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Controversies in lipid management

LDL-C vs. Non-HDL-C targets

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Disclosures

- Honoraria for Speakers Bureau (Pharma)
  AstraZeneca, Sanofi, Pfizer

- Advisory Boards: Sanofi, Aegerion, AstraZeneca

- Research Funding: Pfizer

Impact of 1mmol/L reduction on LDL-C upon major cardiovascular events and mortality
CTT 2010

	Relative Risk (95% CI)	
All cause mortality	0.90 (0.87-0.93), p<0.0001**	10%
CHD mortality	0.80 (0.74—0.87); p<0.0001**	20%
Other cardiac deaths	0.89 (0.81—0.98); p=0.002**	11%
Stroke deaths	0.96 (0.84—1.09); p=0.5	
Major vascular events	0.78 (0·76—0·80); p<0.0001	22%
Non-fatal MI	0.73 (0.70 − 0.77); p<0.0001	27%
Myocardial revascularization	0.75 (0.72 − 0.78); p<0.0001	25%
Ischemic stroke	0.79 (0.74 − 0.85); p<0.0001	21%
Cancer incidence	1.00 (0.96 − 1.04); p=0.9	
Hemorrhagic stroke	1.12 (0.93 − 1.35); p=0.2	

Adapted from The Lancet 2010.; 376:1670-81

**- CI 99%

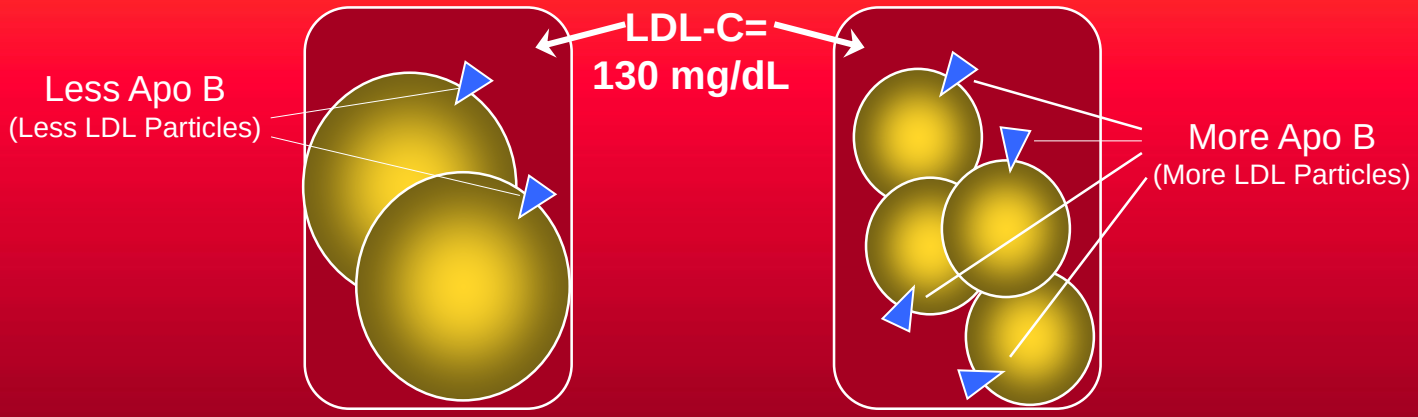
Residual Risk in Statin trials

	Event Rate (No Diabetes)		Event Rate (Diabetes)	
	On Statin	On Placebo	On Statin	On Placebo
HPS* (CHD patients)	19.8%	25.7%	33.4%	37.8 %
CARE†	19.4%	24.6%	28.7%	36.8%
LIPID‡	11.7%	15.2%	19.2%	22.8%
PROSPER§	13.1%	16.0%	18.4%	23.1%
ASCOT-LLA‡	4.9%	8.7%	9.6%	11.4%
TNT‖	7.8%	9.7%	13.8%	17.9%

HPS Collaborative Group. *Lancet*. 2003;361:2005-2016.
Sacks FM, et al. *N Engl J Med*. 1996;335:1001-1009.
LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357.
Shepherd J, et al. *Lancet*. 2002;360:1623-1630.
Sever PS, et al. *Lancet*. 2003;361:1149-1158.
Shepherd J, et al. *Diabetes Care*. 2006;:29:1220-1226.

* CHD death, nonfatal MI, stroke, revascularizations
† CHD death, nonfatal MI, CABG, PTCA
‡ CHD death and nonfatal MI
§ CHD death, nonfatal MI, stroke
‖ CHD death, nonfatal MI, resuscitated cardiac arrest, stroke (80 mg vs 10 mg atorvastatin)

Differences in Lipoprotein Cholesterol Distribution



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

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.

5

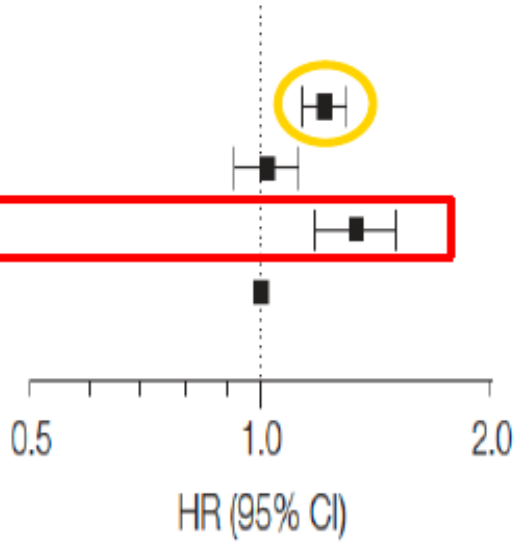
When discordant, risk follows non-HDL-C, not LDL-C

Discordance Meta-Analysis

Risk of Major CV Events during Statin Therapy

HRs adjusted for sex, age, smoking, diabetes, systolic BP and trial

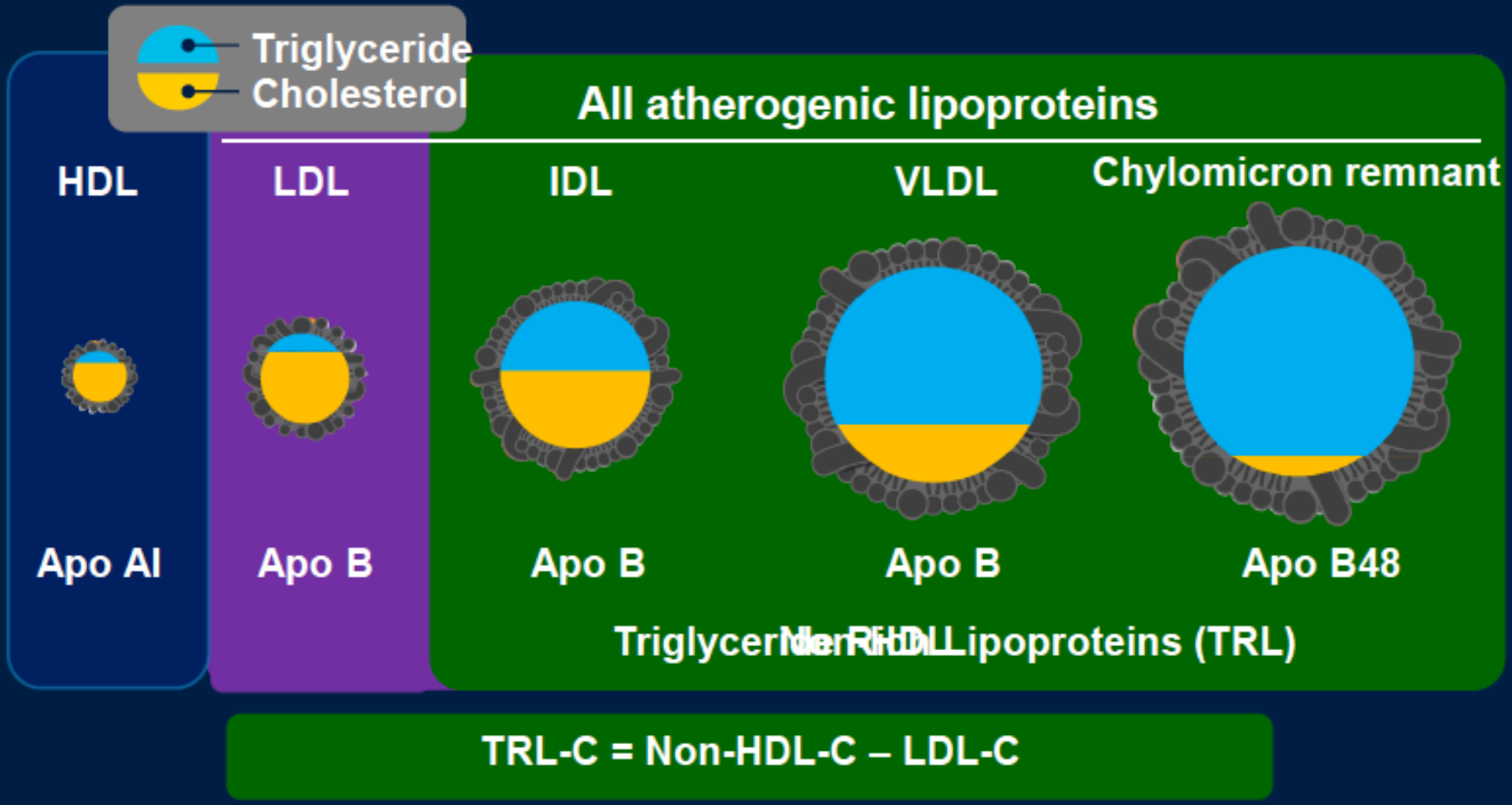
Target Level		No. of Major Cardiovascular Events	Total No. of Participants	HR (95% CI)
LDL-C	Non–HDL-C			
≥100 mg/dL	≥130 mg/dL	1877	10419	1.21 (1.13-1.29)
≥100 mg/dL	<130 mg/dL	467	2873	1.02 (0.92-1.12)
<100 mg/dL	≥130 mg/dL	283	1435	1.32 (1.17-1.50)
<100 mg/dL	<130 mg/dL	2760	23426	1.00 [Reference]



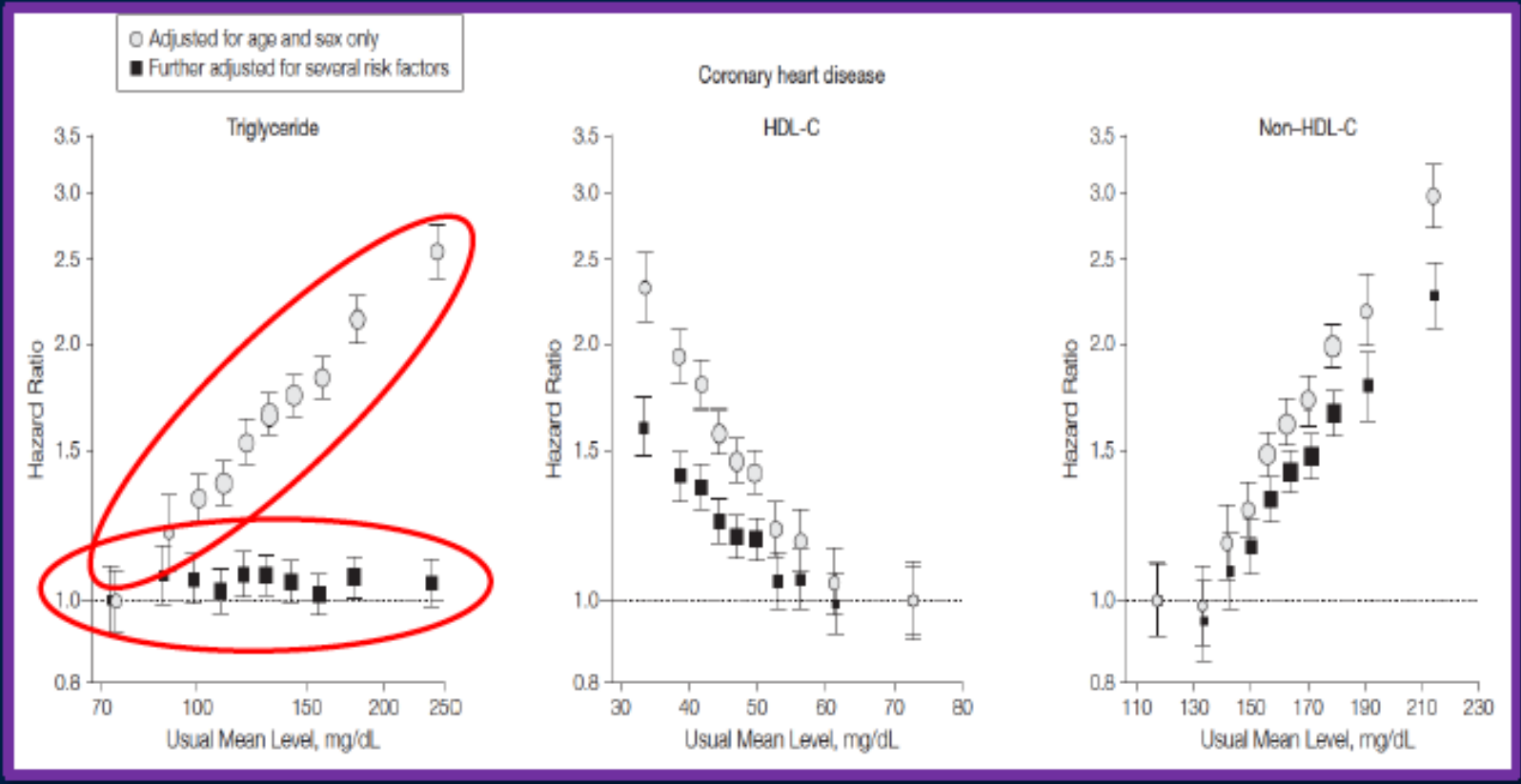
Boekholdt SM, et al. JAMA. 2012;307:1302-1309

Non-HDL Cholesterol

Triglyceride Rich Lipoproteins



CHD Risk for TG Elevation is Contained within Non-HDL-C and HDL-C

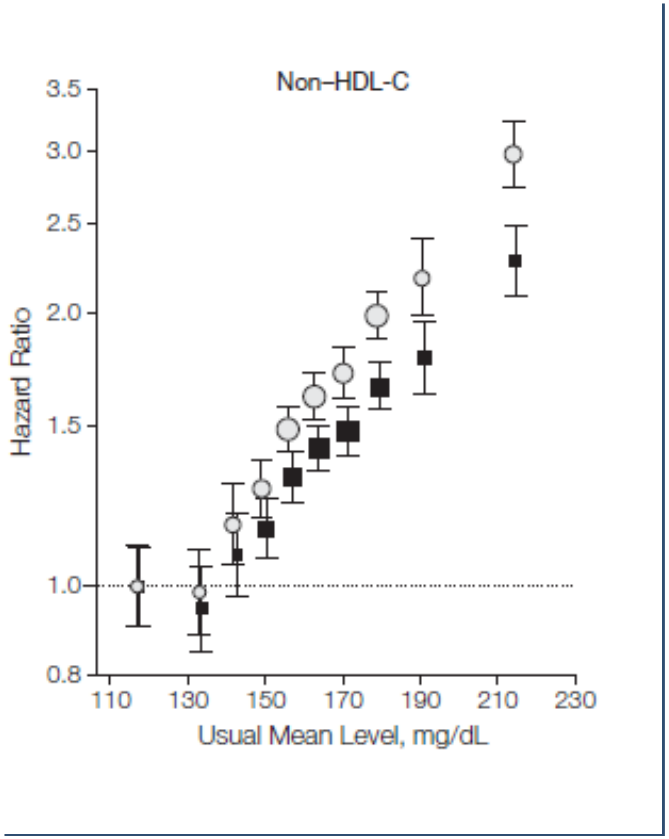


Analyses of $\log_e$ TG were adjusted for HDL-C and non-HDL-C.
Analyses of HDL-C were adjusted for non-HDL-C and $\log_e$ TG.
Analyses of non-HDL-C were adjusted for HDL-C and $\log_e$ TG.

Emerging Risk Factors Collaboration. JAMA. 2009;302:1993-2000

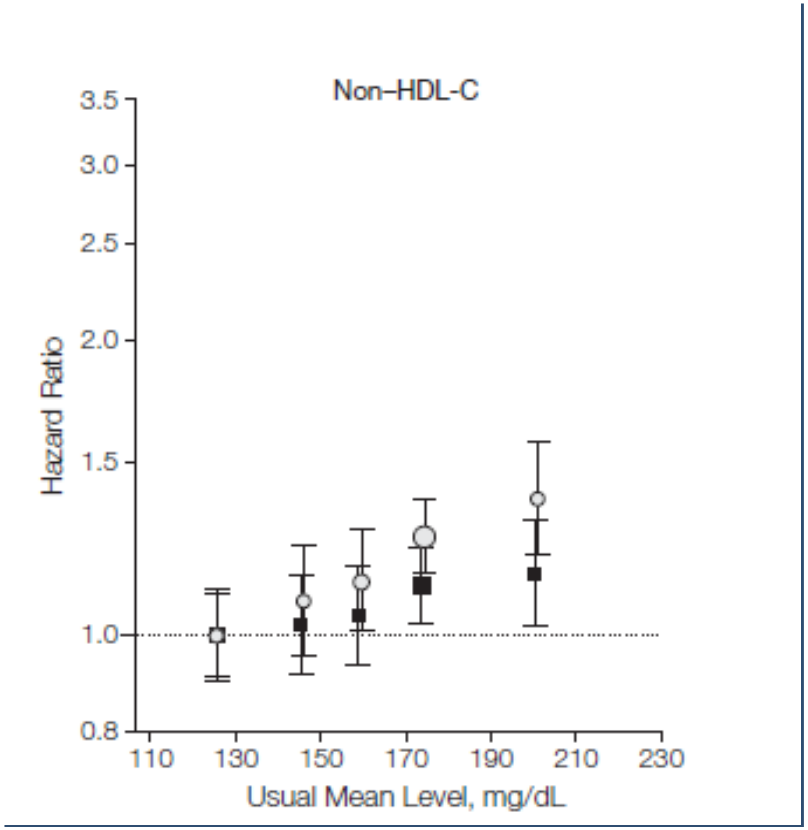
Emerging Risk Factors Collaboration
Meta-analysis

N=302.430



CAD

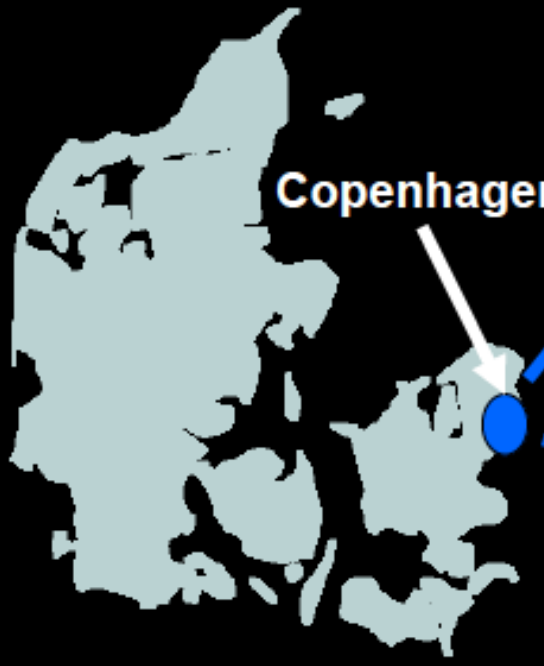
N=173.312



Stroke

JAMA 2009;302:1993-2000

Copenhagen City Heart Study (CCHS)



N=9,558

22 yrs follow-up

No losses to follow-up 1977-2014

N=88,404

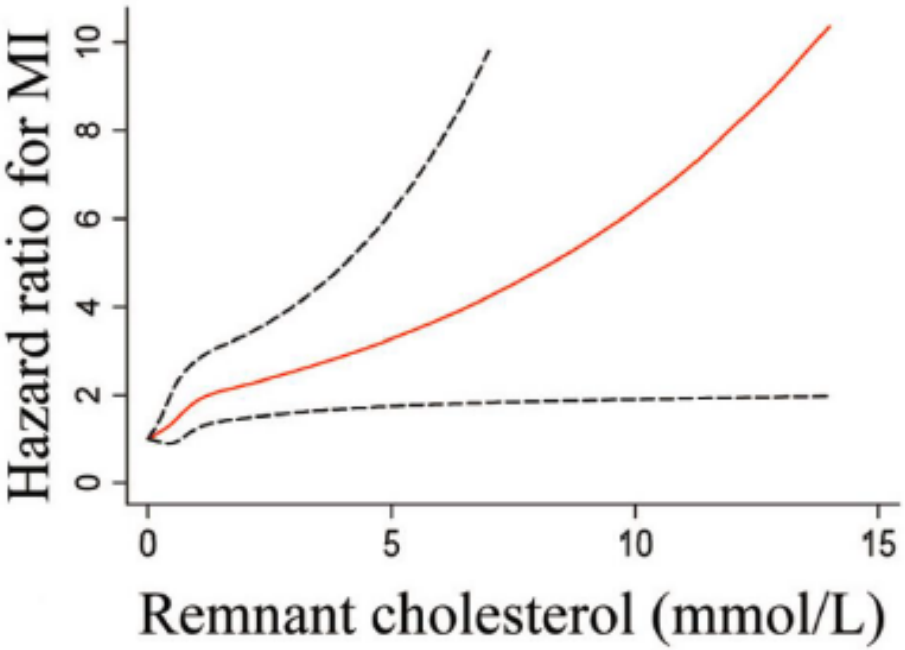
10 yrs follow-up

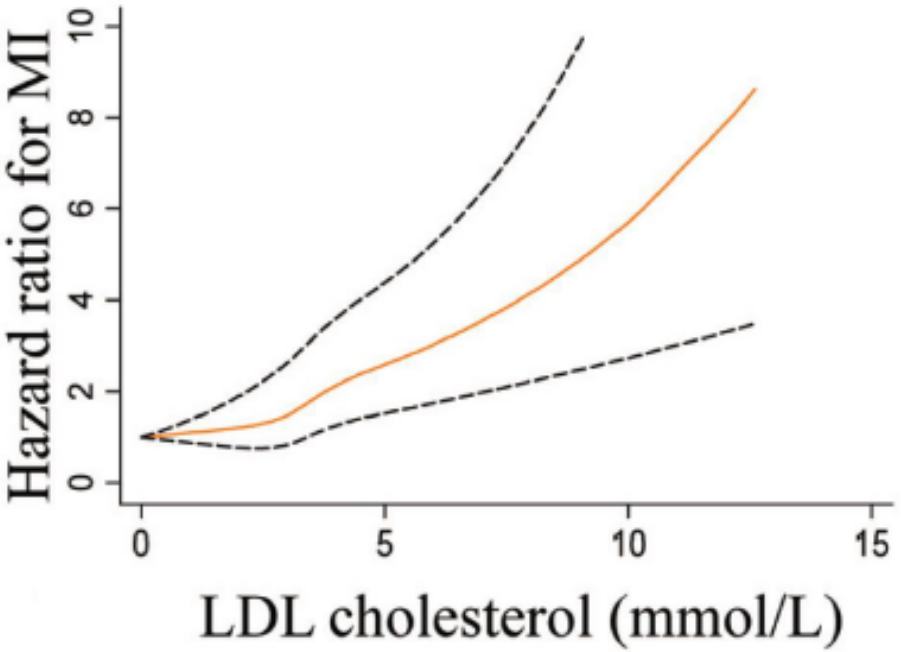
Copenhagen General Population Study (CGPS)

Varbo, Freiberg, Nordestgaard. Clin Chem 2015; 61: 533-543

~90,000 individuals from CGPS & CCHS combined

Myocardial Infarction





Varbo, Freiberg, Nordestgaard. Clin Chem 2015; 61: 533-543

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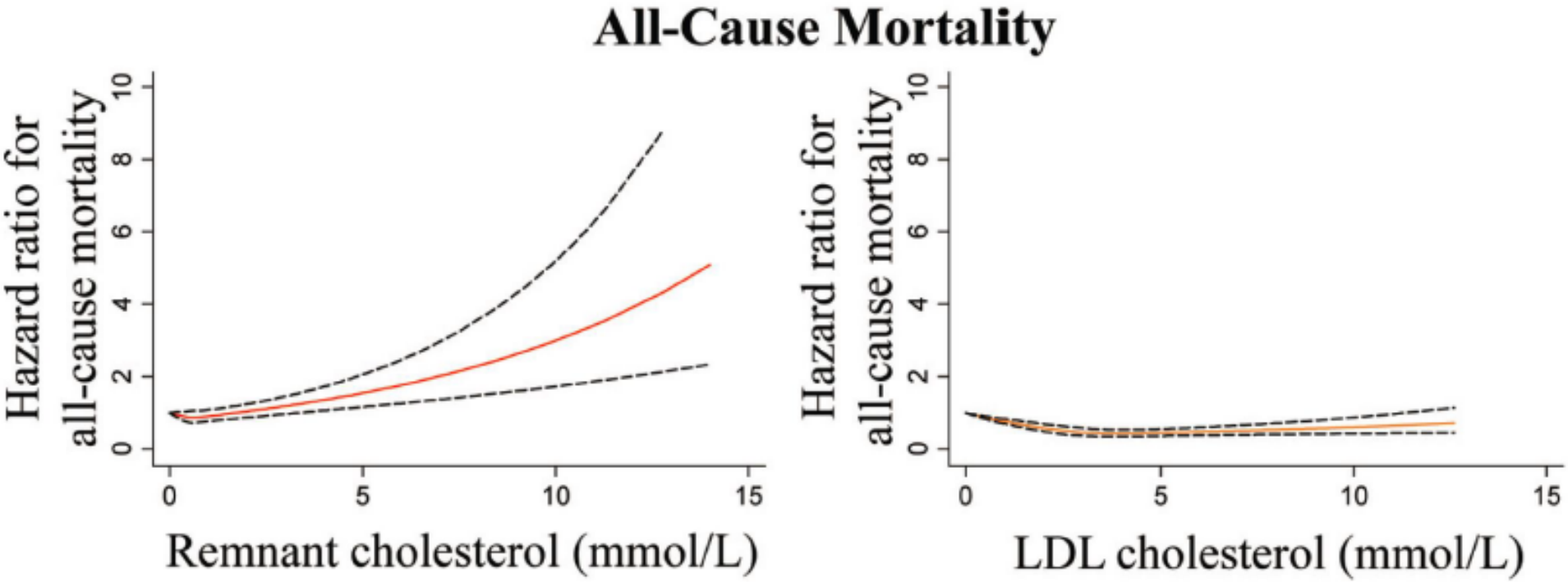
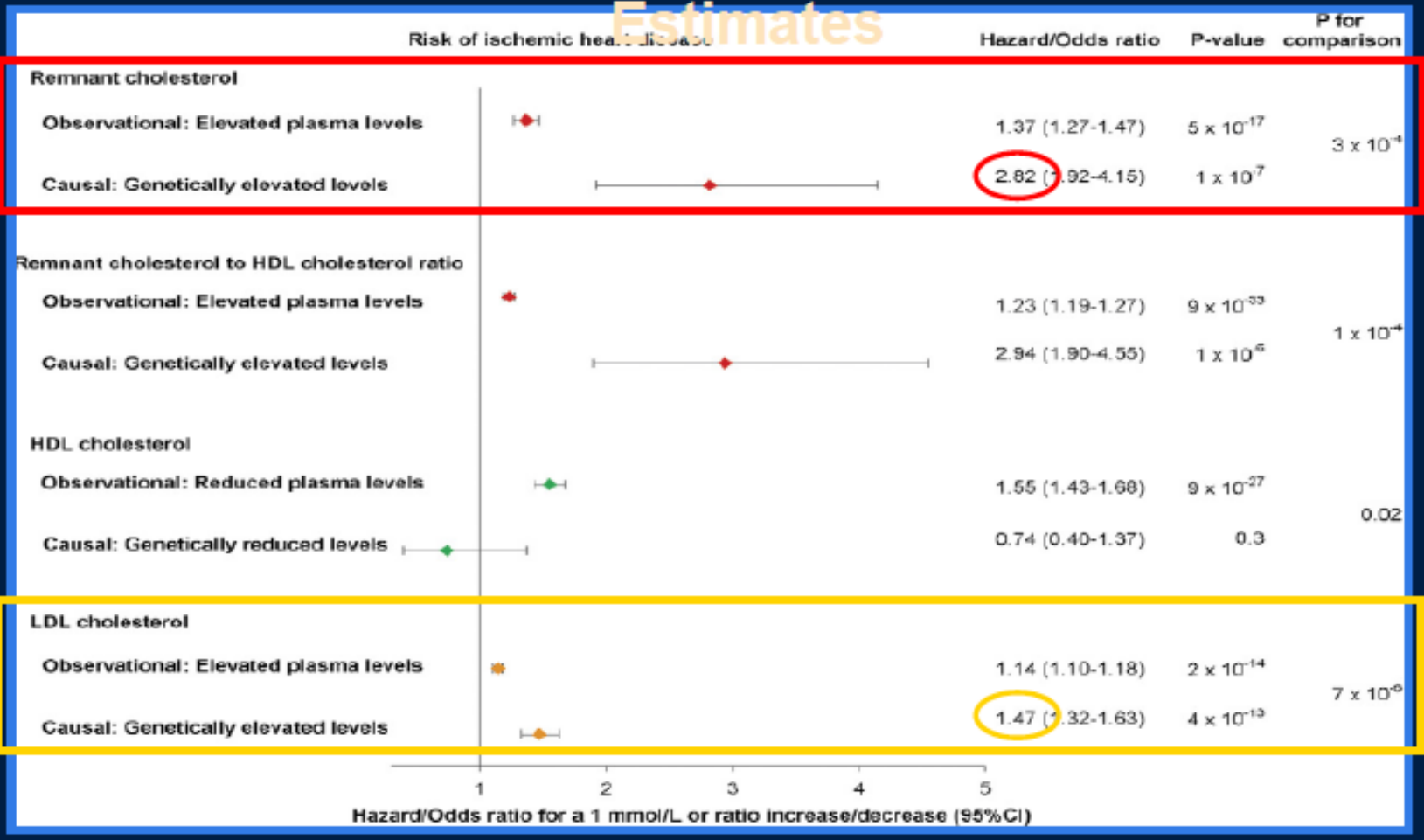


Varbo, Freiberg, Nordestgaard. Clin Chem 2015; 61: 533-543

Lipoprotein Genotypes and IHD

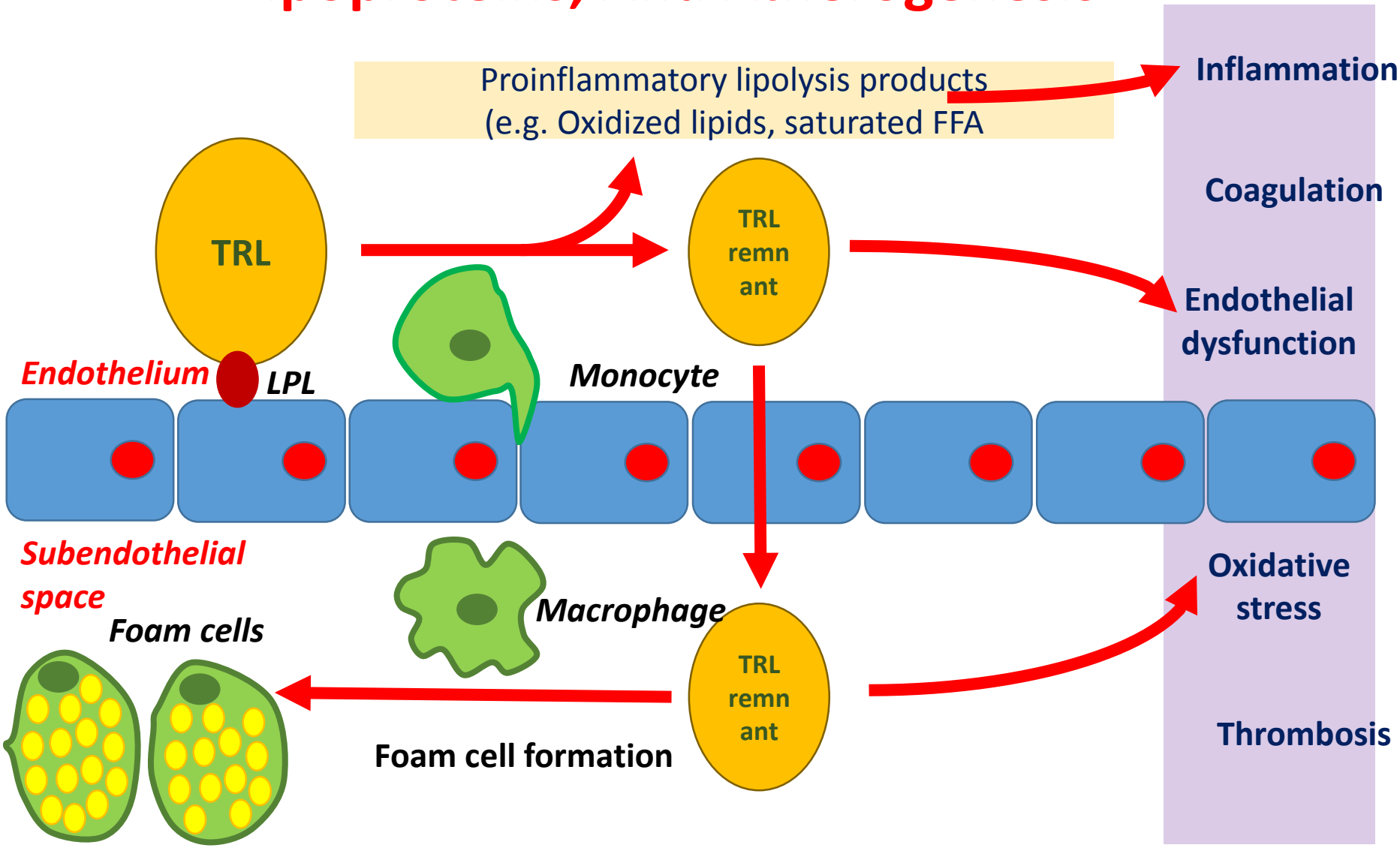
Copenhagen Studies: Causal vs Observational Risk Estimates



HRs for 1 mmol/l or a 1 ratio unit increase or decrease in plasma lipoprotein levels

Varbo et al. JACC 2013;61:427-436.

Hypertriglyceridaemia, Triglyceride-rich Lipoproteins, And Atherogenesis



Watts GF, Ooi EMM, Chan DC. Nature Reviews Cardiology 2013, 10, 648–661

Therapies for TG-rich Lipoproteins

Drug	Description
Fibrates (gemfibrozil, fenofibrate)	• Upregulate PPARα → increase FA oxidation and decrease FA synthesis. Reduce DGAT and VLDL synthesis and TG content and CETP activity. Increase LDL size. Reduce multiple inflammatory markers. • Upregulate apoA-V and LPL, downregulate apoC-III, all of which increase TG-rich lipoprotein lipolysis. • Increase apoA-I and apoA-II synthesis. Trigger LXR upregulation of ABCA1 and increased macrophage RCT. Increase hepatic delipidation of mature HDL.
Niacin (immediate, slow, and extended release)	• Decreases hepatic FA synthesis, increases FA oxidation. Decreases adipocyte TG lipolysis. Inhibits DGAT. Reduces TG-rich VLDL and CETP activity. Increases LDL size. • Delays lipolysis of mature HDL, increasing apoA-I. Through a PPAR- γ effect, triggers LXR upregulation of ABCA1 and increased macrophage RCT. Improves inflammatory markers.
Omega-3 fatty acids	• Increase lipolysis of TG-rich lipoproteins via their effect on multiple nuclear transcription factors; DGAT effect; increase LPL activity; increase LDL size; have potential anti-arrhythmic properties via their effect on ion channels.

Statins Reduce CVD Events in HTG Patients

Trial (Subgroup, mg/dL) (Drug)	Risk difference vs placebo		P-value	
	Main Study	Subgroup	Main Study	Subgroup
WOSCOPS (TG ≥148) (Pravastatin)	**–31%**	**–32%**	**<0.001**	**0.003**
CARE (TG ≥144) (Pravastatin)	**–24%**	**–15%**	**0.003**	**0.07**
PPP Project (TG ≥200) (Pravastatin)	**–23%**	**–15%**	**<0.001**	**0.029**
4S (TG >159, HDL-C <39) (Simvastatin)	**–34%**	**–52%**	**<0.001**	**<0.001**
JUPITER (TG ≥150) (Rosuvastatin)	**–44%**	**–21%**	**<0.001**	**NS**
CTT (TG >177) (Various)	**–21%**	**–24%**	**<0.001**	**<0.001**

TG lowering Rx

Nicotinic acid:

- AIM-HIGH no CV-benefit
- HPS2-THRIVE no CV-benefit

Fibrates

- ACCORD no CV-benefit
- FIELD no CV-benefit

Fibrates, EPA, Niacin – CV Outcome Trials

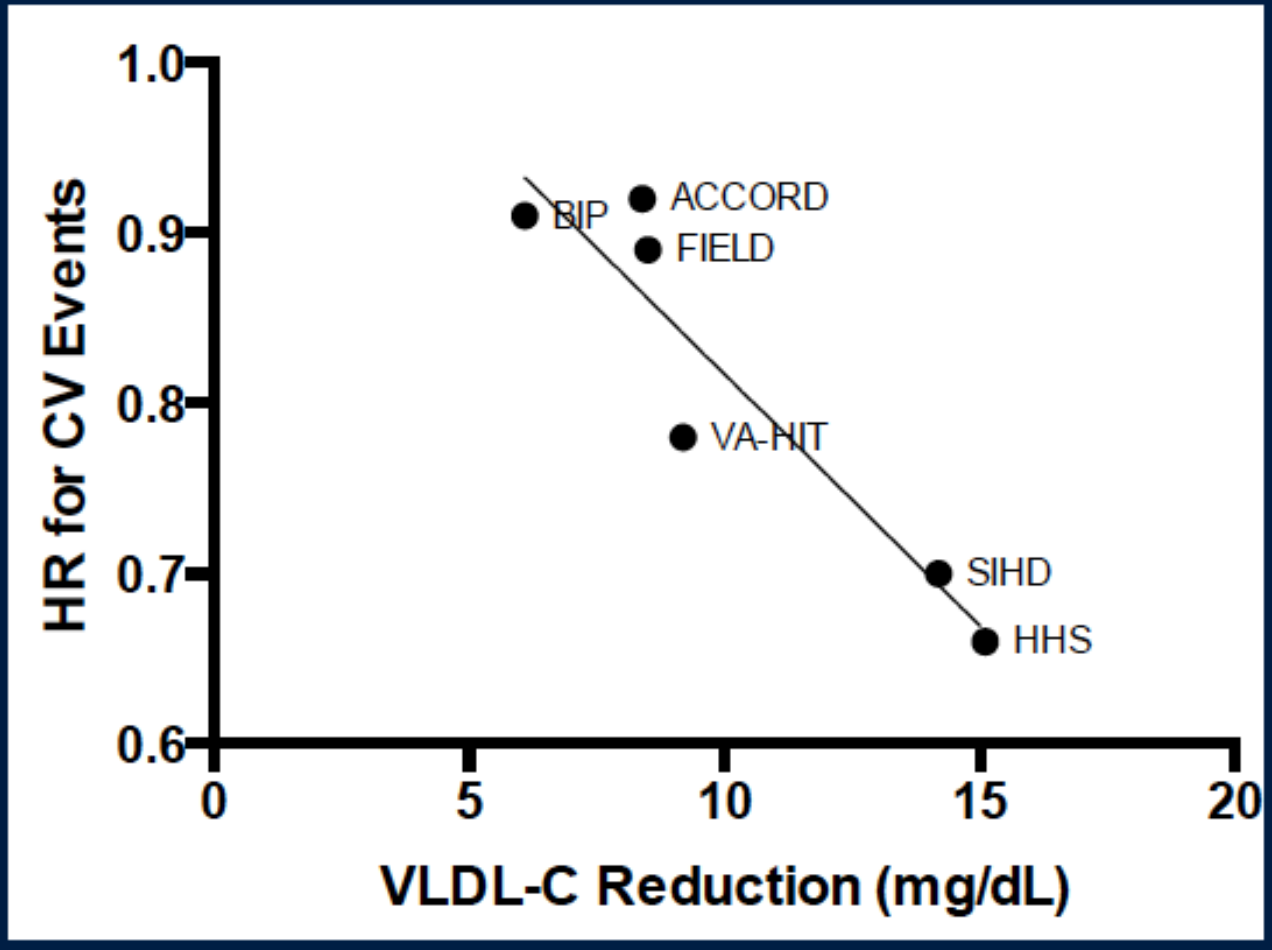
Larger Risk Reductions in Hypertriglyceridemia

Trial (drug)	Entire cohort HR (95% CI)	Subgroup	Subgroup HR (95% CI)
HHS (gemfibrozil)	0.66 (0.47, 0.92)	TG ≥184 mg/dL BMI >27.5 kg/m^2	0.30 (0.15, 0.58)
BIP (bezafibrate)	0.91 (NR)	TG ≥200 mg/dL	0.60 (NR)
VA-HIT (gemfibrozil)	0.78 (0.65, 0.93)	TG ≥151 mg/dL	0.73 (0.58, 0.93)
FIELD (fenofibrate)	0.89 (0.75, 1.05)	TG ≥204 mg/dL HDL-C <42 mg/dL	0.73 (0.58, 0.91)
ACCORD (fenofibrate)	0.92 (0.79, 1.08)	TG ≥204 mg/dL HDL-C ≤34 mg/dL	0.69 (NR)
JELIS (ethyl-EPA)	0.81 (0.69, 0.95)	TG >150 mg/dL HDL-C <40 mg/dL	0.47 (0.23, 0.98)
AIM-HIGH (niacin)	1.02 (0.87, 1.21)	TG >198 mg/dL HDL-C <33 mg/dL	0.74 (0.50, 1.09)

Maki et al. J Clin Lipidol. 2012;6:413. Guyton et al. JACC 2013;62:1580.

Meta-regression Demonstrates that VLDL-C Lowering is Highly Correlated with a Reduction in the Hazard Ratio for a Major CV Event

Each 8.9 mg/dL reduction in VLDL-C (equivalent to 0.5 mmol/L for TG) in the fibrate outcome trials is associated with a reduction of 26% in the hazard for a CV event



Calculated from: Nordestgaard BG, Varbo A. Lancet. 2014;384:626-635. Maki KC, et al. J Clin Lipidol. 2012;6:413-426. SIHD is Carlson LA, Rosenhamer G. Acta Med Scand. 1988;223:405-418.

STRENGTH (EPA+DHA) vs. REDUCE-IT (EPA only): STRENGTH Targets Patients Most Likely to Benefit from Non-HDL-C Reduction

Clinical factors	STRENGTH	REDUCE-IT
Number of patients	~13,000	~8,000
Inclusion criteria	TG ≥200 mg/dL, <500 mg/dL HDL-C <40 mg/dL (men) HDL-C <45 mg/dL (women)	TG ≥200 mg/dL, <500 mg/dL (started with TG ≥150 mg/dL)
	≥4 weeks on statin	≥4 weeks on statin
	Established CVD or at high risk for development of CVD	Established CVD or at high risk for development of CVD
Primary endpoint	MACE	MACE
Dosing regimen	4 g/d	4 g/d
Placebo	Corn oil	Mineral oil

ESC/EAS 2016 Guidelines

Recommendations	Class [a]	Level [b]	Ref [c]
LDL-C is recommended as the primary target for treatment.	I	A	64, 68
TC should be considered as a treatment target if other analyses are not available.	IIa	A	64, 123
Non-HDL-C should be considered as a secondary treatment target.	IIa	B	103
ApoB should be considered as a secondary treatment target, when available.	IIa	B	103, 124
HDL-C is not recommended as a target for treatment.	III	A	92, 93
The ratios apoB/apoAI and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	B	103

ESC/EAS 2016 Guidelines

Lipids LDL-C is the primary target[a]	**Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline[b] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
	High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline[b] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
	Low to moderate risk: LDL-C <3.0 mmol/L (115 mg/dL).
	Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively.
	HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk.
	TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.

NLA Recommendation for Patient centered management of Dyslipidemia

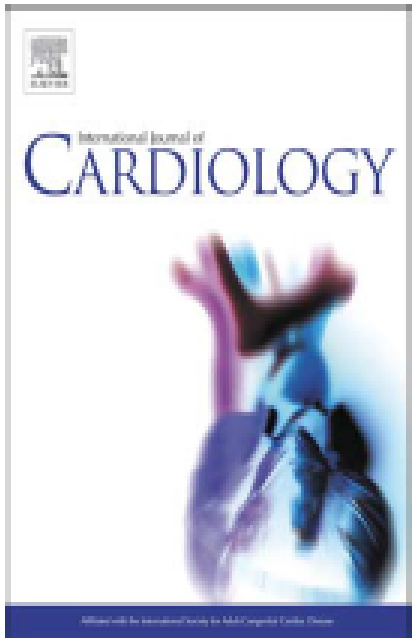
Table 2 Treatment goals for non-HDL-C, LDL-C, and Apo B in mg/dL

	Treatment Goal		
Risk Category	Non-HDL-C	LDL-C	Apo B*
Low	<130	<100	<90
Moderate	<130	<100	<90
High	<130	<100	<90
Very High	<100	<70	<80

Journal of Clinical Lipidology (2014) 8, 473–488

Consensus clinical recommendations for the management of plasma lipid disorders in the Middle East

Nasreen Al Sayed, Khalid Al Waili, Fatheya Alawadi, Saeed Al-Ghamdi, Wael Al Mahmeed, Fahad Al-Nouri, Mona Al Rukhaimi, Khalid Al-Rasadi, Zuhier Awan, Mohamed Farghaly, Mohamed Hassanein, Hani Sabbour, Mohammad Zubaid, Philip Barter



Box 4. Plasma lipid treatment goals

Primary treatment goal: LDL-C

High-risk patients

- A 50% reduction (initial goal) AND <1.8 mmol/L (<70 mg/dL) (after 50% reduction achieved)

Moderate-risk patients

- A 30% reduction (initial goal) AND <2.6 mmol/L (<100 mg/dL) (after 30% reduction achieved)

Primary treatment goal: Non-HDL-C

- 0.8 mmol/L (30 mg/dL) higher than LDL-C target [4, 71]

HDL, high-density lipoprotein; LDL-C, low-density lipoprotein; TG, triglyceride

Conclusion

- Evidence is now accumulating that TGs and TG-rich lipoproteins (TRLs) are causally involved in the pathogenesis of atherosclerotic CV disease.
- Non-HDL-C is a suitable target for dyslipidemia therapy.
- Fibrate, niacin fish oil appear to have CV benefits in the patients with high TG/Low HDL-c but may not benefit other dyslipidemic subgroups.
- Ongoing trials will better define optimal therapy beyond statins.