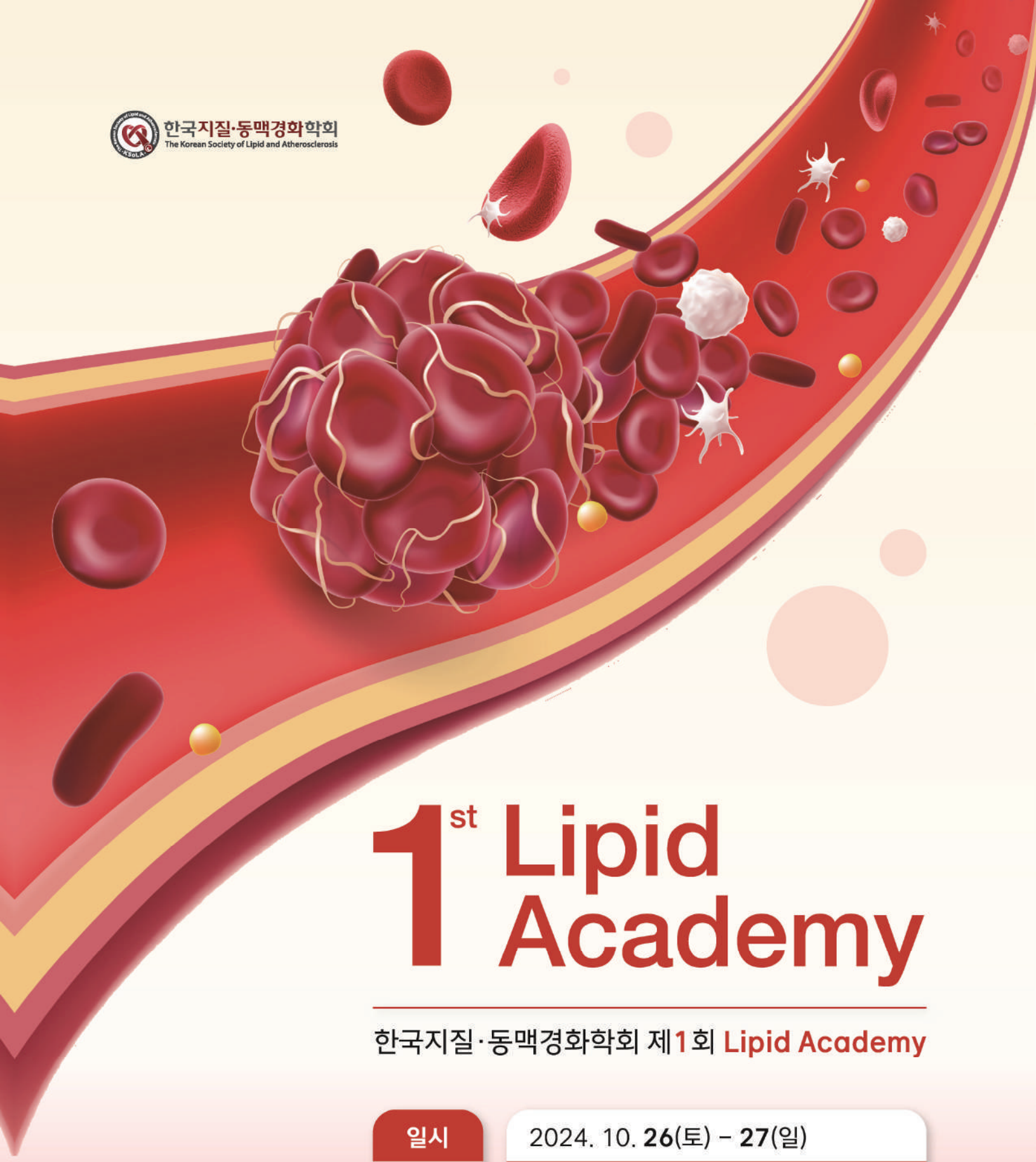
한국지질·동맥경화학회
The Korean Society of Lipid and Atherosclerosis



1st Lipid Academy

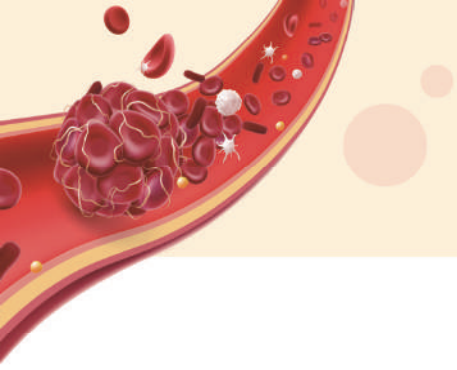
한국지질·동맥경화학회 제1회 Lipid Academy

일시	2024. 10. **26**(토) – **27**(일)
장소	앰배서더 서울 풀만, B1 레거시룸
주최	한국지질·동맥경화학회 교육위원회

PROGRAM

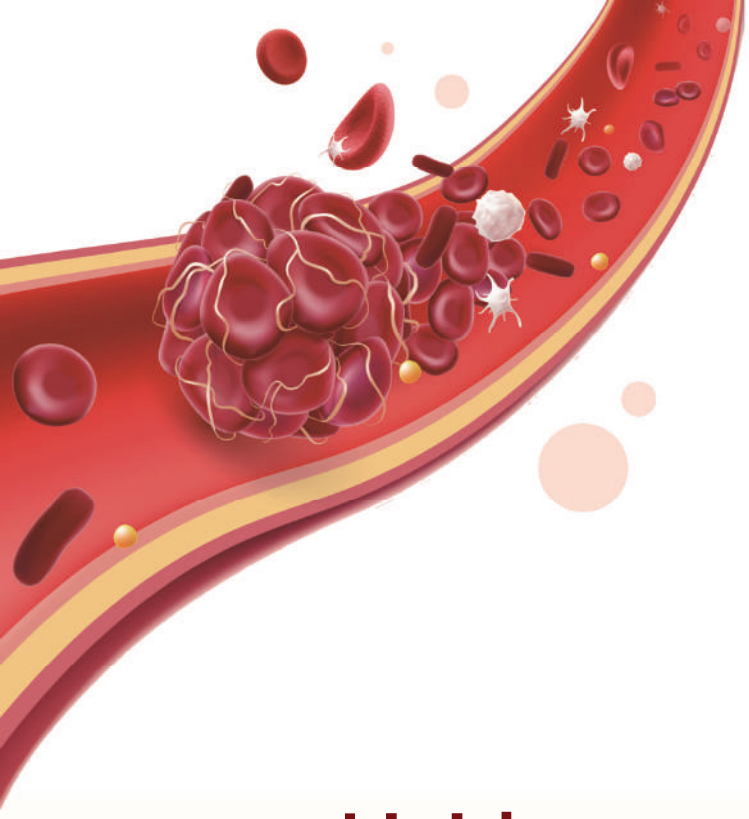
Day 1

08:50 – 08:55	Opening Remarks	김재택 (중앙의대 내분비내과)
08:55 – 09:00	Greeting and Welcome	정익모 (이화의대 순환기내과)
Session 1. Lipidogenesis and Metabolism: Decoding the Complexity		
09:00 – 09:30	Lipids: Functions and Metabolism	문영아 (인하의대 의예과) / 3
09:30 – 10:00	Clinical Application of Apolipoprotein: An Updated Overview Focused on ApoB	김신곤 (고려의대 내분비내과) / 21
10:00 – 10:20	토론	
10:20 – 10:30	*Break Time*	
Session 2. Deciphering LDL Cholesterol Dynamics		
10:30 – 11:00	Insights into Genetic and Enzymatic Machinery of Cholesterol Synthesis and Metabolism	박상욱 (연세의대 생화학분자생물학교실) / 45
11:00 – 11:30	Current Landscape of LDL Cholesterol Lowering Therapies: Pharmaceuticals and RCTs Overview	김상현 (서울의대 순환기내과) / 55
11:30 – 12:00	토론	
12:00 – 13:00	*점심식사 및 photo time*	
Session 3. Exploring Residual Lipid Risks(I)		
13:00 – 13:30	Unveiling the Genetic and Enzymatic Machinery of Triglyceride Synthesis and Metabolism	남궁준 (연세원주의대 생화학교실) / 59
13:30 – 14:00	Latest Insights into TG-lowering Therapies: Pharmaceuticals and RCTs Summary	김병진 (성균관의대 순환기내과) / 75
14:00 – 14:20	토론	
14:20 – 14:30	*Break Time*	
Session 4. Exploring Residual Lipid Risks(II)		
14:30 – 15:00	Unraveling the Enigma of LP(a) and Perspectives on LP(a) Treatment	이장훈 (경북의대 순환기내과) / 111
15:00 – 15:30	Role of HDL Cholesterol and Current Evidence on HDL Cholesterol Treatments	박훈준 (가톨릭의대 순환기내과) / 143
15:30 – 15:50	토론	
15:50 – 16:20	*Break Time*	
16:20 – 17:00	Humanities Lecture	조성준 (성균관의대 정신건강의학과) / 169
18:00 –	*Dinner*	



Day 2

Session 1. Understanding of Severe Dyslipidemia		
09:00 – 09:30	Key Points You Need to Know About FH	이상학 (연세의대 심장내과) / 173
09:30 – 10:00	Insights into the Etiology, Diagnosis, and Treatment of Severe Hypertriglyceridemia	정인경 (경희의대 내분비내과) / 175
10:00 – 10:20	토론	
10:20 – 10:40	*Break Time*	
Session 2. Atherosclerosis Pathophysiology		
10:40 – 11:20	Lipid Measurement Methods and Interpretation	이상국 (연세의대 진단검사의학과) / 199
11:20 – 11:40	토론	
11:40 –	Closing Remarks	김병진 (성균관의대 순환기내과)



Day 1

Session 1

Lipidogenesis and Metabolism: Decoding the Complexity

(09:00 – 10:20)

09:00 – 09:30	Lipids: Functions and Metabolism	문영아 (인하의대 의예과)
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문 영 아

[기본정보]

성함	문 영 아
소속(근무처)	인하대학교 의과대학 분자의학교실

[학력]

해당년도	세부사항
1986-1992	연세대학교 의과대학 (M.D.)
1992-1994	연세대학교 대학원 의학과 (M.S.)
1994-1997	연세대학교 대학원 의학과 (Ph.D.)

[경력]

해당년도	세부사항
1998-2003	Postdoctoral Fellow, University of Texas Southwestern Medical Center
2003-2015	Assistant Professor, University of Texas Southwestern Medical Center
2015-현재	인하대학교 의과대학 분자의학교실- 조교수, 부교수, 교수

[관심분야]

Fatty acid metabolism
Cholesterol metabolism
Metabolic dysfunction-associated steatotic liver disease
Hepatocyte differentiation

[논문]

A male mouse model for metabolic dysfunction-associated steatotic liver disease and hepatocellular carcinoma. Nat Commun. 2024 (Coauthor)

Deletion of Elovl5 leads to dyslipidemia and atherosclerosis in LDLR-deficient mice. Biochem Biophys Res Commun. 2024 (Corresponding author)

Spinocerebellar ataxia 38: structure-function analysis shows ELOVL5 G230V is proteotoxic, conformationally altered and a mutational hotspot. Hum Genet. 2023 (Coauthor)

Tumor-mediated 4-1BB induces tumor proliferation and metastasis in the colorectal cancer cells. Life Sci. 2022 (Corresponding author)

Increased hepatic lipogenesis elevates liver cholesterol content. Mol Cells. 2021 (Corresponding author)

Lipids: Functions and Metabolism

문 영 아

인하의대 의예과

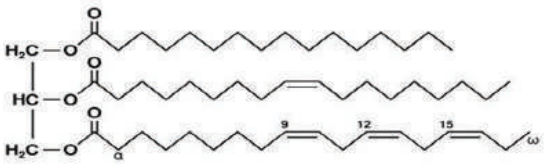
Contents:

1. Features and functions

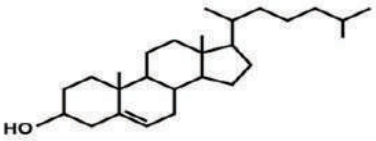
Lipids:

- Fats, oils, waxes, steroids
- Common properties:
  - insoluble in water
  - soluble in nonpolar solvents

<Fatty acid based lipids>



<Cholesterol based lipids>



1. Features and functions

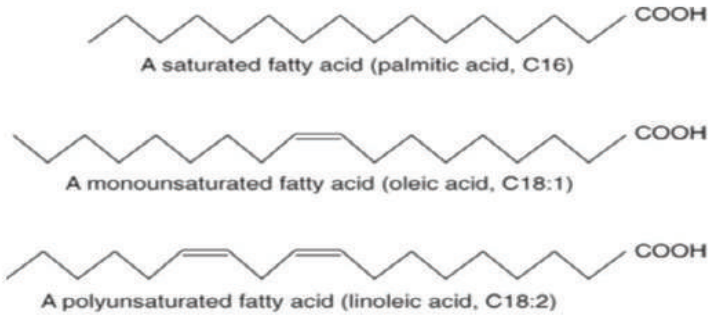
Functions:

- Storage of energy
- Major structural elements of biological membranes
- Other functions: Enzyme cofactors,
  Electron carriers,
  Light-absorbing pigments,
  Hydrophobic anchors for proteins,
  Emulsifying agents in digestive tract,
  Hormones,
  Intracellular messengers

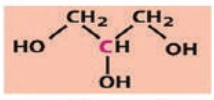
2. Fatty acids

Fatty acids:

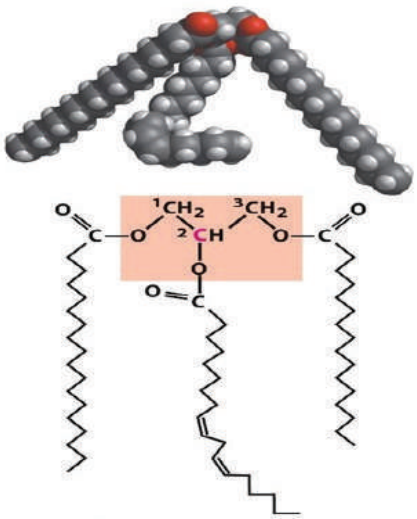
- Aliphatic carboxylic acids (C_4 to C_{36}).
- Contain even number of carbon atoms.
- Saturated or unsaturated.
- As esters in natural fats and oils, as free fatty acids.



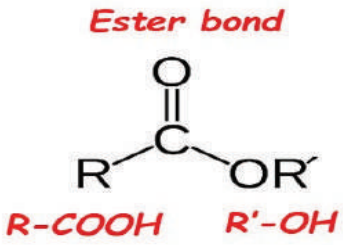
2. Fatty acids



Glycerol



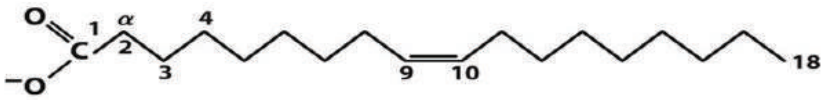
1-Stearoyl, 2-linoleoyl, 3-palmitoyl glycerol,
a mixed triacylglycerol



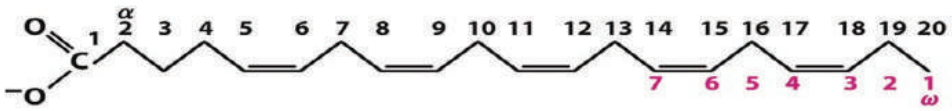
2. Fatty acids

❖ Nomenclature of Fatty acids

<systemic name>
- anoic for saturated fatty acids: octadecanoic acid (C_{18}, stearic acid)
- enoic for unsaturated fatty acids: octadecenoic acid (C_{18}, oleic acid)
- Δ for indicating the number and position of double bonds (count from 1)
- monounsaturated, polyunsaturated fatty acids
- ω9, ω6, ω9: position of double bonds (count from methyl end- ω carbon)



(a) 18:1(Δ^9) *cis*-9-Octadecenoic acid



(b) 20:5($\Delta^{5,8,11,14,17}$) Eicosapentaenoic acid (EPA), an omega-3 fatty acid

2. Fatty acids

Fatty acids with chain lengths of 4 to 10 carbons are found in significant quantities in milk.

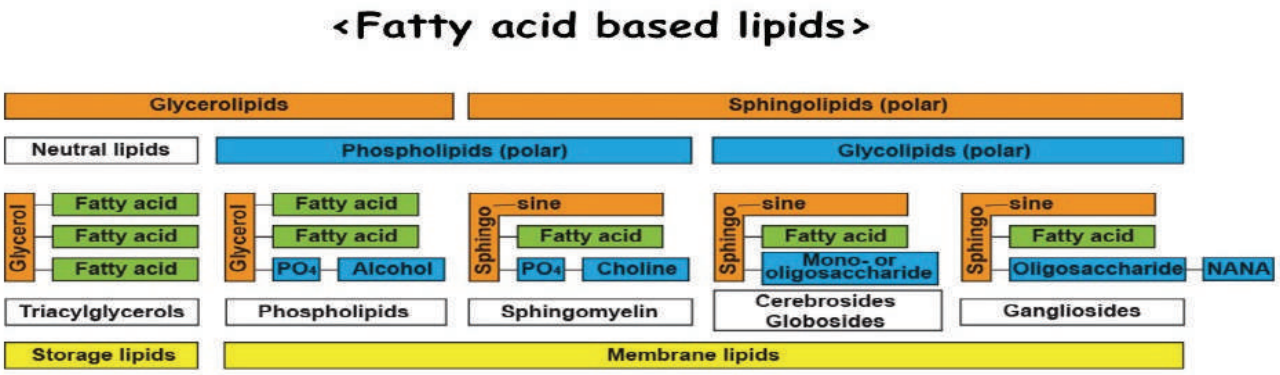
Structural lipids and triacylglycerols contain primarily fatty acids of at least 16 carbons.

COMMON NAME	STRUCTURE	
Formic acid	1	
Acetic acid	2:0	
Propionic acid	3:0	
Butyric acid	4:0	
Capric acid	10:0	
Palmitic acid	16:0	
Palmitoleic acid	16:1(9)	C16:1, ω-7
Stearic acid	18:0	
Oleic acid	18:1(9)	C18:1, ω-9
Linoleic acid	18:2(9,12)	C18:2, ω-6
α-Linolenic acid	18:3(9,12,15)	C18:3, ω-3
Arachidonic acid	20:4(5, 8,11,14)	C20:4, ω-6
Lignoceric acid	24:0	
Nervonic acid	24:1(15)	

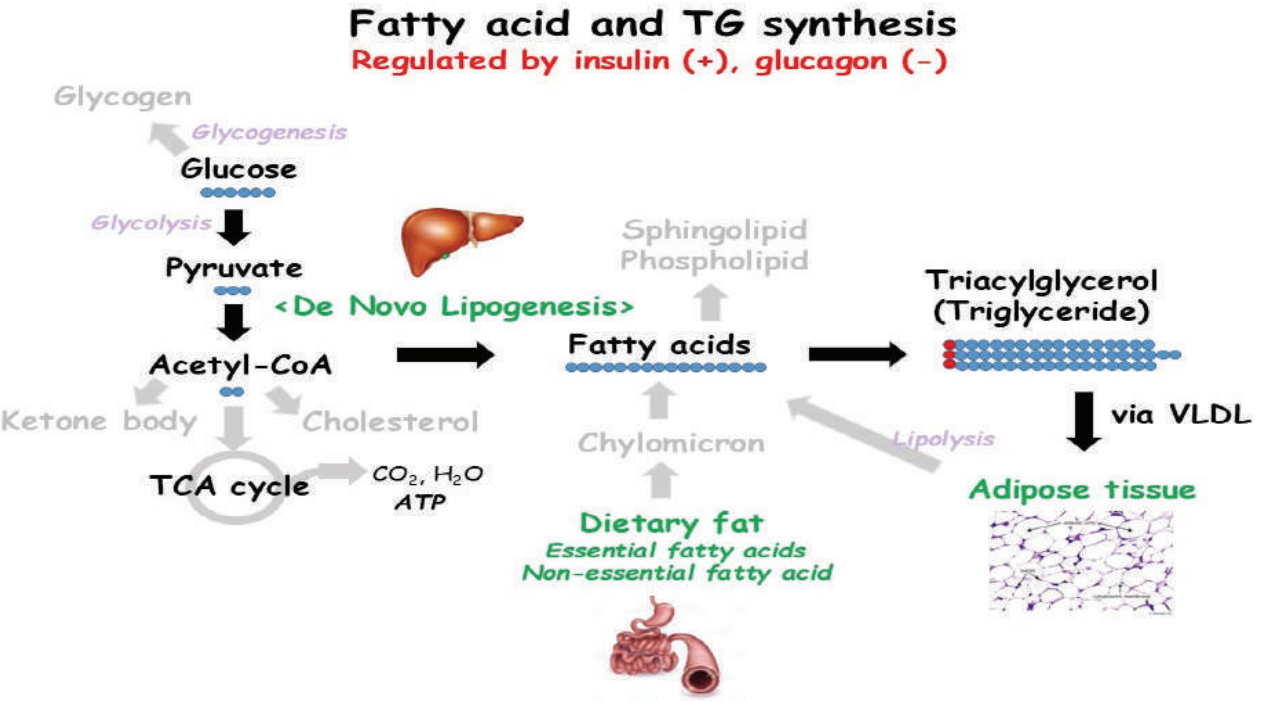
Precursor of prostaglandins

Essential fatty acids

3. Classification of lipids

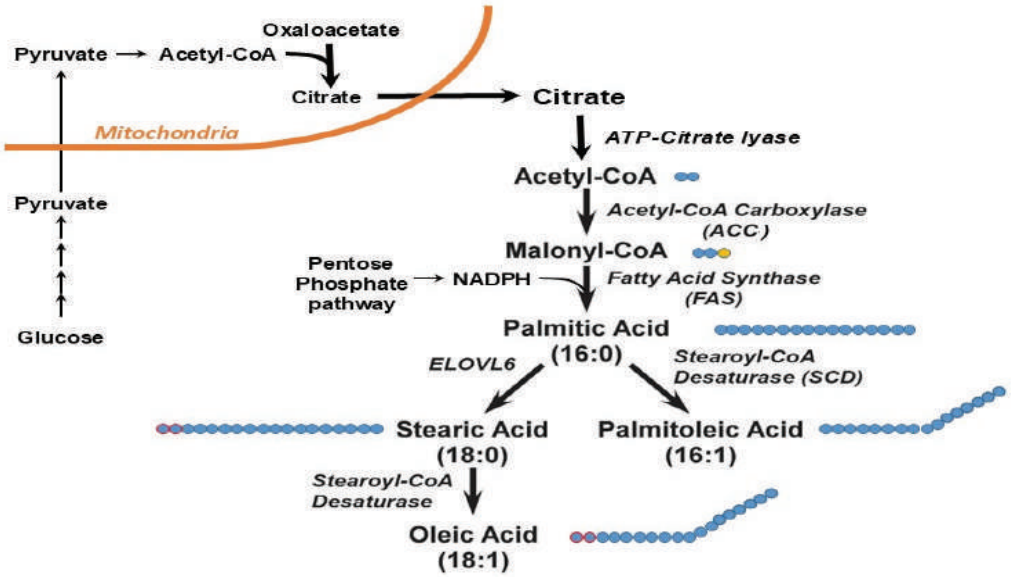


4. De novo synthesis of fatty acid and triacylglycerol



4. De novo synthesis of fatty acid and triacylglycerol

De novo synthesis of fatty acids

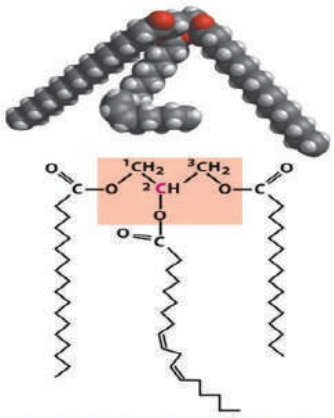


4. De novo synthesis of fatty acid and triacylglycerol

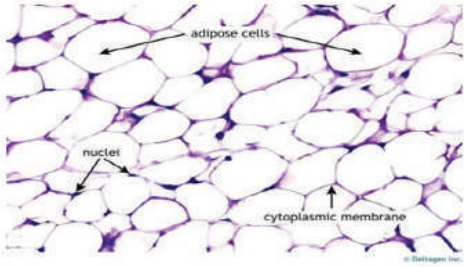
Biosynthesis of triacylglycerols

1. Storage of fatty acids as components of TAG
   - Structure: 3 fatty acids esterified to a glycerol molecule
   - Cytosolic lipid droplet as the major energy reservoir

Glycerol



1-Stearoyl, 2-linoleoyl, 3-palmitoyl glycerol, a mixed triacylglycerol



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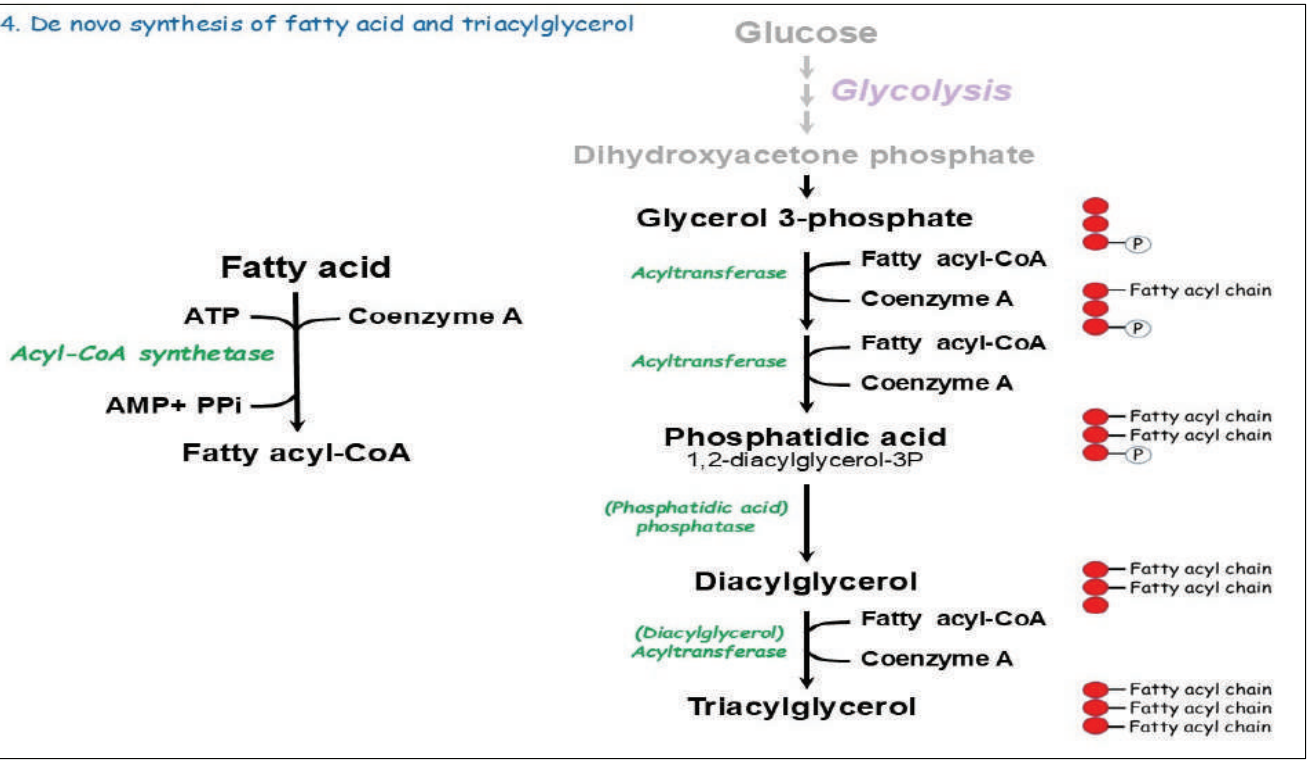
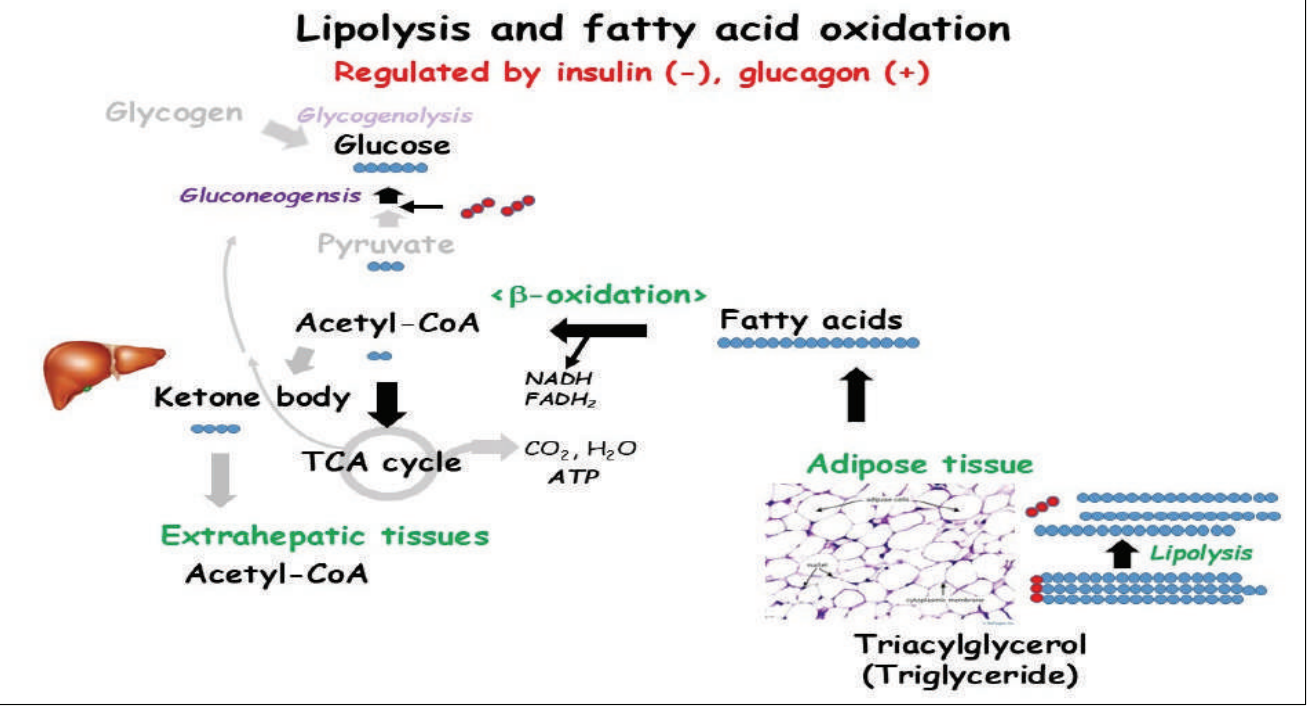
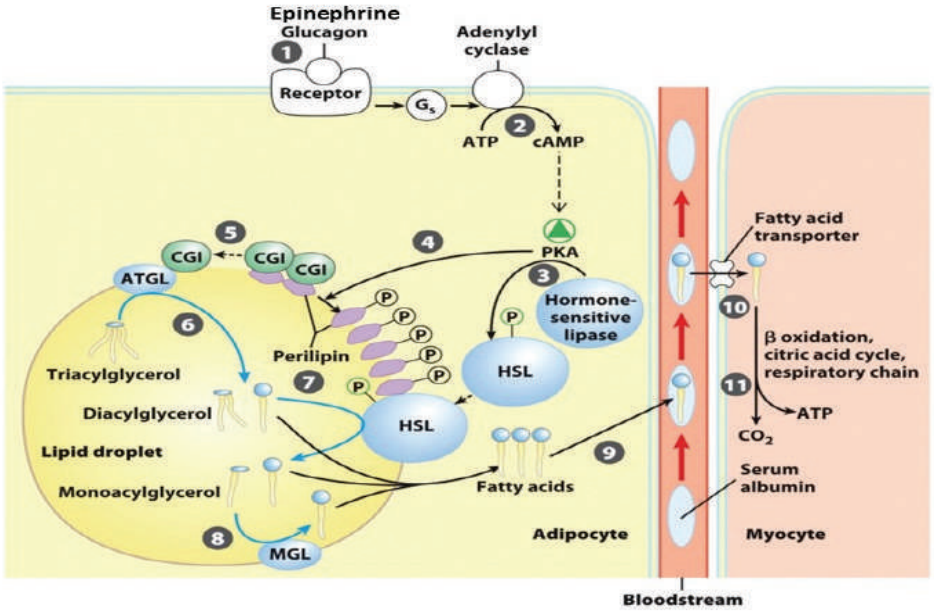


5. Lipolysis and fatty acid β-oxidation



5. Lipolysis and fatty acid β-oxidation

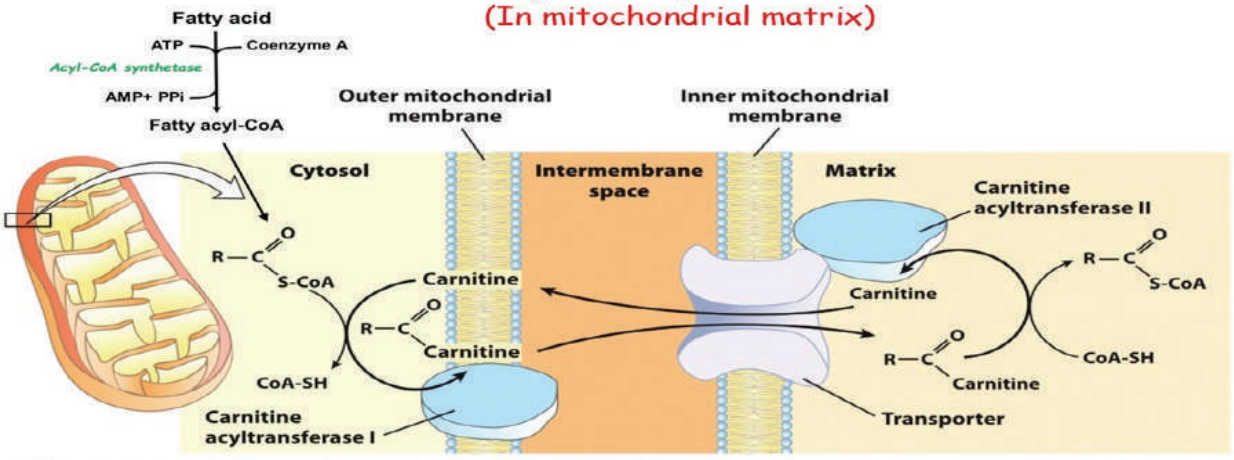
Mobilization of stored TAG triggered by hormones (from adipocytes)



5. Lipolysis and fatty acid β-oxidation

Fatty acid β-oxidation

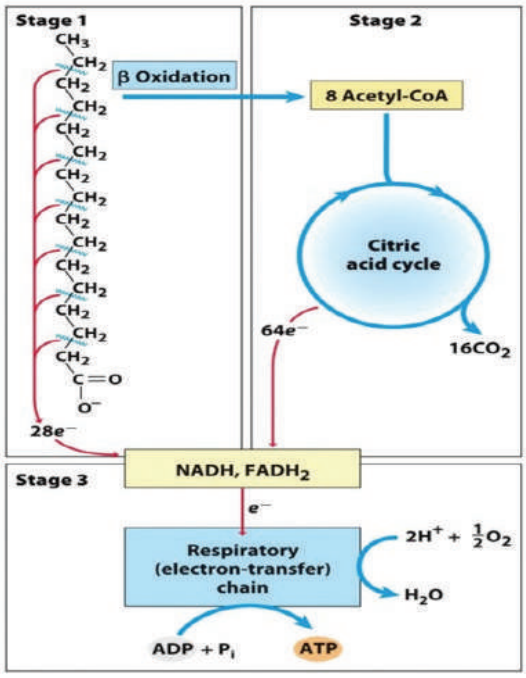
(In mitochondrial matrix)



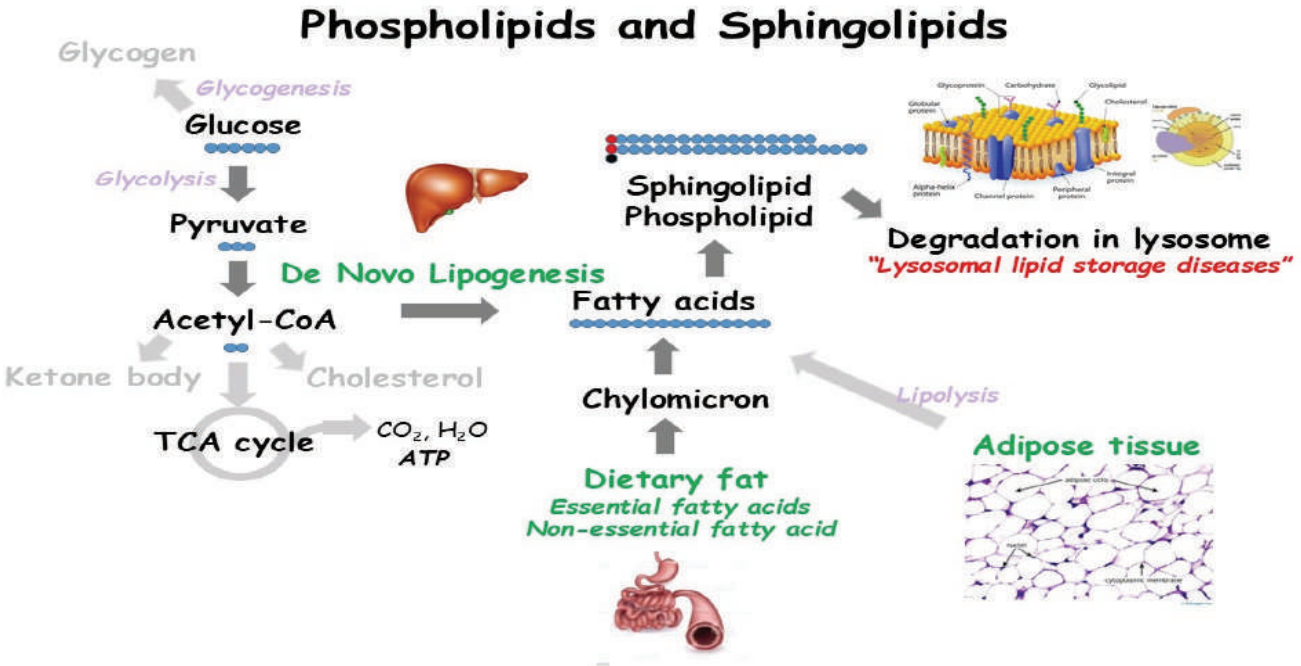
(Carnitine palmitoyltransferase I, CPT-1)

- Malonyl-CoA inhibits Carnitine acyltransferase-1, preventing the entry of acyl group to mitochondrial matrix.

5. Lipolysis and fatty acid β-oxidation



6. Phospholipids



6. Phospholipids

Glycerophospholipids:

- phospholipids containing glycerol as a backbone (phosphatidic acid)
- major class of phospholipids
- predominant lipids in membranes

Serine + PA: phosphatidylserine (PS)

Ethanolamine + PA: phosphatidylethanolamine (PE)

Choline + PA: phosphatidylcholine (PC)

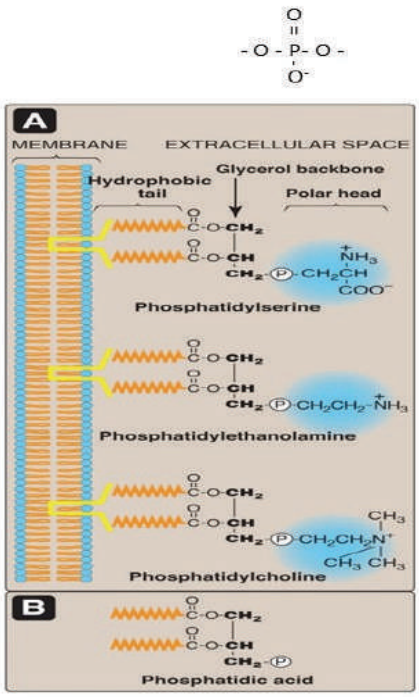
Inositol + PA: phosphatidylinositol (PI)

Glycerol + PA: phosphatidylglycerol (PG)

Cardiolipin

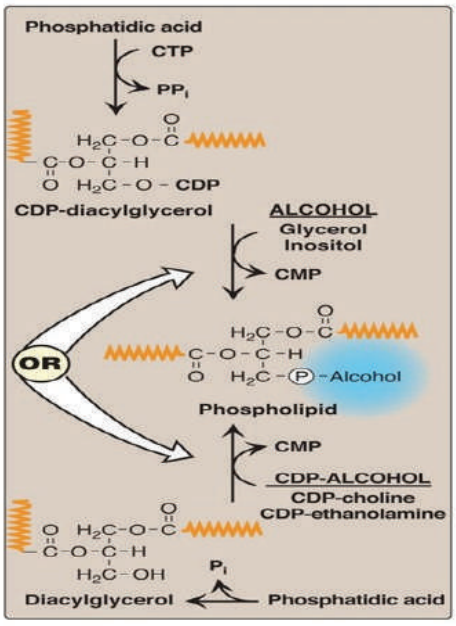
Plasminogens

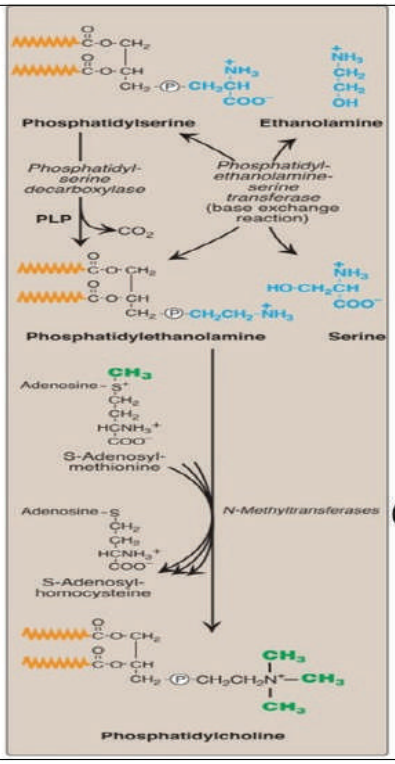
Platelet-activating factor (PAF)



6. Phospholipids

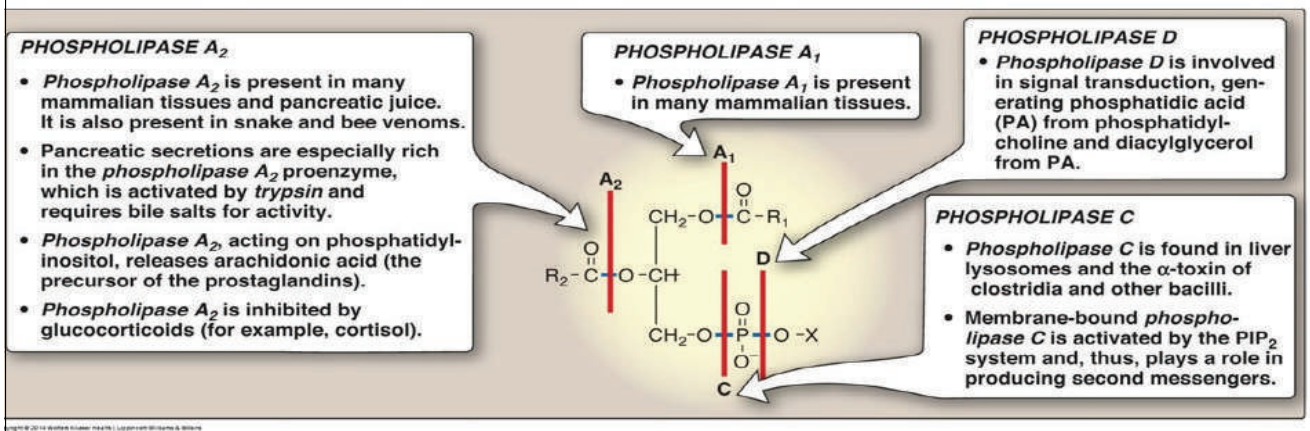
PC synthesis from PS, PE





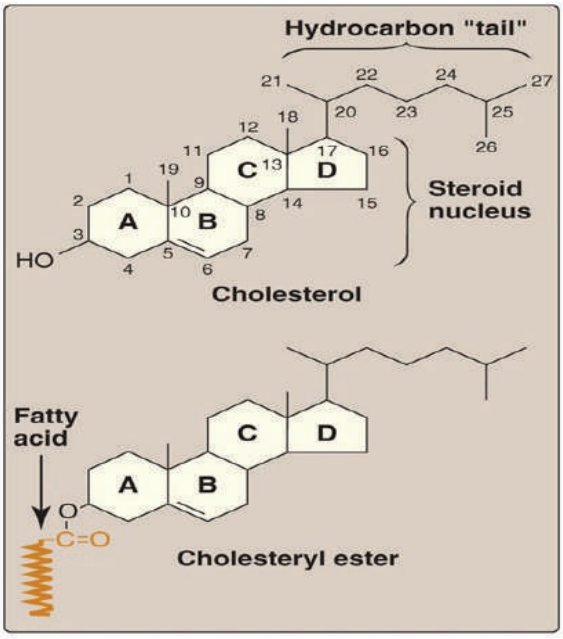
6. Phospholipids

Degradation of phospholipids by phospholipases



7. Cholesterol

Cholesterol



7. Cholesterol

Cholesterol

- Essential component of animal tissues
  - -Component of cell membrane
  - -Precursor of
    - bile acids
    - steroid hormones
    - vitamin D
- Not an energy source
- Hydrophobic molecule
- In lipoproteins in plasma

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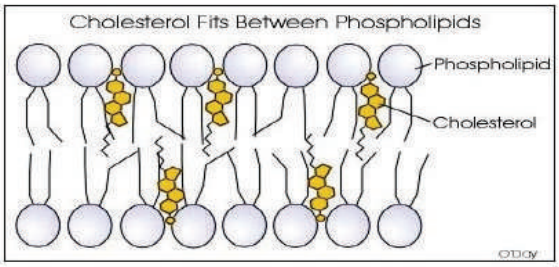
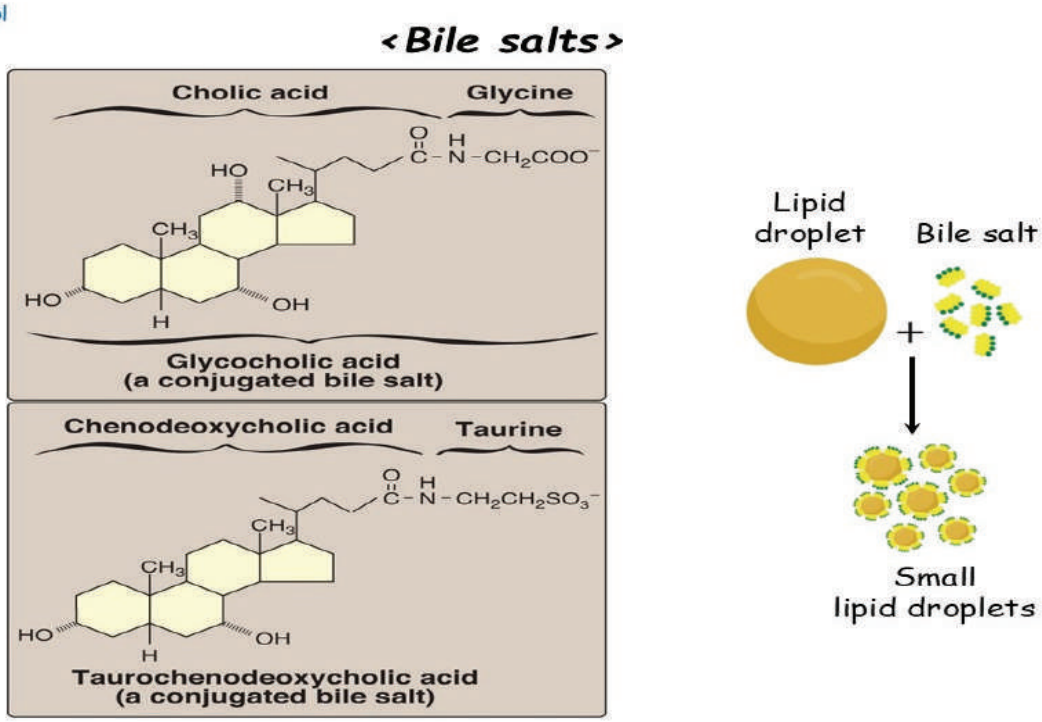


- Regulate membrane fluidity and stability (more cholesterol, less fluid, more stable)
- Reduce permeability

7. Cholesterol



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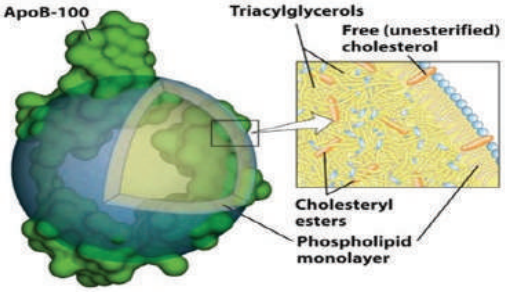
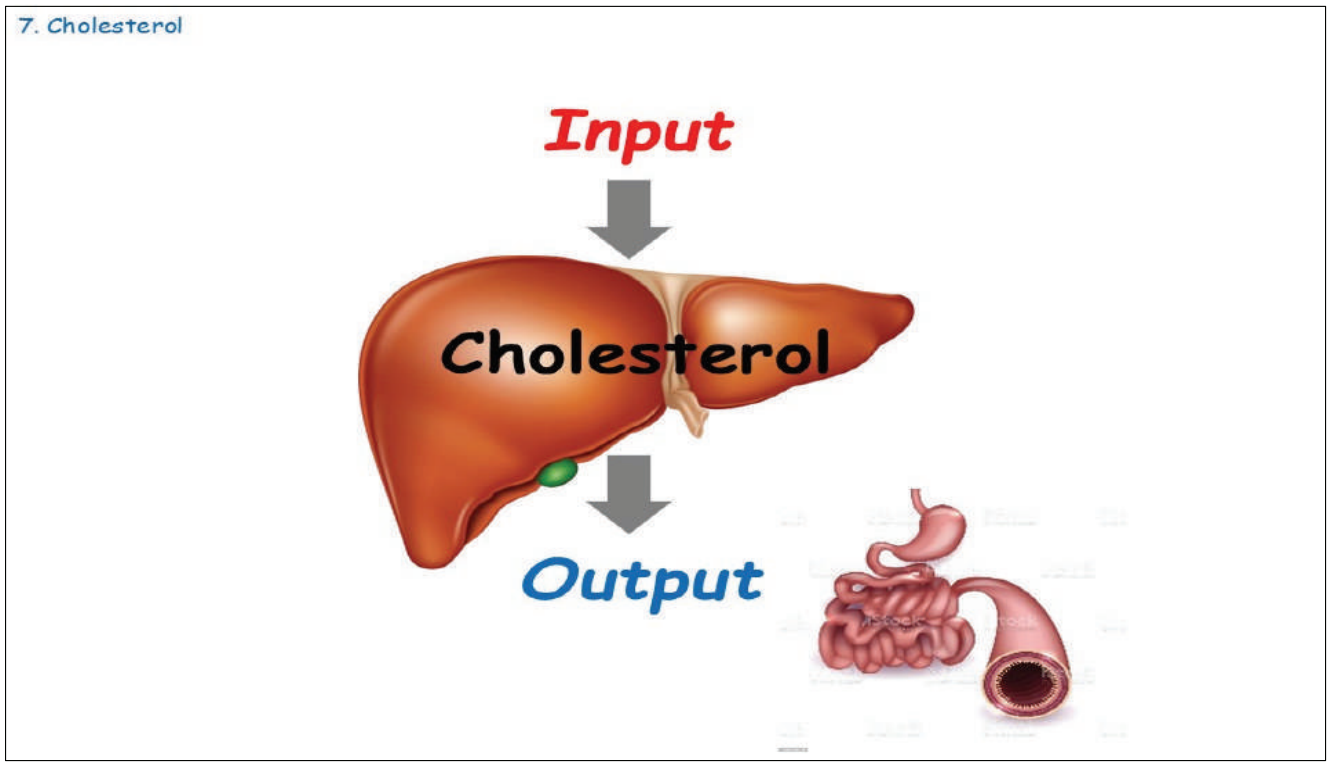
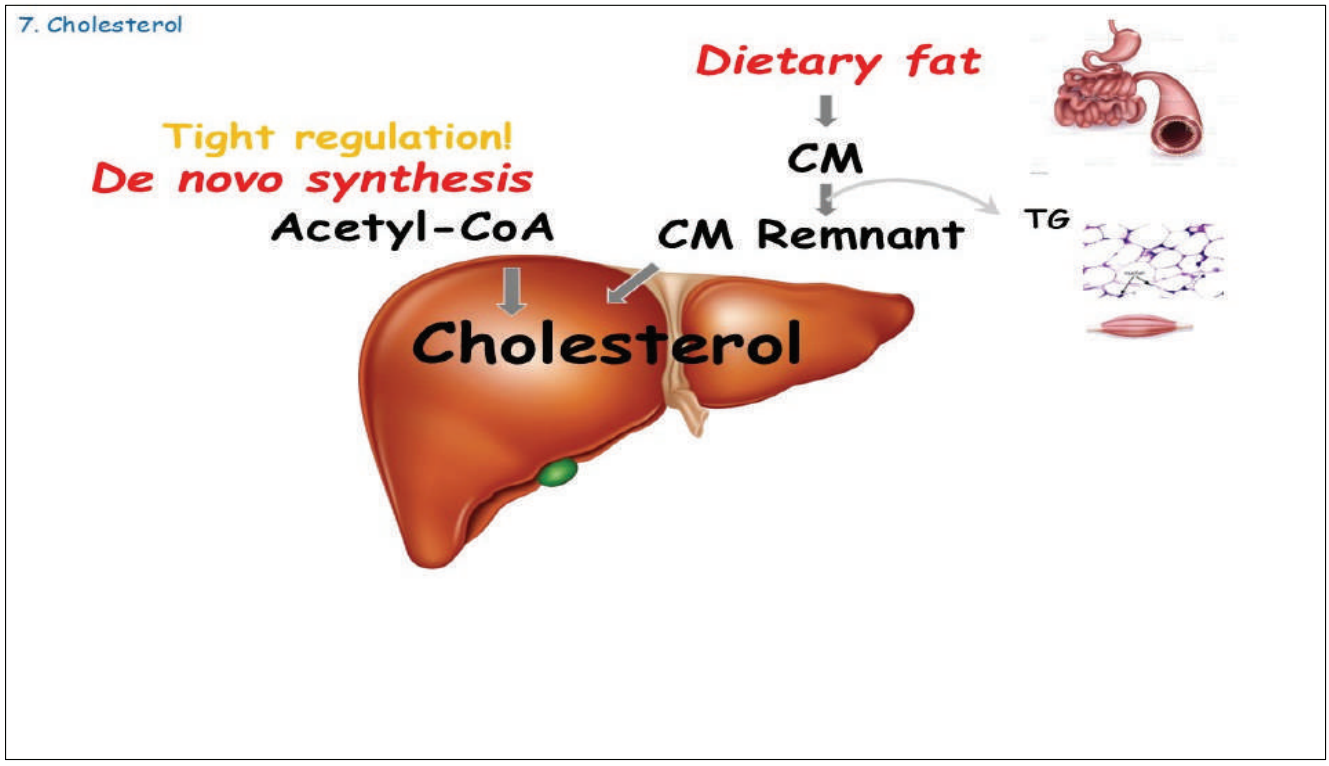
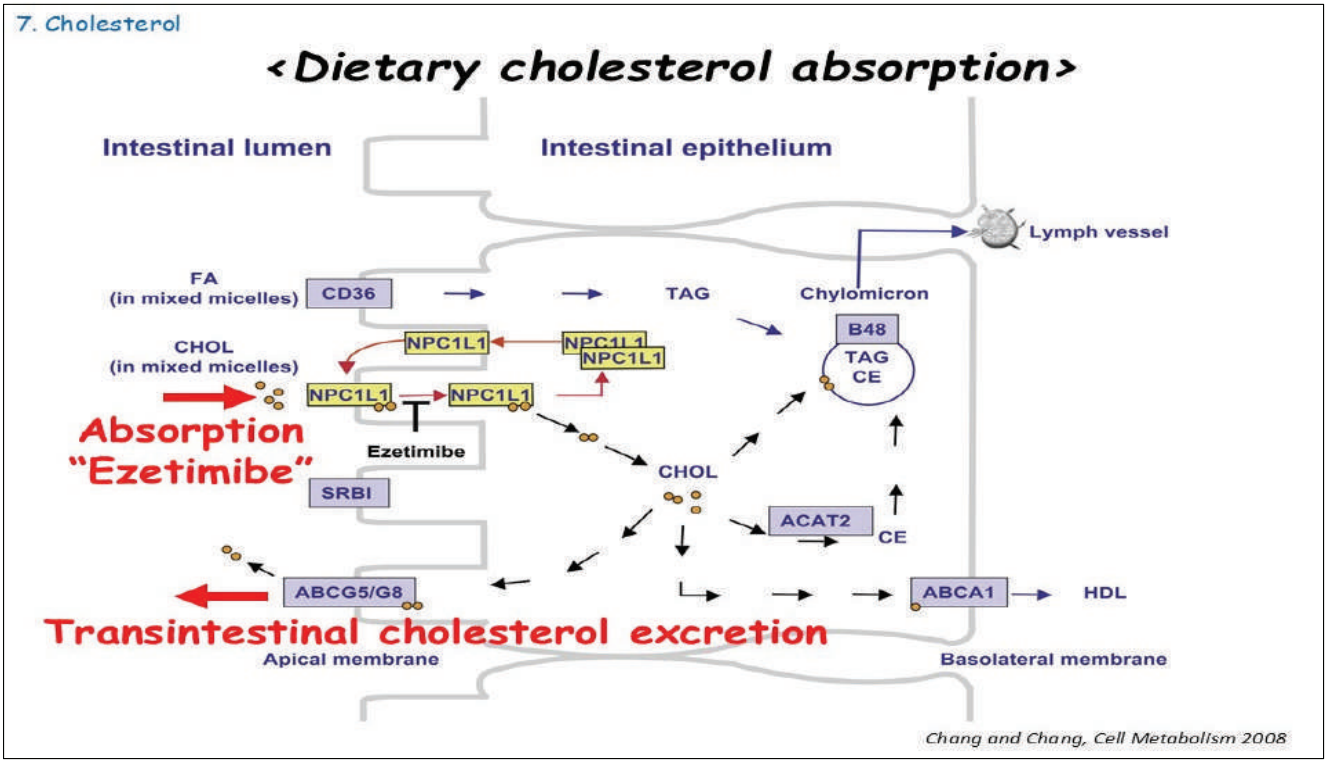


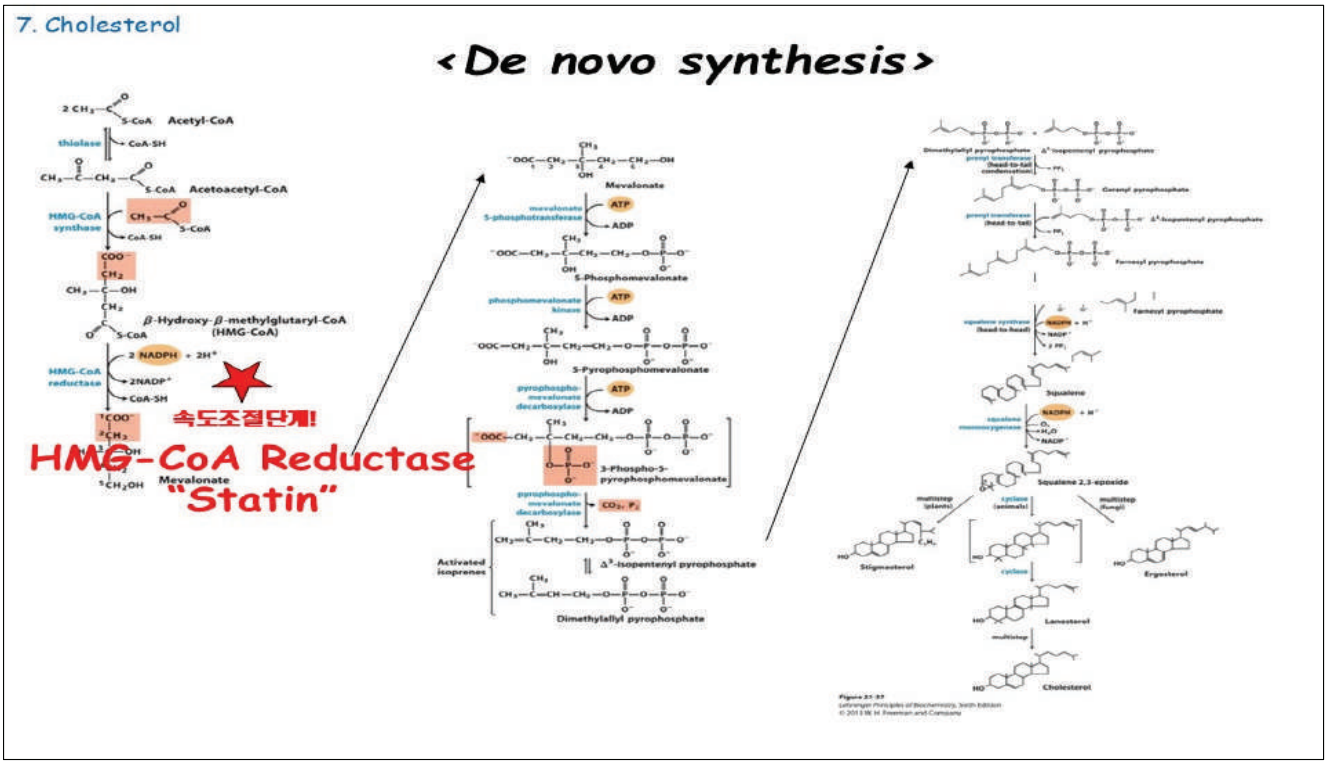

7. Cholesterol
Input
Cholesterol
Output

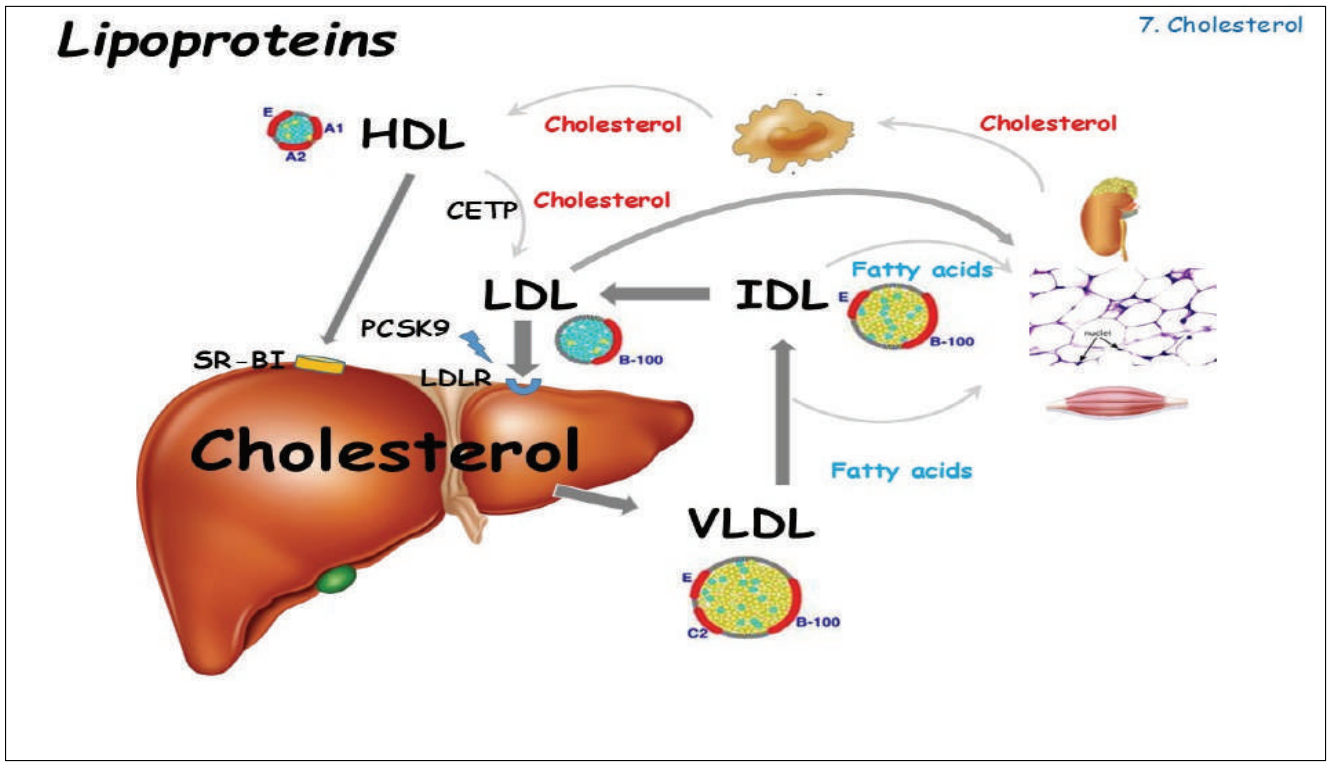

7. Cholesterol
Dietary fat
CM
Tight regulation!
De novo synthesis
Acetyl-CoA
CM Remnant
TG
Cholesterol

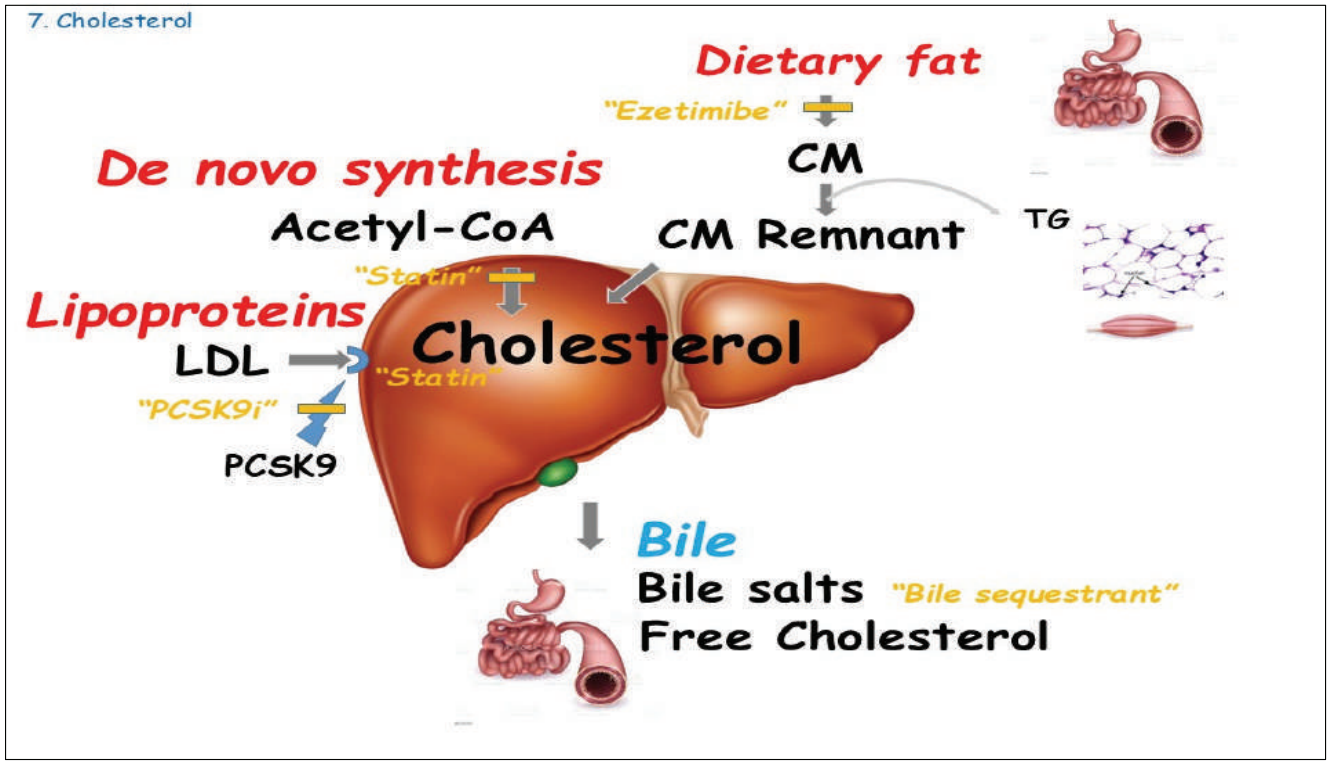
7. Cholesterol



7. Cholesterol




Lipoproteins
7. Cholesterol
HDL
Cholesterol
Cholesterol
CETP
Cholesterol
LDL
IDL
Fatty acids
PCSK9
B-100
SR-BI
LDLR
Cholesterol
Fatty acids
VLDL
B-100


7. Cholesterol
Dietary fat
"Ezetimibe"
CM
De novo synthesis
Acetyl-CoA
CM Remnant
TG
"Statin"
Lipoproteins
LDL
Cholesterol
"Statin"
"PCSK9i"
PCSK9
Bile
Bile salts
"Bile sequestrant"
Free Cholesterol

김 신 곤

[기본정보]

성함	김 신 곤
소속(근무처)	고려대학교 의과대학 내과, 고려대학교병원 내분비내과

[학력]

해당년도	세부사항
1986-1993	고려대학교 의과대학 의학사
1997-2005	고려대학교 의과대학 의학석사, 의학박사

[경력]

해당년도	세부사항
2024-현재	대한당뇨병학회 학술이사
2021-현재	대한내분비학회 기획이사
2016-현재	고려대학교병원 당뇨센터장
2006-현재	고려대학교 의과대학 내분비내과 교수

[관심분야]

Clinical trial, Real world Evidence

[논문]

1. Deerochanawong C, Kim SG, Chang YC. Role of Fenofibrate Use in Dyslipidemia and Related Comorbidities in the Asian Population: A Narrative Review. Diabetes Metab J. 2024 Mar;48(2):184-195
2. Kim NH, Kim JY, Choi J, Kim SG. Associations of omega-3 fatty acids vs. fenofibrate with adverse cardiovascular outcomes in people with metabolic syndrome: propensity matched cohort study. Eur Heart J Cardiovasc Pharmacother. 2024 Feb 23;10(2):118-127
3. Kim JY, Choi J, Kim SG, Kim NH. Relative contributions of statin intensity, achieved low-density lipoprotein cholesterol level, and statin therapy duration to cardiovascular risk reduction in patients with type 2 diabetes: population based cohort study. Cardiovasc Diabetol. 2022 Feb 22;21(1):28
4. Kim NH, Kim SG. Fibrates Revisited: Potential Role in Cardiovascular Risk Reduction. Diabetes Metab J. 2020 Apr;44(2):213-221.
5. Kim NH, Han KH, Choi J, Lee J, Kim SG. Use of fenofibrate on cardiovascular outcomes in statin users with metabolic syndrome: propensity matched cohort study. BMJ. 2019 Sep 27;366:l5125.

Clinical Application of Apolipoprotein: An Updated Overview Focused on ApoB

김 신 곤

고려의대 내분비내과

용어 - 개념 이해

Lipoprotein이란? (1)

- **Lipoproteins** contain an "oil droplet" core of hydrophobic lipids (TGs and cholesteryl esters) surrounded by a shell of hydrophilic lipids (phospholipids, unesterified cholesterol) and proteins (called **apolipoproteins**) that interact with body fluids.
- The plasma lipoproteins are divided into major classes based on their relative density: **chylomicrons**, very-low-density lipoproteins (**VLDLs**), intermediate-density lipoproteins (**IDLs**), low-density lipoproteins (**LDLs**), and high-density lipoproteins (**HDLs**).

Harrison's Principles of Internal Medicine, 21e

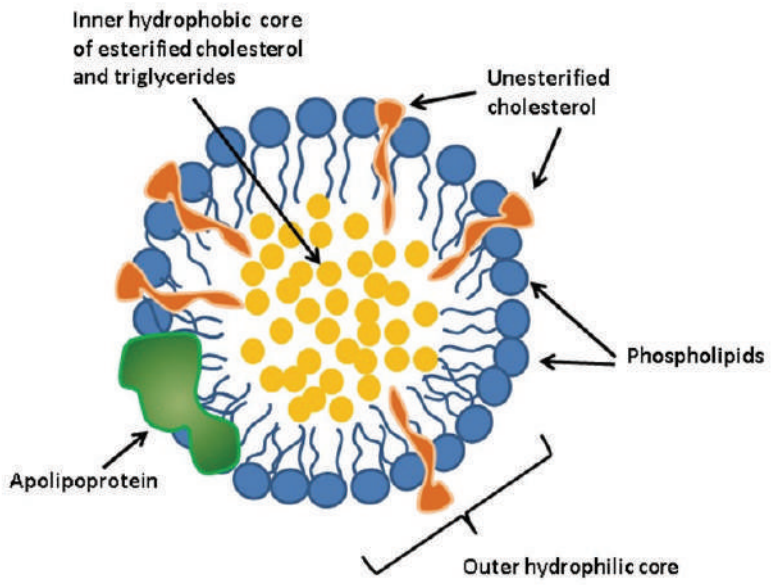
Lipoprotein이란? (2)

- Lipoproteins are **complexes of lipids and proteins** that are essential for **transport** of cholesterol, triglycerides (TGs), and fat-soluble vitamins in the blood. Lipoproteins play essential roles in the **absorption** of dietary cholesterol, long-chain fatty acids, and fat-soluble vitamins; the **transport** of TGs, cholesterol, and fat-soluble vitamins from the liver to peripheral tissues; and the **transport** of cholesterol from peripheral tissues back to the liver and intestine for excretion.

Harrison's Principles of Internal Medicine, 21e

Lipoprotein이란? (3)

- Lipids, such as cholesterol and triglycerides, are insoluble in plasma. **Circulating lipid is carried in lipoproteins that transport the lipid to various tissues for energy utilization, lipid deposition, steroid hormone production, and bile acid formation**. The lipoprotein consists of esterified and unesterified cholesterol, triglycerides, phospholipids, and **proteins referred to as apolipoproteins (apo).**



Schematic drawing of lipoprotein structure. Information derived from Champe et al. 2005.

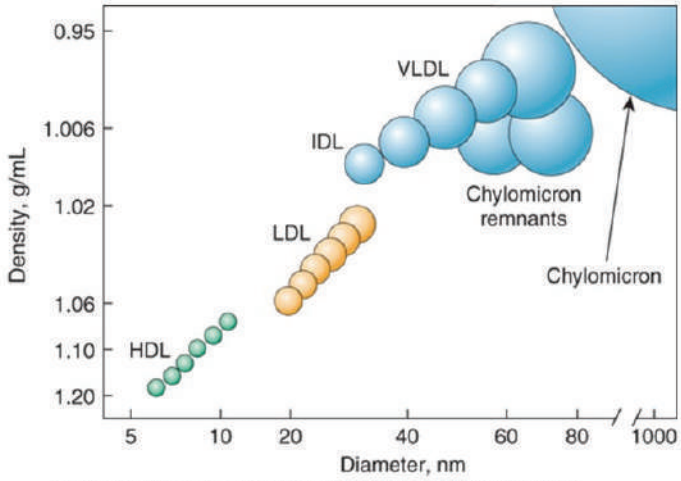
Apolipoprotein이란? (1)

- **Each class of lipoprotein particle** contains protein that is referred to as **apolipoprotein**. Understanding the major functions of the different apolipoproteins is important clinically, because variants in their structure or alterations in their metabolism can lead to abnormalities in lipid handling.
- The **six major lipoproteins particles** are **chylomicrons and chylomicron remnants, VLDL, intermediate-density lipoprotein (IDL), LDL, HDL, and lipoprotein(a)** (Lp(a)). All six lipoproteins carry cholesterol and triglycerides to varying degrees. These particles have been classified based on their physicochemical characteristics (eg, size, density) and apolipoprotein composition. LDL and HDL have been divided into subclasses.

Apolipoprotein이란? (2)

- The proteins associated with lipoproteins, called apolipoproteins, are required for **the assembly, structure, function, and metabolism of lipoproteins**. Apolipoproteins provide **a structural basis for lipoproteins, activate enzymes** important in lipoprotein metabolism, and act as **ligands for cell surface receptors.**

Harrison's Principles of Internal Medicine, 21e



The density and size distribution of the major classes of lipoprotein particles. Lipoproteins are classified by density and size, which are inversely related. HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

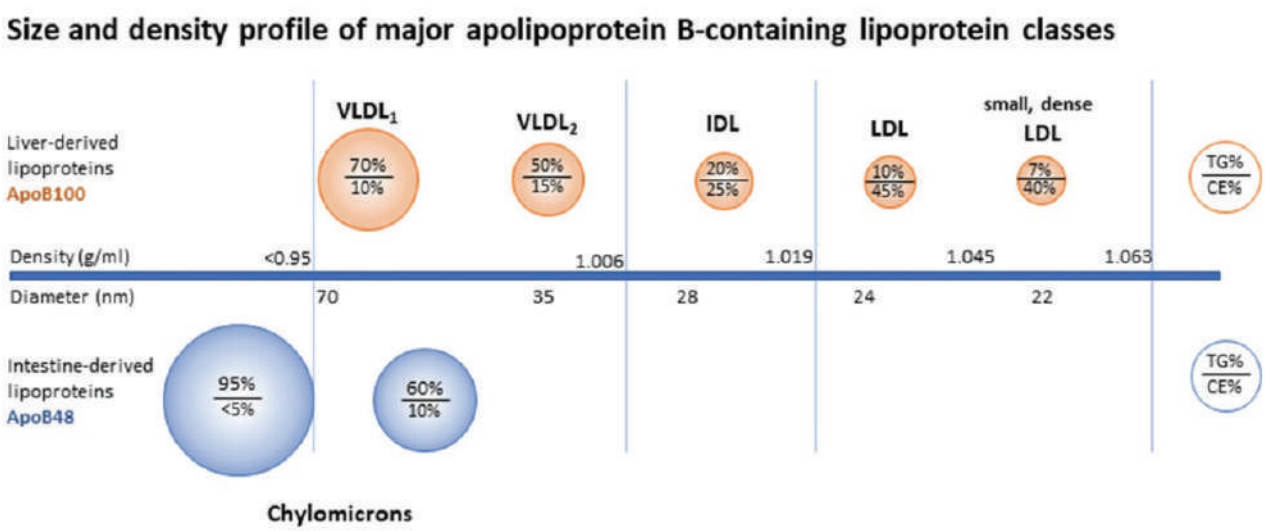
Harrison's Principles of Internal Medicine, 21e >Disorders of Lipoprotein Metabolism

Joseph Loscalzo, Anthony Fauci, Dennis Kasper, Stephen Hauser, Dan Longo, J. Larry Jameson+

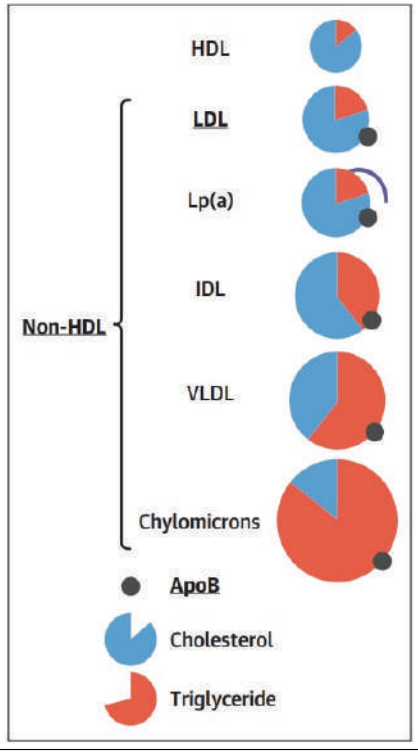
TABLE 407-1Major Apolipoproteins

APOLIPOPROTEIN	PRIMARY SOURCE	LIPOPROTEIN ASSOCIATION	FUNCTION
ApoA-I	Intestine, liver	HDL, chylomicrons	Core structural protein for HDL, promotes cellular lipid efflux via ABCA1, activates LCAT
ApoA-II	Liver	HDL, chylomicrons	Structural protein for HDL
ApoA-V	Liver	VLDL, chylomicrons	Promotes LPL-mediated triglyceride lipolysis
Apo(a)	Liver	Lp(a)	Structural protein for Lp(a)
ApoB-48	Intestine	Chylomicrons, chylomicron remnants	Core structural protein for chylomicrons
ApoB-100	Liver	VLDL, IDL, LDL, Lp(a)	Core structural protein for VLDL, LDL, IDL, Lp(a); ligand for binding to LDL receptor
ApoC-II	Liver	Chylomicrons, VLDL, HDL	Cofactor for LPL
ApoC-III	Liver, intestine	Chylomicrons, VLDL, HDL	Inhibits LPL activity and lipoprotein binding to receptors
ApoE	Liver	Chylomicron remnants, IDL, HDL	Ligand for binding to LDL receptor and other receptors

Abbreviations: HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

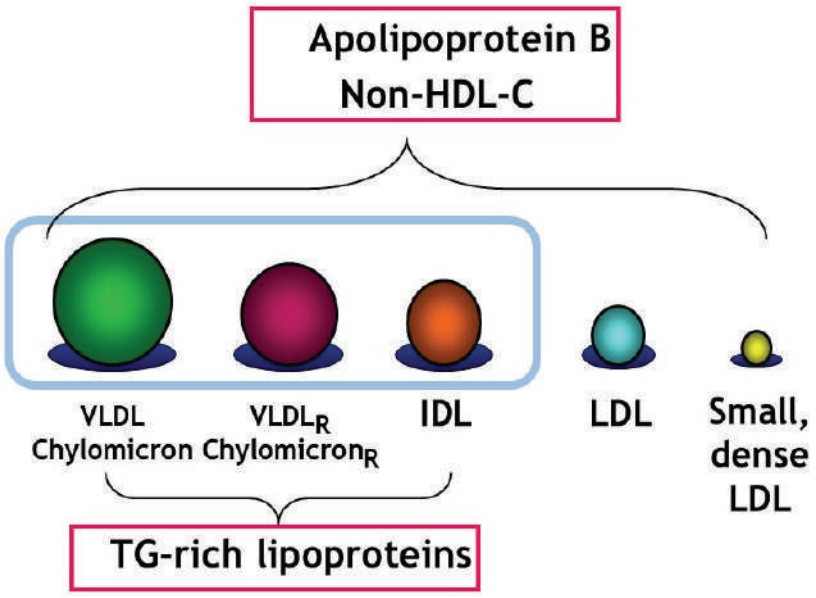


European Heart Journal (2021) 42, 4791–4806



Johannesen, C.D.L. et al. J Am Coll Cardiol. 2021;77(11):1439-50.

Atherogenic Particles

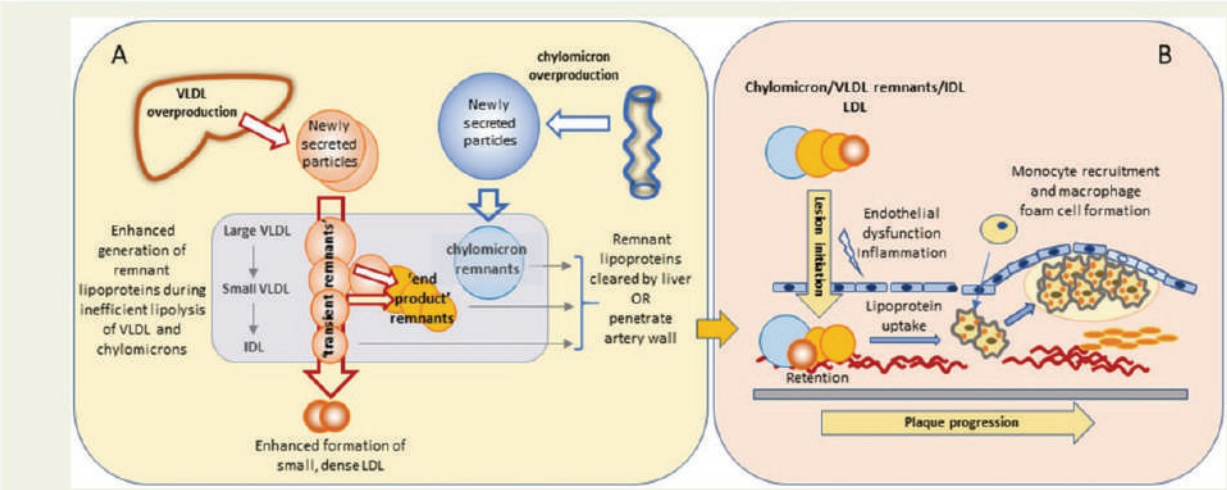


" Conventional Lipid battery "

Total Cholesterol	Cholesterol in VLDL, IDL, and LDL Cholesterol ester in HDL Free fatty acids	Apo B (esp. 100)
Triglycerides	Chylomicron VLDL and IDL	Apo B48, C, E
HDL	Cholesterol ester	Apo A

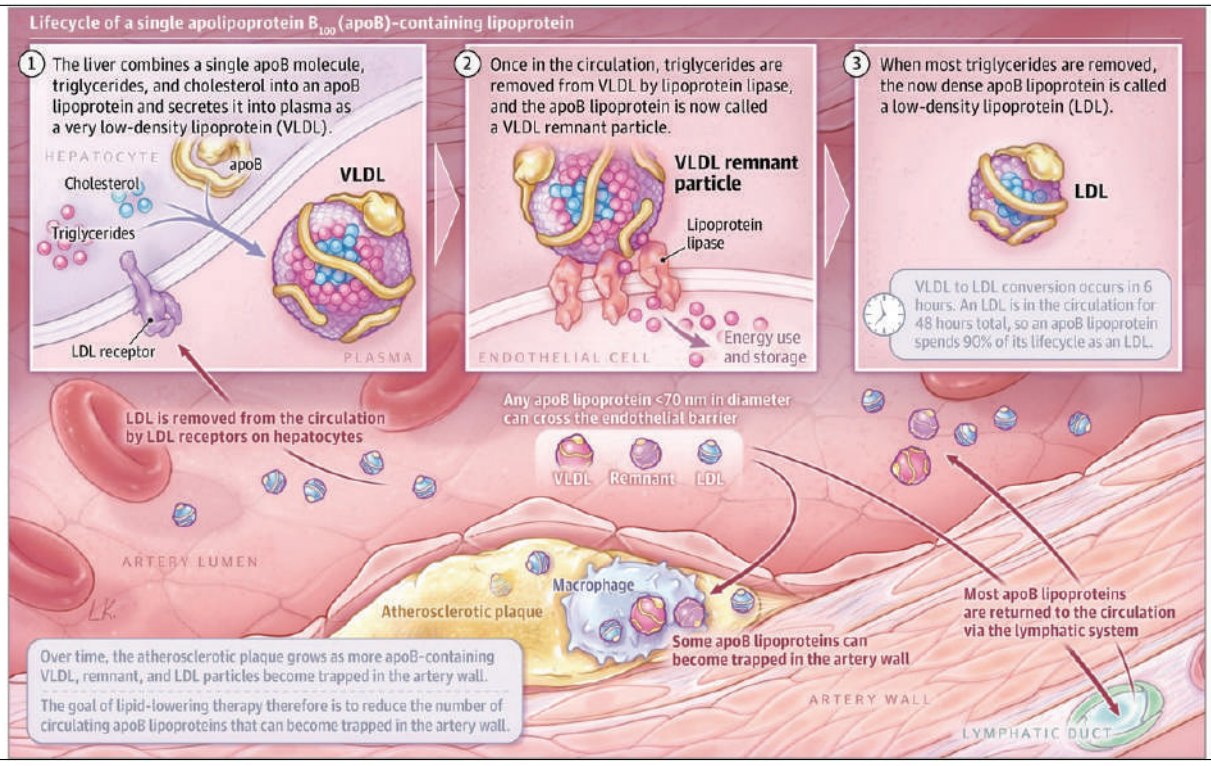
Friedewald formula

LDL cholesterol = TC – TG/5 – HDL-C (VLDL-C = Triglycerides/5)



Formation of triglyceride-rich lipoprotein remnants and their role in atherogenesis. Metabolic scheme for the generation and clearance of triglyceride-rich lipoprotein remnant particles (A). In hypertriglyceridaemia, overproduction and inefficient lipolysis of both very low-density lipoprotein and chylomicrons lead to increased remnant formation. Triglyceride-rich lipoprotein remnants contribute to the initiation and progression of atherosclerotic lesions (B). Particle retention in the subendothelial space is followed by inflammation, cholesterol deposition, and macrophage foam cell formation.

European Heart Journal (2021) 42, 4791–4806



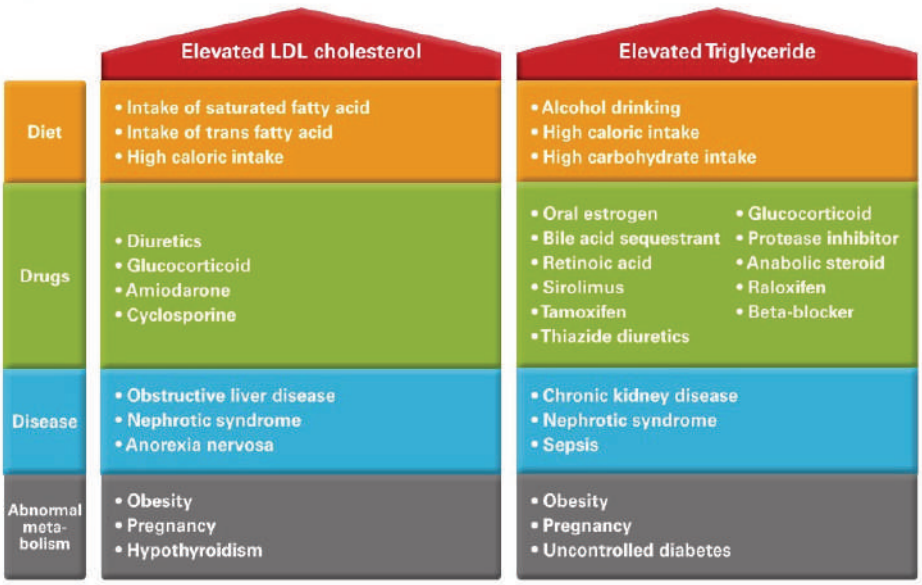
Atherogenic Lipoproteins

- **Non-HDL-C** = TC – HDL-C
- **Non-HDL-C = atherogenic cholesterol**
- **Apo B** concentration represents total number of lipoprotein particles (LDL + IDL + VLDL)

증례

- 46세 남자
- 20년간 흡연자/ 주 2회 소주 2병 정도 음주
- 키 170 cm, 체중 79 kg, BMI 27, 허리둘레 97 cm
- 혈압 140/100 mmHg
- 공복혈당 125 mg/dl, 공복 인슐린 25 uIU/ml, HbA1c 6.7%
- 총콜레스테롤 210, TG 330, HDL 44, LDL 100 mg/dl

Secondary causes of hypercholesterolemia or hypertriglyceridemia

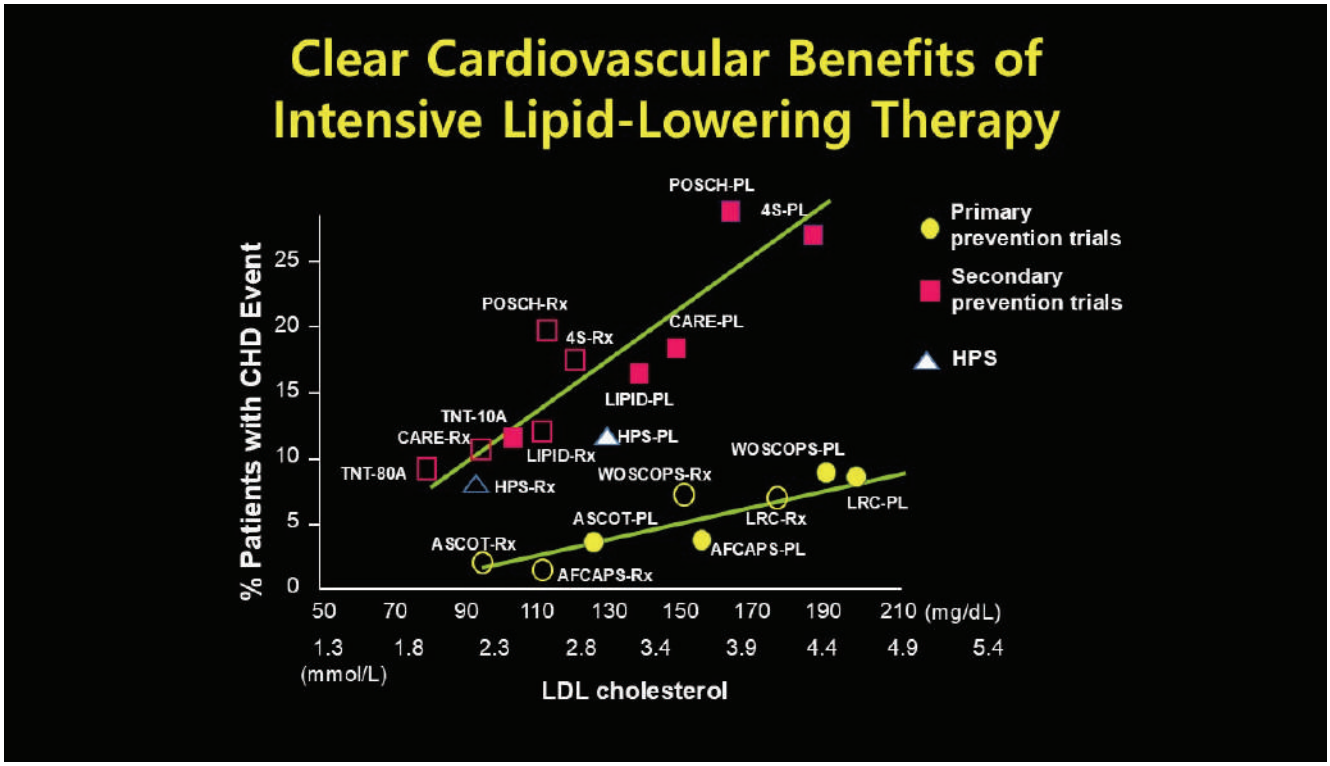


LDL, low-density lipoprotein

증례

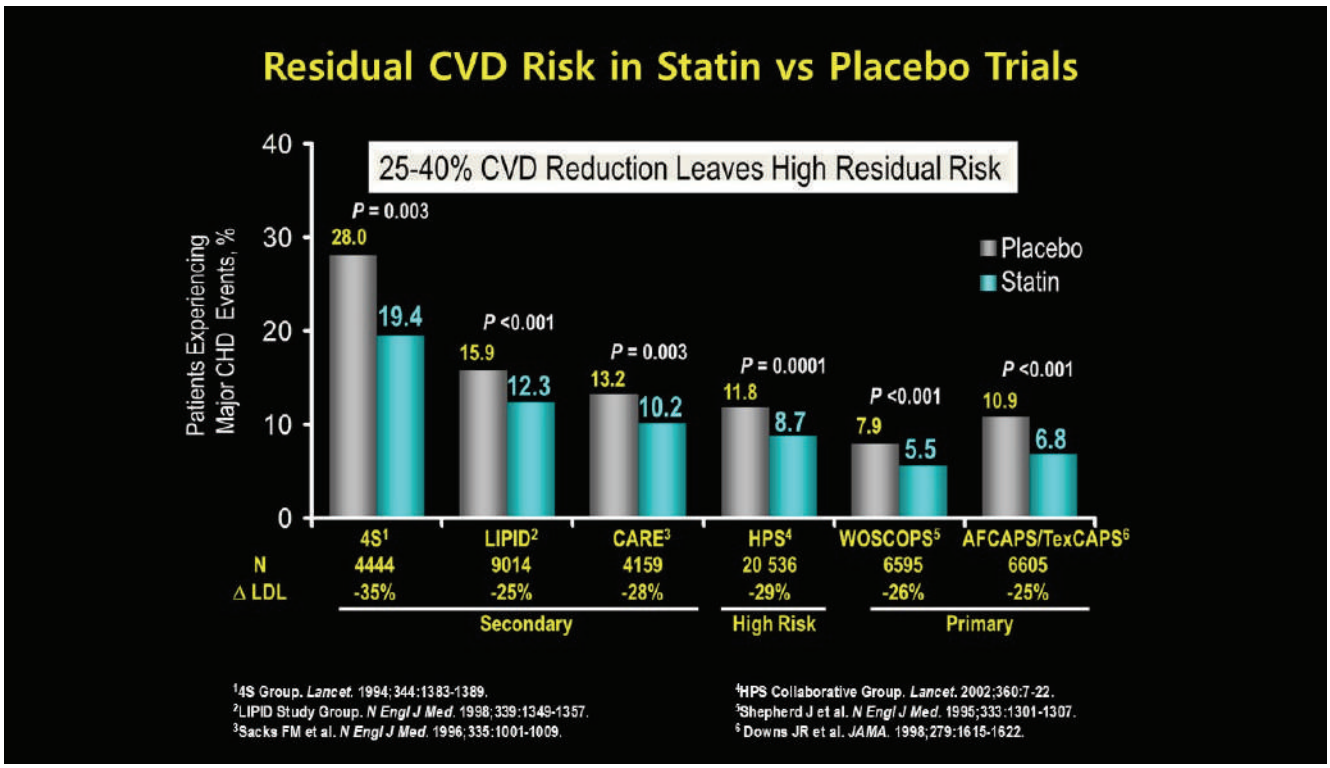
당뇨약과 Rosuvastatin 10mg 투여 중이다
이상지질혈증에 대한 추가적인 투약이 필요한가?

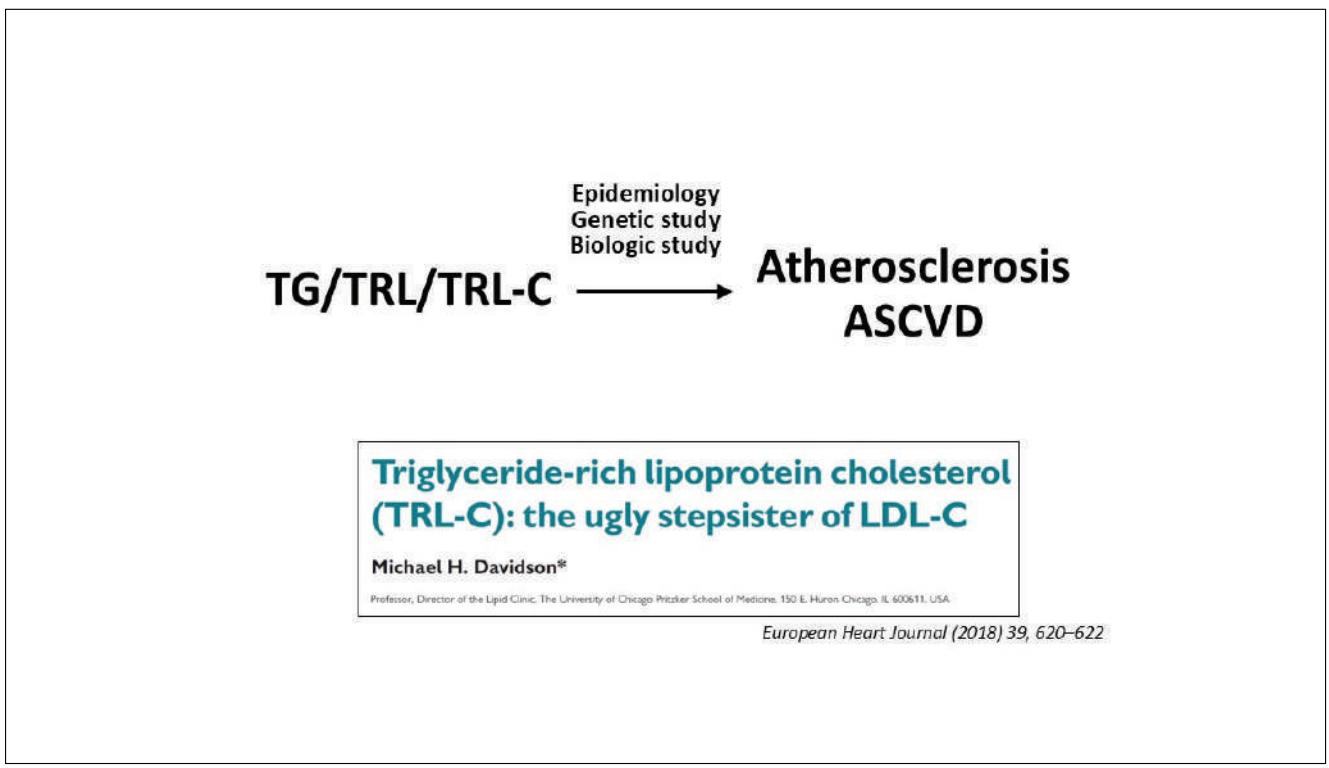
총콜레스테롤 210 mg/dl,
중성지방 330 mg/dl,
HDL 콜레스테롤 44 mg/dl,
LDL 콜레스테롤 100 mg/dl

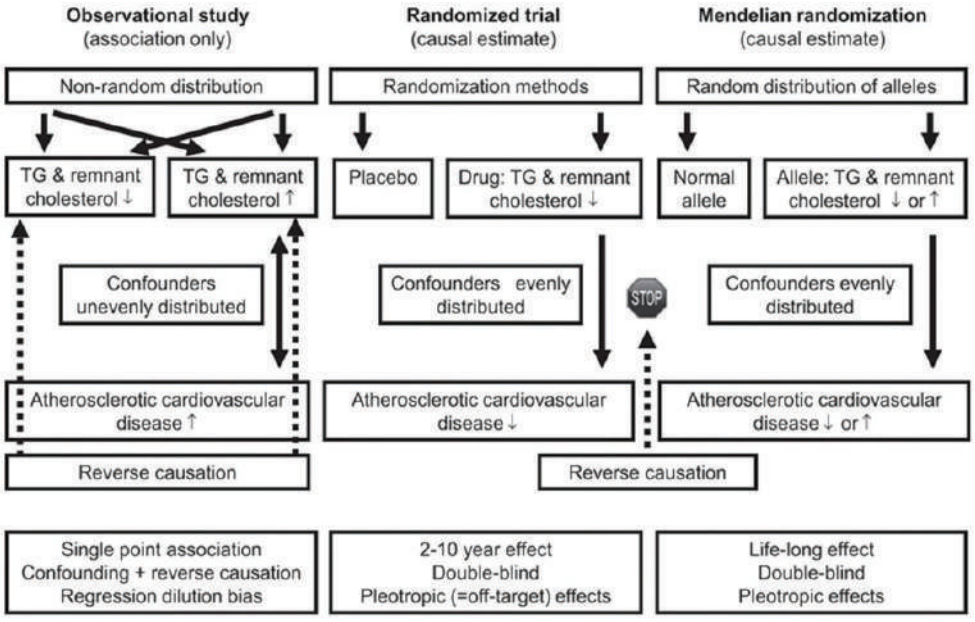


Estimated residual risk even in statin?

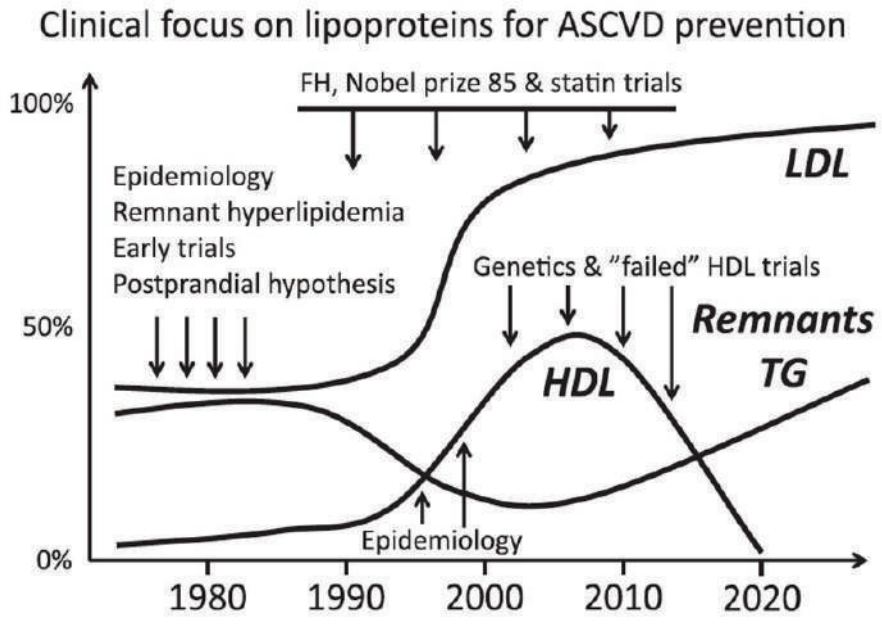
1. 20%
2. 30%
3. 40%
4. 50%
5. 60% 이상


Residual CVD Risk in Statin vs Placebo Trials
25-40% CVD Reduction Leaves High Residual Risk
Patients Experiencing Major CHD Events, %
Placebo
Statin
P = 0.003
28.0
19.4
P <0.001
15.9
12.3
P = 0.003
13.2
10.2
P = 0.0001
11.8
8.7
P <0.001
7.9
5.5
P <0.001
10.9
6.8
4S[1]
LIPID[2]
CARE[3]
HPS[4]
WOSCOPS[5]
AFCAPS/TexCAPS[6]
N
4444
9014
4159
20 536
6595
6605
Δ LDL
-35%
-25%
-28%
-29%
-26%
-25%
Secondary
High Risk
Primary
[1]4S Group. Lancet. 1994;344:1383-1389.
[2]LIPID Study Group. N Engl J Med. 1998;339:1349-1357.
[3]Sacks FM et al. N Engl J Med. 1996;335:1001-1009.
[4]HPS Collaborative Group. Lancet. 2002;360:7-22.
[5]Shepherd J et al. N Engl J Med. 1995;333:1301-1307.
[6]Downs JR et al. JAMA. 1998;279:1615-1622.


Epidemiology
Genetic study
Biologic study
TG/TRL/TRL-C
Atherosclerosis
ASCVD
Triglyceride-rich lipoprotein cholesterol (TRL-C): the ugly stepsister of LDL-C
Michael H. Davidson*
Professor, Director of the Lipid Clinic, The University of Chicago Pritzker School of Medicine, 150 E. Huron Chicago, IL 60611, USA
European Heart Journal (2018) 39, 620–622

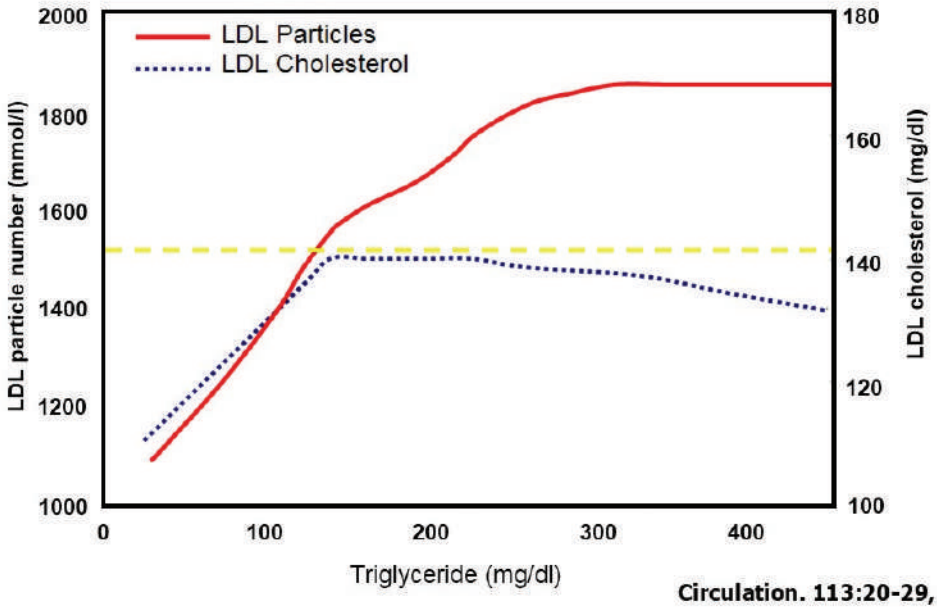


Circ Res. 2016;118:547-563



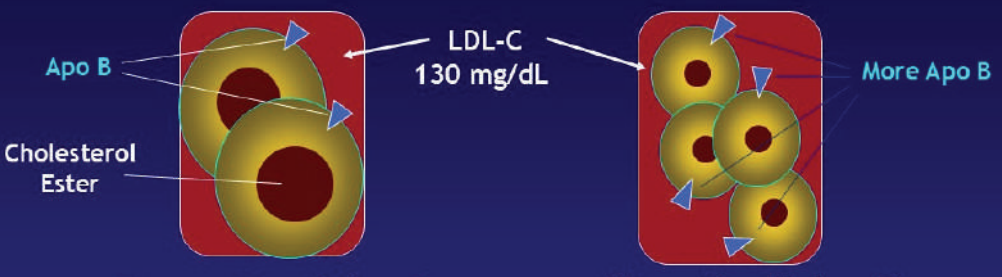
Circ Res. 2016;118:547-563

Relations of LDL particle number and LDL cholesterol value to TG level



Circulation. 113:20-29, 2006

LDL-C Doubly Underestimates CVD Risk in Cases of Small, Dense LDL



Fewer Particles & Less Risk/Particle

Lipid profile:

TC	198 mg/dL
LDL-C	130 mg/dL
TG	90 mg/dL
HDL-C	50 mg/dL
Non-HDL-C	148 mg/dL

More Particles & More Risk/Particle

Lipid profile:

TC	210 mg/dL
LDL-C	130 mg/dL
TG	250 mg/dL
HDL-C	30 mg/dL
Non-HDL-C	180 mg/dL

Otvos JD, et al. *Am J Cardiol*. 2002;90:22i-29i.

Non-HDL-C vs. Apo B

Favoring Non-HDL-C

- *Cholesterol* content conceptually better
- *Free* with lipid profile (*no* extra testing needed)
- Well standardized
- Already incorporated in guidelines

Favoring Apo B

- **Apo B play *causal* role in atherosclerosis**
- **May stronger CVD factor in the recent studies**

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 111–188
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

Changes in recommendations	
Upgrades	
2016	**2019**
Lipid analyses for CVD risk estimation	**Lipid analyses for CVD risk estimation**
ApoB should be considered as an alternative risk marker whenever available, especially in individuals with high TG.	ApoB analysis is recommended for risk assessment, particularly in people with high TG, DM, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG, DM, obesity, or very low LDL-C.

- In general, LDL-C, non-HDL-C, and ApoB concentrations are very highly correlated. As a result, under most circumstances, they provide very similar information about ASCVD risk.
- Considering **the potential inaccuracy of LDL-C in dyslipidaemia,** among patients with **DM or high TG levels, and in patients with very low LDL-C levels**, **measurement of both ApoB and non-HDL-C is recommended as part of routine lipid analysis** for risk evaluation in patients with elevated plasma TGs.
- Because **ApoB provides an accurate estimate of the total concentration of atherogenic particles under all circumstances**, it is **the preferred measurement to further refine the estimate of ASCVD risk** that is modifiable by lipid-lowering therapy.

European Heart Journal (2020) 41, 111188

Recommendations for lipid analyses for cardiovascular disease risk estimation

Recommendations	Class[a]	Level[b]
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.	I	C
LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.	I	C
TG analysis is recommended as part of the routine lipid analysis process.	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); SCORE = Systematic Coronary Risk Estimation; TC = total cholesterol; TG = triglyceride.

European Heart Journal (2020) 41, 111188

Table 7 Treatment targets and goals for cardiovascular disease prevention

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish.
Physical activity	3.5–7 h moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m^2, and waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg.[a]
LDL-C	**Very-high risk in primary or secondary prevention:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required. **High risk:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL). **Moderate risk:** A goal of <2.6 mmol/L (<100 mg/dL).
Non-HDL-C	Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively.
ApoB	ApoB secondary goals are <65, 80, and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively.

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Attribute	2021 CCS guideline	2019 EAS/ESC guideline	2018 AHA/ACC guideline and 2022 update
Screening demographic for baseline lipid profile	Adults older than 40 years, or younger with specified conditions*	Men older than 40 years, and women older than 50 years or postmenopausal	Broad inclusion; adults older than 20 years
Nonfasting lipid profile acceptable?	Yes; repeat fasting depending on TG level elevation	Yes; repeat fasting depending on TG level elevation	Yes; repeat fasting depending on TG level elevation
Risk algorithm in primary prevention	Either FRS or CLEM	SCORE-2	Pooled cohort equation
Risk modifiers	Relatively few (eg, family history; hsCRP, coronary artery calcium, [Lp(a)]); vulnerable populations	A wide range of clinical conditions resembling those for initial lipid screening in the 2021 CCS guideline*	A wide range of clinical conditions resembling those for initial screening in the 2021 CCS guideline,* plus hsCRP, Lp(a), and ApoB
ApoB vs non-HDL-C	Both are equivalent to LDL-C and preferable to it if TG level > 1.5 mmol/L	Both are equivalent to LDL-C and preferable to it if TG level > 1.5 mmol/L	Non-HDL-C is preferable if nonfasting or TG level elevated; ApoB not generally recommended
Lp(a)	Once in every adult's lifetime as part of ASCVD risk assessment	Once in every adult's lifetime as part of ASCVD risk assessment	Measure only if personal or family history of premature ASCVD
Threshold vs target LDL-C	Thresholds in secondary prevention to emulate RCTs; intensify LDL-C lowering therapy if LDL-C > 1.8 mmol/L or non-HDL-C > 2.4 mmol/L or ApoB > 0.7 g/L	LDL-C targets with 4 levels of risk: • Very high—LDL-C < 1.4 mmol/L • High—LDL-C < 1.8 mmol/L • Moderate—LDL-C < 2.6 mmol/L • Low—LDL-C < 3.0 mmol/L	Thresholds for treatment intensification: • Severe 1° hypercholesterolemia—LDL-C > 2.6 mmol/L • 2° Prevention—LDL-C > 1.8 mmol/L

Canadian Journal of Cardiology 40 (2024) S13eS19

Circulation

ORIGINAL RESEARCH ARTICLE

Comparison of Conventional Lipoprotein Tests and Apolipoproteins in the Prediction of Cardiovascular Disease

Data From UK Biobank

Editorial, see p 553

BACKGROUND: Total cholesterol and high-density lipoprotein cholesterol (HDL-C) measurements are central to cardiovascular disease (CVD) risk assessment, but there is continuing debate around the utility of other lipids for risk prediction.

METHODS: Participants from UK Biobank without baseline CVD and not taking statins, with relevant lipid measurements (n=346 686), were included in the primary analysis. An incident fatal or nonfatal CVD event occurred in 6216 participants (1656 fatal) over a median of 8.9 years. Associations of nonfasting lipid measurements (total cholesterol, HDL-C, non–HDL-C, direct and calculated low-density lipoprotein cholesterol [LDL-C], and apolipoproteins [Apo] A1 and B) with CVD were compared using Cox models adjusting for classical risk factors, and predictive utility was determined by the C-index and net reclassification index. Prediction was also tested in 68 649 participants taking a statin with or without baseline CVD (3515 CVD events).

Claire Welsh, PhD
Carlos A. Celis-Morales, PhD
Rosemary Brown, MSc
Daniel F. Mackay, PhD
James Lewsey, PhD
Patrick B. Mark, MD
Stuart R. Gray, PhD
Lyn D. Ferguson, MBChB
Jana J. Anderson, PhD
Donald M. Lyall, PhD
John G. Cleland, MD
Pardeep S. Jhund, MBChB, PhD
Jason M.R. Gill, PhD
Jill P. Pell, MD
Naveed Sattar, MD*
Paul Welsh, PhD*

CONCLUSIONS:
Measurement of total cholesterol and HDL-C in the nonfasted state is sufficient to capture the lipid-associated risk in CVD prediction, with **no meaningful improvement from addition of apolipoproteins**, direct or calculated LDL-C.

Circulation. 2019;140:542–552

EDITORIAL

Cholesterol Insights and Controversies From the UK Biobank Study

Circulation. 2019;140:553–555

Three Take-Home Messages for the Busy Clinician

Among **the subset of 63520 UK Biobank participants who were discordant** (>10% absolute percentile difference with respect to **apo B and LDL cholesterol**), **only apo B was associated with increased CVD risk** (adjusted hazard ratio per SD, 1.23 [95% CI, 1.12–1.35]; P<0.001), whereas **no increased CVD risk was noted for directly measured LDL cholesterol or for calculated LDL cholesterol**. Likewise, among these discordant individuals, **non-HDL cholesterol also was not associated with increased CVD risk.**

This discordant subset of participants represented ≈**15% of the UK Biobank study population**, which is **a relatively healthier population** compared with the general UK population. In other study populations, the proportion of individuals with discordant apo B and LDL cholesterol test results has been noted to be **at least one-quarter of the general population**, with greater prevalence noted among populations enriched with **cardiometabolic risk factors such as obesity, metabolic syndrome, and diabetes mellitus**.

JAMA Cardiology | Original Investigation

Published online November 13, 2021.

Association of Apolipoprotein B–Containing Lipoproteins and Risk of Myocardial Infarction in Individuals With and Without Atherosclerosis

Distinguishing Between Particle Concentration, Type, and Content

OBJECTIVE To determine whether common measures of cholesterol concentration, TG concentration, or their ratio are associated with cardiovascular risk beyond the number of apolipoprotein B (apoB)–containing lipoproteins.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort analysis included individuals from the population-based UK Biobank and from 2 large international clinical trials, FOURIER and IMPROVE-IT. The median (IQR) follow-up was 11.1 (10.4-11.8) years in UK Biobank and 2.5 (2.0-4.7) years in the clinical trials. Two populations were studied in this analysis: 389 529 individuals in the primary prevention group who were not taking lipid-lowering therapy and 40 430 patients with established atherosclerosis who were receiving statin treatment.

EXPOSURES ApoB, non–high-density lipoprotein cholesterol (HDL-C), LDL-C, and TG.

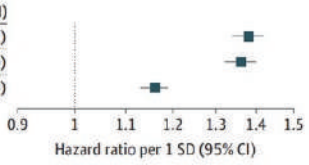
MAIN OUTCOME AND MEASURES The primary study outcome was incident myocardial infarction (MI).

Published online November 13, 2021.

Figure 1. Lipid Parameters and Risk of Myocardial Infarction

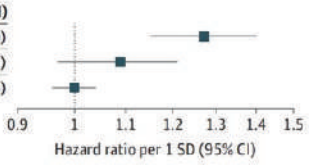
A Primary prevention: clinically adjusted

Lipid parameter	Hazard ratio per 1 SD (95% CI)
Apo B	1.38 (1.34-1.42)
Non-HDL-C	1.36 (1.32-1.40)
TG	1.16 (1.13-1.19)



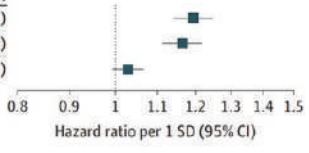
B Primary prevention: clinically and lipid adjusted

Lipid parameter	Hazard ratio per 1 SD (95% CI)
Apo B	1.27 (1.15-1.40)
Non-HDL-C	1.09 (0.97-1.21)
TG	1.00 (0.96-1.04)



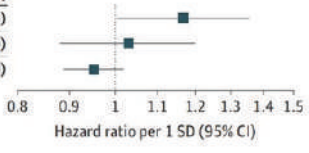
C Secondary prevention: clinically adjusted

Lipid parameter	Hazard ratio per 1 SD (95% CI)
Apo B	1.19 (1.14-1.25)
Non-HDL-C	1.16 (1.11-1.22)
TG	1.03 (0.99-1.07)



D Secondary prevention: clinically and lipid adjusted

Lipid parameter	Hazard ratio per 1 SD (95% CI)
Apo B	1.17 (1.00-1.36)
Non-HDL-C	1.03 (0.88-1.20)
TG	0.94 (0.89-1.00)



All models were adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), smoking status, hypertension, diabetes, ethnicity, and kidney function. The secondary prevention cohort was also adjusted for prior myocardial infarction, stroke, and peripheral artery disease. Clinically and lipid-adjusted models also included apolipoprotein B, non–high-density lipoprotein cholesterol, triglycerides, and high-density lipoprotein cholesterol in addition to the clinical variables.

Apolipoprotein B and Non-HDL Cholesterol Better Reflect Residual Risk Than LDL Cholesterol in Statin-Treated Patients

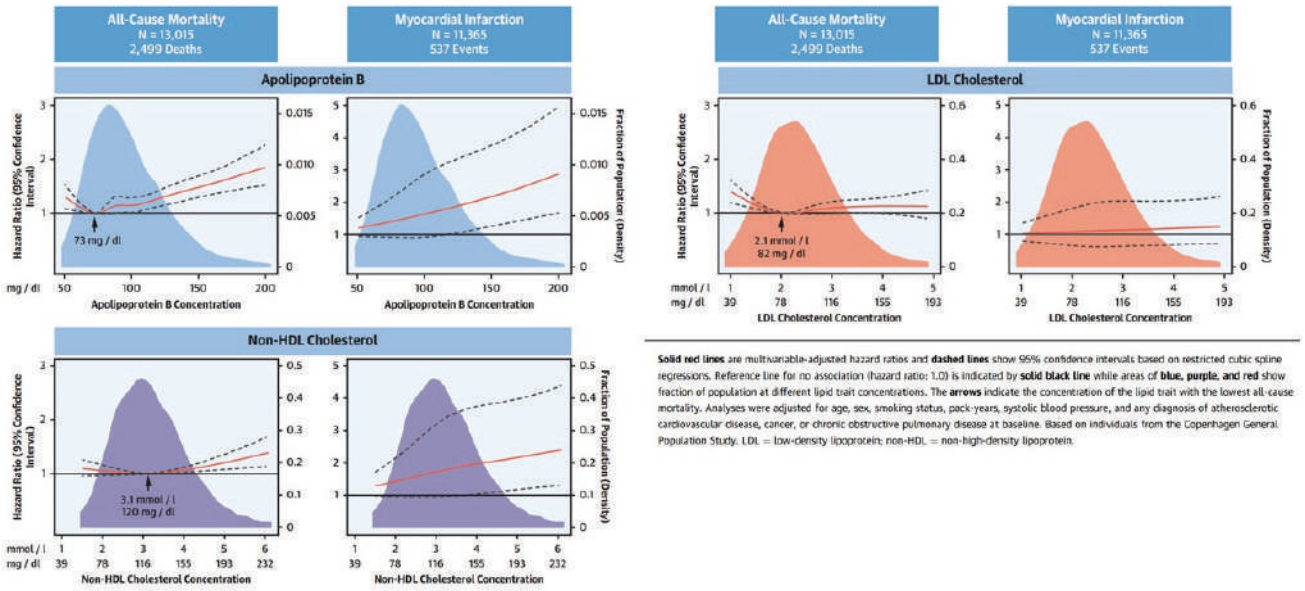
Camilla Ditlev Lindhardt Johannesen, MD,[a,b,c] Martin Bødtker Mortensen, MD, PhD,[a,b,c,d] Anne Langsted, MD, PhD,[a,b,c] Børge Grønne Nordestgaard, MD, DMSc[a,b,c]

J Am Coll Cardiol. 2021;77(11):1439-50.

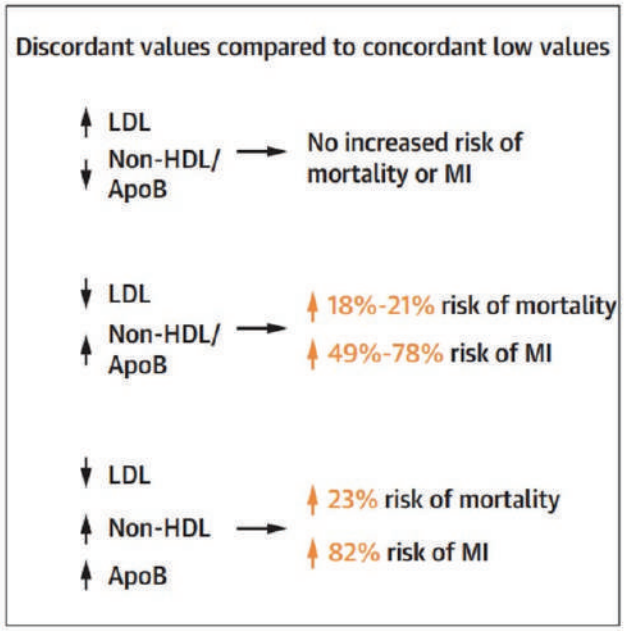
BACKGROUND In cholesterol guidelines, low-density lipoprotein (LDL) cholesterol remains the primary target while apolipoprotein B (apoB) and non-high-density lipoprotein (non-HDL) cholesterol are secondary targets.

OBJECTIVES This study sought to determine if elevated apoB and/or non-HDL cholesterol are superior to elevated LDL cholesterol in identifying statin-treated patients at residual risk of all-cause mortality and myocardial infarction.

METHODS In total, 13,015 statin-treated patients from the Copenhagen General Population Study were included with 8 years median follow-up. Cox regressions among apoB, non-HDL cholesterol, and LDL cholesterol, respectively, and all-cause mortality or myocardial infarction were examined on continuous scales by restricted cubic splines and by categories of concordant and discordant values defined by medians.



Solid red lines are multivariable-adjusted hazard ratios and **dashed lines** show 95% confidence intervals based on restricted cubic spline regressions. Reference line for no association (hazard ratio: 1.0) is indicated by **solid black line** while areas of **blue, purple, and red** show fraction of population at different lipid trait concentrations. The **arrows** indicate the concentration of the lipid trait with the lowest all-cause mortality. Analyses were adjusted for age, sex, smoking status, pack-years, systolic blood pressure, and any diagnosis of atherosclerotic cardiovascular disease, cancer, or chronic obstructive pulmonary disease at baseline. Based on individuals from the Copenhagen General Population Study. LDL = low-density lipoprotein; non-HDL = non-high-density lipoprotein.



Also, **discordant high apoB with low non-HDL cholesterol** yielded **hazard ratios of 1.21 (95% CI: 1.03 to 1.41) for all-cause mortality** and of 0.93 (95% CI: 0.62 to 1.40) for myocardial infarction.

Johannesen, C.D.L. et al. J Am Coll Cardiol. 2021;77(11):1439-50.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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EDITORIAL COMMENT

Tracking Residual Risk

Time for a Change?*

Neil J. Stone, MD, Donald Lloyd-Jones, MD

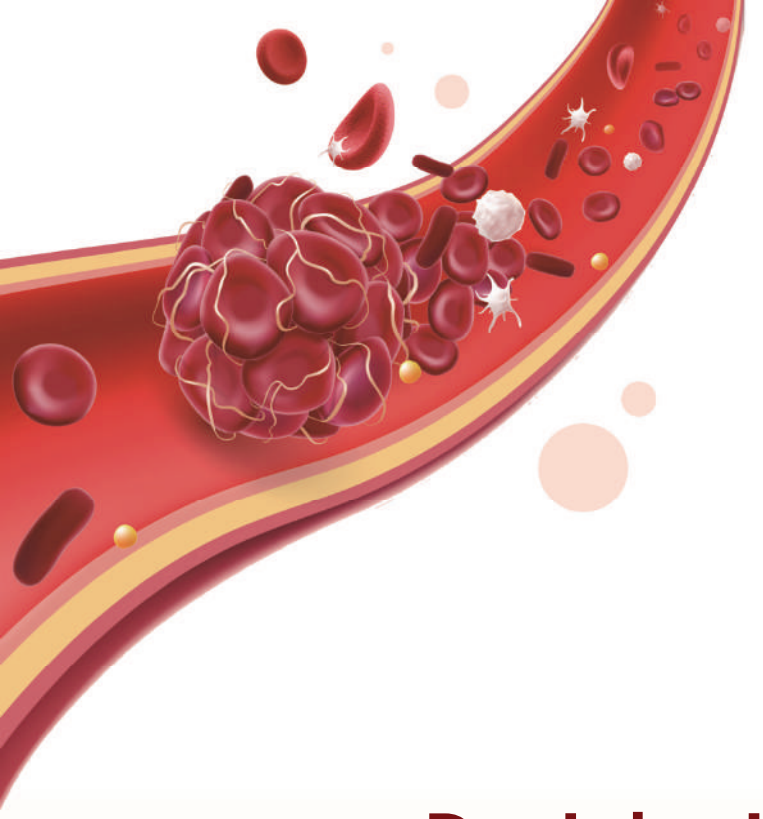
"Progress is impossible without change, and those who cannot change their minds cannot change anything."
–George Bernard Shaw (1)

Current guidelines, both American and European, acknowledge the usefulness of both apoB and non-HDL-C in their risk algorithms, and their use as possible targets to indicate efficacy, but they do not yet strongly recommend measurement of apoB for assessment of residual risk. Subsequent guideline panels should use these observational data and other informative studies to consider how to translate the benefit to improved patient care, and whether these markers should be routinely or selectively measured. In situations where statin use is suboptimal, maximizing statin intensity would appear to be the most important first step in reducing residual risk, and then it may be important to consider how measurement of apoB and non-HDL-C could influence guideline-directed care.

Summaries

- **Non-HDL-C** > LDL-C in certain situation
  (DM or high TG levels, and in very low LDL-C levels)
- **ApoB** ≥ Non-HDL-C
- New lipid battery – **TC, TG, HDL-C and ApoB** *(In my view)*
- More evidence is needed for ApoB targeting therapy

감사합니다



Day 1

Session 2

Deciphering LDL Cholesterol Dynamics

(10:30 – 12:00)

10:30 – 11:00	Insights into Genetic and Enzymatic Machinery of Cholesterol Synthesis and Metabolism	박상욱 (연세의대 생화학분자생물학교실)
11:00 – 11:30	Current Landscape of LDL Cholesterol Lowering Therapies: Pharmaceuticals and RCTs Overview	김상현 (서울의대 순환기내과)
11:30 – 12:00	토론	

1st Lipid Academy

한국지질·동맥경화학회 제1회 Lipid Academy

박 상 욱

[기본정보]

성함	박 상 욱
소속(근무처)	연세대학교 의과대학 생화학 · 분자생물학교실

[학력]

해당년도	세부사항
1988.02	연세대학교 의과대학 의학사
1991.07	연세대학교 대학원 의학석사
1997.02	연세대학교 대학원 의학박사

[경력]

해당년도	세부사항
1988-1996	연세대학교 의과대학 생화학교실 조교, 강사
1997	연세대학교 의과대학 생화학 · 분자생물학교실 조교수
1998-2006	관동대학교 의과대학 생화학교실 조교수, 부교수
2001-2004	UT Southwestern Medical Center, Dallas, Dept. Molecular Genetics, Post-doc
2007-Present	연세대학교 의과대학 생화학 · 분자생물학교실 부교수, 교수

[관심분야]

Cholesterol metabolism, PCSK9, Cardiomyocyte differentiation

[논문]

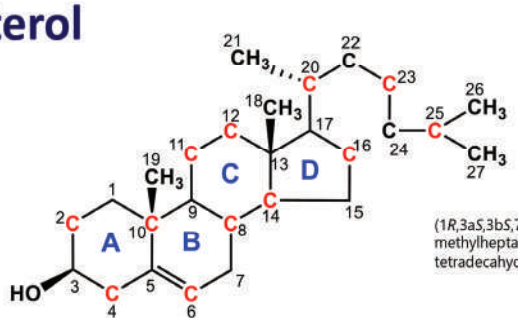
Lee, S.-H., et al. (2024). "Inhibition of TBL1 cleavage alleviates doxorubicin-induced cardiomyocytes death by regulating the Wnt/β-catenin signal pathway." Cardiovascular Research
Jeon, S. B., et al. (2023). "Human induced pluripotent stem cell line YCMi007-A generated from a dilated cardiomyopathy patient with a heterozygous dominant c.613C 〉 T (p. Arg205Trp) variant of the TNNT2 gene." Stem Cell Res **67**: 103048.
Min, D. K., et al. (2015). "In silico Screening of Chemical Libraries to Develop Inhibitors That Hamper the Interaction of PCSK9 with the LDL Receptor." Yonsei Med J **56**(5): 1251-1257.
Park, S. W., et al. (2004). "Post-transcriptional regulation of low density lipoprotein receptor protein by proprotein convertase subtilisin/kexin type 9a in mouse liver." J Biol Chem **279**(48): 50630-50638.

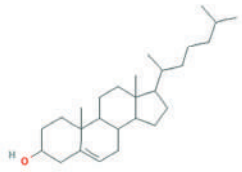
Insights into Genetic and Enzymatic Machinery of Cholesterol Synthesis and Metabolism

박 상 욱

연세의대 생화학분자생물학교실

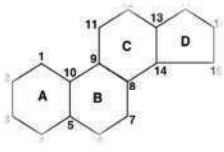
Cholesterol





(1*R*,3a*S*,3b*S*,7*S*,9a*R*,9b*S*,11a*R*)-9a,11a-Dimethyl-1-[(2*R*)-6-methylheptan-2-yl]-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-7-ol

(3β) Cholest-5-en-3β-ol



- **Perhydrocyclopenta[a]phenanthrene nucleus**
- **A single hydroxyl** group at C-3
- **Unsaturated center** between C5 and C6
- An **8-membered branched hydrocarbon chain** at C17
- **Two methyl group** attached at C10 and C13
- Numbering

2

Good? - Normal repertoire of cholesterol

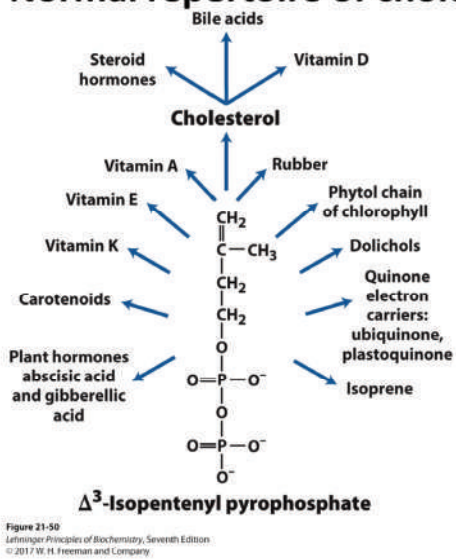


Figure 21-50
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More than 20,000 isoprenoids (terpenoids) in nature

3

Lipoproteins

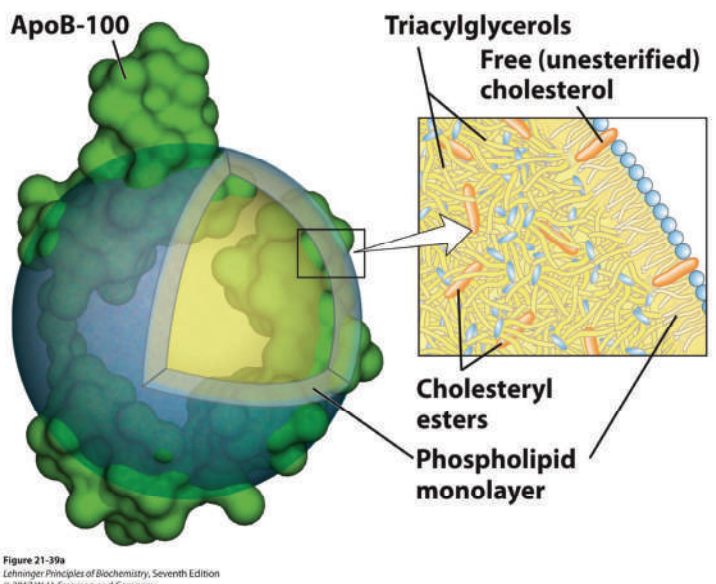

Figure 21-39a
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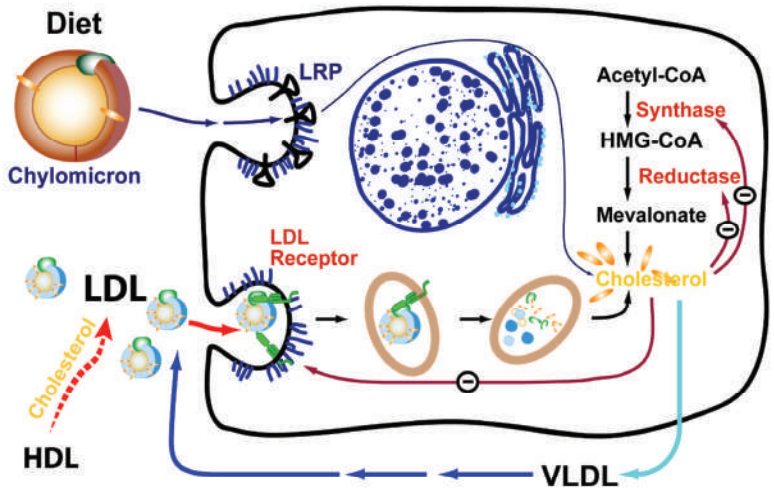
4

Two sources of cellular cholesterol



Lipoprotein and lipid transport

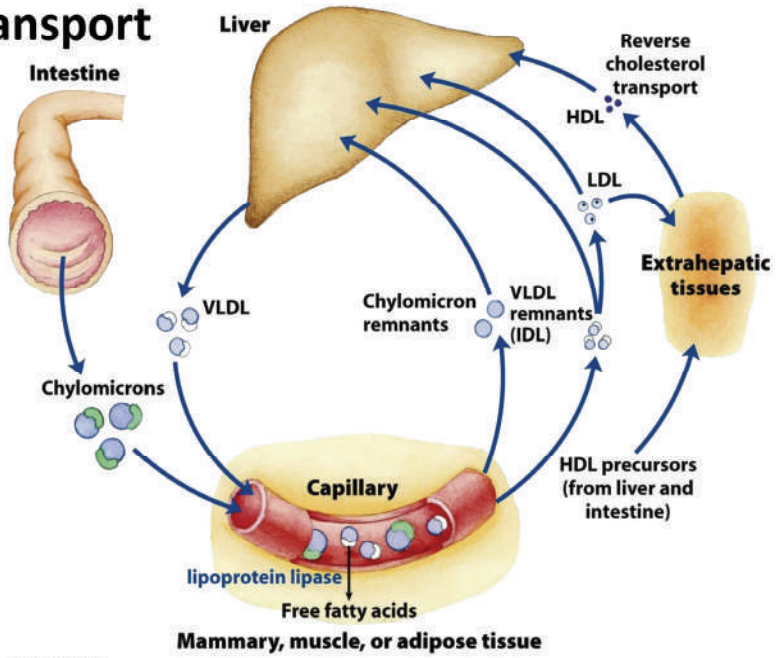


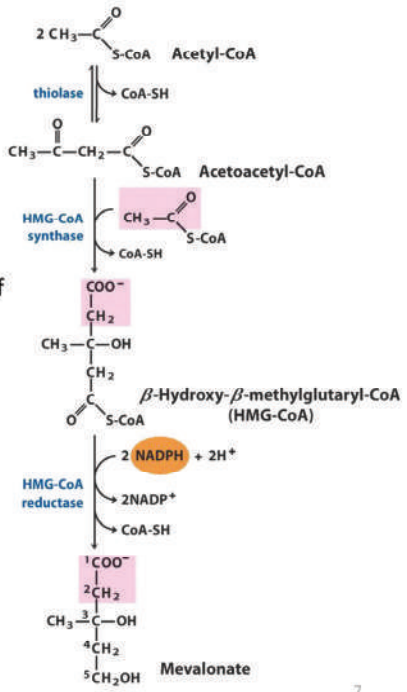
Figure 21-40a
Lehninger Principles of Biochemistry, Fifth Edition

Endogenous cholesterol synthesis from Acetyl CoA in cytosol

1.Synthesis of mevalonate from acetyl-CoA

- Acetyl-CoA acetyl transferase (thiolase I)
- HMG-CoA synthase in cytosol
  - An isozyme of HMG-CoA synthase in mitochondria for synthesis of ketone body
- HMG-CoA reductase
  - The rate-limiting enzyme

- Sources of acetyl CoA & acetoacetyl-CoA
  1. the pyruvate dehydrogenase reaction (from glucose)
  2. the β-oxidation of fatty acids
  3. the oxidation of ketogenic amino acids
  4. by acetyl-coA synthase (acetate thiokinase) from free acetate



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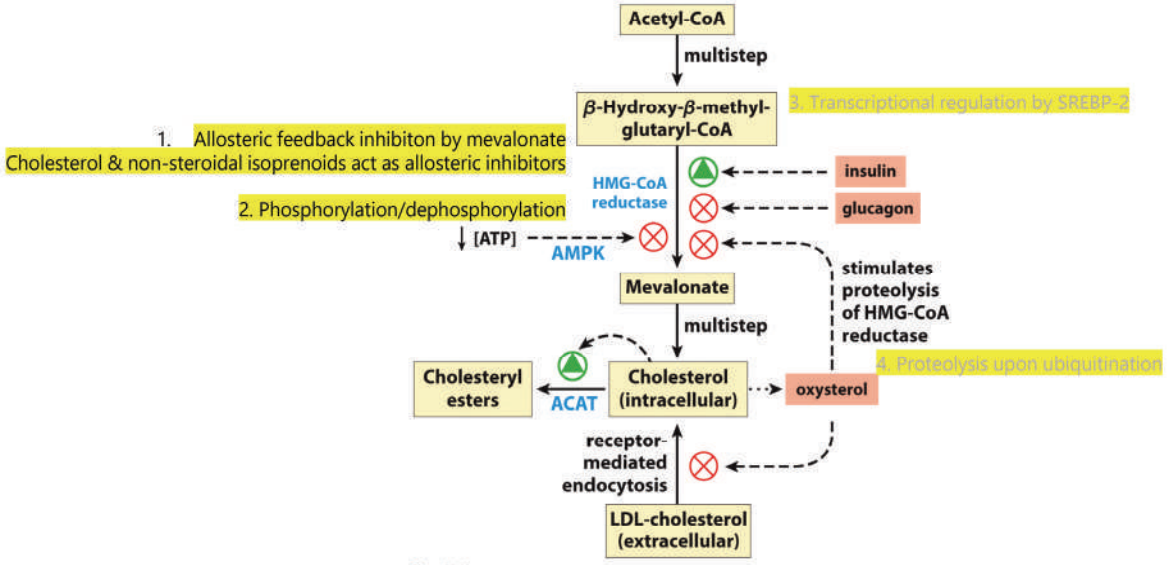
7

Acetyl-CoA
↓ Acetyl-CoA acetyltransferase
Acetoacetyl-CoA
↓ HMG-CoA synthase
β-Hydroxy-β-methylglutaryl-CoA (HMG-CoA)
NADPH +2H+ ↓ HMG-CoA reductase
Mevalonate
ATP ↓ Mevalonate 5-phosphotransferase
5-Phosphomevalonate
2 ATP ↓ Phosphomevalonate kinase / Pyrophosphomevalonate decarboxylase
Δ^3-isopentenyl pyrophosphate
↕
Dimethylallyl phyrophosphate
↓ Geranyl phyrophosphate synthase
Geranyl pyrophosphate
↓ Farnesyl phyrophosphate synthase
Farnesyl pyrophosphate
NADPH +2H+ ↓ Squalene synthase
Squalene
NADPH +2H+ ↓
Squalene 2,3-epoxide
↓ Cyclase
Lanosterol
↓↓↓
Cholesterol
↓ Acyl-CoA cholesterol acyl transferase (ACAT)
Cholesteryl ester

8

Multiple mechanisms of regulation of cholesterol formation



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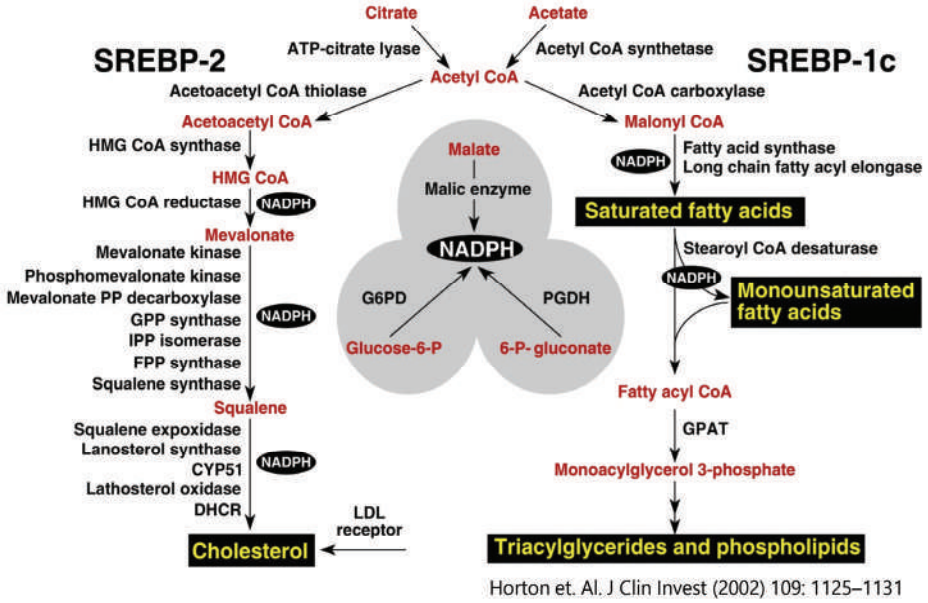
9

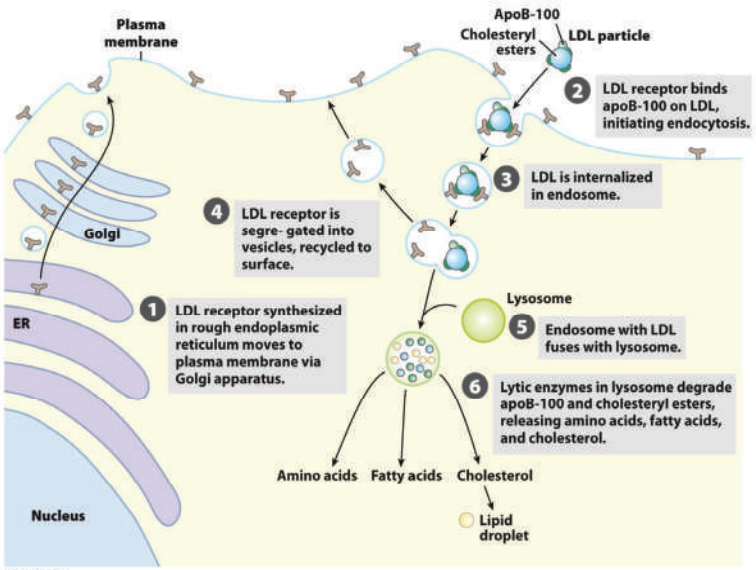
Transcriptional Regulation: SREBPs
(Sterol regulatory element-binding proteins)



Horton et. Al. J Clin Invest (2002) 109: 1125–1131

10

Receptor mediated endocytosis of LDL



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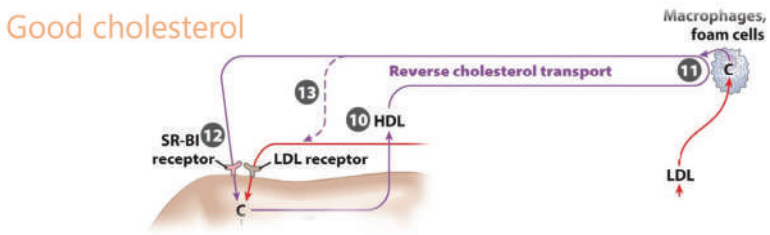
Reverse cholesterol transport: HDL



- **HDL** originates in the liver as small, protein-rich particles, that contain relatively little cholesterol and no cholesteryl ester (**nascent HDL**)
  - contains **apoA-I, A-II**, C-I, C-II, C-III, & **E**
- Nascent HDL also contains **LCAT (lecithin-cholesterol acyl transferase)** which converts peripheral cholesterol (transfer via **ABCA1/G1**) to cholesterol ester, then becomes mature HDL
- Mature HDL returns to liver via **Scavenger receptor type B1 (SR-BI)**
  - **Unloading of sterol via SR-BI does not involve endocytosis**
  - Mediates **partial and selective transfer of cholesterol and other lipids** into cells, then depleted HDL recirculates and reused.
- Some of cholesteryl esters in HDL is transferred to LDL by **cholesteryl ester transfer protein (CETP).**

12

DISORDERS OF LIPOPROTEIN METABOLISM

Primary Hyperlipoproteinemias Caused by Known Single Gene Mutations (Monogenic)

Genetic Disorder	Gene Defect	Lipoproteins Elevated	Clinical Findings	Genetics	Estimated Incidence
Lipoprotein lipase deficiency	LPL (*LPL*)	Chylomicrons	Eruptive xanthomas, hepatosplenomegaly pancreatitis	AR	1/1,000,000
Familial apolipoprotein C-II deficiency	ApoC-II (*APOC2*)	Chylomicrons	Eruptive xanthomas, hepatosplenomegaly-pancreatitis	AR	<1/1,000,000
Familial hepatic lipase deficiency	Hepatic lipase (*LIPC*)	VLDL remnants	Premature atherosclerosis	AR	<1/1,000,000
Familial dysbetalipoproteinemia	**ApoE (*APOE*)**	**Chylomicron and VLDL remnants**	**Palmar and tuberoeruptive xanthomas, CHD, PVD**	**AR AD**	**1/10,000**
Familial hypercholesterolemia	**LDL receptor (*LDLR*)**	**LDL**	**Tendon xanthomas, CHD**	**AD**	**1/500**
Familial defective apoB-100	**ApoB-100 (*APOB*)**	**LDL**	**Tendon xanthomas, CHD**	**AD**	**1/1000**
Autosomal recessive hypercholesterolemia	**ARH (*ARH*)**	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000
Sitosterolemia	*ABCG5* or *ABCG8*	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000
Familial hyper-cholesterolemia 3 (FH3)	***PCSK9***	**LDL**	**CHD**	**AD**	<1/1,000,000 **?**

Note: AR, autosomal recessive; AD, autosomal dominant; VLDL, very low density lipoprotein; CHD, coronary heart disease; PVD, peripheral vascular disease; LDL, low-density lipoprotein.

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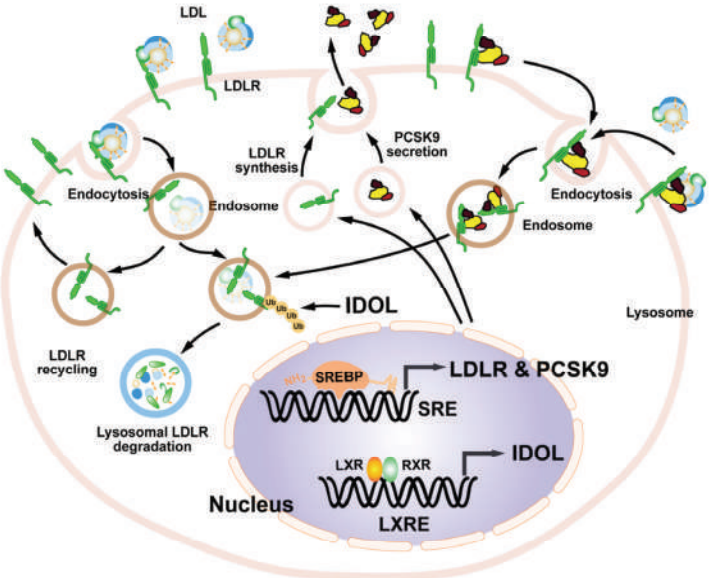
PCSK9

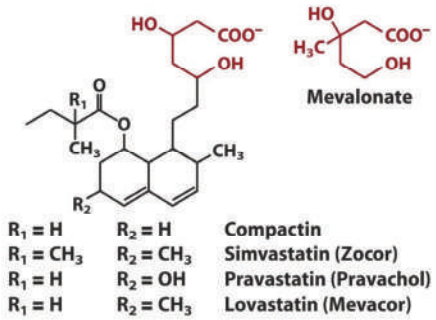
Proprotein convertase subtilisin/kexin type 9



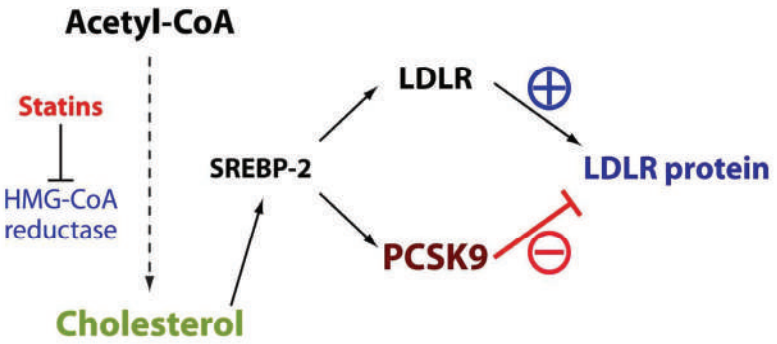
14

Cholesterol biosynthesis is carefully regulated

- **Statin drugs as inhibitors of HMG-CoA reductase,**
  - **a rate-limiting enzyme of cholesterol biosynthesis**



$R_1 = H$	$R_2 = H$	Compactin
$R_1 = CH_3$	$R_2 = CH_3$	Simvastatin (Zocor)
$R_1 = H$	$R_2 = OH$	Pravastatin (Pravachol)
$R_1 = H$	$R_2 = CH_3$	Lovastatin (Mevacor)



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15

Antibodies against PCSK9

Developer	Molecule	Description	Clinical stage
Regeneron/ Sanofi	**Alirocumab (REGN727, SAR236553)**	**Fully human IgG1 mAb**	**Phase 3**
Amgen	**Evolocumab (AMG145)**	**Fully human IgG2 mAb**	**Phase 3**
Pfizer	**Bococizumab (PF-04950615, RN-316)**	**Humanized IgG2a mAb**	**Phase 3**
Roche	RG-7652	mAb	Phase 2[a]
Eli Lilly	LY3015014	mAb	Phase 2
Merk	ID 05-IgG2	mAb	?
Norvatis	LGT209	mAb	Phase2

Dadu RT, Ballantyne CM. Lipid lowering with PCSK9 inhibitors. Nat Rev Cardiol 2014;11:563-75.

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Thank you very much!

김 상 현

[기본정보]

성함	김 상 현
소속(근무처)	서울의대 보라매병원 순환기내과

[학력]

해당년도	세부사항
1985.03-1991.02	서울대학교 의과대학 학사
1999.03-2001.02	서울대학교 의과대학원 석사
2001.03-2005.02	서울대학교 의과대학원 박사

[경력]

해당년도	세부사항
2000-현재	보라매병원 순환기내과 교수
2003-2007	서울대학교 의과대학 조교수
2007-2012	서울대학교 의과대학 부교수
2012-현재	서울대학교 의과대학 부교수

[관심분야]

Lipid, atherosclerosis, preventive cardiology

[논문]

New onset diabetes mellitus and cardiovascular outcomes according to statin intensity in patients after drug-eluting stent implantation in Asian patients. Chung J, Kim HL, Lim WH, Seo JB, Zo JH, Kim MA, Kim SH. Sci Rep. 2023 Sep 25;13(1):16061.

Efficacy, safety and clinical outcome associated with statin use for primary prevention in Korean patients with low-density lipoprotein cholesterol level ≥ 190 mg/dL: A retrospective cohort study.
Kim HL, Lim WH, Seo JB, Zo JH, Kim MA, Kim SH. PLoS One. 2023;18(6):e0280586

One-month changes in blood pressure-adjusted pulse wave velocity for predicting long-term cardiovascular outcomes in patients undergoing percutaneous coronary intervention.
Kim HL, Joh HS, Lim WH, Seo JB, **Kim SH**, Zo JH, Kim MA.J Hypertens. 2023 Mar 1;41(3):437-442.

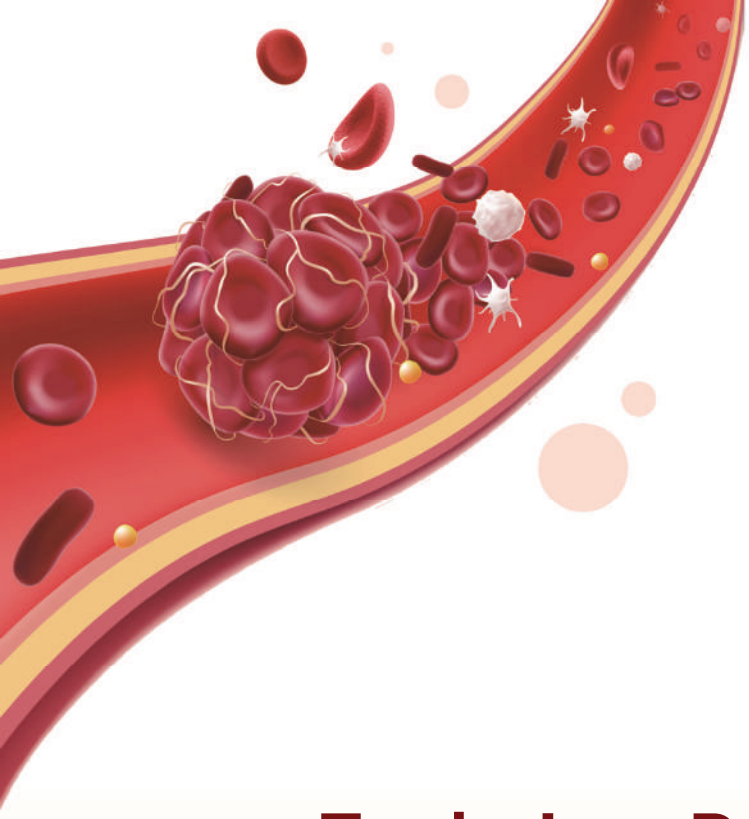
Association between inter-leg blood pressure difference and cardiovascular outcome in patients undergoing percutaneous coronary intervention. Moon IK, Kim HL, Lim WH, Seo JB, Zo JH, Kim MA, Kim SH. PLOS One. 2021;16(10):e0257443

Current Landscape of LDL Cholesterol Lowering Therapies: Pharmaceuticals and RCTs Overview

김 상 현

서울의대 순환기내과

The most important strategy for the management of patients with dyslipidemia is to prevent cardiovascular disease and decrease cardiac death through the comprehensive management of risk factors, especially LDL cholesterol. The current main treatment strategy for lowering LDL cholesterol is to treat the patients with statin-based medications and lifestyle management. Ezetimibe, monoclonal antibody or RNA-based therapy of PCSK9, bempedoic acid and other drugs including lomitapide, mipomersen and angiopoietin-like protein 3 (ANGPLT3) inhibitor/antibody such as evinacumab are valuable for further treatment of dyslipidemia. And upcoming treatment drugs are oral PCSK9 inhibitor and CETP inhibitors.



Day 1

Session 3

Exploring Residual Lipid Risks(I)

(13:00 – 14:20)

13:00 – 13:30	Unveiling the Genetic and Enzymatic Machinery of Triglyceride Synthesis and Metabolism	남궁준 (연세원주의대 생화학교실)
13:30 – 14:00	Latest Insights into TG-lowering Therapies: Pharmaceuticals and RCTs Summary	김병진 (성균관의대 순환기내과)
14:00 – 14:20	토론	

1st Lipid Academy

한국지질·동맥경화학회 제1회 Lipid Academy

남 궁 준

[기본정보]

성함	남 궁 준
소속(근무처)	연세대학교 원주의과대학 생화학교실

[학력]

해당년도	세부사항
2012.02	연세대학교 대학원 의학박사
2006.02	연세대학교 원주의과대학 의학사

[경력]

해당년도	세부사항
2020.03~현재	연세대학교 원주의과대학 생화학교실 부교수
2017.03~2020.02	연세대학교 원주의과대학 생화학교실 조교수
2015.03~2017.02	한국과학기술원 의생명연구센터 연구조교수
2012.03~2015.02	연세대학교 원주의과대학 생화학교실 연구강사

[관심분야]

Metabolic syndrome, Lipid and energy metabolism, Mitochondrial calcium, Mitonuclear signaling

[논문]

Chang JS, **Namkung J**.
Effects of exercise intervention on mitochondrial stress markers in metabolic syndrome patients: a randomized controlled trial.
Int J Environ Res Public Health. 2021 Feb 24;18(5):2242.

Shong KE, Oh CM, **Namkung J**, Park SK, Kim H.
Serotonin regulates de novo lipogenesis in adipose tissues through serotonin receptor 2a.
Endocrinol Metab (Seoul). 2020 Jun;35(2):470-479.

Namkung J, Sohn JH, Chang, JS, Park SW, Kim JY, Koh SB, Kong ID, Park KS.
Increased serum angiopoietin-like 6 as a biomarker for metabolic syndrome: a prospective cohort study.
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Choi W*, **Namkung J***, Hwang I, Kim H, Lim A, Park HJ, Lee HW, Han KH, Park S, Jeong JS, Bang G, Kim YH, Yadav VK, Karsenty G, Ju YS, Choi C, Suh JM, Park JY, Park S, Kim H.
Serotonin signals through a gut-liver axis to regulate hepatic steatosis.
Nat Commun. 2018 Nov 16;9(1):4824. (* co-first author)

Namkung J, Shong KE, Kim H, Oh CM, Park S, Kim H.
Inhibition of Serotonin Synthesis Induces Negative Hepatic Lipid Balance.
Diabetes Metab J. 2018 Jun;42(3):233-243.

Unveiling the Genetic and Enzymatic Machinery of Triglyceride Synthesis and Metabolism

남 궁 준

연세원주의대 생화학교실

Contents

- Clinical significance of triglycerides
- Synthesis of triglyceride
- Triglyceride mobilization
- Regulation of triglyceride metabolism
- Therapeutic approaches

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1. Clinical Significance of Triglycerides

- Hypertriglyceridemia
- Hyperlipoproteinemia
- Metabolic syndrome
- MASLD
- Ectopic fat deposit
- Metabolically healthy obesity

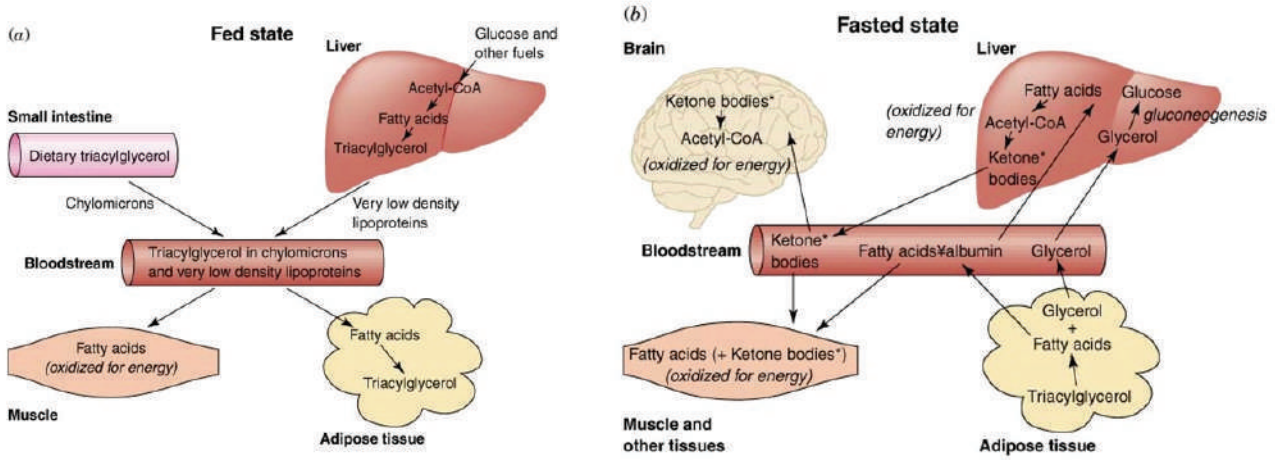
3

Primary Hyperlipoproteinemia by Single Gene Mutations

Genetic Disorder	*Protein (Gene) Defect*	*Lipoproteins Elevated*	*Clinical Findings*	*Genetic Transmission*	*Estimated Incidence*
Lipoprotein lipase deficiency	LPL (*LPL*)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	~1/1,000,000
Familial apoC-II deficiency	ApoC-II (*APOC2*)	Chylomicrons, VLDL		AR	<1/1,000,000
ApoA-V deficiency	ApoA-V (*APOA5*)	Chylomicrons, VLDL		AR	<1/1,000,000
GPIHBP1 deficiency	*GPIHBP1*	Chylomicrons	Eruptive xanthomas, pancreatitis	AR	<1/1,000,000
Familial hepatic lipase deficiency	Hepatic lipase (*LIPC*)	VLDL remnants, HDL	Pancreatitis, coronary heart diseases (CHD)	AR	<1/1,000,000
Familial dysbetalipoproteinemia	ApoE (*APOE*)	Chylomicron remnants, VLDL remnants	Palmar and tuberoeruptive xanthomas, CHD, PVD	AR	~1/10,000
Familial hypercholesterolemia	LDL receptor (*LDLR*)	LDL	Tendon xanthomas, CHD	AD	~1/250 to 1/500
Familial defective apoB-100	ApoB-100 (*APOB*)	LDL		AD	<~1/1500
Autosomal dominant hypercholesterolemia, type 3	PCSK9 (*PCSK9*)	LDL		AD	<1/1,000,000
Autosomal recessive hypercholesterolemia	ARH (*LDLRAP*)	LDL		AR	<1/1,000,000
Sitosterolemia	*ABCG5* or *ABCG8*	LDL		AR	<1/1,000,000

4

Lipid Transport



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Fundamental Concepts of Triglyceride Metabolism

- Changes of triglyceride
  - Functional balance
    - Synthesis vs mobilization
    - Expression of enzymes
    - Flux of substrates
- Locations of existence
  - TRLs in blood
    - Dyslipidemia
  - LDs in cells
    - Insulin resistance
- Altered cellular metabolism
- Targets for therapeutic intervention

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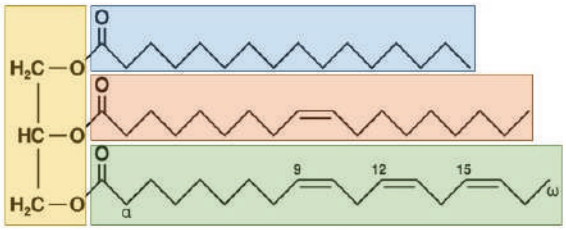
2. Synthesis of Triglyceride

- Esterification of fatty acids to glycerol backbone
  - Decreasing toxicity of fatty acids
    - ➢ To lipid droplet
  - Storage of energy
    - ➢ From ATP to triglyceride

- Major sites
  - Adipose tissue
  - Muscle
  - Liver
  - Intestine



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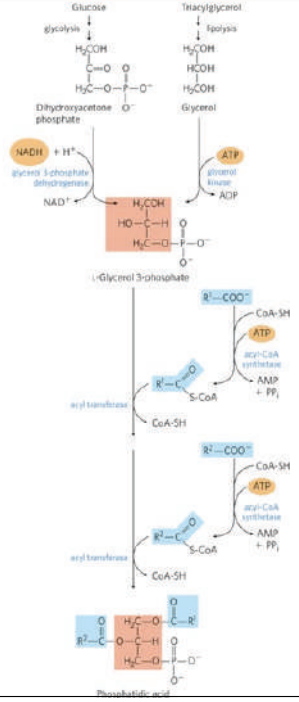
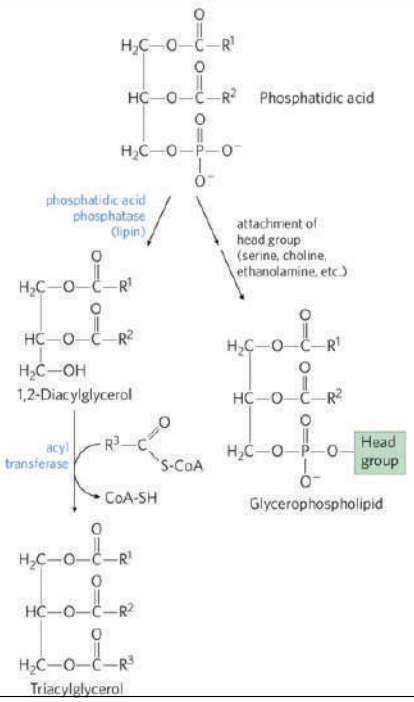
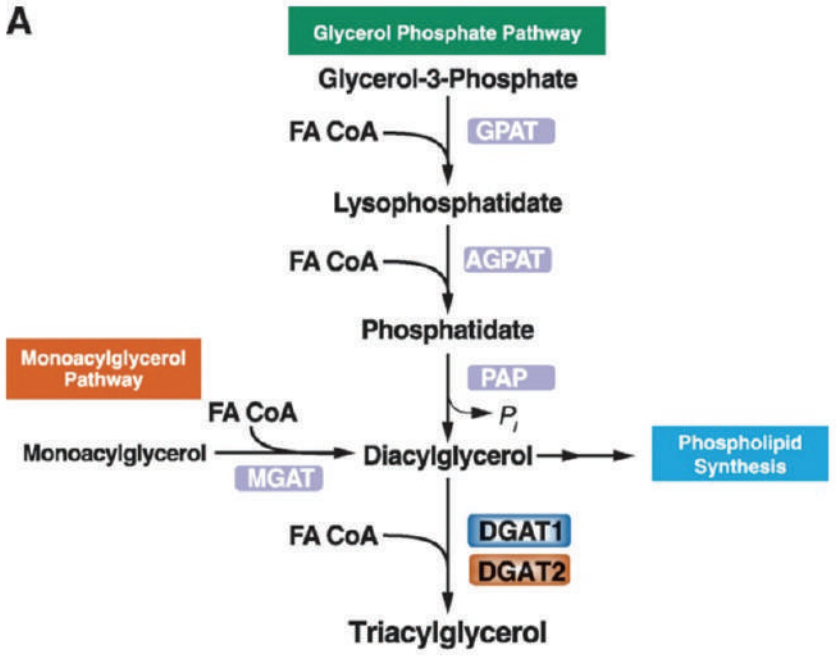
Synthesis of Triglyceride





8

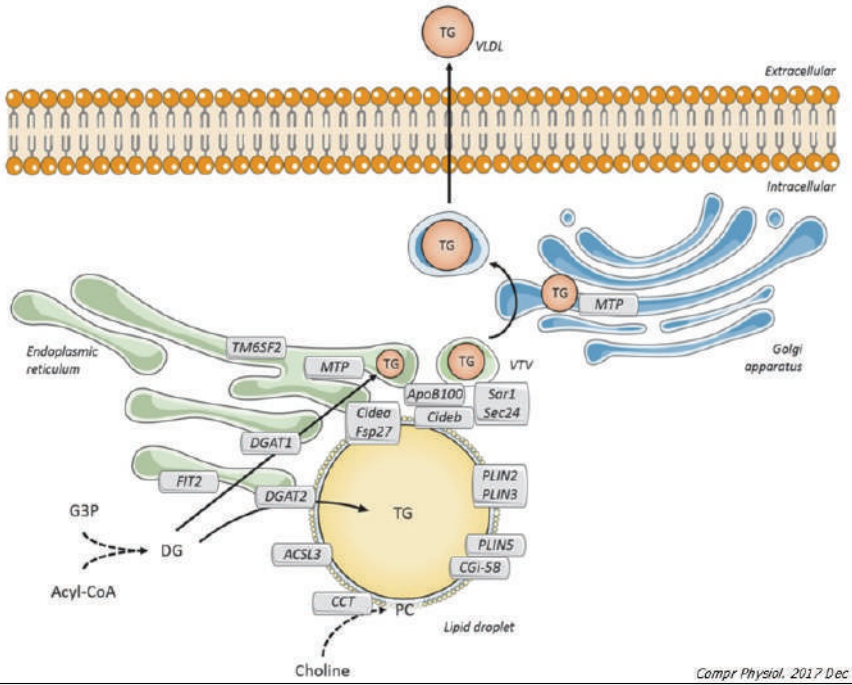
Synthesis of Triglyceride



- GPAT, glycerol 3-phosphate acyltransferase
  - Rate-limiting in TG synthesis
- AGPAT, 1-acylglycerol-3-phosphate o-acyltransferase
- PAP, phosphatidic acid phosphatase (Lipin)
- MGAT, monoacylglycerol acyltransferase
- DGAT, diacylglycerol acyltransferase

9

Triglyceride to LD and VLDL



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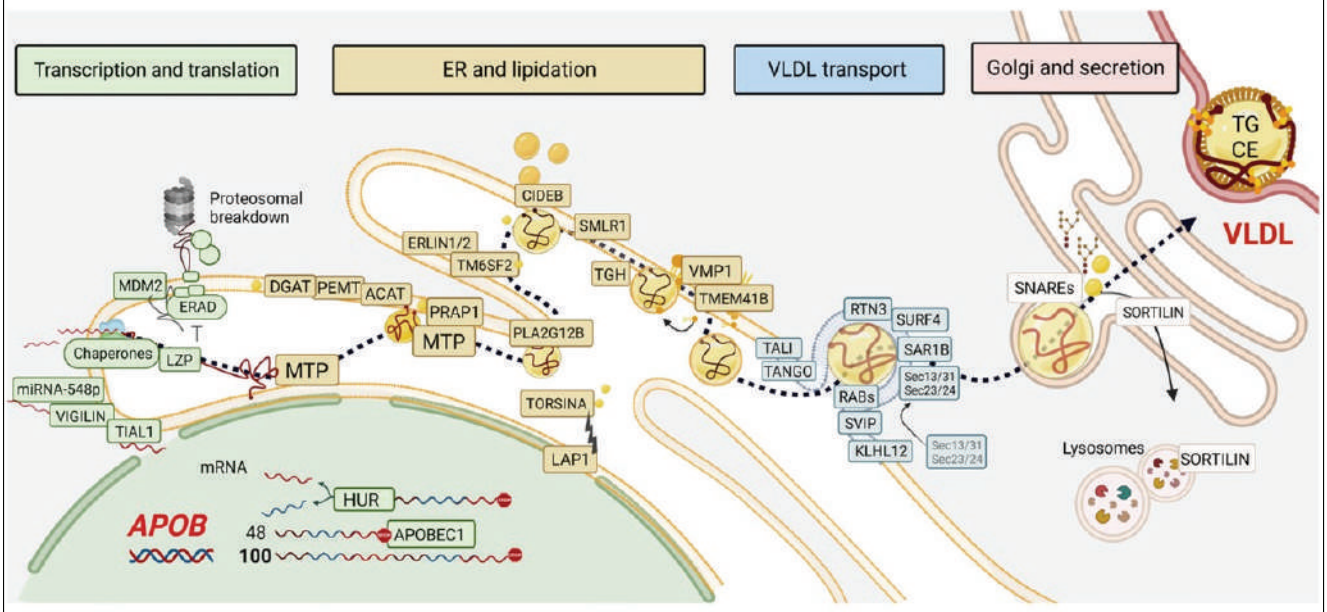
Compr Physiol. 2017 Dec 12;8(1):1-8.

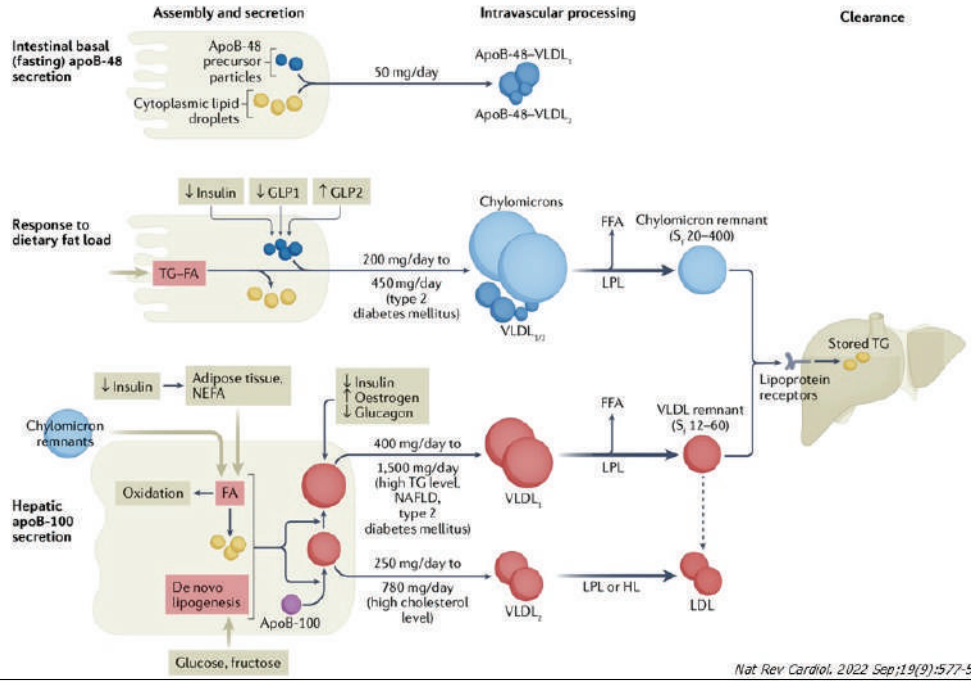
VLDL Assembly and Secretion



11

Circ Res. 2024 Jan 19;134(2):226-244.

Secretion of Triglyceride-Rich Lipoproteins (TRLs)



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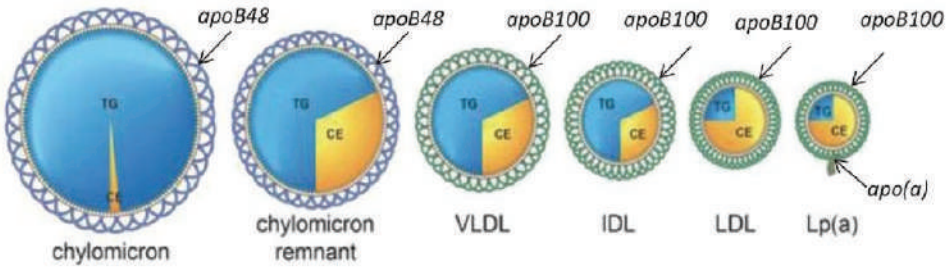
Nat Rev Cardiol. 2022 Sep;19(9):577-592.

ApoB Lipoproteins

- Non-HDL-cholesterol



13

JAMA Cardiol. 2019 Dec 1;4(12):1287-1295.

3. Triglyceride Mobilization

- Lipolysis
  - Lipid droplets
    - ➢ Fatty acids to blood stream
  - Lipoproteins
    - ➢ Endogenous lipid transport
    - ➢ Exogenous lipid transport

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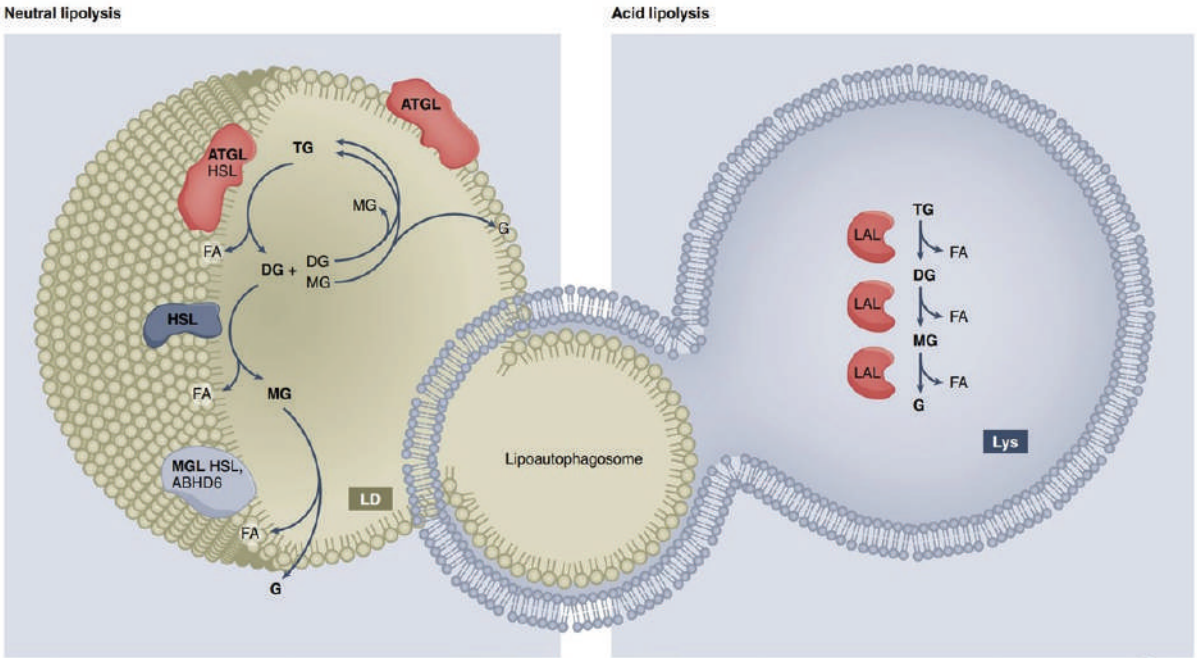
Canonical Pathways of Lipolysis



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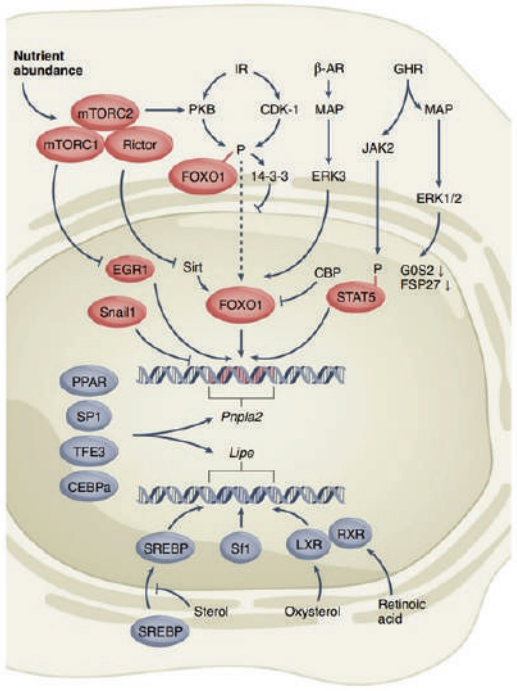
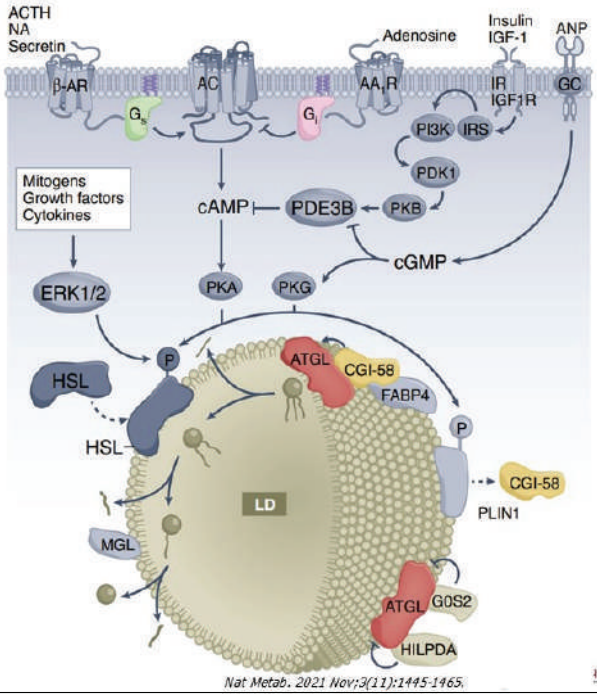
Nat Metab. 2021 Nov;3(11):1445-1465.

Regulations of Canonical Neutral Lipolysis





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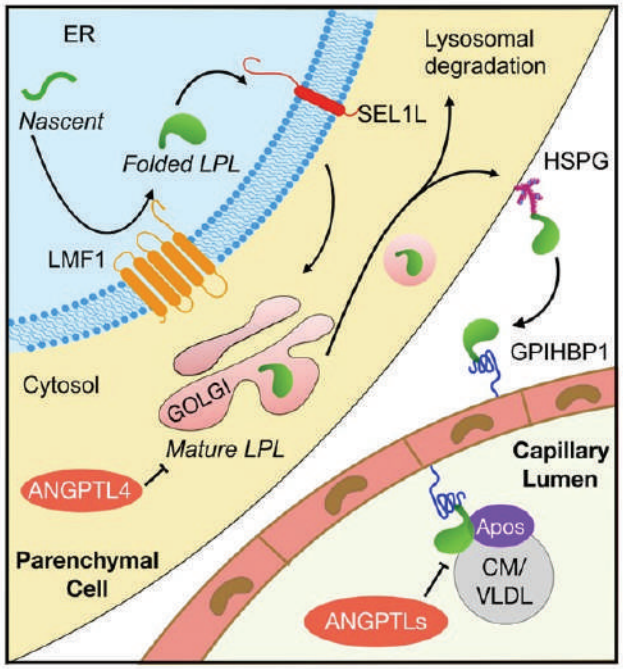
Nat Metab. 2021 Nov;3(11):1445-1465.

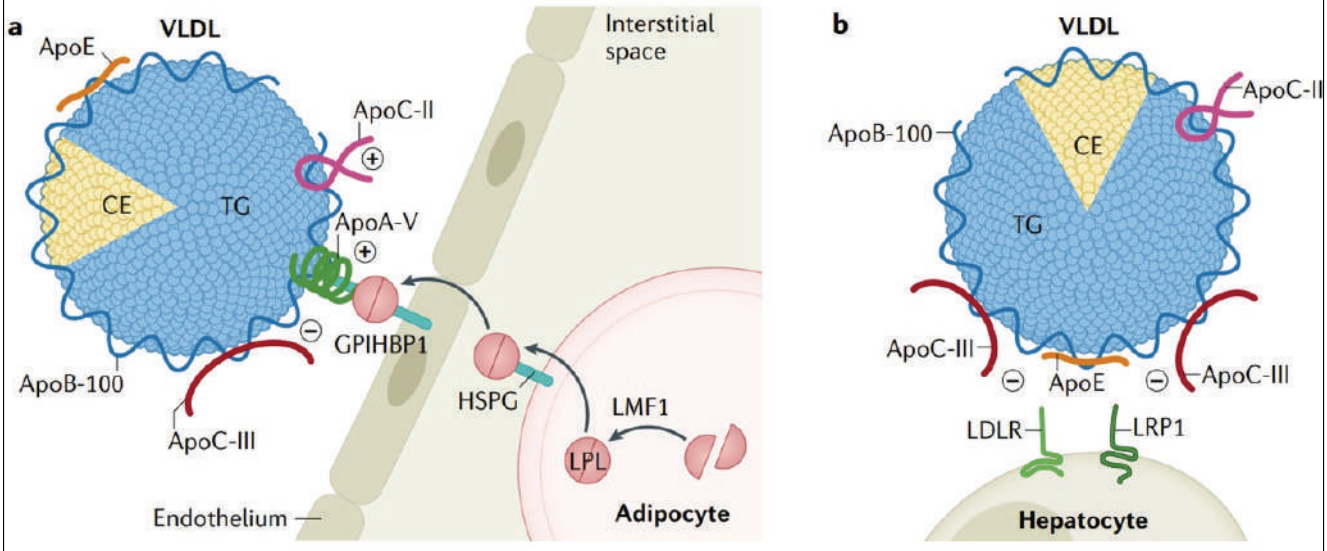
Lipoprotein Lipase



17

Trends Endocrinol Metab. 2021 Jan;32(1):48-61.

ApoC-II and ApoC-III in TRL Metabolism



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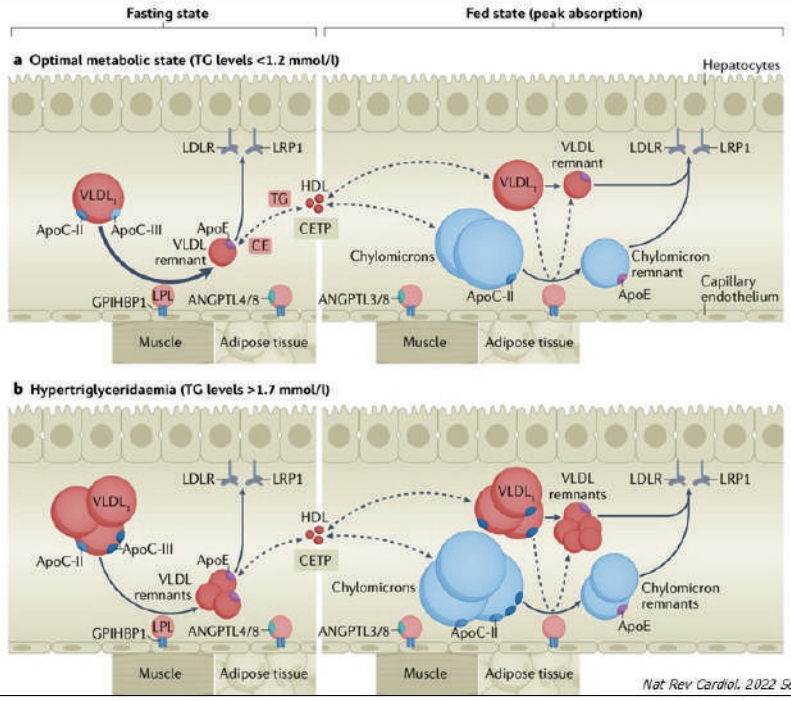
Nat Rev Cardiol. 2022 Sep;19(9):577-592.

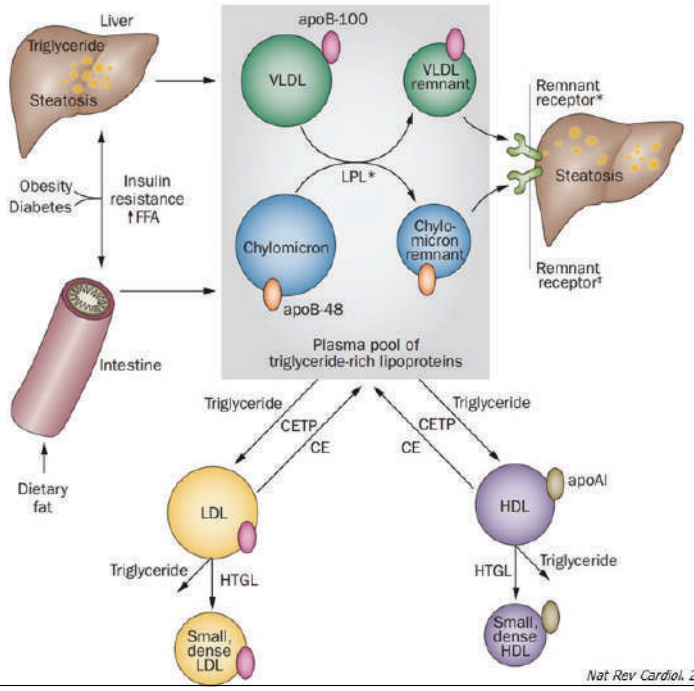
Lipolysis and Clearance of TRLs



Nat Rev Cardiol. 2022 Sep;19(9):577-592.

19

Atherogenic Dyslipidemia



Nat Rev Cardiol. 2013 Nov;10(11):648-61.

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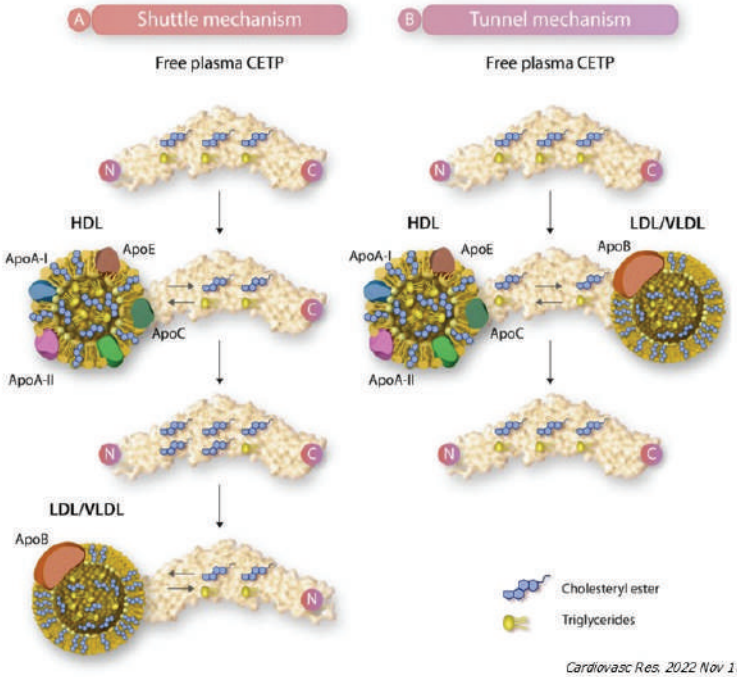
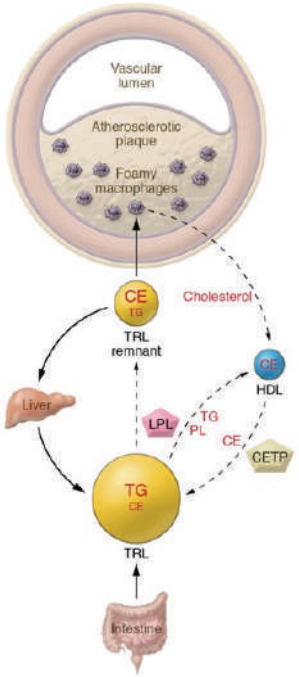
Cholesteryl Ester Transfer Protein (CETP)



21

Cardiovasc Res. 2022 Nov 10;118(14):2919-2931.

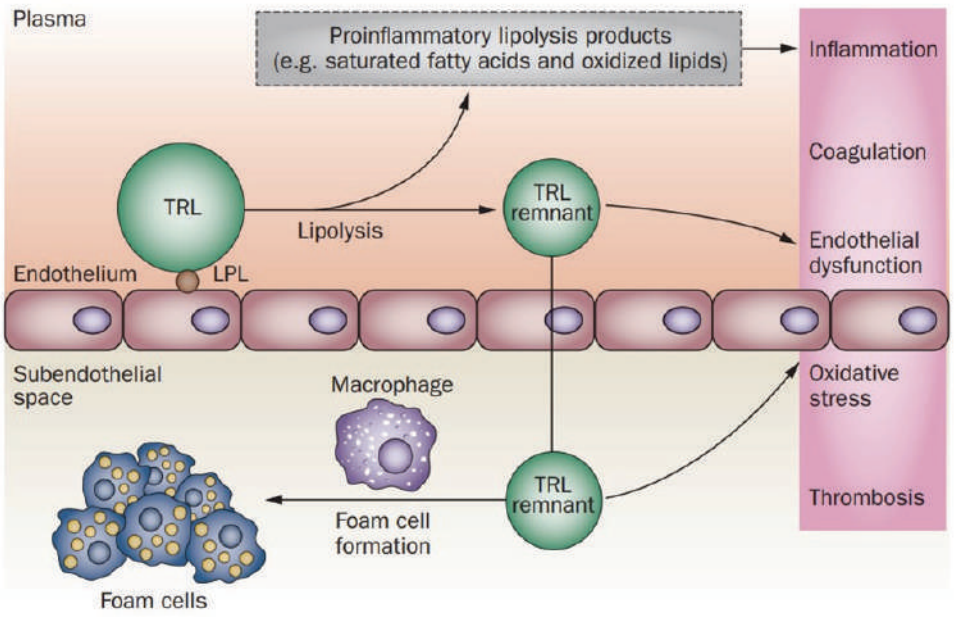
Atherogenic TRL Remnant



22

J Clin Invest. 2022 Jan 4;132(1):e148559.

Atherogenic Dyslipidemia



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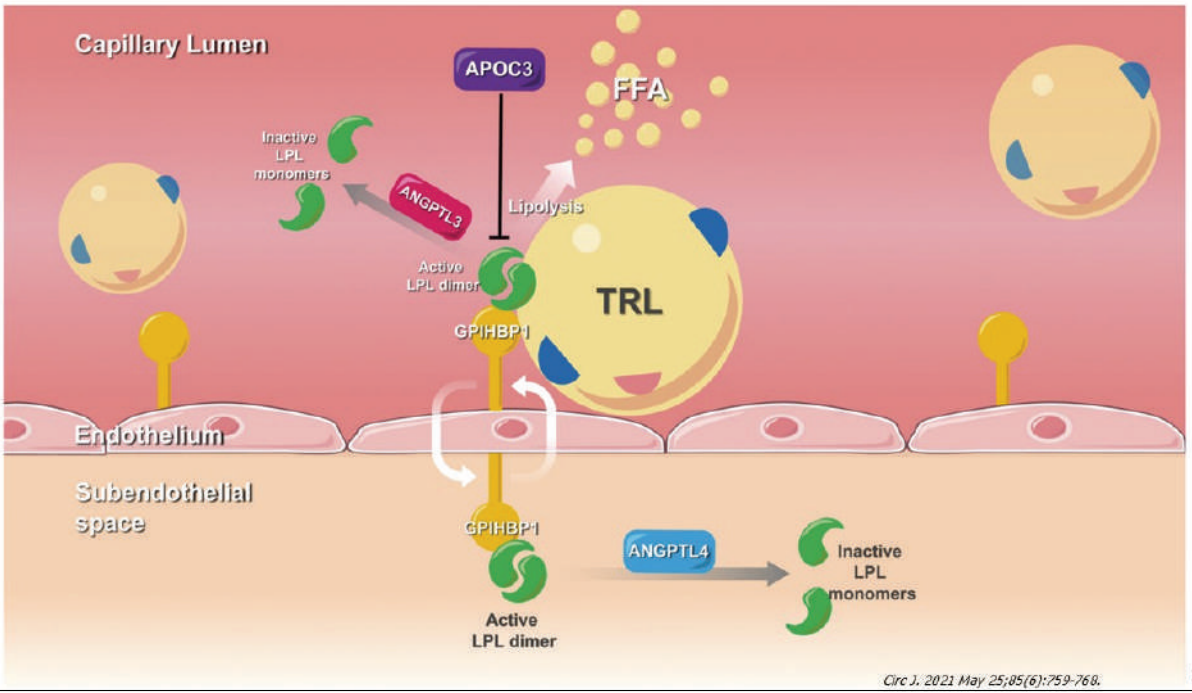
Nat Rev Cardiol. 2013 Nov;10(11):648-61.

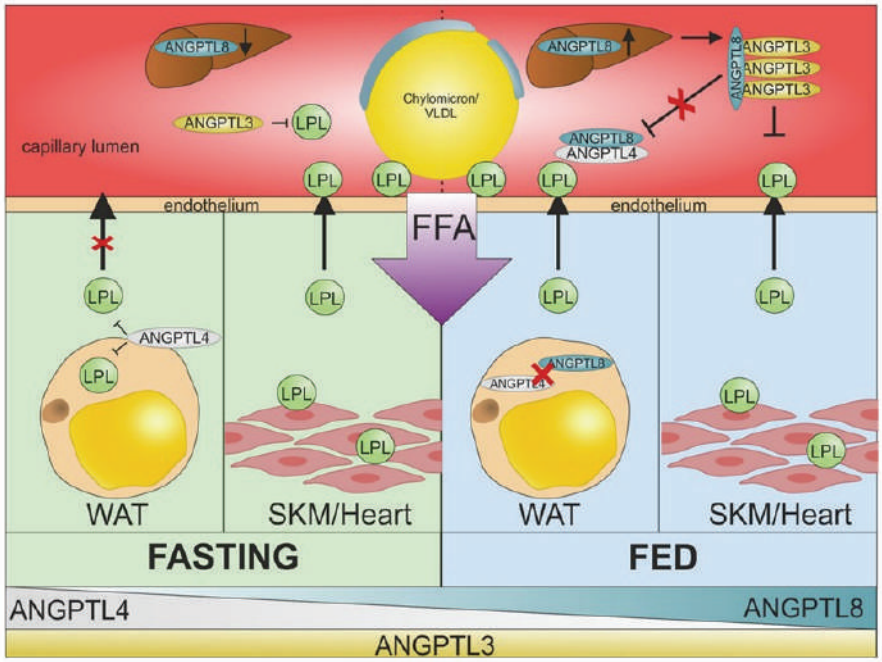
4. Regulation of Triglyceride Metabolism



24

Circ J. 2021 May 25;85(6):759-768.

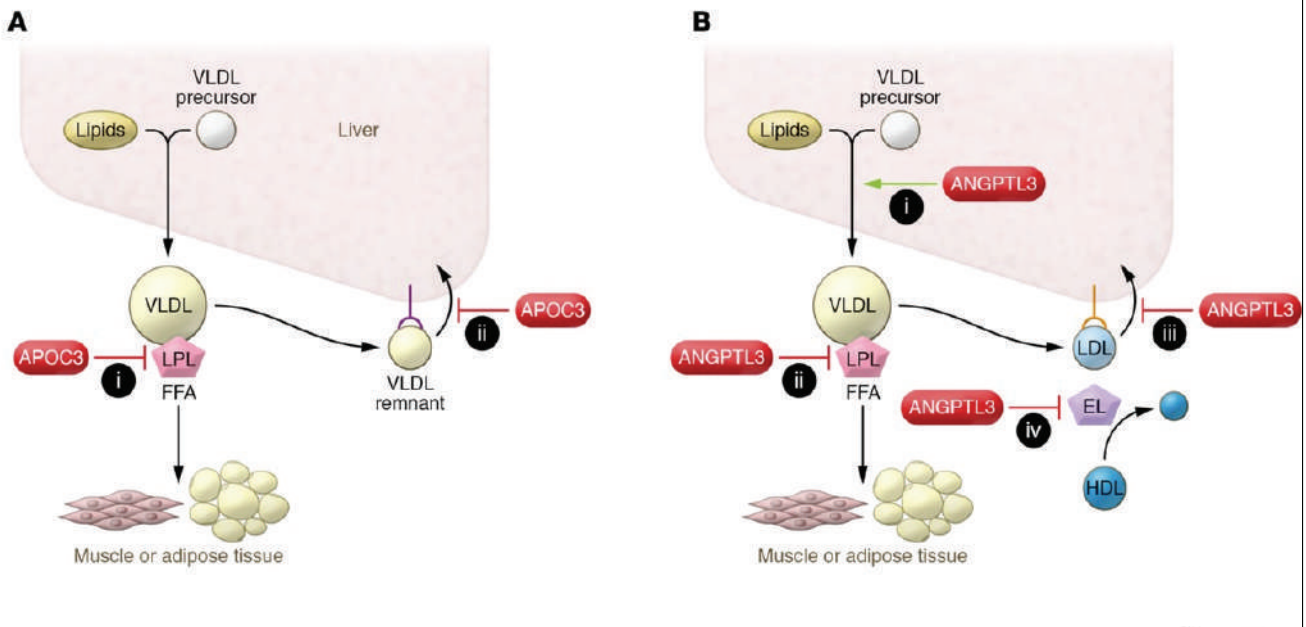
Interplay of ANGPTL3/4/8



25

Front Cell Dev Biol. 2021 Jul 15;9:702508.

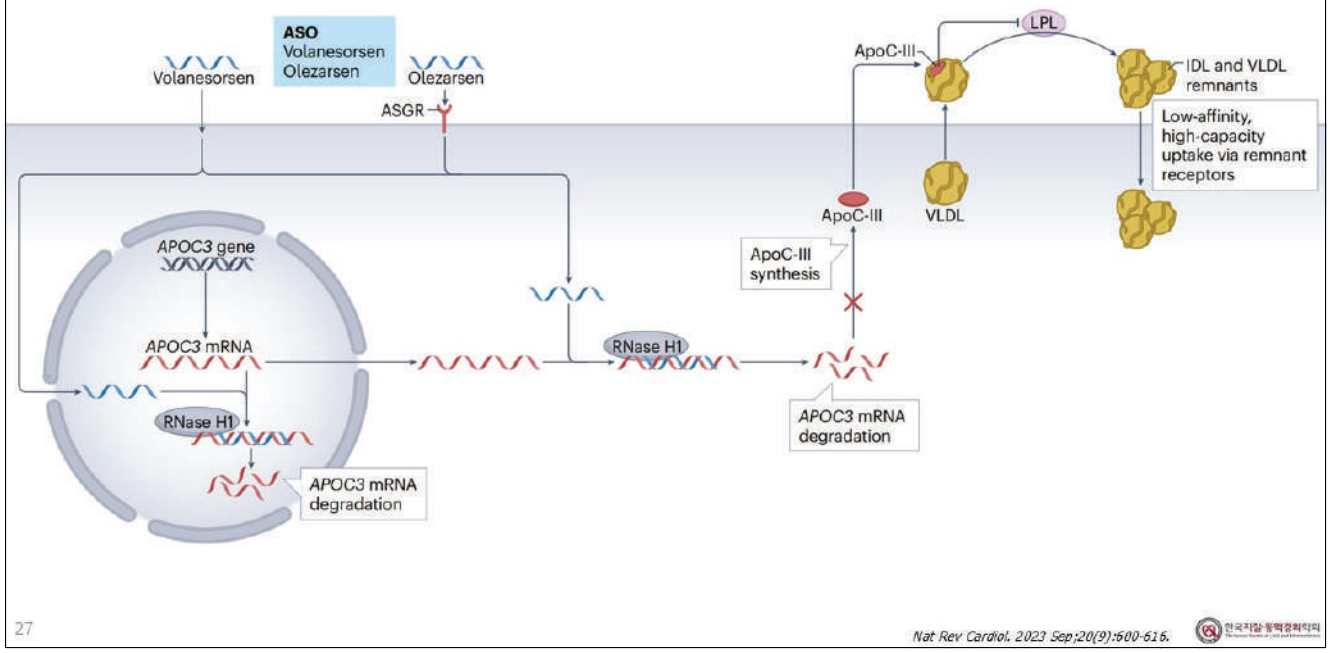
5. Therapeutic approaches



26

J Clin Invest. 2022 Jan 4;132(1):e148559.

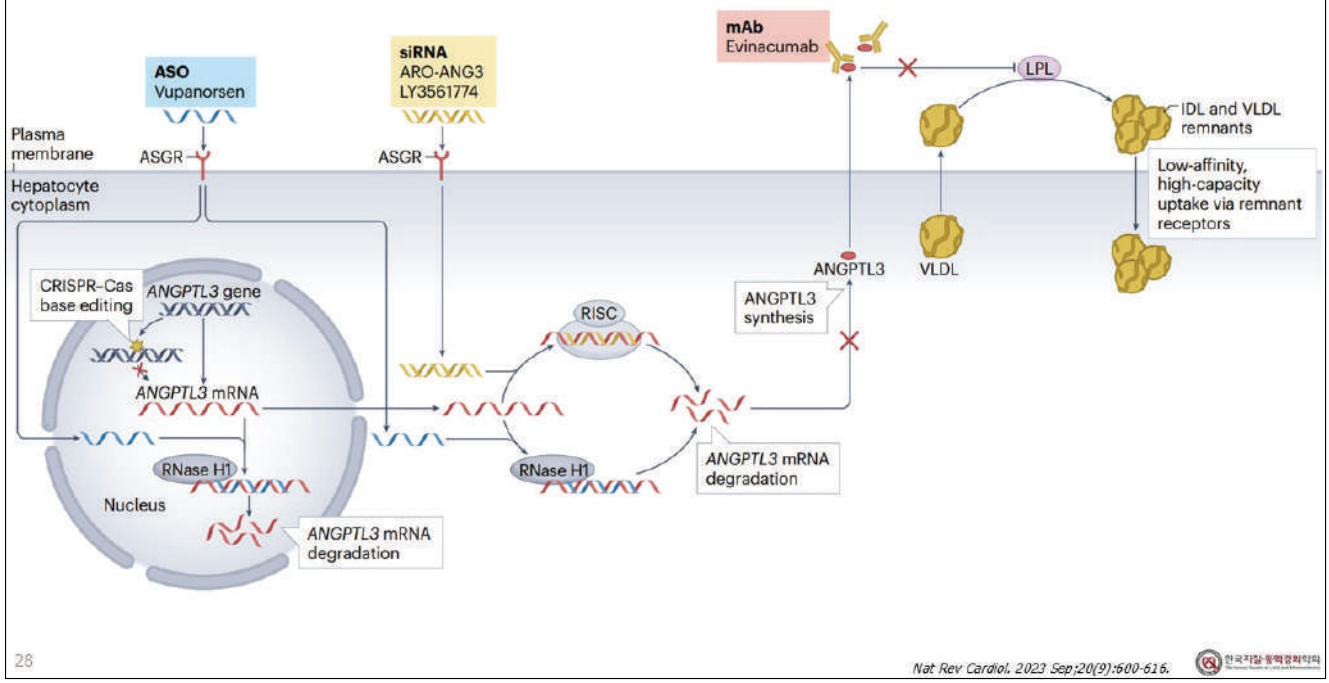
Lipid-lowering Therapies targeting ApoC-III



27

Nat Rev Cardiol. 2023 Sep;20(9):600-616.

Lipid-lowering Therapies targeting ANGPTL3



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Nat Rev Cardiol. 2023 Sep;20(9):600-616.

Summary

- Synthesis
  - LD formation
    - Storage of excess ATP
    - Ectopic fat deposit
    - Metabolically healthy obesity
  - TRL secretion
    - Endogenous and exogenous lipid transport
    - Endothelial dysfunction
    - Dyslipidemia
- Mobilization
  - Free fatty acids
    - Fuel supply
    - Insulin resistance
  - TRL remnant
    - Atherogenic
    - Oxidative stress

29

김 병 진

[기본정보]

성함	김 병 진
소속(근무처)	성균관의대 강북삼성병원 순환기내과

[학력]

해당년도	세부사항
1987-1993	부산의대 졸업
1994-1996	부산의대 석사
2001-2003	부산의대 내과 박사

[경력]

해당년도	세부사항
2001-2003.02	성균관의대 삼성서울병원 순환기내과 임상강사
2003.03-현재	성균관의대 강북삼성병원 순환기내과 조교수(~2008), 부교수(~2014), 정교수(2014~현재)
2007-2008	Dept. of Epidemiology and Preventive Medicine, UC San Diego 연수

[관심분야]

Lipid and atherosclerosis, Preventive cardiology, Hypertension, Epidemiology

[논문]

Lipoprotein(a)-related cardiovascular and all-cause mortalities in Korean adults. Eur J Prev Cardiol 2023;30:308-317
Association between LDLC level and cardiovascular outcomes in Korean adults: a Nationwide cohort study. Diabetes Metab J2023;47:59-71
Cardiovascular outcomes according to comorbidities and LDLC in Korean people with type 2 diabetes mellitus. Diabetes Metab J 2023;47:45-58
Comparison of office BP, automated unattended office BP, home BP, and 24-hour ambulatory BP measurements. JKorean Med Sci 2023;38:e406
2022 Consensus statement on the management of familial hypercholesterolemia in Korea. Korean J Intern Med 2022;37:931-944

Latest Insights into TG-lowering Therapies: Pharmaceuticals and RCTs Summary

김 병 진

성균관의대 순환기내과

CONTENTS

- TG-rich lipoprotein(TRLs)과 remnant cholesterol(RC)은 무엇인가?
- TG와 RC는 CV risk marker인가?
- TG와 RC에 대한 RCT의 CV outcome 결과는 어떠한가?
- TG RCT를 해석시 주의할 점은 없는가?
- TG와 RC에 대한 현재 치료지침은 어떠한가?
- 고중성지방혈증의 치료제 개발

1st Lipid Academy

Conclusions

- TG-rich lipoprotein(TRLs)과 remnant cholesterol(RC)은 무엇인가?
  - 일반적으로, TRL은 VLDL+IDL, RC는 VLDL+IDL에 함유된 cholesterol을 의미한다.
- TG와 RC는 CV risk marker인가?
  - 예
- TG와 RC에 대한 RCT의 CV outcome 결과는 어떠한가?
  - Inconsistent한 결과를 보였지만 좋은 경향을 보인다.
- TG RCT를 해석시 주의할 점은 없는가?
  - 현재 사용가능한 High TG치료제 사용시 TG감소효과를 보기보다는 apoB, LDLC, nonHDLC의 변화를 잘 관찰해야한다.
  - Fibrates사용시 Cr의 변화와 O3FA사용시 new-onset Afib monitoring을 고려해야한다.
- TG와 RC에 대한 현재 치료지침은 어떠한가?
  - RC에 대한 치료지침은 아직 확립되어 있지 않다.
  - TG치료는 고위험군이상에서 statin사용(LDLC lowering therapy)에도 high TG일 경우 fibrates 또는 O3FA의 사용을 고려해 볼수 있겠다.(Class IIb)
- 고중성지방혈증의 치료제 개발
  - apoCIII ASO and siRNA, ANGPTL3 mAb and siRNA의 연구들이 진행중이다.

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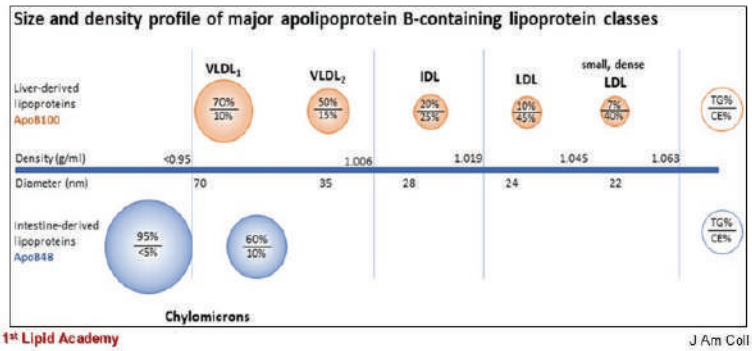
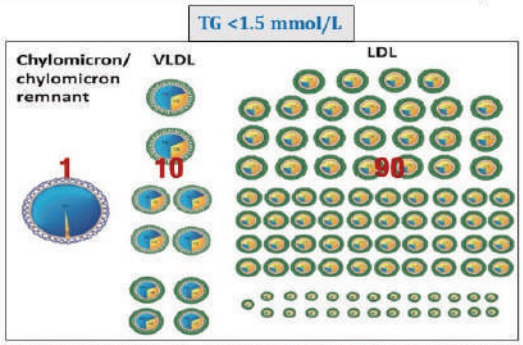
Size, Density, and Core and Surface components of LPs

TABLE 1 Size, Density, and Core and Surface Components of Lipoproteins

	Diameter (nm)	Molecular Weight × 10^6 (Da)	Density (g/ml)	Components (% of Dry Weight)					Main Apolipoproteins
				Core		Surface			
				Triglycerides	Cholesterol Ester	Cholesterol	Phospholipid	Apolipoproteins	
Chylomicrons	75-1,200	50-1,000	0.93	86	3	2	7	2	A, B-48, C, E
VLDL	30-80	10-80	0.93-1.006	55	12	7	18	8	B-100, C, E
IDL	25-35	5-10	1.006-1.019	23	29	9	19	19	B-100, C, E
Lipoprotein(a)	25-30	4-5	1.040-1.090	8	30	8	25	29	B-100, a
LDL	18-25	2.3	1.019-1.063	6	42	8	22	22	B-100
HDL	5-12	0.2-0.4	1.063-1.210	4	15	5	34	42	A, C, E





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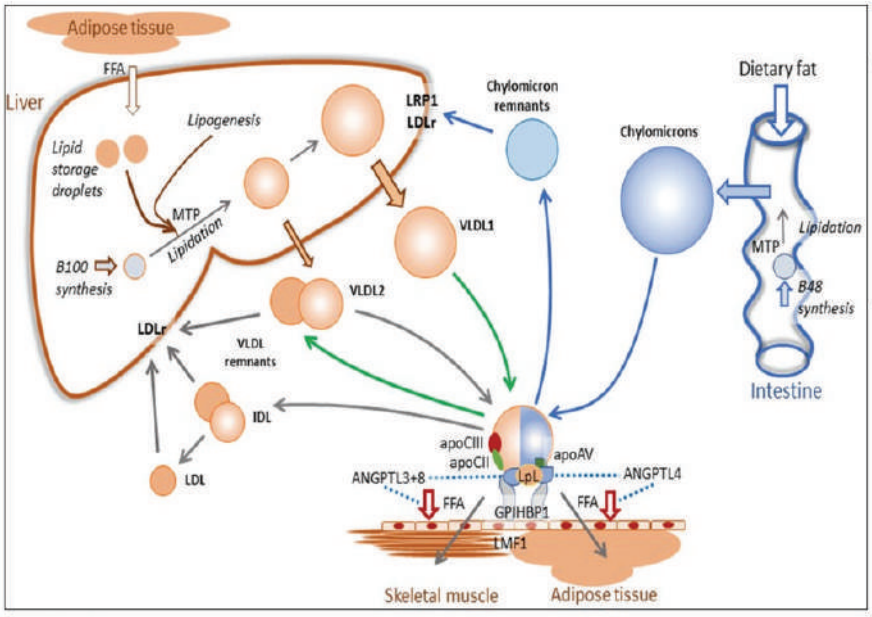
J Am Coll Cardiol 2017;70:1637-46; Eur Heart J 2021;42:4791-4806;JAMA Cardiol 2019;4:1287-1295

Metabolism of apoB-containing lipoproteins



- ✓ ***VLDL to LDL conversion*** occurs in ***6 hours***.
- ✓ ***An LDL is in the circulation*** for ***48 hours*** total, so ***an apoB lipoprotein spends*** ***90%*** of its lifecycle ***as an LDL.***

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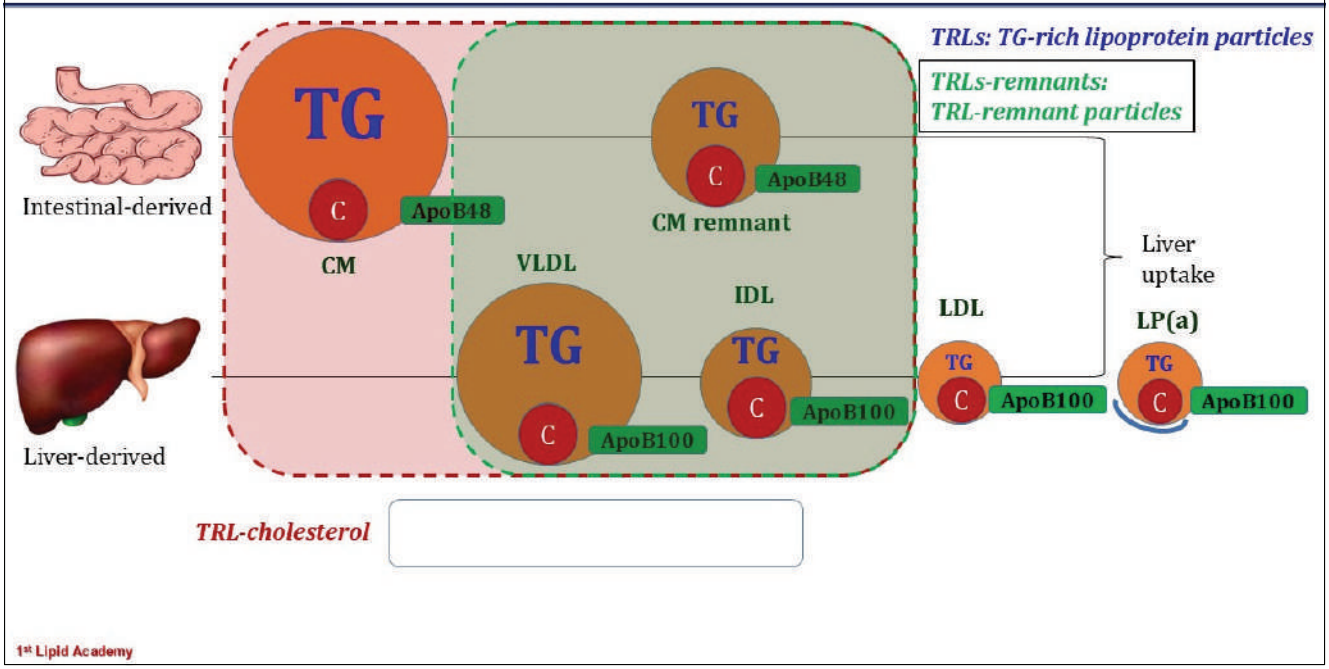
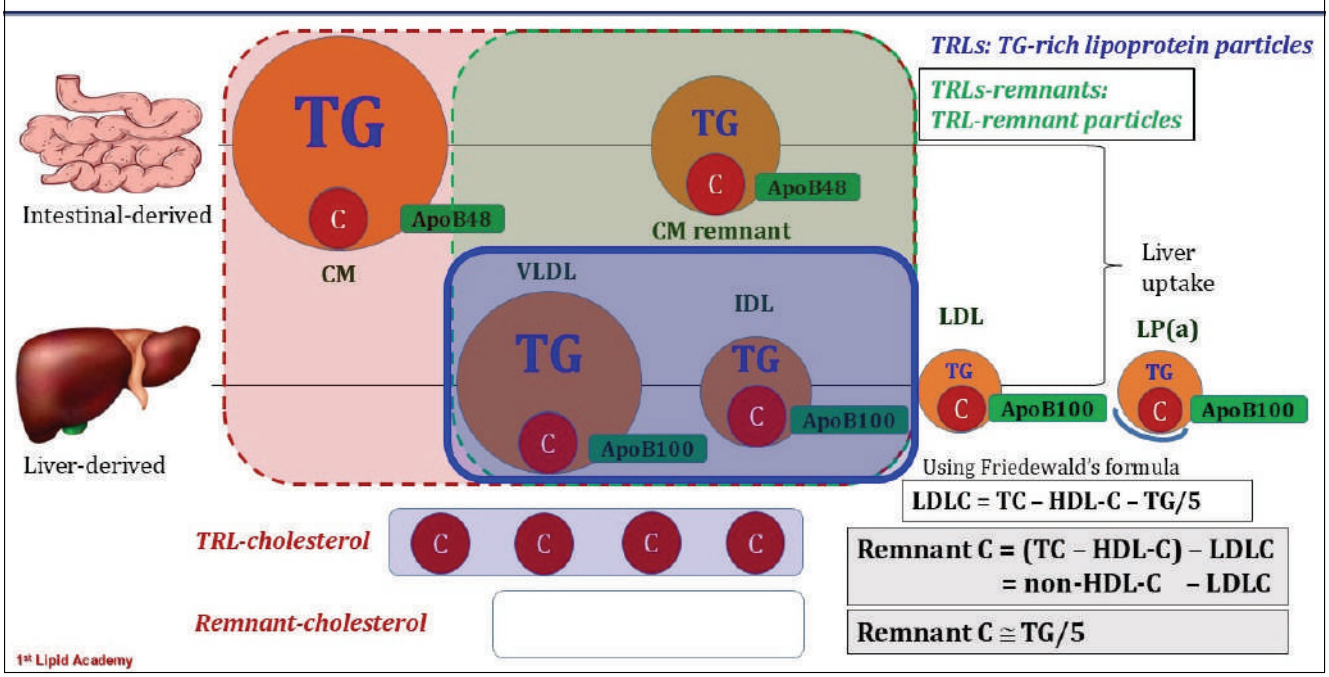
Eur Heart J 2021;42:4791-4806; JAMA 2020;324:595-6

What is TRLs and remnant cholesterol?



What is TRLs and remnant cholesterol?



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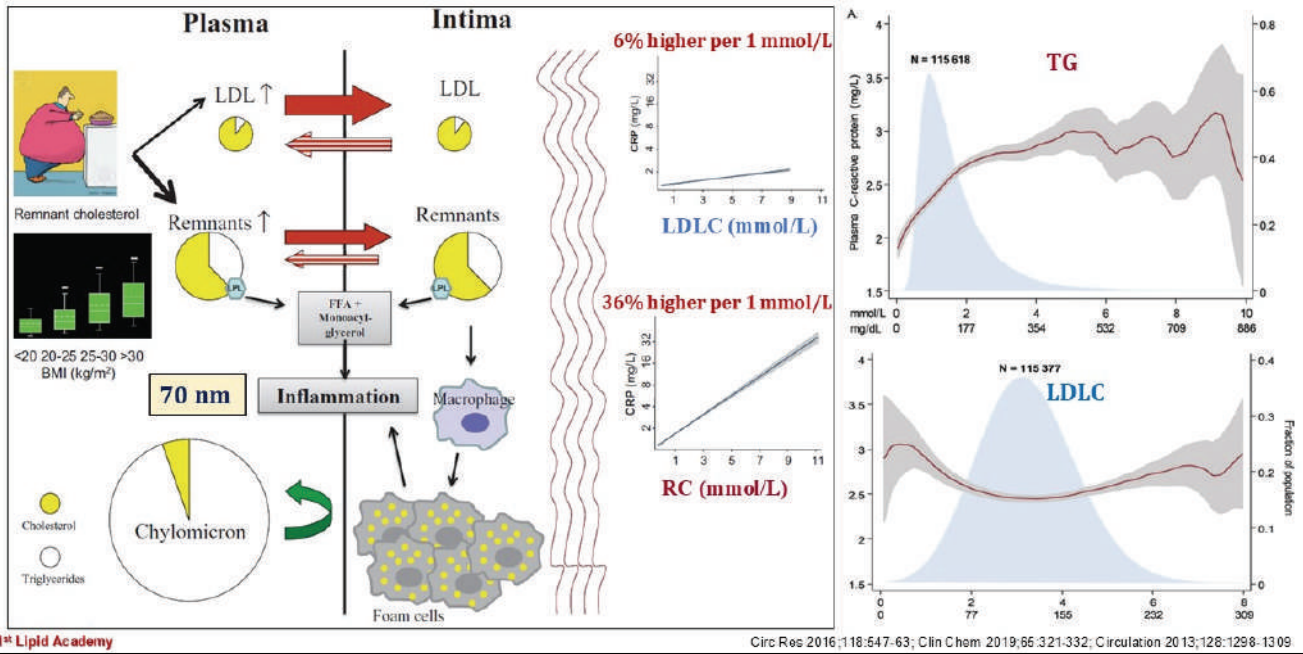
Suggested role of TGs and remnant cholesterol in intimal low-grade inflammation and development of atherosclerosis



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Circ Res 2016;118:547-63; Clin Chem 2019;65:321-332; Circulation 2013;128:1298-1309

Putative effects of TRLs and their remnants on vascular wall biology

- **Impaired vasodilation**
- Upregulated production of **proinflammatory cytokines**
- Enhanced endothelial inflammatory response
- Upregulated expression of **VCAM-1 and monocyte activation**

- Activated **NLRP3 inflammasome** in human monocytes
- Inducing alternative NLRP3 inflammasome via caspase-8 with dimerization of toll-like receptors 2 and 4
- **Impeding endothelial regeneration**

ApoCIII

TRLs

Lipolytically released SFAs and PLs(oxidized FAs)

- ✓ Activated **toll-like receptors** of subendothelial macrophages
- ✓ Producing **ROS** and proinflammatory lipids and proteins

- Plaque rupture and thrombus formation via:
  - ✓ **redox-sensitive mechanisms**
  - ✓ **Tissue factor** secretion form endothelium
  - ✓ Stimulation of monocytes and **thrombin generation.**
  - ✓ **Coagulation factors VII and X** transported by chylomicrons and VLDLs

Biochim Biophys Acta 2012;1821:858-66; Curr Atheroscler Rep 2009;11:199-205; J Lipid Res 2009;50:204-13; Nature Immuno 2020;21:30-41; Circulation 2000;102:670-6; J Clin Pathol 1988;41:940-4

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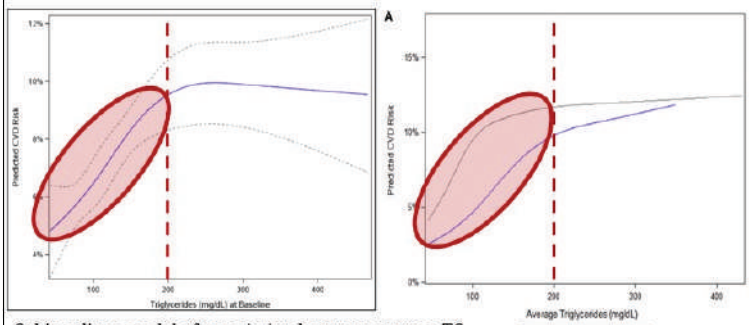
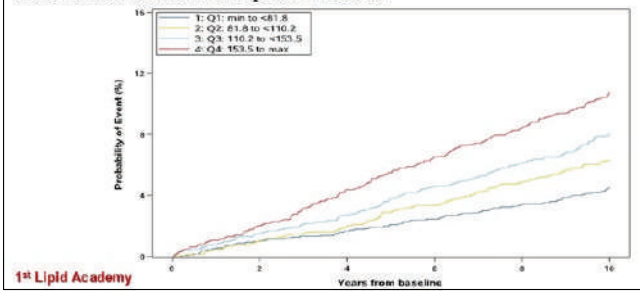
CVD increases dramatically with TG increases

even just "normal" to "upper normal" range



Cubic splines model of association between average TG and CVD risk *Dotted lines represent 95% CI.

- ✓ 8068 primary prevention patients in Atherosclerosis Risk in Communities Study (ARIC) and Framingham Offspring Study
  - 40 to 65 years old
  - No CVD
- ✓ ≥2 TG measurements on record
- ✓ Endpoint: time to MI, stroke, or CV death
- ✓ Follow-up for up to 10 years to first event



CVD events steeply increase across the entire range of TG levels to ~ 200 mg/dL, above which the relationship is less graded.

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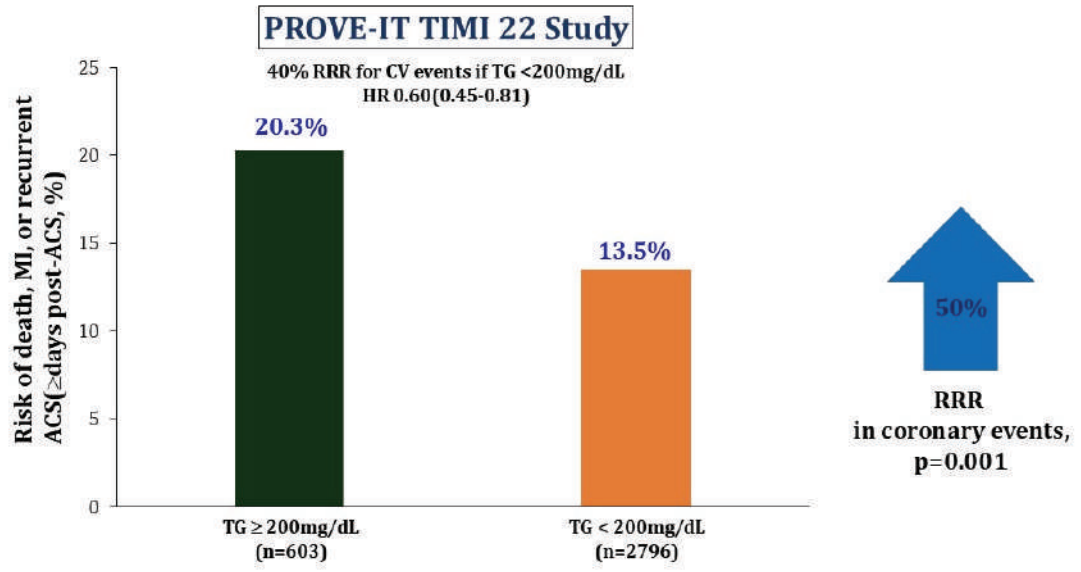
J Clin Lipidol 2020;14:438-447.e3

High TG is a "Red flag" for Residual Risk in Statin Monotherapy, even with LDLC < 70mg/dL



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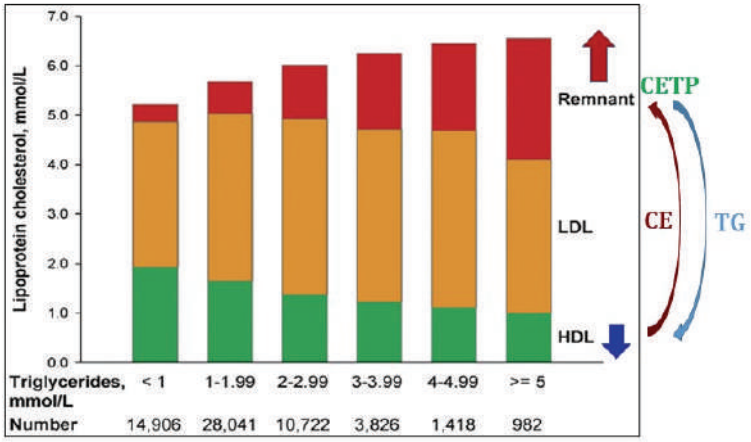
JACC 2008;51:724-730

Copenhagen General Population Study, Copenhagen City Heart study, Copenhagen Ischemic Heart Disease Study

Associations of lipoprotein cholesterol and TGs



R / p-value	Remnant cholesterol	HDL cholesterol	LDL cholesterol	Triglycerides
Remnant cholesterol		-0.45	0.12	0.96
HDL cholesterol	p<0.001		-0.12	-0.42
LDL cholesterol	p<0.001	p<0.001		0.12
Triglycerides	p<0.001	p<0.001	p<0.001	

Increased TGs were associated with increased remnant cholesterol and reduced HDLC.

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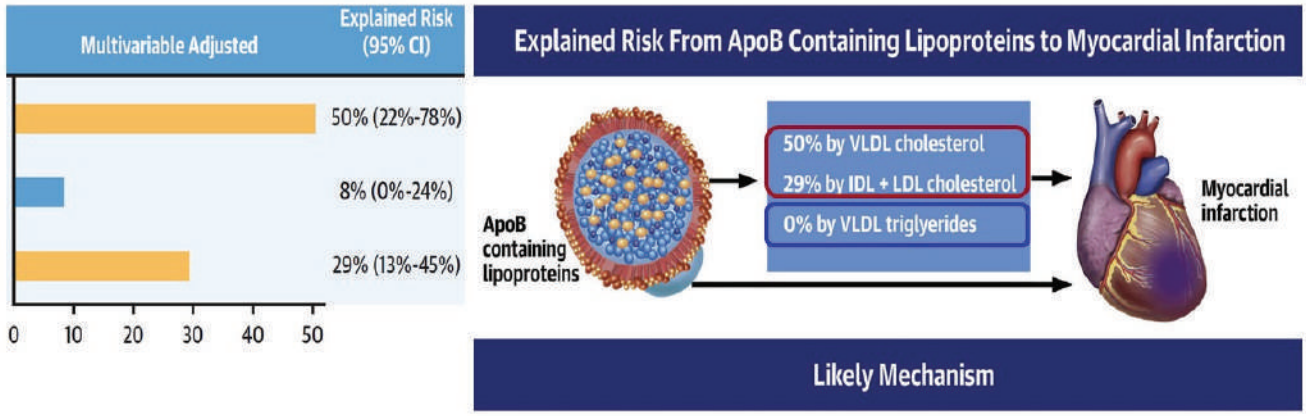
J Am Coll Cardiol 2013;61:427-436

Explained risk from apoB-containing lipoproteins to MI

Copenhagen General Population Study (25,480 subjects free of LLT and MI, median 11-yr FU)



VLDL cholesterol explained one-half of the myocardial infarction risk from elevated apoB-containing lipoproteins, whereas **VLDL triglycerides** did **not** explain risk.

1st Lipid Academy JACC 2020;76:2725-35

Epidemiological studies
TRL-remnant cholesterol and incident CVD

TABLE 1 Triglyceride-Rich Remnants Lipoprotein Cholesterol and Incident Cardiovascular Disease

Study Association (Ref. #)	Sample Size	Fasting Status	Measurement	Outcome	HR (95% CI) Adjusted Risk
CGS, CCHS, CIHS (13)	75,513	Nonfasting	TC-LDL-C-HDL-C	Ischemic heart disease	2.3 (1.7-3.1) for highest vs lowest quintile
CGS (6)	106,213	Nonfasting	TC-LDL-C-HDL-C	MI	Normal weight: 2.0 (1.3-3.2) Overweight: 1.9 (1.4-2.6) Obese: 2.3 (1.4-3.5); for highest vs lowest quartile
CGS (11)	102,964	Nonfasting	TC-LDL-C-HDL-C	Ischemic stroke	1.99 (1.49-2.67) for highest vs lowest quartile
PREDIMED (12)	6,901	Overnight fast	TC-LDL-C-HDL-C	Cardiovascular event (MI, ischemic stroke, CVD death)	1.83 (1.30-2.58) highest (>30.95 mg/dL) vs lowest quartile (<17.5 mg/dL)
Women's Health Study (13,16)	480 cases, 496 controls	Nonfasting	TRL cholesterol	Cardiovascular events (MI, ischemic stroke, PAD, CVD death)	1.87 (1.14-3.06)

CCHS = Copenhagen Community Health Study; CGS = Copenhagen General Study; CI = confidence interval; CIHS = Copenhagen Ischemic Heart Study; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease; PREDIMED = Prevencion con Dieta Mediteranea; TC = total cholesterol; TRLC = triglyceride-rich lipoprotein cholesterol.

1st Lipid Academy JACC 2021;78:1817-30

Association of remnant cholesterol with risk of CVD events, stroke, and mortality: Meta-analysis

Association of remnant cholesterol with risk of cardiovascular disease events, stroke, and mortality: A systemic review and meta-analysis

Aims To evaluate the association of remnant cholesterol (RC) with the risks of cardiovascular diseases (CVDs), coronary heart disease (CHD), stroke, and mortality.

Methods

Five databases screened for 232 studies

31 studies
N=2,857,236

Outcomes
- CVD
- CHD
- Stroke
- Mortality

Results
- **CVD**
  RR = 1.53, 95% CI 1.41–1.66
- **CHD**
  RR = 1.41, 95% CI 1.19–1.67
- **Stroke**
  RR = 1.43, 95% CI 1.24–1.66
- **CVD mortality**
  RR = 1.83, 95% CI 1.53–2.19
- **All-cause mortality**
  RR = 1.39, 95% CI 1.27–1.50

Conclusions Elevated RC is associated with an increased risk of CVD, stroke, and mortality. In addition to the traditional cardiovascular risk factors, such as total cholesterol and LDL-C, clinicians should also pay attention to RC in clinics.

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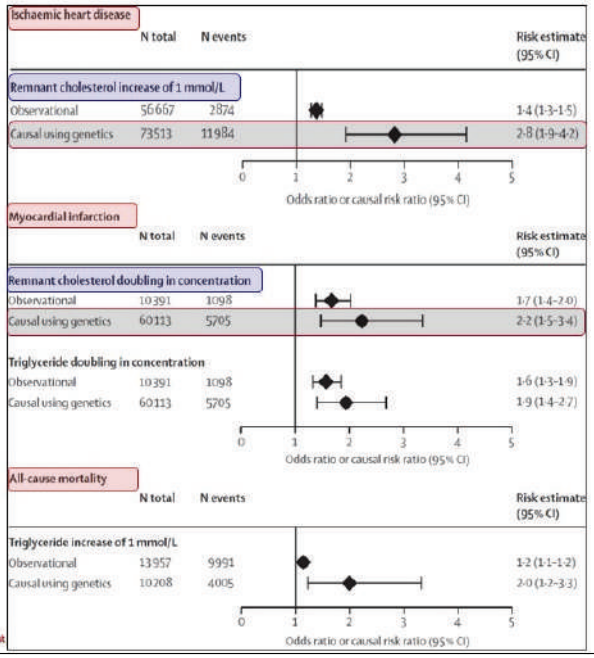
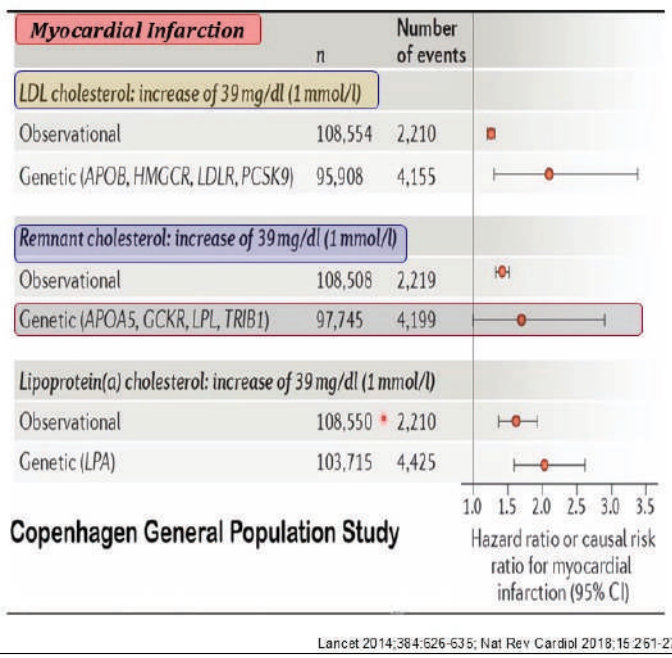
Atherosclerosis 2023;371:21-31

Observational and genetic association of remnant cholesterol and TGs with risk of IHD, MI, and all-cause mortality: Copenhagen General Population Study





Lancet 2014;384:626-635; Nat Rev Cardiol 2018;15:261-272

Remnant cholesterol normal range?

	Quintile	Lipid levels (mmol/L or ratio)	Lipid levels (mg/dL or ratio)	N total	N cases	Hazard Ratio Ischemic Heart Disease	Hazard Ratio (95%CI)	P for trend
	Remnant cholesterol							
No risk	1	<0.4	<15	11,589	311		1	
Low risk	2	0.4-0.6	15-23	11,410	471		1.1 (0.8-1.6)	
Low-medium risk	3	0.6-0.7	23-27	11,265	578		1.2 (0.9-1.6)	1×10^{-14}
High-medium risk	4	0.7-1.1	27-43	11,241	736		2.0 (1.5-2.6)	
High risk	5	>1.1	>43	11,152	778		2.3 (1.7-3.1)	

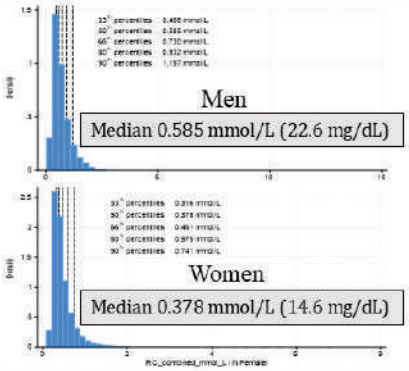
2009 NHIS-HEALS over 8,000,000 individuals

	Q1	Q2	Q3	Q4
Mean Remnant C, mmol/L	≤0.36	0.39-0.54	0.57-0.75	≥0.78

2009-2011 NHID over 3,600,000 individuals
Median[IQs] 0.58 (0.43 – 0.82) mmol/L, 22[17, 32] mg/dL

2003~2016 KSHS over 200,000 individuals

Median RC
- ✓ 0.47[0.33, 0.69] mmol/L for Friedewald's equation (18.1 mg/dL)
- ✓ 0.39[0.23, 0.60] mmol/L for direct LDLC (15.1 mg/dL)



JACC 2013;61:427-436; Diabetes Care 2023;46:305-312; EJPC 2023;30:1142-50

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Omega-3 fatty acid

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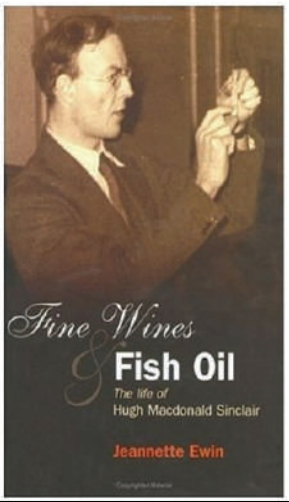
Interesting History of omega-3 fatty acids

Inuit Paradox

Hugh Macdonald Sinclair (1910-1990)



He is best remembered for his belief that diets deficient in essential fatty acids are the cause of most degenerative illnesses, including coronary heart disease. Sinclair's forceful arguments on this matter preceded firm scientific evidence, however; and his self-experimentation, including the infamous 100 day seal-meat diet, were the subject of widespread ridicule and professional ruin.

> Lancet. 1956 Apr 7;270(6919):381-3.

Deficiency of essential fatty acids and atherosclerosis, etcetera

H M SINCLAIR

PMID: 13307939

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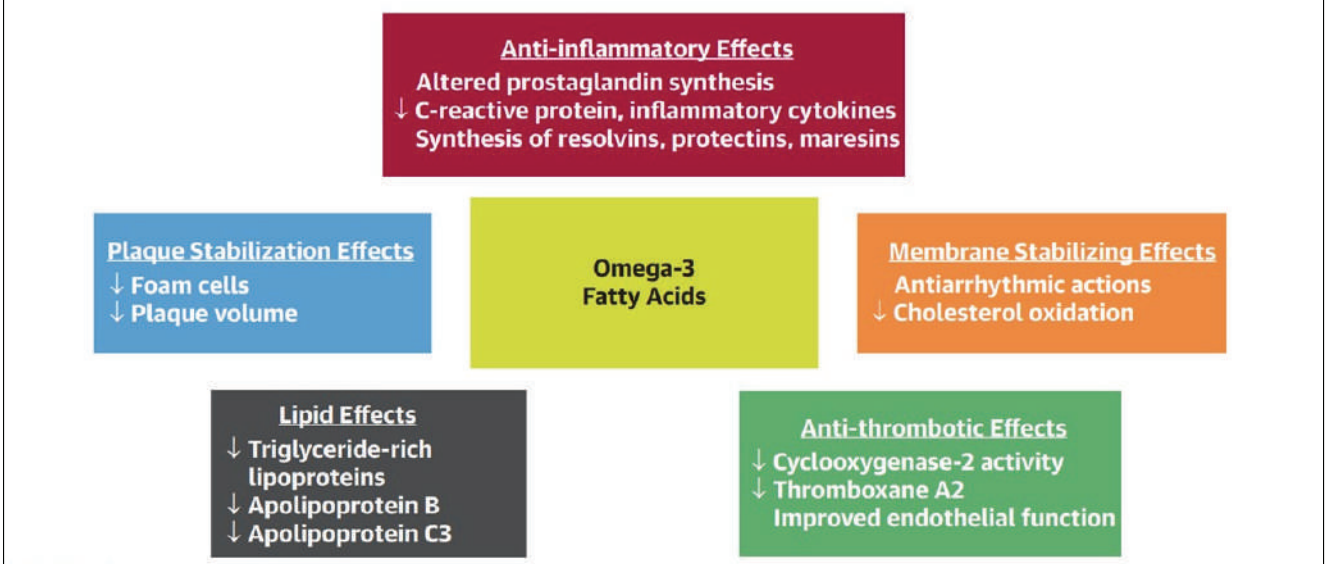
Hypothesized mechanisms of n-3 PUFAs that decrease CVD risk



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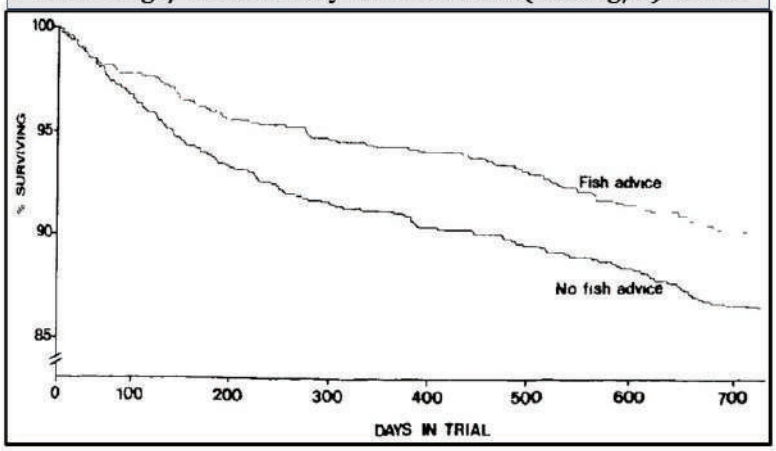
J Am Coll Cardiol 2021;77:593-608

DART(Diet And Reinfarction Trial)(1989)

≥ 2 servings/week of fatty fish or fish oil(500mg/d) vs SOC



✓ 2033 post MI men, 2yr FU

✓ All death: 0.71[0.54-0.93]

✓ IHD events
(IHD death and nonfatal MI)
-0.84[0.66-1.07]

Ingestion of modest amounts of fatty fish reduces mortality in men after MI.

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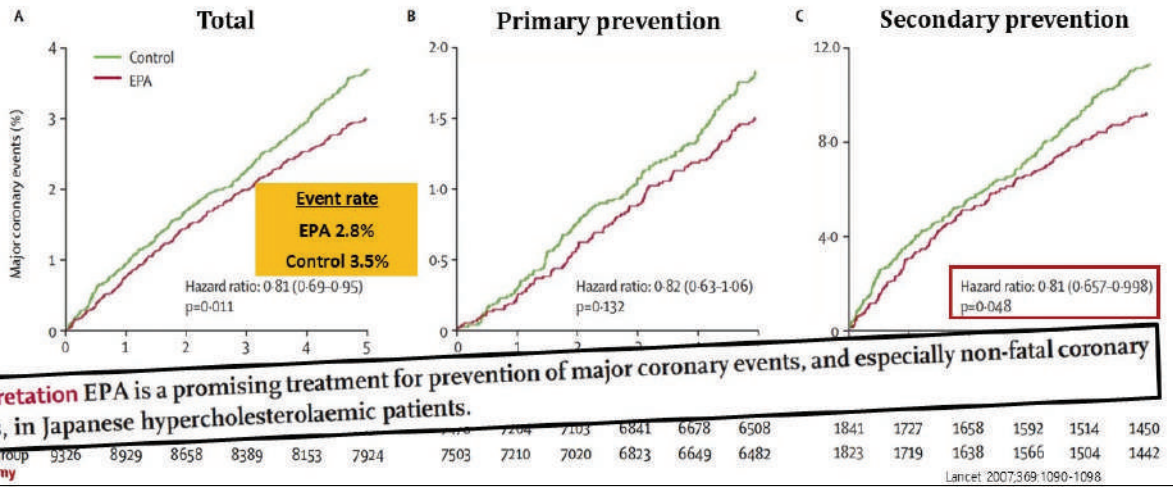
LANCET 1989;2:757-61

JELIS study: statin+EPA 1800 mg vs. statin

Primary any major coronary event: a composite of sudden cardiac death, fatal and nonfatal MI, UAP, angioplasty, stenting, or CABG → HR 0.81 (95% CI: 0.69-0.95); *P=0.011*



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RCTs for omega-3 FA and CVD events (until 2017)

Trials	Type	DHA &/or EPA	Control	Number	duration	Primary outcome
DART	S	2 serving/week(LD)	Standard of care	2,033	2	positive
GISSI-P	S	EPA+DHA(LD)	Standard of care	11,324	3.5	positive
JELIS	P>S	EPA(HD)+statin	Statin	18,645	4.6	positive
GISSI-HF	HF	EPA+DHA(LD)	Oil(unspecified)	6,975	3.9	positive
DOIT	P>S	EPA+DHA(HD)	Corn oil	563	3.0	negative
α OMEGA	S	EPA+DHA(LD)	Magarine(+-ALA)	4,837	3.4	negative
OMEGA	S	EPA+DHA(LD)	Olive oil	3,851	1.0	negative
SU.FOL.OM3	S	EPA+DHA(LD)	Undefined	2,501		negative
ORIGIN	S>P	EPA+DHA(LD)				negative
R & P	P, S					negative
AREDS2	P>S		Undefined	4,203	4.8	negative

Inconsistent!!

P, primary prevention; S, secondary prevention; LD, low-dose; HD, high-dose;EE, ethyl ester; ALA, alpha linolenic acid

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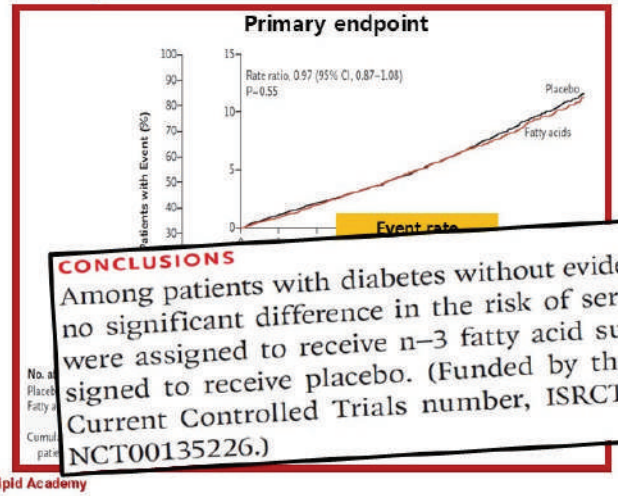
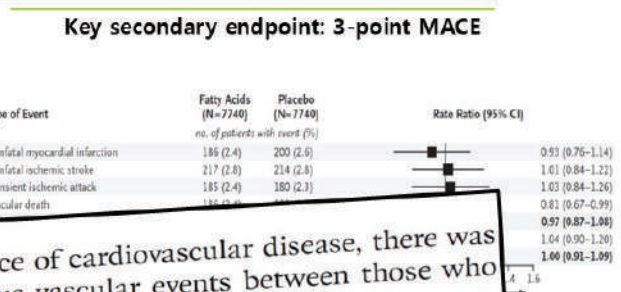
J Am Coll Cardiol 2021;77:593-608

ASCEND study: n-3 FA 1g (EPA 460mg DHA 380mg) vs. Olive oil

Primary serious vascular event: a composite of nonfatal MI or stroke, TIA, or vascular death (excluding confirmed ICH)

HR 0.97 (95% CI: 0.87-1.08); *P=0.55*





CONCLUSIONS

Among patients with diabetes without evidence of cardiovascular disease, there was no significant difference in the risk of serious vascular events between those who were assigned to receive n–3 fatty acid supplementation and those who were assigned to receive placebo. (Funded by the British Heart Foundation and others; Current Controlled Trials number, ISRCTN60635500; ClinicalTrials.gov number, NCT00135226.)

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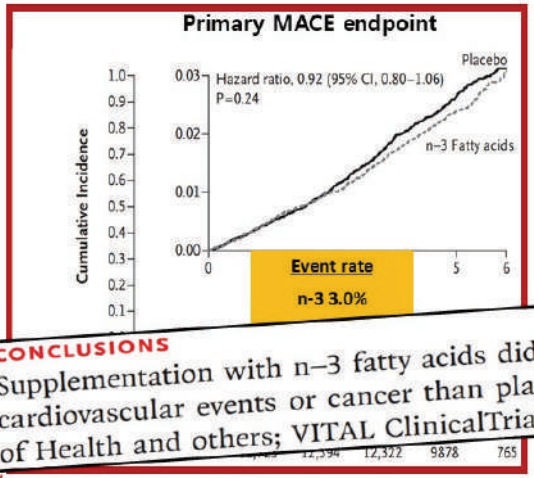
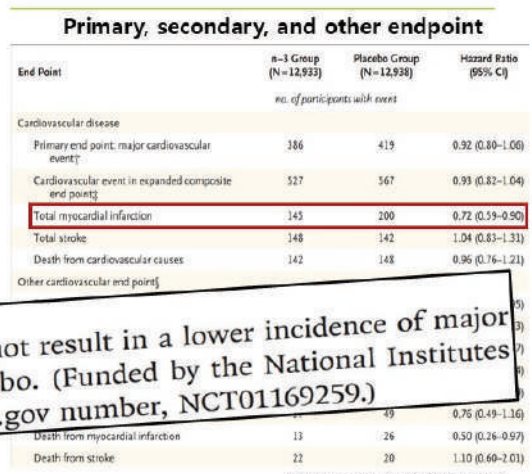
NEJM 2018;379:1540-1550

VITAL study: n-3 FA 1g (EPA 460mg DHA 380mg) vs. placebo

Primary MACE endpoint: a composite of CV death, MI ,and stroke

HR 0.92 (95% CI: 0.80-1.06); *P=0.24*





CONCLUSIONS

Supplementation with n–3 fatty acids did not result in a lower incidence of major cardiovascular events or cancer than placebo. (Funded by the National Institutes of Health and others; VITAL ClinicalTrials.gov number, NCT01169259.)

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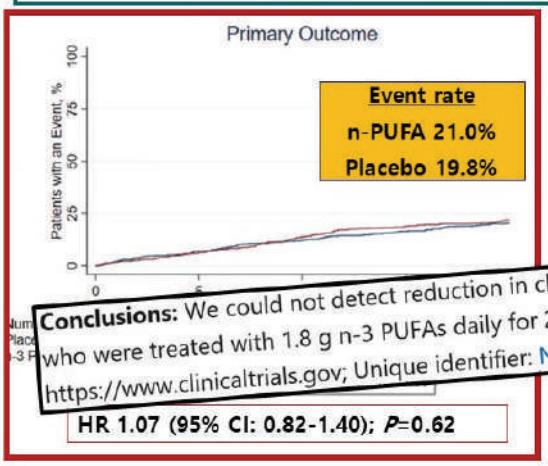
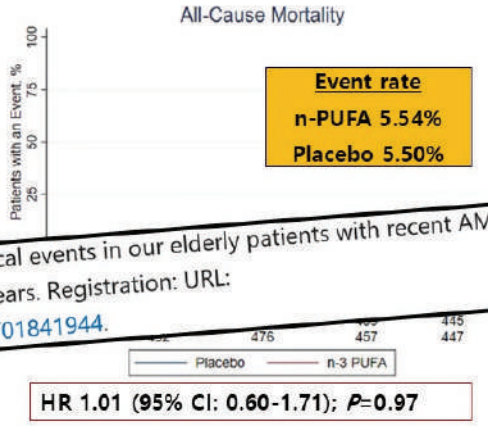
Manson JE, et al. NEJM 2019;380:23-32

OMEMI: 1.8 g n-3 PUFA(930 mg EPA+660 mg DHA) vs. Corn oil

Primary outcome: a composite of non-fatal MI, unscheduled revascularization (stenting or bypass surgery), stroke, HF hospitalization, or all-cause mortality

HR 1.07 (95% CI: 0.82-1.40); *P*=0.62





Conclusions: We could not detect reduction in clinical events in our elderly patients with recent AMI who were treated with 1.8 g n-3 PUFAs daily for 2 years. Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01841944.

1st Lipid Academy

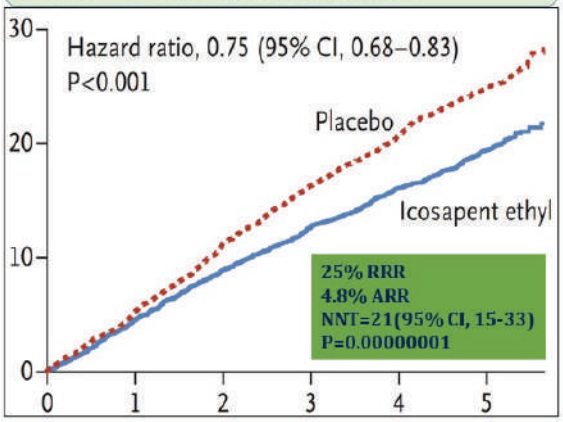
Kalstad AA, et al. Circulation. 2021 Feb 9;143(6):528-539.

REDUCE-IT vs STREGNTH

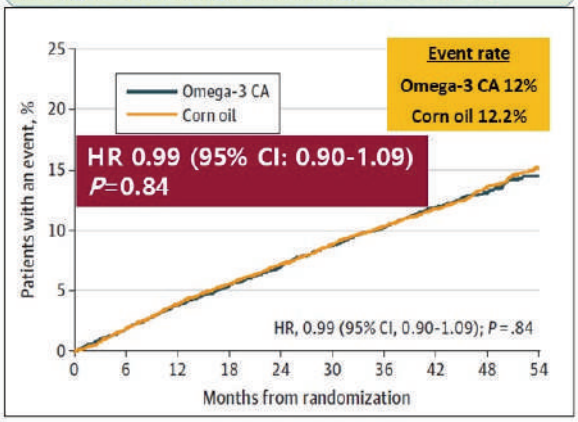
Icosapent ethyl reduces ASCVD risk but Omega-3 carboxylic acid does not

Primary MACE endpoint: a composite of CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina

REDUCE-IT
Icosapent ethyl 4g vs Mineral oil



STRENGTH
Omega-3 carboxylic acid 4g vs Corn oil



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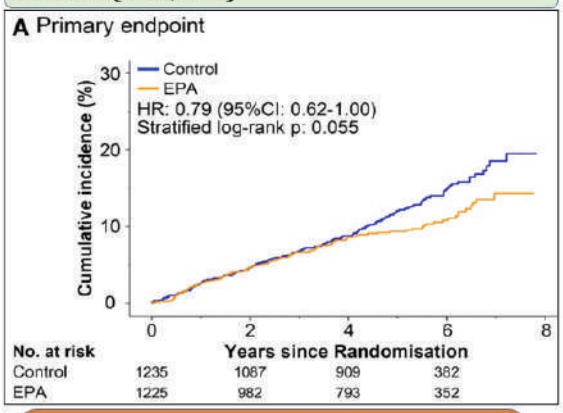
NEJM 2019;380:11-22

RESPECT-EPA

Icosapent ethyl numerically reduces CV events risk without a statistical significance

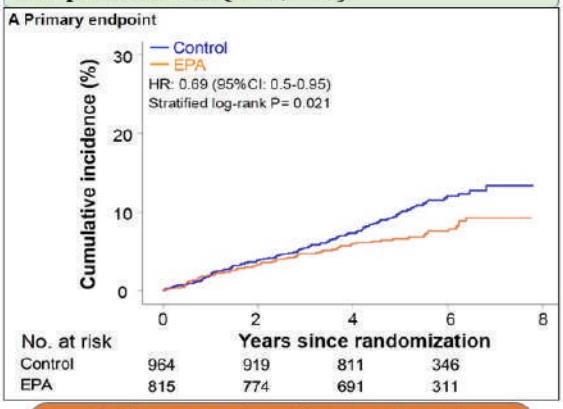
20-79 years, stable CAD with EPA/AA <0.4, Median FU 5 years
Primary MACE endpoint: a composite of CV death, nonfatal MI and stroke, UAP, and coronary revascularization

ITT set (n=2,460)



NOAF 3.1% vs 1.6% p=0.012
NODM 2.1% vs 1.2% p=0.085

Per protocol set (n=1,779)



2 times protocol amendment
Increased sample size and longer FU duration

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Circulation 2024;150:425-434

Omega-3 fatty acid: since 2018

Trials	Type	DHA &/or EPA	Control	Number	duration	Primary outcome
VITAL	P	EPA+DHA(LD)	Inert placebo	25,871	5.3	negative
ASCEND	P(DM)	EPA+DHA(LD)	Olive oil	15,480	7.4	negative
REDUCE IT	S(70%)>P	EPA(HD)	Mineral oil	8,179	4.9	positive
STRENGTH	S(56%)>P	EPA+DHA(HD)	Corn oil	13,078	3.5	negative
OMEMI	S	EPA+DHA(HD)	Corn oil	1,027	2	negative
RESPECT-EPA	S	EPA(HD)	Control(No)	2.506	5.0	negative

P, primary; S, secondary; LD, low-dose; HD, high-dose;EE, ethyl ester

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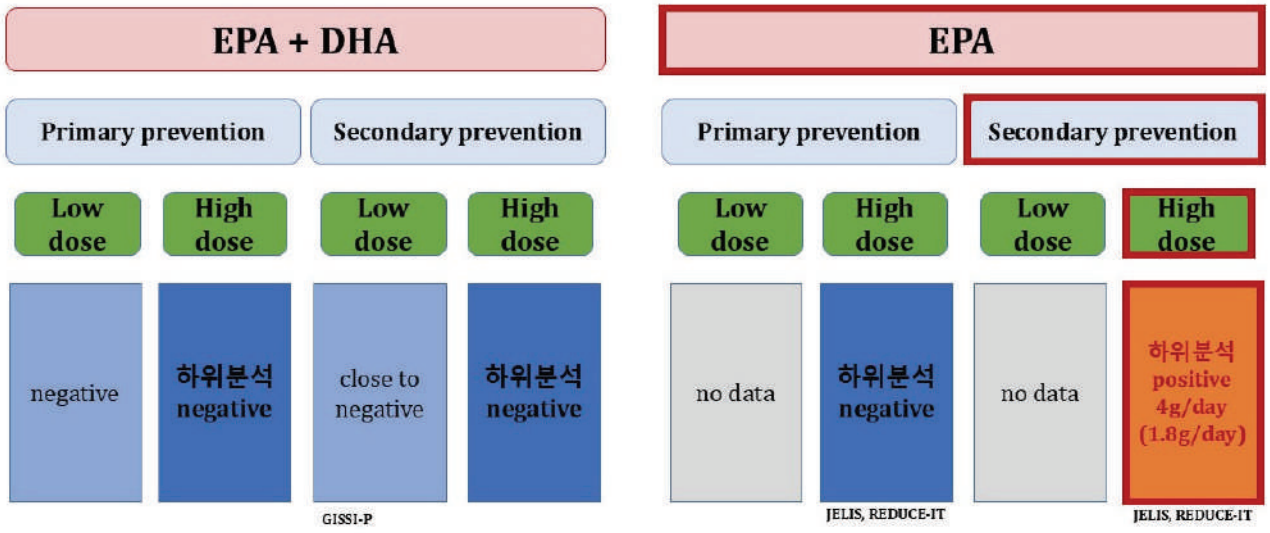
Omega-3 PUFAs and CV outcome studies



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low-dose(<1g/day); high-dose(>1g/day: 1.8 g/day or 4g/day)

Fibrates

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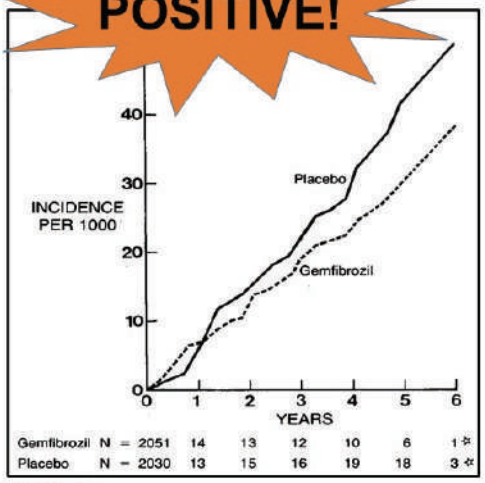
Helsinki Heart Study: 4081 asymptomatic middle-age men

No statin use

Gemfibrozil 600mg bid vs placebo, mean FU 6.2 years

Primary endpoint: nonfatal MI and cardiac death → **34% reduction, p<0.02**

POSITIVE!



Coronary Event	Subjects Receiving Treatment		Subjects Withdrawn from Treatment		Total	
	Gemfibrozil	Placebo	Gemfibrozil	Placebo	Gemfibrozil	Placebo
					no. (rate/1000)	
Definite						
Nonfatal myocardial infarction	40	61	5	10	45 (21.9)	71 (35.0)
Fatal myocardial infarction	3	7	3	1	6 (2.9)	8 (3.9)
Sudden cardiac death	3	3	2	1	5 (2.4)	4 (2.0)
Unwitnessed death	0	1	0	0	0 (0.0)	1 (0.5)
Total	46	72	10	12	56 (27.3)	84 (41.4)*
Possible	14	12	1	4	15 (7.3)	16 (7.9)

*Log-rank chi-square = 6.0; nominal P value <0.02 (two-tailed). Lan–DeMets sequential-procedure critical value = 4.02; overall P value <0.05 (two-tailed).

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NEJM 1987;317:1237-45

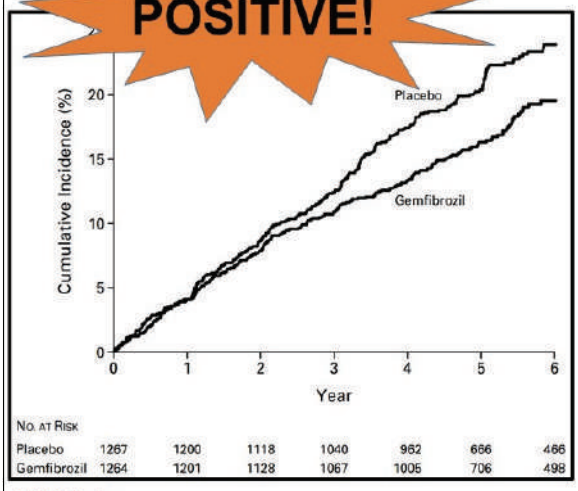
VA-HIT study: 2531 CHD men

No statin use

Gemfibrozil 1200mg/day vs placebo, median FU 5.1 years

Primary endpoint: nonfatal MI and death from coronary causes → **22% reduction, p=0.006**

POSITIVE!



Event	Placebo (N=1267)	Gemfibrozil (N=1264)	Risk Reduction (95% CI)	P Value
	no. (%)		%	
Nonfatal myocardial infarction or death due to CHD	275 (21.7)	219 (17.3)	22 (7 to 35)	0.006
Nonfatal myocardial infarction or death due to CHD (excluding silent myocardial infarction)	241 (19)	195 (15.4)	21 (4 to 34)	0.02
Nonfatal myocardial infarction, death due to CHD, or confirmed stroke†	330 (26)	258 (20.4)	24 (11 to 36)	<0.001
Nonfatal myocardial infarction	184 (14.5)	146 (11.6)	23 (4 to 38)	0.02
Death due to CHD	118 (9.3)	93 (7.4)	22 (−2 to 41)	0.07
Death from any cause	220 (17.4)	198 (15.7)	11 (−8 to 27)	0.23
Investigator-designated stroke	88 (6.9)	64 (5.1)	29 (2 to 48)	0.04
Confirmed stroke	76 (6.0)	58 (4.6)	25 (−6 to 47)	0.10
Transient ischemic attack	53 (4.2)	22 (1.7)	59 (33 to 75)	<0.001
CABG	173 (13.7)	164 (13.0)	6 (−17 to 24)	0.60
PTCA	147 (11.6)	120 (9.5)	21 (−1 to 38)	0.06
CABG or PTCA	287 (22.7)	266 (21.0)	9 (−8 to 23)	0.29
Peripheral vascular surgery	28 (2.2)	19 (1.5)	38 (−20 to 68)	0.18
Carotid endarterectomy	44 (3.5)	16 (1.3)	65 (37 to 80)	<0.001
Hospitalization for unstable angina	453 (35.8)	457 (36.2)	−0.4 (−14 to 12)	0.95
Hospitalization for congestive heart failure	168 (13.3)	134 (10.6)	22 (2 to 38)	0.04

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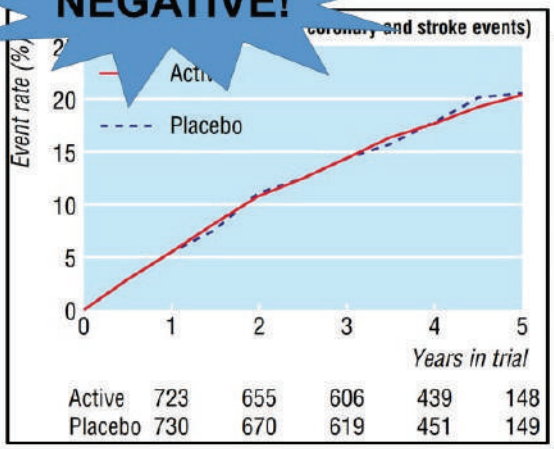
NEJM 1999;341:410-418

LEADER study: 1568 men with lower extremity arterial disease

Bezafibrate 400mg qd vs placebo, median FU 4.6 years

Primary endpoint: combination of CHD and stroke → HR 0.96 (95% CI: 0.76-1.21)

NEGATIVE!



	Active (n=783; 3029 person years)		Placebo (n=785; 3076 person years)			
	Events	Rate	Events	Rate	RR (95% CI)†	P value
All primary end points	150	49.5	160	52.0	0.96 (0.76 to 1.21)	0.72
Coronary heart disease:						
Fatal	64	21.1	65	21.1	0.95 (0.66 to 1.37)	0.79
Non-fatal	26	8.6	46	15.0	0.60 (0.36 to 0.99)	0.05
All	90	29.7	111	36.1	0.81 (0.60 to 1.08)	0.15
Stroke:						
Fatal	13	4.3	9	2.9	1.24 (0.46 to 3.37)	0.67
Non-fatal	47	15.5	40	13.0	1.34 (0.86 to 2.10)	0.19
All	60	19.8	49	15.9	1.34 (0.80 to 2.01)	0.49
Deaths, all causes‡	204	63.9	195	59.6	1.03 (0.83 to 1.26)	0.81

*Calculated as time to first event or time in trial for event-free men.
†Adjusted for entry characteristics.
‡Mainly cancer (47 active treatment, 47 placebo), heart failure, and respiratory disease (see text).

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BMJ 2002;325:1139-1141

BIP study: 3090 patients with previous MI or SAP

No statin use

Bezafibrate 400mg qd vs placebo, mean FU 6.2 years

Primary endpoint: fatal MI, fatal MI, sudden death → 13.6% vs 15.0%, p=0.26

NEGATIVE!

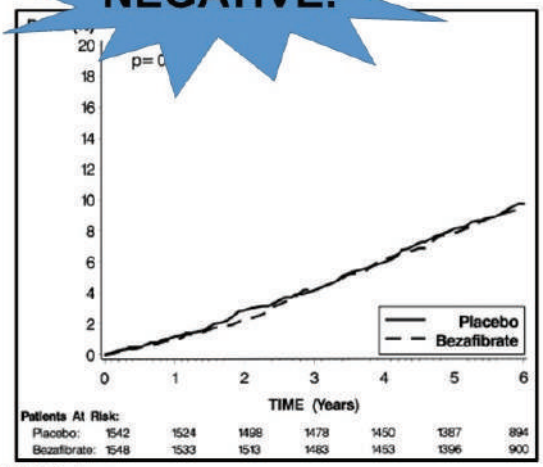

TABLE 3. Cumulative Probability of Primary End Points at 6.2 Years of Follow-Up by Baseline Triglycerides and HDL-C Levels

	Bezafibrate, n (%)	Placebo, n (%)	Reduction, %	P
Triglycerides				
<150 mg/dL	938 (12.6)	901 (13.7)	7.9	0.43
≥150 mg/dL	603 (16.3)	629 (17.1)	4.6	0.48
≥175 mg/dL	407 (15.9)	385 (20.3)	21.6	0.07
≥200 mg/dL	234 (12.0)	225 (19.7)	39.5	0.02
HDL-C <35 mg/dL and triglycerides				
<150 mg/dL	378 (13.5)	382 (15.5)	12.4	0.46
≥150 mg/dL	420 (18.5)	436 (19.4)	4.5	0.56
≥175 mg/dL	294 (17.2)	286 (22.2)	22.6	0.09
≥200 mg/dL	184 (13.0)	162 (22.3)	41.8	0.02

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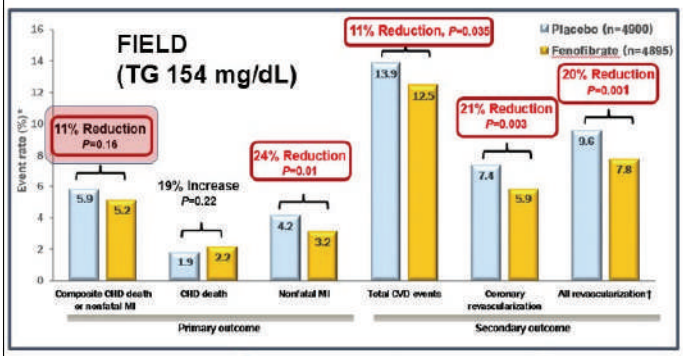
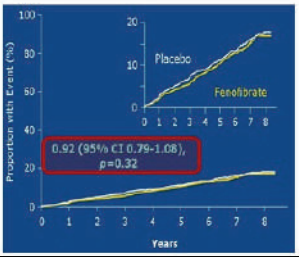
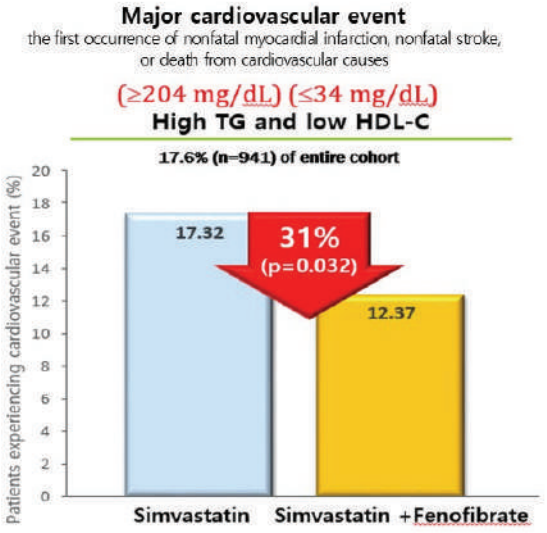
Circulation 2000;102:21-27

Two Fenofibrate trials: FIELD and ACCORD-LIPID Trials





ACCORD
(TG 162 mg/dL)



Lancet 2005;366:1849-1861; J Clin Lipidol 2011;6:9-20; N Engl J Med 2010;362:1563-1574.

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Landmark Fibrates CV outcome studies: Posthoc or subgroup analyses

Trials	Drugs	population	Baseline TG	Primary endpoint	Lipid subgroup criteria	Subgroup endpoint
HHS	Gemfibrozil 1200mg/day	Primary, Only men	176 mg/dL	-34%(p=0.02)	TG ≥204 mg/dL HDLC <42 mg/dL	-71%(p=0.005)
VA-HIT	Gemfibrozil 600mg bid	CHD, Only Men	160 mg/dL	-22%(p=0.006)	TG ≥151 mg/dL HDLC <31.5 mg/dL	-27%(p=0.01) -30%(p=0.003)
BIP	Bezafibrate 400mg/day	MI or SAP	145 mg/dL	-7.3%(p=0.24)	TG ≥200 mg/dL HDLC <35 mg/dL	-41.8%(p=0.02)
LEADER	Bezafibrate 400mg/day	PAD, Only Men	188 mg/dL	-4%(p=0.72)	TG ≥200 mg/dL	-40%(p=0.02)
FIELD	Fenofibrate	DM	154 mg/dL	-11%(p=0.16)	TG ≥204 mg/dL HDLC <42 mg/dL	-27%(p=0.005)
ACCORD	Fenofibrate	DM	162 mg/dL	-8%(p=0.32)	TG ≥204 mg/dL HDLC >34 mg/dL	-31%(p=0.032)

HHS, Helsinki Heart Study; VA-HIT, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; BIP, Bezafibrate Infarction Prevention; LEADER, Lower Extremity Arterial Disease Event Reduction; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; ACCORD, Action to Control Cardiovascular Risk in Diabetes

N Engl J M Med 1987;317:1237-1245; N Engl J Med 1999;341:410-418; Circulation 2000;102:21-27; BMJ 2002;325:1139-1141; Lancet 2005;366:1849-1851;N Engl J Med 2010;362:1563-1574.

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PROMINENT: Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes

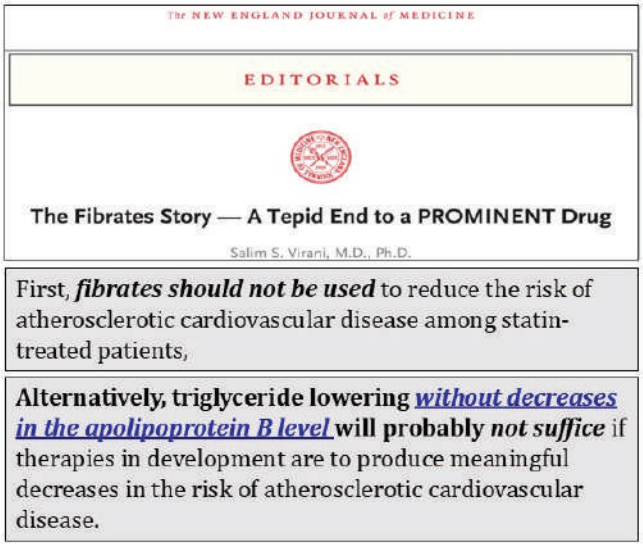
10497 patients with type 2 DM, fasting TG 200-500 mg/dL, and HDLC ≤ 40mg/dL
Primary prevention cohort 33.1%, median FU 3.4 years (early termination)

Any statin: about 96%. High-intensity statin: about 70%

Primary Endpoints: nonfatal MI, ischemic stroke, coro. revasc. or CV death.

	Placebo (N= 5257)	Pemafibrate (N= 5240)	HR (95%CI)	P value
Primary Composite Endpoint	560	572	1.03 (0.91-1.15)	0.67
Components				
Nonfatal MI	178	205	1.16 (0.95-1.42)	-
Nonfatal Ischemic Stroke	104	95	0.92 (0.69-1.21)	-
Coronary revascularization	344	334	0.98 (0.84-1.13)	-
Death from CV causes	133	133	1.00 (0.79-1.28)	-

- The overall incidence of serious adverse events did not differ significantly between the groups, but pemafibrate was associated with **a higher incidence of adverse renal events and VTE** and **lower incidence of NAFLD**.


The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

The Fibrates Story — A Tepid End to a PROMINENT Drug

Salim S. Virani, M.D., Ph.D.

First, ***fibrates should not be used*** to reduce the risk of atherosclerotic cardiovascular disease among statin-treated patients,

Alternatively, triglyceride lowering *without decreases in the apolipoprotein B level* will probably *not suffice* if therapies in development are to produce meaningful decreases in the risk of atherosclerotic cardiovascular disease.

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CONTENTS

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CV outcome개선에 과연 EPA가 EPA+DHA보다 좋은가?

REDUCE-IT vs STRENGTH: Indirect comparison

Trial (% of patients with established cardiovascular disease at baseline)	Groups	Patients with event/total patients, n/N (%)		Hazard ratio (95% CI)
		Omega-3	Placebo	
REDUCE-IT (70.7%) 4.9 years		Icosapent ethyl	Mineral oil	
	All participants	705/4089 (17.2%)	901/4090 (22%)	0.75 (0.68–0.83)*
	Primary prevention	146/1197 (12.2%)	163/1197 (13.6%)	0.88 (0.70–1.10)
X 1.4	Secondary prevention	559/2982 (19.3%)	738/2893 (25.5%)	0.73 (0.65–0.81)
STRENGTH (56%) 3.5 years		Eicosapentaenoic acid + Docosahexaenoic acid	Corn oil	
	All participants	785/6539 (12%) 16.8%	795/6539 (12.2%) 17.1%	0.99 (0.90–1.09)
	Primary prevention	216/2901 (7.4%) 10.4%	185/2861 (6.5%) 9.1%	1.16 (0.95–1.41)
	Secondary prevention	569/3638 (15.6%) 21.8%	610/3678 (16.6%) 23.2%	0.94 (0.84–1.05)

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Revised from Circulation 2021;144:183-185

REDUCE-IT vs STRENGTH: indirect comparison

Presumed estimated MACE incidence adjusted for FU period

		REDUCE-IT		STRENGTH	
		Mineral oil	IPE	EPA+DHA	Corn oil
Event/total patients, n/N(%)	All patients	22%	17.2%	16.8%	17.1%
	Primary prevention	13.6%	12.2%	10.4%	9.1%
	Secondary prevention	25.5%	19.3%	21.8%	23.2%

MACE incidence

EPA ≅ EPA+DHA ≅ Corn oil < Mineral oil

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REDUCE-IT Biomarker Substudy(II): Mineral oil > Icosapent ethyl

	Median percent difference
LP(a)	2.4%
Homocysteine	3.0%
Oxidized LDLC	4.2%
IL-6	19.8%
Lp-PLA2	26.2%
hsCRP	38.5%
IL-1ß	48.7%
LDLC	7.0%
TG	13.0%

Among participants in REDUCE-IT, allocation to ***icosapent ethyl*** had ***minimal effects*** on a series of ***biomarkers*** associated with ASCVD, whereas ***levels increased*** over time among those allocated to ***placebo***.

The effect of these findings on the interpretation of the REDUCE-IT trial results remains unclear and will ***require further investigation***.

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Circulation 2022;146:372-379

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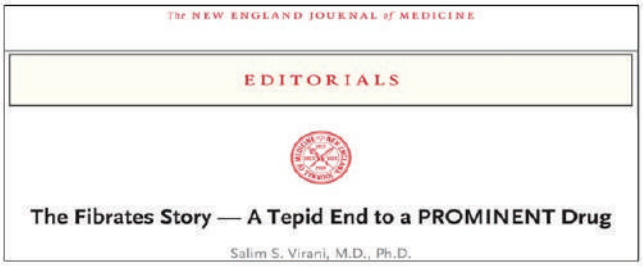
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Presented by Aruna D Pradhan, BRIGHAM AND WOMEN'S HOSPITAL, Boston, MA; Scientific Sessions 2022. © 2022 American Heart Association. All rights reserved.
N Engl J Med 2022;387:1923-34; N Engl J Med 2022;387:1991-1992

Variable	Pemafibrate (N=5240)	Placebo (N=5257)	PROMINENT
	Median Value (IQR)		MACE 1.03 ⟷
Triglyceride-related biomarkers			
Triglyceride level, measured			
Baseline — mg/dl	273 (227 to 342)	269 (226 to 338)	
4 Mo — mg/dl	189 (143 to 253)	254 (193 to 341)	TG ↓
Median change from baseline — %	−31.1 (−48.9 to −9.6)	−6.9 (−28.4 to 20.2)	−26.2 (−28.4 to −24.10)
Remnant cholesterol level, measured			
Baseline — mg/dl	56 (43 to 73)	56 (43 to 72)	
4 Mo — mg/dl	30 (23 to 41)	44 (32 to 61)	Remnant C ↓
Median change from baseline — %	−43.6 (−57.8 to −24.1)	−20.2 (−38.3 to 3.8)	−25.6 (−27.3 to −24.0)
LDL cholesterol level, measured			
Baseline — mg/dl	79 (60 to 104)	78 (59 to 102)	
4 Mo — mg/dl	91 (71 to 115)	80 (62 to 105)	LDLC ↑
Median change from baseline — %	14.0 (−6.3 to 41.4)	2.9 (−13.5 to 24.6)	12.3 (10.7 to 14.0)
Non-HDL cholesterol level, calculated§			
Baseline — mg/dl	128 (106 to 159)	128 (104 to 157)	
4 Mo — mg/dl	125 (102 to 153)	122 (100 to 154)	nonHDLC ⟷
Median change from baseline — %	−2.4 (−18.0 to 15.0)	−2.5 (−16.3 to 13.0)	−0.2 (−1.3 to 1.0)
Apolipoprotein B level, measured			
Baseline — mg/dl	90 (75 to 108)	89 (74 to 107)	
4 Mo — mg/dl	93 (77 to 111)	87 (73 to 105)	ApoB ↑
Median change from baseline — %	3.2 (−12.0 to 19.7)	−1.6 (−13.4 to 11.8)	4.8 (3.8 to 5.8)

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Landmark Fibrates CV outcome studies vs PROMINENT

Trials	FU TGs (mg/dL)	FU LDLC (mg/dL)	FU NonHDLC (mg/dL)	FU Remnant C (mg/dL)
HHS	43% reduction ↓	10% reduction ↓	-14% ↓	≅40%
VA-HIT	31% reduction ↓	113 vs 113 ⟷	145(P) vs 136 ↓	32(P) vs 23 ↓
BIP	21% reduction ↓	≅145(P)vs ≅139	173(P) vs 160 ↓	-41.8% ↓
LEADER	23% reduction ↓	8.1% reduction ↓		
FIELD	29% reduction ↓	100(P) vs 94 ↓	133(P) vs 120 ↓	32.4(P) vs 25.9 ↓
ACCORD	13.5% reduction ↓	80.0(P) vs 81.1 ⟷	113(P) vs 110 ↓	33.2(P) vs 28.8 ↓
PROMINENT	26.2% reduction ↓	**5.1% elevation (ApoB 4.8%) ↑**	**-0.2% ⟷**	**44(P) vs 30 ↓**

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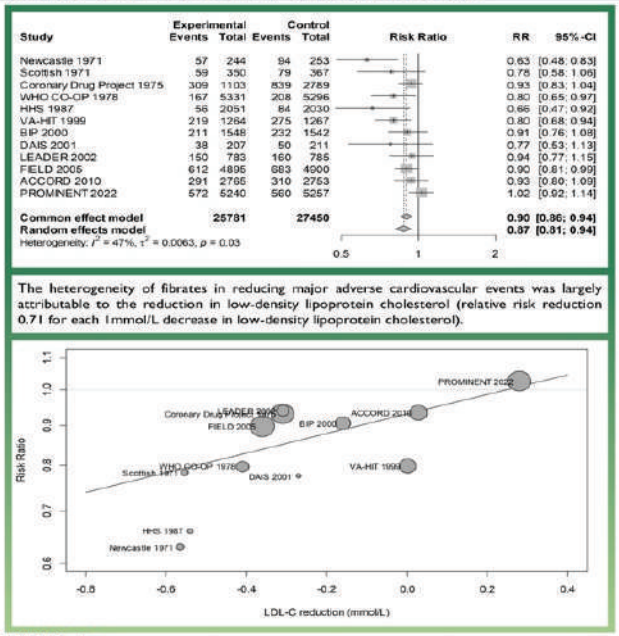
Meta-analysis: the effect of fibrates on lowering LDLC and CV risk reduction



- 12 trials
- Primary outcome:

a composite of CV death, AMI, Stroke, Coro REVASC

Fibrate therapy was associated with decreased risk of MACE [RR 0.87, 95% confidence interval (CI) 0.81–0.94] with moderate heterogeneity (I^2 = 47%).

Each 1 mmol/L reduction in LDLC after fibrate treatment reduced MACE (RR 0.71, 95% CI 0.49–0.94, P = 0.01)

TG level changes did not show a significant association (RR per 1mmol/L reduction 0.96, 95% CI 0.53–1.40, P = 0.86).

Treatment with fibrates was associated with decreased risk of MACE. The reduction in MACE risk with fibrate therapy appears to be attributable to LDL-C reduction rather than a decrease in triglyceride levels.

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Eur J Prev Cardiol 2024;31:291-301

Variable	Pemafibrate (N=5240)	Placebo (N=5257)	PROMINENT
	Median Value (IQR)		MACE 1.03
Triglyceride-related biomarkers			
Triglyceride level, measured			
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Baseline — mg/dl	56 (43 to 73)	56 (43 to 72)	Remnant C
4 Mo — mg/dl	30 (23 to 41)	44 (32 to 61)	
Median change from baseline — %	-43.6 (-57.8 to -24.1)	-20.2 (-38.3 to 3.8)	-25.6 (-27.3 to -24.0)
LDL cholesterol level, measured			
Baseline — mg/dl	79 (60 to 104)	78 (59 to 102)	
4 Mo — mg/dl	91 (71 to 115)	80 (62 to 105)	LDLC
Median change from baseline — %	14.0 (-6.3 to 41.4)	2.9 (-13.5 to 24.6)	12.3 (10.7 to 14.0)
Non-HDL cholesterol level, calculated§			
Baseline — mg/dl	128 (106 to 159)	128 (104 to 157)	
4 Mo — mg/dl	125 (102 to 153)	122 (100 to 154)	nonHDLC
Median change from baseline — %	-2.4 (-18.0 to 15.0)	-2.5 (-16.3 to 13.0)	-0.2 (-1.3 to 1.0)
Apolipoprotein B level, measured			
Baseline — mg/dl	90 (75 to 108)	89 (74 to 107)	
4 Mo — mg/dl	93 (77 to 111)	87 (73 to 105)	ApoB
Median change from baseline — %	3.2 (-12.0 to 19.7)	-1.6 (-13.4 to 11.8)	4.8 (3.8 to 5.8)

REDUCE-IT	STRENGTH
MACE 0.75	MACE 0.99
EPA Placebo	EPA+DHA placebo
TG -18.3% vs +2.2%	TG -19% vs -0.9%
Remnant C -20.5% vs -5.9%	Remnant C -20.0% vs -4.0%
LDLC +3[illegible]% vs +10.2%	+1.2% vs -1.1%
nonHDLC -3[illegible]% vs +10.4%	-6.1% vs -1.1%
ApoB -2.5% vs +7.8%	-2.0% vs -1.0%

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Omega-3 PUFAs and Afib

Trials	Active arm	Placebo	Afib Incidence	Change	P value
VITAL	EPA+DHA 840mg	Inert placebo	7.2% vs 6.6%	9% 증가	0.19
OMEMI	EPA+DHA 1.8g	Corn oil	7.2% vs 4.0%	84% 증가	0.06
STRENGTH	EPA+DHA 4g	Corn oil	2.2% vs 1.3%	69% 증가	<0.001
REDUCE-IT	EPA 4.8g	Mineral oil	5.3% vs 3.9%	36% 증가	0.003
RESPECT-EPA	EPA 1.8g	No drug	3.1% vs 1.6%	94% 증가	0.017

✓ 메타분석연구들

고용량 54% 증가
저용량 12% 증가

n3FA 1g증가할 때
AF risk 11% 증가

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Circulation 2019;140:e673-691; Cardiovasc Drug Ther 2021;35:793-800;Circulation 2021;144:1981-1990

Fenofibrate and serum creatinine

FIELD

	Baseline	FU (p<0.001)	8 wks after D/C
Fenofibrate	77.7 umol/L (0.88 mg/dL)	91 umol/L (1.03 mg/dL)	77 umol/L (0.87 mg/dL)
Placebo	77.4 umol/L (0.88 mg/dL)	80 umol/L (0.90 mg/dL)	79 umol/L (0.89 mg/dL)

✓ The rate of progression to albuminuria was significantly reduced by fenofibrate.
- Progression: 11%(Placebo) > 10%(Fenofibrate)
- Regression: 8%(Placebo) < 9%(Fenofibrate)

Fenofibrate투약전 투약 3개월 후 혈중 Cr을 확인하고, 이후에 이상이 없다면 6개월마다 추적관찰(class II, B)

ACCORD-LIPID

Baseline	All patients	Fenofibrate	Placebo	
Serum creatinine — mg/dl	0.9±0.2	0.9±0.2	0.9±0.2	0.96
Estimated glomerular filtration rate — no. (%)				
30–49 ml/min/1.73 m²	141 (2.6)	71 (2.6)	70 (2.5)	0.89
>50 ml/min/1.73 m²	5347 (97.4)	2668 (97.4)	2679 (97.5)	

Follow-Up	Fenofibrates	Placebo	
Serum creatinine elevation			
Women ever > 1.3 mg/dl	235 (27.9%)	157 (18.7%)	<0.001
Men ever > 1.5 mg/dl	698 (36.7%)	350 (18.5%)	<0.001
Post-randomization incidence of microalbuminuria (≥ 30 to < 300 mg/g**)	1050 (38.2%)	1137 (41.6%)	0.01
Post-randomization incidence of macroalbuminuria (> 300 mg/g**)	289 (10.5%)	337 (12.3%)	0.04

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Lancet 2005;366:1849-1861; N Engl J Med 2010;362:1563-1574

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2019 ESC/EAS 진료지침:중성지방

2016 ESC Guideline

Table 18 Recommendations for drug treatments of hypertriglyceridaemia

Recommendations	Class[a]	Level[b]	Ref[c]
Drug treatment should be considered in high-risk patients with TG >2.3 mmol/L (200 mg/dL).	IIa	B	261, 262
Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia.	IIb	B	263, 264
In high-risk patients with TG >2.3 mmol/L (200 mg/dL) despite statin treatment, fenofibrate may be considered in combination with statins.	IIb	C	261–264

CVD = cardiovascular disease; TG = triglycerides.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

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2019 ESC Guideline

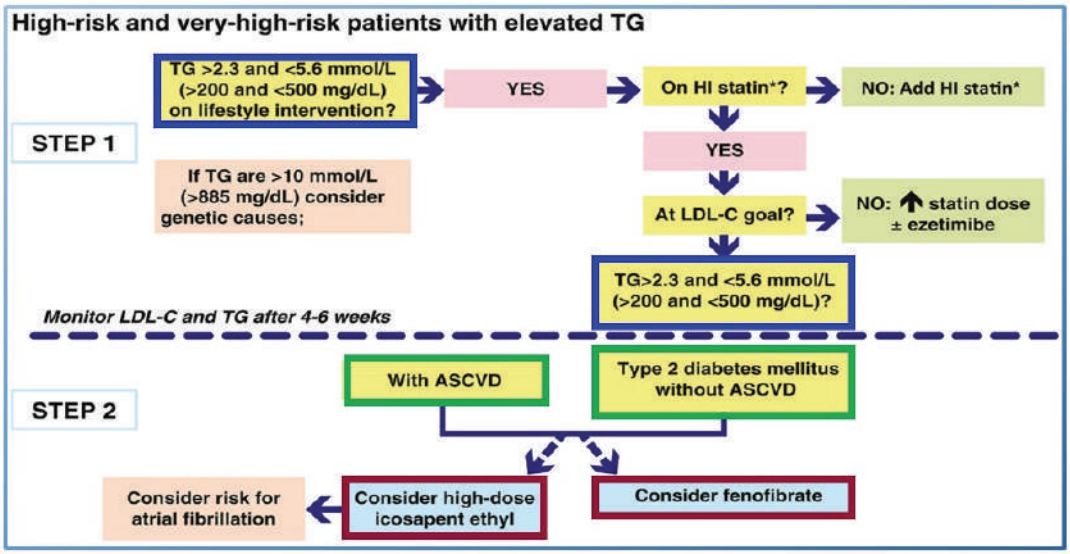
Recommendations for drug treatment of patients with hypertriglyceridaemia

Recommendations	Class[a]	Level[b]
TG 200 mg/dL이상인 고위험군 환자들은 CVD risk를 감소시키기 위해 statin을 우선적으로 사용해야 한다. (Class I)	I	B
스타틴을 복용하고 있는 고위험군 이상의 환자들에서 TG가 135~499 mg/dL이면 icosapent ethyl(EPA) 2X2 g/day를 고려해야 한다. (Class IIa)		
TG 200 mg/dL이상인 일차예방을 위한 환자들은 스타틴과 함께 fenofibrate나 bezafibrate를 고려해 볼 수 있겠다. (Class IIb)	IIb	B
TG 200 mg/dL이상인 고위험군 환자들은 스타틴과 함께 fenofibrate나 bezafibrate를 고려해 볼 수 있겠다. (Class IIb)	IIb	C

2021 ESC Guideline for CVD prevention

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [triglycerides >2.3 mmol/L (200 mg/dL)].[533]	I	A
In patients taking statins who are at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered.[534–536]	IIb	B
스타틴을 복용하고 있는 고위험군 이상의 환자들에서 TG가 135 mg/dL이상이면 icosapent ethyl(EPA) 2X2 g/day를 고려해 볼 수 있겠다. (Class IIb)		

A statement from EAS Task Force:
Suggested algorithm for high and very-high-risk patients with high TG



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Atherosclerosis 2021;325:99-109

2022 Korean Dyslipidemia Guidelines

Others including TG lowering therapy

이상지질혈증의 약물요법 II (1) 권고안

내용	권고등급	근거수준
중성지방이 500 mg/dL 이상인 경우 급성췌장염의 예방을 위한 즉각적인 약물치료와 생활습관개선을 시작할 것을 권고한다.	I	A
중성지방이 지속적으로 500 mg/dL 이상인 경우, 중성지방 조절을 위한 약제로 피브린산 유도체를 고려한다.	IIa	A
중성지방이 지속적으로 500 mg/dL 이상인 경우, 중성지방 조절을 위한 약제는 오메가-3 지방산을 고려한다.	IIa	A
중성지방이 200~499 mg/dL 인 경우, 먼저 일차적인 치료 목표는 계산된 심혈관계 위험도에 따라 LDL 콜레스테롤을 목표치 미만으로 낮추는 것이며, 이를 위해 우선적으로 치료적 생활습관개선 및 스타틴 약물치료를 권고한다.	I	A
중성지방이 200~499 mg/dL 인 경우, LDL 콜레스테롤 목표달성 후 중성지방이 200 mg/dL 이상이거나 non-HDL 콜레스테롤 목표치 이상이면 약물치료를 고려한다.	IIa	B

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Others including TG lowering therapy

이상지질혈증의 약물요법 II (2) 권고안

내용	권고등급	근거수준
죽상경화성 심혈관질환이나 당뇨병 환자에서 생활습관 개선 및 스타틴 투약 후에도 200 mg/dL 이상의 고중성지방혈증이 지속될 때, 심혈관질환의 예방을 위하여 IPE (하루 4 g)를 추가 투약하는 것을 고려할 수 있다.	IIb	B
죽상경화성 심혈관질환이나 당뇨병 환자에서 생활습관 개선 및 스타틴 투약 후에도 200 mg/dL 이상의 고중성지방혈증이 지속될 때, 심혈관질환의 예방을 위하여 피브린산 유도체를 추가 투약하는 것을 고려할 수 있다.	IIb	B
죽상경화성 심혈관질환이나 당뇨병 환자에서 생활습관 개선 및 스타틴투약후에도 200 mg/dL 이상의 고중성지방혈증이 지속될 때, 심혈관질환 예방을 위하여 EPA와 DHA를 혼합한 오메가-3 지방산을 추가 투약하는 것을 고려할 수 있다.	IIb	E
저HDL 콜레스테롤혈증 환자에서도 일차치료목표로 LDL 콜레스테롤을 목표 수치로 조절하는 것을 권고한다.	I	A
HDL 콜레스테롤을 상승시키기 위한 약물치료는 권고하지 않는다.	III	A
Gemfibrozil과 스타틴의 병용 치료는 근육병증의 발생 위험을 증가시키므로 권고하지 않는다.	III	B

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2021 ACC Expert Consensus Decision Pathway for hyperTG

Adults with ASCVD and fasting TG ≥150 mg/dL or nonfasting TG ≥175 mg/dL and TG <500 mg/dL

Adults with diabetes mellitus aged ≥40 years, no ASCVD, and fasting TG ≥150 mg/dL or nonfasting TG ≥175 mg/dL and TG <500 mg/dL

Adults aged ≥20 years with no ASCVD or diabetes mellitus and fasting TG ≥150 mg/dL or nonfasting TG ≥175 mg/dL and TG <500 mg/dL

Adults aged ≥20 years with TG ≥500 mg/dL

Factors to Consider

- Evaluate and manage secondary causes
- Optimize diet and lifestyle interventions for hypertriglyceridemia
- Implement guideline-directed statin therapy and optimize statin adherence
- Optimize glycemic control
- Monitor response to therapy and adherence
- Conduct clinician-patient discussion of potential benefits, potential harms, and patient preferences

Persistent Fasting Hypertriglyceridemia

Optional Interventions to Consider

- Referral to registered dietitian nutritionist
- Addition of a triglyceride risk-based pharmacological agent

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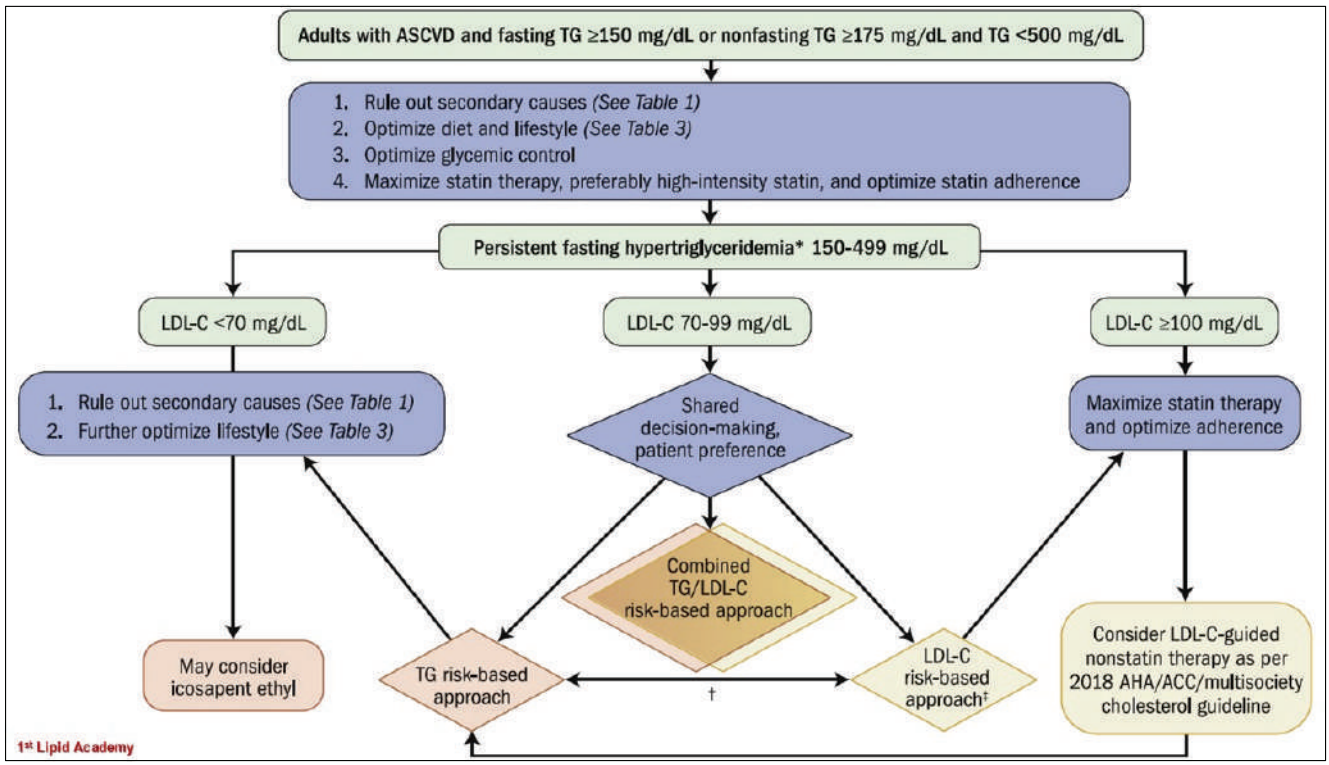
Adults with ASCVD and fasting TG ≥150 mg/dL or nonfasting TG ≥175 mg/dL and TG <500 mg/dL
1. Rule out secondary causes (See Table 1)
2. Optimize diet and lifestyle (See Table 3)
3. Optimize glycemic control
4. Maximize statin therapy, preferably high-intensity statin, and optimize statin adherence
Persistent fasting hypertriglyceridemia* 150-499 mg/dL
LDL-C <70 mg/dL
LDL-C 70-99 mg/dL
LDL-C ≥100 mg/dL
1. Rule out secondary causes (See Table 1)
2. Further optimize lifestyle (See Table 3)
Shared decision-making, patient preference
Maximize statin therapy and optimize adherence
Combined TG/LDL-C risk-based approach
May consider icosapent ethyl
TG risk-based approach
†
LDL-C risk-based approach‡
Consider LDL-C-guided nonstatin therapy as per 2018 AHA/ACC/multisociety cholesterol guideline
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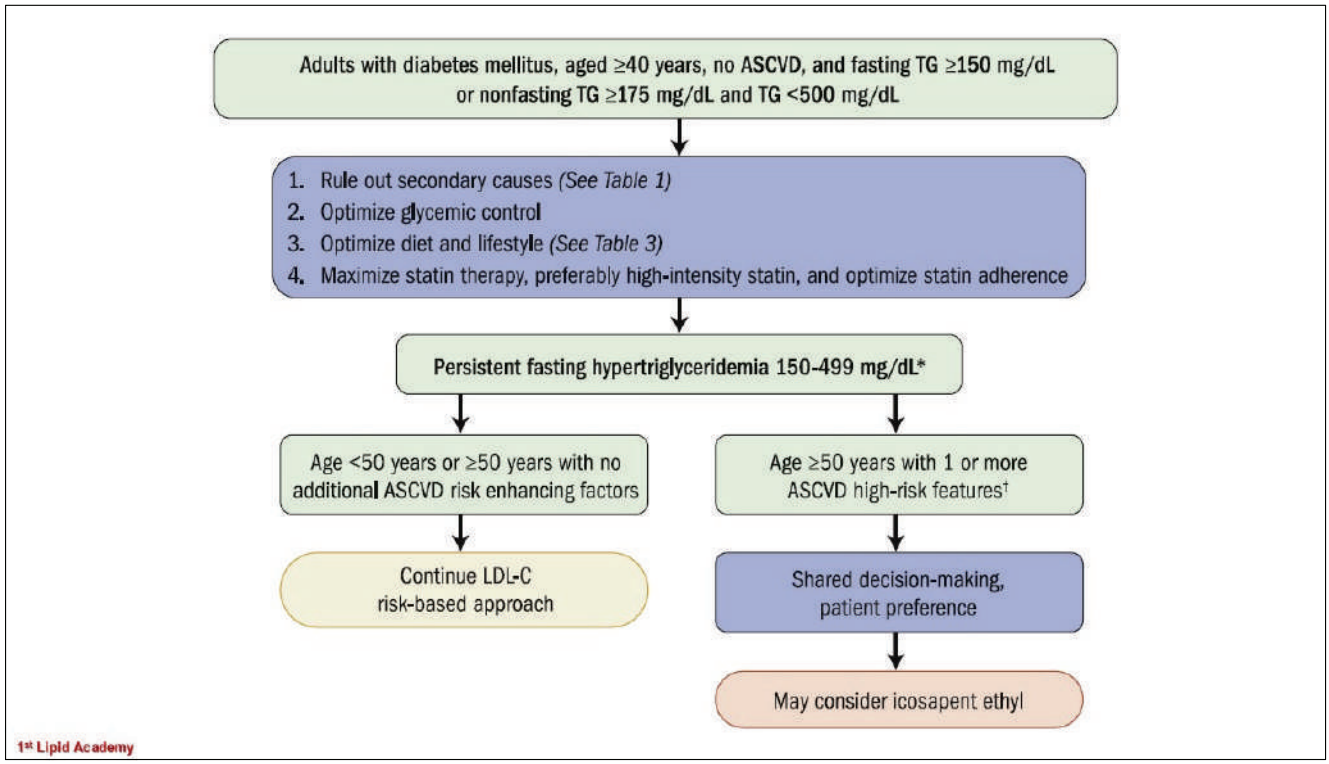
Adults with diabetes mellitus, aged ≥40 years, no ASCVD, and fasting TG ≥150 mg/dL or nonfasting TG ≥175 mg/dL and TG <500 mg/dL
1. Rule out secondary causes (See Table 1)
2. Optimize glycemic control
3. Optimize diet and lifestyle (See Table 3)
4. Maximize statin therapy, preferably high-intensity statin, and optimize statin adherence
Persistent fasting hypertriglyceridemia 150-499 mg/dL*
Age <50 years or ≥50 years with no additional ASCVD risk enhancing factors
Age ≥50 years with 1 or more ASCVD high-risk features†
Continue LDL-C risk-based approach
Shared decision-making, patient preference
May consider icosapent ethyl
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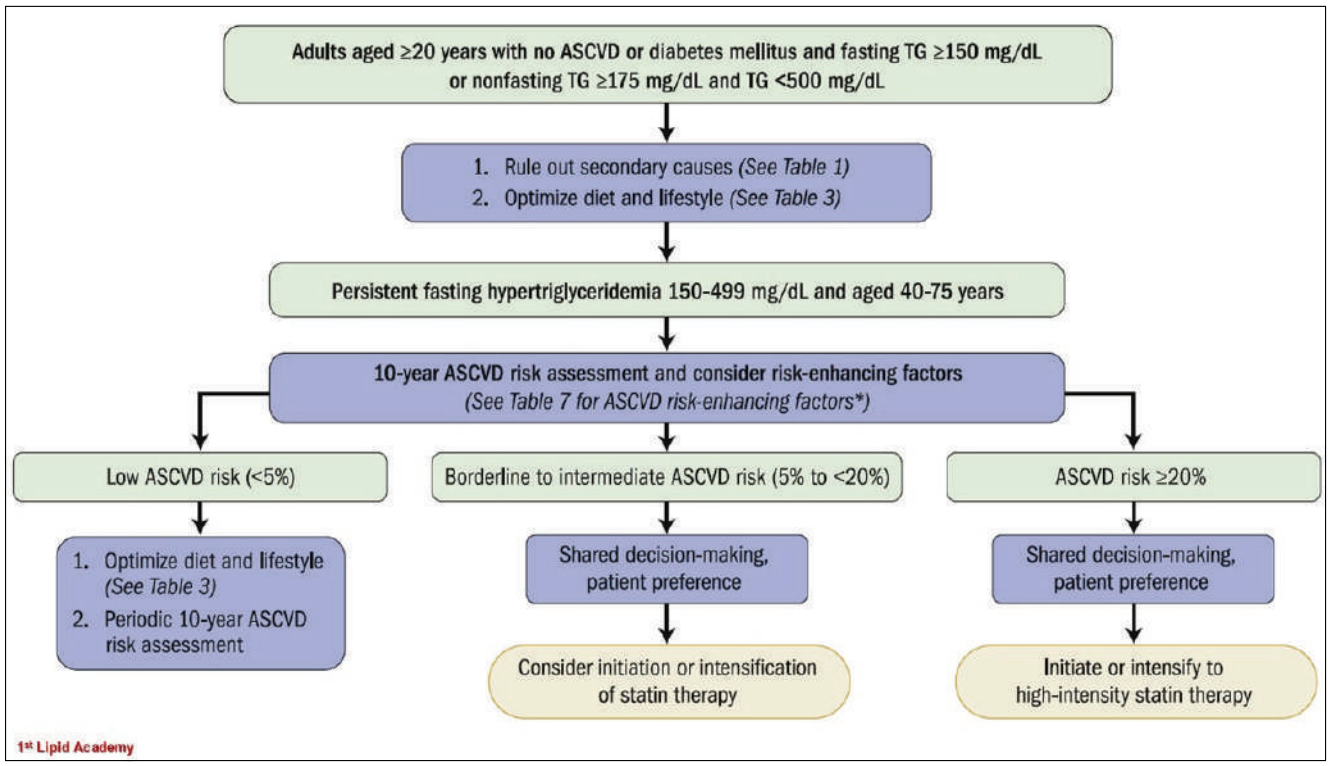
Adults aged ≥20 years with no ASCVD or diabetes mellitus and fasting TG ≥150 mg/dL or nonfasting TG ≥175 mg/dL and TG <500 mg/dL
1. Rule out secondary causes (See Table 1)
2. Optimize diet and lifestyle (See Table 3)
Persistent fasting hypertriglyceridemia 150-499 mg/dL and aged 40-75 years
10-year ASCVD risk assessment and consider risk-enhancing factors
(See Table 7 for ASCVD risk-enhancing factors*)
Low ASCVD risk (<5%)
Borderline to intermediate ASCVD risk (5% to <20%)
ASCVD risk ≥20%
1. Optimize diet and lifestyle (See Table 3)
2. Periodic 10-year ASCVD risk assessment
Shared decision-making, patient preference
Shared decision-making, patient preference
Consider initiation or intensification of statin therapy
Initiate or intensify to high-intensity statin therapy
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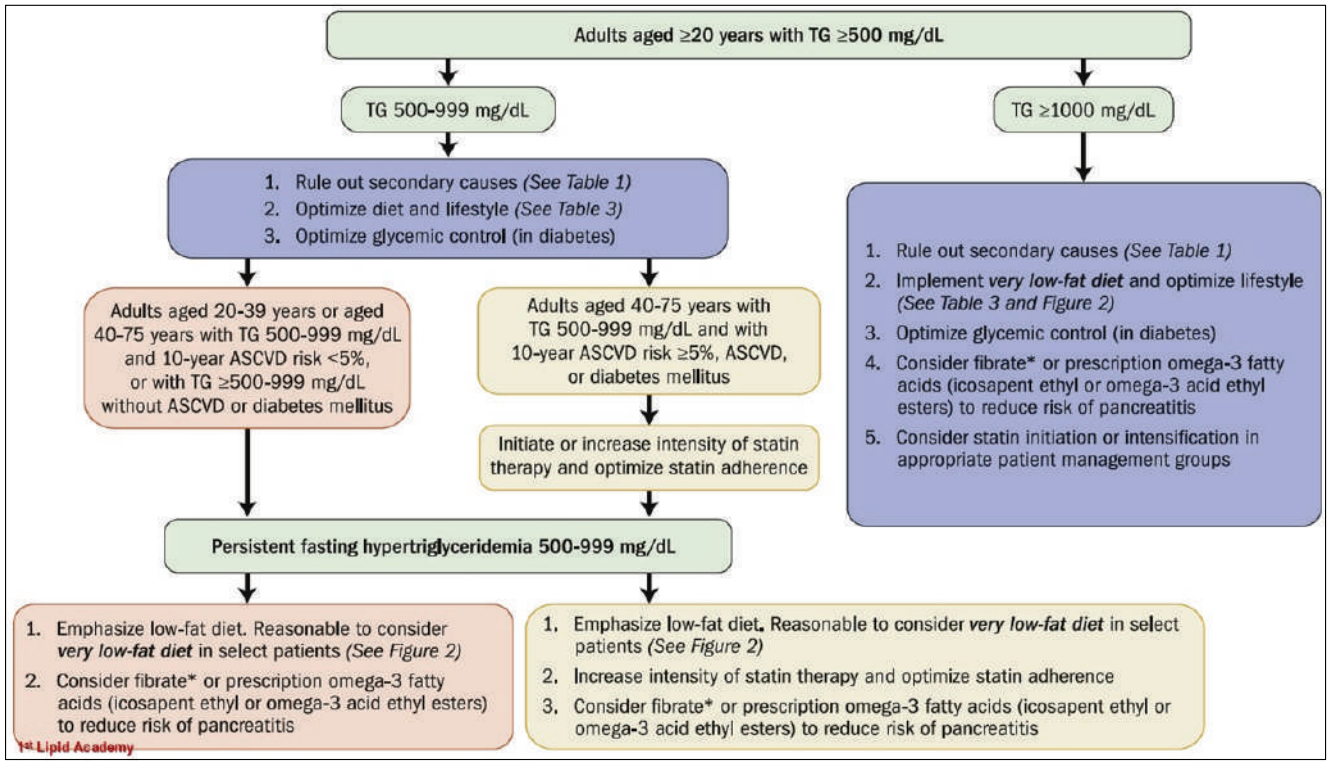
Adults aged ≥20 years with TG ≥500 mg/dL
TG 500-999 mg/dL
TG ≥1000 mg/dL
1. Rule out secondary causes (See Table 1)
2. Optimize diet and lifestyle (See Table 3)
3. Optimize glycemic control (in diabetes)
Adults aged 20-39 years or aged 40-75 years with TG 500-999 mg/dL and 10-year ASCVD risk <5%, or with TG ≥500-999 mg/dL without ASCVD or diabetes mellitus
Adults aged 40-75 years with TG 500-999 mg/dL and with 10-year ASCVD risk ≥5%, ASCVD, or diabetes mellitus
Initiate or increase intensity of statin therapy and optimize statin adherence
1. Rule out secondary causes (See Table 1)
2. Implement very low-fat diet and optimize lifestyle (See Table 3 and Figure 2)
3. Optimize glycemic control (in diabetes)
4. Consider fibrate* or prescription omega-3 fatty acids (icosapent ethyl or omega-3 acid ethyl esters) to reduce risk of pancreatitis
5. Consider statin initiation or intensification in appropriate patient management groups
Persistent fasting hypertriglyceridemia 500-999 mg/dL
1. Emphasize low-fat diet. Reasonable to consider very low-fat diet in select patients (See Figure 2)
2. Consider fibrate* or prescription omega-3 fatty acids (icosapent ethyl or omega-3 acid ethyl esters) to reduce risk of pancreatitis
1. Emphasize low-fat diet. Reasonable to consider very low-fat diet in select patients (See Figure 2)
2. Increase intensity of statin therapy and optimize statin adherence
3. Consider fibrate* or prescription omega-3 fatty acids (icosapent ethyl or omega-3 acid ethyl esters) to reduce risk of pancreatitis
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CONTENTS

- TG-rich lipoprotein(TRLs)과 remnant cholesterol(RC)은 무엇인가?
- TG와 RC는 CV risk marker인가?
- TG와 RC에 대한 RCT의 CV outcome 결과는 어떠한가?
- TG RCT를 해석시 주의할 점은 없는가?
- TG와 RC에 대한 현재 치료지침은 어떠한가?
- 고중성지방혈증의 치료제 개발

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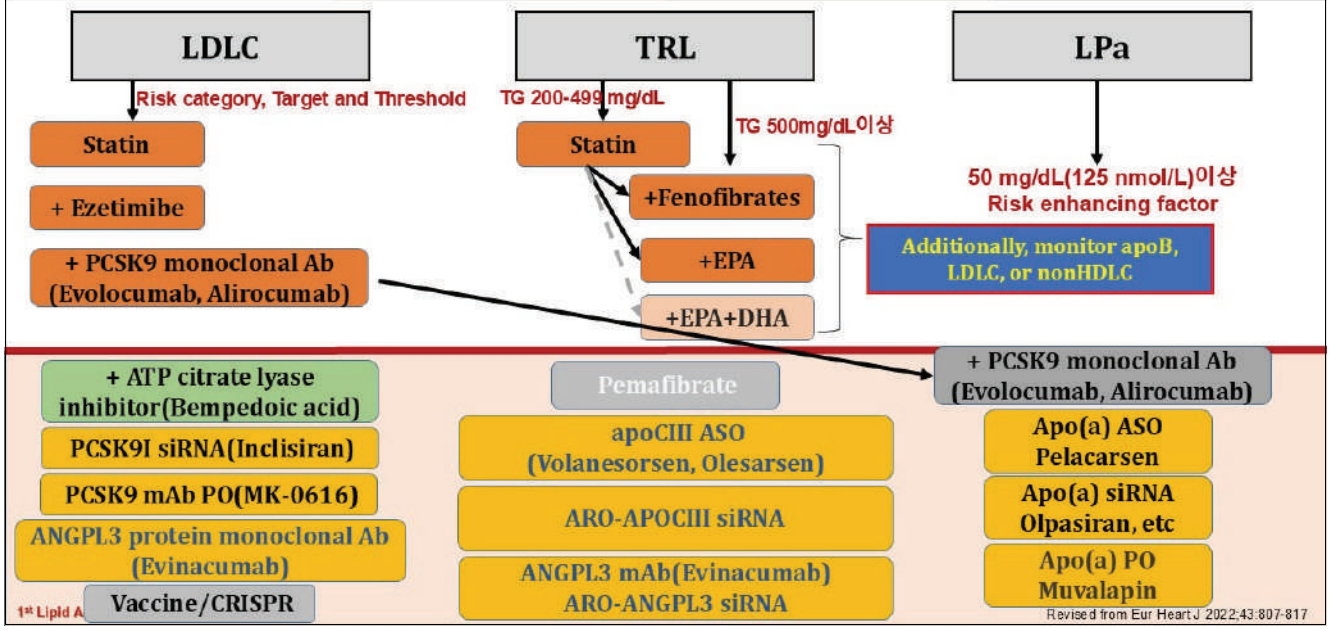
Perspectives
Dyslipidemia Treatment for prevention and reduction of ASCVD



Conclusions

- TRL은 VLDL+IDL, RC는 VLDL+IDL에 함유된 cholesterol을 의미한다.
- TG와 RC는 CV risk marker이다.
- TG와 RC에 대한 RCT의 CV outcome 결과는 Inconsistent한 결과를 보였지만 좋은 경향을 보인다.
- 현재 사용 가능한 High TG치료제 사용시 TG감소효과를 보기보다는 apoB, LDLC, nonHDLC의 변화를 잘 관찰해야한다.
- Fibrates사용시 Cr의 변화와 O3FA사용시 new-onset Afib monitoring을 고려해야한다.

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Conclusions

- RC에 대한 치료지침은 아직 확립되어 있지 않다.
- TG치료는 고위험군이상에서 statin사용(LDLC lowering therapy)에도 high TG일 경우 fibrates 또는 O3FA의 사용을 고려해 볼 수 있겠다.(Class IIb)
- apoCIII ASO and siRNA, ANGPTL3 mAb and siRNA의 연구들이 진행중이다.

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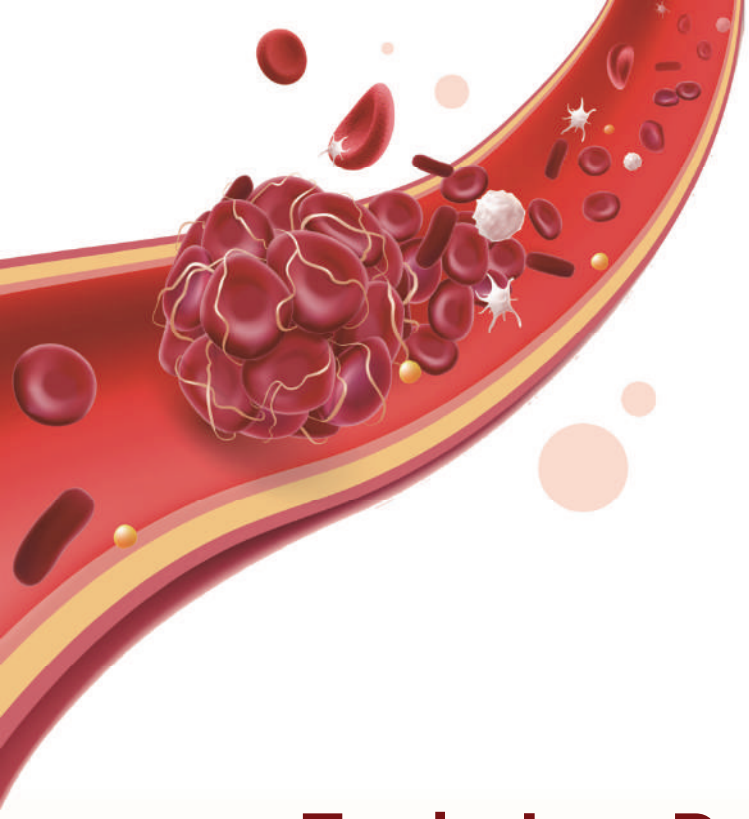
감사합니다!!



Day 1

Session 4

Exploring Residual Lipid Risks(II)

(14:30 – 17:00)

14:30 – 15:00	Unraveling the Enigma of LP(a) and Perspectives on LP(a) Treatment	이장훈 (경북의대 순환기내과)
15:00 – 15:30	Role of HDL Cholesterol and Current Evidence on HDL Cholesterol Treatments	박훈준 (가톨릭의대 순환기내과)
15:30 – 15:50	토론	
16:20 – 17:00	Humanities Lecture	조성준 (성균관의대 정신건강의학과)

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한국지질·동맥경화학회 제1회 Lipid Academy

이 장 훈

[기본정보]

성함	이 장 훈
소속(근무처)	경북대학교병원

[학력]

해당년도	세부사항
1993.3.2-1999.2.25	경북대학교 의과대학 학사
2008.3.3-2011.2.25	경북대학교 의과대학 석사
2008.3.3-2011.2.25	경북대학교 의과대학 박사

[경력]

해당년도	세부사항
2020.10.1-현재	경북대학교병원 순환기내과 교수
2020.10.1-현재	대구경북 권역심뇌혈관센터 심혈관센터장

[관심분야]

Intervention cardiology

[논문]

1. Intravascular modality-guided versus angiography-guided percutaneous coronary intervention in acute myocardial infarction. Kim N, Lee JH, Jang SY, Bae MH, Yang DH, Park HS, Cho Y, Jeong MH, Park JS, Kim HS, Hur SH, Seong IW, Cho MC, Kim CJ, Chae SC; Korea Acute Myocardial Infarction Registry - National Institute of Health Investigators. Catheter Cardiovasc Interv. 2020 Mar 1;95(4):696-703. doi: 10.1002/ccd.28359. Epub 2019 May 27.
2. Usefulness of Calculation of Cardiovascular Risk Factors to Predict Outcomes in Patients With Acute Myocardial Infarction. Kim CY, Lee JH, Jang SY, Bae MH, Yang DH, Park HS, Cho Y, Jeong MH, Park JS, Kim HS, Hur SH, Seong IW, Cho MC, Kim CJ, Chae SC; Korea Acute Myocardial Infarction Registry - National Institute of Health Investigators. Am J Cardiol. 2019 Sep 15;124(6):857-863. doi: 10.1016/j.amjcard.2019.06.010. Epub 2019 Jun 25.
3. Coronary Endothelial Dysfunction and the Index of Microcirculatory Resistance as a Marker of Subsequent Development of Cardiac Allograft Vasculopathy. Lee JH, Okada K, Khush K, Kobayashi Y, Sinha S, Luikart H, Valantine H, Yeung AC, Honda Y, Fearon WF. Circulation. 2017 Mar 14;135(11):1093-1095. doi: 10.1161/CIRCULATIONAHA.116.025268. No abstract available.
4. Coronary Collaterals Function and Clinical Outcome Between Patients With Acute and Chronic Total Occlusion. Lee JH, Kim CY, Kim N, Jang SY, Bae MH, Yang DH, Cho Y, Chae SC, Park HS. JACC Cardiovasc Interv. 2017 Mar 27;10(6):585-593. doi: 10.1016/j.jcin.2016.12.009.
5. Pulling the RIPCORD: FFRCT to Improve Interpretation of Coronary CT Angiography. Fearon WF, Lee JH. JACC Cardiovasc Imaging. 2016 Oct;9(10):1195-1197. doi: 10.1016/j.jcmg.2016.01.037. Epub 2016 Aug 24.

Unraveling the Enigma of LP(a) and Perspectives on LP(a) Treatment

이 장 훈

경북의대 순환기내과

KNUH 경북대학교병원

Lp(a): Unraveling its Enigma and Perspectives on Treatment

- Brief history

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Short overview on important milestones in Lp(a) research

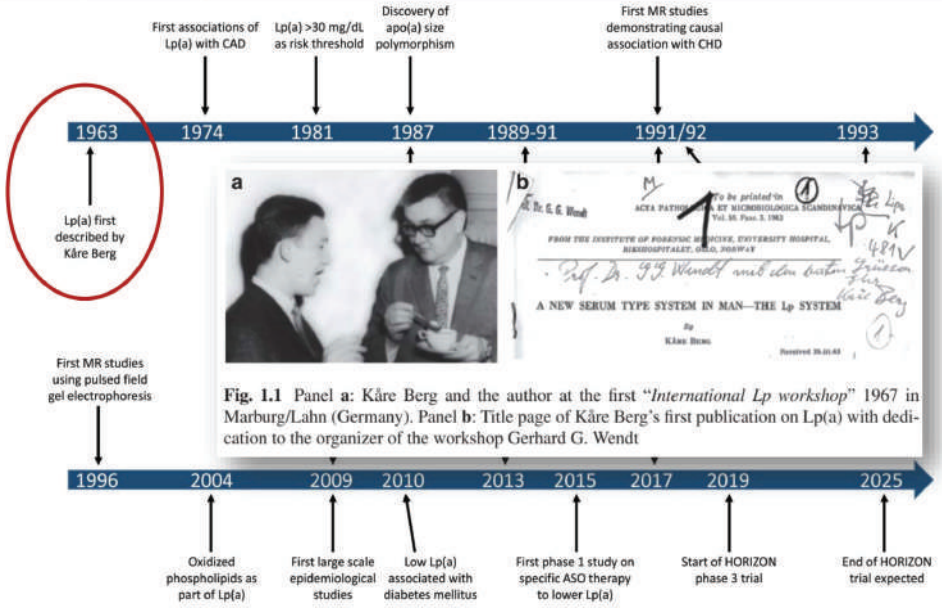

Fig. 1.1 Panel **a**: Kåre Berg and the author at the first "*International Lp workshop*" 1967 in Marburg/Lahn (Germany). Panel **b**: Title page of Kåre Berg's first publication on Lp(a) with dedication to the organizer of the workshop Gerhard G. Wendt

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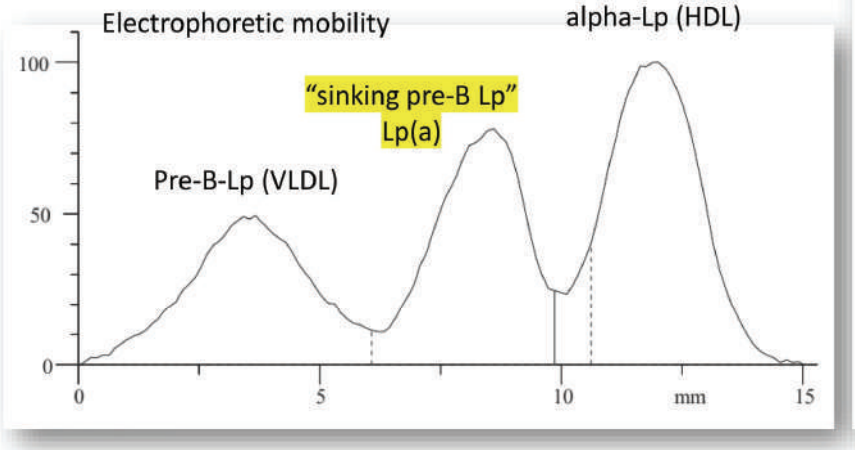
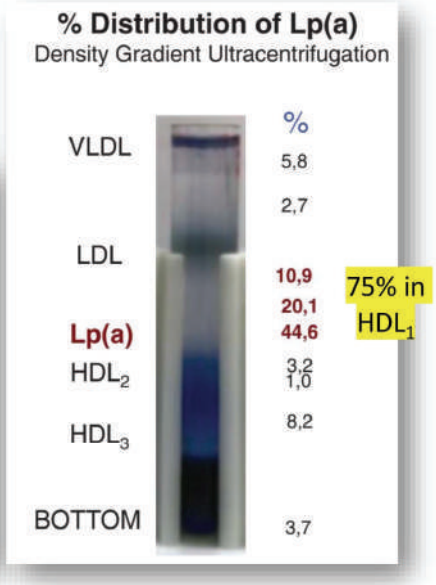
Koschinsky ML, et al. Atherosclerosis. 2022;349:1-6

Qualitative and Quantitative separation of Lp(a)

- **Electrophoresis**: mobility; alpha-, B-, and pre-B Lp
- **Ultracentrifugation**: Density; VLDL, LDL, and HDL
- **Immune-affinity methods**: Lp-A, Lp-B, and Lp-C





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Lp(a): Unraveling its Enigma and Perspectives on Treatment

- Brief history
- Structure

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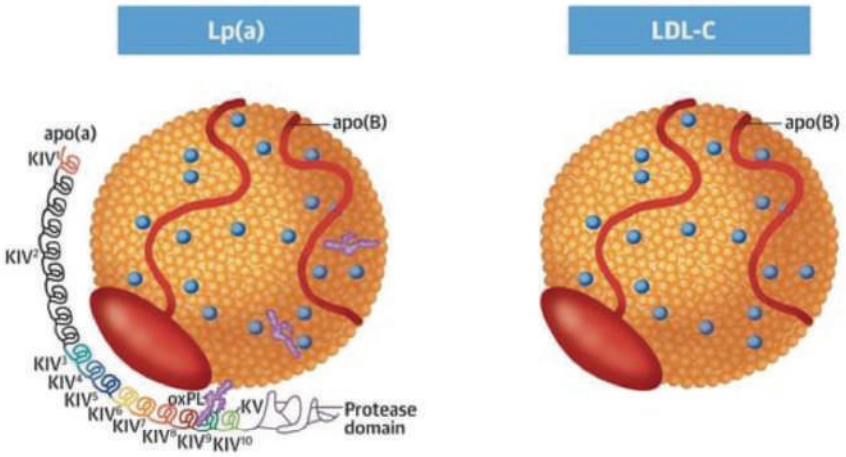
Structure of Lp(a) versus LDL



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Chemical composition of Lp(a) in comparison with LDL

Compound	Lp(a) % w/w	LDL % w/w
Protein	26-30	21.0
Carbohydrates	4-8	1.3
Cholesterol ester	31-37	42.0
Free cholesterol	7-8	9.0
Phospholipids	16-20	20.7
Triglycerides	4-6	6.0

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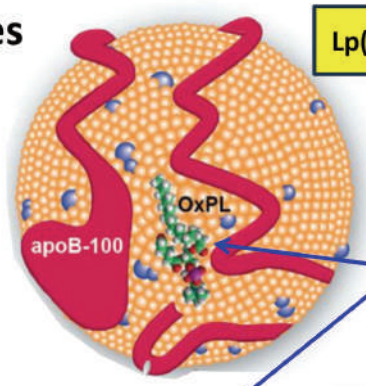
What is Lp(a)?

- KIV domain expanded to 10 subtypes (KIV_1 to KIV_{10})
- KIV_2 repeats vary from 2 to >40

Danish Pastry

Kringles

LDL-Like Particle



Lp(a) = LDL + apo(a) + OxPLs

Postulated sites where OxPL are present on Lp(a)

KIV_{10} is important in OxPL binding

Apo(a)

KIV_9 connects to apoB via disulfide bond

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Lp(a) is found only in the plasma of humans

Species	Kringles III	Kringles IV	Kringles V	Attachment to LDL	Protease Domain	Protease Activity	Fibrin Binding	OxPL (E06) Binding
Plasminogen of all mammals Apolipoprotein(a)	✓	✓	✓	No	✓	✓	✓	✓
Human		✓	✓	✓	✓	No	✓	✓
Bonobo		✓	✓	✓	✓	No	No*	No
Chimpanzee		✓	✓	✓	✓	No	No*	No
Gorilla		✓	✓	✓	✓	No	No*	No
Orangutan		✓	✓	✓	✓	No	No	?
Baboon		✓		✓	✓	No	No†	No
Cynomolgous		✓		✓	✓	No	No*	No
Rhesus		✓		✓	✓	No	No*	No
Hedgehog	✓			✓	No	No	✓	No

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Tsimikas S. et al. J Am Coll Cardiol. 2022;80:934-946.

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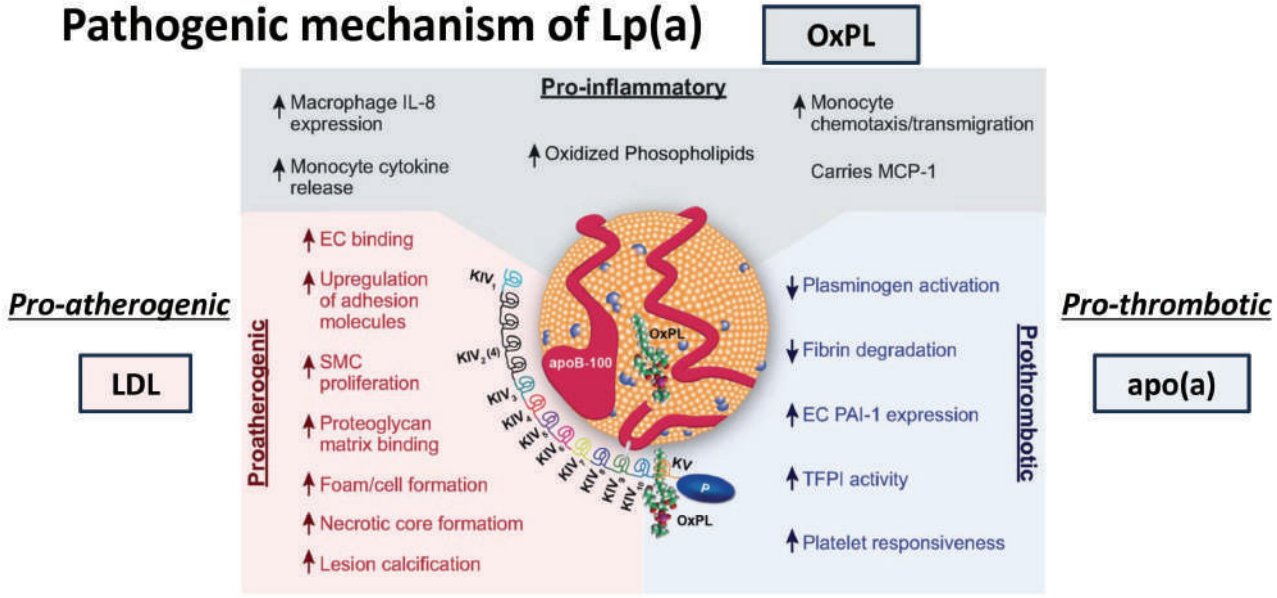
Pathogenic mechanism of Lp(a)



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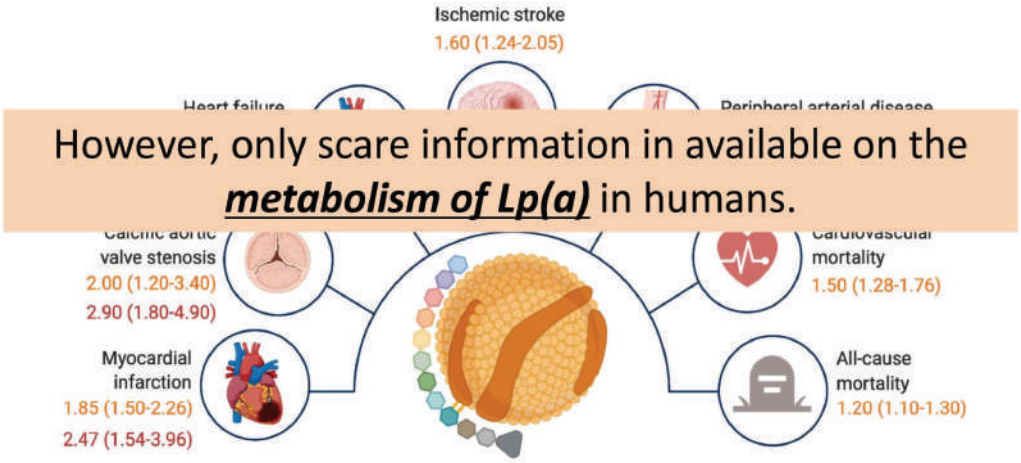
Elevated Lp(a) and CVD Outcomes Data from the Copenhagen Studies



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Arsenault and Kamstrup. Atherosclerosis. 2022;349:7-16.

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Lp(a): Unraveling its Enigma and Perspectives on Treatment

- Brief history
- Structure
- Biosynthesis – interconversion or not

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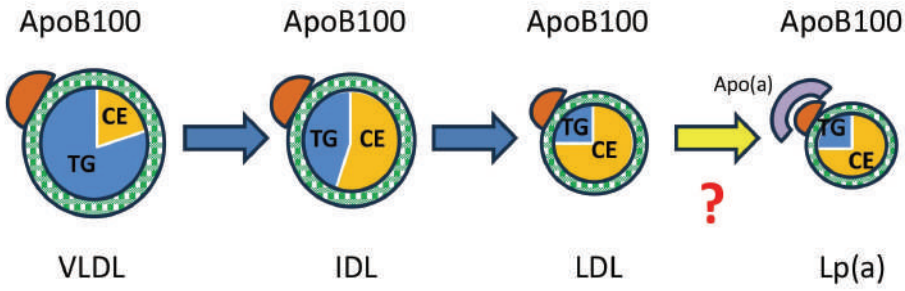
Potential for VLDL, LDL and Lp(a) Interconversion



- VLDL and LDL are not precursors to Lp(a).
- There is ***no interconversion*** of the apoB 100 moiety.
- Lp(a) is secreted as a separate lipoprotein.

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Krempler F, et al. Biochim Biophys Acta. 1979;575:63-70.

Assembly of Lp(a): apo(a) + ApoB

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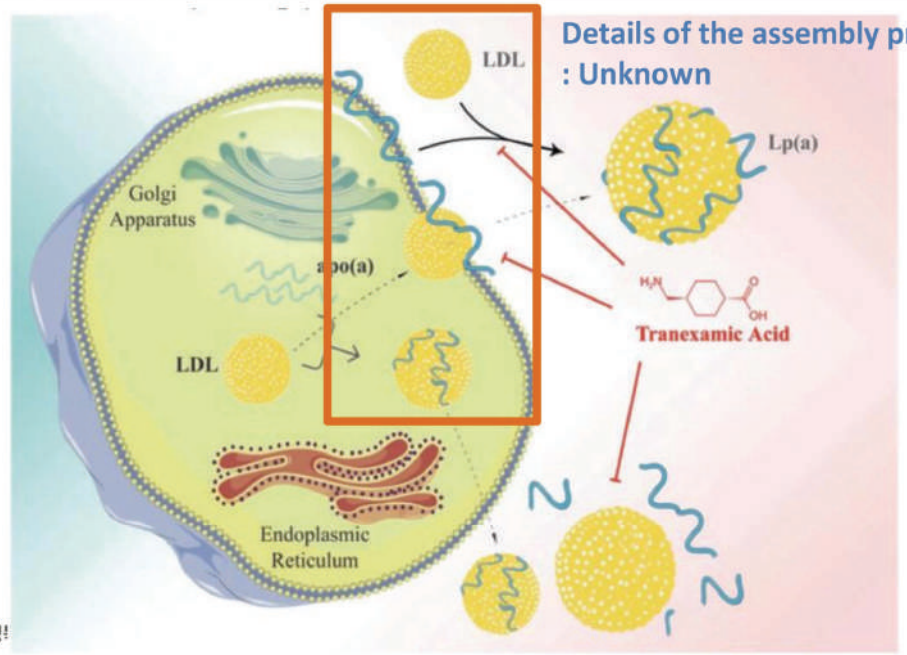

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Biosynthesis of mature Lp(a)

	Hepatocyte	Mature Lp(a)
A		
B		
C		

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Impact of the Assembly on Plasma Concentrations of Lp(a): Apo(a)

- Gene sequencing of APOA in Caucasian individuals with almost zero Lp(a) levels revealed a G→A substitution at the 1+ donor splice site of K-IV type 8 introns. This nonsense mutation led to the expression of a truncated form of apo(a) that consisted of a N-terminal fragment lacking all entities after kringle-IV-T7.
- Since K-IV T9 in apo(a) contains the single free –SH group that is necessary for the covalent binding to apoB-100, such ***truncated apo(a) are not able to stably assemble with LDL***.
- Interestingly, there are small amounts of free truncated apo(a) found in plasma indicating that the liver secretes such apo(a) mutants, but it seems that they are very rapidly catabolized.
- This opens up the question ***whether plasma Lp(a) levels might be drastically reduced in general by inhibition of Lp(a) assembly.***

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Impact of the Assembly on Plasma Concentrations of Lp(a): Apo(a)

- It was speculated that individuals with ***apo(a) mutations or polymorphisms that cause reduced plasma Lp(a) levels might be at a lower risk for CAD***.
- This was addressed in a cohort of the PROCARDIS study published by Kyriakou (Kyriakou et al. 2014).
- It was found that the LPA null allele as identified by the rs41272114 SNP not only is associated with reduced plasma Lp(a) concentrations but also with a significantly reduced CAD risk.

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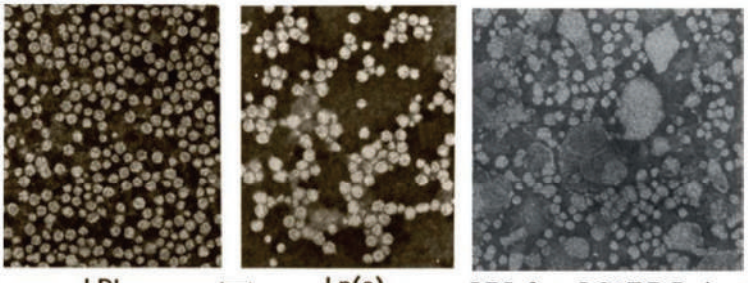
Impact of the Assembly on Plasma Concentrations of Lp(a): LDL-C

- ***Why apo(a) only assembles with LDL and not with other serum proteins?***
- The composition and morphology of ***LDL have just the right prerequisites*** for this assembly.
- ***Whereas wild-type LDL mixed with apo(a) complexed under the given experimental conditions between 15% and 44% with apo(a), LDL from a homozygous familial defective apoB-100 (FDB) patient showed only 2–16% association and heterozygous FDB individuals showed 2–30%.***



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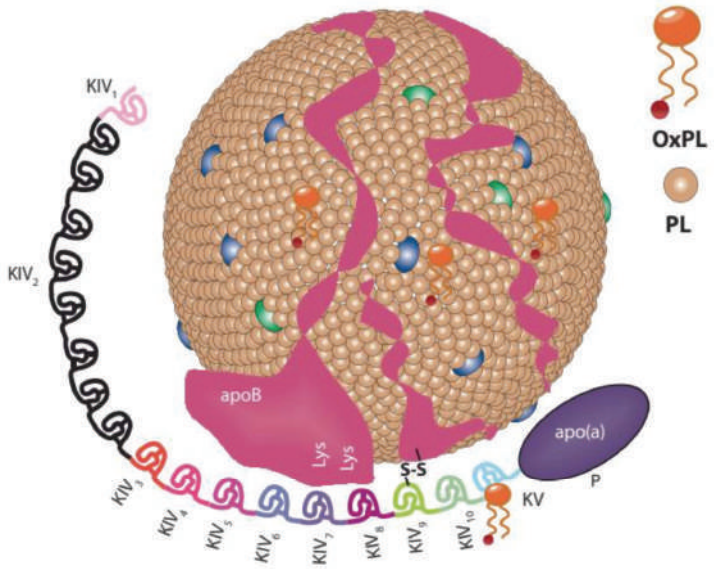
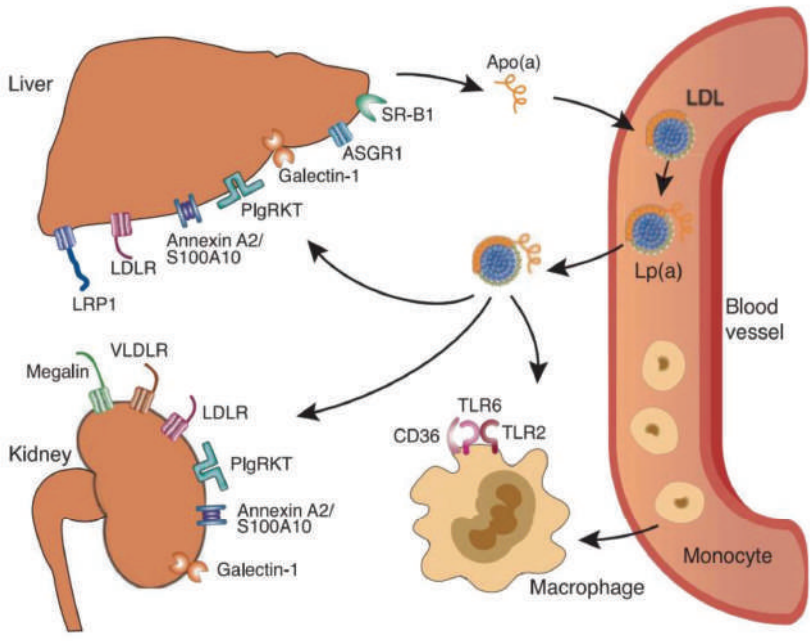
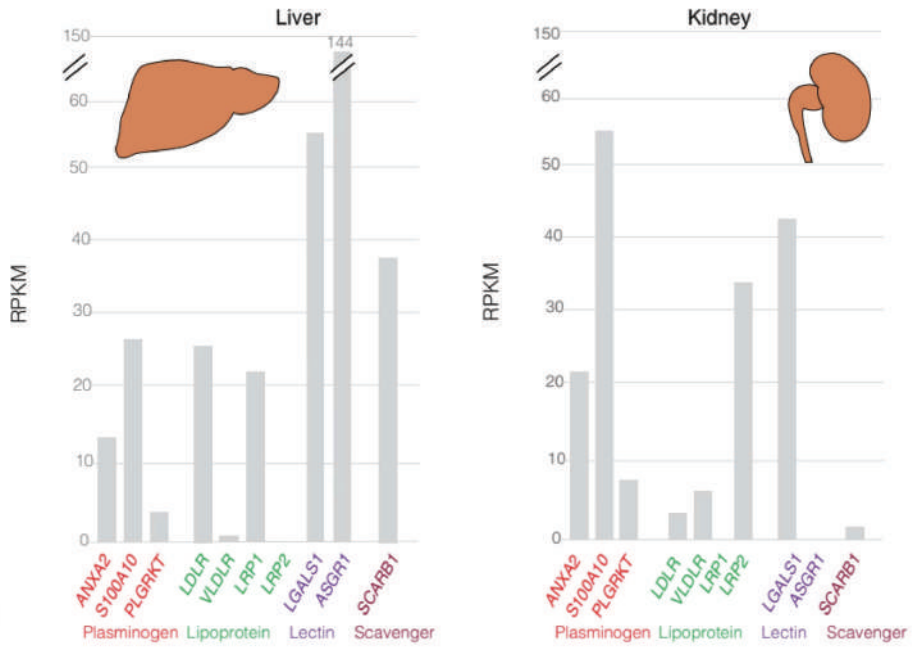
Catabolism of Lp(a)



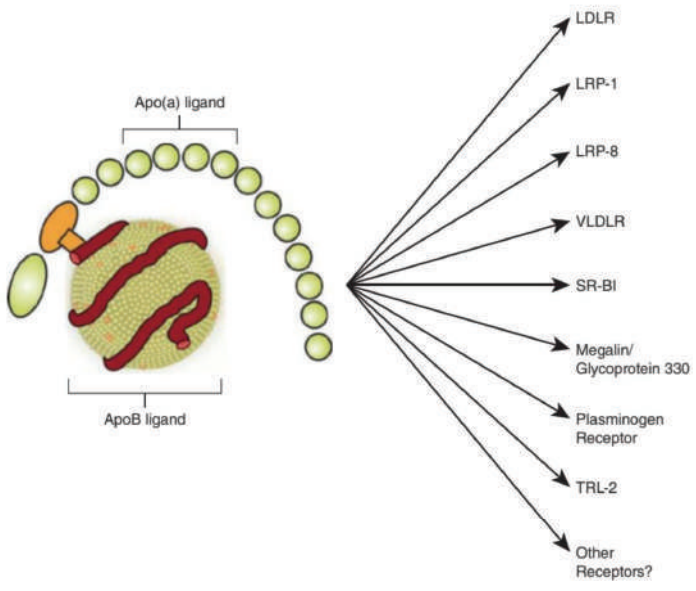
Catabolism of Lp(a)

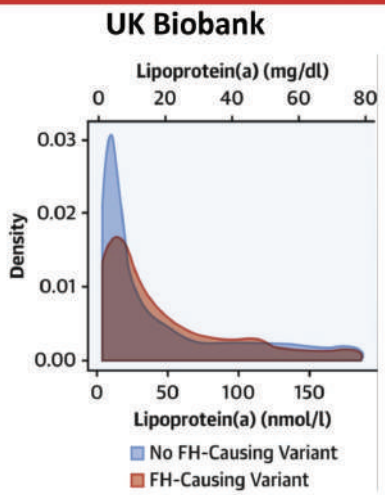


Catabolism of Lp(a)



Catabolism of Lp(a)

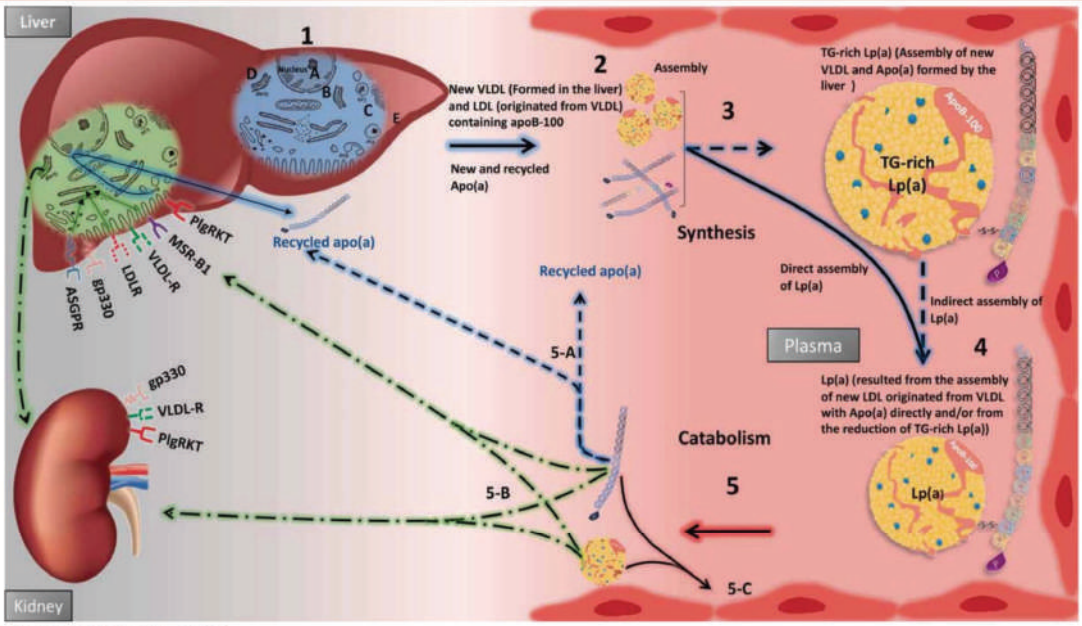




The genetic data do not strongly support a role for the LDL receptor in directly mediating the catabolism of Lp(a)

Trinder M, et al. J Am Coll Cardiol. 2020;75:2682-2693.

Synthesis, Assembly, Secretion, and Catabolis of Lp(a)



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Jawi MM et al. J Lipids. 2020;2020:3491764.

Lp(a): Unraveling its Enigma and Perspectives on Treatment

- Brief history
- Structure
- Biosynthesis – interconversion or not
- Determinants of Lp(a) concentration
  - Kringles isoform?

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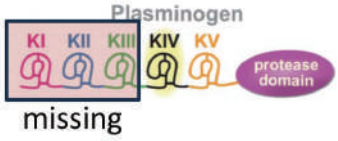
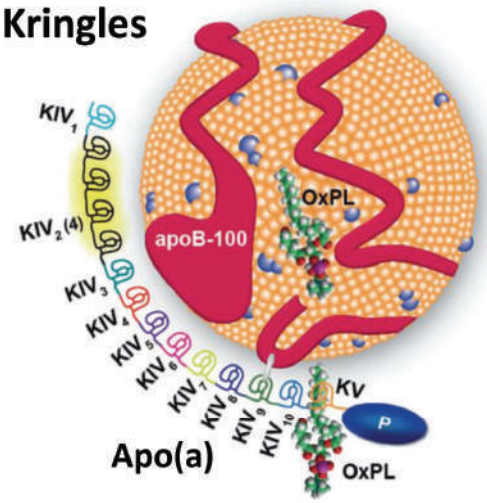
What is Lp(a)?



The kringles are the same as in ***Plasminogen***



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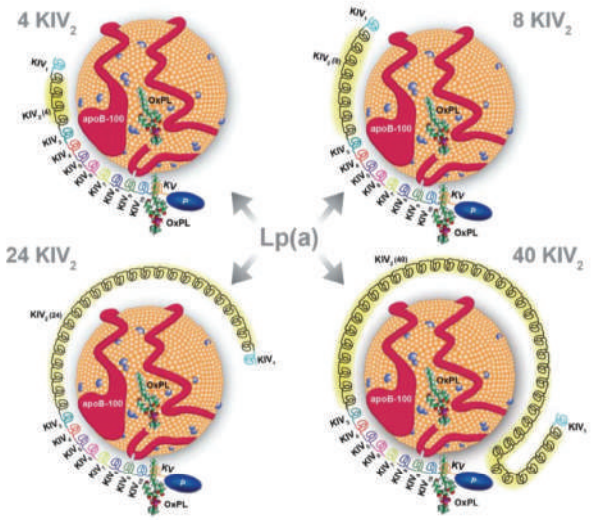
Composition of Lp(a)

- Lp(a) comes in different sizes depending on the Kringles length.
- The Kringles length is genetically determined.
- The number of particles determines the activity of the Lp(a).



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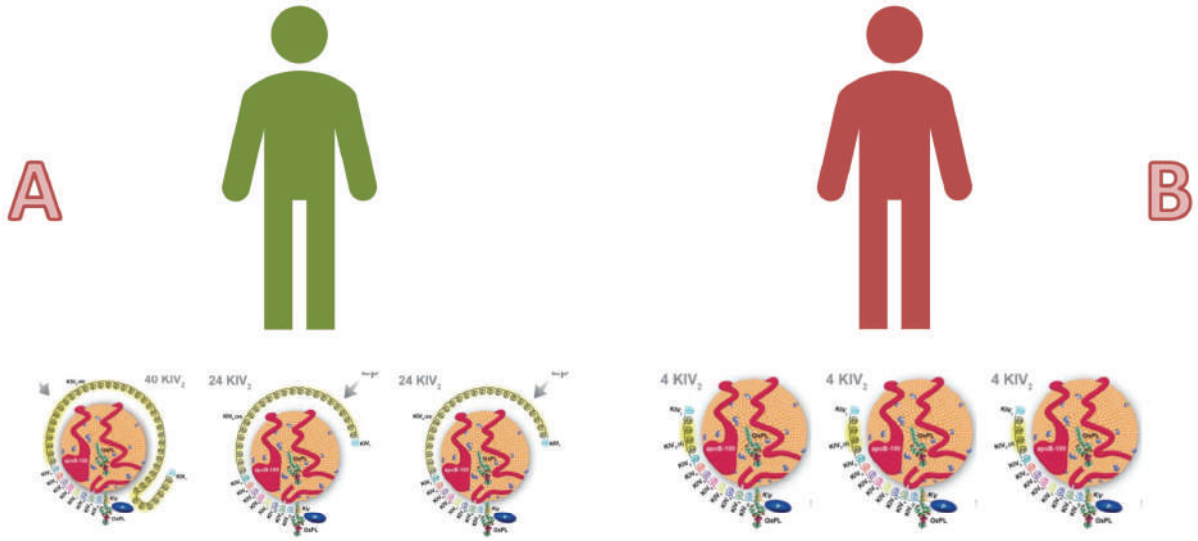
Same Lp(a) levels?



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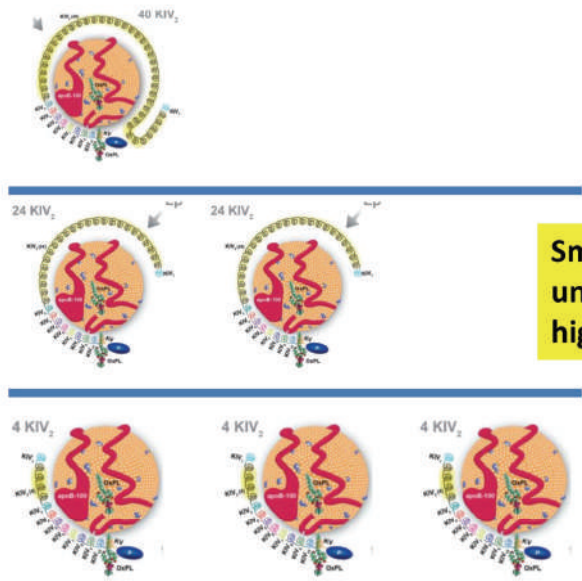
The Kringle length is genetically determined



High KIV-2 repeat number
→ Long Kringle length
→ Low particle number
→ Low Lp(a) concentration

Small isoforms can be produced faster per unit time in the hepatocyte, thus leading to higher plasma Lp(a) levels.

Low KIV-2 repeat number
→ Short Kringle length
→ Higher particle number
→ High Lp(a) concentration

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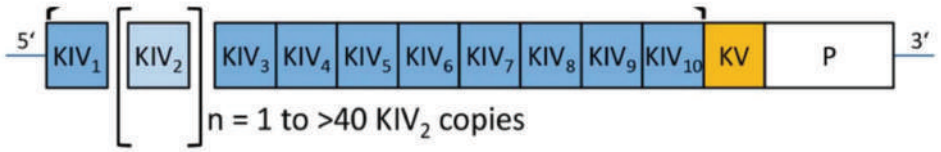
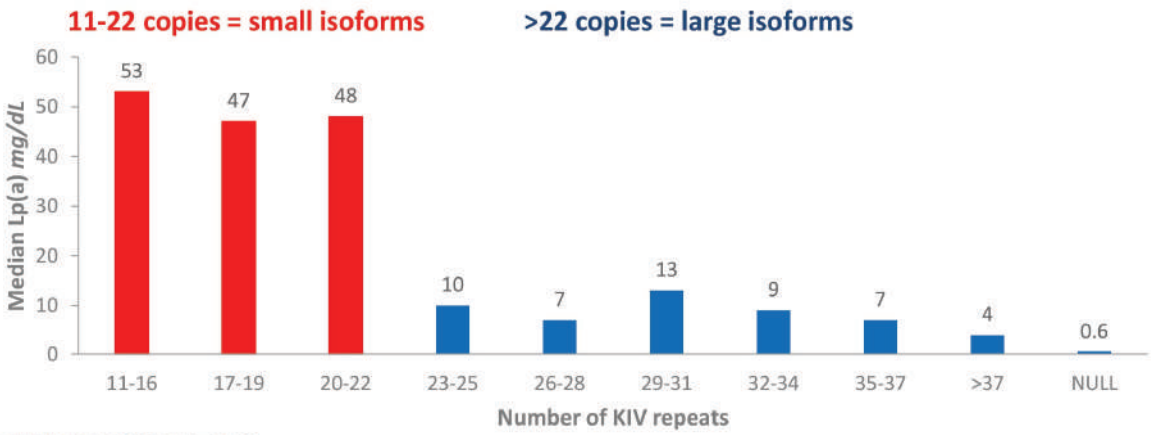
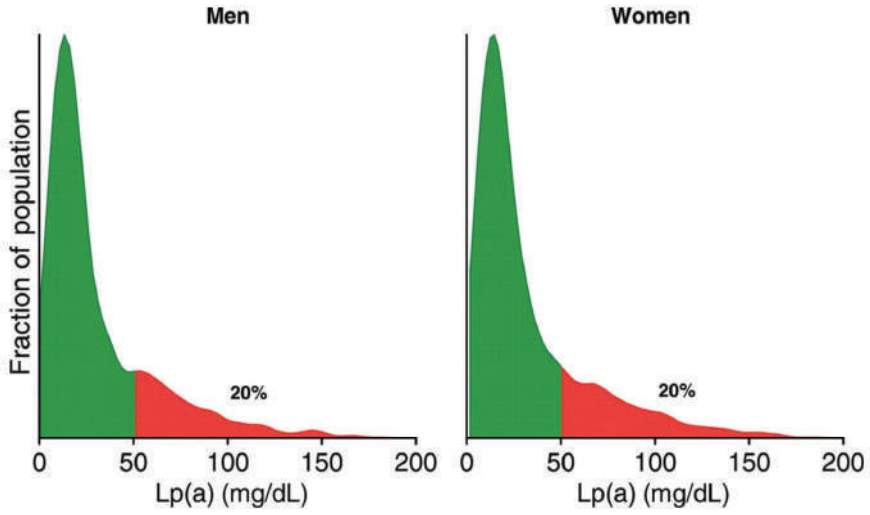
KIV_2 Repeats in Apo(a) and Lp(a) Concentration





Laschkolnig et al. CV Reasearch. 2014;103:26-36.

Copenhagen General Population Study



Nordestgaard et al. EHJ. 2010;31:2844-2853.

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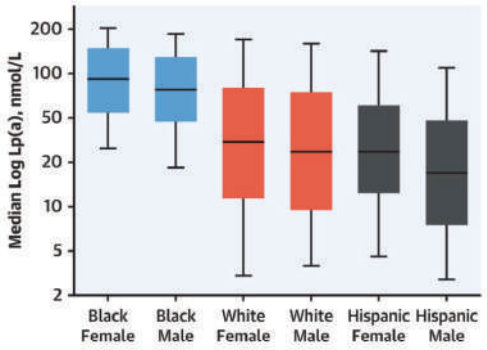
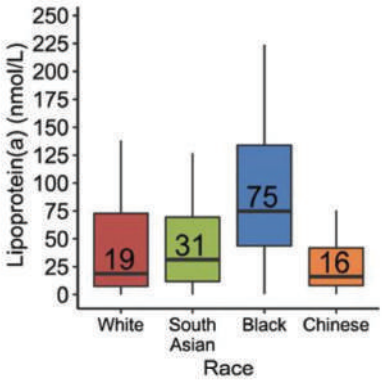
Lp(a) Concentration by Ethnicity

Dallas Heart Study



Tsimikas S. et al. J Am Coll Cardiol. 2022;80:934-946.

Dallas Heart Study



Patel et al. ATVB. 2021;41:465-474.

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Global 2022 Prevalence of Elevated (≥100-125 nmol/L) Lp(a) Level

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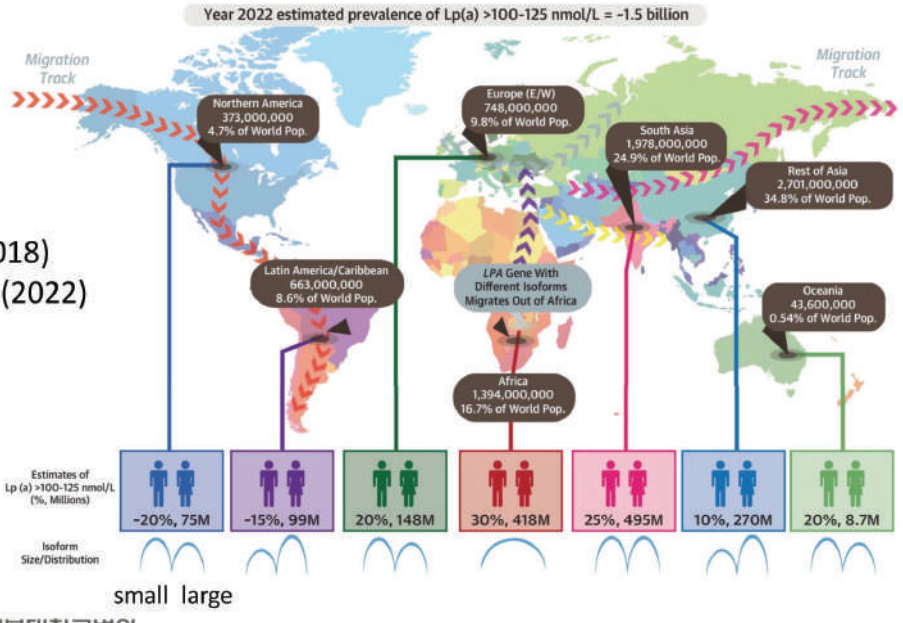

1.4 billion (2018)
→ 1.5 billion (2022)

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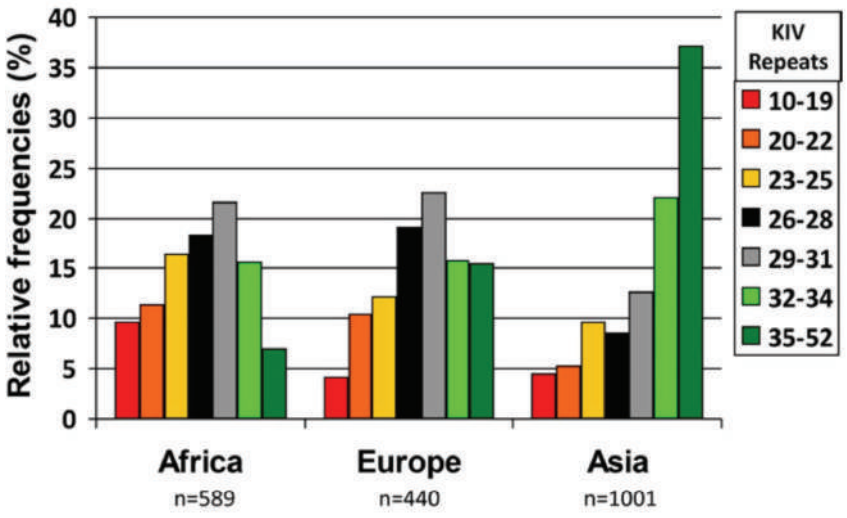
Tsimikas S. et al. J Am Coll Cardiol. 2022;80:934-946.



Schmidt K, et al. J Lipid Res. 2016;57:1339-59.

Lp(a): Unraveling its Enigma and Perspectives on Treatment

- Brief history
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- Biosynthesis – interconversion or not
- Determinants of Lp(a) concentration
  - Kringles isoform?
  - production or clearance?

Same Lp(a) levels?

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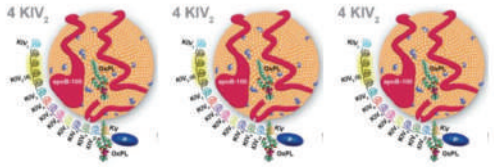
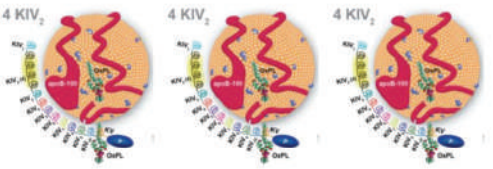
A



B



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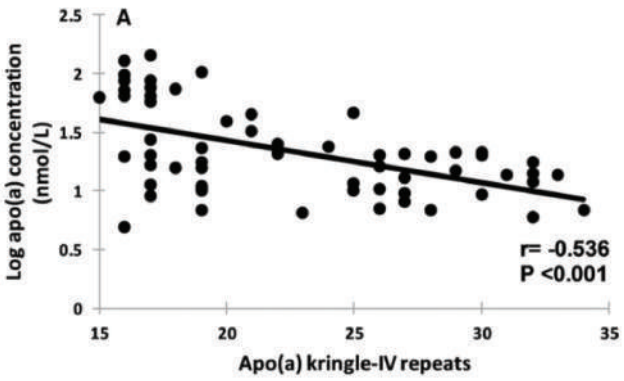

Smaller apo(a) isoforms are more readily secreted from hepatocytes, likely due to more efficient intracellular processing

Characteristics	Apo(a) levels	
	Low (≤ 22 nmol/L)	High (>22 nmol/L)
Predominant apo(a) isoform KIV	24 (22–26)†	18 (17–19)
Apo(a), nmol/L	12 (11–14)‡	56 (45–72)
Apo(a) FCR, pool/day	0.45 (0.40–0.52)*	0.33 (0.28–0.38)
Apo(a) PR, nmol/kg/day	0.25 (0.21–30)†	0.83 (0.63–1.08)
LDL-apoB-100, mg/L	481±146	420±132
LDL-apoB-100 FCR, pools/day	0.46±0.13	0.45±0.13
LDL-apoB-100 PR, mg/kg/day	9.8±3.7	8.6±4.1

Values expressed as mean±SD or geometric mean (95% confidence interval); Apo, apolipoprotein; FCR, fractional catabolic rate; LDL, low-density lipoprotein; PR, production rate.
*$P < 0.01$.
†$P < 0.001$.

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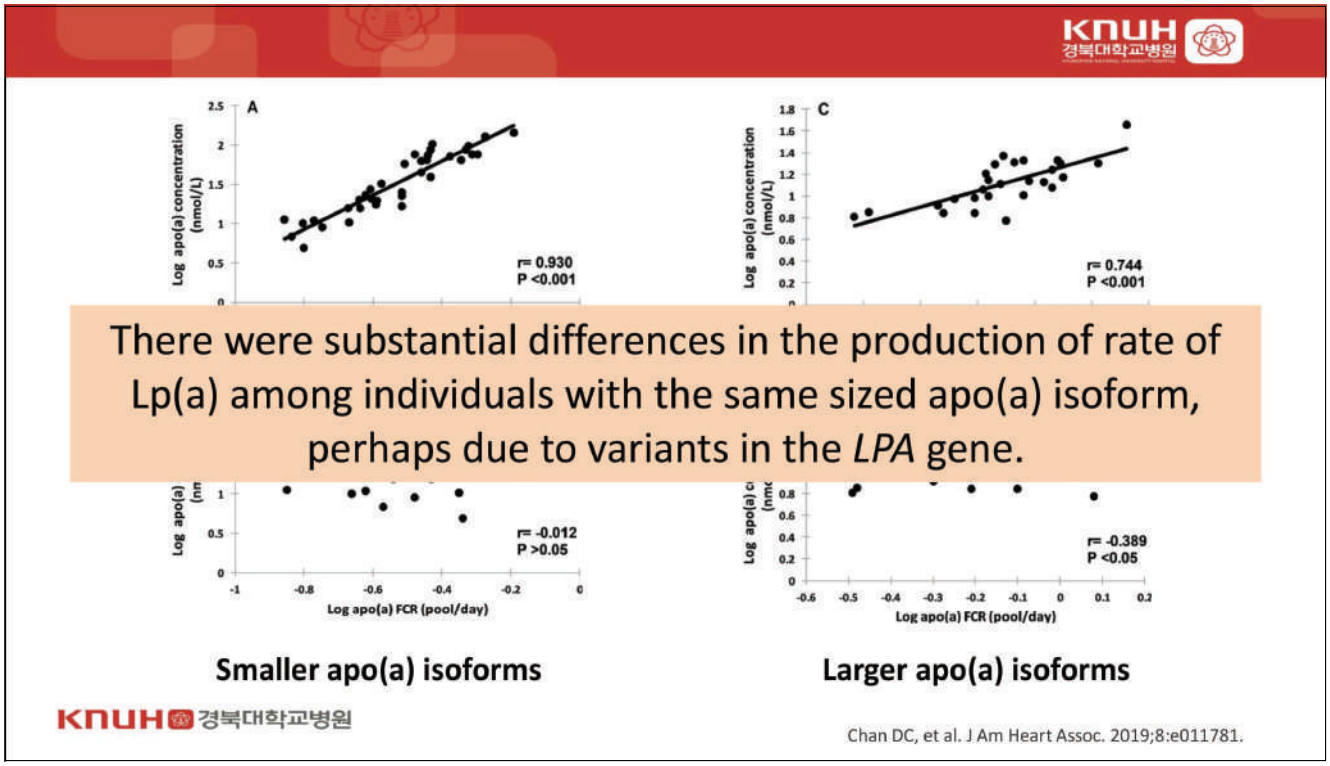
Chan DC, et al. J Am Heart Assoc. 2019;8:e011781.


A
Log apo(a) concentration (nmol/L)
r= 0.930
P <0.001
C
Log apo(a) concentration (nmol/L)
r= 0.744
P <0.001
There were substantial differences in the production of rate of Lp(a) among individuals with the same sized apo(a) isoform, perhaps due to variants in the LPA gene.
r= -0.012
P >0.05
Log apo(a) FCR (pool/day)
r= -0.389
P <0.05
Log apo(a) FCR (pool/day)
Smaller apo(a) isoforms
Larger apo(a) isoforms
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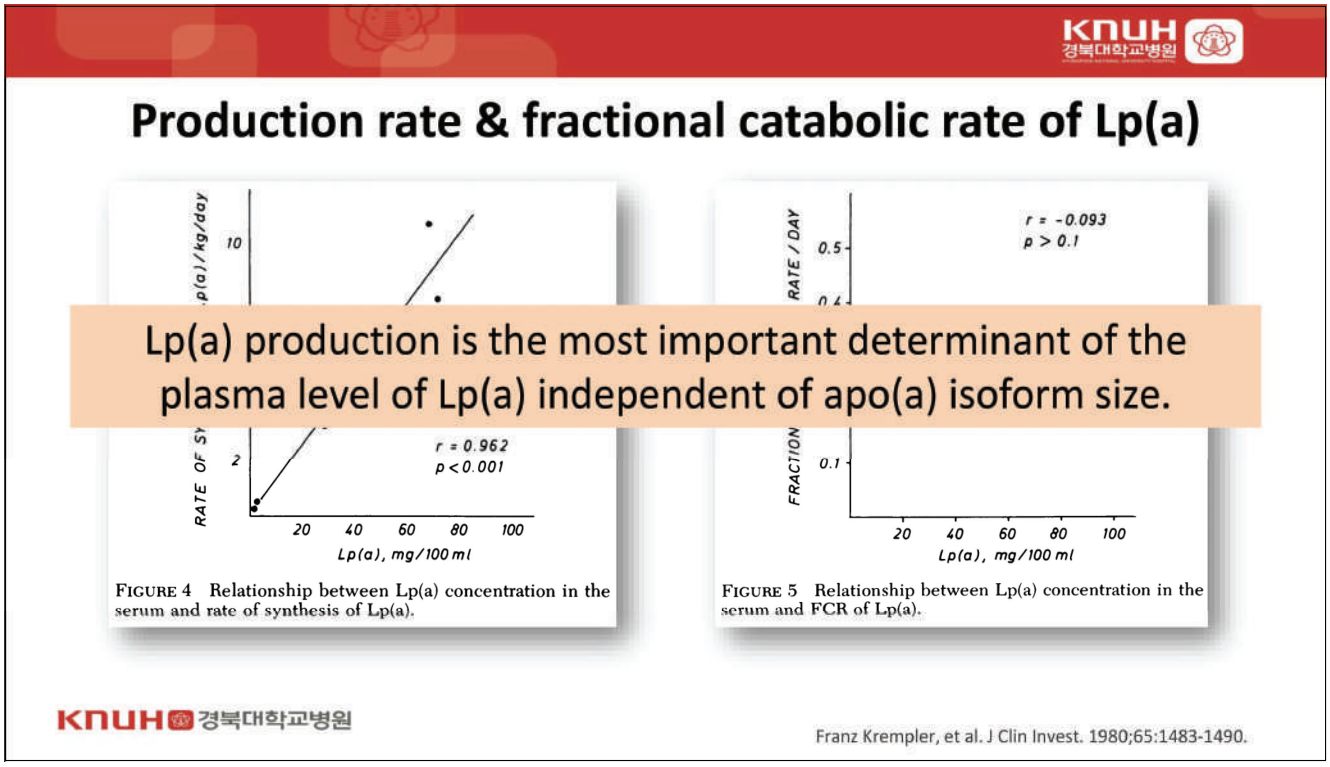
Chan DC, et al. J Am Heart Assoc. 2019;8:e011781.


Production rate & fractional catabolic rate of Lp(a)
Lp(a) production is the most important determinant of the plasma level of Lp(a) independent of apo(a) isoform size.
r = 0.962
p < 0.001
Lp(a), mg/100 ml
FIGURE 4 Relationship between Lp(a) concentration in the serum and rate of synthesis of Lp(a).
r = -0.093
p > 0.1
Lp(a), mg/100 ml
FIGURE 5 Relationship between Lp(a) concentration in the serum and FCR of Lp(a).
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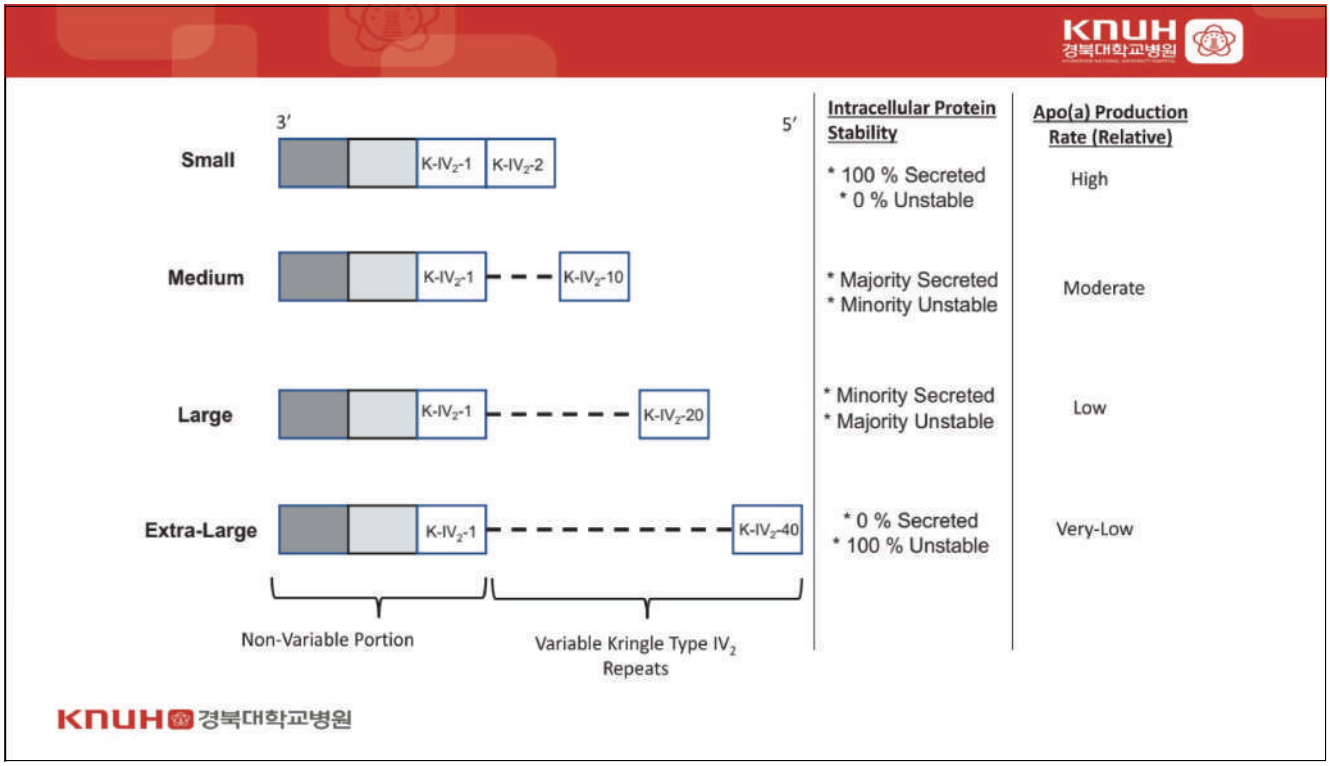
Franz Krempler, et al. J Clin Invest. 1980;65:1483-1490.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3′
5′
Small
Medium
Large
Extra-Large
K-IV2-1
K-IV2-2
K-IV2-10
K-IV2-20
K-IV2-40
Intracellular Protein Stability
* 100 % Secreted
* 0 % Unstable
* Majority Secreted
* Minority Unstable
* Minority Secreted
* Majority Unstable
* 0 % Secreted
* 100 % Unstable
Apo(a) Production Rate (Relative)
High
Moderate
Low
Very-Low
Non-Variable Portion
Variable Kringle Type IV2 Repeats
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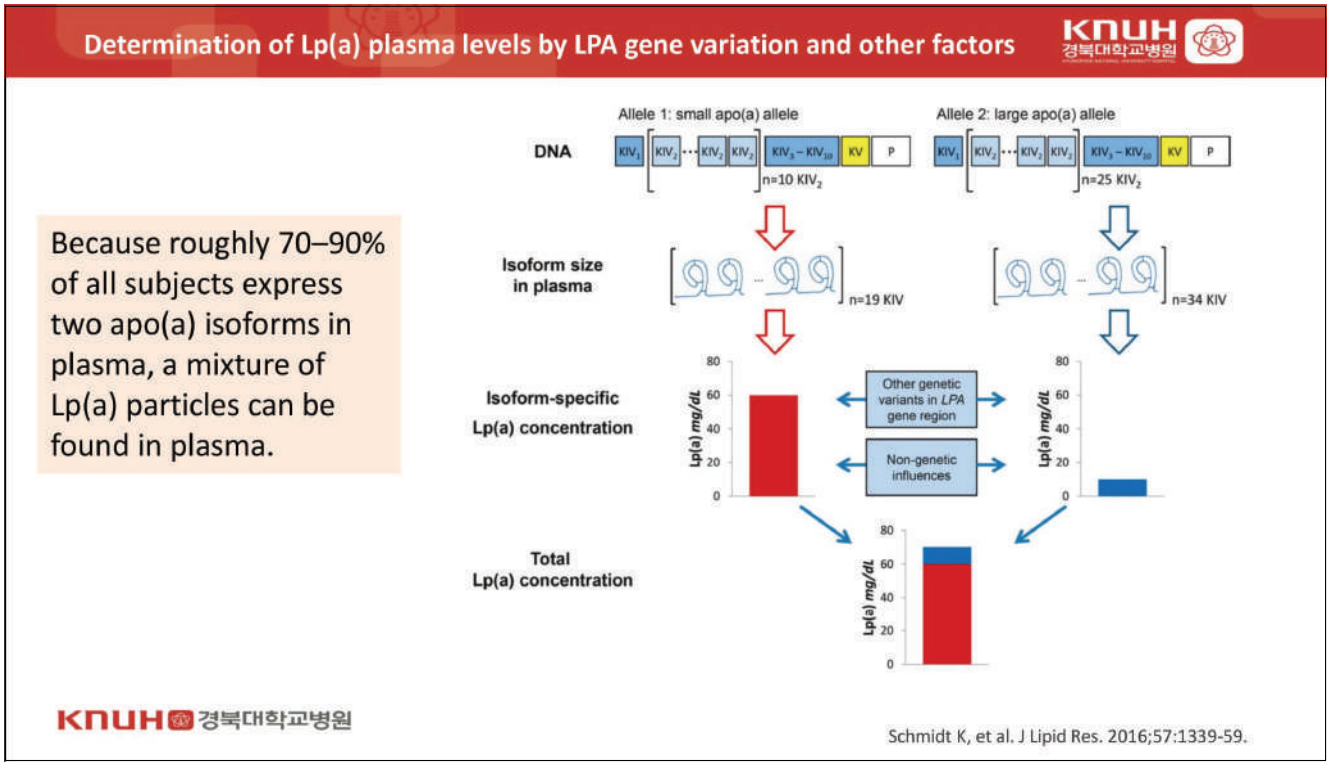
Determination of Lp(a) plasma levels by LPA gene variation and other factors
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Because roughly 70–90% of all subjects express two apo(a) isoforms in plasma, a mixture of Lp(a) particles can be found in plasma.
Allele 1: small apo(a) allele
Allele 2: large apo(a) allele
DNA
n=10 KIV2
n=25 KIV2
Isoform size in plasma
n=19 KIV
n=34 KIV
Isoform-specific Lp(a) concentration
Other genetic variants in LPA gene region
Non-genetic influences
Lp(a) mg/dL
Total Lp(a) concentration
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Schmidt K, et al. J Lipid Res. 2016;57:1339-59.

Combined effects of the KIV-2 VNTR and SNPs in the LPA gene

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- **This basic situation is modulated by SNPs.**
- Allele 2 in subject A carries the Lp(a) decreasing SNPs KIV-8 IVS+1G>A and KIV-2 R21X which are in strong LD and result in a null allele.
- Allele 4 in subject B which codes for an isoform of intermediate size and carries the variant 4733G>A in KIV-2 which affects splicing and moderately decreases Lp(a).
- The total plasma Lp(a) concentration in a subject is the sum of the two allele-associated concentrations.
- Other loci may have minor effects by unknown mechanisms

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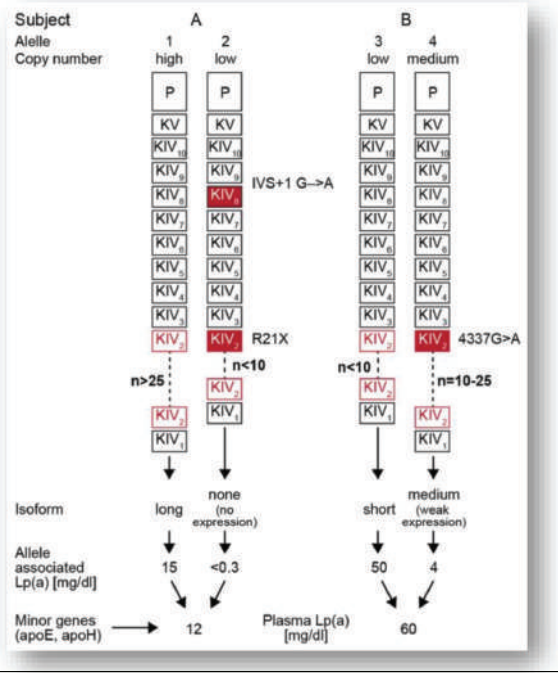

Copenhagen Baby Heart Study: Lp(a) Concentration

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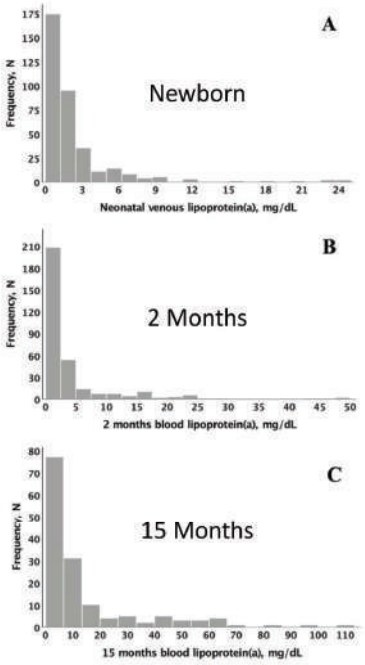

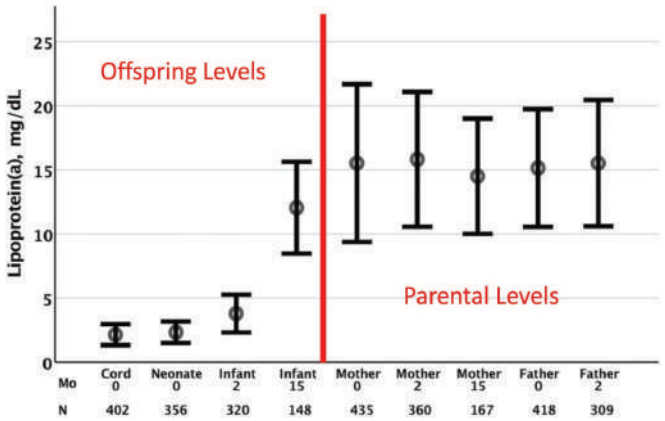

- Lp(a) at birth predicts Lp(a) at 15 months of age
- Lp(a) at birth >90th %ile predicts Lp(a) >42 mg/dL at 15 months
- Lp(a) at birth >90th %ile predicts ≥1 parent with Lp(a) >42 mg/dL

Strandkjær N, et al. The COMPARE Study. J Clin Endocrinol Metab. 2022;107:324-335.

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Lp(a): Unraveling its Enigma and Perspectives on Treatment

- Brief history
- Structure
- Biosynthesis – interconversion or not
- Determinants of Lp(a) concentration
  - Kringles isoform?
  - production or clearance?
- Lipid-regulating agents on Lp(a) metabolism

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Apo(a) Isoform size and PR/FCR

- Smaller apo(a) isoforms have been shown to have a ***shorter retention time in the endoplasmic reticulum and probably lesser intracellular apo(a) proteasome degradation, resulting in a more efficiently secretion from hepatocytes*** (White et al. 1994; Brunner et al. 1996; Lobentanz et al. 1998).
- On the other hand, Lp(a) with apo(a) isoforms of different sizes may have ***different binding affinities for the LDL receptor or other receptors*** (März et al. 1993).
- Lp(a) particles with ***larger isoform size have been shown to be more effectively removed via LDL receptor independent pathways***.

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Apo(a) Isoform size and PR/FCR

- Plasma Lp(a) concentration is predominantly determined by the rate of production of Lp(a) particles, irrespective of apo(a) isoform size and background statin use.
- Lp(a) particle catabolism may only play a ***modest role in determining Lp(a) concentration in subjects with larger apo(a) isoform size***.
- These observations also support the clinical use of agents that target the hepatic production and secretion of Lp(a) (Tsimikas 2017).

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Mechanism of action of lipid-regulating agents

- A major challenge in managing patients with elevated Lp(a) is a lack of effective and specific treatment for lowering Lp(a) concentrations (Tsimikas 2017; Tsimikas et al. 2018; Reyes-Soffer et al. 2022; Schwartz and Ballantyne 2022).
- Diet and lifestyle interventions, such as weight loss or physical activity, do not seem to influence Lp(a) concentrations.
- Lipoprotein apheresis is the only FDA approved treatment for elevated Lp(a).
- Currently, there are no approved pharmacologic therapies that specifically target Lp(a) concentrations (Cegla et al. 2009; Tsimikas 2017).

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Statin

- Statins competitively inhibit HMG CoA reductase, thereby decreasing cholesterol biosynthesis, reciprocally ***upregulating hepatic LDL receptors and enhancing clearance of LDL and other apoB-100-containing particles***, including TRLs (Ginsberg 2006).
- Given the structural similarities between LDL and Lp(a), one would speculate that ***statins could lower Lp(a) concentration by increasing the clearance of Lp(a)***.
- However, ***the effect of statins on Lp(a) levels is conflicting***: some studies show a neutral role (Wang et al. 2021; de Boer et al. 2022), while others report a decrease (Takagi and Umemoto 2012) or increase of plasma Lp(a) levels (Tsimikas et al. 2020).

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Statin

- The statin-induced increase in Lp(a) level is supported by experimental evidence in HepG2 cells showing a ***higher LPA mRNA level in response to atorvastatin*** (Tsimikas et al. 2020).
- In a study of healthy normolipidemic subjects, ***atorvastatin (80 mg daily) did not significantly alter the FCR or PR of apo(a)*** (Watts et al. 2017). This finding does not support a role of LDL receptor in the regulation of apo(a) FCR under physiological condition.
- However, it remains unclear whether statin has a potential impact on Lp(a) metabolism in subjects with high Lp(a) concentration. There is also evidence showing that ***statins increase Lp(a) levels exclusively in patients with a small size apo(a) defined as ≤22 KIV repeats*** (Yahya et al. 2019).
- The precise mechanisms of action of this effect on Lp(a) metabolism remain to be investigated.

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Author (year)	Subjects	Agents	concentration	FCR	PR
Watts et al. (2018)	Healthy normolipidemic men	Atorvastatin	↔	↔	↔

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Niacin

- Experimental data suggest that ***niacin decreases the expression of LPA mRNA*** (Chennamsetty et al. 2012).
- This is consistent with a kinetic study showing that ***niacin lowered Lp(a) concentration by decreasing the production of apo(a)*** in non-diabetic, obese and hypertriglyceridemic men (Croyal et al. 2015).
- The lowering of the PR of apo(a) by niacin was confirmed in another postprandial kinetic study in statin-treated patients with type 2 diabetes (Ooi et al. 2015). In this study, extended-release niacin (1–2 g/day) significantly decreased plasma Lp(a) concentration and the production rates of apo(a), with greater treatment effect in individuals with elevated Lp(a) concentration.
- Extended-release niacin was more effective in lowering Lp(a) level in subjects with small apo(a) isoform than those with large isoform (Artemeva et al. 2015).

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Author (year)	Subjects	Agents	concentration	FCR	PR
Watts et al. (2018)	Healthy normolipidemic men	Atorvastatin	↔	↔	↔
Ooi et al. (2015)	Statin-treated men with T2DM	ER niacin	↓↓	↔	↓↓
Croyal et al. (2015)	Non-DM, Obese men with HyperTG	ER niacin	↓↓	↓↓	↓↓↓

PCSK9 Inhibition

- PCSK9 mAbs can lower plasma Lp(a) concentration.
- The effectiveness of PCSK9 mAbs in reducing ASCVD events is also found to be most pronounced in patients with high Lp(a) and that the reduction in Lp(a) could also partly mediate the cardiovascular benefit of PCSK9 mAbs (Bittner et al. 2020; Schwartz et al. 2021).
- In a kinetic study of healthy normolipidemic men, evolocumab monotherapy significantly decreased plasma Lp(a) concentration chiefly by ***reducing the PR of apo(a) with no effect on the corresponding FCR*** (Watts et al. 2018).
- The mechanistic effect of evolocumab may involve reduced hepatic production of Lp(a) ***by decreasing the assembly of Lp(a) particles through the reduction of apo(a) binding with LDL on the surface of hepatocytes*** (Lambert et al. 2017).
- This speculation is supported by in vitro studies showing that ***PCSK9 induces Lp(a) intracellular assembly and secretion, whereas PCSK9 mAbs reduce the extracellular release of Lp(a)*** (Villard et al. 2016).

PCSK9 Inhibition

- However, as combination therapy with high-dose atorvastatin, evolocumab reduced the plasma concentration of Lp(a) chiefly by a ***significant increase in the FCR of apo(a)*** (Watts et al. 2018). The PR of Lp(a) was not significantly altered with the combination.
- However, the increase in apo(a) FCR in the latter study was ***not statistically significant***, probably owing to greater variability in study subject characteristics.
- The mechanistic effect of evolocumab in combination with atorvastatin may involve ***supraphysiological upregulation of the activity of LDL receptors*** and ***decreased competition of Lp(a) with very low concentrations of LDLs for clearance*** by these receptors.
- This mechanism suggests that the ***LDL receptor likely plays a significant role in mediating Lp(a) clearance only when its expression is markedly upregulated and when LDL plasma levels are substantially lowered, allowing decreased competition between LDL and Lp(a) for receptor-mediated uptake in the liver.***

PCSK9 Inhibition

- Using stable isotopes, PCSK9 inhibition with alirocumab-lowered plasma Lp(a) concentration by increasing apo(a) FCR in patients with elevated Lp(a) receiving maximally tolerated statin therapy (Watts et al. 2020).
- However, in patients with very high-Lp(a) concentration, alirocumab signifcantly lowered plasma Lp(a) concentration by a dual mode of action involving both increased clearance and decreased production of apo(a) (Ying et al. 2022).
- Taken together, the mechanistic action of PCSK9 mAbs on the PR and FCR of apo(a) appears to be dependent on background statin use and Lp(a) concentration at baseline.

Author (year)	Subjects	Agents	concentration	FCR	PR
Watts et al. (2018)	Healthy normolipidemic men	Atorvastatin	↔	↔	↔
Ooi et al. (2015)	Statin-treated men with T2DM	ER niacin	↓↓	↔	↓↓
Croyal et al. (2015)	Non-DM, Obese men with HyperTG	ER niacin	↓↓	↓↓	↓↓↓
Reyes-Soffer et al. (2017)	Healthy normolipidemic men and women	Alirocumab	↓	↑	↔
Watts et al. (2020)	Statin-treated men and women with high Lp(a)	Alirocumab	↓↓	↑↑	↔
Ying et al. (2022)	Statin-treated men and women with very high Lp(a)	Alirocumab	↓↓↓	↑↑	↓↓
Watts et al. (2018)	Healthy normolipidemic men	Evolocumab	↓↓	↔	↓↓
Watts et al. (2018)	Healthy normolipidemic men	Evolocumab + Atorvastatin	↓↓	↑↑	↔

CETP inhibitors

- Treatment with CETP inhibitors, either alone or in combination with statin, can lower Lp(a) concentrations up to 30% (Schmidt et al. 2021).
- In a kinetic study of patients with hypercholesterolaemia (Thomas et al. 2017), CETP inhibition with anacetrapib lowered Lp(a) concentration by reducing the PR of apo(a) with no effect on the corresponding FCR.
- However, there is ***no clear explanation*** for the reduction in apo(a) PR with anacetrapib.
- Despite these metabolic changes, CETP inhibitors did overall not have clinically meaningful effects in large clinical trials.
- Two clinical trials with a newer CETP inhibitor obicetrapib (TA-8995; 10 mg) has been shown to increase HDL-cholesterol by 160%, and reduce LDL-cholesterol, apoB and Lp(a) levels approximately by 50–60%, 30–50% and ***25–50%***, respectively, in patients treated with atorvastatin or rosuvastatin (Hovingh et al. 2015; Ray 2022).

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Author (year)	Subjects	Agents	concentration	FCR	PR
Watts et al. (2018)	Healthy normolipidemic men	Atorvastatin	↔	↔	↔
Ooi et al. (2015)	Statin-treated men with T2DM	ER niacin	↓↓	↔	↓↓
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Reyes-Soffer et al. (2017)	Healthy normolipidemic men and women	Alirocumab	↓	↑	↔
Watts et al. (2020)	Statin-treated men and women with high Lp(a)	Alirocumab	↓↓	↑↑	↔
Ying et al. (2022)	Statin-treated men and women with very high Lp(a)	Alirocumab	↓↓↓	↑↑	↓↓
Watts et al. (2018)	Healthy normolipidemic men	Evolocumab	↓↓	↔	↓↓
Watts et al. (2018)	Healthy normolipidemic men	Evolocumab + Atorvastatin	↓↓	↑↑	↔
Thomas et al. (2017)	Mildly hypercholesterolaemic men with women	Anacetrapib (CETP inhibitor)	↓↓	↔	↓↓

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ApoB Antisense Oligonucleotides (ASO)

- Mipomersen is an antisense oligonucleotide (ASO) directed to liver mRNA of apoB that inhibits apoB synthesis (Parham and Goldberg 2019).
- Accordingly, mipomersen has been shown to significantly lower plasma concentrations of apoB-containing lipoproteins including LDL and Lp(a).
- In a kinetic study of healthy volunteers, treatment with mipomersen caused a significant decrease of plasma Lp(a) levels that was associated with ***a significant increase in the FCR of Lp(a), with no effect on corresponding apo(a) PR*** (Nandakumar et al. 2018).
- These results were unexpected because inhibition of apoB synthesis with mipomersen would reduce the availability of apoB100 substrate for the assembly of hepatic apoB with apo(a) to form an Lp(a).
- It is noteworthy that mipomersen also did not reduce VLDL apoB secretion in the same subjects studied (Reyes-Soffer et al. 2016). These observations appear to support the presence of spare apoB pool in the liver that would be utilized for the assembly of Lp(a) in order to maintain hepatic homeostasis for apoB.

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Author (year)	Subjects	Agents	concentration	FCR	PR
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Croyal et al. (2015)	Non-DM, Obese men with HyperTG	ER niacin	↓↓	↓↓	↓↓↓
Reyes-Soffer et al. (2017)	Healthy normolipidemic men and women	Alirocumab	↓	↑	↔
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Ying et al. (2022)	Statin-treated men and women with very high Lp(a)	Alirocumab	↓↓↓	↑↑	↓↓
Watts et al. (2018)	Healthy normolipidemic men	Evolocumab	↓↓	↔	↓↓
Watts et al. (2018)	Healthy normolipidemic men	Evolocumab + Atorvastatin	↓↓	↑↑	↔
Thomas et al. (2017)	Mildly hypercholesterolaemic men with women	Anacetrapib (CETP inhibitor)	↓↓	↔	↓↓
Nandakumar et al. (2018)	Healthy normolipidemic men and women	Mipomersen (ApoB ASO)	↓↓	↑↑	↔

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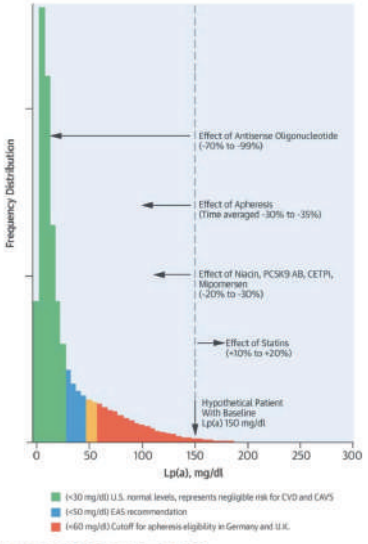
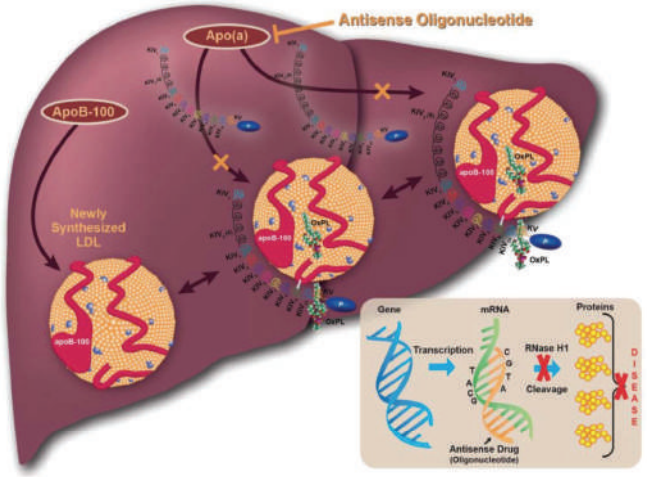
Mechanism of ASO Targeted to Apo(a) to reduce Lp(a) levels





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Study Name, Phase (Therapy)	Therapy Mechanism	Therapy Formulation	Population	Outcome
ORION-11,[c] phase 3 (inclisiran)	siRNA that inhibits PCSK9 synthesis	SC injection of 300 mg on day 1 and day 90, then every 6 months vs. placebo	• ≥18 years of age • LDL-C level ≥70 mg/dL • History of ASCVD	• Secondary outcome evaluating effect of inclisiran on Lp(a) level • Preliminary results: percent reduction of Lp(a) level by 28.5%
Lp(a) HORIZON,[d] phase 3 (pelacarsen [TQJ230])	ASO against Apo(a)	SC injection of 80 mg monthly vs. placebo	• 8,323 participants • 18-90 years of age • Lp(a) level ≥70 mg/dL • Established CVD	• Time to occurrence of MACE in 4 years
TQJ230,[f] phase 3 (pelacarsen [TQJ230])	ASO against Apo(a)	SC injection of 80 mg monthly vs. placebo	• 60 participants • Established ASCVD • Currently undergoing lipoprotein apheresis for isolated Lp(a)	• Superiority of pelacarsen over placebo in reducing the rate of lipoprotein apheresis sessions

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Take Home Message

- Major advances have been made in our understanding of the factors that regulate Lp(a) metabolism for 60 years.
- The synthesis of apo(a) is largely under genetic control and ultimately determines the production rate and concentration of Lp(a) in plasma.
- A single receptor that regulates Lp(a) clearance has not been identified to date; the LDL receptor does not appear to play a major physiological role.
- Niacin and cholesteryl ester transfer protein inhibitors lower plasma Lp(a) concentration by increasing the clearance or catabolism of apo(a).
- ApoB ASO lower plasma Lp(a) concentration by decreasing hepatic production.
- PCSK 9 inhibitors can lower plasma Lp(a) concentration by a dual mode of action involving both increased clearance and decreased production of apo(a), further studies should investigate nucleic acid-based inhibitors for apo(a), angiopoietin-like 3 and apoC-III inhibitors on the metabolism of Lp(a) and other lipoproteins.

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박 훈 준

[기본정보]

성함	박 훈 준
소속(근무처)	가톨릭의대 의정부성모병원 순환기내과

[학력]

해당년도	세부사항
2009.03-2012.02	가톨릭대학교 의과대학 내과학 박사
2006.09-2008.08	가톨릭대학교 의과대학 내과학 석사
1991.03-1997.02	가톨릭대학교 의과대학 의학과 학사

[경력]

해당년도	세부사항
2024.04-현재	의정부성모병원 교수
2019.03-2024.03	서울성모병원 교수
2012.03-2013.07	미국 Emory University 방문교수

[관심분야]

심근경색, 중재시술. 심부전. 줄기세포, 심장재생

[논문]

Kim C, Kim H, Sim WS, et al. Spatiotemporal control of neutrophil fate to tune inflammation and repair for myocardial infarction therapy. Nat Commun 2024;15:8481
Pham QH, Bui TVA, Sim WS, et al. Daily oral administration of probiotics engineered to constantly secrete short-chain fatty acids effectively prevents myocardial injury from subsequent ischemic heart disease. Cardiovasc Res.2024;:cvae128.
Min S, Kim S, Sim WS, et al. Versatile human cardiac tissues engineered with perfusable heart extracellular microenvironment for biomedical applications. Nat Commun 2024;15:2564.
Jeong SY, Park BW, Kim J, et al. Hyaluronic acid stimulation of stem cells for cardiac repair: a cell-free strategy for myocardial infarct. J Nanobiotechnology 2024;22:149.
Park KH, Truong TT, Park JH, et al. Robust and customizable spheroid culture system for regenerative medicine. Biofabrication 2024;16(4).

Role of HDL Cholesterol and Current Evidence on HDL Cholesterol Treatments

박 훈 준

가톨릭의대 순환기내과

High Density Lipoprotein - HDL

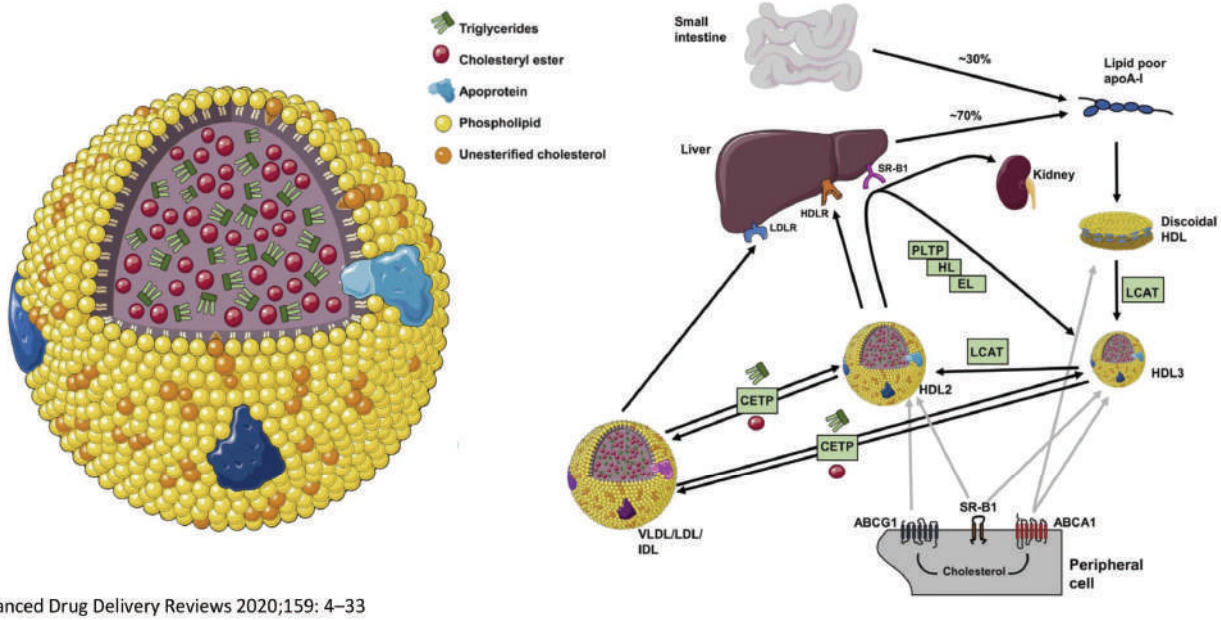
Michel Macheboeuf (프랑스)

"소 혈청에서 단백질 59%, 지질 41% (18% 콜레스테롤, 23% 인지질)로 구성된 고밀도 (HDL) 지단백질 분리" (1929년)

"혈장 지단백질의 아버지"

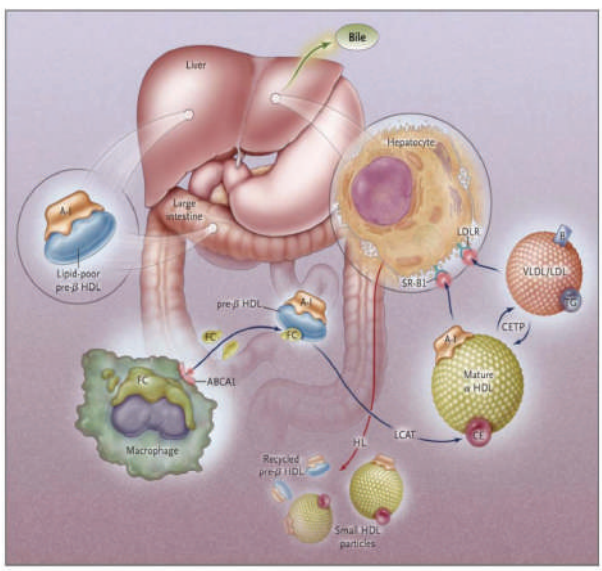
"Lipid albumin index"

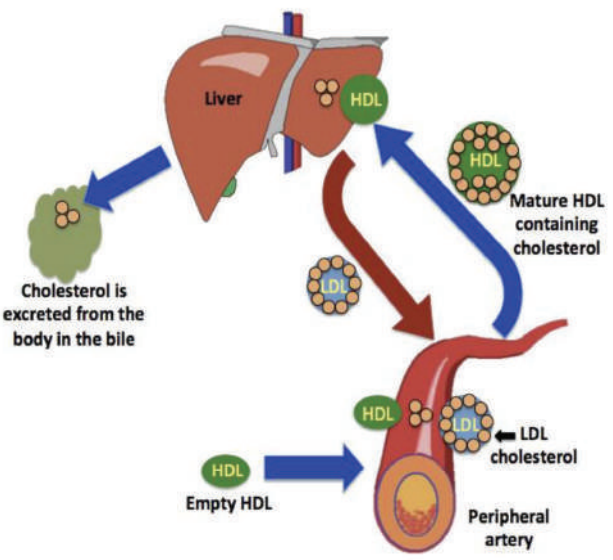
HDL structure & metabolism



Advanced Drug Delivery Reviews 2020;159: 4–33

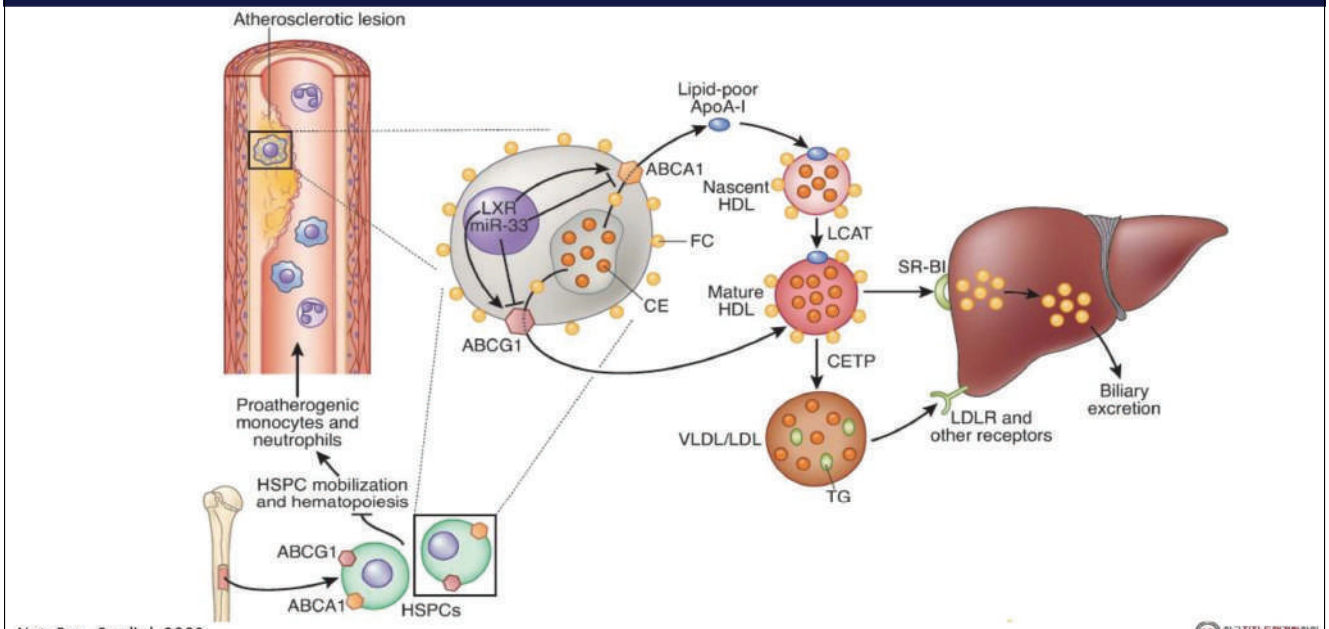
Role of HDL in circulation





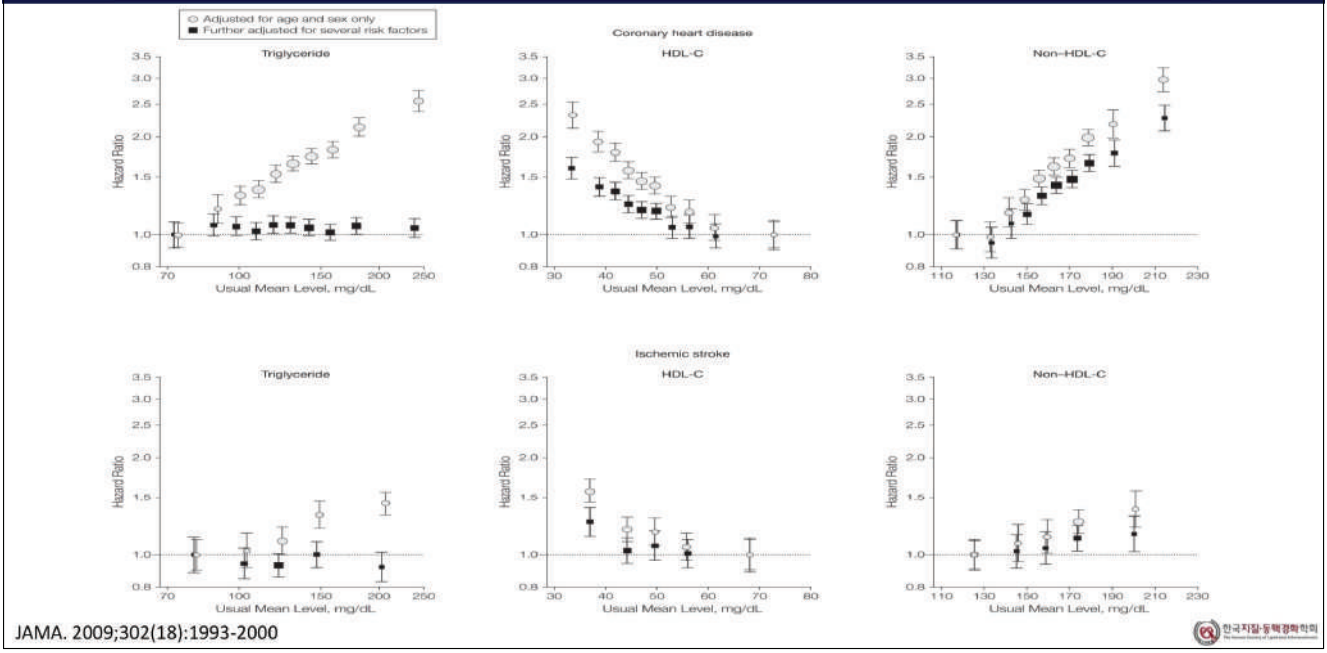
N Engl J Med 2005;353:1252-60.

Reverse cholesterol transport



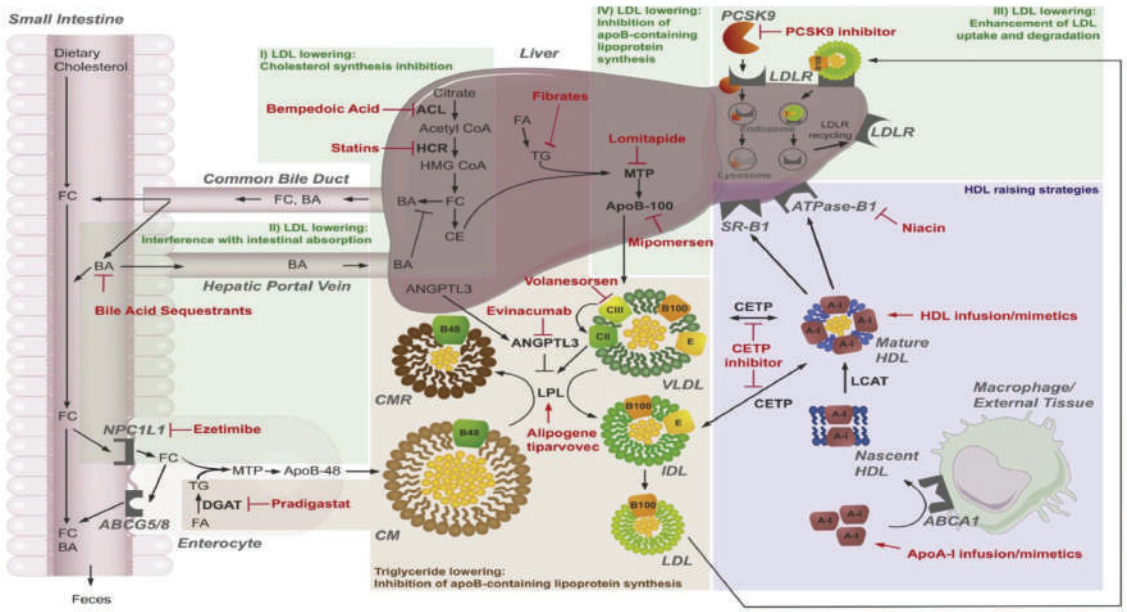
Nat. Rev. Cardiol. 2009

Hazard Ratio for CHD & Stroke Across HDL-C Levels



JAMA. 2009;302(18):1993-2000

Emerging targets for management of dyslipidemia



Advanced Drug Delivery Reviews 2020;159: 4–33

Lipid-lowering medication & effects of HDL-C

Medication	HDL Increase†	Mechanism	Specific Agents	Contraindications by Class	Common and Serious Side Effects by Class
Niacin	20–35%	Inhibits hepatic uptake of apolipoprotein A-I and enhances plasma pre-β HDL cholesterol; improves endothelial function and enhances endothelial nitric oxide synthase activity	Extended-release niacin (Niaspan), 1000–2000 mg orally nightly Niacin (nicotinic acid), 1–2 g orally two or three times daily Sustained-release niacin (Slo-Niacin), 250–750 mg orally once or twice daily	Hypersensitivity, hepatic dysfunction, active peptic ulcer, unexplained elevations of liver-function tests, alcoholism	Common: flushing,‡ pruritus, nausea, vomiting, rash, dyspepsia, elevated liver aminotransferase levels, hypotension, paresthesias, abdominal pain, hyperglycemia,§ elevated lactate dehydrogenase levels, hyperuricemia Serious: hepatotoxicity, arrhythmias, severe hypotension or hemorrhage (rare reports with nicotinic acid and Slo-Niacin)
Fibrates	10–25%	Activates PPARα, which stimulates apolipoprotein A-I expression[38]	Fenofibrate, micronized (Antara), 43–130 mg orally once daily Fenofibrate, micronized (Lofibra), 67–200 mg orally once daily Fenofibrate (Tricor), 48–145 mg orally once daily Gemfibrozil (Lopid), 600 mg orally twice daily	Hypersensitivity, gallbladder disease, hepatic dysfunction, severe renal dysfunction, unexplained elevations of liver-function tests, primary biliary cirrhosis	Common: elevated liver aminotransferase levels, abnormal liver-function tests, abdominal pain, elevated creatine kinase levels, nausea, respiratory disorders, back pain, headache, rhinitis, constipation Serious: myositis, myopathy, cholelithiasis, hepatitis, pancreatitis
Statins	5–15%	Increases apolipoprotein A-I synthesis	Rosuvastatin (Crestor), 5–40 mg orally once daily Fluvastatin (Lescol), 20–40 mg orally nightly Fluvastatin (Lescol XL), 80 mg orally nightly Simvastatin (Zocor), 5–80 mg orally every evening	Hypersensitivity, active liver disease, unexplained elevations of liver-function tests, pregnancy, breast-feeding	Common: myalgia, elevated creatine kinase levels, elevated liver aminotransferase levels, dyspepsia, abdominal pain, diarrhea, nausea, headache, back pain, flu-like syndrome, urinary tract infection, rhinitis or sinusitis, constipation, arthralgia or arthritis, rash, paresthesias, peripheral edema, pharyngitis, asthenia Serious: myopathy, hepatotoxicity, pancreatitis, angioedema, leukopenia, thrombocytopenia, vesiculobullous rash, photosensitivity, rhabdomyolysis (rare)
	2–12%		Pravastatin (Pravachol), 10–80 mg orally once daily		
	2–10%		Atorvastatin (Lipitor), 10–80 mg orally once daily		
	2–8%		Lovastatin (Altoprev), 10–60 mg orally nightly		
Combination statin and niacin	21–26%		Lovastatin–niacin (Advicor), 20–500 mg to 20–1000 mg orally nightly	Hypersensitivity, active liver disease, unexplained elevations of liver-function tests, active peptic ulcer, arterial bleeding, pregnancy, breast-feeding	Common: flushing, warm sensation, redness of skin, pruritus, tingling, nausea or vomiting, diarrhea, dyspepsia, flatulence, constipation, paresthesias, rash, asthenia, myalgia, hyperglycemia, elevated creatine kinase levels, elevated liver aminotransferase levels, hyperuricemia, hypotension Serious: hepatotoxicity, fulminant hepatic necrosis, thrombocytopenia, peptic ulcer, arrhythmias, myopathy, pancreatitis

N Engl J Med 2005;353:1252-60.

Clinical trials for HDL-C in therapy: Niacin

Drugs	Trials	Outcomes
Niacin alone	Coronary Drug Prevention project (1975)[68]	Reduced MI and stroke in 3,906 patients with prior MI.
Add on colestipol versus placebo	Cholesterol Lowering Atherosclerosis study (CLAS) (1987)[69]	Significant atherosclerosis regression was noted in treatment group compared to placebo. Fewer people were found to develop new lesions in grafts and coronary arteries.
Add on statin	HDL Atherosclerosis Treatment study (HATS) (2001)[70]	Simvastatin plus niacin showed notable angiographic and clinical benefits among patients with CAD and low HDL-C levels.
Add on statin	Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 (2004)[71]	ERN added to statins slowed the progress of atherosclerotic disease among patients with previous CAD and moderately-low HDL-C.
Add on statin	ARBITER 3 (2006)[72]	When added to statins, ERN significantly increased HDL-C and regression of CIMT.
Add on statin	ARBITER-6 HDL and LDL Treatment Strategies (HALTS) (2010)[73]	Niacin showed superiority to ezetimibe for regression of CIMT among patients on statins.
Add on statin	Atherothrombosis Intervention in Metabolic Syndrome with low HDL-C/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) (2011)[14]	This trial was ended early as it did not show increased benefit on ASCVD outcomes, in spite of a 10% increment in HDL-C.
Add on statin; niacin/laropiprant	Heart Protection Study 2: Treatment of HDL to reduce the incidence of vascular events (HPS2-THRIVE) (2013)[15]	No reduction in CVD events compared to statins alone over a mean follow-up of 3 years.

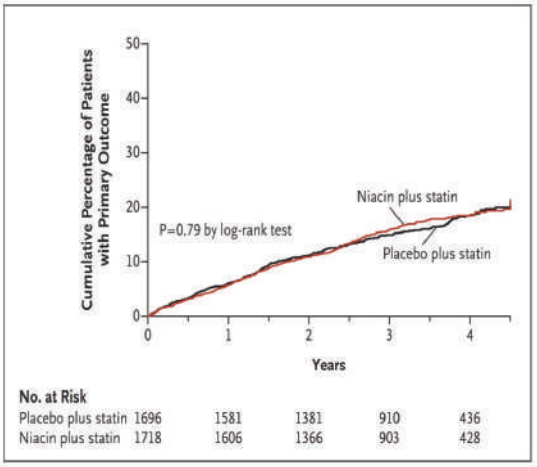
Vascular Health and Risk Management 2014

AIM-HIGH trial

- Randomly assigned eligible patients to receive ER niacin, 1500 to 2000 mg/day, or matching placebo.
- All patients received 40-80 mg/day simvastatin, plus 10mg/day ezetimibe to maintain LDL-C of 40- 80 mg/dl
- Primary end point was the composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an ACS, or symptom-driven coronary or cerebral revascularization.

Table 2. Lipid Values at Baseline and during Follow-up.*

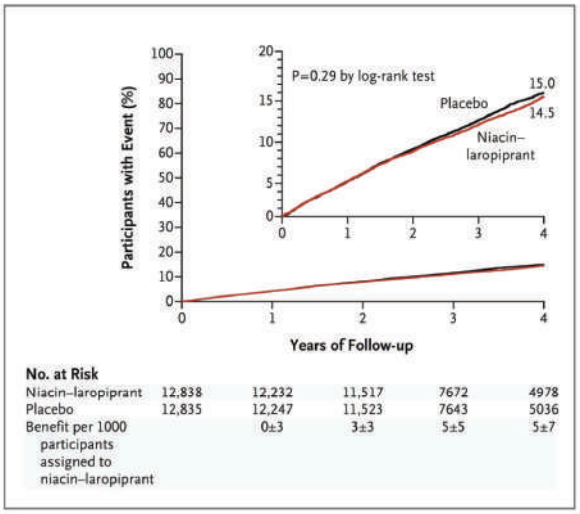
Variable	Placebo plus Statin (N=1696)				Extended-Release Niacin plus Statin (N=1718)			
	Baseline (N=1696)	Year 1 (N=1554)	Year 2 (N=1326)	Year 3 (N=873)	Baseline (N=1718)	Year 1 (N=1561)	Year 2 (N=1329)	Year 3 (N=865)
LDL cholesterol								
Mean (mg/dl)	74.0±22.7	70.4±18.9	69.5±19.9	68.3±19.3	74.2±23.4	66.4±19.9	65.0±20.5	65.2±21.8
Median (mg/dl)	72	69	68	67	73	64	62	62
Interquartile range (mg/dl)	60–85	59–79	57–78	56–78	59–86	54–75	52–74	51–74
Median change from baseline (%)		-4.3	-5.5	-7.6		-10.0	-12.0	-13.6
Triglycerides								
Median (mg/dl)	163	155	153	152	167.5	121	122	120
Interquartile range (mg/dl)	131–216	118–208	117–210	114–204	131–219	86–170	85–170	84–172
Median change from baseline (%)		-5.0	-8.1	-9.9		-28.2	-28.6	-30.8
HDL cholesterol								
Mean (mg/dl)	34.9±5.6†	38.4±7.6	38.7±7.4	39.1±7.7	34.5±5.6	43.6±10.9	43.9±10.6	44.1±11.3
Median (mg/dl)	35	38	38	38	35	42	42	42
Interquartile range (mg/dl)	31–39	34–43	34–43	34–44	30–39	36–49	37–50	36–50
Median change from baseline (%)		9.1	9.8	11.8		23.3	25.0	25.0

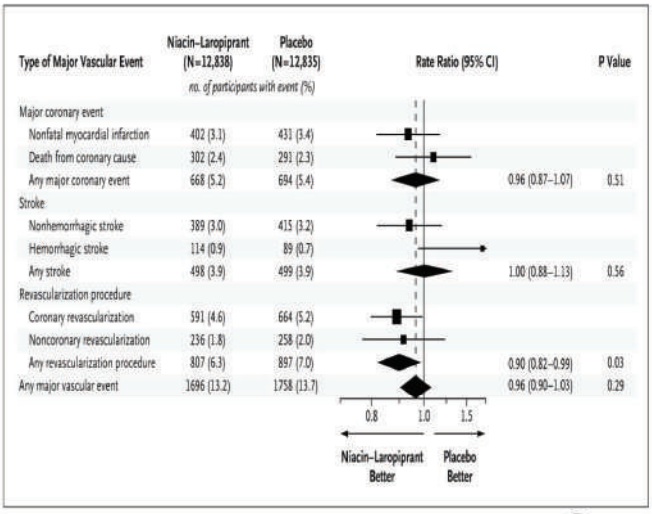


N Engl J Med 2011;365:2255-67.

HPS2-THRIVE trial

- Randomly assigned 25,673 adults with vascular disease to receive 2 g of extended-release niacin and 40 mg of laropiprant or a matching placebo daily.
- Primary outcome was the first major vascular event (nonfatal MI, death from CHD, stroke, or arterial revascularization).





N Engl J Med 2014;371:203-12.

Clinical trials for HDL-C in therapy: CETP inhibitors

Drugs	Trials	Outcomes
Torcetrapib	Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial (2007)[74]	Increased mortality, possibly from off-target effects on blood pressure and electrolytes.
	Rating Atherosclerotic Disease Change by Imaging With A New CETP Inhibitor(RADIANCE) (2007)[75]	Elevated HDL-C and lowered LDL-C substantially; also increased systolic BP and did not change CIMT.
	Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) (2007)[76]	Reduced LDL-C and enhanced HDL-C markedly. Study group had elevated BP. There was no significant decrease in evolution of coronary atheroma.
Dalcetrapib	Efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome (dal-OUTCOMES) (2012)[77]	Increased HDL-C up to 40%, without altering LDL-C, with no improvement on CVD outcomes.
	Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (Dal-PLAQUE) Phase IIb (2011)[78]	Increased HDL-C by 31% with decreased CETP over a mean of 2 years. Failed to show plaque progression at 2 years or inflammatory response at 6 months. No increased adverse events noted.
Anacetrapib	Determining the Efficacy and Tolerability of CETP INhibition with AnacEtrapib (DEFINE) (2010)[79]	Improved HDL-C by 138%, decreased LDL-C by 40%, and decreased Lp(a) by 36%. No significant variation in BP compared with placebo noted.
	Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) (ongoing)[80]	Will test effects of anacetrapib 100 mg daily added to atorvastatin in reducing CHD events among 30,000 individuals with ASCVD or diabetes. To be completed in 2017.
Evacetrapib	A randomized trial (2011)[81]	Evacetrapib alone or combined with statins reduced LDL-C (14%–36%) and augmented HDL-C (54%–129%). No discernible effects on BP or production of aldosterone or cortisol were noted. To test the effects on ASCVD events among 11,000 postacute coronary syndrome patients.

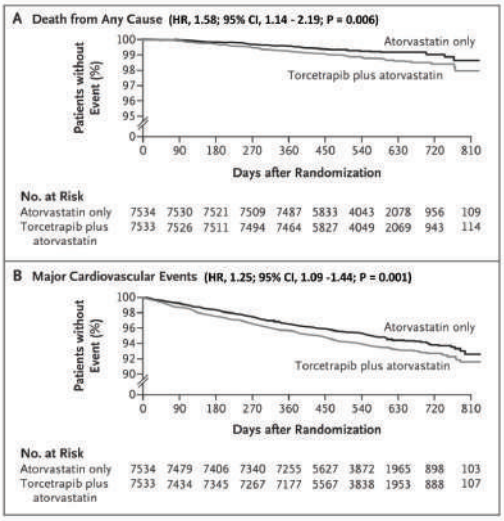
Vascular Health and Risk Management 2014

ILLUMINATE trial

- Randomly assigned 15,067 patients at high CV risk to torcetrapib plus atorvastatin or atorvastatin alone.
- Primary outcome was the time to the first MACE (death from CHD, nonfatal MI, stroke, or UA.

Table 2. Changes from Baseline at 3 Months and 12 Months in Selected Measures.*

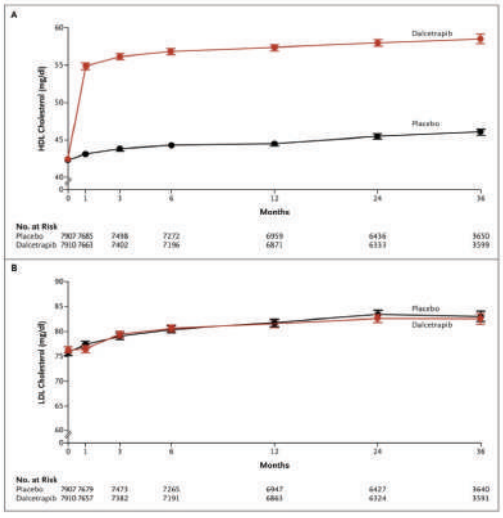
Variable	Change at 3 Months			Change at 12 Months		
	Atorvastatin Only	Torcetrapib plus Atorvastatin	P Value	Atorvastatin Only	Torcetrapib plus Atorvastatin	P Value
Lipids (absolute change) — mg/dl						
Cholesterol						
Total	+1.6±20.5	+5.1±23.9	<0.001	+2.1±22.4	+9.3±26.3	<0.001
High-density lipoprotein	+0.5±6.2	+29.0±14.4	<0.001	+0.5±6.8	+34.2±17.0	<0.001
Low-density lipoprotein	+0.6±15.8	−20.5±20.8	<0.001	+0.9±17.1	−21.5±22.7	<0.001
Triglycerides						
Median	+1	−10	<0.001	+1	−10	<0.001
Interquartile range	−23 to 26	−38 to 12		−23 to 29	−38 to 14	
Apolipoprotein						
A-I	+0.4±16.0	+30.8±21.9	<0.001	NA	NA	NA
B	+0.6±11.1	−10.1±14.4	<0.001	NA	NA	NA
Lipids (percent change) — %						
Cholesterol						
Total	+1.7±13.3	+4.2±16.0	<0.001	+2.2±14.5	+7.0±17.7	<0.001
High-density lipoprotein	+1.7±12.7	+60.9±28.7	<0.001	+1.8±14.0	+72.1±34.7	<0.001
Low-density lipoprotein	+2.5±21.7	−24.0±25.1	<0.001	+3.0±23.7	−24.9±28.5	<0.001
Triglycerides						
Median	+1	−9	<0.001	+1	−9	<0.001
Interquartile range	−17 to 23	−26 to 11		−18 to 25	−27 to 13	
Apolipoprotein						
A-I	+1.3±18.6	+25.3±24.4	<0.001	NA	NA	NA
B	+2.0±16.6	−12.5±19.2	<0.001	NA	NA	NA

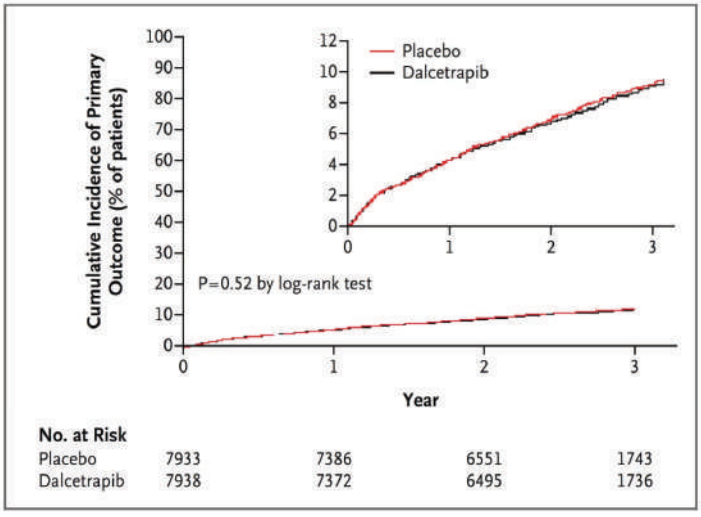


N Engl J Med 2007;357:2109-22.

dal-OUTCOMES trial

- Randomly assigned 15,871 patients with ACS to receive dalcetrapib, at a dose of 600mg daily, or placebo.
- Primary end point was a composite of death from CHD, nonfatal MI, ischemic stroke, UA, or cardiac arrest with resuscitation.





N Engl J Med 2012;367:2089-99.

REVEAL trial

- Randomized, double-blind, placebo-controlled trial involving 30,449 adults with atherosclerotic vascular disease who were assigned to receive either 100 mg of anacetrapib once daily or matching placebo.
- Primary end point was a composite of coronary death, MI, or coronary revascularization.

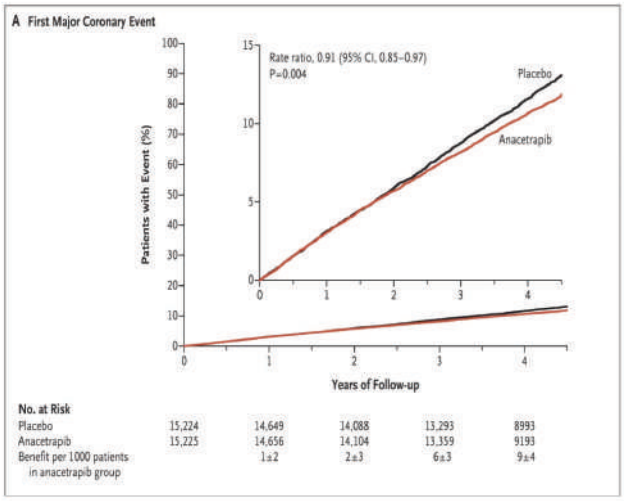


Table 2. Effects of Anacetrapib on Blood Lipids and Lipoproteins at Trial Midpoint.*

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

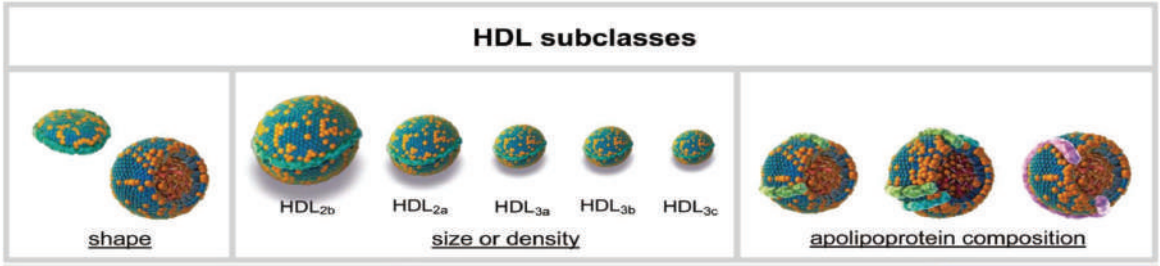
B First Major Coronary Event, According to Year of Follow-up

Year of First Event	Anacetrapib (N=15,225)	Placebo (N=15,224)	Rate Ratio (95% CI)	P Value
	no. of patients with event (%)			
1	465 (3.1)	476 (3.1)	0.98 (0.86–1.11)	
2	398 (2.7)	414 (2.8)	0.96 (0.84–1.10)	
3	370 (2.6)	427 (3.0)	0.86 (0.75–0.99)	
≥4	407 (3.0)	486 (3.7)	0.83 (0.73–0.94)	
>1	1175 (8.0)	1327 (9.1)	0.88 (0.81–0.95)	0.001
All	1640 (10.8)	1803 (11.8)	0.91 (0.85–0.97)	0.004

Test for trend across years, χ^2=4.87 (P=0.03)
Test for heterogeneity between ≤1 yr and >1 yr, χ^2=1.82 (P=0.18)
Anacetrapib Better
Placebo Better

N Engl J Med 2017;377:1217-27

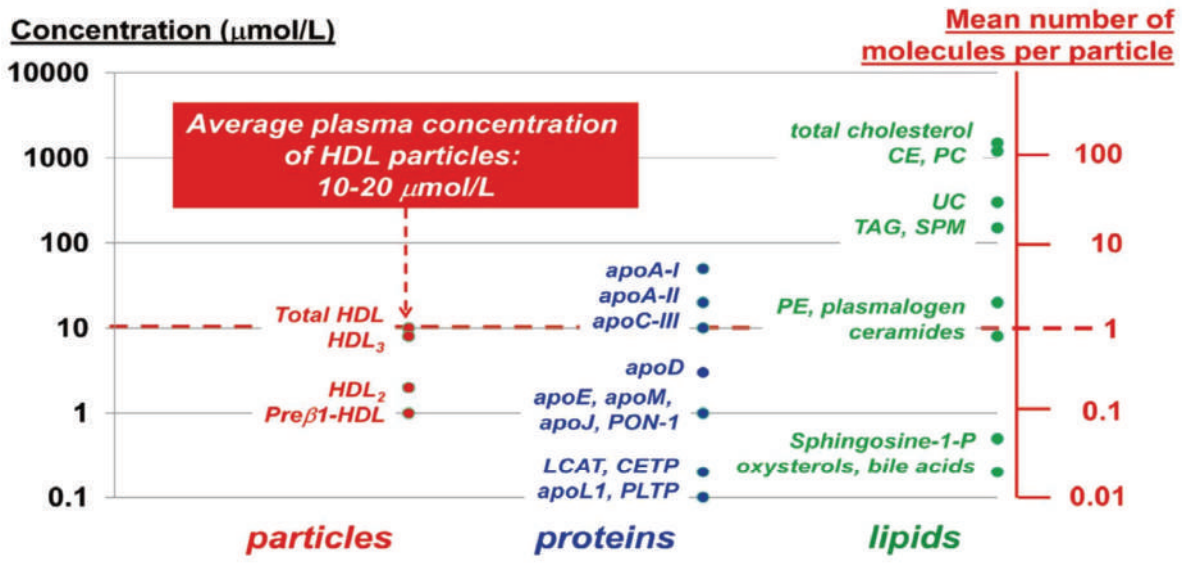
HDL heterogeneity – structure & components



> 80 proteins or peptides	> 200 lipid species	microRNAs
Apolipoproteins and lipocalins: apoA-I, apoA-II, apoA-IV apoA-V, apoC-I, apoC-II, apoC-III, apoC-IV, apoD, apoE, apoF, apoH, apoJ, apoL-I, apoM	Isoprenoids: esterified and unesterified cholesterol, oxysterols, bile acids, steroid hormones	miR-223 miR-126 miR-92a miR-150
Enzymes: LCAT, CETP, PLTP, PON1, PON3, GPx, Lp-PLA$_2$, MPO	Acylglycerols: triglycerides	
Other proteins: SAA1, SAA2, SAA4, Coe, Hp, Hb, HRP, hPBP, PSP, C3, C4, α_1-AT, α_2-HS-GP, α_2-AP, TTR, αFib, α_1-PI	Glycerophospholipids: (lyso)-phosphatidylcholines, -ethanolamines, - serines, -inositols, plasmalogens, cardiolipins	miR-30c* miR-145* miR-146a* miR-155 miR-378*
	Sphingolipids: sphingomyelins, ceramides, glycolipids, sphingosine-1-phosphate	
	Vitamins: α-tocopherol, carotenoids, retinoids	

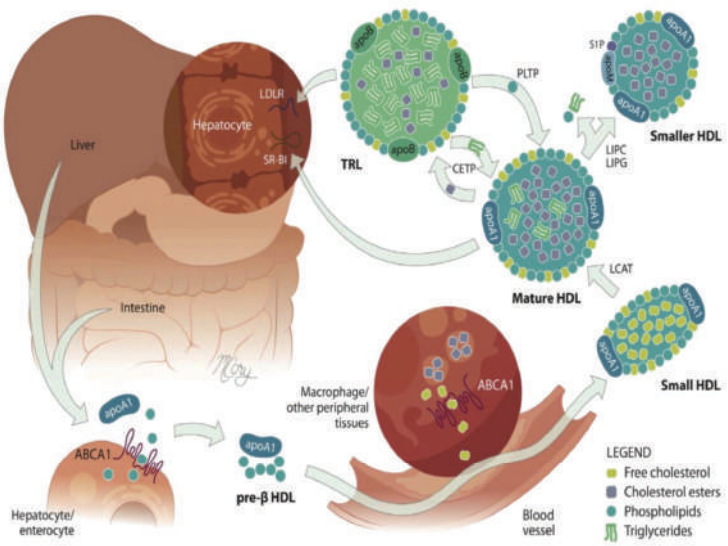
Circ J 2013; 77: 2432 - 2448

HDL heterogeneity – concentration & number



Circ J 2013; 77: 2432 - 2448

Human genetics for HDL-C & risk of CVD



Gene	Effect on HDL-C	Effect on CVD
APOA1	↓	↑
ABCA1	↓	↑/-
LCAT	↓	↑/-
CETP	↑	↓/-
LPL	↓	↑/-
LPIC	↑	↑
LPIG	↑	↓/-
APOC2	↓	ND
APOC3	↑	↓
GALNT2	↑	ND
PLTP	↓	ND
SCARB1	↑	↑?

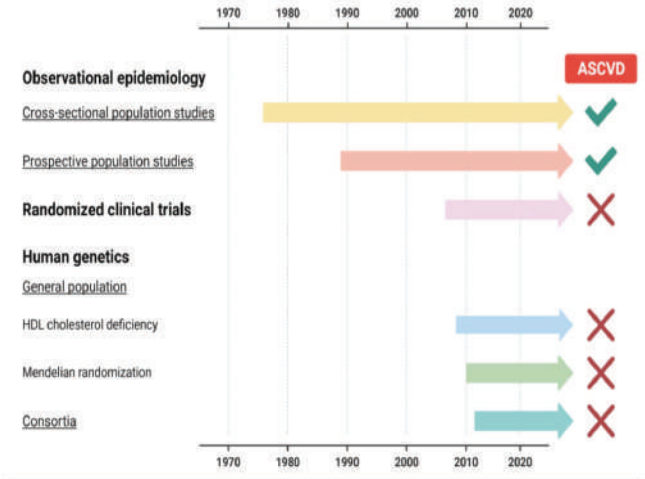
Progress in Lipid Research 2015;58: 14–25

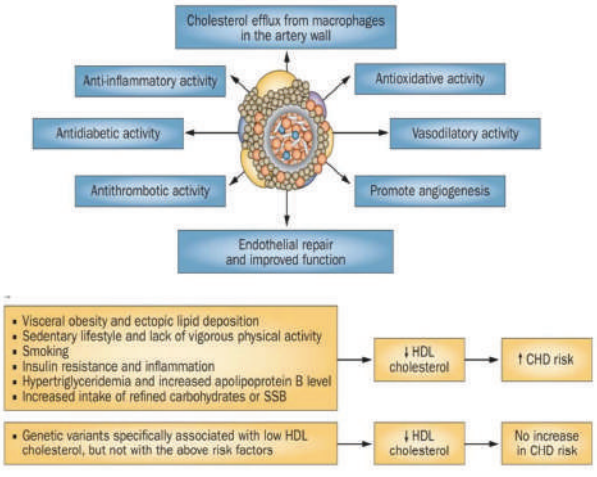
Genetic variants of HDL & risk of CVD

Gene	Chromosomal location	Study design	Variant type	Effect on HDL-C levels	CHD association	Comments	Refs
ABCA1	9q31.1	Observational; kindreds	Homozygous LOF	Severe deficiency	Variable	In classic Tangier disease, LDL-C levels are low, which might mitigate the association	132
		Mendelian randomization	Homozygous LOF	Reduced by 0.44 mmol/l	None	A decrease in HDL-C levels predicts increased risk of CHD (OR 1.70, 95% CI 1.56–1.85)	17
APOA1	11q23.3	Observational; kindreds	Homozygous LOF	Severely deficient to absence	Strong for premature CHD	Apolipoprotein A-I deficiency with most *APOA1* variants associated with CHD	132
CETP	16q13	Observational; kindreds	Homozygous LOF	Increased by 80–100%	Variable to none	Some families with CETP deficiency have paradoxically increased risk of CHD	133
		Mendelian randomization	Common SNPs; rare, heterozygous LOF	Increased by 20–30%	Variable	Some studies show reduced risk of CHD, especially with rare LOF variants, but meta-analyses have neutral results	35, 134
LCAT	16q22.1	Observational; kindreds	Homozygous LOF	Severe deficiency	None	LCAT deficiency or fish eye disease have multisystemic manifestations; no early CHD	132
		Mendelian randomization	Homozygous LOF (p.S208T)	Reduced by 0.21 mmol/l	None	A decrease in HDL-C levels predicts increased risk of CHD (OR 1.18, 95% CI 1.12–1.24)	51

Nat. Rev. Cardiol. 2018

Timeline for evidence between HDL-C & ASCVD





Nat. Rev. Cardiol. 2013
BBA - Molecular and Cell Biology of Lipids 2022

A causative role of HDL in CVD

Evidence in favour

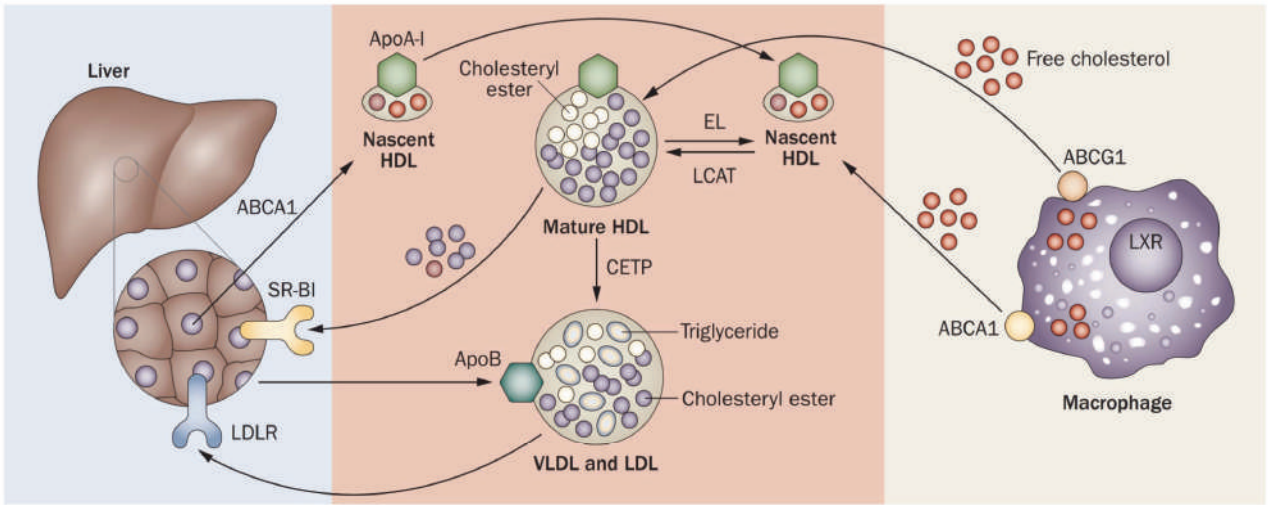
- Inverse association of HDL cholesterol level with CVD risk in epidemiological studies
- HDL has a role in reverse cholesterol transport from *in vitro* and animal studies
- HDL has pleiotropic effects *in vitro* and *ex vivo*, for example anti-inflammatory, anti-oxidative and anti-thrombotic effects
- Atherosclerosis lesion regression occurs in animals and humans after infusion of HDL or its components
- Some human genetic evidence, for example early atherosclerosis in some ApoA-I-deficient or ABCA1-deficient families
- Early clinical trials from the prestatin era of gemfibrozil and niacin
- Association between biomarkers of cholesterol efflux and CVD risk

Evidence against

- Frequent neutral relationships between rare monogenic disorders affecting HDL and CVD risk
- Negative findings in Mendelian randomization studies of the association between CVD and both common and rare genetic variants affecting HDL
- Negative findings in terms of CVD risk in clinical trials of niacin and fibrates published in the past few years
- Negative findings or deleterious effects of CETP inhibitors on CVD risk

Nat. Rev. Endocrinol. 2013; 9:308–312

HDL metabolism & reverse cholesterol transport



Nat. Rev. Cardiol. 2009

HDL cholesterol efflux capacity

- We measured cholesterol efflux capacity in 203 healthy volunteers, 442 patients with CAD, & 351 patients without CAD.
- We quantified efflux capacity by incubation of macrophages with apolipoprotein B–depleted serum from the study participants.

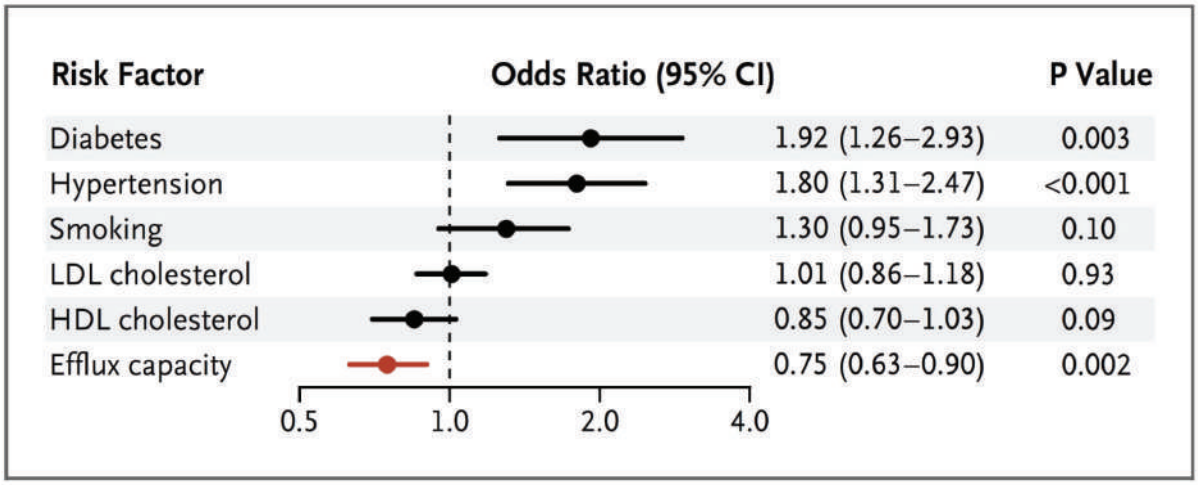
Table 3. Coronary Artery Disease Status According to Quartile of Efflux Capacity.

Variable	No. of Patients	Odds Ratio for Coronary Artery Disease (95% CI)*		
		Adjusted for Cardiovascular Risk Factors	Adjusted for Cardiovascular Risk Factors and HDL Cholesterol	Adjusted for Cardiovascular Risk Factors and Apolipoprotein A-I
Quartile 1	198	1.00	1.00	1.00
Quartile 2	198	0.75 (0.48–1.16)	0.79 (0.51–1.24)	0.77 (0.49–1.21)
Quartile 3	198	0.58 (0.37–0.89)	0.64 (0.41–1.00)	0.63 (0.40–0.99)
Quartile 4	199	0.40 (0.25–0.63)	0.48 (0.30–0.78)	0.46 (0.28–0.75)
P value for trend		<0.001	0.002	0.002

N Engl J Med 2011;364:127-35.

HDL cholesterol efflux capacity

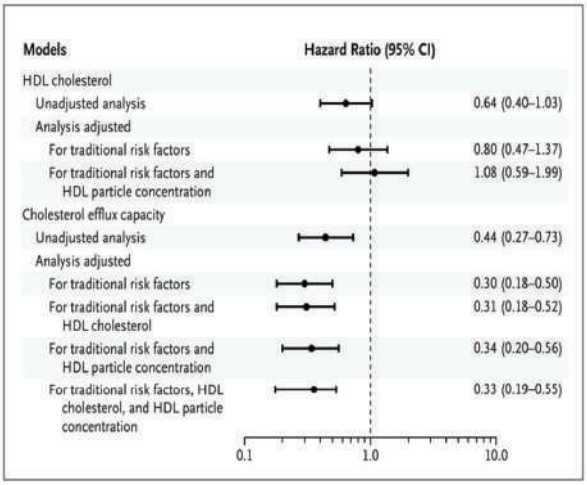
- We measured cholesterol efflux capacity in 203 healthy volunteers, 442 patients with CAD, & 351 patients without CAD.
- We quantified efflux capacity by incubation of macrophages with apolipoprotein B–depleted serum from the study participants.

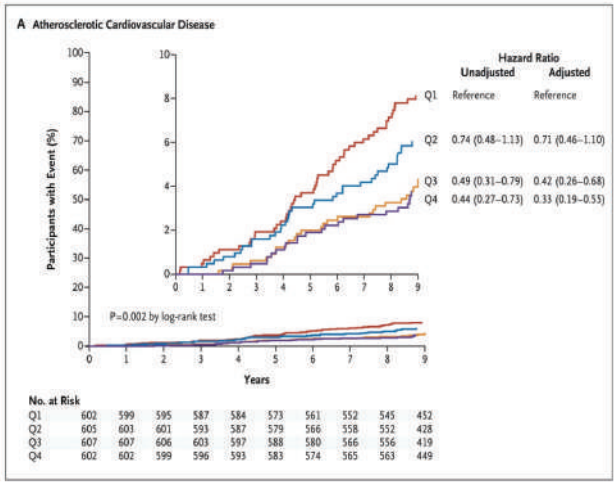


N Engl J Med 2011;364:127-35.

HDL cholesterol efflux capacity

- We measured HDL-C level, HDL particle concentration, and cholesterol efflux capacity at baseline in 2924 adults free from CVD who were participants in the Dallas Heart Study
- The primary end point was ASCVD, defined as a first nonfatal MI, nonfatal stroke, or coronary revascularization or CV death.



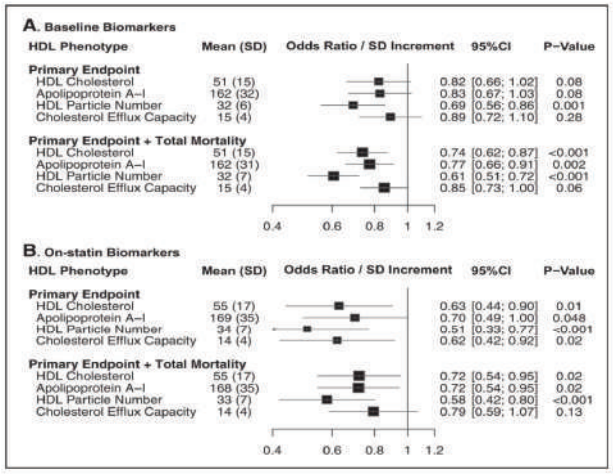


N Engl J Med 2014;371:2383-93.

HDL particles & Ischemic Events

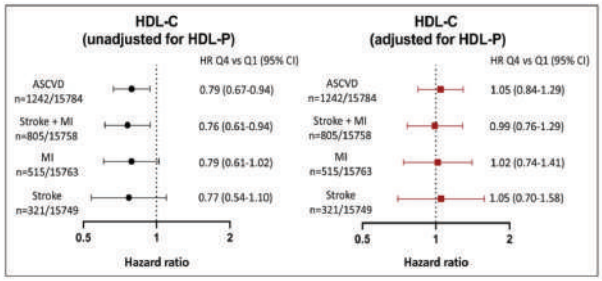
ORIGINAL RESEARCH ARTICLE

Cholesterol Efflux Capacity, High-Density Lipoprotein Particle Number, and Incident Cardiovascular Events



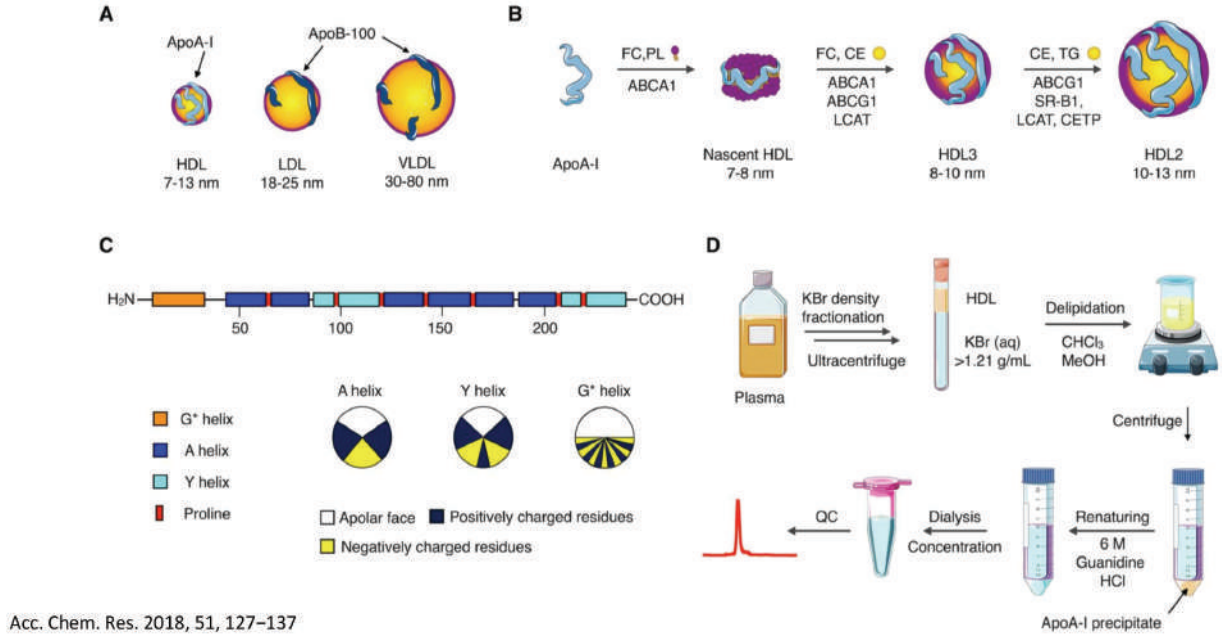
ORIGINAL RESEARCH ARTICLE

Associations Between High-Density Lipoprotein Particles and Ischemic Events by Vascular Domain, Sex, and Ethnicity



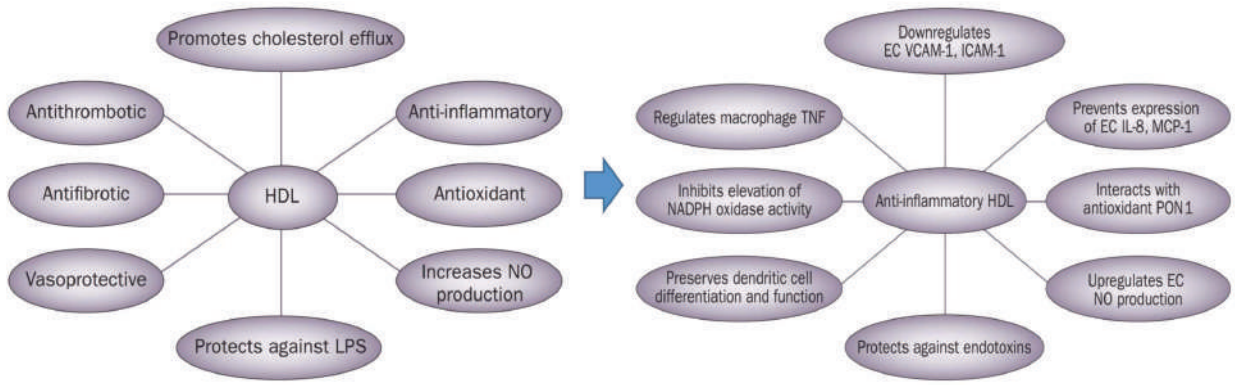
Circulation. 2017;135:2494–2504
Circulation. 2020;142:657–669

HDL particles & apoA-I structure



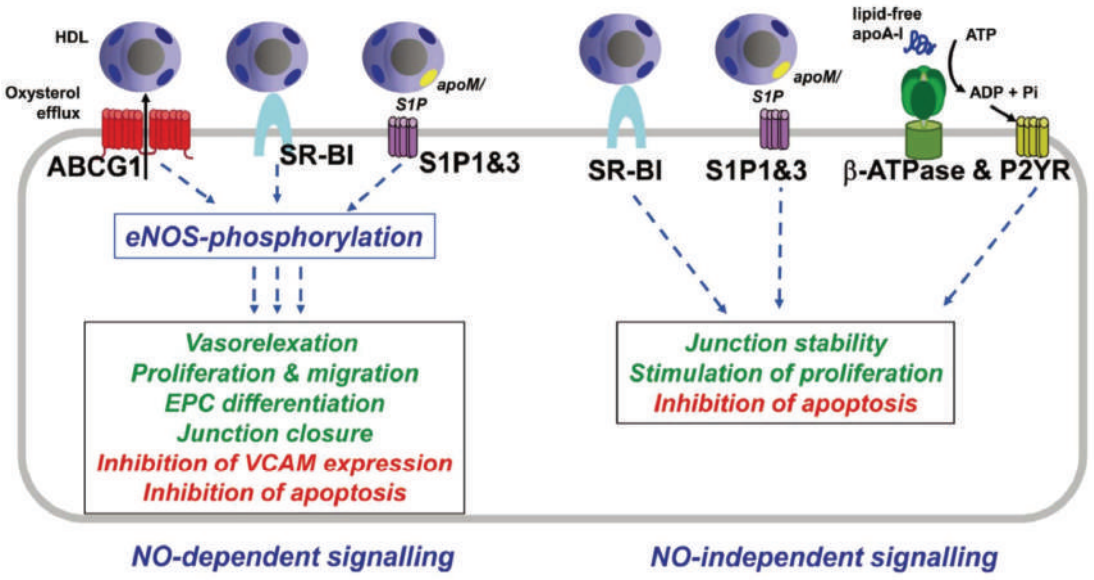
Acc. Chem. Res. 2018, 51, 127–137

HDL function & Anti-inflammatory properties



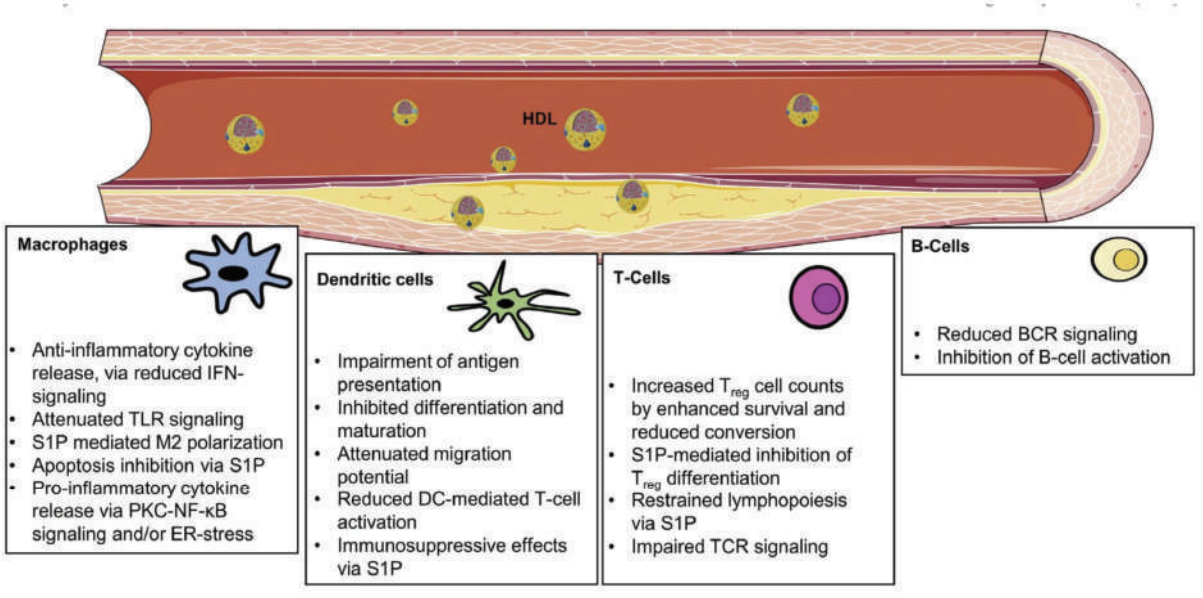
Nat. Rev. Cardiol. 2011;8: 222–232

HDLs & Endothelial function



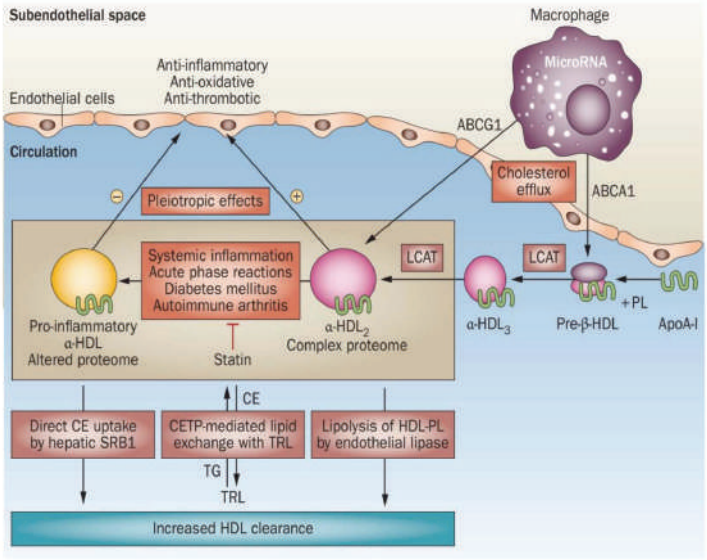
Circ J 2013; 77: 2432 - 2448

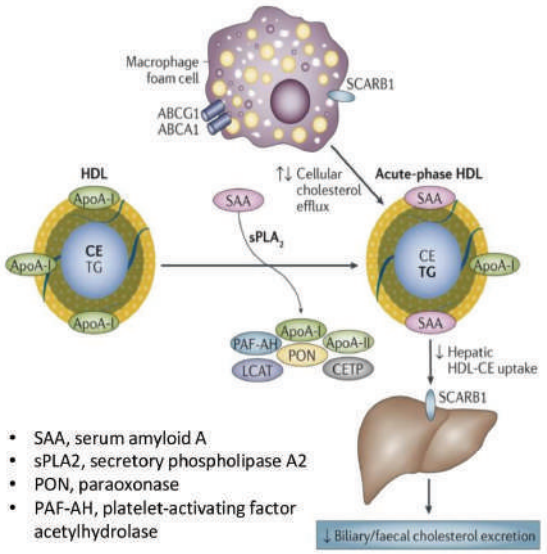
HDL & Coronary atherosclerosis



Nat. Rev. Cardiol. 2009

HDL remodelings during inflammation

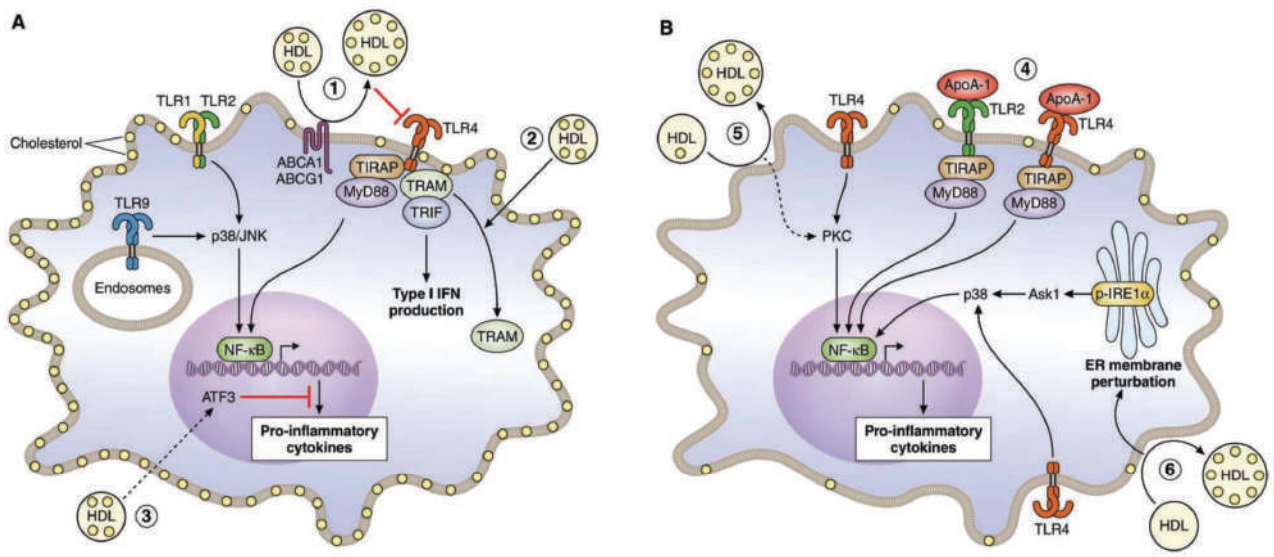




- SAA, serum amyloid A
- sPLA2, secretory phospholipase A2
- PON, paraoxonase
- PAF-AH, platelet-activating factor acetylhydrolase

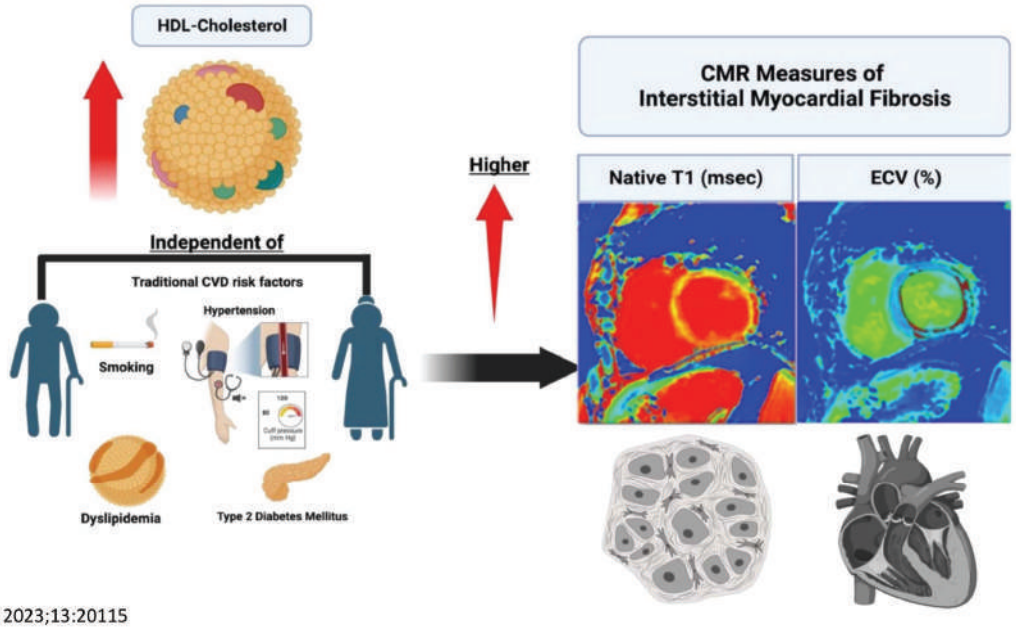
Nat. Rev. Endocrinol. 2013; 9:308–312

HDLs & Macrophages



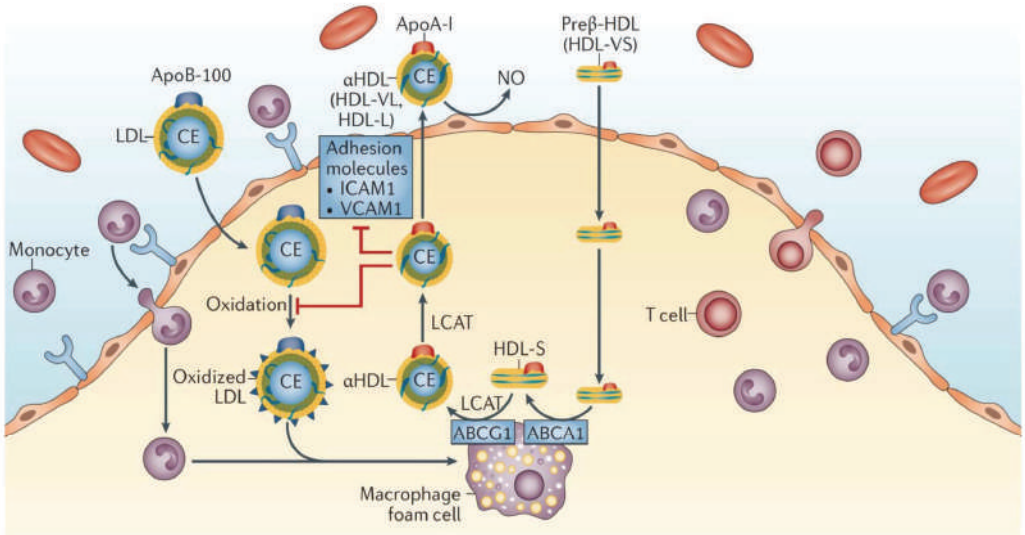
Nat. Rev. Cardiol. 2009

High HDL-C: Interstitial myocardial fibrosis



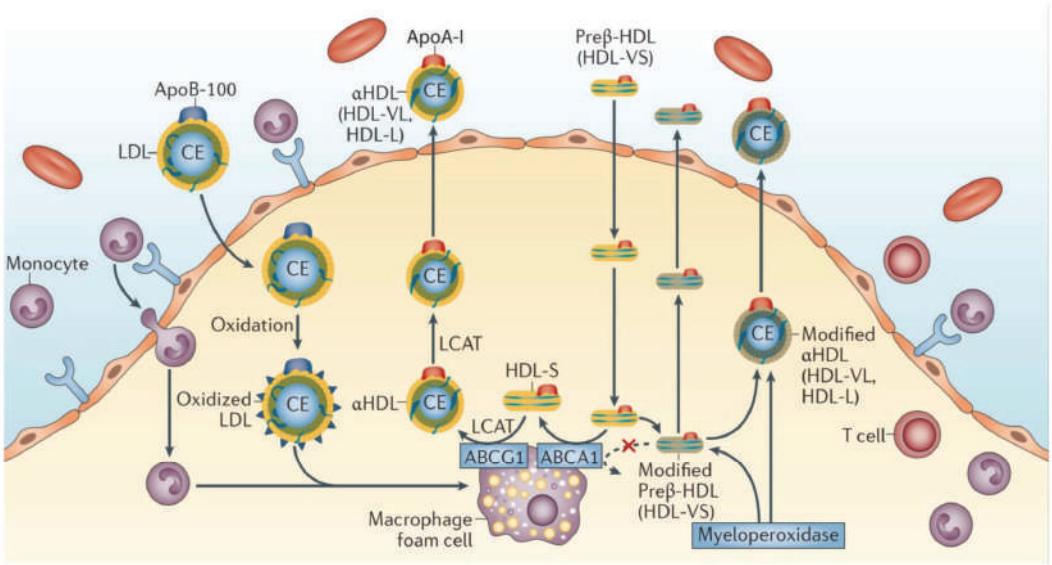
Scientific Reports 2023;13:20115

HDL & Coronary atherosclerosis – Good !



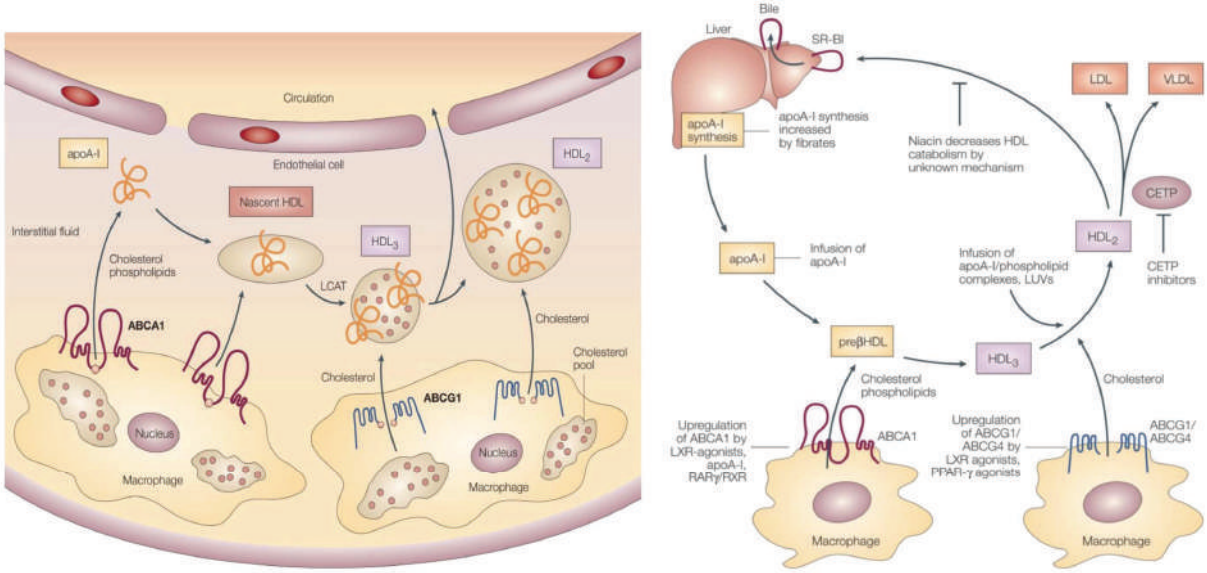
Nat. Rev. Cardiol. 2016

HDL & Coronary atherosclerosis – Bad !



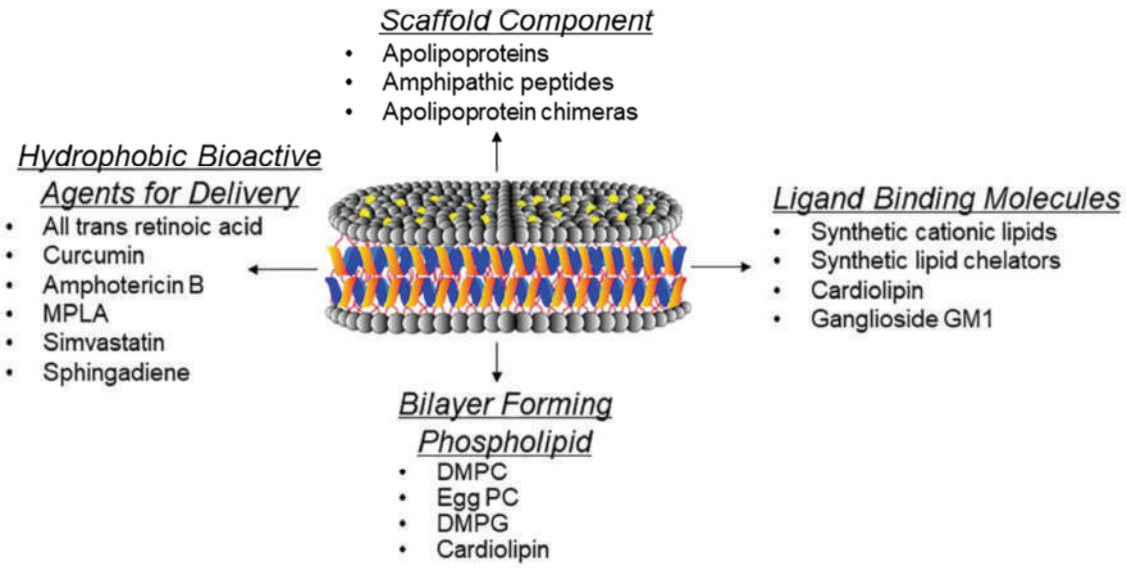
Nat. Rev. Cardiol. 2016

Therapeutic targets in HDL metabolism



Nat. Rev. Drug Discovery. 2005

Reconstituted HDL



BBA - Molecular and Cell Biology of Lipids. 2021;1866:159025

Clinical trials of reconstituted HDL

PRELIMINARY COMMUNICATION

Effects of Reconstituted High-Density Lipoprotein Infusions on Coronary Atherosclerosis

A Randomized Controlled Trial

Table 2. Intravascular Ultrasound Results

	Placebo (n = 47)	CSL-111 (Reconstituted HDL) (n = 89)
Plaque volume, mm³		
Baseline, mean (SD)	158.3 (66.3)	151.0 (64.1)
Baseline, median (IQR)	151.4 (118.2 to 201.3)	146.0 (105.2 to 195.1)
Follow-up, mean (SD)	154.6 (65.7)	147.1 (62.5)
Follow-up, median (IQR)	144.2 (116.4 to 193.3)	136.6 (98.2 to 189.5)
Median change (IQR)	−2.33 (−9.41 to 3.31)	−5.34 (−9.11 to 2.25)
P value vs baseline	.04	<.001
P value vs placebo		.39
Change in atheroma volume, %		
Median change (IQR)	−1.62 (−5.95 to 1.94)	−3.41 (−6.55 to 1.88)
P value for change	.07	<.001
P value vs placebo		.48

JAMA, 2007, Am Coll Cardiol 2010

A First-in-Man, Randomized, Placebo-Controlled Study to Evaluate the Safety and Feasibility of Autologous Delipidated High-Density Lipoprotein Plasma Infusions in Patients With Acute Coronary Syndrome

Ron Waksman, MD,* Rebecca Torguson, MPH,* Kenneth M. Kent, MD, PhD,* Augusto D. Pichard, MD,* William O. Suddath, MD,* Lowell F. Satler, MD,* Brenda D. Martin, RN,* Timothy J. Perlman, BSME,† Jo-Ann B. Maltais, PhD,† Neil J. Weissman, MD,* Peter J. Fitzgerald, MD,‡ H. Bryan Brewer, Jr, MD*†

Washington, DC, and Pleasanton and Palo Alto, California

Table 6 IVUS Parameters, With Change Defined as Post-Delipidation Treatments Minus Baseline ACS Presentation

Variable	Delipidated Group (n = 14)	Control Group (n = 12)	p Value
Total atheroma volume baseline, mm³	229.3 ± 82.5	213.4 ± 104.0	0.594
Total atheroma volume follow-up, mm³	217.1 ± 72.1	216.2 ± 102.8	0.629
Plaque burden baseline, %	45 ± 8	45 ± 8	0.899
Plaque burden follow-up, %	44 ± 9	45 ± 6	1.00
Mean max atheroma thickness baseline, mm	1.86 ± 0.34	1.7 ± 0.35	0.238
Mean max atheroma thickness follow-up, mm	1.78 ± 0.47	1.73 ± 0.36	0.859
Change in mean max atheroma thickness from baseline	−0.06 ± 0.17	0.01 ± 0.08	0.309
Atheroma volume follow-up, most diseased 10-mm subsegment	78.76 ± 22.05	80.49 ± 30.01	0.899
Change from baseline atheroma volume, most diseased 10-mm subsegment	−6.24 ± 17.94	−1.73 ± 11.21	0.494
Atheroma volume, least diseased 10-mm subsegment, baseline	50.1 ± 28.6	55.8 ± 22.3	0.494
Atheroma volume follow-up, least diseased 10-mm subsegment	49.02 ± 24.09	57.37 ± 24.12	0.325

Clinical trials of reconstituted HDL

IVUS parameter	ETC-216	CSL-111	Autologous HDL	Atorvastatin 80 mg
Duration of therapy	5 weeks	4 weeks	7 weeks	18 months
Baseline atheroma volume (mm^3)	268.4	151.0	229.3	184.4
Change in total atheroma volume (mm^3; %)	–14.1; –1.1	–5.3; –3.4	–12.2; –1.0	–0.4; –0.2

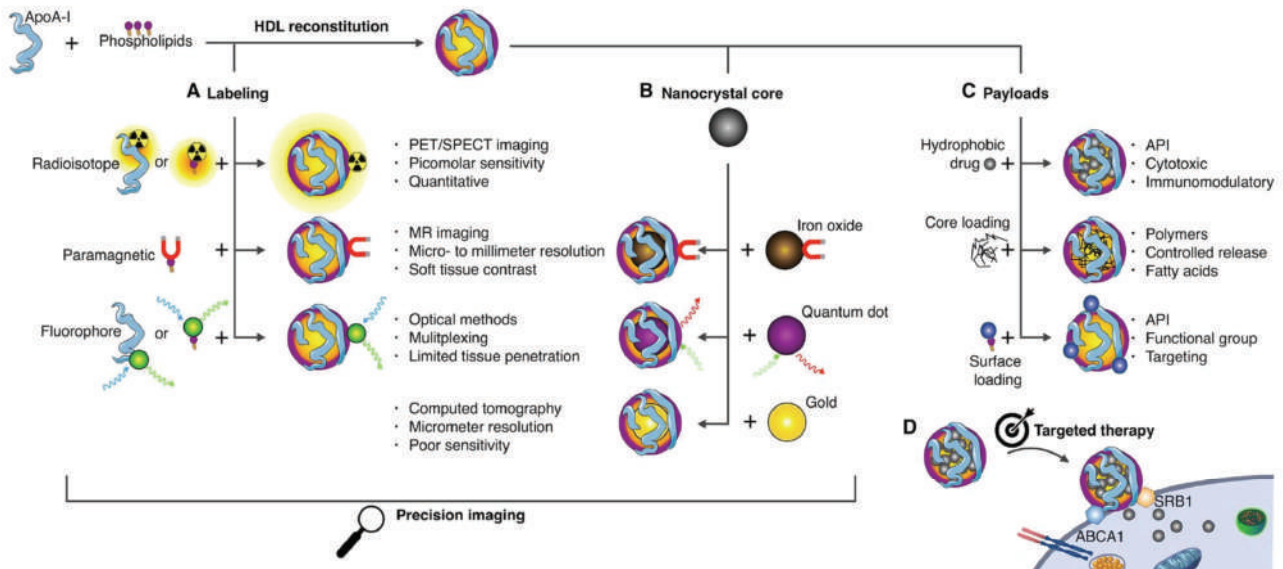
JAMA, 2007

Reconstituted HDL – Clinical trials

Study	Agent	Phase	Intervention	Population	Patient #	Primary outcome	Reference
Clin-Pharma Research AG	Soybean PC-rHDL	1	Single i/v doses of 25mg/kg or 40mg/kg	Healthy volunteers	7	Change in plasma lipoprotein levels	(Nanjee et al., 1999)
Recombinant apoA-I Milano	ETC-216	2	Placebo vs. 5 weekly infusions of 15 mg/kg or 45 mg/kg	Acute coronary syndromes (ACS)	47	% Change in atheroma volume (IVUS)	(Nissen et al., 2003)
Recombinant apo A-I Milano	ETC-216	2	Placebo vs. 5 weekly infusions of 15 mg/kg or 45 mg/kg	Acute coronary syndromes (ACS)		% Change in atheroma volume (IVUS)	(Nicholls et al., 2006)
ERASE	CSL-111	2	Placebo vs. 4 weekly infusions of 40mg/kg or 80mg/kg	Acute coronary syndromes (ACS)	60	% Change in atheroma volume (IVUS)	(Tardif et al., 2007a)
Alfred Hospital	CSL-111		Placebo vs. single infusion of 80mg/kg	Type 2 diabetes mellitus	13	Anti-inflammatory effects of plasma HDL	(Patel et al., 2009)
NCT01129661	CSL-112	1	Placebo vs. single escalating doses	Healthy volunteers	57	Safety	(Gille, A., Easton, R., Wright, S. & Shear, 2012)
NCT01281774	CSL-112		Placebo vs. multiple ascending infusions of CSL112	Healthy volunteers	36	Safety	(Gille, A., Easton, R., Wright, S. & Shear, 2012)
NCT01499420	CSL-112	2a	Placebo vs 1.7, 3.4, 6.8 g single infusion of CSL112	Stable atherothrombotic disease	33	Alanine aminotransferase (ALT), aspartate aminotransferase (AST)	(Tricoci et al., 2013)
NCT01201837	CER-001	2	Placebo vs. 6 weekly infusions of 3 mg/kg, 6 mg/kg, or 12 mg/kg of CER-001	Acute coronary syndromes (ACS)	~400	%Changes in atheroma volume (IVUS) and coronary scores (QCA) ultrasonography	(Tardif et al., 2014)
CHI-SQUARE	CER-001	2	Placebo vs. biweekly infusions of CER-001 for 24 weeks	Homozygous familial hypercholesterolemia	30	% Change in total carotid plaque volume (MRI)	(Tardif et al., 2014)
NCT01499420	CSL-112	2a	Placebo vs CSL-112 (single escalating i/v doses)	Stable atherothrombotic disease	40	Safety	Dr Russell Basser, CSL Limited, 2014 (no publications provided)
NCT01281774	CSL-112	1	Placebo vs. multiple ascending infusions of CSL112	Healthy volunteers	36	Safety	(Easton et al., 2014)
CER-001 in FPHA patients	CER-001	2	Open-label uncontrolled study, 20 infusions of CER-001 (8 mg/kg) over 6 months	Familial hypoalphalipoproteinemia (FPHA) deficiencies		plasma-mediated cellular cholesterol efflux, fecal sterol excretion (FSE), carotid artery wall dimension (MRI) and artery wall inflammation by (^{18})F-fluorodeoxyglucose-positron emission tomograhy/computed tomography scans	(Kootte et al., 2015)
MODE	CER-001	2	Placebo vs. biweekly infusion of CER-001 for 24 weeks	Homozygous familial hypercholesterolemia	30	% Change in total carotid plaque volume (MRI)	(Hovingh et al., 2015)

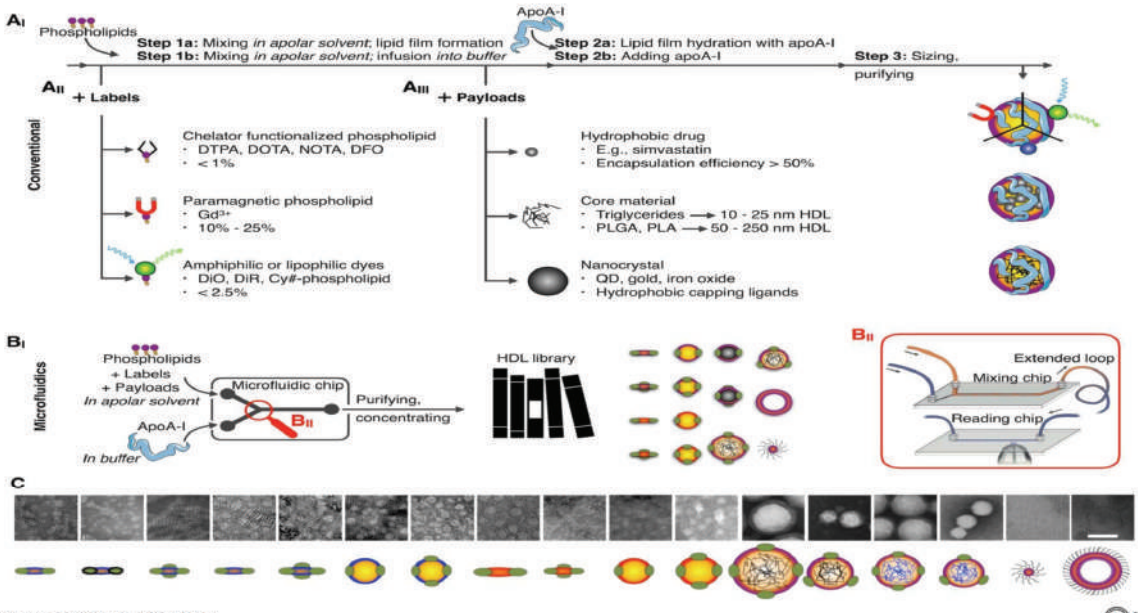
Pharmacology & Therapeutics 2016;157: 28–42

HDL nanobiologic platform technology



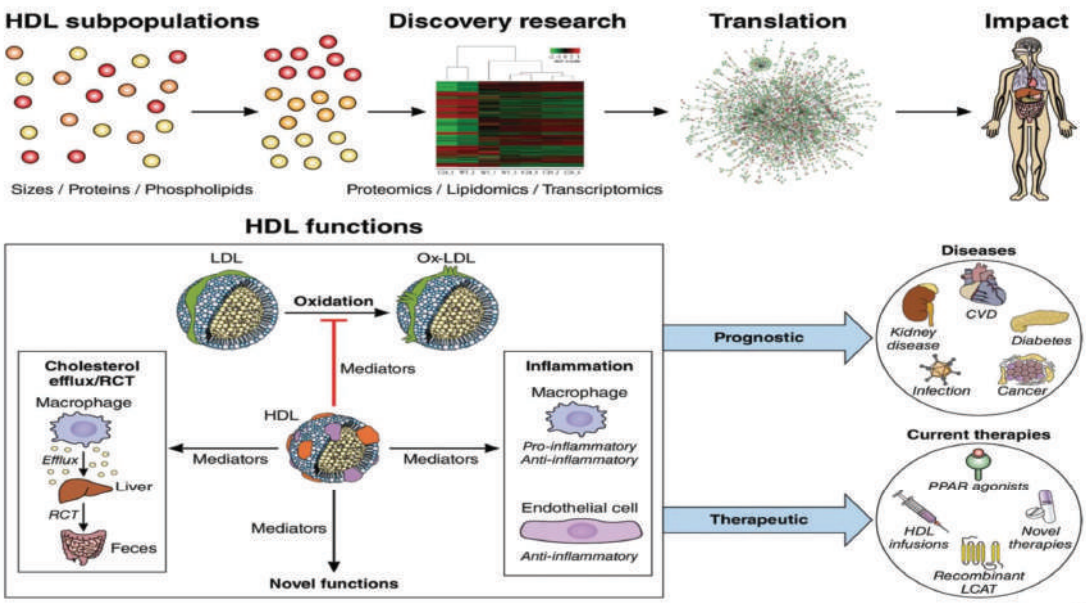
Acc. Chem. Res. 2018, 51, 127−137

HDL nanobiologics production



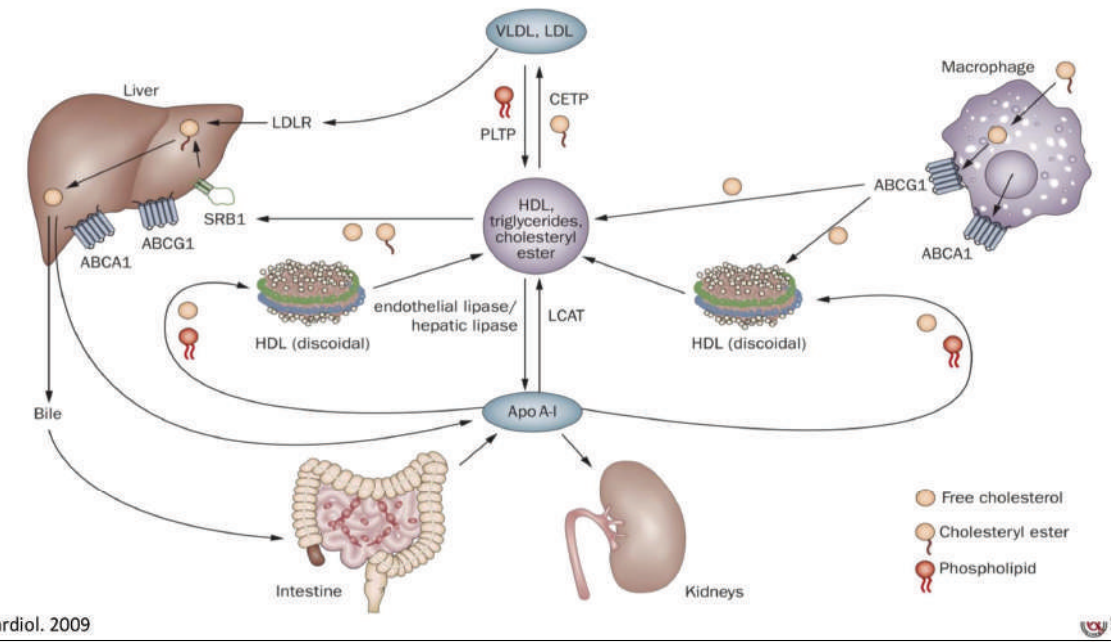
Acc. Chem. Res. 2018, 51, 127−137

HDL: Future direction



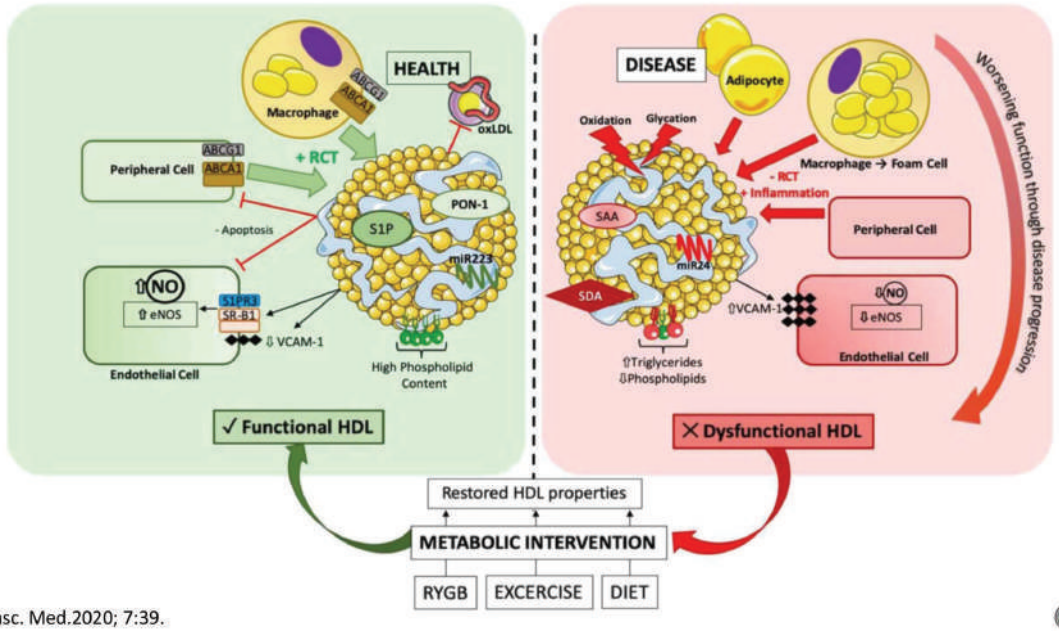
Nat. Rev. Cardiol. 2009

Take Home Message 1: HDL reverse cholesterol transport



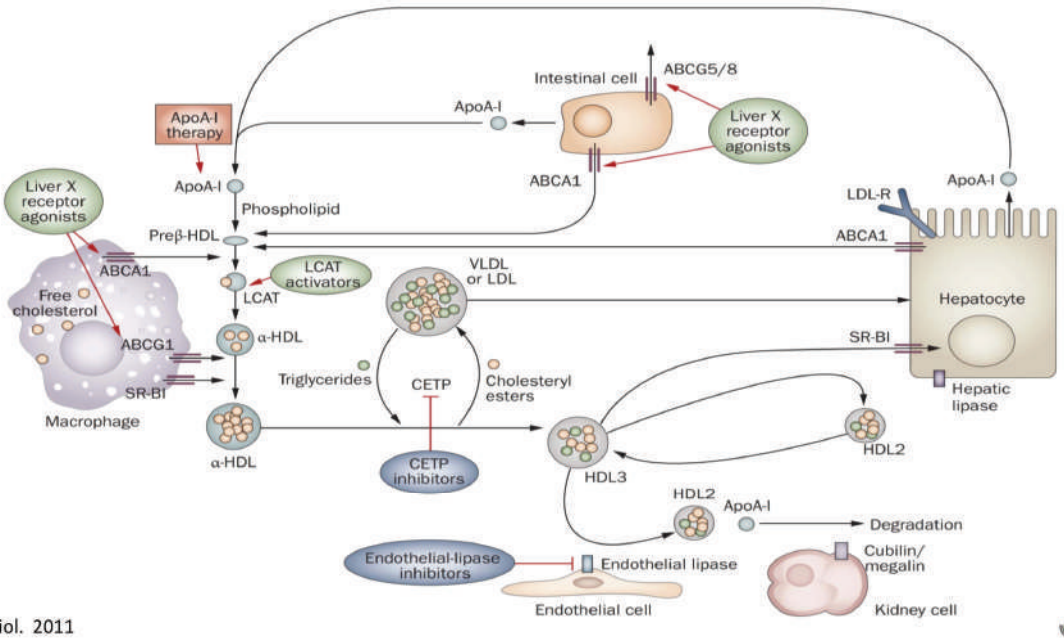
Nat. Rev. Cardiol. 2009

Take Home Message 2: Improving HDL functionality



Front. Cardiovasc. Med.2020; 7:39.

Take Home Message 3: Therapeutic targets in HDL metabolism



Nat. Rev. Cardiol. 2011


Thank you.

조 성 준

[기본정보]

성함	조 성 준
소속(근무처)	성균관의대 강북삼성병원 정신건강의학과

[학력]

해당년도	세부사항
2007	차의과학대학교 졸업
2010	차의과학대학교 대학원 석사 졸업
2019	차의과학대학교 대학원 박사 졸업

[경력]

해당년도	세부사항
2008-2012	차의과학대학교 분당차병원 정신건강의학과 전공의
2015-2019	서울대학교병원 정신건강의학과 전임의 및 진료조교수
2019-	성균관의대 강북삼성병원 정신건강의학과

[관심분야]

사회정신의학, 기분장애, 공황장애, 조현병

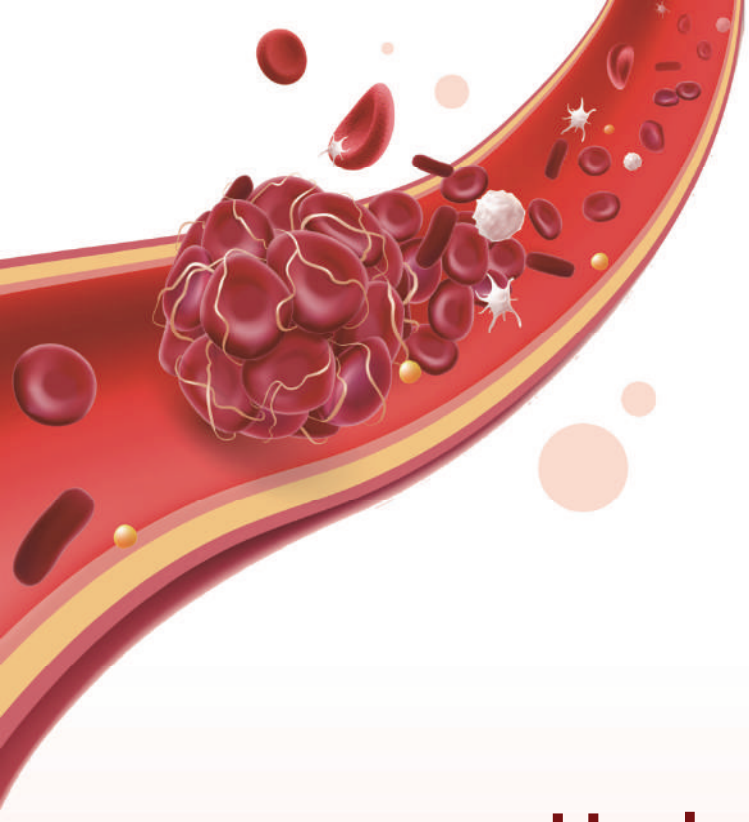
[논문]

Psychological Distress Trends and Effect of Media Exposure Among Community Residents After the Seoul Halloween Crowd Crush (2024) JKMS, correspond
Medication burden reduction and early clinical benefit through aripiprazole once monthly in schizophrenia patients with polypharmacy (2024) Progress in Neuropsychopharmacology and Biological Psychiatry, correspond
The gender difference of moderated mediating effect of grit between occupational stress and suicidal ideation in Korean workers (2024) JKMS, correspond
Sex Differences in the Association between Prolonged Sitting Time and Anxiety Prevalence among Korean Adults (2024) Brain Science, correspond
Exploring the Association between Elevated Anxiety Symptoms and Low Skeletal Muscle Mass among Asymptomatic Adults: A Population-Based Study in Republic of Korea (2024) Brain Science, correspond

Humanities Lecture

조 성 준

성균관의대 정신건강의학과



Day 2

Session 1

Understanding of Severe Dyslipidemia

(09:00 – 10:20)

09:00 – 09:30	Key Points You Need to Know About FH	이상학 (연세의대 심장내과)
09:30 – 10:00	Insights into the Etiology, Diagnosis, and Treatment of Severe Hypertriglyceridemia	정인경 (경희의대 내분비내과)
10:00 – 10:20	토론	

1st Lipid Academy

한국지질·동맥경화학회 제1회 Lipid Academy

이 상 학

[기본정보]

성함	이 상 학
소속(근무처)	연세의대 심장내과

[학력]

해당년도	세부사항
1988-1994	연세의대 학사
1997-1999	연세대 대학원 석사
2002-2005	연세대 대학원 박사

[경력]

해당년도	세부사항
2003-2006	한림의대 강남성심병원
2007-현재	연세의대 세브란스병원
2010-2012	미국 UCSD 방문연구원

[관심분야]

예방심장학, 지단백 대사, 심혈관 유전학

[논문]

Kim J, et al. Statin therapy in individuals with intermediate cardiovascular risk. Metabolism 2024;150:155723
An DB, et al. Hepatic Cdkal1 deletion regulates HDL catabolism and promotes reverse cholesterol transport. Atherosclerosis 2023;375:21-29
Lee CJ, et al. Cardiovascular risk and treatment outcomes in severe hypercholesterolemia: a nationwide cohort study. J Am Heart Assoc 2022;11:e024379
Ann SJ, et al. Role of lncRNA HSPA7 in human atherosclerotic plaque in sponging miR-223 and promoting proinflammatory vascular smooth muscle cell transition. Exp Mol Med 2021;53:1842-1849.
Roh JW, et al. Pravastatin versus fluvastatin after statin intolerance: the PRUV-Intolerance study with propensity score matching. Am J Med 2019;132:1320-1326

Key Points You Need to Know About FH

이 상 학

연세의대 심장내과

정 인 경

[기본정보]

성함	정 인 경
소속(근무처)	경희의대 강동경희대학교병원 내분비대사내과

[학력]

해당년도	세부사항
1988.3-1994.2	경희대학교 의과대학 의학사
1995.3-1997.2	경희대학교 대학원 의학석사
1997.3-1999.2	경희대학교 대학원 의학박사

[경력]

해당년도	세부사항
2008.3-2009.7	Harvard University Joslin Diabetes Center visiting researcher
2015.3-현재	경희대학교 부속 강동경희대학교병원 내과 교수
2022.3-2024.7	경희대학교 부속 강동경희대학교병원 내과 부장
2024.8-현재	경희대학교 부속 강동경희대학교병원 연구부원장

[관심분야]

- Glucose and lipid metabolism (탄수화물 및 지방대사) - Vascular biology and diabetic vascular complication (당뇨병 혈관합병증 연구)
- Non-alcoholic fatty liver disease and energy metabolism (지방간 연구) - Pancreatic beta cell biology and insulin secretion (베타세포 연구)

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2. Jeong IK, Han A, Jun JE, Hwang YC, Ahn KJ, Chung HY, Kang BS, Choung SY. A Compound Containing Aldehyde Dehydrogenase Relieves the Effects of Alcohol Consumption and Hangover Symptoms in Healthy Men: An Open-Labeled Comparative Study. Pharmaceuticals (Basel). 2024 Aug 20;17(8):1087. doi: 10.3390/ph17081087. PMID: 39204192; PMCID: PMC11357502.
3. Jeong IK. Letter by In-Kyung Jeong Regarding Article, Trends in Prevalence of Hypertriglyceridemia and Related Factors in Korean Adults: A Serial Cross-Sectional Study. J Lipid Atheroscler2024 Jan;13(1):80-81.
4. Kim HJ, Noh JH, Moon MK, Choi SH, Ko SH, Rhee EJ, Hur KY, Jeong IK. A Multicenter, Randomized, Open-Label Study to Compare the Effects of Gemigliptin Add-on or Escalation of Metformin Dose on Glycemic Control and Safety in Patients with Inadequately Controlled Type 2 Diabetes Mellitus Treated with Metformin and SGLT-2 Inhibitors (SO GOOD Study). J Diabetes Res. 2024 Jan 5;2024:8915591
5. Yang YS, Kim NH, Baek JH, Ko SH, Son JW, Lee SH, Rhee SY, Kim SK, Sohn TS, Jun JE, Jeong IK, Kim CH, Song K, Rhee EJ, Noh J, Hur KY; Committee of Clinical Practice Guidelines, Korean Diabetes Association. Real-World Treatment Patterns according to Clinical Practice Guidelines in Patients with Type 2 Diabetes Mellitus and Established Cardiovascular Disease in Korea: Multicenter, Retrospective, Observational Study. Diabetes Metab J. 2024 Mar;48(2):279-289.

Insights into the Etiology, Diagnosis, and Treatment of Severe Hypertriglyceridemia

정 인 경

경희의대 내분비내과

Contents

Definition of hypertriglyceridemia

Korean guidelines for dyslipidemia management

Risk	Triglyceride
Very High	≥ 500
High	200~499
Border-line	150~199
Optimal	< 150

Clinical Practice Guideline of Korean Society of Lipid and Atherosclerosis

Consensus of European atherosclerosis society

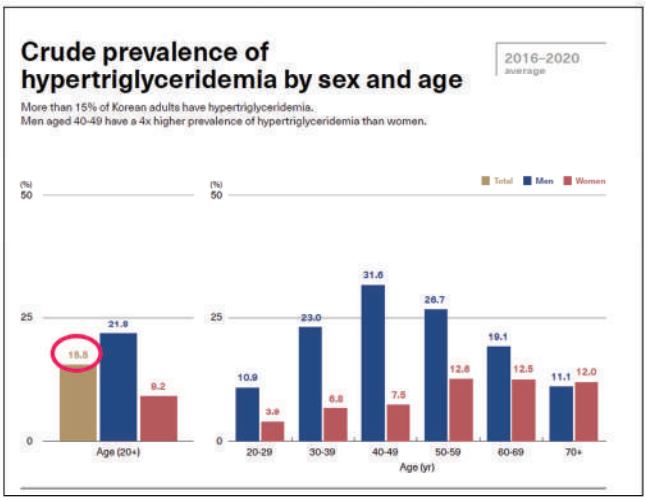
Category	Triglyceride level mmol/L (mg/dL)
Optimal	<1.2 (<~100)
Borderline	1.2–1.7 (100–150)
Moderately elevated	1.7–5.7 (150–500)
Severe	5.7–10.0 (500–880)
Extreme	>10 (>880)

Henry Ginsberg et al. European Heart Journal (2021) 42, 4791–4806

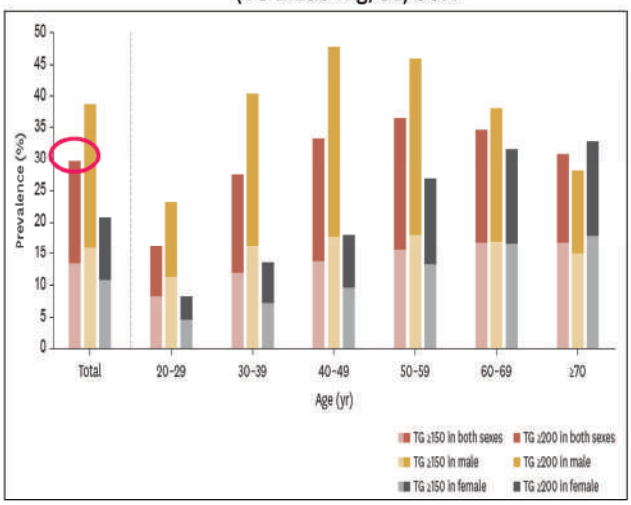
Prevalence of hypertriglyceridemia in Korea

KNHANES data

(TG≥200 mg/dL) 15.5%



(TG ≥ 150 mg/dL) 30%



Jeong IK et al J Lipid Atheroscler. 2023 Sep;12(3):237-251

Prevalence of hypertriglyceridemia (TG>150 mg/dL) in USA

NHANES 2007–2014

Table 1 Weighted prevalence of TG levels ≥ 150 mg/dl among adults ≥ 20 years of age in NHANES 2007–2014

	Prevalence, %	Patients with TG levels ≥ 150 mg/dl, millions[a]	Total number of patients, millions[a]
Overall	25.9	56.9	219.9
Statin treated	31.6	12.3	38.9
Statin treated and LDL-C < 100 mg/dl	27.6	6.0	21.7
Statin treated and diabetes	39.5	4.9	12.4
Statin treated and ASCVD	30.5	3.1	10.1
Statin treated and diabetes or ASCVD	34.4	6.4	18.6

ASCVD atherosclerotic cardiovascular disease, *LDL-C* low-density lipoprotein cholesterol, *NHANES* National Health and Nutrition Examination Survey, *TG* triglyceride

[a] Projected number of US adults

Cardiol Ther (2020) 9:207–213

Epidemiology of severe hypertriglyceridemia

	Plasma TG concentration		Prevalence
	mmol/L	mg/dL	
Normal	< 1.7	< 150	
Mild to moderate	2.0 – 9.9	177- 884	common (obesity, T2DM)
Severe[1]	> 10	> 885	0.1-0.2%
Very severe[2]	> 20	> 1770	0.014%

1. J Clin Lipidol 2019;13:80–88.2. J Clin Lipidol 2019;13:89–99.

Contents

1. Current status of hypertriglyceridemia
2. Etiology
3. Clinical relevance of TG, TRL, and remnants
4. Diagnosis
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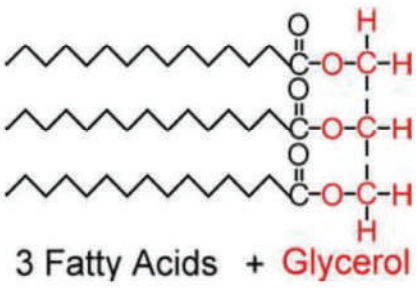
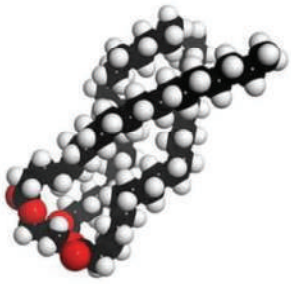
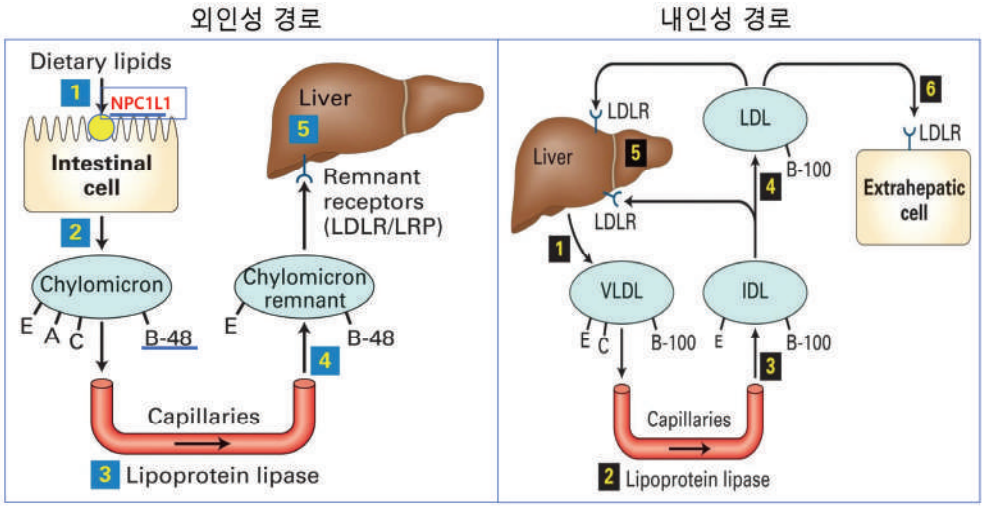
Triglycerides ?





Sources of triglycerides



Related factors with hypertriglyceridemia in Korea

KNHANES data

- Obesity
- Diabetes
- Alcohol drinking
- Smoking status
- Low income status

Table 2. Prevalence of age- and sex-specific hypertriglyceridemia (95% confidence intervals) according to smoking status, alcohol drinking pattern, and exercise

Variables	Age groups (yr)	Current smoking		High-risk alcohol drinking		Regular exercise	
		Male	Female	Male	Female	Male	Female
No	20–29	18.6 (15.4–21.8)	8.8 (6.7–10.9)	19.7 (16.5–22.8)	7.7 (5.9–9.6)	21.4 (16.4–26.4)	9.3 (6.5–12.1)
	30–39	34.5 (30.6–38.4)	15.7 (13.2–18.2)	38.4 (34.9–41.8)	14.7 (12.4–17.1)	43.5 (38.5–48.5)	15.3 (12.4–18.3)
	40–49	45.4 (41.5–49.3)	15.4 (13.3–17.6)	46.4 (43.1–49.8)	15.3 (13.2–17.5)	53.8 (49.7–57.9)	16.8 (13.8–19.7)
	50–59	41.0 (37.4–44.6)	23.9 (21.6–26.1)	42.5 (39.1–45.8)	24.1 (21.8–26.3)	48.8 (45.1–52.6)	24.8 (21.8–27.9)
	60–69	33.1 (29.9–36.3)	26.7 (24.3–29.0)	34.4 (31.3–37.6)	27.0 (24.6–29.3)	40.1 (36.0–44.1)	31.1 (28.0–34.2)
	≥70	24.6 (21.7–27.5)	27.2 (24.6–29.9)	25.0 (22.2–27.9)	27.3 (24.7–29.9)	25.5 (21.9–29.2)	27.3 (24.1–30.5)
Yes	20–29	27.2 (21.8–32.6)	9.5 (3.8–15.2)	33.5 (25.2–41.7)	18.3 (10.1–26.5)	21.9 (18.3–25.5)	8.7 (6.0–11.4)
	30–39	50.6 (45.1–56.2)	18.1 (10.6–25.6)	49.8 (42.5–57.0)	27.8 (19.3–36.4)	38.0 (33.7–42.4)	16.9 (13.3–20.5)
	40–49	56.8 (52.5–61.2)	21.9 (13.3–30.6)	60.0 (54.3–65.6)	22.4 (14.9–30.0)	45.4 (41.0–49.9)	15.4 (12.4–18.3)
	50–59	56.7 (51.8–61.5)	40.9 (28.0–53.7)	61.1 (55.4–66.8)	34.4 (22.7–46.1)	43.3 (38.6–48.1)	24.3 (20.8–27.8)
	60–69	47.6 (42.3–52.9)	37.5 (23.4–51.7)	48.3 (41.7–54.9)	33.2 (18.3–48.1)	34.0 (29.8–38.1)	19.5 (16.2–22.9)
	≥70	35.5 (27.5–43.4)	33.4 (16.9–49.9)	41.4 (31.0–51.7)	7.1 (6.8–21.0)	27.4 (22.6–32.2)	23.7 (19.0–28.5)

Table 1. Prevalence of sex-specific hypertriglyceridemia (95% confidence intervals) according to income and education level

Variables	Male	Female
Income		
Quartile 1	41.2 (36.0–46.4)	20.5 (17.0–24.1)
Quartile 2	38.3 (35.5–41.0)	19.1 (17.3–21.0)
Quartile 3	39.2 (36.9–41.5)	18.2 (16.4–20.0)
Quartile 4	36.8 (34.6–39.0)	15.7 (13.9–17.5)
p for trends	0.040	<0.001
Education		
≤Elementary school	43.1 (18.1–68.0)	24.4 (14.7–34.1)
Middle school graduate	45.3 (34.1–56.4)	26.4 (18.6–34.1)
High school graduate	38.9 (36.5–41.2)	17.5 (15.7–19.2)
≥University graduate	38.3 (36.4–40.2)	16.5 (14.8–18.2)
p for trends	0.038	<0.001

The prevalence was calculated using the direct standardization method based on a 2005 population projection.

Table 3. Prevalence of age- and sex-specific hypertriglyceridemia (95% confidence intervals) according to presence of obesity, abdominal obesity, hypertension, and diabetes mellitus

Variables	Age groups (yr)	Obesity		Abdominal obesity		Hypertension		Diabetes mellitus	
		Male	Female	Male	Female	Male	Female	Male	Female
No	20–29	15.0 (11.8–18.3)	5.4 (3.6–7.3)	16.2 (13.0–19.4)	6.2 (4.4–8.0)	20.9 (17.8–23.9)	8.6 (6.6–10.6)	21.1 (18.0–24.1)	8.2 (6.3–10.1)
	30–39	28.2 (24.0–32.4)	9.2 (7.0–11.4)	30.3 (26.3–34.3)	9.0 (6.9–11.2)	36.7 (33.2–40.1)	14.3 (12.1–16.5)	39.1 (35.8–42.5)	14.7 (12.4–17.0)
	40–49	38.3 (34.4–42.3)	10.9 (8.9–12.8)	40.3 (36.6–44.0)	11.9 (10.0–13.9)	44.9 (41.4–48.5)	14.3 (12.1–16.4)	47.7 (44.7–50.8)	14.7 (12.7–16.7)
	50–59	39.3 (35.4–43.3)	18.9 (16.4–21.3)	39.2 (35.5–42.9)	19.5 (17.0–22.0)	42.1 (38.4–45.7)	21.9 (19.2–24.5)	44.3 (41.1–47.5)	22.5 (20.2–24.7)
	60–69	34.1 (30.4–37.7)	22.7 (19.9–25.5)	30.2 (26.6–33.7)	22.8 (19.9–25.7)	32.1 (28.2–36.0)	24.6 (21.6–27.7)	34.5 (31.4–37.7)	24.8 (22.3–27.4)
	≥70	23.1 (19.6–26.6)	23.2 (20.1–26.4)	19.7 (16.4–23.0)	20.9 (17.2–24.6)	25.9 (21.4–30.4)	27.9 (23.7–32.2)	24.6 (21.2–27.9)	25.2 (22.3–28.1)
Yes	20–29	32.1 (26.6–37.5)	23.7 (17.5–29.9)	37.6 (30.8–44.4)	30.2 (20.9–39.5)	33.4 (22.0–44.7)	22.5 (6.2–38.9)	45.7 (1.6–89.7)	51.5 (13.6–89.5)
	30–39	52.0 (47.6–56.3)	38.4 (32.5–44.4)	55.7 (50.7–60.6)	44.1 (37.1–51.1)	61.0 (53.2–68.8)	51.4 (37.8–65.0)	63.1 (46.4–79.9)	73.8 (55.6–92.0)
	40–49	63.2 (59.1–67.4)	29.7 (24.5–34.9)	64.2 (59.8–68.6)	30.3 (24.4–36.2)	62.3 (56.8–67.7)	27.9 (21.1–34.6)	68.2 (59.8–76.6)	45.3 (32.2–58.5)
	50–59	56.8 (52.3–61.3)	37.4 (33.0–41.9)	58.4 (54.0–62.8)	37.3 (32.7–41.9)	54.7 (50.1–59.4)	31.1 (26.6–35.7)	58.3 (51.6–65.0)	43.2 (34.6–51.8)
	60–69	41.2 (36.7–45.6)	34.5 (30.3–38.7)	46.7 (42.2–51.1)	32.2 (28.4–36.1)	42.5 (38.5–46.6)	29.3 (25.8–32.9)	42.9 (37.2–48.7)	36.9 (30.7–43.2)
	≥70	33.3 (28.0–38.6)	33.6 (29.9–37.4)	33.9 (29.2–38.6)	33.2 (29.8–36.5)	31.3 (25.7–36.8)	33.5 (28.5–38.5)	26.3 (22.8–29.8)	27.1 (24.3–30.0)

Causes of hypertriglyceridemia

Primary causes

A. Severe HTG (TG >10 mmol/L)

Monogenic chylomicronaemia (formerly HLP Type 1 or familial chylomicronaemia syndrome)
- Lipoprotein lipase deficiency (Bi-allelic *LPL* gene mutations)
- Apo C-II deficiency (Bi-allelic *APOC2* gene mutations)
- Apo A-V deficiency (Bi-allelic *APOA5* gene mutations)
- Lipase maturation factor 1 deficiency (Bi-allelic *LMF1* gene mutations)
- GPIHBP1 deficiency (Bi-allelic *GPIHBP1* gene mutations)

Multifactorial or polygenic chylomicronaemia (formerly HLP Type 5 or mixed hyperlipidaemia)
- Complex genetic susceptibility, including
- Heterozygous rare large-effect gene variants for monogenic chylomicronaemia (see above); and/or
- Accumulated common small-effect TG-raising polymorphisms (e.g. numerous GWAS loci including *APOA1-C3-A4-A5; TRIB1, LPL, MLXIPL, GCKR, FADS1-2-3, NCAN, APOB, PLTP, ANGPTL3*)
- Other
  - Transient infantile HTG (glycerol-3-phosphate dehydrogenase 1 deficiency) from bi-allelic *GPD1* gene mutations

B. Mild-to-moderate HTG (TG 2.0–9.9 mmol/L)

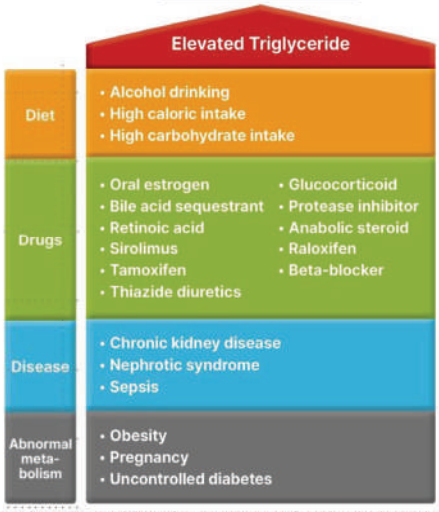
Multifactorial or polygenic HTG (formerly HLP Type 4 or familial HTG)
- Complex genetic susceptibility (see above)

Dysbetalipoproteinaemia (formerly HLP Type 3 or dysbetalipoproteinaemia)
- Complex genetic susceptibility (see above), plus
- *APOE* E2/E2 homozygosity or
- *APOE* dominant rare variant heterozygosity

Combined hyperlipoproteinaemia (formerly HLP Type 2B or familial combined hyperlipidaemia)
- Complex genetic susceptibility (see above), plus
- Accumulation of common small effect LDL-C-raising polymorphisms

Laufs U et al Eur Heart J 2020;41, 99

Secondary causes



Clinical Practice Guideline of Korean Society of Lipid and Atherosclerosis

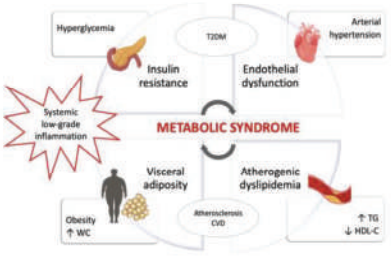
High TG = Insulin resistance => Metabolic syndrome

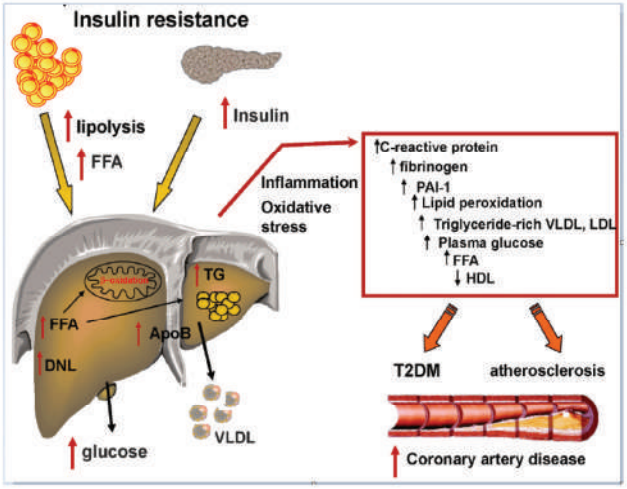
Hypertriglyceridemia, Insulin Resistance, and the Metabolic Syndrome

Scott M. Grundy, MD, PhD

The metabolic syndrome consists of a cluster of metabolic disorders, many of which promote the development of atherosclerosis and increase the risk of cardiovascular disease events. Insulin resistance may lie at the heart of the metabolic syndrome. Elevated serum triglycerides commonly associate with insulin resistance and represent a valuable clinical marker of the metabolic syndrome. Abdominal obesity is a clinical marker for insulin resistance. The metabolic syndrome manifests 4 categories of abnormality: atherogenic dyslipidemia (elevated triglycerides, increased small low-density lipoproteins, and decreased high-density lipoproteins), increased blood pressure, elevated plasma glucose, and a prothrombotic state. Various therapeutic approaches for the patient with the metabolic syndrome should be implemented to decrease the risk of cardiovascular disease events. These interventions include decreasing obesity, increasing physical activity, and managing dyslipidemia; the latter may require the use of pharmacotherapy with cholesterol-lowering and triglyceride-lowering drugs. ©1999 by Excerpta Medica, Inc.

Am J Cardiol 1999;83:25F–29F





Scott M. Grundy, Am J Cardiol 1999;83:25F–29F, Noce A, Nutrients 2021, 13, 630

Gaggini M et al, Nutrients 2013, 5, 1544-1560

Major Apolipoproteins

Apo	Primary source	Location	Funciton	Atherosclerosis
A-I	Intestine, liver	HDL, CM	Core structural protein for HDL, promotes cellular lipid efflux via ABCA1, activates LCAT	↓↓↓
A-II	liver	HDL, CM	Structural protein for HDL	↓?
A-V	liver	VLDL, CM	Promote LPL-mediated triglyceride lipolysis	↓?
B-48	Intestine	CM, CM remnants,	Core structural protein for CM, Exogeous pathway	↑?
B-100	liver	VLDL, IDL, LDL, LP(a)	Core structural protein for VLDL, LDL, IDL, Lp(a); ligand for binding to LDL receptor	↑↑↑
C-II	liver	CM, VLDL, HDL	Cofactor for LPL, LPL activity ↑	↓
C-III	Intestine, liver	CM, VLDL, HDL	LPL activity ↓	↑
E	liver	CM remnants, IDL, HDL	Ligand for binding to LDL receptor and other receptors	↓?
(a)	liver	Lp(a)	Structural protein for Lp(a)	↑↑↑

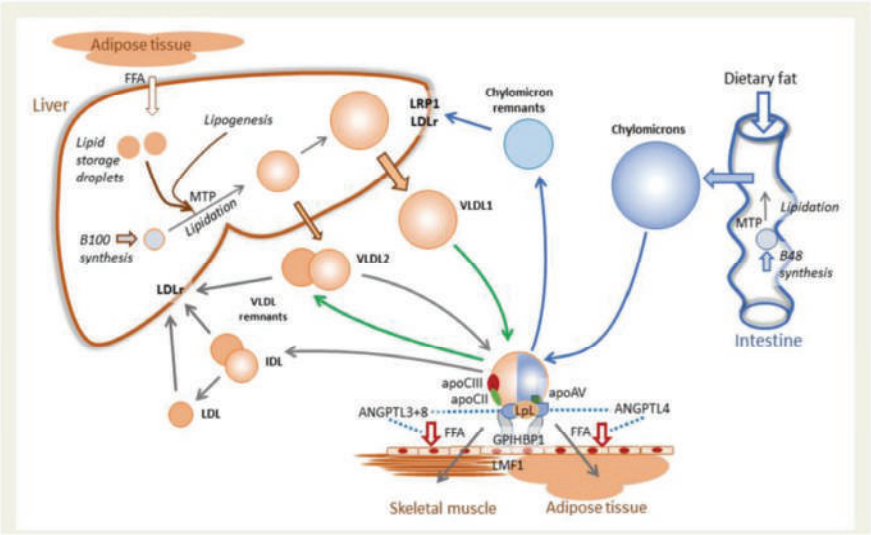
HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

Genetic Severe HTG/ Mixed dyslipidemia

Name	Mutated genes	Phenotype	Genetic transmission	Clinical findings
Severe hypertriglyceridemia				
Familial hyperchylomicronemia (Type I) = Familial chylomicronemia syndrome (FCS)	Biallelic LoF mutations LPL , APOC2, APOA5, GPIBHP1, LMF1	CM, TG ↑↑ HDL ↓↓	AR	Pancreatitis, eruptive xanthomas, hepatosplenomegaly
Familial partial lipodystrophy (FPLD)	Heterozygous LoF mutations in: *LMNA, PPARG, PLIN1, AKT2, ADRA2A*	CM, LDLC, TG ↑↑ HDL ↓	AD	Insulin resistance, fatty liver disease, pancreatitis, central obesity, lack of subcutaneous adipose in extremities
Mixed dyslipidemia				
Hepatic lipase deficiency	Biallelic LoF mutations in *LIPC*	CM remnants, TG ↑, IDL, HDL↑	AR	Premature ASCVD
Familial dysbetalipoproteinemia (Type III) (FDBL)	APOE polymorphism Remnant clearance ↓	CM remnants, TG, IDL↑↑	AR	Palmar and tuberoeruptive xanthomas, premature ASCVD

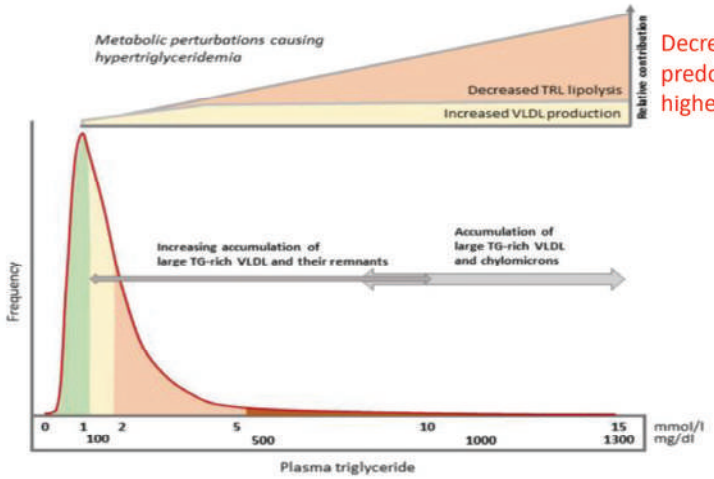
LMF1: lipase mutation factor1

Key factors of hypertriglyceridemia



- ApoCII : an activator of LPL
- ApoCIII : an inhibitor of LPL
- ApoAV: increases LPL-mediated lipolysis
- GPIHBP1(glycophosphatidylinositol-anchored high-density lipoproteinbinding protein-1)
- LMF1: lipase maturation factor 1;
- LRP1: LDL receptor-related protein 1;
- ANGPTL3, 4, 8 (angiopoietin-like proteins): inhibit LPL

Causes of hypertriglyceridemia in the population

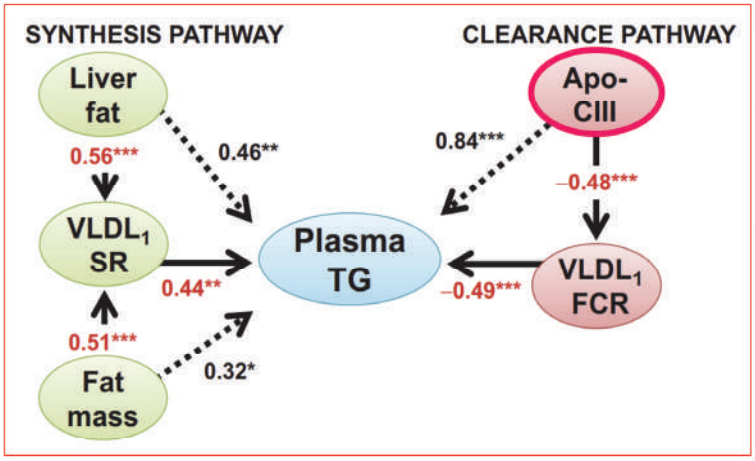


Decreased lipolysis is the predominant feature at higher TG concentrations.

Distribution of plasma triglyceride levels in a population (adapted from a survey of >100 000 individuals in the Copenhagen General Population Study).

Key predictors of plasma triglycerides.

- A multicenter study using dual stable isotopes (deuterated leucine and glycerol) and multicompartmental modeling was performed to elucidate the **kinetics of triglycerides and apoB in VLDL1 in 46 subjects with abdominal obesity.**



Liver fat (r = 0.46, p < 0.01)

Fat mass (r = 0.32, p < 0.05)

Plasma apoC-III concentration (r = 0.84, p < 0.001)

Plasma apoC-II concentration (r = 0.60, p < 0.001)

Plasma apoE concentration (r = 0.60, p < 0.001)

Conclusions—Reduction in liver fat and targeting apoC-III may be an effective approach for correcting triglyceride metabolism atherogenic dyslipidemia in obesity.

Jan Borén et al. Arterioscler Thromb Vasc Biol. 2015;35:2218-2224

Contents

1. **Current status of hypertriglyceridemia**
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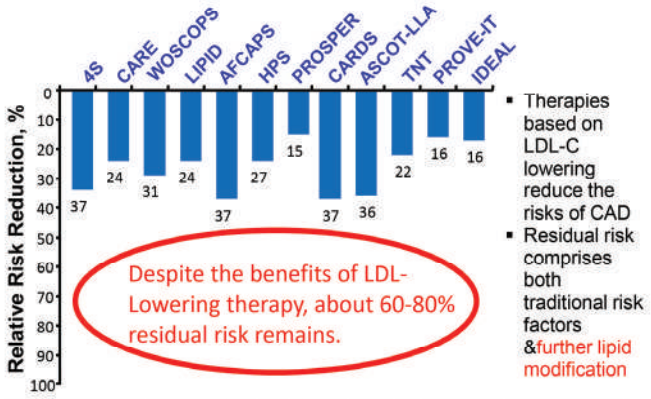
5. **Treatment**

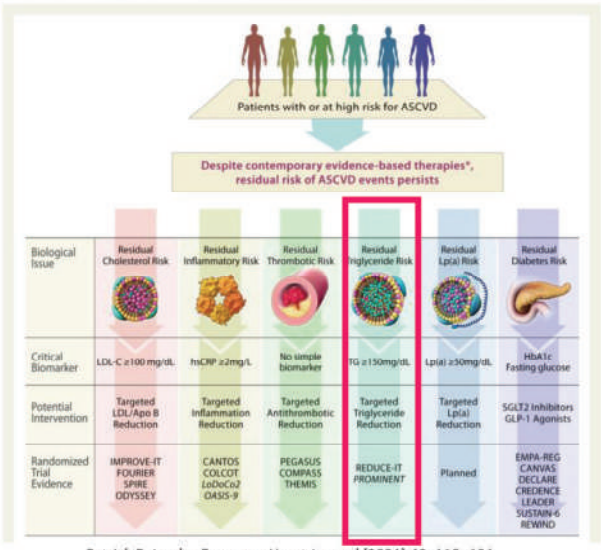
Residual CV risk after LDL-C lowering therapy



- Therapies based on LDL-C lowering reduce the risks of CAD
- Residual risk comprises both traditional risk factors &further lipid modification

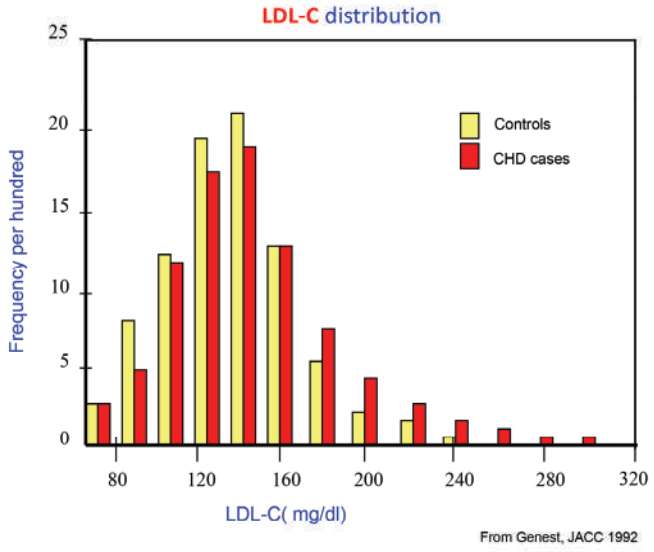
4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol And Recurrent Events; WOSCOPS = West of Scotland Coronary Prevention Study; LIPID= Long-term Intervention with Pravastatin in Ischemic Disease; AFCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; HPS = Heart Protection Study; PROSPER = Prospective Study of Pravastatin in Elderly at Risk; CARDS = Collaborative Atorvastatin Diabetes Study; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm; TNT = Treating to New Targets; PROVE-IT = PRavastatin Or atorVastatin Evaluation and Infection Therapy; IDEAL = Incremental Decrease in End points through Aggressive Lipid lowering; CV = cardiovascular.

Adapted from Chapman J. *Eur Heart J.* 2005;7(suppl F):F58–F62.
[4S Study Group]. *Lancet.* 1994;344:1383–1389; Sacks FM et al. *N Engl J Med.* 1996;335:1001–1009; Shepherd J et al. *N Engl J Med.* 1995;333:1301–1307; The Long-Term Intervention With Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med.* 1998;339:1349–1357; Downs JR et al. *JAMA.* 1998;279:1615–1622; Heart Protection Study Collaborative Group. *Lancet.* 2002;36:7–22; Shepherd J et al. *Lancet.* 2002;360:1623–1630; Colhoun HM et al. *Lancet.* 2004;364:685–696; Sever PS et al. *Lancet.* 2003;361:1149–1158; LaRosa JC et al. *N Engl J Med.* 2005;352:1425–1435; Cannon CP et al. *N Engl J Med.* 2004;350:1495–1505; Pedersen TR et al. *JAMA.* 2005;294:2437–3092.

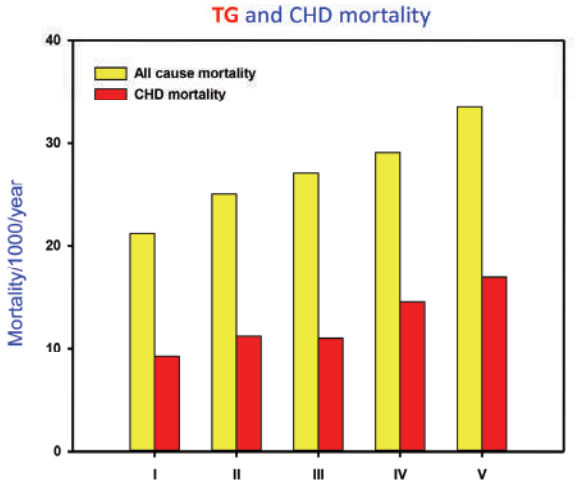


Patrick R. Lawler European Heart Journal (2021) 42, 113–131

Lipid & CHD Mortality



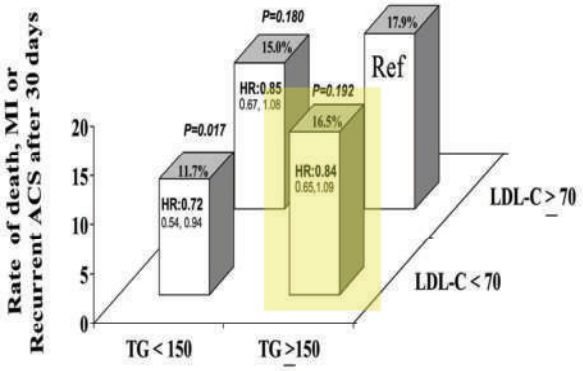
From Genest, JACC 1992



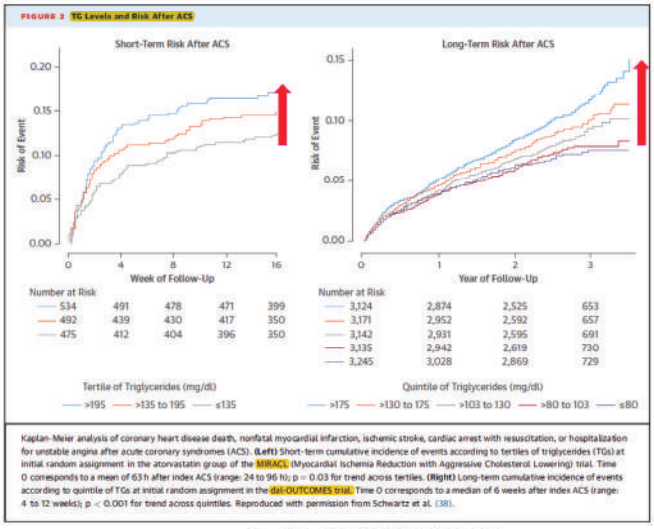
Age adjusted all cause and CHD mortality per 1000 persons in male
TG I<94.3, II 94.3~124.4, III 124.4~160.7, IV 160.7~217, V>217 mg/dl
Haim et al, Circulation 1999;100:475

High TG is dangerous even after high dose statin treatment

Impact of TG Levels beyond LDL-C after ACS in the PROVE IT-TIMI 22 Trial



Canadian J Cardiol 1988;4:5A, JACC 2008:724–30



J Am Coll Cardiol. 2018 Jul 17;72(3):330-343.

Does lowering TG reduce ASCVD risk ?

Previous **landmark clinical trials of TG-lowering therapy** have **failed** to establish a **consistent association between TG lowering and reduction in MACE.**

MACE : major adverse cardiovascular events

TABLE 1 Clinical Trials of Fibrates for Reduction of TG

Study, Ref. #	Year	Population	Sample Size (n)	Fibrate and Dose	TG Lowering Effect	Primary Outcome	Primary Outcome HR (95% CI)
Helsinki Heart Study[2]	1987	Asymptomatic middle-aged men (ages 40-55 y) with non-HDL <200 mg/dL	4,081	Gemfibrozil 600 mg twice daily	−43% at 2 y	Fatal and nonfatal MI and cardiac death	0.66 (0.474-0.918)
VA-HIT[3]	1999	Men with known coronary heart disease, HDL-C ≤40 mg/dL, LDL-C ≤140 mg/dL	2,531	Gemfibrozil 1,200 mg daily	−31% at 1 y	Nonfatal MI or death from coronary causes	0.78 (0.65-0.93)
BIP[25]	2000	Patients with previous MI or stable angina, TC 180-250 mg/dL, HDL-C ≤45 mg/dL, TG ≤300 mg/dL, LDL-C ≤180 mg/dL	3,090	400 mg bezafibrate daily	−21% at 1 y	Fatal or nonfatal MI or sudden death	0.91 (P = 0.26)
FIELD[12]	2005	Participants age 50-75 y with type 2 diabetes and not on statin therapy	9,795	Fenofibrate 200 mg daily	−29% at 4 mo	Coronary events (coronary heart disease death or nonfatal MI)	0.89 (0.75-1.05)
ACCORD-Lipid[11]	2010	Participants with type 2 diabetes being treated with simvastatin	5,518	Fenofibrate 160 mg daily	−25.6% at 5 y	First occurrence of nonfatal MI, nonfatal stroke, or death from CV causes	0.92 (0.79-1.08)
PROMINENT[12]	2022	Participants with type 2 diabetes, TG 200-499 mg/dL, HDL-C ≤40 mg/dL on guideline statin therapy	10,497	Pemafibrate 0.2 mg BID 12.3% increase in LDL-C and 4.8% increase in apoB	−26.2% at 3.4 y	Composite of nonfatal MI, stroke, hospitalization for UA requiring revascularization, and CV death	1.03 (0.91-1.15)

TABLE 2 Clinical Trials of Omega-3 Fatty Acids

Study, Ref. #	Year	Population	Sample Size (n)	Omega-3 PUFA and Dose (g)	TG-Lowering Effect Compared With Placebo	Primary Outcome HR (95% CI)
EPA clinical trials						
JELIS[29]	2007	Hypercholesterolemia patients with baseline LDL-C ≥182 mg/dL	18,645	EPA EE 1.8 g	−5.0%	0.81 (0.69-0.95)
REDUCE-IT[13]	2019	Diabetic patients and patients with ASCVD	8,179	EPA EE 4 g	−20.5%	0.75 (0.68-0.83)
RESPECT-EPA[16]	2022	Patients with chronic coronary artery disease with EPA/AA ratio <0.4	2,506	EPA 1.8 g	–	0.785 (0.62-1.00)
EPA/DHA clinical trials						
VITAL[27]	2018	Healthy volunteers (men >50 y or women >55 y)	25,871	EPA EE 0.46 g DHA EE 0.38 g	Unknown	0.92 (0.8-1.06)
ASCEND[23]	2018	Diabetic patients without ASCVD	15,480	EPA EE 0.46 g DHA EE 0.38 g	Unknown	0.97 (0.87-1.08)
STRENGTH[15]	2020	Diabetic patients, patients with ASCVD, and high-risk patients	13,078	EPA 2.2 g DHA 0.8 g	−18.1%	0.99 (0.9-1.09)

These results suggested that apo B or remnant cholesterol of triglyceride-rich lipoproteins (TRLs), rather than HTG per se, are more important pathophysiologic factors in ASCVD.

Malick WA Am Coll Cardiol. 2023 Apr 25;81(16):1646-1658.

TG, TRLs, and TRL remnants

- TRLs (Triglyceride-rich lipoproteins) : CM, CM-Rm, VLDL, VLDL-Rm, IDL
- Remnant cholesterol : cholesterol component of TRL = [TC-HDLC-LDLC]

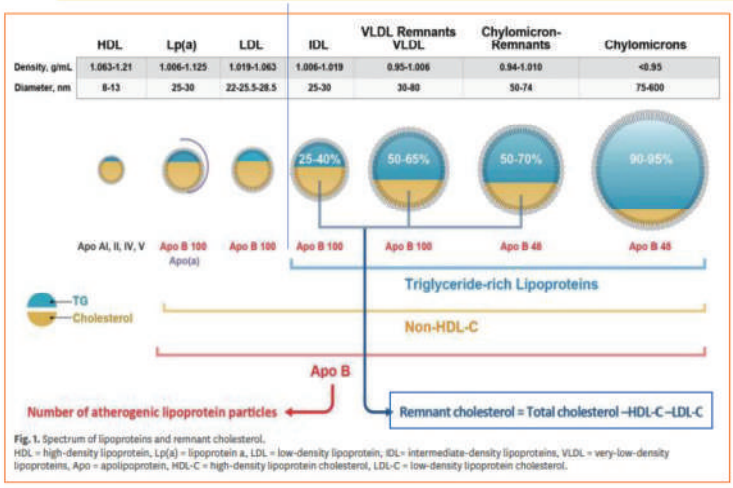
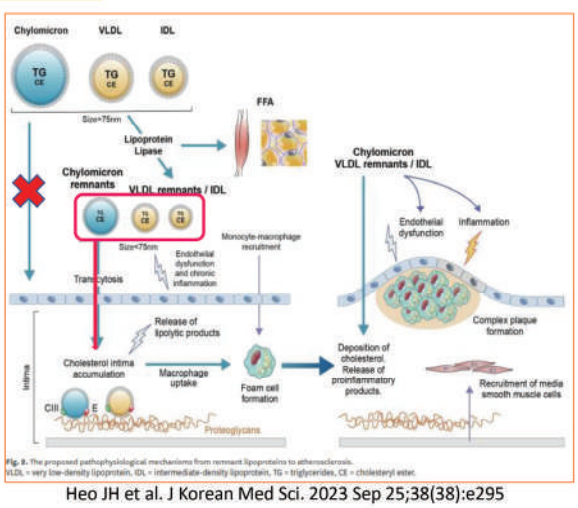
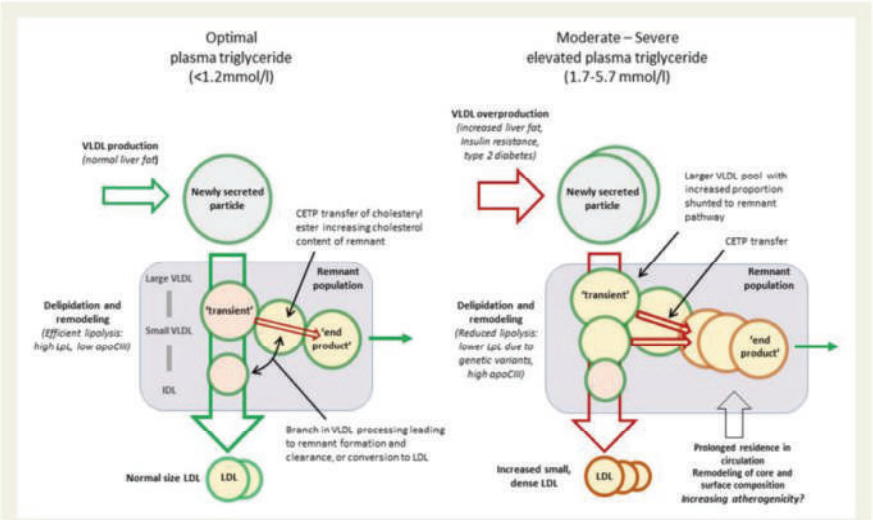


Fig. 1. Spectrum of lipoproteins and remnant cholesterol.
HDL = high-density lipoprotein, Lp(a) = lipoprotein a, LDL = low-density lipoprotein, IDL= intermediate-density lipoproteins, VLDL = very-low-density lipoproteins, Apo = apolipoprotein, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.



Heo JH et al. J Korean Med Sci. 2023 Sep 25;38(38):e295

Metabolism of remnant lipoproteins in optimal vs hypertriglyceridemia



Henry Ginsberg et al. European Heart Journal (2021) 42, 4791–4806

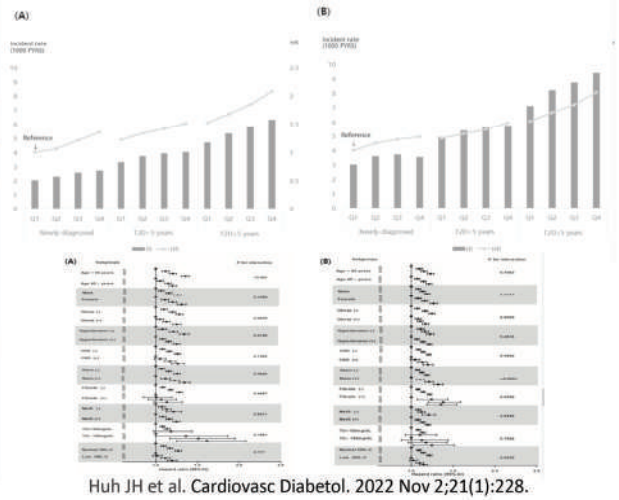
Remnant cholesterol and ASCVD

A nonfasting remnant cholesterol increase of 1 mmol/l (39 mg/dl) is associated with a 2.8-fold causal risk for ischemic heart disease.

Ischemic heart disease	N total	N events	Risk estimate (95% CI)
Remnant cholesterol increase of 1 mmol/L			(All p <0.001)
Observational: Elevated plasma levels	56667	2874	1.4 (1.3–1.5)
Causal: Genetically elevated levels	73513	11984	2.8 (1.9–4.2)
Myocardial infarction			
Remnant cholesterol doubling in concentration			
Observational: Elevated plasma levels	10391	1098	1.7 (1.4–2.0)
Causal: Genetically elevated levels	60113	5705	2.2 (1.5–3.4)
Myocardial infarction			
Remnant cholesterol increase of 1 mmol/L			
Observational: Elevated plasma levels	108508	2219	1.4 (1.3–1.5)
Causal: Genetically elevated levels	97745	4199	1.7 (1.0–3.0)

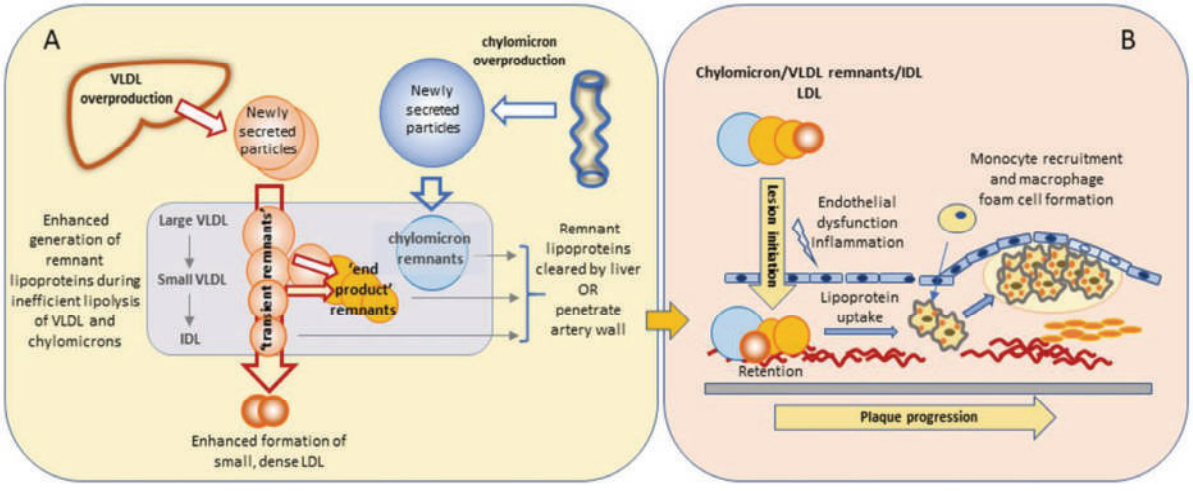
Wang K et al. Front Cardiovasc Med. 2022 Oct 17;9:913869.

In Korean patients with T2D, remnant-C was a/w CVD, independent of the LDL-C level or other conventional CVD risk factors.



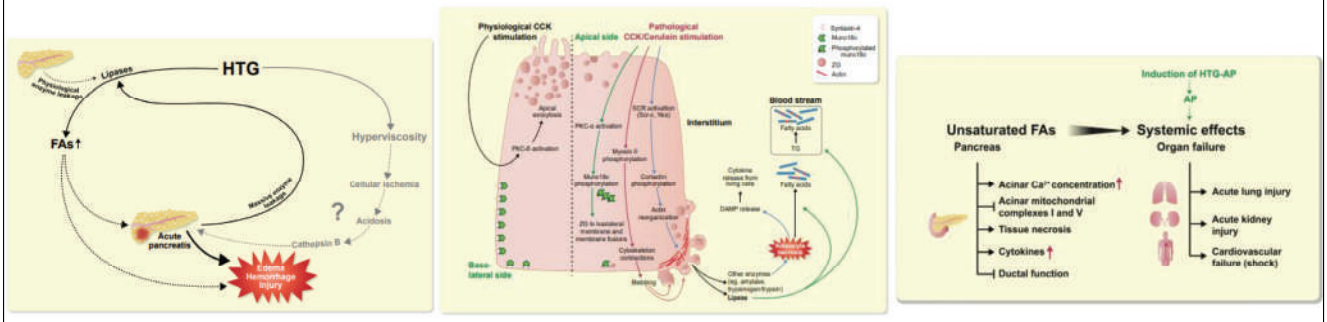
Huh JH et al. Cardiovasc Diabetol. 2022 Nov 2;21(1):228.

Role of TG-rich lipoprotein remnants in atherogenesis



Henry Ginsberg et al. European Heart Journal (2021) 42, 4791–4806

Linking severe hypertriglyceridemia to acute pancreatitis



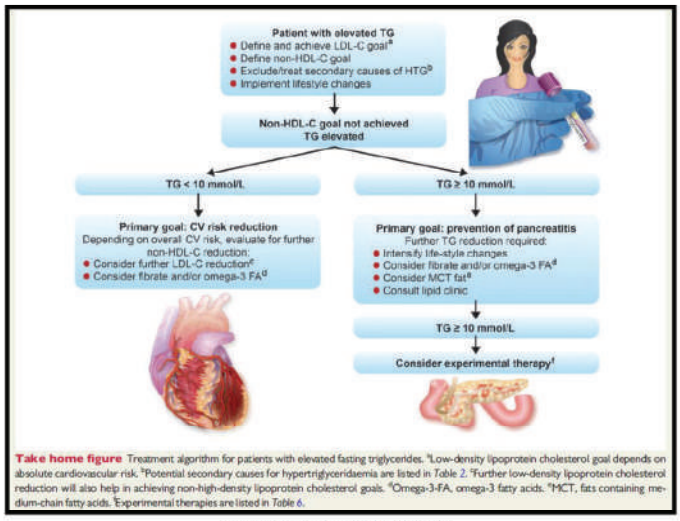
Lóránd Kiss et al Acta Physiologica. 2023;237:e13916

Major goals of treatment of hypertriglyceridemia

1. Prevention of cardiovascular disease
2. Prevention of Pancreatitis
3. Improvement of insulin resistance and MAFLD

Contents

Treatment of hypertriglyceridemia: GUIDELINE



Take home figure Treatment algorithm for patients with elevated fasting triglycerides. [a]Low-density lipoprotein cholesterol goal depends on absolute cardiovascular risk. [b]Potential secondary causes for hypertriglyceridaemia are listed in *Table 2*. [c]Further low-density lipoprotein cholesterol reduction will also help in achieving non-high-density lipoprotein cholesterol goals. [d]Omega-3-FA, omega-3 fatty acids. [e]MCT, fats containing medium-chain fatty acids. [f]Experimental therapies are listed in *Table 6*.

Laufs U et al Eur Heart J 2020:41, 99

12	For individuals with a triglyceride concentration of 500 mg/dL or higher, immediate drug therapy and lifestyle modification are important to prevent acute pancreatitis.	I	A
13	For individuals with a triglyceride concentration of 200–499 mg/dL, the primary treatment goal is to lower the LDL-C to the targeted level based on the calculated cardiovascular risk.	I	A
14	For individuals with a triglyceride concentration of 200–499 mg/dL, pharmacological therapy should be considered to lower triglyceride concentration after achieving the targeted LDL-C level if triglyceride concentration is >200 mg/dL with cardiovascular risk factors, or if non-HDL-C concentration is above the target.	IIa	B
15	If indicated, fibrates should be used to control triglyceride concentration.	I	B
16	If indicated, omega-3 fatty acids should be considered to control triglyceride concentration.	IIa	B
17	Combination drug therapy may be considered if targeted triglyceride level is not met after monotherapy.	IIb	C
18	The primary goal for low HDL cholesterolemia treatment is to control LDL-C to below the target.	I	A

Jeong IK et al. Korean J Intern Med 2019;34:723-771

고중성지방혈증에 대한 비약물요법

- 체중 조절 : 이상체중 유지
- 규칙적인 운동
- 과음하지 않기
- 금연
- 고탄수화물 식사 피하기

약물 요법

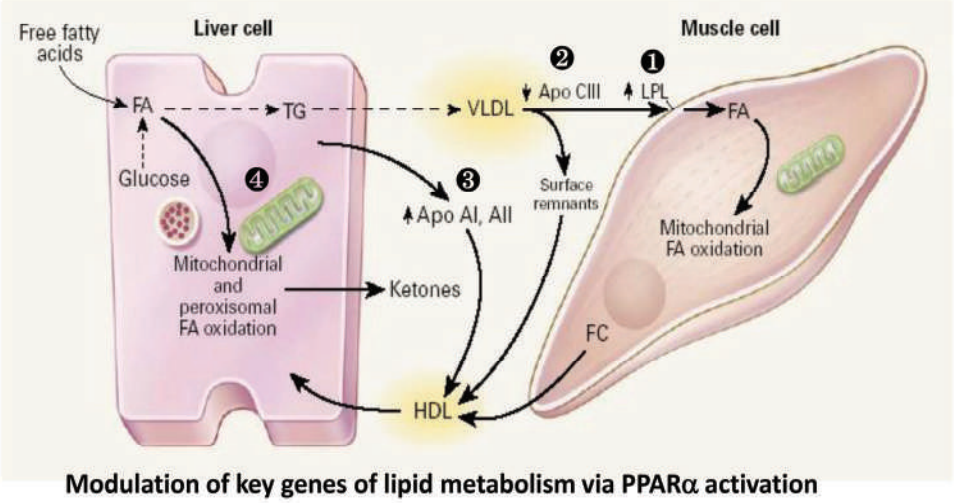
Drug class/agents	HDL-C effect	LDL-C effect	Triglyceride effect
Statins	↑ 5–15%	↓ 18–55%	↓ 7–30%
Fibriates	↑ 10–20%	↓ 5–20%	↓ 20–50%
Niacin	↑ 15–35%	↓ 5–25%	↓ 20–50%
Ezetimibe	↑ 1%	↓ 18%	↓ 8%
Bile acid sequestrants	↑ 3–5%	↓ 15–30%	No change or increase

약물 요법

약제	주요 적응증	약물 작용 기전	주요 이상반응
스타틴 (HMG-CoA reductase inhibitor)	LDL-C↑ 고CV위험군	Cholesterol synthesis↓ Hepatic LDL-R↑ ↓VLDL production	Myalgia, arthralgia, elevated transaminases, dyspepsia
에제티미브 (cholesterol absorption inhibitor)	LDL-C↑	Intestinal cholesterol absorption↓ LDL-R↑	Elevated transaminases
Bile acid sequestrants	LDL-C↑	Bile acid excretion↑ LDL-R↑	Bloating, constipation, elevated TG
PCSK9 inhibitor	LDL-C↑	Hepatic LDL-R↑	Itching at the injection site, flu-like symptoms
Fibric acid derivatives	중성지방↑	LPL↑ VLDL synthesis↓	Dyspepsia, myalgia, gallstones, elevated transaminases
Omega-3 fatty acids	중성지방↑	TG catabolism↑	Dyspepsia, diarrhea, fishy odor to breath

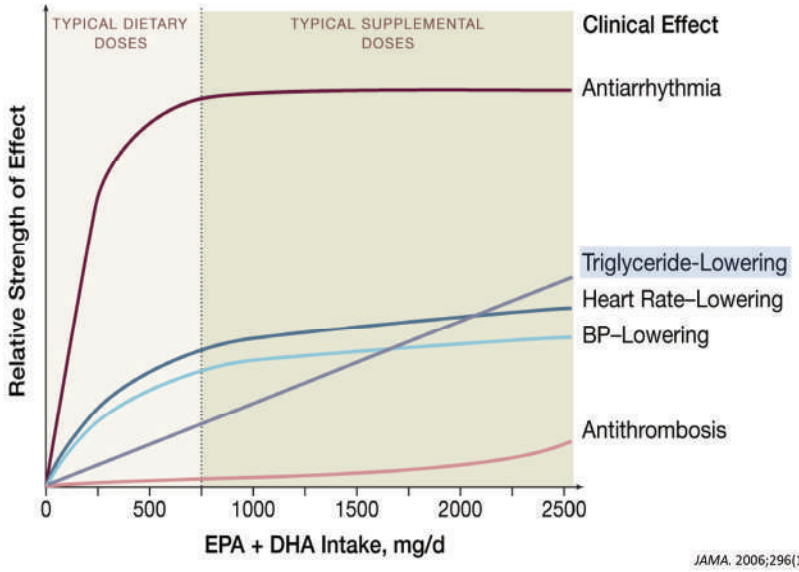
Fibrates

- gemfibrozil, fenofibrate, bezafibrate, pemafibrate



Modulation of key genes of lipid metabolism via PPARα activation

Omega-3 relative strength of effect



JAMA. 2006;296(15):1885-1899

Strategy to lowering of TRL and remnants for ASCVD prevention

1. Inhibiting lipoprotein production

1) **Mipomersen** [**an antisense oligonucleotide (ASO) inhibitor of apoB-100 translation**] : block apoB synthesis : HoFH
2) **Lomitapide** **(an inhibitor of microsomal triglyceride transport protein)** block VLDL assembly : HoFH

➔ Adverse events : elevated liver enzyme and hepatic fat accumulation

2. Reducing cholesterol ester enrichment of remnants

CETP inhibitor : evacetrapib or anacetrapib

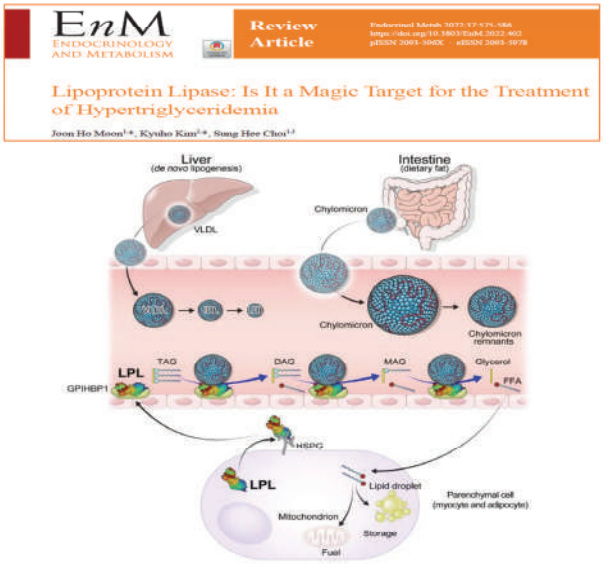
- marked decrease in the cholesterol/TG ratio in VLDL
- While anacetrapib treatment led to a small risk reduction, putatively linked to a decrease in LDL-C, greater LDL-C reduction with evacetrapib did not confer cardiovascular benefit.

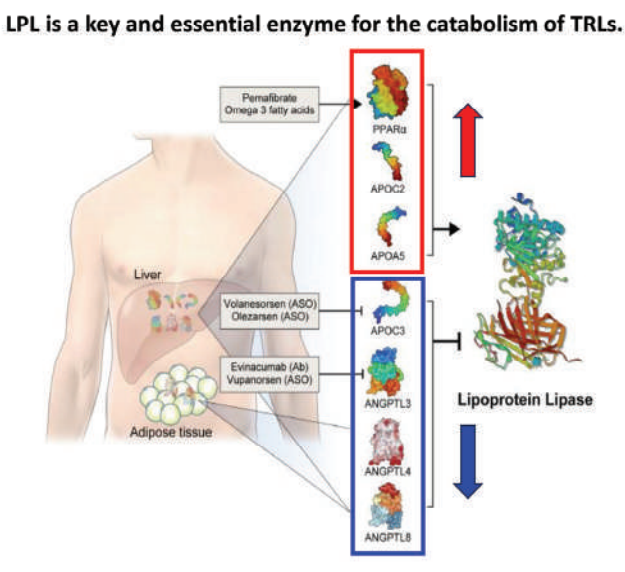
3. Stimulating lipolysis

Key factors of hypertriglyceridemia management

1. TG synthesis ↓
   1) CM : Intestine from dietary fat
   2) VLDL : Hepatic synthesis
2. TG clearance ↑
   1) Lipolysis of TG by Lipoprotein lipase (LPL)
   2) Hepatic clearance of remnants

TG catabolism : Lipoprotein lipase (LPL)





TG catabolism : Lipoprotein lipase (LPL)

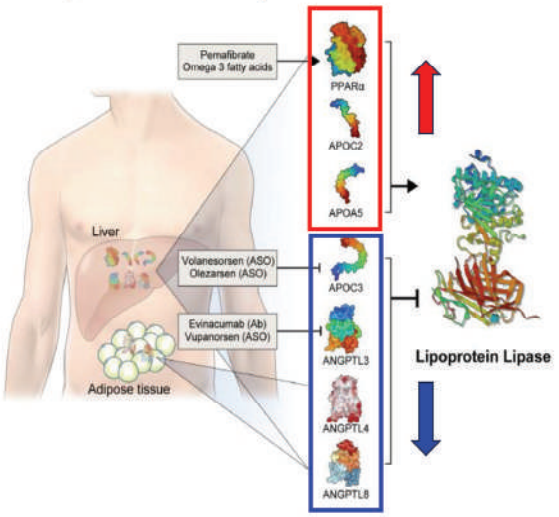

EnM ENDOCRINOLOGY AND METABOLISM
Review Article
Lipoprotein Lipase: Is It a Magic Target for the Treatment of Hypertriglyceridemia
Joon Ho Moon[1,*], Kyuho Kim[2,*], Sung Hee Choi[1,]

Emerging two therapeutic targets.

1) ApoC-III

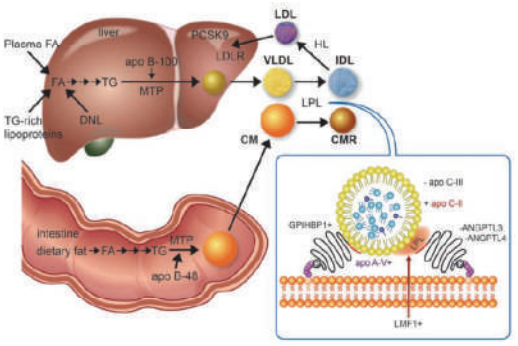
2) ANGPTL3

LPL is a key and essential enzyme for the catabolism of TGRLs.



Novel emerging drugs for TG

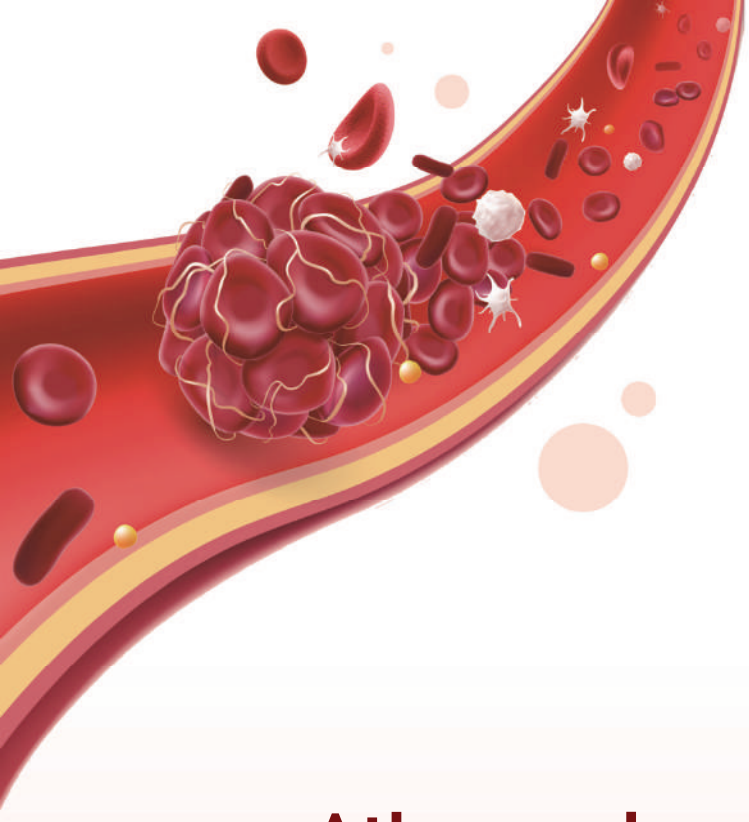
1. Treatment to reduce **Apo C-III**
   - Volanesorsen (Waylivra; ISIS 304801 or IONIS-APOCIIIRx; Ionis/Akcea)
   - Olezarsen (ASO targeting APOC3 mRNA)
   - Plozasiran (siRNA of APOC3)
2. Treatment targeting **angiopoietin-like protein 3**
   - Evinacumab or IONIS-ANGPTL3-LRx
3. FGF 21 analogue



Laufs U et al Eur Heart J 2020:41, 99

Take home message

1. The prevalence of hypertriglyceridemia (≥ 150 mg/dl) is 30% in Korean adults aged 20 years older.
2. TRL, Remnant cholesterol, rather than hyperTG itself, are more important pathophysiologic factors in ASCVD.
3. Stimulation of Lipolysis through Inhibition of ApoC3 or ANGPTL3 : novel target for management of HTG.
4. ApoC3 inhibits the LPL and decreases the clearance of TRL and remnants, and results in hyperTG.
5. Recent clinical, epidemiological and genetic studies : causal relationships of apoC3 with hyperTG
6. Volanesosen (ASO targeting APOC3 mRNA) : reduced TG, ApoC3, prevent AP, improved insulin sensitivity. but, injection site reactions and thromobocytopenia were common adverse events.
7. Olezarsen (ASO targeting APOC3 mRNA) : reduced TG, ApoC3, prevent AP. Adverse events was mild.
8. Plozasiran (siRNA of APOC3) : reduced TG, ApoC3, in phase 2 study.
9. Pegozafermin (FGF 21 analogue) : reduced TG, improved NASH.
10. Despite the significant reduction in TGs with apoC-III, ANGPTL3 inhibitors, and FGF 21 analogues it remains to be seen whether these reductions in TG can translate to reductions in MACE.



Day 2

Session 2

Atherosclerosis Pathophysiology

(10:40 – 11:40)

10:40 – 11:20	Lipid Measurement Methods and Interpretation	이상국 (연세의대 진단검사의학과)
11:20 – 11:40	토론	

1st Lipid Academy

한국지질·동맥경화학회 제1회 Lipid Academy

이 상 국

[기본정보]

성함	이 상 국
소속(근무처)	연세대학교 의과대학 세브란스병원 진단검사의학과

[학력]

해당년도	세부사항
2005	연세대학교 의학사
2009	연세대학교 의학 석사 (진단검사의학)
2017	연세대학교 의학 박사 (진단검사의학)

[경력]

해당년도	세부사항
2013-2014	연세의대 진단검사의학과 강사
2014-2020	연세의대 진단검사의학과 조교수
2020-	연세의대 진단검사의학과 부교수

[관심분야]

Clinical metabolomics, clinical mass spectrometry, metabolic disorders, laboratory results standardization

[논문]

1. Lee KS, Lee YH, Lee SG. Alanine to glycine ratio is a novel predictive biomarker for type 2 diabetes mellitus. Diabetes, obesity & metabolism. 2024;26(3):980-8.
2. Yun SY, Rim JH, Kang H, Lee SG, Lim JB. Associations of LDL Cholesterol, Non-HDL Cholesterol, and Apolipoprotein B With Cardiovascular Disease Occurrence in Adults: Korean Genome and Epidemiology Study. Annals of laboratory medicine. 2023;43(3):237-43.
3. Ahn S, Lee SH, Chung KS, Ku NS, Hyun YM, Chun S, et al. Development and validation of a novel sepsis biomarker based on amino acid profiling. Clinical nutrition. 2021;40(6):3668-76.
4. Kim SR, Lee SG, Kim SH, Kim JH, Choi E, Cho W, et al. SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. Nature communications. 2020;11(1):2127.
5. Nam HS, Ha J, Ji D, Kwon I, Lee HS, Han M, et al. Elevation of the Gut Microbiota Metabolite Trimethylamine N-Oxide Predicts Stroke Outcome. Journal of stroke. 2019;21(3):350-2.

Lipid Measurement Methods and Interpretation

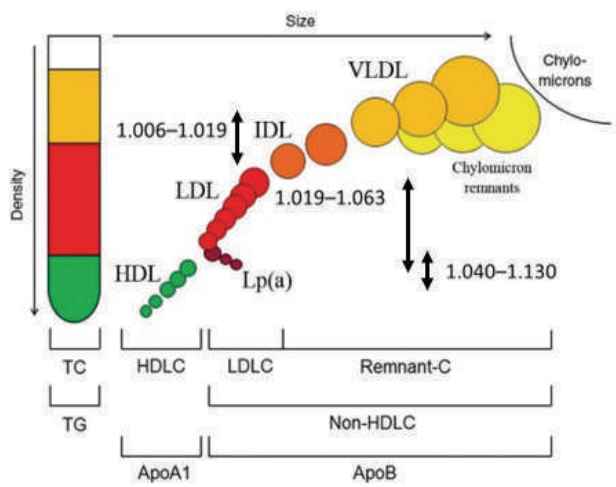
이 상 국
연세의대 진단검사의학과

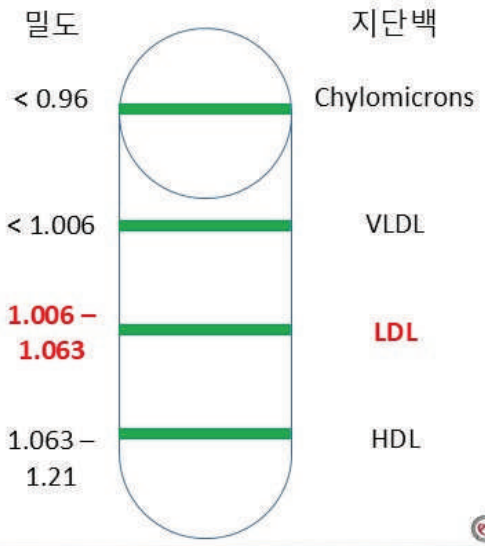
Contents

- LDL-C 측정방법의 종류 및 원리
- Lipoprotein(a) 측정방법
- LDL subfraction, sdLDL-C 소개

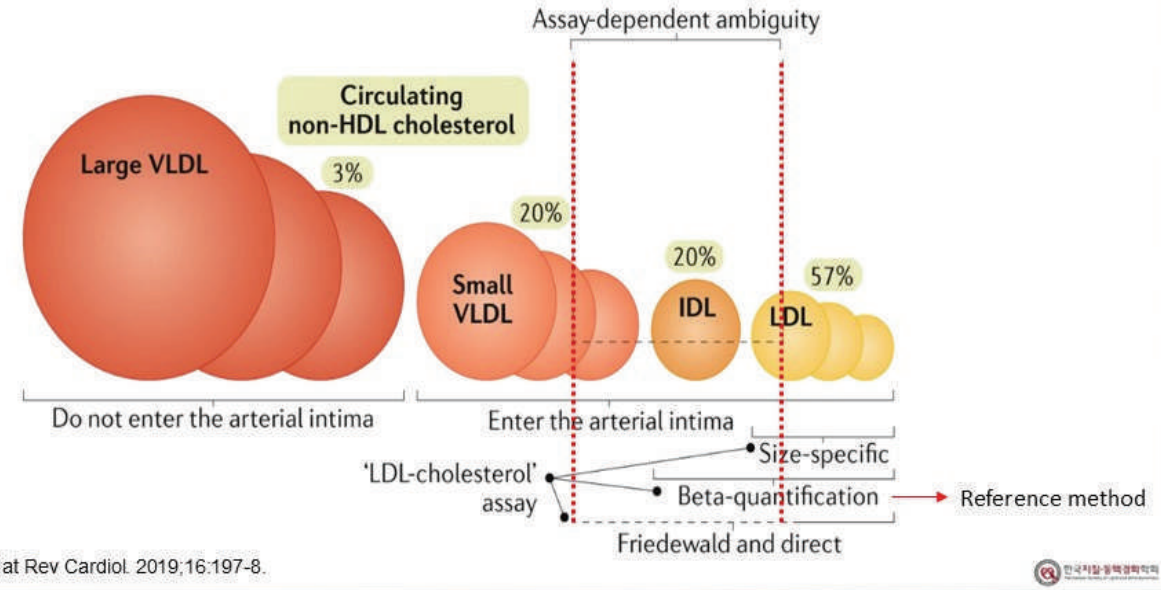
LDL-C 측정방법의 종류 및 원리

혈장 지단백 (lipoprotein)의 종류





LDL-C assay: assay dependent ambiguity



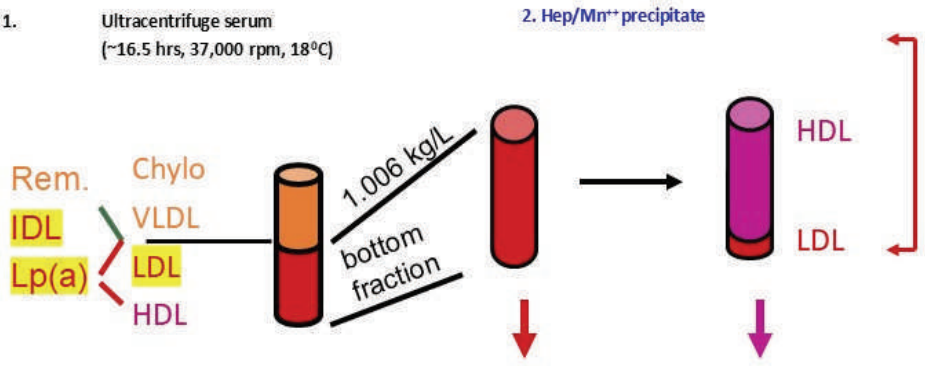
Nat Rev Cardiol. 2019;16:197-8.

Beta-quantification (ultracentrifuge and polyanion precipitation)

Ultracentrifuge laboratory
1952년 Donner Laboratory에서 운영 중인 초원심분리기 실험실

J Clin Lipidol. 2007;1:100-3.

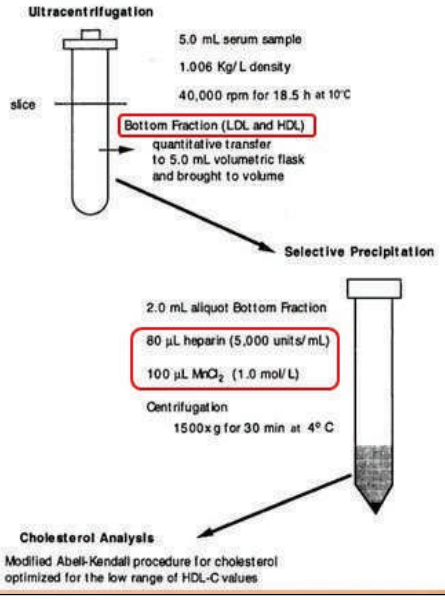
Heparin/Mn^{2+} HDL and beta-quantification LDL RMP separates lipid classes according to their densities



Ultracentrifugation 장비

Beckman-Coulter Preparative Centrifuge

J Clin Invest. 1955;34:1345-53.



Chemical Precipitation with polyanions

TABLE 2 LIPOPROTEINS PRECIPITATED BY VARIOUS SULFATED POLYSACCHARIDES AND DIVALENT CATIONS

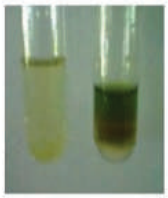
	Sulfated Polysaccharide		
Cation	Heparin	Dextran Sulfate	Dextran Sulfate 2000
Mg^{++}, Ca^{++}	Chylomicrons VLDL	Chylomicrons VLDL LDL	Chylomicrons VLDL LDL HDL
Mn^{++}	Chylomicrons VLDL LDL	Chylomicrons VLDL LDL HDL	

TABLE 3 FINAL CONCENTRATIONS OF REAGENTS REQUIRED FOR THE PRECIPITATION OF LIPOPROTEINS

Reagents	Chylomicrons plus VLDL	LDL	HDL
Heparin Mn^{++}	0.01% 0.05 M	0.1% 0.05 M	no ppt
Dextran sulfate Mg^{++} (Ca^{++})	0.01% 0.1 M	0.1% 0.1 M	no ppt
Dextran sulfate Mn^{++}		0.05% 0.05 M	0.65% 0.2 M
Dextran sulfate 2000 Ca^{++}		0.05% 0.1 M	0.55% 0.2 M
NaPhT Mg^{++}	0.05% 0.1 M	0.2% 0.1 M	2.0% 0.2 M
NaPhT Mn^{++}		0.08% 0.05 M	0.6% 0.2 M

J Lipid Res. 1970;11:583-95.

CDC has two reference methods for cholesterol



Abell-Kendall Method

- Serum (250 uL)
- Hydrolysis (EtOH/KOH 50 °C, 60 min)
- Liquid/Liquid Extraction (Hexane)
- Evaporate Hexane (Vacuum)
- Liebermann Burchard Reaction
- Spectrophotometric Measurement

GC/MS Method

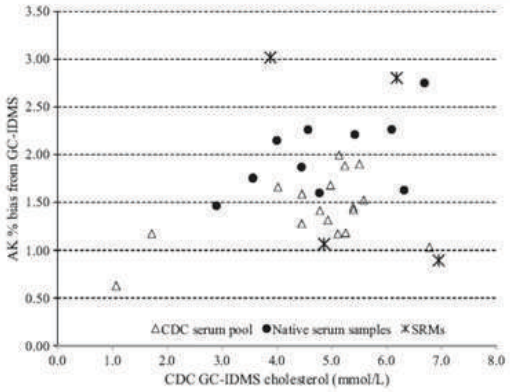
- Serum (250 uL)
- Add Internal Standard ([$^{13}C_2$]-cholesterol)
- Hydrolysis (EtOH/KOH, 50 °C, 60 min)
- Liquid/Liquid Extraction (Hexane)
- Evaporate Hexane (Vacuum)
- Derivatize (trisil BSA, 70 °C, 90 min)
- GC/MS analysis

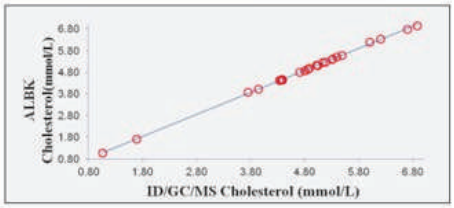
From the Dr. Hubert W. Vesper's presentation in Korea, 2011

Relative bias between AK and GC-ID-MS for the serum samples examined

The mean %bias of AK RMP against ID-GC-MS RMP was **1.6%**
Ellerbe P, et al. Clin Chem 1990;36:370-5.

Proposed master equation for epidemiological comparison:
AK = **1.0181**(GC-IDMS)- 0.0937
r^2 = 0.9996
Edwards SH, et al. Clin Chem 2011;57:614-22.





- Good correlation between the methods for total cholesterol measurements
- AK RMP has small positive difference to ID/GC/MS

베타정량법의 단점

- 초원심분리 과정이 필요, 검사 소요시간이 길고 검사 과정이 복잡함
- 염분 농도 및 원심력에 의해 지단백이 검사 과정 중에 변할 수 있음
- 고가의 장비와 다양한 기구가 필요, 검사 조건에 따른 편차가 크며 검사자의 경험과 기술에 따라 분리결과에 차이가 있음
- 일상적인 검사로 사용하기에 부적합

Friedewald 공식

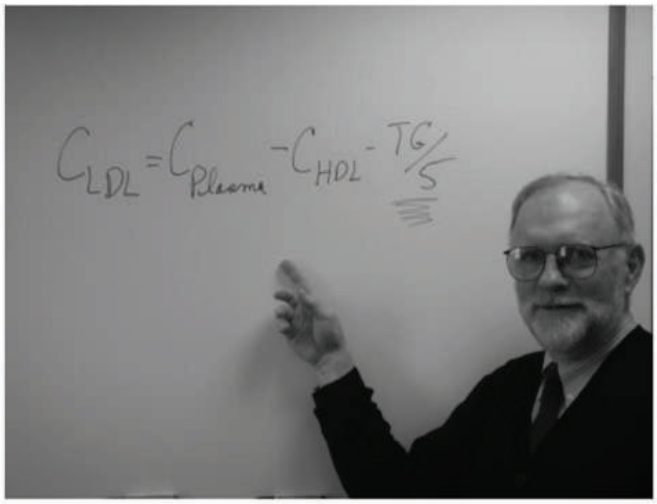


Fig. 1. William Friedewald.

Clin Chem. 2004;50(10):1861-70.

Friedewald 공식의 제한점

LDL-C (mg/dL) = TC – HDL-C – TG/5

- 중성지방이 400 mg/dL 이상일 경우
- 검체에 킬로미크론이 있는 경우 (금식 >12시간을 지키지 않은 경우)
- 검체에 베타초저밀도지단백이 (VLDL remnant)있는 경우 (Type III hyperlipoproteinemia)
- 간질환, 당뇨병, 신장질환 등에 속발한 고지혈증
- Friedewald 공식에 의한 LDL-C 값의 variability는 3개 측정값의 variability가 합해짐 (Friedewald 공식의 평균 CV_a : 4.0% 표준화된 지질 검사실, ~12% 임상검사실)

Clin Chem. 1972;18:499-502.

Friedewald 공식의 제한점

TABLE 7. *Estimates of total analytical variation in LDL-cholesterol measurements*

Sample	No. of Laboratories	LDL-chol Concentration mg/dL (mmol/L)	CV_a (%)	$\frac{CV_a\ (LDL\text{-}chol)}{CV_a\ (Total\ chol)}$
C03	1,149	138 (3.57)	10.8	1.9
C04	1,138	167 (4.32)	11.3	2.0
C08	1,282	171 (4.42)	11.4	2.0
C09	1,271	195 (5.04)	12.6	2.1
C13	1,405	132 (3.41)	11.8	2.0
C14	1,393	153 (3.95)	11.7	2.1
C16	1,349	191 (4.94)	13.3	2.2
C17	1,340	159 (4.11)	12.3	2.1

Source: CAP data taken from College of American Pathologists Comprehensive Chemistry Survey, 1989.

NIH Publication No. 95-3044
September 1995

Direct Methods

- **First-generation methods (chemical precipitation)**

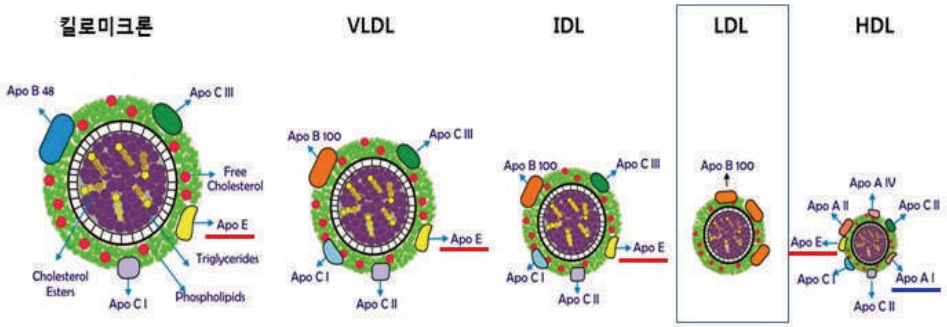
Precipitant	
Heparin at pH 5.12	Merck, Genzyme, Polymedco
Polyvinylsulfate	Roche Diagnostics
Unspecific amphiphatic polymers	BioMérieux
Dextran sulfate	Progen

$$LDL\text{-}C_{prec} = TC - \text{supernate (non-LDL) C}$$

Clin Chem. 2002;48(2):236-54.

Direct Methods

- **Second-generation methods**
  - Resin에 결합된 apo A-I과 apo E에 대한 다클론성 항체를 이용하여 LDL이외의 지단백(VLDL, IDL, HDL)을 침전시킴

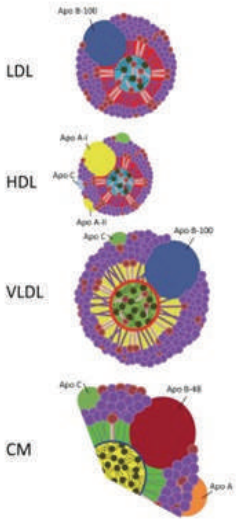


resin - polyclonal Abs (apo A-I, apo E)

Direct Methods

- **Third-generation methods (Homogeneous assays)**
  - 1998년 최초의 LDL-C 균질법이 일본에서 보고됨
  - 전과정 자동화가 가능해짐
  - 자동화를 통한 정확한 파이펫팅, 시간, 온도 조절로 정밀도 개선
  - LDL-C 이외의 지단백을 억제 또는 가용화(solubilization)시켜 선택적으로 측정하는 방법

Homogeneous Methods - 선택적 LDL-C 측정법



Redrawn from Anal Methods. 2013;5:3612.

Homogeneous Methods의 장점

- 중성지방이 400 mg/dL 이상인 경우도 측정 가능
- 금식 하지 않은 검체에서도 측정 가능
- 3가지 항목 (중성지방, 콜레스테롤, HDL-C)을 각각 측정하면서 발생하는 변이에 비해 단일 측정치에 의한 비정밀도의 개선

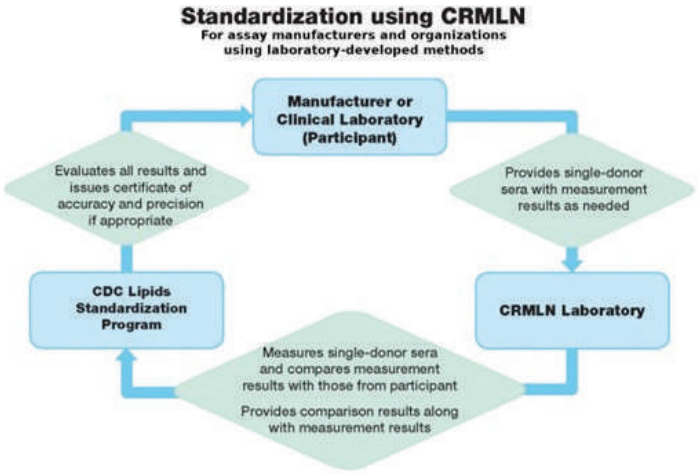
Accuracy – CRMLN program

CDC
SAFER·HEALTHIER·PEOPLE™

CHOLESTEROL REFERENCE METHOD LABORATORY NETWORK (CRMLN)

LIST OF ANALYTICAL SYSTEMS & REAGENTS CERTIFIED FOR LDLC

Date Updated: March 2019



미국 CDC의 CRMLN (Cholesterol Reference Method Laboratory Network) 프로그램을 통한 제조사 인증 – 표준검사법과 일치

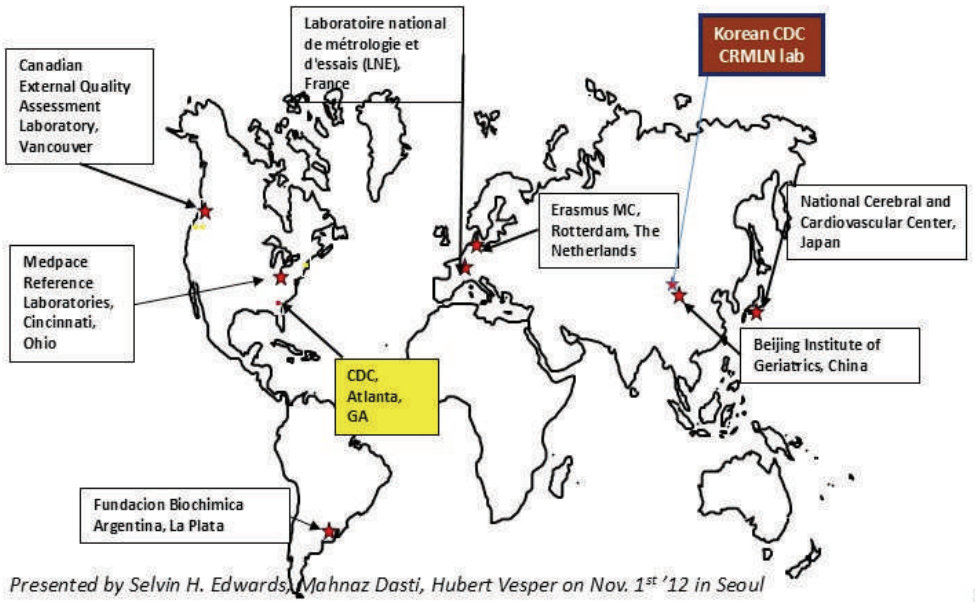
NCEP Recommendations for Analytical Performance of Lipid and Lipoprotein Measurements

		CONSISTENT WITH	
	Total Error, %	Bias, %	CV, %
Cholesterol	8.9	≤ ±3	≤ 3
Triglycerides	≤ 15	≤ ±5	≤ 5
HDL cholesterol	≤ 13	≤ ±5	≤ 4
LDL cholesterol	≤ 12	≤ ±4	≤ 4

Roche Diagnostics GmbH
Dr. H. Klima
Nonnenwald 2
Penzberg, Germany
Phone: -

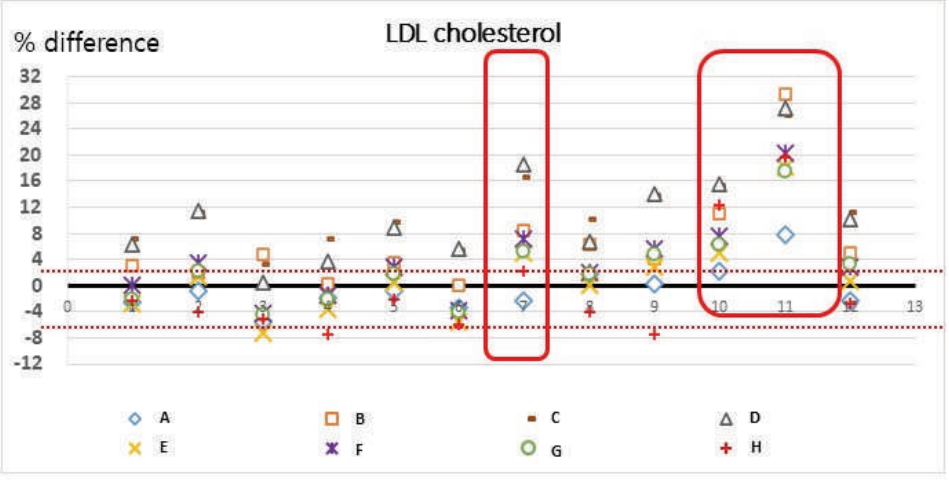
Instrument	Reagent	Reagent Lot(s)	Calibrator	Calibrator Lot(s)	Matrix	Certification Date	Network Laboratory	POC
Roche Diagnostics GmbH Cobas	Roche Diagnostics GmbH LDLC3	658154	Roche Diagnostics GmbH Cfas Lipids	469280	Serum	2/16/2023	Erasmus MC	No

CRMLN USA and international members are regional reference laboratories



Presented by Selvin H. Edwards, Mahnaz Dasti, Hubert Vesper on Nov. 1st '12 in Seoul

LDL-Cholesterol accuracy evaluation



LDL-C/TG ratio is associated with LDL-C bias

Sample number	TC	HDL-C	LDL-C	TG	LDL-C/TG ratio	LDLC Average %Bias
1	212	52	130	150	0.87	0.8
2	229	43	147	179	0.82	3.4
3	143	55	77	71	1.08	-2.2
4	188	57	116	77	1.51	-0.7
5	214	52	131	136	0.96	3.0
6	192	49	121	100	1.21	-1.5
7	152	38	85	155	0.55	7.6
8	174	65	95	60	1.57	3.2
9	193	47	118	118	1.00	4.8
10	183	48	102	153	0.66	9.4
11	178	43	81	218	0.37	20.8
12	163	55	91	83	1.11	3.5

Difference of test results among routine methods for measuring LDL-cholesterol

Clinical chemistry 2010;56:977-986

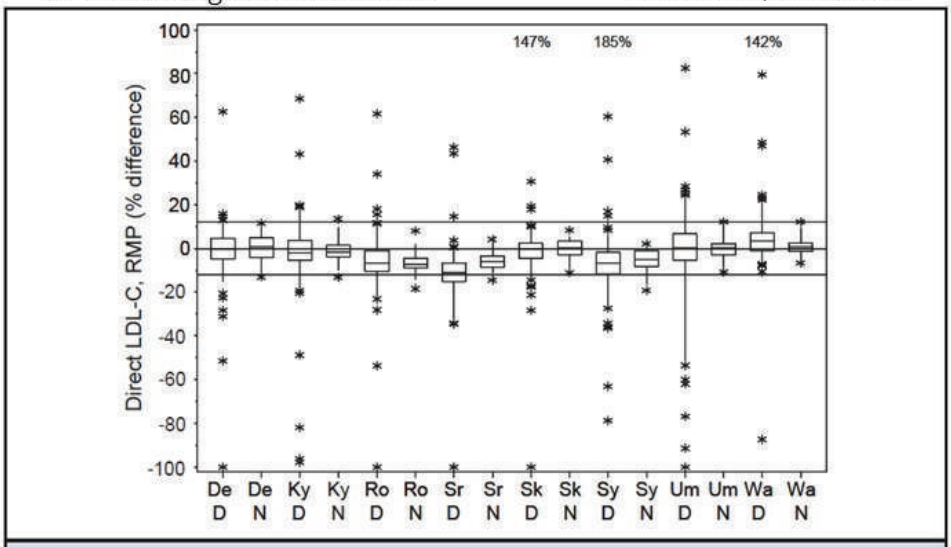


Fig. 2. Box-and-whisker plot of the differences in percentage between the direct and RMP results for LDL-C for each direct method (abbreviations as defined in the Fig. 1 legend).

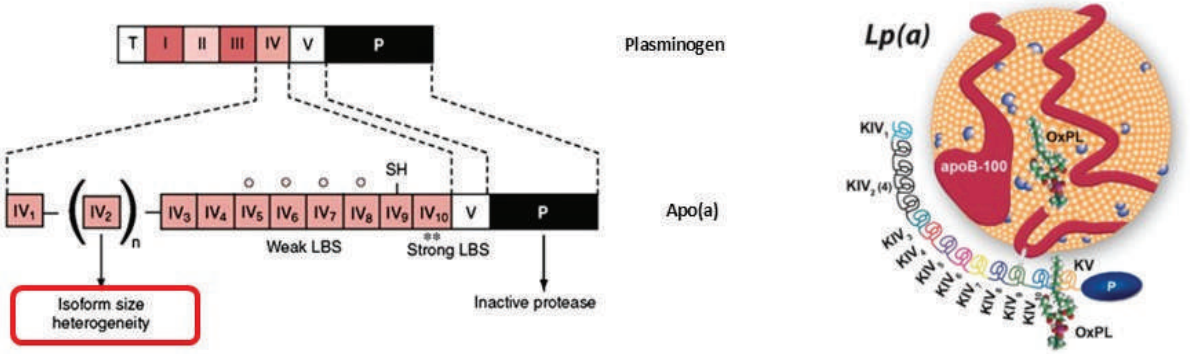
The median is the center line, the ends of the box represent 25th and 75th percentiles, the end of the lines extend to the 10th and 90th percentiles, and individual results are shown beyond the lines.

CRMLN certification: Samples from patients with dyslipidemia

- Additional five specimen that are collected (not part of certification) must:
  - Include at least one sample from donor with **Diabetes Mellitus (type I and type II)**
  - Include at least one sample from donor with **Hypertriglyceridemia**
  - Include at least one sample from donor with **Cirrhosis**
  - Include two additional sample types (Lipid-lowering drugs, Dyslipidemias, CVD, ESRD)

Lp(a) measurement

Immunochemical heterogeneity of Lp(a)



- Size polymorphism of apo(a)
  - 2~43 copies of the KIV type 2 (KIV_2) elements
  - Molecular weight (~250– 800 kDa)

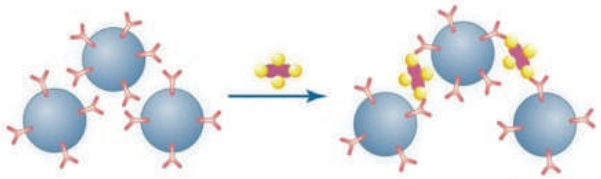
Lp(a) measurement

Polyclonal antibody

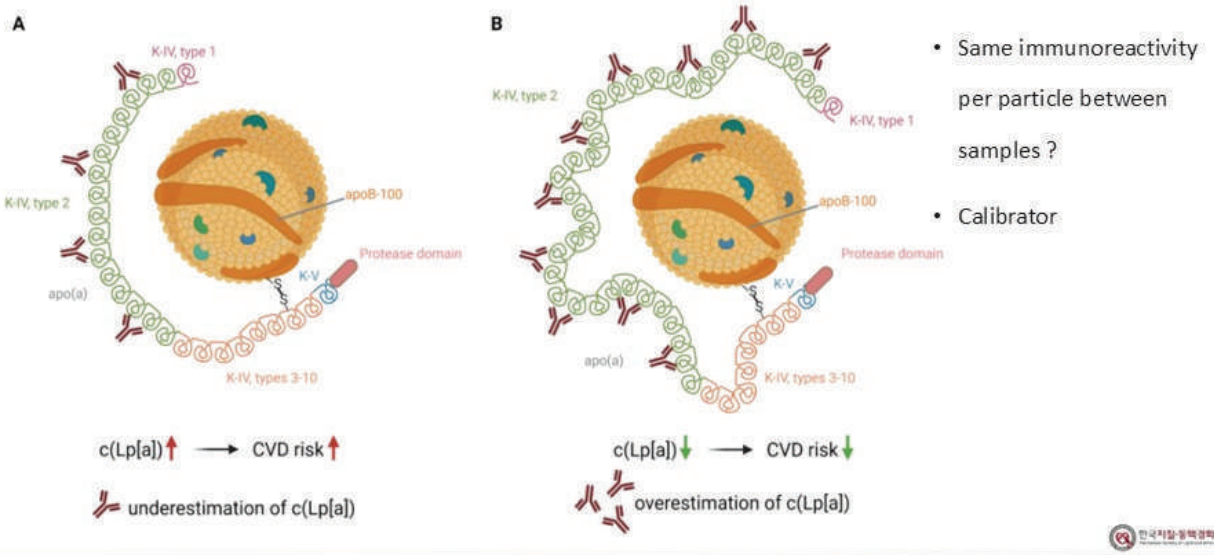
- Raised in animals and are of polyclonal nature.
- If an antibody is directed against this **repetitive motif**, the protein might be recognized by the antibody more than once, which makes a measurement in molar terms hardly possible.
- Monoclonal antibody against non-repeated region?

Immunoturbidimetric assay

- Monoclonal antibodies yield very low signals in homogenous turbidimetric assays and are thus not applicable for such tests.

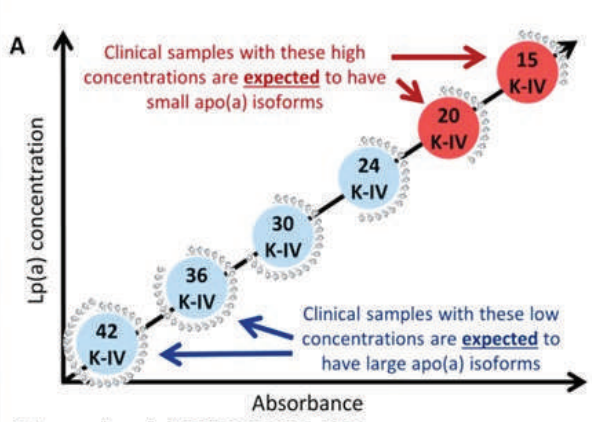


Influence of KIV_2-dependent immunological assays on quantification

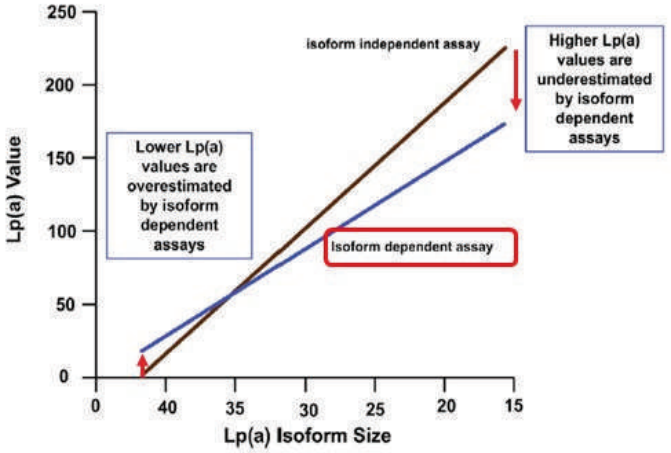


- Same immunoreactivity per particle between samples ?
- Calibrator

Lp(a) concentration and Lp(a) isoform size



Atherosclerosis 2022;349:123–135

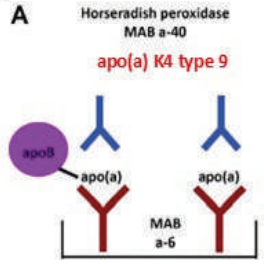


Journal of Clinical Lipidology 2018;12:1313–1323

Lp(a) standardization

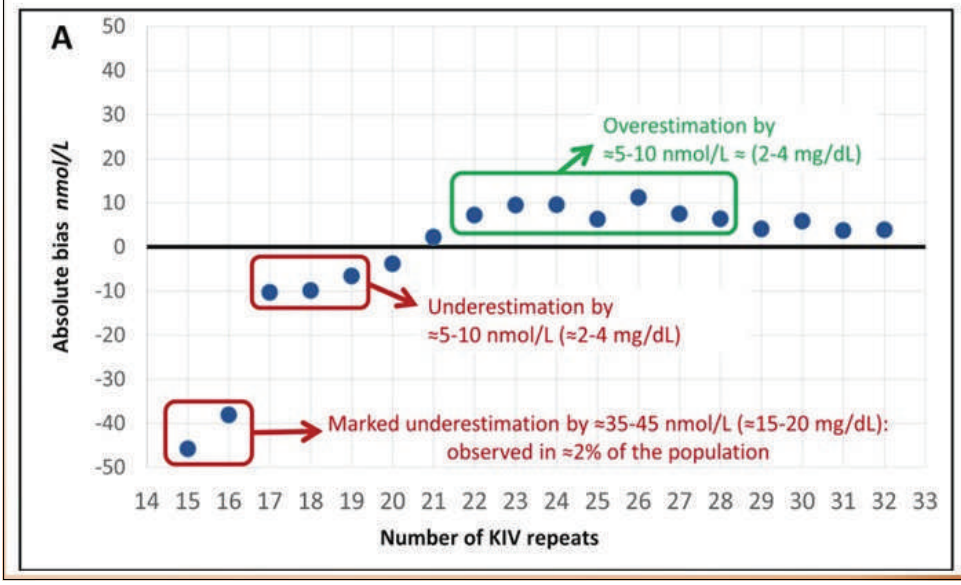
- **Isoform sensitive assay** ⇒ Isoform insensitive assay

- **Lack of an international reference material and hence the non-traceability of manufacturers' Lp(a) calibrators to a reference material**
  - In 1995, the IFCC (International Federation of Clinical Chemistry) Working Group for Lp(a) Assay Standardization
  - Candidate reference method (Northwest Lipid Metabolism and Diabetes Research Laboratories (NLMDRL), **University of Washington**, Seattle, USA): ELISA using MAB a-40
  - In 2003, IFCC Standard Reference Material (SRM) 2B (107 nmol/L) was approved.
  - SRM 2B: used for value assignment of manufacturer's calibrators



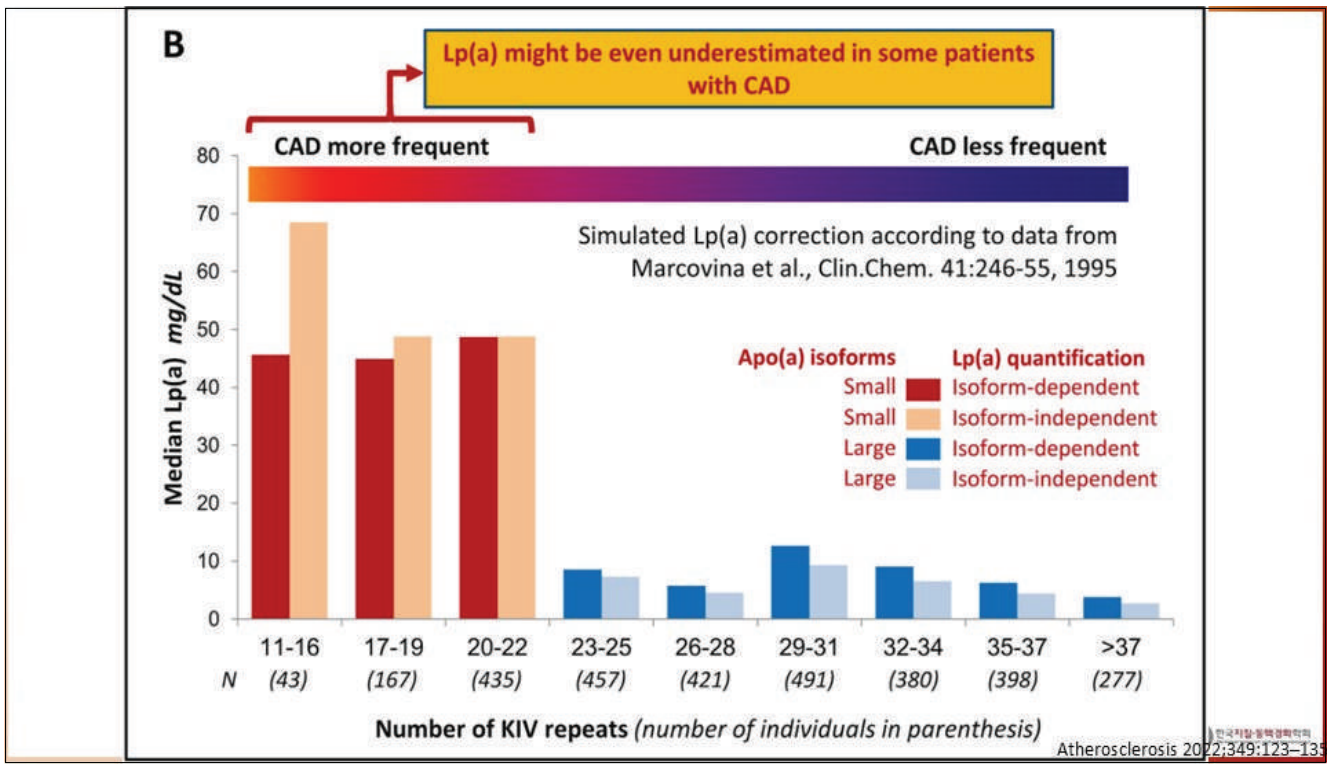
Journal of Clinical Lipidology 2018;12:1313–1323

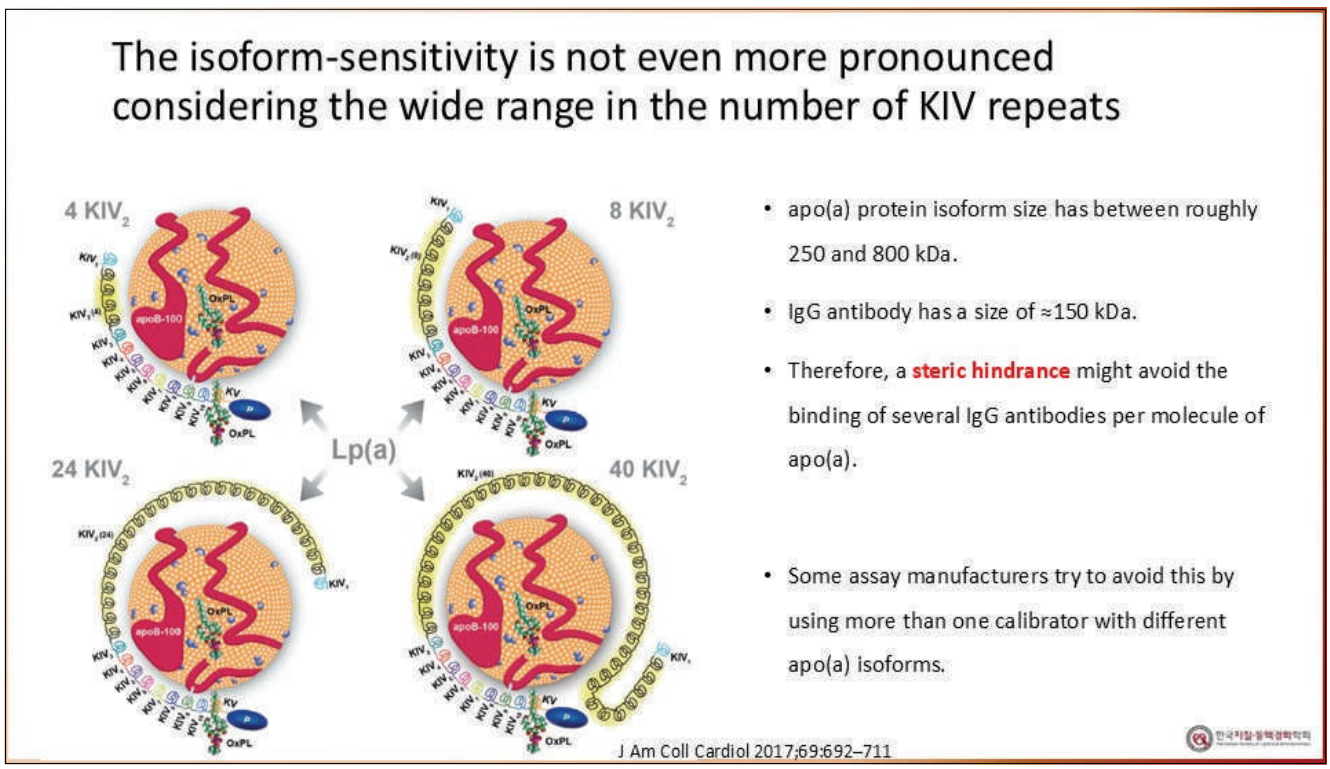
Comparisons between an isoform-sensitive and an isoform-insensitive assay



- Both assays used same calibrator (K4, 21 repeats).
- Still bias in isoform-sensitive assay.

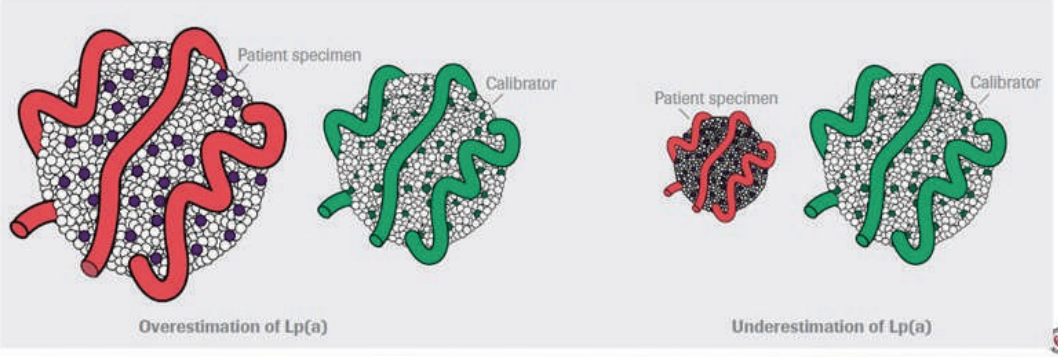
Atherosclerosis 2022;349:123–135


B
Lp(a) might be even underestimated in some patients with CAD
CAD more frequent
CAD less frequent
Simulated Lp(a) correction according to data from Marcovina et al., Clin.Chem. 41:246-55, 1995
Median Lp(a) mg/dL
80
70
60
50
40
30
20
10
0
Apo(a) isoforms
Lp(a) quantification
Small Isoform-dependent
Small Isoform-independent
Large Isoform-dependent
Large Isoform-independent
11-16 17-19 20-22 23-25 26-28 29-31 32-34 35-37 >37
N (43) (167) (435) (457) (421) (491) (380) (398) (277)
Number of KIV repeats (number of individuals in parenthesis)
Atherosclerosis 2022;349:123–135

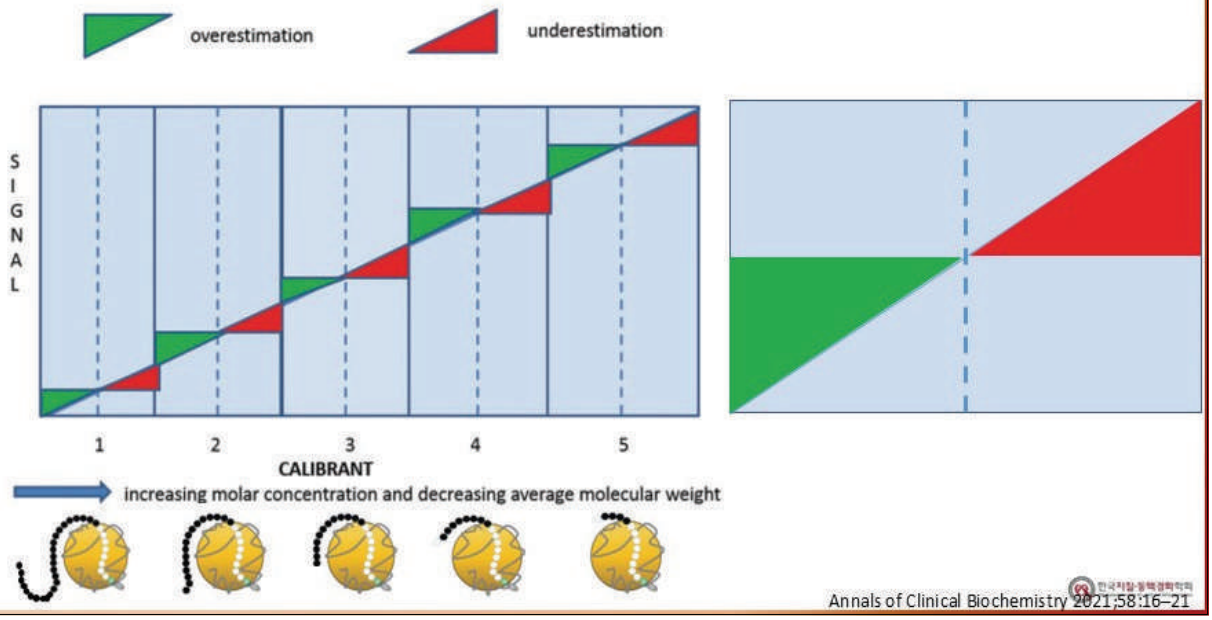

The isoform-sensitivity is not even more pronounced considering the wide range in the number of KIV repeats
4 KIV2
8 KIV2
24 KIV2
40 KIV2
Lp(a)
apoB-100
OxPL
KIV
P
• apo(a) protein isoform size has between roughly 250 and 800 kDa.
• IgG antibody has a size of ≈150 kDa.
• Therefore, a steric hindrance might avoid the binding of several IgG antibodies per molecule of apo(a).
• Some assay manufacturers try to avoid this by using more than one calibrator with different apo(a) isoforms.
J Am Coll Cardiol 2017;69:692–711

Size-calibrated polyclonal immunoassays

- Calibrator
  - Serial dilution from high concentration
  - Independent calibrator with different isoform



Size-calibrated polyclonal immunoassays



Annals of Clinical Biochemistry 2021;58:16–21

Table 4 Relationship of the assigned Lp(a) value to the observed value for 30 samples.[a]

Participant	System	Method[b]	Slope	y-Intercept	Average absolute bias, nmol/l
Daiichi Pure Chemicals Co. Ltd.	Hitachi 717	ITA	0.85	4.1	12.4
DakoCytomation A/S (formerly Dako A/S)	Cobas Fara II	ITA	0.82	20.5	18.4
Denka Seiken Co. Ltd.	Hitachi 917	ITA	0.99	1.7	4.4
DiaSys Diagnostic Systems GmbH	EPOS 5060	ITA	0.81	25.5	19.3
DiaSorin Inc. (formerly Incstar)	Cobas Fara II	ITA[c]	0.86	3.8	13.2
DiaSorin Inc. (formerly Incstar)	Cobas Fara II	ITA[d]	0.89	15.8	17.4
Nitto Boseki Co. Ltd.	Hitachi 7150	ITA	0.89	22.6	19.6
Orion Diagnostica[e]	Kone Specific	ITA	0.78	74.3	59.3
Roche Diagnostics GmbH	Cobas Integra	ITA	0.92	11.1	13.7
Roche Diagnostics GmbH (formerly Boehringer Mannheim GmbH)	Hitachi 911	ITA	0.74	20.0	19.8
Immuno AG	BN100	INA	0.79	8.9	16.1
Beckman Coulter, Inc. (formerly Beckman Instruments)	Beckman Array	INA	0.93	10.0	15.8
Beckman Coulter, Inc. (formerly Beckman Instruments)	IMMAGE	INA	0.88	20.5	21.8
Children's Hospital, Boston	BNII	INA	0.81	15.1	17.1
Dade Behring Marburg GmbH (formerly Behringwerke AG)	BNII	INA	0.79	13.6	16.7
Cliniqa Corp. (formerly International Enzymes Inc.)	Beckman Array	INA	0.91	16.1	19.7
Princess Alexandra Hospital, Brisbane	Beckman Array	INA	0.90	7.4	12.6
Tenon Hospital, Paris	Beckman Array	INA	0.90	10.6	15.0
Medical Biochemistry Institute, Graz	DELFIA (a/B)	FIA	0.78	7.9	16.7
Medical Biochemistry Institute, Graz	DELFIA (a/a)	FIA	0.66	18.9	23.8
SEBIA		EID	0.72	12.1	20.1
Baylor College of Medicine, Houston		ELISA	0.77	18.4	19.4

- **22 assay systems** were calibrated traceable to **IFCC SRM 2B.**
- Despite the use of a common reference preparation, no harmonization in Lp(a) values among the different methods.
- Low level of impact of apo(a) size variation observed by the Denka method is primarily due to **the use of five independent calibrators.**

Clin Chem Lab Med 2004;42(6):670–676

Current immunoassays for Lp(a)

Reporting units	Assay name	Calibration traceability	Calibrators (n)	Method	Measurement range
nmol/L	Roche Lp(a) Tina-Quant	SRM2B	5	Turbidimetry	7–240
	Randox Lipoprotein(a) Assay	SRM2B	5	Turbidimetry	5.23 - 206
	Sentinel Lp(a) Ultra	SRM2B	5	Turbidimetry	
	Diasys Lp(a) 21FS	SRM2B	5	Turbidimetry	6 – 260
mg/dL	Roche Lp(a) Tina-Quant converted			Calculation (nmol/L X 0.4167)	
	Randox Lipoprotein(a) Assay	Manufacturer's internal standard	5	Turbidimetry	3–90
	Sentinel Lp(a) Ultra	Manufacturer's internal standard	5	Turbidimetry	10–100
	Diasys Lp(a) 21FS	Manufacturer's internal standard	5	Turbidimetry	3 – 110
	Denka Seiken Lp(a)-Latex SEIKEN	Manufacturer's internal standard	5	Turbidimetry	0.5–80
	Abbott Alinity c Lp(a)	Manufacturer's internal standard	5	Turbidimetry	3–90
	Sekisui Lp (a) Latex "DAIICHI"	Manufacturer's internal standard	3	Turbidimetry	1–100
	Siemens Healthineers Atellica CH	Manufacturer's internal standard	5	Turbidimetry	10–85
	Siemens Healthineers N Latex Lp(a)[c]	Manufacturer's internal standard	5, serial dilution	Nephelometry	10–100

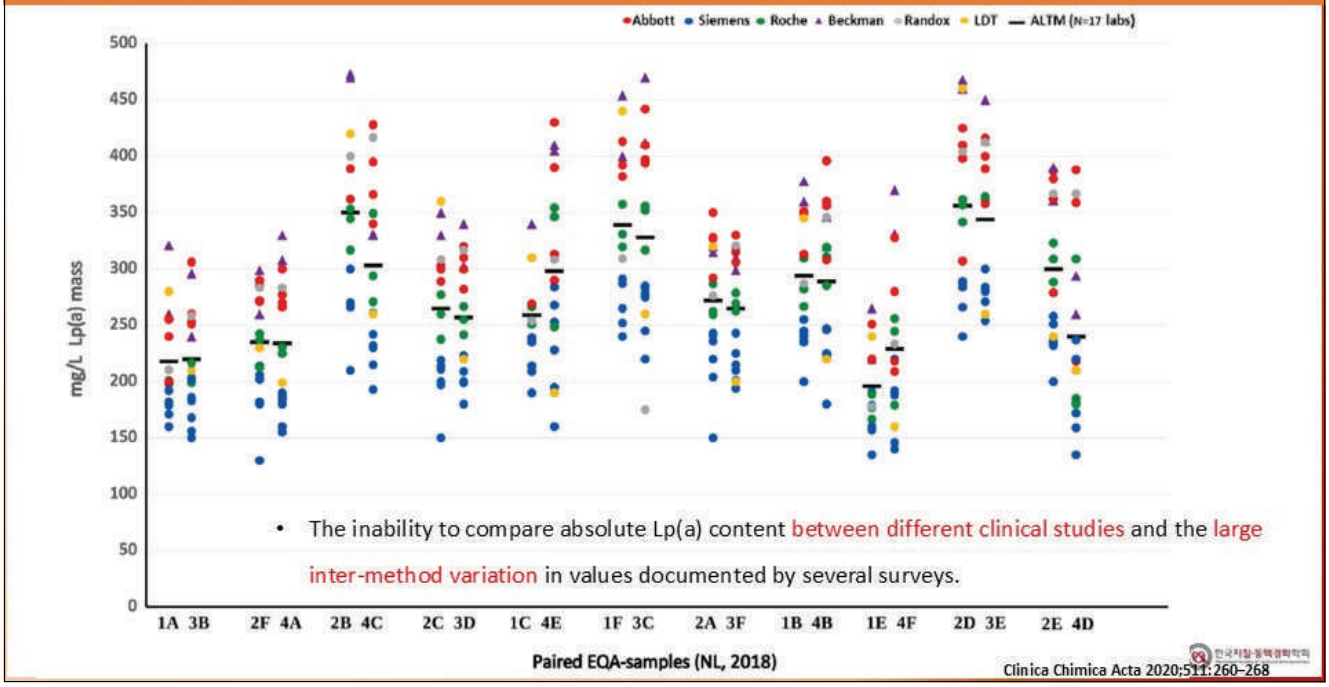
Clinical Chemistry 2023;69:262–272

2024년 01차 정확도기반 지질검사 공통보고서

CAL-24-02 Target value: 36.85 mg/dL

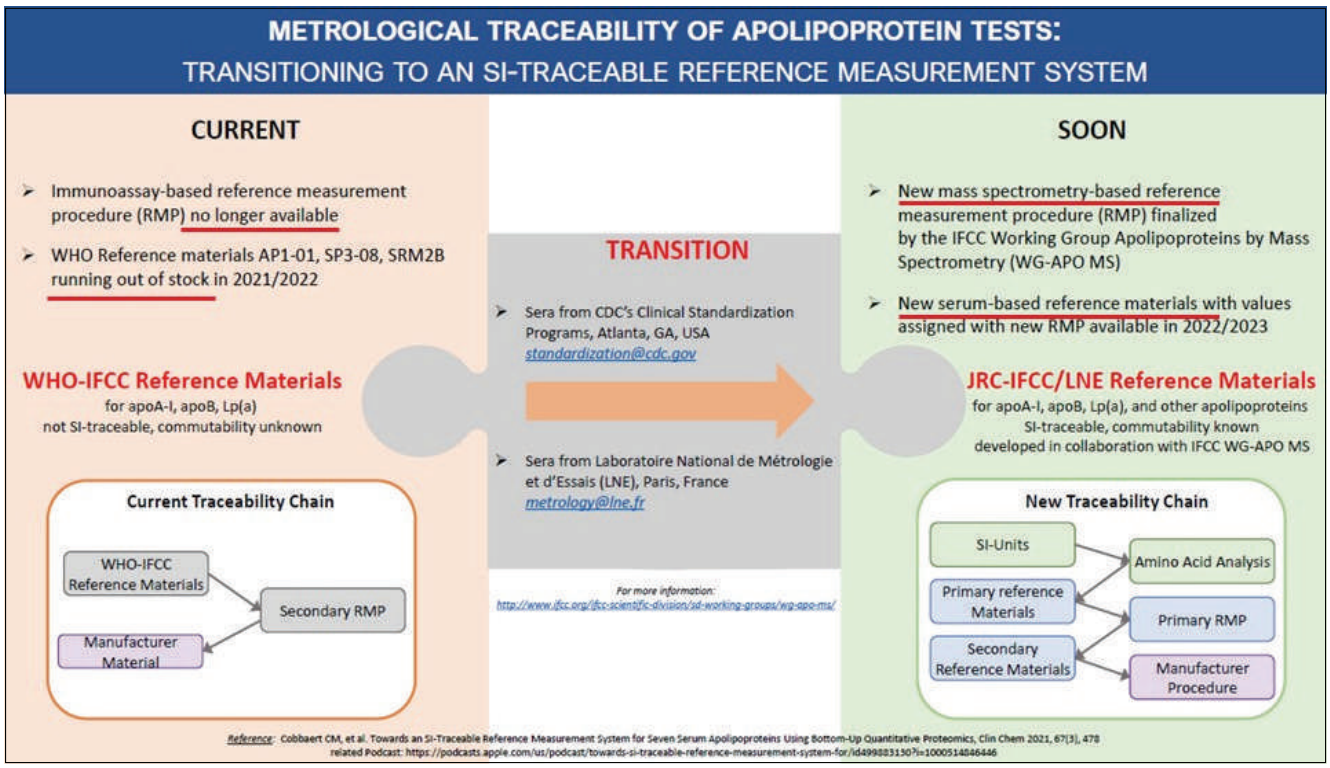
	N	Mean	SD	CV(%)	Median	Min	Max
All	90	36.85	7.42	20.1	40.4	22.6	88.7
Abbott	2					25.6	28.1
Alinity c system	2					25.6	28.1
Beckman Coulter Inc.	13	30.67	6.42	20.9	31.4	22.6	41.1
AU5800 Series	12	30.61	6.70	21.9	29.2	22.6	41.1
AU680	1				31.4		
Canon Medical Systems (구 Toshiba Medical Systems)	4				38.3	24.0	46.9
TBA-2000FR	1				46.9		
TBA-c8000	1				24.0		
TBA-FX8	2					31.8	44.7
Hitachi high-technologies corporation	13	25.12	0.77	3.1	25.2	24.0	39.0
Hitachi 7180	1				25.4		
Hitachi 7600	2					25.6	39.0
Hitachi Labospect 006	2					24.1	24.8
Hitachi Labospect 008AS(S)	3				24.6	24.0	25.2
Labospect 008	5				25.8	25.0	27.5
Roche	51	41.17	1.81	4.4	41.4	31.6	88.7
cobas pro c503	4				41.5	39.1	83.3
cobas6000 c501 with Electrolyte Module	4				40.1	39.3	41.7
cobas8000 c502	2					38.1	41.3
cobas8000 c702	41	41.53	1.66	4.0	41.4	31.6	88.7
Siemens Healthineers	7				44.7	27.9	47.5
Atellica CH 930 Analyzer	6				45.3	43.7	47.5
BN™ II System	1				27.9		

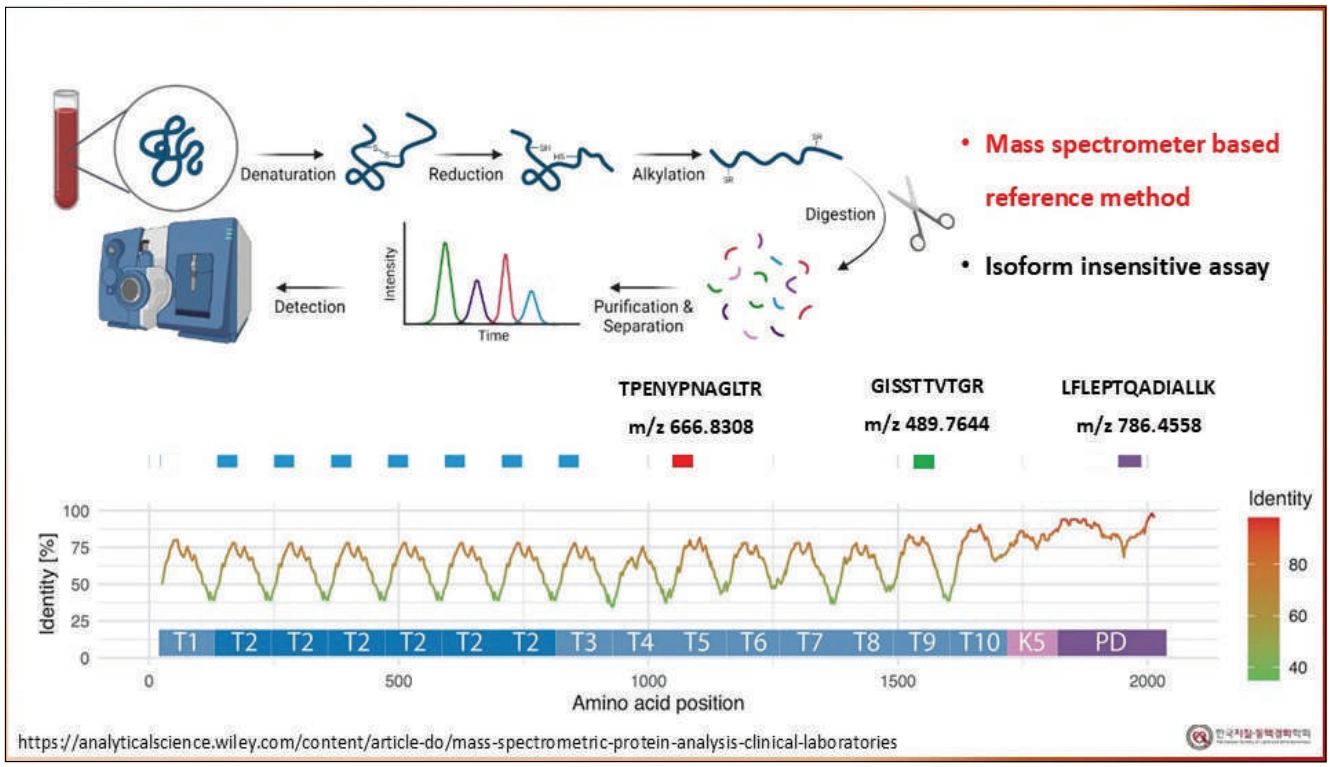
National External Quality Assessment -results of Lp(a) surveys held in 2018 in the Netherlands.
17 labas, 11 rounds



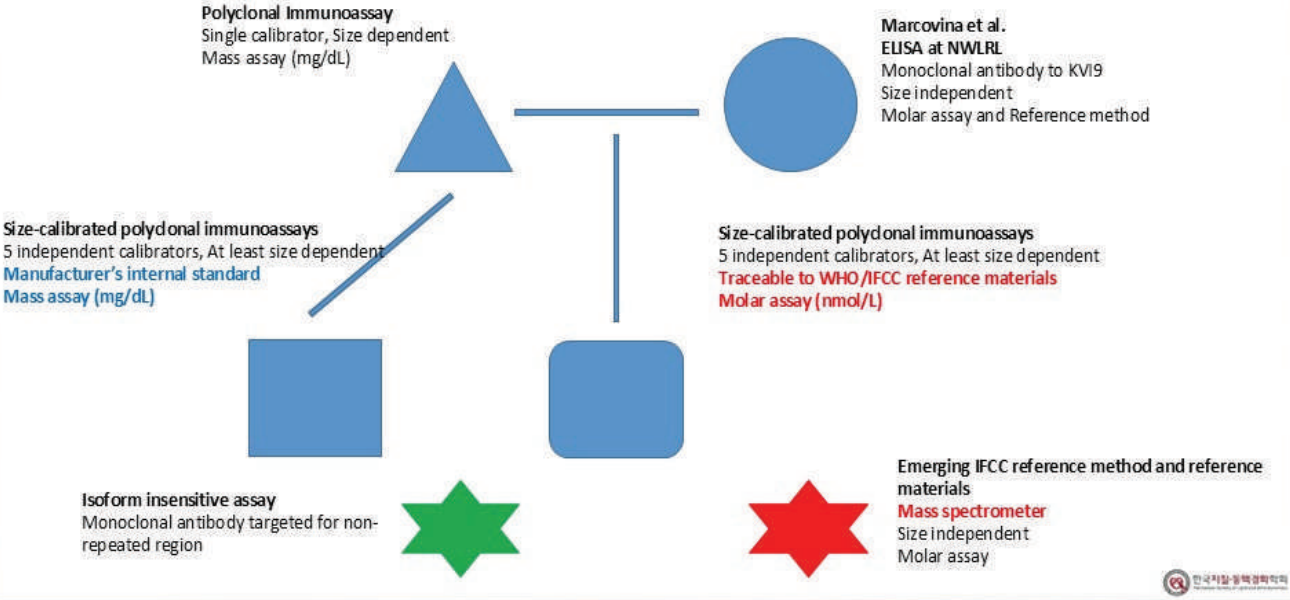
- The inability to compare absolute Lp(a) content between different clinical studies and the large inter-method variation in values documented by several surveys.

Clinica Chimica Acta 2020;511:260–268


METROLOGICAL TRACEABILITY OF APOLIPOPROTEIN TESTS:
TRANSITIONING TO AN SI-TRACEABLE REFERENCE MEASUREMENT SYSTEM
CURRENT
Immunoassay-based reference measurement procedure (RMP) no longer available
WHO Reference materials AP1-01, SP3-08, SRM2B running out of stock in 2021/2022
WHO-IFCC Reference Materials
for apoA-I, apoB, Lp(a)
not SI-traceable, commutability unknown
Current Traceability Chain
WHO-IFCC Reference Materials
Manufacturer Material
Secondary RMP
TRANSITION
Sera from CDC's Clinical Standardization Programs, Atlanta, GA, USA
standardization@cdc.gov
Sera from Laboratoire National de Métrologie et d'Essais (LNE), Paris, France
metrology@lne.fr
For more information:
http://www.ifcc.org/ifcc-scientific-division/sd-working-groups/wg-apo-ms/
SOON
New mass spectrometry-based reference measurement procedure (RMP) finalized by the IFCC Working Group Apolipoproteins by Mass Spectrometry (WG-APO MS)
New serum-based reference materials with values assigned with new RMP available in 2022/2023
JRC-IFCC/LNE Reference Materials
for apoA-I, apoB, Lp(a), and other apolipoproteins
SI-traceable, commutability known
developed in collaboration with IFCC WG-APO MS
New Traceability Chain
SI-Units
Primary reference Materials
Secondary Reference Materials
Amino Acid Analysis
Primary RMP
Manufacturer Procedure
Reference: Cobbaert CM, et al. Towards an SI-Traceable Reference Measurement System for Seven Serum Apolipoproteins Using Bottom-Up Quantitative Proteomics, Clin Chem 2021, 67(3), 478
related Podcast: https://podcasts.apple.com/us/podcast/towards-si-traceable-reference-measurement-system-for/id499883130?i=1000514546446

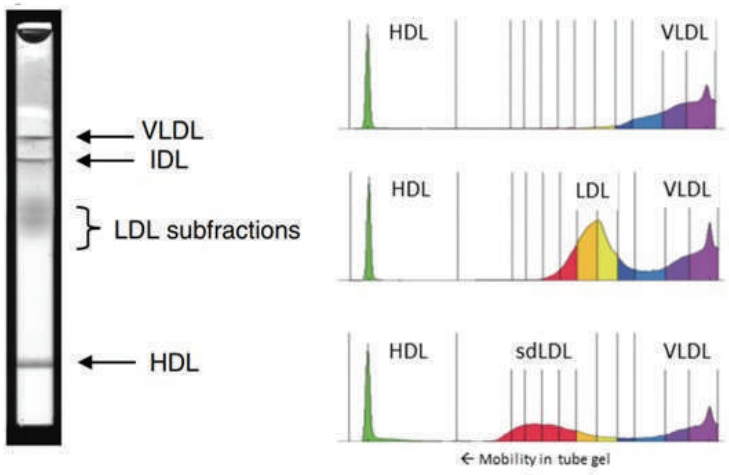

Denaturation
Reduction
Alkylation
Digestion
Purification & Separation
Detection
Intensity
Time
• Mass spectrometer based reference method
• Isoform insensitive assay
TPENYPNAGLTR
m/z 666.8308
GISSTTVTGR
m/z 489.7644
LFLEPTQADIALLK
m/z 786.4558
Identity [%]
Identity
T1 T2 T2 T2 T2 T2 T2 T3 T4 T5 T6 T7 T8 T9 T10 K5 PD
Amino acid position
https://analyticalscience.wiley.com/content/article-do/mass-spectrometric-protein-analysis-clinical-laboratories

Current status of Lp(a) method

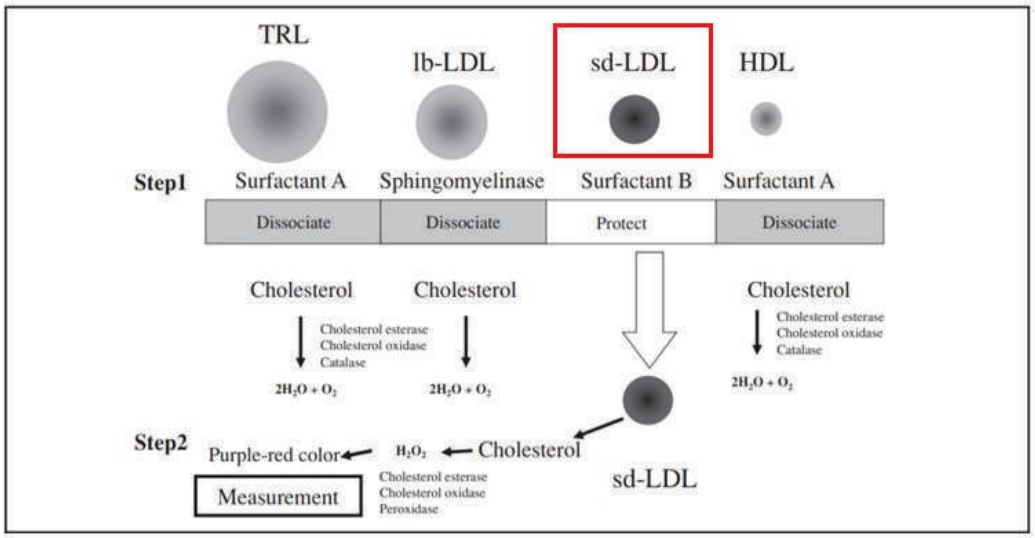


LDL subfraction & sdLDL-C

LDL subfraction separation



Homogenous assay for sd-LDL-C



Clin Chem. 2011;57:57-65.

Thank you!

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발행일 2024년 10월 26일

발행처 한국지질 · 동맥경화학회
[04168] 서울시 마포구 마포대로 68
마포아크로타워 707호
Tel 02-3272-5330, **Fax** 02-3272-5331
E-mail ksla@lipid.or.kr
Homepage www.lipid.or.kr

인쇄소 한국학술정보㈜
Tel 031-940-1007, **Fax** 031-940-9933
E-mail booktory1007@kstudy.com