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Review

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Lipoproteins, Cholesterol, and Atherosclerotic Cardiovascular Disease in East Asians and Europeans

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One fifth of the world population live in East Asia comprising Japan, Korea, and China where ischemic heart disease, a major component of atherosclerotic cardiovascular disease (ASCVD), is the second most frequent cause of death. Each of low-density lipoproteins (LDL), remnant lipoproteins, and lipoprotein(a), summarized as non-high-density lipoproteins (non-HDL) or apolipoprotein B (apoB) containing lipoproteins, causes ASCVD. However, a significant proportion of the evidence on lipoproteins and lipoprotein cholesterol with risk of ASCVD came from White people mainly living in Europe and North America and not from people living in East Asia or of East Asian descent. With a unique biological, geohistorical, and social background in this world region, East Asians have distinctive characteristics that might have potential impact on the association of lipoproteins and lipoprotein cholesterol with risk of ASCVD. Considering the movement across national borders in the World, understanding of lipoprotein and lipoprotein cholesterol evidence on ASCVD in East Asia is important for both East Asian and non-East Asian populations wherever they live in the World.

In this review, we introduce the biological features of lipoproteins and lipoprotein cholesterol and the evidence for their association with risk of ASCVD in East Asian and European populations. We also provide an overview of guideline recommendations for prevention of ASCVD in these two different world regions. Finally, specific preventive strategies and future perspectives are touched upon.

Key words: **Lipid, Triglycerides, Atherosclerosis, Cardiovascular event, Angina, Epidemiology**

Introduction

One fifth of the world population live in East Asia[1)] where atherosclerotic cardiovascular disease (ASCVD) including ischemic heart disease is the second most frequent cause of death next to cancer[2-4)]. Growing attention has been on lipoproteins and lipoprotein cholesterol as causal risk factors for ASCVD; however, a significant proportion of the evidence on lipoproteins and lipoprotein cholesterol with risk of ASCVD come from White people mainly living in Europe and North America and not from people living in East Asian countries or of East Asian descent.

East Asian populations in Japan, Korea, and China have a shared biological background, which could affect the distribution of lipoprotein cholesterol levels, the efficacy of pharmacological interventions, and the incidence of ASCVD, each of which could differ from those in individuals with European and North American background. Geohistorical and social background also influence our lifestyle including food intake, daily exercise, and smoking habits. These unique characteristics of East Asian populations relative to Europeans may have potential impact on the association of lipoproteins with ASCVD.

In this review, we will first introduce the biological features of lipoproteins and lipoprotein cholesterol and compare the lipoprotein and lipoprotein cholesterol levels in different populations.

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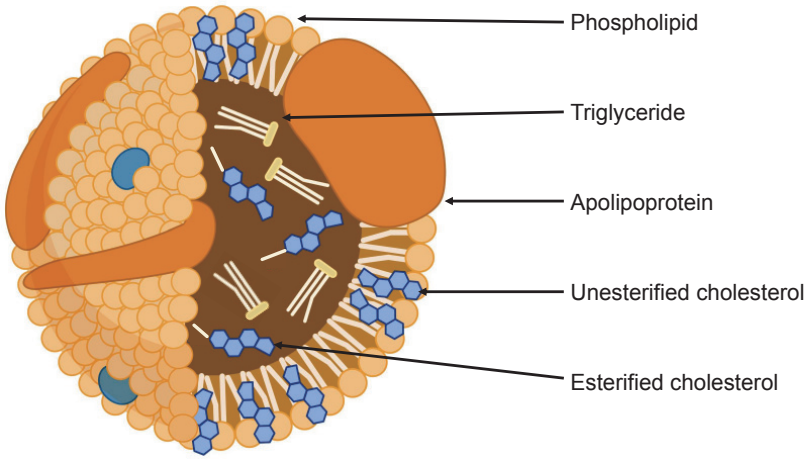

Fig. 1. Structure of a lipoprotein particle

Table 1. Characteristics of human plasma lipoproteins

	Chylomicron	VLDL	IDL	LDL	Lp(a)	HDL
Density, g/mL	<0.95	0.95 – 1.006	1.006 – 1.019	1.019 – 1.063	1.040 – 1.130	1.063 – 1.210
Diameter, nm	>70	27 – 70	22 – 24	19 – 23	27 – 30	4 – 10
Lipid composition, % of total mass						
Cholesterol*	5	19	38	50	38	20
Triglycerides	86	55	23	6	8	4
Major apolipoproteins	B48	B100	B100	B100	B100	
	A-I	C-I	E		(a)	A-I
	C-I	C-II				A-II
	C-II	C-III				
	C-III	E				

*Cholesterol is unesterified and esterified cholesterol combined.
HDL=high-density lipoprotein; IDL=intermediate-density lipoprotein; LDL=low-density lipoprotein; Lp(a)=lipoprotein(a); VLDL=very-low-density lipoprotein.
Data are from [5], modified.

Next, the role of lipoproteins in atherosclerosis and atherothrombosis will be discussed. Further, the current evidence of different lipoprotein and lipoprotein cholesterol in the association with risk of ASCVD will be described. We also provide an overview of guideline recommendations for prevention of ASCVD in East Asian and European populations. Finally, specific preventive strategies and future perspectives are touched upon.

Lipoproteins

Lipoproteins are spherical macromolecular complex particles that primarily transport hydrophobic lipid molecules in water such as blood plasma[5, 6]. Like a micelle, lipoproteins contain more hydrophobic lipids (e.g. triglycerides and esterified cholesterol) in their core and more hydrophilic lipids (e.g. phospholipid and unesterified cholesterol) on their surface[7] **(Fig. 1)**.

Lipoproteins have different physical and chemical characteristics because they contain different proportions of core lipids and surface lipids and proteins. They also contain one or more apolipoproteins in order to 1) maintain the structure of the lipoprotein particles, 2) facilitate uptake of lipoproteins into cells through recognition by receptors, and 3) activate or inhibit enzymes in metabolic pathways[8].

Lipoproteins are categorized mainly on the basis of their densities determined by ultracentrifugation **(Table 1)**[9]. The major lipoprotein fractions include chylomicrons, VLDL (very-low-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), HDL (high-density lipoprotein), and Lp(a) [lipoprotein(a)]. Traditionally, lipoprotein

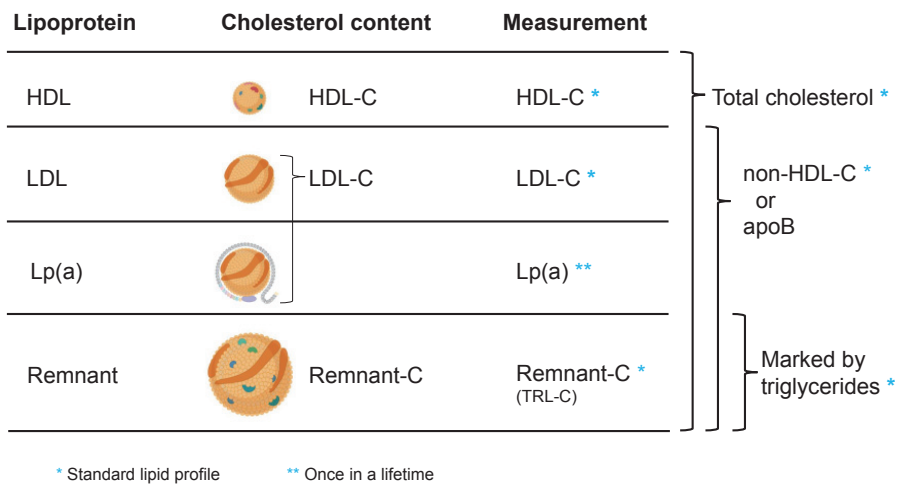

Fig. 2. Lipoprotein particles, cholesterol content of the particles, and laboratory measurement for lipid profiles

Cholesterol content of lipoprotein particles can be measured by quantitative enzymatic methods in routine assay. This means cholesterol content of HDL, LDL, and remnants are measured as HDL cholesterol, LDL cholesterol, and remnant cholesterol. Apolipoprotein B-containing lipoprotein cholesterol includes LDL cholesterol, remnant cholesterol, and cholesterol content of Lp(a), summarized as non-HDL cholesterol. Remnant cholesterol or triglyceride-rich lipoprotein cholesterol are marked by plasma triglyceride levels.
Remnant cholesterol can be calculated as total cholesterol *minus* LDL cholesterol *minus* HDL cholesterol or measured directly by an automated assay from Denka Co. Ltd. (Tokyo, Japan) called triglyceride-rich lipoprotein cholesterol (TRL-C)[72].
*represents standard lipid panel.
**Lp(a) should be measured at least one in a lifetime.
HDL=high-density lipoprotein; HDL-C=high-density lipoprotein cholesterol, LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; Lp(a)=lipoprotein(a); non-HDL-C=non-high-density lipoprotein cholesterol; Remnant-C=remnant cholesterol; TRL-C=triglyceride-rich lipoprotein cholesterol.

concentrations have been measured and expressed in terms of mass concentration of their cholesterol content (total cholesterol, LDL cholesterol, HDL cholesterol, etc.)[10]. Non-HDL cholesterol represents the cholesterol content of apolipoprotein B containing lipoproteins [ApoB-containing lipoproteins; LDL, remnants, and Lp(a)] which cause atherosclerosis and/or atherothrombosis resulting in ASCVD. A standard lipid profile includes total cholesterol, HDL cholesterol, and triglycerides historically; however, it can be expanded to include LDL cholesterol[11-13], non-HDL cholesterol, and remnant cholesterol (as currently in use in Copenhagen, Denmark) because they can be calculated free of charge and are all important as good predictors of ASCVD risk **(Fig. 2)**. In addition, lipoprotein(a) should be measured in all at least once in a lifetime, while apolipoprotein B is useful together with non-HDL cholesterol to evaluate residual ASCVD risk in individuals with low LDL cholesterol.

Lipoprotein and Lipoprotein Cholesterol Levels in Different Populations

Typical mean levels of LDL cholesterol, remnant cholesterol, and Lp(a) total mass in different populations are shown in **Fig. 3**. LDL cholesterol levels are lower in East Asians than in Europeans; however, remnant cholesterol levels appear to be similar amongst East Asians and Europeans. Lp(a) levels differ slightly among individuals in these countries. However, when comparing Lp(a) levels to those in Africans (up to 4-fold higher than levels in Europeans[14]), the minor differences between East Asians and Europeans are mitigated. LDL cholesterol levels are distributed normally, while levels of remnant cholesterol and Lp(a) are skewed with a tail toward higher levels. The distributions are similar between East Asians and Europeans **(Fig. 4)**.

Pathophysiological Link from Elevated Lipoproteins with Atherosclerosis and Atherothrombosis

After the first description by Adolf Windaus in 1910, numerous studies has confirmed the association of elevated lipoproteins with atherosclerosis[15].

Atherosclerosis starts with the retention and accumulation of cholesterol-rich apoB-containing lipoproteins in the arterial intima **(Fig. 5)**. Human

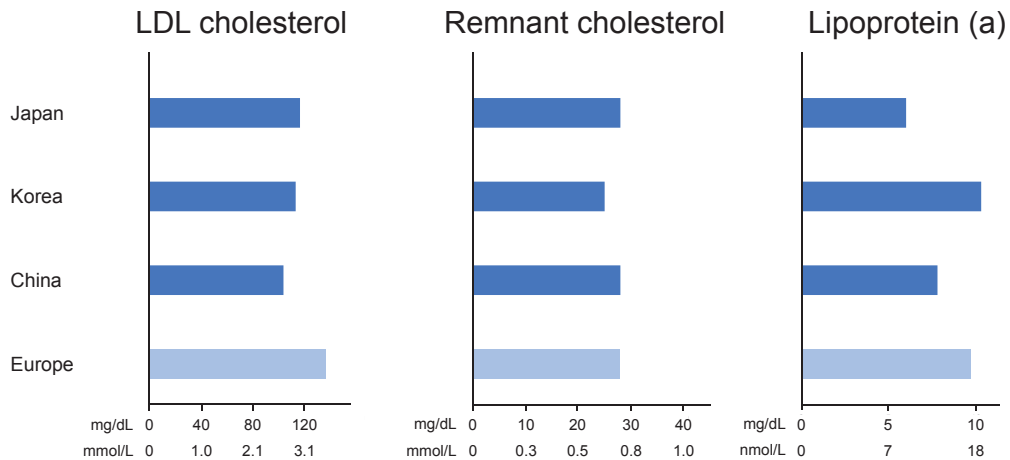

Fig. 3. Lipid levels in East Asians and Europeans

Mean levels of LDL and remnant cholesterol and median levels of Lp(a) are shown. Data are from the National Health and Nutrition Survey in Japan, 2019 (n=1,917)[151], Hamamura *et al.* (n=674)[152], the Korea National Health and Nutrition Examination Survey, 2005 (n=5,323)[153], the Kangbuk Samsung Health Study [n=41,860 for Lp(a) to include only individuals using Cobas 8000 c702 (Roche Diagnostics)][120], the China National Diabetes and Metabolic Disorders Study (n=46,239)[154], the INTERHEART study (n=2,407 for Chinese population without history of heart disease)[119] and the Copenhagen General Population Study (n=6,747 with fasting blood samples without lipid lowering treatment)[155]. All data are from fasting blood samples. Chinese data includes individuals on lipid lowering therapy whereas Japanese, Korean, and European data are from individuals without lipid lowering therapy.
LDL cholesterol shown was calculated by the Friedewald formula.
Mean remnant cholesterol was calculated from mean total cholesterol *minus* mean LDL cholesterol *minus* mean HDL cholesterol.
The conversions were done by the following equation: LDL cholesterol (mmol/L)=LDL cholesterol (mg/dL) * 0.026, Remnant cholesterol (mmol/L)=Remnant cholesterol (mg/dL) * 0.026, Lp(a) (nmol/L)=2.18 * Lp(a) (mg/dL)−3.83 [156].
HDL=high-density lipoprotein; LDL=low-density lipoprotein; Lp(a)=lipoprotein(a).

and animal studies have demonstrated that apo-B containing lipoproteins <70 nm in diameter including LDL, remnants, and Lp(a) can enter into the arterial intima and that they cannot penetrate further into the media due to their large size relative to the fenestra of the media[16-18]. Some of these lipoprotein particles do not return to the blood stream and stay in the intima partly due to the blood pressure gradient from high pressure in the arterial lumen to low pressure at the adventitia as well as due to binding of lipoproteins to proteoglycans in the intima. These lipoproteins then become susceptible to oxidation and other chemical modifications.

Leukocytes including monocytes and T-lymphocytes are recruited to the lesion after the accumulation of lipoprotein particles. Once monocytes are recruited to the arterial intima, they internalize lipids, become foam cells or lipid-laden macrophages **(Fig. 5)**[19]. From this process, nascent atheroma or so-called fatty streaks are developed. Subsequently, arterial smooth muscle cells from the underlying media advances into the intima or arise from blood-borne precursors to advance atheroma[20]. Extracellular matrix macromolecules including interstitial collagens and proteoglycans also contribute to the advancement of atheroma[21] and ultimately can lead to ASCVD. Inflammatory cytokines formed by intimal cells secondary after degradation of triglycerides to tissue toxic free fatty acids from lipoprotein particles[22] and other causes[23-26] may also contribute to the accumulation of inflammatory and arterial smooth muscle cells, the advancement of extracellular matrix macromolecules, and the vulnerability of the arterial plaque which may subsequently lead to atherothrombotic events.

Atherosclerotic plaques and in particular unstable plaques can rupture, leading to development of atherothrombus with activated platelets and fibrin deposits. Lp(a) might inhibit fibrinolysis due to homology of apolipoprotein(a) with plasminogen, which indirectly could support atherothrombus growth **(Fig. 5)** leading to myocardial infarction, unstable angina and stroke.

LDL

LDL is an apoB-containing, cholesterol-rich lipoprotein with a diameter of 19-23 nm **(Table 1)** and is the key deliverer of cholesterol to the arterial intima in most individuals. Entrance into the intima of LDL and other lipoproteins is increased by leakiness of the arterial wall, by higher lipoprotein

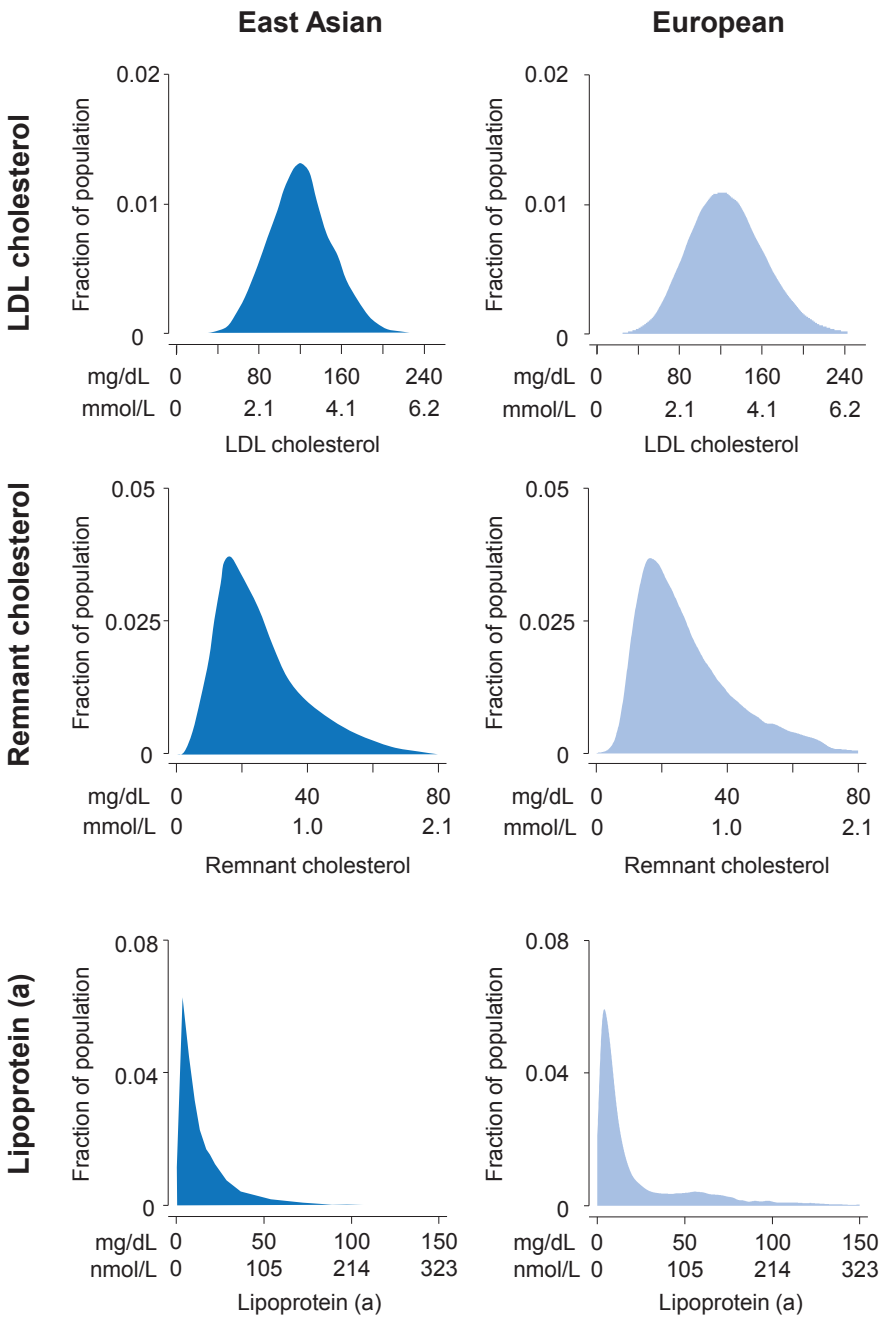

Fig. 4. Distribution of lipid levels in East Asians and Europeans

Data are from the National Health and Nutrition Survey in Japan, 2019 (LDL cholesterol and remnant cholesterol, $n=1,917$)[151], the report by Lin L. *et al.* [Lp(a), $n=411,634$][157], and the Copenhagen General Population Study ($n=6,747$)[71]. All data are from fasting blood samples
In East Asian populations, the distributions of LDL cholesterol and remnant cholesterol were drawn manually by the authors based on the values reported. This means these figures might be slightly different from the real distribution; however, the authors provide best possible information in order to improve readers' understanding. The distribution of Lp(a) was from the report by Lin L. *et al* with modification.
The conversions were done by the following equation: LDL cholesterol (mmol/L)=LDL cholesterol (mg/dL) * 0.026, Remnant cholesterol (mmol/L)=Remnant cholesterol (mg/dL) * 0.026, Lp(a) (nmol/L)=2.18 * Lp(a) (mg/dL)−3.83 [156].
Remnant cholesterol (mg/dL) was calculated from triglycerides in mg/dL divided by 5.
LDL=low-density lipoprotein; Lp(a)=lipoprotein(a).

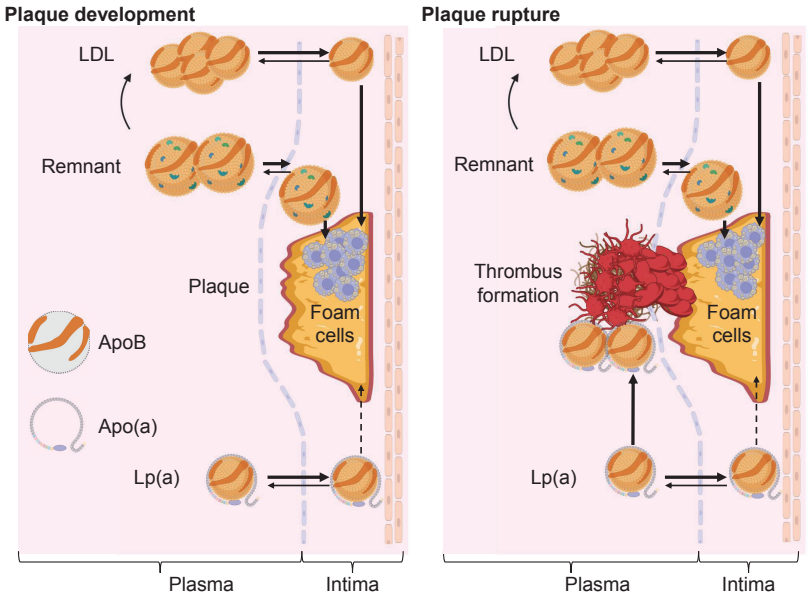

Fig. 5. Role of lipoproteins in atherosclerotic plaque development, rupture and thrombus formation

Plaque development: LDL and remnants enter the intima and are trapped there partly due to pressure gradient and due to the attachment of glycosaminoglycan. Both lipoproteins can be taken up by macrophages to produce foam cells which are a principal component of initial atherosclerosis. Lp(a) also enters to the intima like LDL and remnants; however, it is still unclear whether Lp(a) is taken up by macrophages and produce foam cell. Under the high plasma levels of LDL and remnants and possibly Lp(a) as well, growing number of inflammatory cells including foam cells develop resulting in enhanced formation of atherosclerotic plaques.
Plaque rupture: Plaque can be ruptured with mechanical stress resulting thrombus formation with activated platelets and fibrin deposits. Lp(a) might inhibit fibrinolysis which indirectly support thrombus formation causing acute complication of atherosclerosis including myocardial infarction, unstable angina, and stroke.
LDL=low-density lipoprotein; Lp(a)=lipoprotein(a).

concentration in plasma, and by higher blood pressure[27]. Accumulated LDL in the subendothelial space is phagocyted by macrophage-derived foam cells after lipid and protein components have experienced oxidation, aggregation, or other modifications. Through these processes, LDL contribute to develop atherosclerosis and finally cause ASCVD.

Measurement or Calculation of LDL Cholesterol

Historically, the cholesterol content of LDL (or LDL cholesterol) can be measured by indirect methods called the CDC (center for disease control) reference method or beta-quantification[10]. In this method, VLDL and chylomicrons are removed by ultracentrifugation of plasma or serum as a floating layer at the top of centrifuge tube (density ≤ 1.006 g/mL) **(Table 1)**. After removing this layer (density ≤ 1.006 g/mL) and measuring HDL cholesterol directly, LDL cholesterol is calculated by the following:

LDL cholesterol=(cholesterol in particles with density >1.006 g/mL) *minus* (HDL cholesterol).

In this context, measurement of LDL cholesterol includes cholesterol in IDL and Lp(a); however, cholesterol content of IDL and Lp(a) in most individuals contribute with a minor fraction of the total LDL cholesterol value.

LDL cholesterol can also be calculated using plasma total cholesterol, HDL cholesterol, and plasma triglycerides levels by the Friedewald[11], Martin-Hopkins[12], and Sampson-NIH[13] equations. Further, LDL cholesterol can be measured directly using a homogeneous assay.

LDL and ASCVD

From prospective epidemiologic observational studies, genetic Mendelian randomization studies, to randomized clinical trials, elevated LDL cholesterol levels are consistently causally associated with increased risk of ASCVD[28, 29]. Animal models likewise support this conclusion.

The Emerging Risk factors Collaboration have shown the results of meta-analysis of 68 prospective cohort studies[30]. In sub-analyses of this meta-analysis, individuals with directly measured LDL cholesterol (44,234 individuals with 2,076 cases from 8 studies), elevated LDL cholesterol levels were associated with increased risk of coronary heart disease [hazard ratio (HR) 1.39, 95% confidence interval (CI) 1.09-1.78

Table 2. Evidence for lipoproteins related to atherosclerotic cardiovascular disease

	Observational	Causal	
		Genetic Mendelian randomization	Randomized controlled trial
LDL cholesterol	Yes[30-37]	Yes[38-41]	Yes[42-44]
Remnant cholesterol	Yes[30, 80, 82-88]	Yes[41, 89, 90]	Conflicting[74, 95-100]
Lp(a)	Yes[118-121]	Yes[114, 115]	Ongoing[131, 132]
HDL cholesterol	Yes[30, 139]	No[89, 90]	No[95-98, 145-147]

HDL=high-density lipoprotein; LDL=low-density lipoprotein; Lp(a)=lipoprotein(a).

in an age and sex adjusted model]. The association of elevated LDL cholesterol levels with increased risk of ASCVD is likewise reported from prospective cohort studies in East Asia[31-37].

Genetic Mendelian randomization studies from European ancestry consistently revealed that variants associated with lower LDL cholesterol levels are associated with reduced risk of ASCVD[38-41]. When plotting the effect of every LDL cholesterol associated variant on risk of ASCVD, there is dose-dependent association between the absolute difference in LDL cholesterol and the risk of ASCVD[28].

Randomized controlled studies using statins provided the evidence that lowering of LDL cholesterol reduced the risk of ASCVD[42-44]. From a meta-analysis of individual-participant data from 14 randomized controlled trials comparing statin treatment with placebo including 90,056 individuals, statin treatment reduced the risk of myocardial infarction or coronary death by 23%, any vascular event by 21%, and all-cause mortality by 12% when LDL cholesterol was reduced by 39 mg/dL (1 mmol/L)[42]. Similar risk reductions were observed in a meta-analysis including data from 39,612 individuals in 5 randomized controlled trials comparing more versus less intensive statin therapy[43]. Other lipid lowering therapies ranging from conventional bile acids, lifestyle interventions, and surgical ileal bypass to the more current ezetimibe, PCSK9 inhibitors, and bempedoic acid have also documented decreased risk of ASCVD[45-50].

In an East Asian context, several important randomized controlled trials have been carried out. Among 3,966 individuals from Japan for primary prevention enrolled in the MEGA study, diet modification plus treatment with 10-20 mg pravastatin daily lowered the incidence of coronary heart disease more than diet modification alone (HR 0.67, 95%CI 0.49-0.91; P=0.01)[51]. The efficacy of intensive statin therapy was demonstrated in the REAL-CAD study that enrolled 13,054 Japanese individuals with stable coronary artery disease[52]. In this trial, the high-dose pitavastatin group (4 mg/day) experienced a lower incidence of the primary cardiovascular composite end point (HR 0.81, 95%CI 0.69–0.95, P=0.01) and all-cause mortality (HR 0.81, 95%CI 0.68–0.98, P=0.03) than low dose group (1 mg/day).

The results from epidemiological observational studies, genetic Mendelian randomization studies, and randomized controlled trials provide strong evidence that LDL cholesterol is causally associated with the risk of ASCVD **(Table 2)**.

Treatment Strategy

From the accumulated evidence that high LDL cholesterol causes ASCVD, current Japanese, Korean, Chinese, European, and American guidelines recommend targeting high LDL cholesterol levels for primary and secondary prevention purposes **(Table 3, 4)**[53-62].

Statins inhibiting the HMG-CoA reductase in liver cells and thereby endogenous cholesterol synthesis are recommended as first line therapy to decrease levels of LDL cholesterol and the incidence of ASCVD. The intensity of statins is defined by the doses reducing LDL cholesterol to a certain extent: high-intensity is for LDL cholesterol reduction by ≥ 50% while moderate-intensity is for 30-50% reduction – intensity is however not defined as the specific statin dose[61, 62], which is especially important in an East Asian context. Indeed, there is considerable variation of the LDL cholesterol reduction obtained with the same doses of statins between people of East Asian and European descent **(Fig. 6)**. To reach LDL cholesterol reduction by 50%, atorvastatin 80 mg/day or rosuvastatin 20 mg/day are needed in a combined population mainly from Europe and America while atorvastatin 20 mg/day or rosuvastatin 5-10 mg/day are enough in the Japanese population[63, 64]. There are also significant interindividual variation of statin doses to reach similar percent reductions of LDL cholesterol. Therefore, treat-to-target statin treatment is recommended especially in the East Asian context

Table 3. Lipid profile assessment

	ASCVD causality	Pancreatitis causality	Assessment for
LDL cholesterol	Yes		ASCVD risk
Remnant cholesterol	Yes		ASCVD risk
Lp(a)	Yes		ASCVD risk
non-HDL cholesterol			ASCVD residual risk
Apolipoprotein B			ASCVD residual risk
Total cholesterol			
HDL cholesterol			
Triglycerides		Yes	Pancreatitis risk

ASCVD=atherosclerotic cardiovascular disease; HDL=high-density lipoprotein; LDL=low-density lipoprotein; Lp(a)=lipoprotein(a).

Table 4. Lipoprotein target for prevention of atherosclerotic cardiovascular disease in different guidelines

Target	Japan 2022 [53, 54]	Korea 2022 [55-57]	China 2021 [58-60]	Europe 2019 [61]	US 2018 [62]
Primary prevention: Diabetes, CKD, and absolute 10-year risk based					
LDL cholesterol	Yes	Yes	Yes	Yes	Yes
non-HDL cholesterol	Yes	Yes	Yes	Yes	
Apolipoprotein B				Yes	
Primary prevention: Familial hypercholesterolemia					
LDL cholesterol	Yes	Yes	Yes	Yes	Yes
Secondary prevention: ASCVD					
LDL cholesterol	Yes	Yes	Yes	Yes	Yes
non-HDL cholesterol	Yes	Yes	Yes	Yes	Yes
Apolipoprotein B				Yes	

ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; HDL=high-density lipoprotein; LDL=low-density lipoprotein.

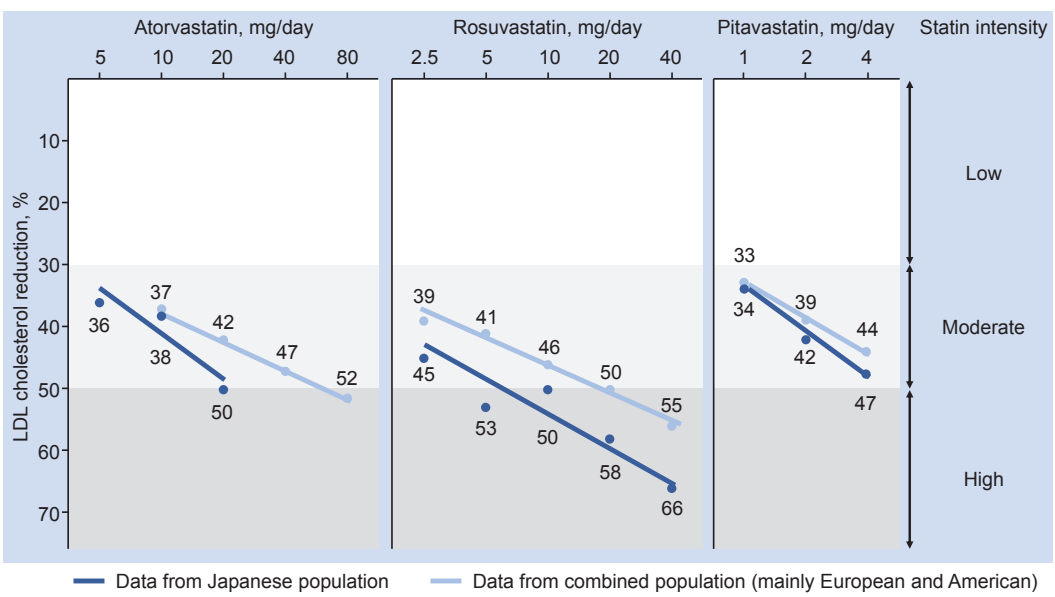

Fig. 6. Statin dose and LDL cholesterol reduction in East Asians and Europeans

LDL cholesterol reduction in different doses of statins in East Asian (Japanese, dark blue)[64, 158, 159] and mixed population mainly Whites in Europe and North America (light blue)[63, 160, 161] are drawn from results of randomized clinical trials and meta-analyses of such studies. LDL=low-density lipoprotein.

Table 5. Expected low-density lipoprotein cholesterol reduction by lipid-lowering therapies

	Average LDL cholesterol reduction
Treatment	
Low-intensity statin	<30%
Moderate-intensity statin	≈30%
Moderate-intensity statin + ezetimibe	≈45%
High-intensity statin	≈50%
High-intensity statin + ezetimibe	≈65%
PCSK9 inhibitor	≈60%
High-intensity statin + PCSK9 inhibitor	≈75%
High-intensity statin + ezetimibe + PCSK9 inhibitor	≈85%

LDL=low-density lipoprotein; PCSK9=proprotein convertase subtilisin/kexin type 9.
Table contents are modified from Mach *et al*[61].

although some guidelines recommended to initiate statin treatment with high-intensity statin. In fact, among 4,400 Korean individuals, non-inferiority of treat-to-target statin versus high-intensity statin for prevention of ASCVD has been shown in individuals with coronary artery disease[65].

Ezetimibe inhibiting transmembrane protein NPC1L1 (Niemann/Pick C1 like 1) which lowers intestinal uptake of dietary and biliary cholesterol reduces LDL cholesterol levels by 20% or an additional 15% when given on top of a statin **(Table 5)**. Monoclonal antibodies inhibiting PCSK9 (proprotein convertase subtilisin/kexin 9) which lower the rate of LDL receptor degradation reduce LDL cholesterol levels up to 60% in monotherapy **(Table 5)**. These two lipid-lowering drugs have evidence of efficacy for prevention of ASCVD on top of statin in large randomized controlled studies[47-49]. In addition, lipid-lowering therapies through gene silencing technology which need less frequent administration have been developed. Twice-yearly administration of inclisiran, a small interfering RNA (siRNA) which inactivates PCSK9 decreases LDL cholesterol levels by up to 50%[66]. Also, lomitapide[67], a microsomal triglyceride transfer protein (MTP) inhibitor and mipomersen, an antisense oligonucleotide targeting apolipoprotein B100 are also possible treatments for specific population (e.g. homozygous familial hypercholesterolemia)[68, 69]. Finally, in individuals who cannot or will not take a statin, bempedoic acid inhibiting ATP citrate lyase in liver cells and thereby inhibiting endogenous cholesterol synthesis can reduce LDL cholesterol by 21% and consequently the risk of ASCVD by 13%[50].

Remnants (Remnant Lipoproteins or Triglyceride- & Cholesterol-Rich Lipoproteins)

Remnants (chylomicron remnants, VLDL, and IDL) include the lipolytic products of the nascent very large triglyceride-rich lipoproteins including VLDL and chylomicrons, with apoB as the major structural protein like in LDL. Remnants are larger in size and contain both more triglycerides and cholesterol per particle in terms of mass than LDL. Remnants when including IDL contain one third of total plasma cholesterol[70]. On a relative scale, the triglyceride content is larger and the cholesterol content is smaller in remnants than in LDL **(Table 1)**.

Immediately after entering the plasma, lipoprotein lipase degrades the triglyceride component of chylomicrons, VLDL and their remnants releasing free fatty acids[22]. During lipolysis while remnants become smaller, the triglyceride content decreases, and cholesterol ester content increase due to the cholesteryl ester-transporter protein (CETP) mediated pathway.

Measurement or Calculation of Remnant Cholesterol

The cholesterol content of remnants [or remnant cholesterol, triglyceride-rich lipoprotein cholesterol (TRL-C)] can be calculated as[71]

Remnant cholesterol=total cholesterol−HDL cholesterol−LDL cholesterol

Using this equation, remnant cholesterol can be calculated by directly measured total cholesterol, HDL cholesterol, and LDL cholesterol, or for the latter by LDL cholesterol calculated as mentioned above. When using the Friedewald equation to calculate LDL cholesterol, remnant cholesterol levels are equal to triglycerides in mg/dL divided by 5 or triglycerides in mmol/L divided by 2.2. From these equations, plasma triglyceride levels can be a good surrogate for remnants

(Fig. 2). Remnant cholesterol can also be measured by a direct assay from Denka, Tokyo, Japan (TRL-C assay)[72-74]. In some studies, the term remnant-like particle cholesterol (RLP-C) is also used; however, this captures only a fraction of the remnant cholesterol referred to above, typically around 15%.

Remnants and ASCVD

Prospective population-based cohort studies from Copenhagen in Denmark (the Copenhagen General Population Study: the CGPS and the Copenhagen City Heart Study: the CCHS) with >100,000 individuals demonstrated the association of elevated remnant cholesterol levels with increased risk of ASCVD. Individuals with calculated remnant cholesterol ≥ 58 mg/dL (1.5 mmol/L) had HRs of 2.4(95%CI 1.9–2.9) for ischemic heart disease (IHD)[75], 4.8(3.1–7.5) for peripheral artery disease[76], and 1.4(1.1-1.8) for aortic valve stenosis[77] in a primary prevention setting and a sub-hazard ratio for recurrent major adverse cardiovascular events (MACE) of 1.8(1.3–2.5) in a secondary prevention setting[78], all compared to those with remnant cholesterol <19 mg/dL (0.5 mmol/L)[71]. Similar results for myocardial infarction have been shown using directly measured remnant cholesterol in the CGPS[73]. Another study from China analyzed 1,716 individuals with previous acute coronary syndrome and found that individuals with calculated remnant cholesterol levels >30 mg/dL (0.79 mmol/L; 75th percentile) had a higher incidence of MACE than those with remnant cholesterol levels ≤ 30 mg/dL (HR: 1.57, 95%CI:1.25-1.98, $P<0.001$)[79].

Consistent results were reported when using plasma triglycerides levels as a surrogate of remnant cholesterol[30, 80]. From the detailed analyses in the Emerging Risk Factors Collaboration, HRs for coronary heart disease per 1-standard deviation higher plasma triglycerides were 1.37(1.31-1.42) in a multivariable adjusted model. However, corresponding HR was 0.99(0.94-1.05) after further adjustment for HDL cholesterol and non–HDL cholesterol[30]. These results reflect that non-HDL cholesterol is the sum of LDL and remnant cholesterol and that triglycerides and HDL cholesterol are highly inversely correlated[81]. Said differently, when the association of elevated plasma triglycerides with increased ASCVD risk is adjusted for the cholesterol content of remnants (and additionally for the long-term marker of elevated triglycerides: HDL cholesterol[81]), the association is no longer apparent. The association of elevated remnant cholesterol levels or plasma triglycerides levels with increased risk of ASCVD is also reported in several prospective cohort studies from East Asia[82-88].

From genetic Mendelian randomization studies, elevated remnant cholesterol is causally associated with increased risk of ASCVD. In a study including 73,513 individuals from the CGPS, the CCHS, and the Copenhagen Ischemic Heart Study analyzing gene variants associated with both high remnant cholesterol and low HDL cholesterol and gene variants only associated with low HDL cholesterol, they found the causal risk estimates of ischemic heart disease (IHD) were 2.82(95%CI: 1.92-4.15) for a 1 mmol/L increase in remnant cholesterol and 0.74(0.40-1.37) for 1 mmol/L decrease in HDL cholesterol[89]. These analyses mean that gene variants related to lifelong elevated remnant cholesterol and reduced HDL cholesterol levels were causally associated with increased risk for IHD, whereas gene variants only related to lifelong reduced HDL cholesterol levels were not associated with increased risk for IHD. Moreover, analyses including 188,577 individuals and 185 common variants carefully assessed the association with lipid levels including triglycerides, HDL cholesterol, and LDL cholesterol, demonstrated that gene variants which increase or decrease triglyceride levels are genetically associated with increased or decreased risk of coronary artery disease[90]. From these analyses, they concluded that there is a causal role of triglyceride-rich lipoproteins (= remnants) in the development of coronary artery disease even after accounting for the variants' effect on HDL cholesterol and/or LDL cholesterol levels, and that elevated remnant cholesterol *per se* is causally related to increased risk for coronary artery disease. Later numerous later Mendelian randomization studies have confirmed this conclusion[91].

Even with these accumulated evidence from epidemiologic observational studies and genetic Mendelian randomization studies, most randomized controlled trials especially published in the statin era did not confirm whether lowering of triglycerides and remnant cholesterol reduce the risk of ASCVD. This could be partly because many trials have excluded individuals with elevated triglycerides >400 mg/dL (4.5 mmol/L) and included individuals with both low and mild-to-moderately elevated triglycerides. Concomitant administration of statins which also contributes to clear remnant cholesterol from the blood is another reason why it is difficult to demonstrate the efficacy of other remnant cholesterol lowering therapies for prevention of ASCVD, that is, when it is given on top of statins, plasma triglycerides and remnant cholesterol have already reduced to some extent. In fact, although several fibrate and niacin trials have shown positive results for prevention of ASCVD in the pre-statin era[92-94], clinical trials did not show clear benefit on prevention of ASCVD

mainly on top of statin treatment[74, 95-98]. Moreover, randomized placebo-controlled trials using omega-3 fatty acids as well as statins for prevention of ASCVD showed contrasting results mainly in the Western population (REDUCE-IT and STRENGTH)[99, 100]. These contrasting results could be explained by the different composition of the omega-3 fatty acids (eicosapentaenoic acid, EPA and EPA+docosahexaenoic acid, DHA) or different comparator oil (placebo)[101].

In the East Asian context, in the JELIS trial with 18,645 Japanese individuals with hypercholesterolemia, EPA on top of statins showed a 19% relative reduction of major coronary events[102]. From these results as well as the results from the REDUCE-IT trial[99], EPA not EPA+DHA could be beneficial; however, further investigations are needed to conclude the efficacy of omega-3 fatty acids.

In summary, the results from epidemiological observational studies and genetic Mendelian randomization studies showed a causal association of elevated remnant cholesterol with increased risk of ASCVD **(Table 2 and Table 3)**. Results from randomized controlled trials need further evidence **(Table 2)**, as we need randomized trials in people included due to elevated remnant cholesterol (and not just elevated plasma triglycerides) with the use of drugs that not only lower remnant cholesterol and plasma triglycerides but also secure at reduction of total atherogenic cholesterol in plasma (=remnant cholesterol+LDL cholesterol=non-HDL cholesterol) and a reduction in the total number of atherogenic particles marked a lower apoB levels in plasma.

Treatment Strategy

The available pharmacological interventions include statins, PCSK9 inhibitors, fibrates, and omega-3 fatty acids[61]. LDL receptor upregulation by statins and PCSK9 inhibitors reduce the risk of ASCVD by reducing LDL cholesterol as well as remnant cholesterol; the remnant cholesterol lowering is most pronounced for high-intensity statins and less for lower intensity statins or for PSCK9 inhibitors.

Other triglyceride- and remnant cholesterol-lowering agents includes angiopoetin-like 3 protein (ANGPTL3) inhibitors[103-106] and apolipoprotein C3 inhibitors[107, 108], but these are still under development and not yet ready for clinical use[109]. These new therapeutic agents may change the strategies toward primary and secondary prevention purposes in individuals with elevated remnant cholesterol levels if positive results of randomized controlled trials to reduce the risk of ASCVD are demonstrated.

Lipoprotein(a)

Lipoprotein(a) [Lp(a)] is a lipoprotein particle with one apolipoprotein B-100 (apoB-100) per particle and with a similar lipid composition as LDL, but distinctive in structure compared to LDL[110]. With an apolipoprotein(a) [apo(a)] bound to apoB-100, Lp(a) has a homology sequence with plasminogen which releases plasmin, a key enzyme in the fibrinolytic system. However, unlike plasminogen, Lp(a) is not considered as an active protease.

Apo(a), which is synthesized almost exclusively in the liver[111], has a huge variation of length in its peptide chain because of its variable number of Kringle domains. Unlike plasminogen which contains five Kringle domains [Kringle 1 to 5, (KI to KV)], apo(a) possesses only Kringles 4 and 5 (KIV and KV). In 10 distinct classes of the Kringle 4-like domains [Kringle 4 type 1 to type 10 (KIV-I to KIV-X)] in apo(a), Kringle 4 type 2 (KIV-II) has a variable number of repeats determined by genes while Kringle 4 type 1 (KIV-I) and Kringle 4 type 3 to 10 (KIV-III to KIV-X) only have a single copy[112]. As a result, there are different molecular weighted isoforms of apo(a). Because small apo(a) isoforms can be made in higher particle numbers per unit time than large isoforms[113], the size of the apo(a) isoform determined by the number of Kringle 4 type 2 repeats is inversely correlated to plasma Lp(a) levels[114, 115]. Lp(a) levels are determined almost exclusively by variants in the *LPA* gene, that is, without significant dietary or environmental influences[116]. Therefore, Lp(a) measurement is recommended at least once in a lifetime in several guidelines **(Fig. 2)**[58, 61, 117].

The cholesterol content of Lp(a) is included mainly in LDL cholesterol and to a minor extent in HDL cholesterol values in the CDC defined reference method[10]. However, the cholesterol content of Lp(a) usually contributes minor fraction of the total LDL cholesterol and the total HDL cholesterol values.

Commercially available Lp(a) measurement are usually based on polyclonal antibodies to apo(a). To measure Lp(a) accurate, an assay needs to be largely isoform independent and use 5-6 calibrator points based on Lp(a) with different apo(a) isoform size. The currently best available assay (including calibrator) is the one developed by Denka, Tokyo, Japan and today used for the majority of autoanalysers.

Lipoprotein(a) and ASCVD

A meta-analysis of epidemiological observational studies revealed that elevated Lp(a) levels are associated with increased risk of ASCVD in the primary prevention setting. In these analyses including

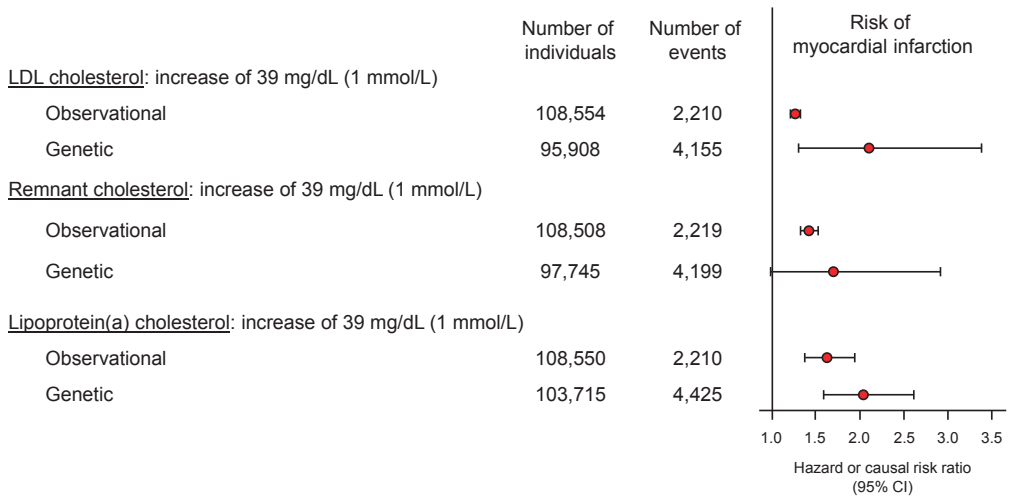

Fig. 7. Lipoprotein cholesterol and risk of myocardial infarction

Risk of myocardial infarction with 1 mmol/L (39 mg/dL) higher levels of LDL cholesterol, remnant cholesterol, and cholesterol content of Lp(a) [Lp(a) cholesterol] according to observational and genetic study data in the Copenhagen General Population Study. Modified with permission from [135].
LDL=low-density lipoprotein; Lp(a)=lipoprotein(a).

126,634 participants with individual participant data from 36 prospective studies, mainly from non-Asian countries, the multivariable adjusted relative risk ratios for coronary heart disease per 3.5-fold higher Lp(a) levels were 1.13(95%CI, 1.09-1.18)[118]. There is also evidence showing the association of elevated Lp(a) with increased risk of ASCVD in East Asian cohorts[119-121]. Moreover, elevated Lp(a) levels above the 75th percentile and above the 90th percentile increased risk for aortic valve stenosis[122] and heart failure[123] in European cohorts.

Generic Mendelian randomization studies from Europe strongly support a causal association between elevated Lp(a) and increased risk for ASCVD. By using both the number of Kringle 4 type 2 repeats and variants in the *LPA* gene, genetically elevated Lp(a) levels are causally associated with increased risk of ASCVD **(Table 2)**[115, 124-126].

Treatment Strategy

Despite the strong evidence of a causal association of elevated Lp(a) with risk of ASCVD and aortic valve stenosis, specific Lp(a)-lowering drugs are not yet approved. The lipid-lowering agents, niacin, PCSK9 inhibitors, and mipomersen approved for other diseases, have Lp(a) lowering effect[95, 127, 128]; none of them are currently approved for this purpose. Statin treatment may slightly increase levels of Lp(a)[129, 130]. Despite this, current European expert consensus statement recommended to continue statin because cardiovascular benefits in individuals with high Lp(a) outweigh any potential risk associated with modest increase in Lp(a) levels[126].

Novel antisense oligonucleotides (ASOs) and siRNAs inhibiting apo(a) production decrease Lp(a) concentration dramatically. The HORIZON trial for GalNAc-conjugated ASO drug pelacarsen (also known as IONIS-APO(a)-LRx, AKCEA-APO(a)-LRx, or TQJ 230)[131] and the OCEAN(a) trial for GalNAc-conjugated siRNA drugs, such as olpasiran (also known as AMG 890)[132] are ongoing to show the efficacy for prevention of ASCVD in individuals with high Lp(a) levels. Moreover, SLN360 is in early devemopment **(Table 2)**[133]. Moreover, LDL apheresis is approved for elevated Lp(a) levels in some countries; however, not all the countries approved due to its availability and cost issue[134] .

Non-HDL Cholesterol and ApoB

Non-HDL cholesterol (total cholesterol *minus* HDL cholesterol) includes LDL cholesterol, remnant cholesterol, and the cholesterol content of Lp(a), all of which are the cholesterol content of apoB-containing lipoproteins **(Fig. 2)**. Although many believe that cholesterol in these three different lipoproteins probably have an equal contribution to ASCVD risk, the HRs for myocardial infarction were higher per 39 mg/dL (1 mmol/L) higher levels of remnant cholesterol and cholesterol content of Lp(a) than for correspondingly higher LDL cholesterol observationally in the Copenhagen General Population Study **(Fig. 7)**[135].

Moreover, the corresponding genetically determined 39 mg/dL (1 mmol/L) higher levels of LDL cholesterol, remnant cholesterol and cholesterol content of Lp(a) were all to the right side of the observational estimates, again demonstrating that the three different lipoproteins each represent an independent causal risk factor for ASCVD. From these results, as well as from previously published articles **(Table 2 and Table 3)**, targeting LDL cholesterol alone is challenging due to lack of consideration of risk associated with the other two lipoproteins. Consequently, non-HDL cholesterol is a recommended target for secondary prevention purposes in Japanese, Korean, Chinese, European, and American guidelines and for primary prevention purposes in Japanese. Korean, Chinese, and European guidelines **(Table 4)**[53, 55, 57-59, 61, 62]. In European guidelines, apoB levels are also recommended to be a target for both primary and secondary prevention purposes[61].

Non-HDL cholesterol and apoB levels reflect residual cardiovascular disease risk better than LDL cholesterol in statin-treated individuals. In 13,015 statin-treated individuals from the Copenhagen General Population Study, the HRs for myocardial infarction were 1.78 (95%CI 1.35-2.34) in individuals with high non-HDL cholesterol levels (≥ 120 mg/dL, 3.1 mmol/L) compared to those with low non-HDL cholesterol levels (<120 mg/dL, 3.1 mmol/L) and 1.49 (1.15-1.92) in individuals with high apoB levels (≥ 92 mg/dL, 0.92 g/L) compared to those with low apoB levels (<92 mg/dL, 0.92 g/L) in individuals with low LDL cholesterol levels (<89 mg/dL, 2.3 mmol/L), while risk of myocardial infarction was not statistically significant in individuals with high LDL cholesterol levels (≥ 89 mg/dL, 2.3 mmol/L) compared to those with low LDL cholesterol levels (<89 mg/dL, 2.3 mmol/L)[136].

However, in the general population setting including both statin and non-statin users, it is still unclear whether non-HDL cholesterol or apolipoprotein B identifies ASCVD more effectively than LDL cholesterol[30, 137, 138]. From these results as well as from a biological point of view, both non-HDL cholesterol and apolipoprotein B can be good indicators for residual risk assessment, especially in individuals on lipid-lowering therapy. **(Table 3)**.

HDL

For more than half a century, it was recognized that elevated HDL cholesterol and apolipoprotein A1, which is the major apolipoprotein in HDL **(Table 1)**, are associated with reduced risk of ASCVD as observed in many prospective observational studies[30, 139].

The proposed pathway of the "atheroprotective" property of HDL has been reverse cholesterol transport or HDL-mediated trafficking of cholesterol and this pathway has urged to progress various therapeutic measurement to increase HDL cholesterol levels[140, 141]. In fact, fibrate and niacin clinical trials which modestly increase HDL cholesterol and reduce triglycerides[92-94, 142] and recombinant apolipoprotein A-I infusion therapy[143] succeeded in the early stage. However, later larger trials of HDL cholesterol raising treatment concomitantly taken with statin have resulted in little or no benefit **(Table 2)**[96-98]. These results are in line with genetic Mendelian randomization studies, using genetic variants known to affect only HDL cholesterol levels and not to affect other covariates including LDL and remnant cholesterol as instruments, which have shown no evidence of a causal association between high HDL cholesterol levels and reduced risk of ASCVD **(Table 2)**[89, 90, 144]. Further, major cardiovascular outcome studies of CETP inhibitors which largely increase HDL cholesterol levels have shown at most limited beneficial effect[145-147].

Cholesterol efflux capacity is assessing the ability to remove excess cholesterol from peripheral tissues including atherosclerotic plaques to the liver. Cholesterol efflux capacity of HDL was found to be significantly inversely associated with ASCVD even after additional adjustment for HDL cholesterol in healthy volunteers and in individuals with familial hypercholesterolemia[148, 149]. Currently, a phase 3, randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of plasma-derived apolipoprotein A-I among high-risk patients with myocardial infarction is under way[150].

Future Perspectives on Potential Treatment for Elevated Lipoprotein Cholesterol

Besides small-molecule and monoclonal antibodies (e.g., statins, ezetimibe, fibrates, bempedoic acid, and PCSK9 inhibitors), gene silencing technology including ASOs, siRNAs and gene editing technologies targeting proteins that have an important role in lipoprotein production or removal (e.g., the protein products of *ANGPTL3*, *APOB*, *APOC3*, *LPA*, and *PCSK9*) are under development. Using these technologies, plasma levels of LDL cholesterol, remnant cholesterol, and Lp(a) can be reduced dramatically with less frequent dosing. Long-term reductions of these lipoproteins may help fill unmet medical needs by improving compliance to medical therapy and by risk reduction of residual ASCVD risk.

Conclusion

Lipoproteins and lipoprotein cholesterol research on risk of ASCVD is still on the way. Accumulation of evidence is warranted especially in the East Asian population.

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Conflict of Interest

BGN reports consultancies or talks sponsored by AstraZeneca, Sanofi, Regeneron, Akcea, Ionis, Amgen, Amarin, Kowa, Denka, Novartis, Novo Nordisk, Esperion, Abbott, Silence Therapeutics, and Mankind. TD and AL declare no competing interests.

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