacetrapib

Patients with Event (%)

Years of Follow-up
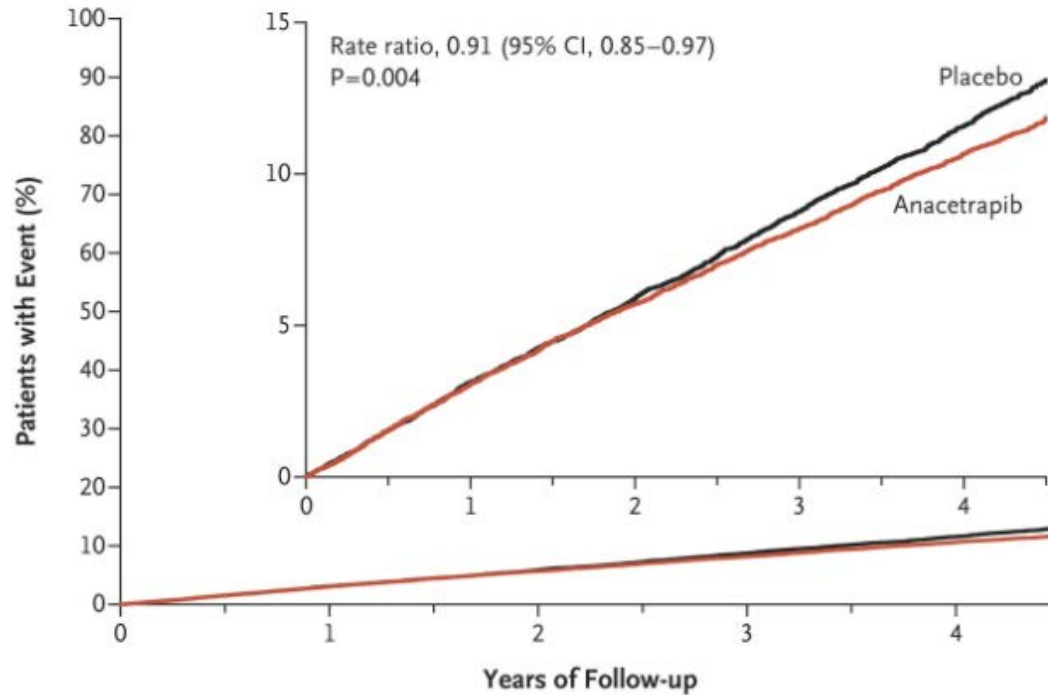
No. at Risk					
Placebo	15,224	14,649	14,088	13,293	8993
Anacetrapib	15,225	14,656	14,104	13,359	9193
Benefit per 1000 patients in anacetrapib group		1±2	2±3	6±3	9±4

* Coronary heart disease death, non-fatal MI, or coronary revascularization

The HPS3/TIMI55–REVEAL Collaborative Group. N Engl J Med. 2017;377:1217-1227

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HDL-C as a Surrogate Endpoint
Summary conclusions

- While HDL-C is an appears to be an established epidemiologic predictor of CV risk, the modification of HDL-C levels by CETP inhibition, in and of itself, does not appear to provide clinical benefit

- The modest CV risk reduction seen in the REVEAL study can be accounted for by the additional LDL-C and non-HDL-C lowering

- **Non-acceptance of HDL-C as a surrogate endpoint and requiring further clinical trial evidence was the appropriate action**

Lipids and Surrogate Endpoint Qualification
Summary

- The identification of cholesterol as a causal agent of vascular injury, in both man, and some animals, was the foundation for its eventual acceptance as a surrogate biomarker of risk

- With the identification of subsets of lipoproteins that transported circulating cholesterol, as predictive of cardiovascular risk, it became feasible to attempt to modify their levels, in the assessment of safety and efficacy of potential treatments

- It subsequently became possible to demonstrate the dose related efficacy of novel lipid modifying agents which showed a direct correlation between the level of the circulating biomarker (LDL-C) and clinical outcomes

- This same paradigm for biomarker validation revealed the failure of HDL-C to meet the same standard as a surrogate of clinical benefit

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Question and Answer Session

- LDL lowering has been shown to reduce risk of cardiac events with several different mechanisms.
  - Do you think there is sufficient proof of universality or should the regulators require post marketing studies to proof the reduction in cardiac events?

- Increasing HDL has not been accepted as a surrogate for cardiovascular benefit.
  - Important to understand different mechanisms & effects on a surrogate (safety vs. efficacy)
    - i.e. Impacts of negative outcome of increased BP with Torcetrapib

- Does a single neutral or negative correlation to outcome eliminate potential for surrogacy?
  - Increase HDL (i.e. different class) - what is required or what additional evidence is needed?

- Influence of approved drugs on future decision-making?
  - PCSK9 was given a fairly broad label with approval
  - Would future drugs (classes) with strong genetic causality be treated similarly?

- Could the elevation of HDL and reduction of LDL "in combination" be a possible surrogate?

- Strength of Causality (robust genetics) & Plausibility (inference of correlations to outcomes)
  - Different weights applied to level of evidence