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Review article

Quantifying atherogenic lipoproteins for lipid-lowering strategies: Consensus-based recommendations from EAS and EFLM

Børge G. Nordestgaard[a,*], Michel R. Langlois[b,**], Anne Langsted[a], M. John Chapman[c], Kristin M. Aakre[d], Hannsjörg Baum[e], Jan Borén[f], Eric Bruckert[g], Alberico Catapano[h], Christa Cobbaert[i], Paul Collinson[j], Olivier S. Descamps[k], Christopher J. Duff[l], Arnold von Eckardstein[m], Angelika Hammerer-Lercher[n], Pia R. Kamstrup[a], Genovefa Kolovou[o], Florian Kronenberg[p], Samia Mora[q], Kari Pulkki[r], Alan T. Remaley[s], Nader Rifai[t], Emilio Ros[u], Sanja Stankovic[v], Ana Stavljenic-Rukavina[w], Grazyna Sypniewska[x], Gerald F. Watts[y], Olov Wiklund[f], Päivi Laitinen[z], for the European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Joint Consensus Initiative

Quantifying atherogenic lipoproteins for lipid-lowering strategies: consensus-based recommendations from EAS and EFLM

Primary lipid panel nonfasting
Total cholesterol
Triglycerides
HDL cholesterol
LDL cholesterol
non-HDL cholesterol
(remnant cholesterol)

Lipoprotein(a)
measured once

Residual risk of ASCVD under optimal LDL - evaluate:
1. Non-HDL cholesterol
- from LDL, remnants & Lp(a)
2. Apolipoprotein B
- From LDL, remnants & Lp(a)

Particularly at
mild-to-moderate
hypertriglyceridemia
(2-10 mmol/L)

Laboratories shall flag
abnormal lipid values
with reference to
therapeutic decision thresholds

Nordestgaard, Langlois, et al. EAS-EFLM consensus. Atherosclerosis 2020; online Jan 9

Key EAS/EFLM recommendations for testing of atherogenic lipoproteins [1,2].

Pre-preanalytical phase (test ordering)

Comprehensive testing of atherogenic lipoproteins should include tests to asses the risk conferred by LDL particles, remnant particles and, in selected cases, Lp(a).

Preanalytical phase (test sampling)

Fasting is not routinely required for assessing the lipid profile.

Consider fasting sample when nonfasting TG are ≥ 4.5 mmol/L (400 mg/dL); however, this is not a requirement.

Take 2 to 3 serial blood specimens, at least 1 week apart, to allow to average for biological variation (importantly when test results are near the treatment decision thresholds).[a]

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Key EAS/EFLM recommendations for testing of atherogenic lipoproteins [1,2].

Analytical phase (test measurement)

Follow-up of measured or calculated LDLC and non-HDLC of a patient, from baseline to on-treatment measurements, should be ideally performed with the same method (and preferably the same laboratory). [b]

Clinicians should be notified when the laboratory test changes from a method to another.

The Martin-Hopkins equation may be preferable for calculation of LDLC in patients with low LDLC concentration < 1.8 mmol/L (70 mg/dL) and/or TG concentration 2.0–4.5 mmol/L (175–400 mg/dL), and in nonfasting samples.

Direct LDLC assays should be used for calculation of RemnantC and for assessment of LDLC when TG concentration is ≥ 4.5 mmol/l (400 mg/dL).

Lp(a)-corrected LDLC should be assessed at least once in patients with suspected or known high Lp(a), or if the patient shows a poor response to LDL-lowering therapy.

ApoB assays currently provide the most accurate measurement of overall burden of atherogenic particles in the fasting and nonfasting state.

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Key EAS/EFLM recommendations for testing of atherogenic lipoproteins [1,2].

Postanalytical phase (test reporting)

Laboratories should automatically calculate and report non-HDLC on all lipid profiles; RemnantC could also be reported.

Laboratory reports should flag abnormal concentrations based on decision thresholds.

Extremely high concentrations beyond the reference limits should alert clinicians (interpretative commenting on test report).

Post-postanalytical phase (test interpretation and use)

LDLC is the primary target of lipid-lowering therapy.

When LDLC goal is achieved, non-HDLC or apoB should be preferred as secondary treatment targets in patients with TG 2–10 mmol/L (175–880 mg/dL), diabetes, obesity or metabolic syndrome.

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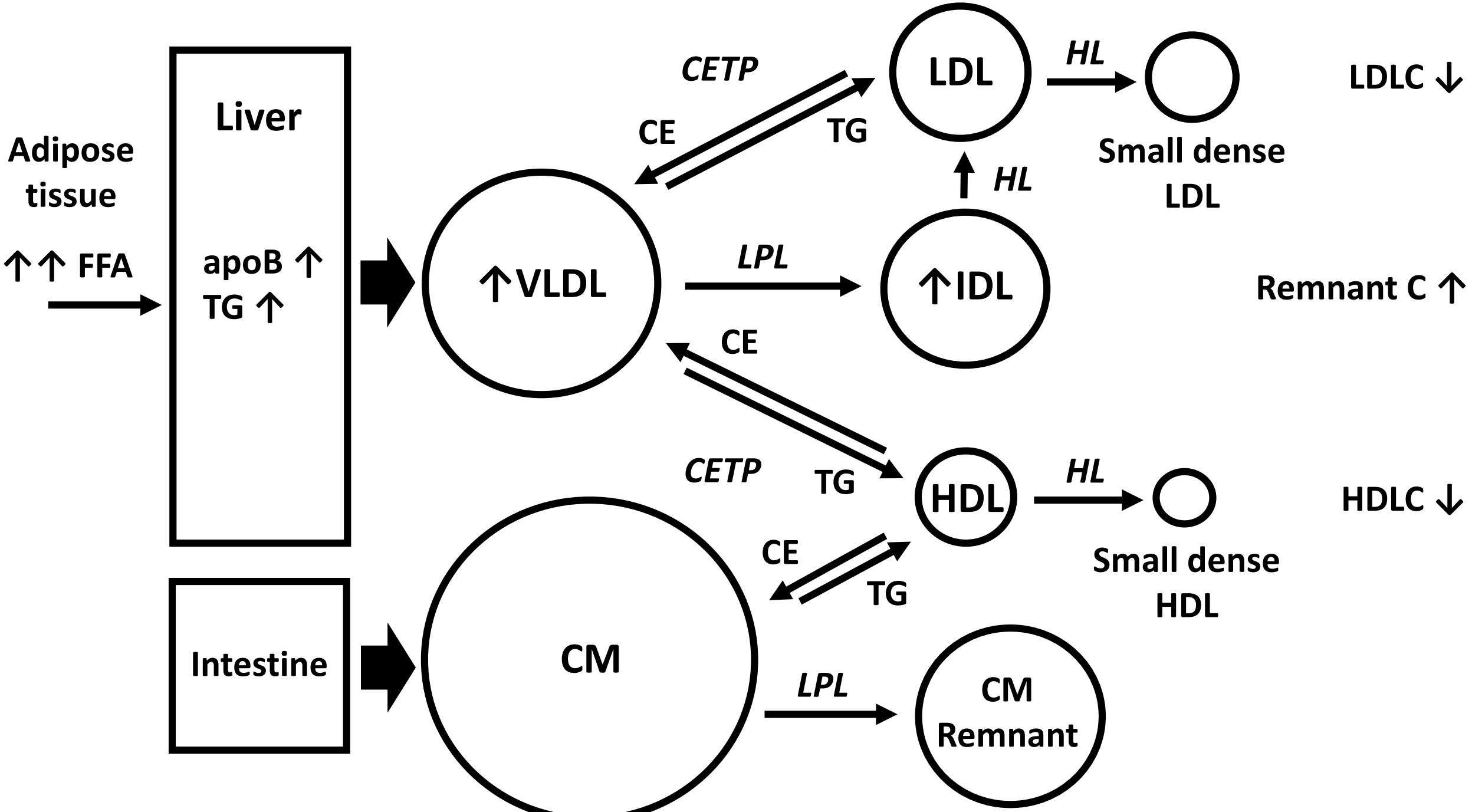

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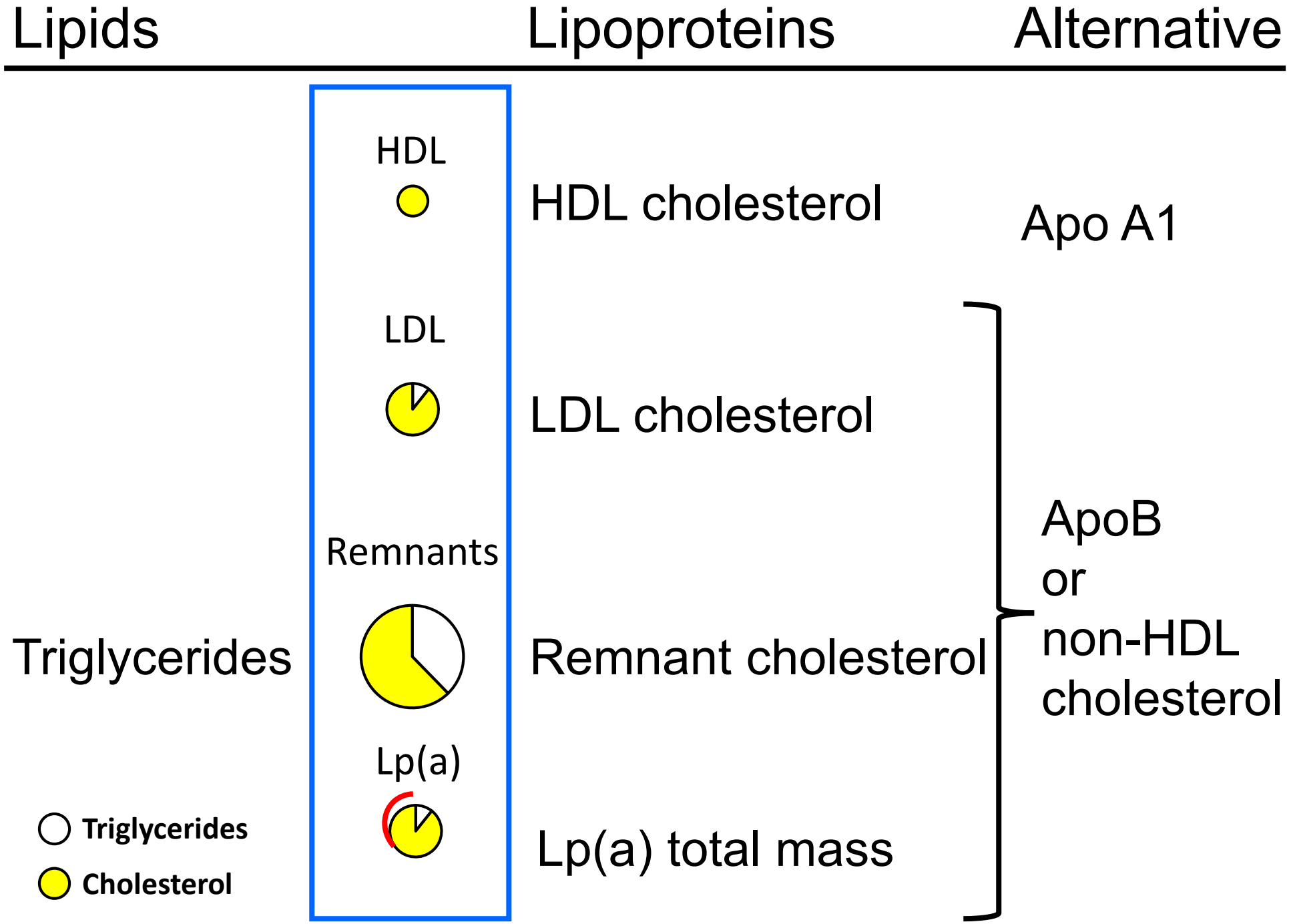

Nordestgaard et al. EAS EFLM joint Consensus Panel. Eur Heart J 2016; 37:1944-58

Concentration distribution of nonfasting lipids, lipoproteins, and apolipoproteins in 54,129 women in the Copenhagen General Population Study not on lipid-lowering therapy.

	Percentiles									
	2.5		25		50		75		97.5	
Age group	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL
Triglycerides										
20–39	0.45	40	0.73	65	0.98	87	1.4	121	2.8	248
40–65	0.50	44	0.84	74	1.2	103	1.7	148	3.6	317
66–100	0.59	52	0.98	87	1.4	120	1.9	170	3.8	340
Total cholesterol										
20–39	3.3	127	4.2	162	4.7	182	5.3	205	6.9	267
40–65	3.8	147	5.0	193	5.6	217	6.3	244	7.9	306
66–100	4.3	166	5.5	213	6.1	236	6.8	263	8.2	317
LDL cholesterol										
20–39	1.4	54	2.1	81	2.6	101	3.1	120	4.4	170
40–65	1.7	66	2.6	101	3.2	124	3.8	147	5.3	205
66–100	1.9	73	3.0	116	3.5	135	4.1	159	5.5	213
Remnant cholesterol										
20–39	0.19	7.4	0.33	13	0.45	17	0.62	24	1.2	48
40–65	0.21	8.1	0.38	15	0.53	20	0.76	29	1.5	60
66–100	0.26	10	0.45	17	0.61	24	0.86	33	1.6	62
Non-HDL cholesterol										
20–39	1.7	67	2.6	99	3.1	118	3.7	142	5.3	203
40–65	2.1	82	3.1	121	3.8	147	4.6	176	6.3	242
66–100	2.4	93	3.5	137	4.2	162	4.9	190	6.5	251
HDL cholesterol										
20–39	0.91	35	1.3	51	1.6	61	1.9	73	2.5	98
40–65	0.93	36	1.4	55	1.7	67	2.1	80	2.8	108
66–100	0.98	38	1.5	58	1.9	72	2.2	86	3.0	117
Lipoprotein(a)										
	nmol/L	mg/dL	nmol/L	mg/dL	nmol/L	mg/dL	nmol/L	mg/dL	nmol/L	mg/dL
20–39	1.1	1.4	5.4	4.3	15	8.5	43	22	207	97
40–65	1.6	1.5	6.8	4.9	17	9.8	60	30	242	113
66–100	1.9	1.6	7.4	5.2	19	10	64	31	250	116
Apolipoprotein B										
	g/L	mg/dL	g/L	mg/dL	g/L	mg/dL	g/L	mg/dL	g/L	mg/dL
20–39	0.51	51	0.69	69	0.82	82	0.98	98	1.47	147
40–65	0.59	59	0.83	83	1.00	100	1.21	121	1.79	179
66–100	0.67	67	0.94	94	1.11	111	1.31	131	1.87	187

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Concentration distribution of nonfasting lipids, lipoproteins, and apolipoproteins in 42,126 men in the Copenhagen General Population Study not on lipid-lowering therapy. Laboratory measurements and calculations were performed as described in the footnote of Table 2 [3].

	Percentiles									
	2.5		25		50		75		97.5	
Age group	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL
Triglycerides										
20–39	0.54	48	0.96	85	1.4	128	2.2	190	5.1	454
40–65	0.61	54	1.10	100	1.7	146	2.5	219	5.5	485
66–100	0.62	55	1.10	98	1.6	140	2.3	201	4.6	404
Total cholesterol										
20–39	3.3	128	4.3	166	4.9	189	5.6	217	7.2	278
40–65	3.9	151	5.0	193	5.6	217	6.3	244	7.9	305
66–100	3.8	147	5.0	193	5.6	217	6.3	244	7.6	294
LDL cholesterol										
20–39	1.5	58	2.4	93	2.9	112	3.5	135	5.0	193
40–65	1.8	70	2.8	108	3.4	131	4.0	155	5.4	209
66–100	1.8	70	2.7	104	3.3	128	3.9	151	5.0	193
Remnant cholesterol										
20–39	0.22	8.5	0.43	17	0.64	25	0.95	37	1.8	71
40–65	0.26	10	0.51	20	0.74	29	1.1	43	2.0	76
66–100	0.27	10	0.50	19	0.71	27	1.0	39	1.7	67
Non-HDL cholesterol										
20–39	2.0	76	3.0	115	3.6	140	4.4	170	6.2	238
40–65	2.4	92	3.6	137	4.3	164	5.5	213	6.6	255
66–100	2.3	89	3.4	133	4.1	158	4.8	184	6.1	237
HDL cholesterol										
20–39	0.67	26	1.0	39	1.2	85	1.5	56	2.0	76
40–65	0.72	28	1.1	42	1.3	52	1.7	64	2.4	93
66–100	0.76	29	1.2	46	1.5	56	1.8	70	2.6	101
Lipoprotein(a)										
	nmol/L	mg/dL	nmol/L	mg/dL	nmol/L	mg/dL	nmol/L	mg/dL	nmol/L	mg/dL
20–39	1.0	1.2	5.5	4.3	14	8.3	49	24	219	102
40–65	1.1	1.4	5.8	4.4	15	8.9	51	25	226	105
66–100	1.1	1.4	6.2	4.6	17	9.5	50	25	211	99
Apolipoprotein B										
	g/L	mg/dL	g/L	mg/dL	g/L	mg/dL	g/L	mg/dL	g/L	mg/dL
20–39	0.56	56	0.81	81	0.99	99	1.22	122	1.86	186
40–65	0.67	67	0.96	96	1.16	116	1.41	141	2.04	204
66–100	0.66	66	0.93	93	1.11	111	1.32	132	1.86	186

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Recommendations for the clinical indications for lipid and (apo)lipoprotein quantitation [1,4].

	ASCVD risk estimation	Dyslipidemia characterization	Treatment choice	Treatment target
Primary tests				
TC[a]	YES[a]	Optional[b]	Optional[b]	Optional[b]
HDLC[c]	YES[d]	YES	NO	NO
TG	YES	YES	YES	NO
LDLC	YES	YES	YES	YES
RemnantC[a]	Optional[e]	Optional[e]	NO	Optional[e]
Non-HDLC[a]	YES	NO[f]	NO	YES[g]
Additional tests				
ApoB[h]	YES[g]	YES[g]	NO	Optional[g]
Lp(a)	YES[i]	YES[i]	Not yet[j]	Not yet[j]

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Example of between-laboratory uncertainty when lipids are measured by different methods in a hypertriglyceridemic patient.

Test	Assumed total error	Defined concentration in model patient		Range of uncertainty	
		mg/dL	(mmol/L)	mg/dL	(mmol/L)
TC	9% [a]	200	(5.2)	182 to 218	(4.7–5.7)
TG	15% [a]	250	(2.8)	212 to 288	(2.4–3.3)
dHDLC	−20% to +36% [b]	40	(1.0)	32 to 54	(0.8–1.4)
Non-HDLC	(derived from TC and dHDLC)	160	(4.1)	128 to 186	(3.3–4.8)
cLDLC (Friedewald)	(derived from TC, dHDLC and TG)	110	(2.8)	70 to 144	(1.8–3.7)
cLDLC (Martin-Hopkins)	(derived from TC, dHDLC, TG and non-HDLC)	122	(3.2)	91 to 151	(2.4–3.9)
dLDLC	−26% to +32% [b]	122	(3.2)	90 to 161	(2.3–4.2)

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Primary and secondary goals of preventive therapy according to cardiovascular mortality risk categories assessed with the SCORE system [4].

Risk (SCORE) [a]	LDLC mmol/L (mg/dL)	Non-HDLC [b] mmol/L (mg/dL)	ApoB [b] g/L (mg/dL)
Very high	< 1.4 (55) and ≥50% reduction in LDLC	< 2.2 (85) [c]	< 0.65 (65) [d]
High	< 1.8 (70) and ≥50% reduction in LDLC	< 2.6 (100)	< 0.80 (80)
Moderate	< 2.6 (100)	< 3.3 (130)	< 1.00 (100)
Low	< 3.0 (115)		

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Contemporary evidence for the medical use of LDLC, non-HDLC, apoB, and LDLP based on essential test characteristics [1]. Test characteristics defined by the EFLM Test Evaluation Working Group [70].

Test characteristics	LDLC	non-HDLC	ApoB	LDLP
Analytical performance[a]				
Precise assays	Yes	Yes	Yes	Yes
Accurate assays (method independency)	No	No	Yes	No
Nonfasting measurement possible	cLDLC at TG < 4.5 mmol/L	Yes	Yes	Yes
Widely accessible assays	Yes	Yes	Yes	No
Reasonable operational costs	Yes	No extra measurement	Yes	Not yet
Clinical performance[b]				
Robust associations with incident ASCVD?	Yes	Yes	Yes	Yes
Novel information beyond existing markers?	(Reference)	Yes	Yes	Yes
Validated decision thresholds?	No	No	No	No
Clinical effectiveness[c]				
Superiority to existing tests?	(Reference)	Probably	Probably	Probably
Modifiable risk association (treatment target)?	Yes	Yes	Yes	Yes
Test-guided treatment reduces ASCVD risk?	Yes	Probably	Probably	Unknown
Cost effectiveness[d]				
Test-guided treatment saves healthcare costs?	Yes	Unknown	Unknown	Unknown

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Flagging of abnormal lipid and (apo)lipoprotein concentrations based on risk prediction thresholds and of extremely abnormal concentrations [2].

Parameter	Thresholds	Interpretative commenting
TG [a]	Fasting ≥1.7 mmol/L (150 mg/dL) Nonfasting ≥2 mmol/L (175 mg/dL)	> 10 mmol/L (880 mg/dL): severe hypertriglyceridemia with high risk of acute pancreatitis
TC	≥5 mmol/L (190 mg/dL)	
LDLC	≥3 mmol/L (115 mg/dL)	> 13 mmol/L (500 mg/dL): consider homozygous FH > 5 mmol/L (190 mg/dL): consider heterozygous FH
RemnantC	Fasting ≥0.8 mmol/L (30 mg/dL) Nonfasting ≥0.9 mmol/L (35 mg/dL)	
Non-HDLC	Fasting ≥3.8 mmol/L (145 mg/dL) Nonfasting ≥3.9 mmol/L (150 mg/dL)	
ApoB	≥1 g/L (100 mg/dL)	< 0.1 g/L (10 mg/dL): genetic abetalipoproteinemia
HDLC	Men ≤1 mmol/L (40 mg/dL) Women ≤1.2 mmol/L (45 mg/dL)	
ApoA-I	Men ≤1.2 g/L (120 mg/dL) Women ≤ 1.4 g/l (140 mg/dL)	< 0.1 g/L (10 mg/dL): genetic hypoalphalipoproteinemia
Lp(a)	≥50 mg/dL (> 105 nmol/L)[b,c]	> 120 mg/dL: very high risk for myocardial infarction and aortic valve stenosis

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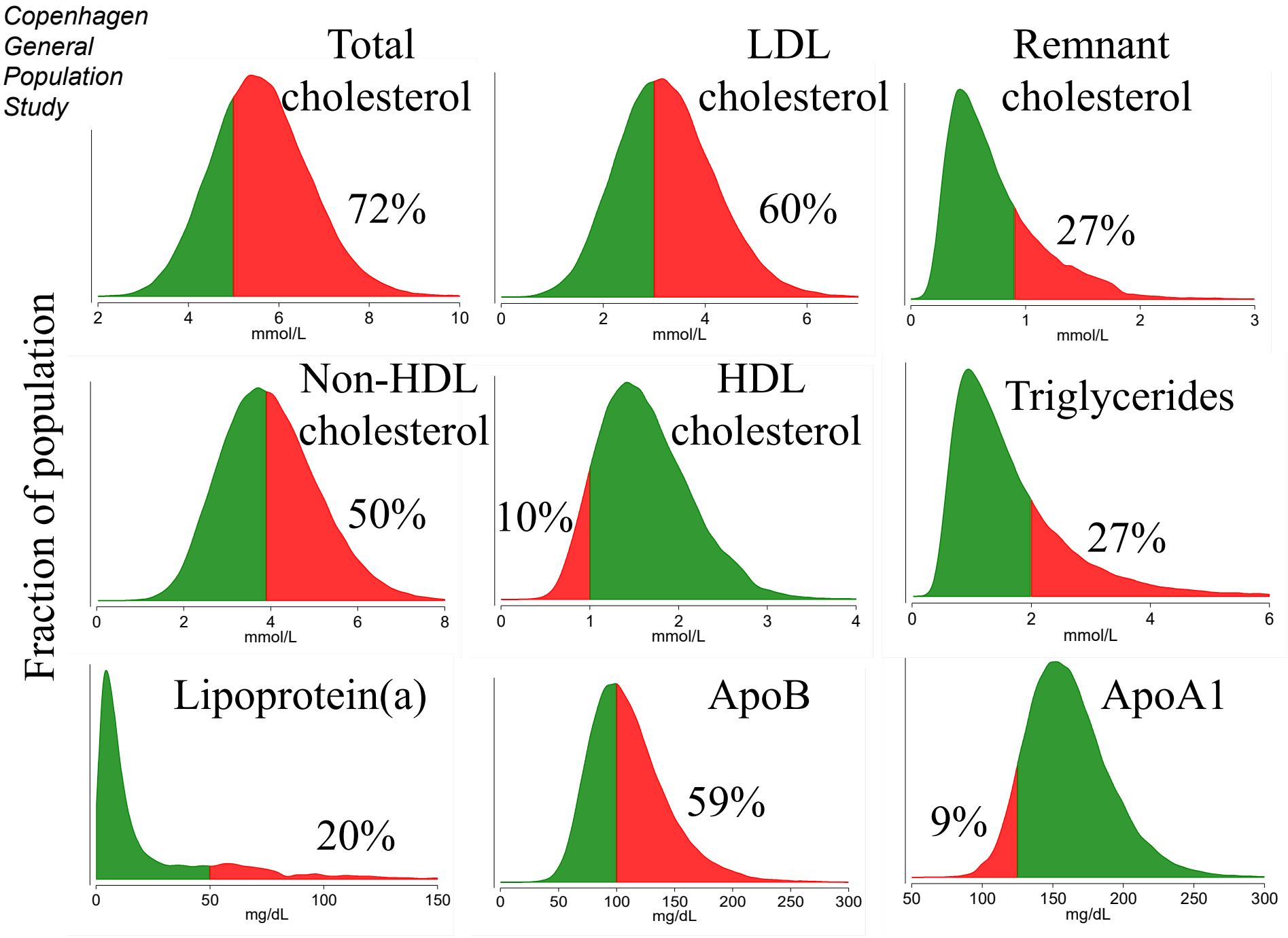
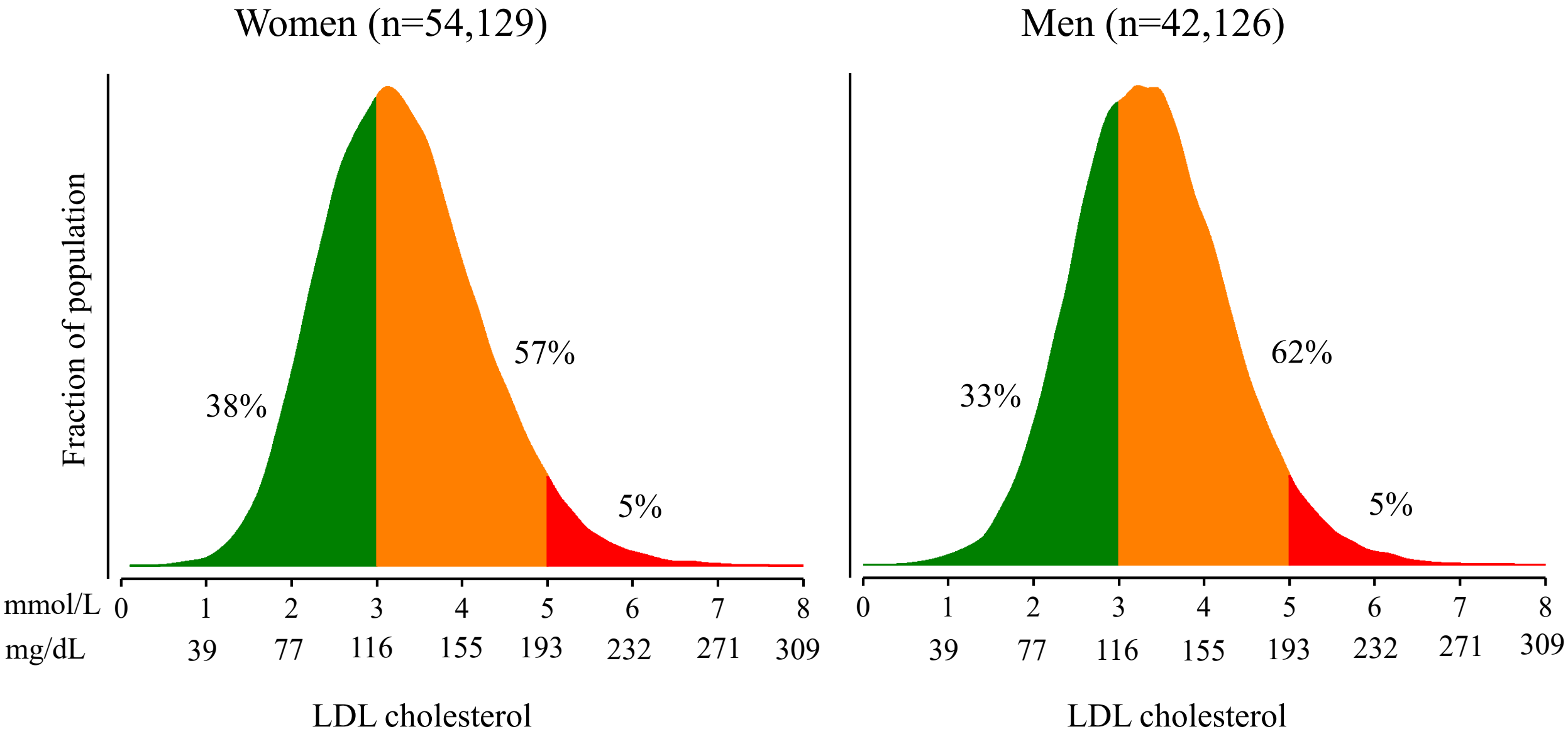


Nordestgaard et al. EAS EFLM joint Consensus Panel. Eur Heart J 2016; 37:1944-58

Copenhagen General Population Study



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