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7th EMIRATES FAMILY MEDICINE SOCIETY CONGRESS 2024

DUBAI | UAE | 22 to 24 APRIL

DUBAI WORLD TRADE CENTRE

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WiredIN

DECLARATION OF INTERESTS

Carlos Aguiar has received payments for speaker services, consultancy, and research activities from the following entities:

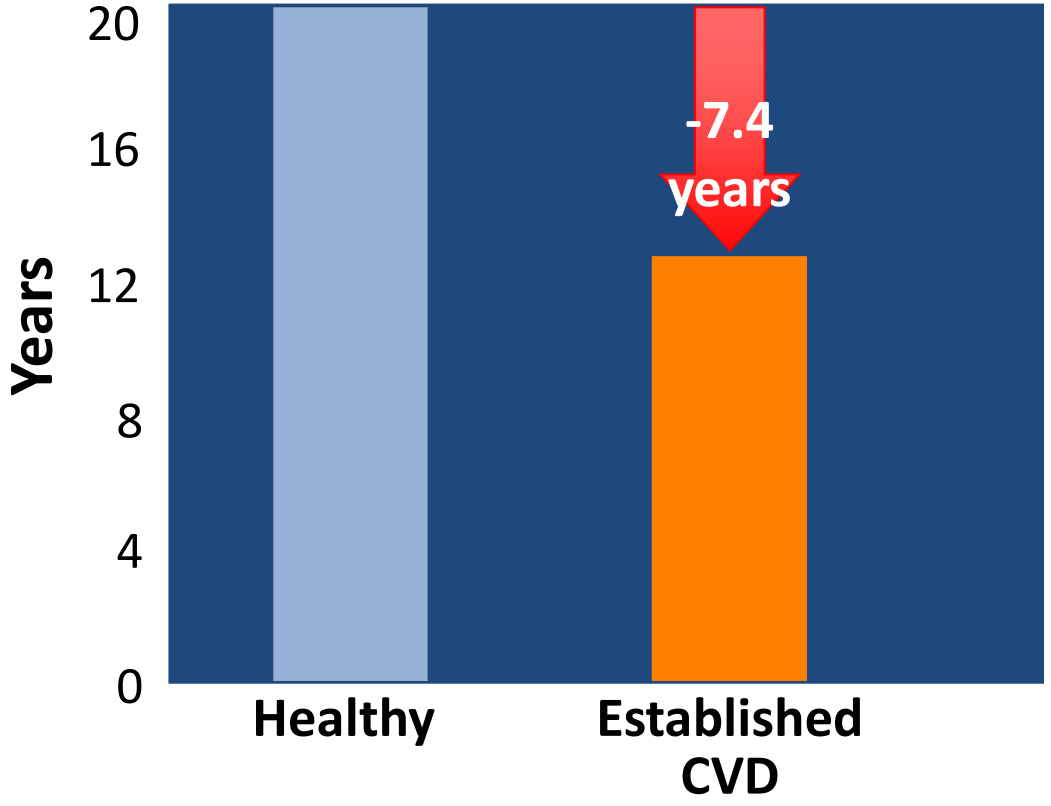
Abbott, Abbvie, Amgen, Alnylam, AstraZeneca, Bayer, BiAL, Boehringer-Ingelheim, Daiichi-Sankyo, Ferrer, Gilead, GSK, Lilly, Novartis, Pfizer, Sanofi, Servier, Takeda, Tecnimede

KEY MESSAGE #1

LDL-C goal attainment is a fundamental intervention to reduce mortality and morbidity in high risk individuals … **but CVD risk can remain very high even when LDL-C is at goal**

BURDEN OF CARDIOVASCULAR DISEASE

Average life expectancy for a man, age 60 years, Framingham



Lipid-lowering interventions are truly meant to prevent the occurrence of cholesterol-related complications that substantially reduce life expectancy and quality of life.

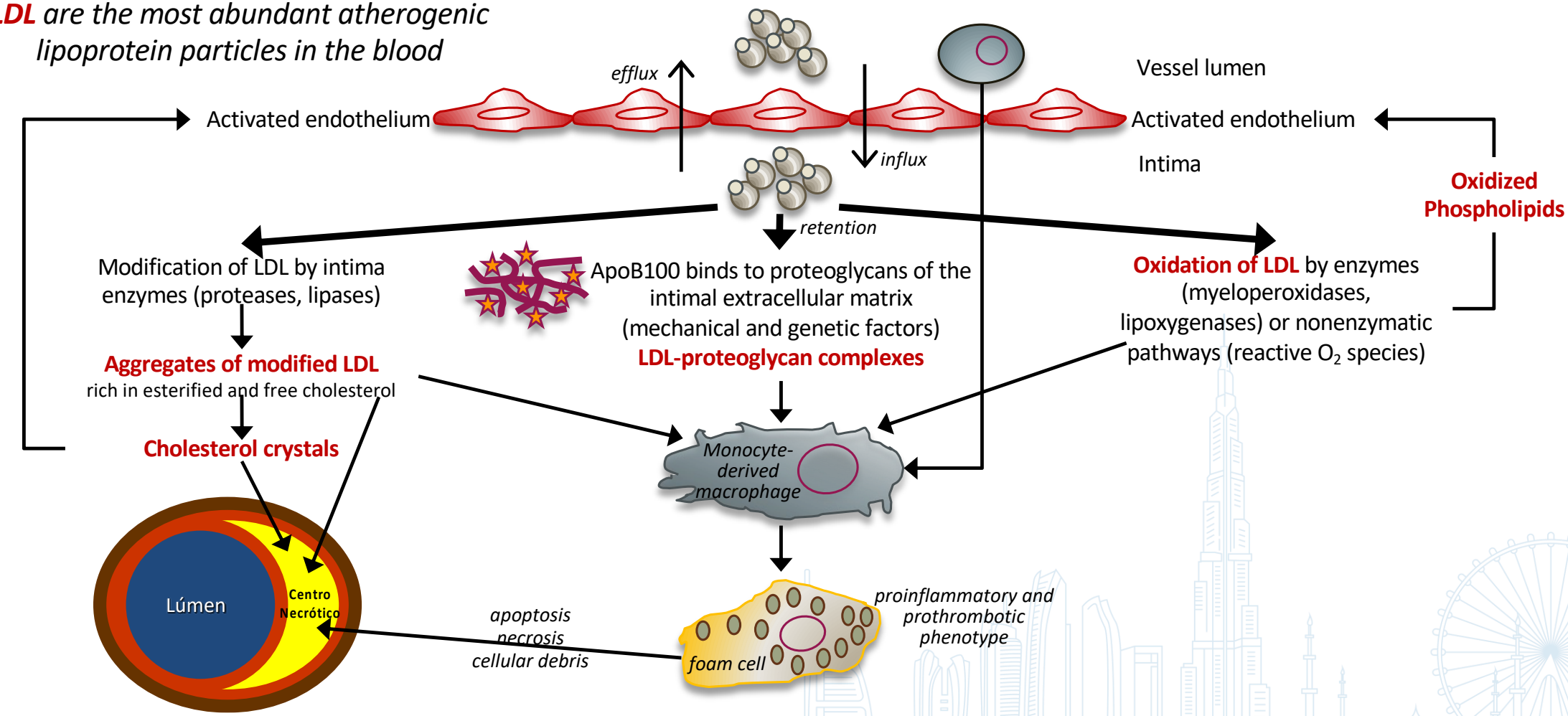
Average life expectancy for a woman, age 60 years: 24.5 years if healthy; 16.1 if established CVD; 11.6 if prior MI; 9.81 if prior stroke; 8.26 if heart failure.

CVD, cardiovascular disease. MI, myocardial infarction.

LDL-CHOLESTEROL

Primary driver of atherogenesis

***LDL** are the most abundant atherogenic lipoprotein particles in the blood*

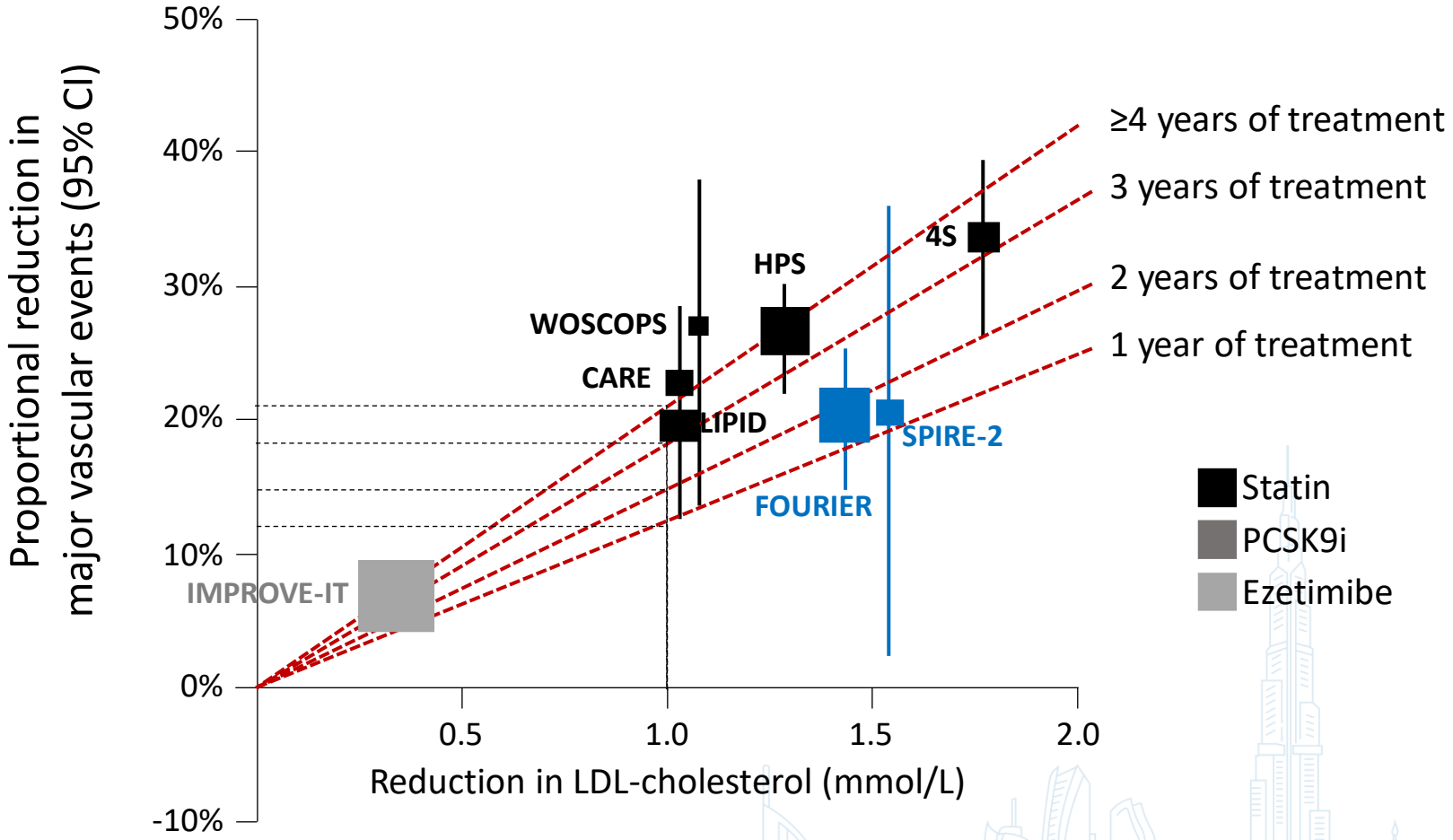


LDL-c, low density lipoproteins

Boren J et al. *Eur Heart J* **2020**;41:2313

LDL-CHOLESTEROL LOWERING THERAPY

Lower is better … and so is longer

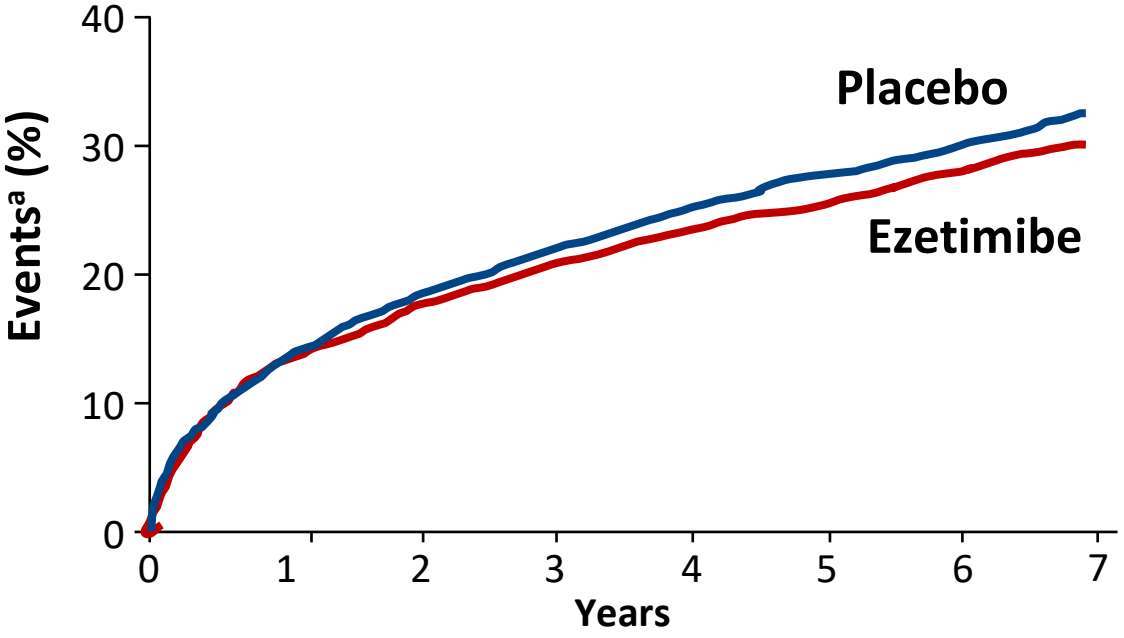


4S, Scandinavian Simvastatin Survival Study. CARE, Cholesterol and Recurrent Events Trial. FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk. HPS, Heart Protection Study. IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial. LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease. SPIRE-2, Studies of PCSK9 Inhibition and the Reduction of Vascular Events 2. WOSCOPS, West Of Scotland Coronary Prevention Study.

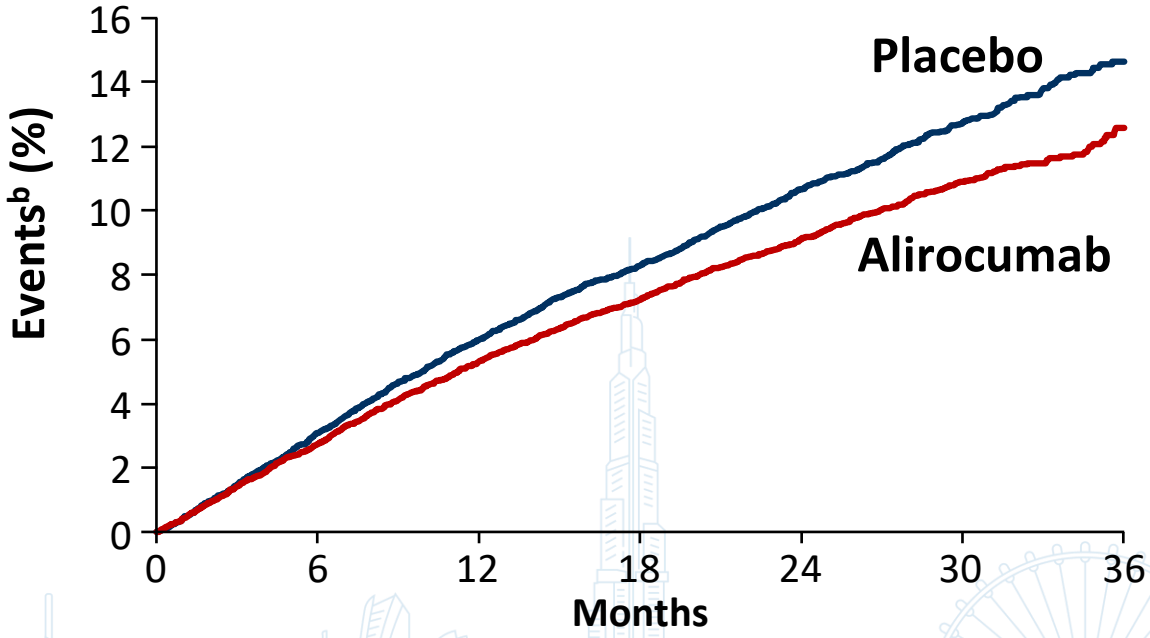
TRENDS IN CARDIOVASCULAR DISEASE

Residual risk despite LDL-c reducing therapies

IMPROVE-IT[1]:
Simvastatin vs Simva+Ezetimibe
LDL-c: 69 vs 54 mg/dL
Risk reduction 6%



ODYSSEY-OUTCOMES[2]:
High-potency statin vs +Alirocumab
LDL-c: 96 vs 48 mg/dL
Risk reduction 15%



[a] CVD death, MI, ischemic stroke, hospitalisation for unstable angina, myocardial revascularisation
[b] Coronary death, MI, ischemic stroke, hospitalisation for unstable angina

1. Cannon CP et al. *N Engl J Med* **2015**;372:2387. 2. Schwarz GG et al. *N Engl J Med* **2018**;379:2097.

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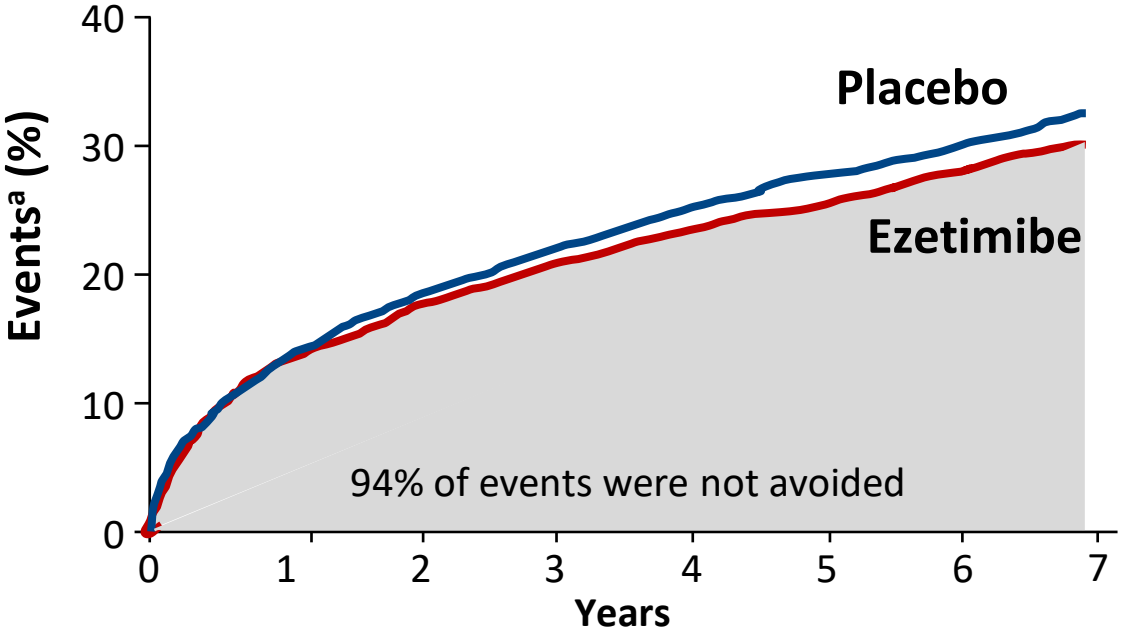

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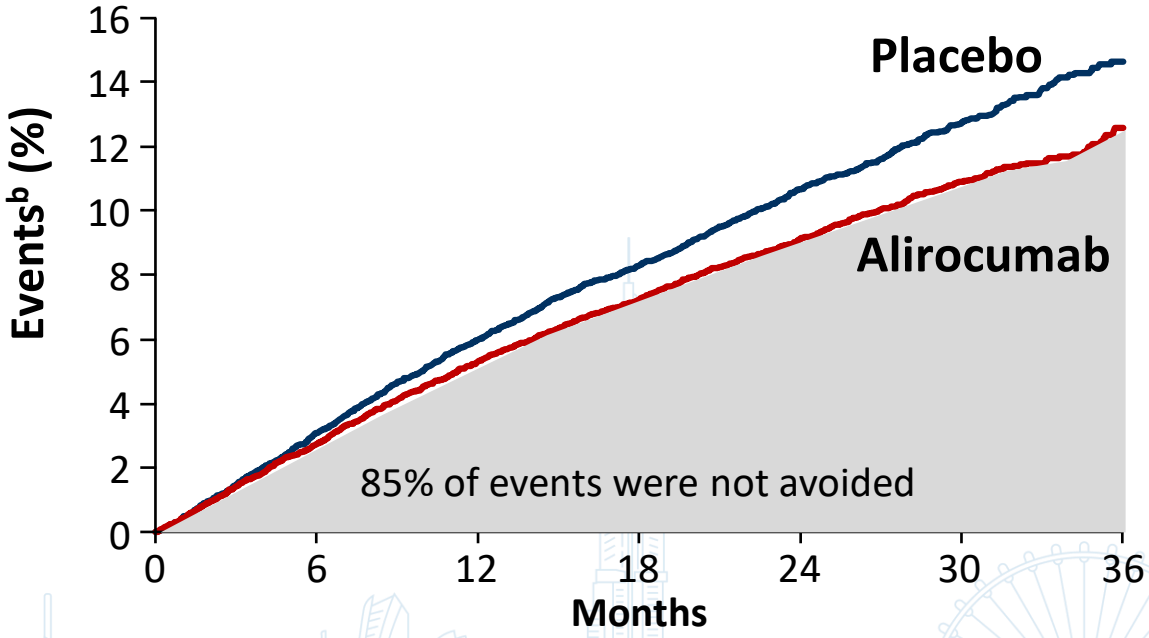

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1. Cannon CP et al. *N Engl J Med* **2015**;372:2387. 2. Schwarz GG et al. *N Engl J Med* **2018**;379:2097.

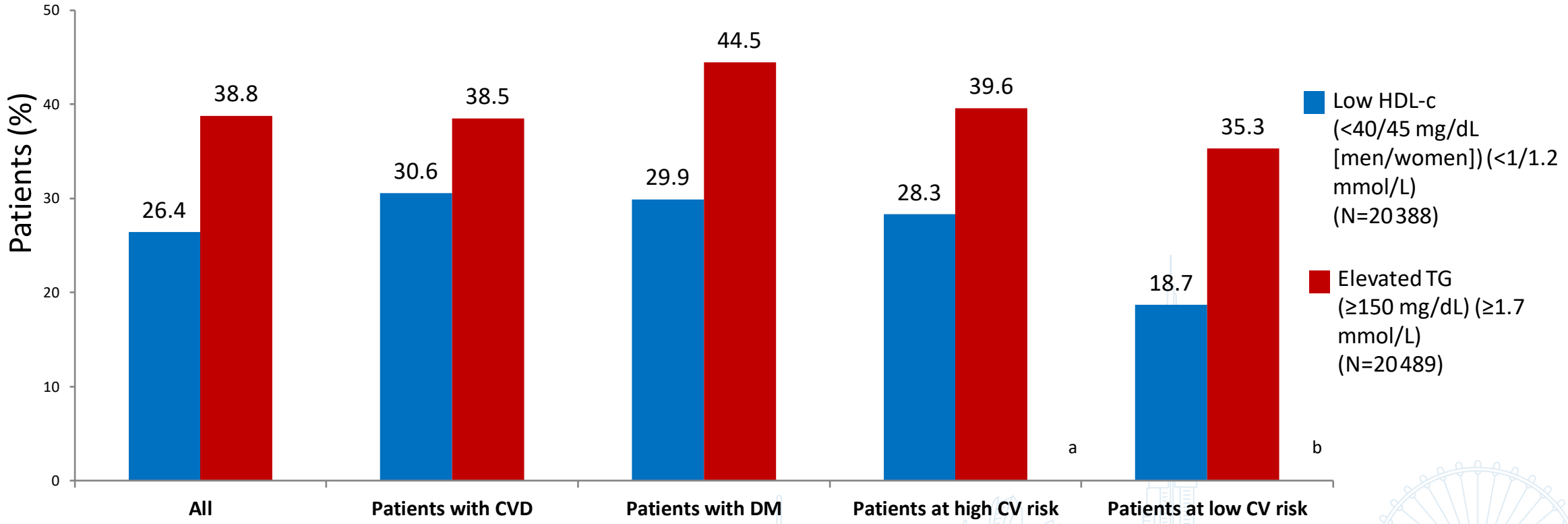
KEY MESSAGE #2

A common feature of individuals who have a persistently high residual risk of CVD events, despite taking LDL-C lowering treatments … is a **TG level >1.7 mmol/L**

MIXED DYSLIPIDEMIA

Highly prevalent condition, despite statin therapy[1,2]

Proportion of patients with TGs or HDL-c abnormalities in the DYSIS study[1]



DYSIS[1]: 22,063 patients from 2954 sites across 11 European countries and Canada between April 2008 and February 2009

[a]Defined as CVD and DM and/or SCORE ≥5%; [b]Defined as SCORE <5%

1. Gitt AK et al. *Eur J Prev Cardiol* **2012**;19:221. 2. Leiter LA et al. *Diabet Med* **2011**;28:1343.

MIXED DYSLIPIDEMIA

Contribution to excess risk of cardiovascular disease

Elevated TGs and low levels of HDL-c have a synergistic detrimental impact on residual CVD risk in patients on target LDL-c

Odds ratio for Coronary Heart Disease*		TG quintile				
		≤72 mg/dL (0.8 mmol/L)	72–102 mg/dL (0.8-1.2 mmol/L)	102–133 mg/dL (1.2-1.5 mmol/L)	133–190 mg/dL (1.5-2.1 mmol/L)	>190 mg/dL (2.1 mmol/L)
HDL-c quintile	>53 mg/dL (1.4 mmol/L)	1.0				0.6
	42–53 mg/dL (1.1-1.4 mmol/L)		**1.3**			1.2
	36–42 mg/dL (0.9-1.1 mmol/L)			**2.0**		2.4
	30–36 mg/dL (0.8-0.9 mmol/L)				**4.1**	5.0
	≤30 mg/dL (0.8 mmol/L)	3.1	4.2	5.6	7.6	**10.3**

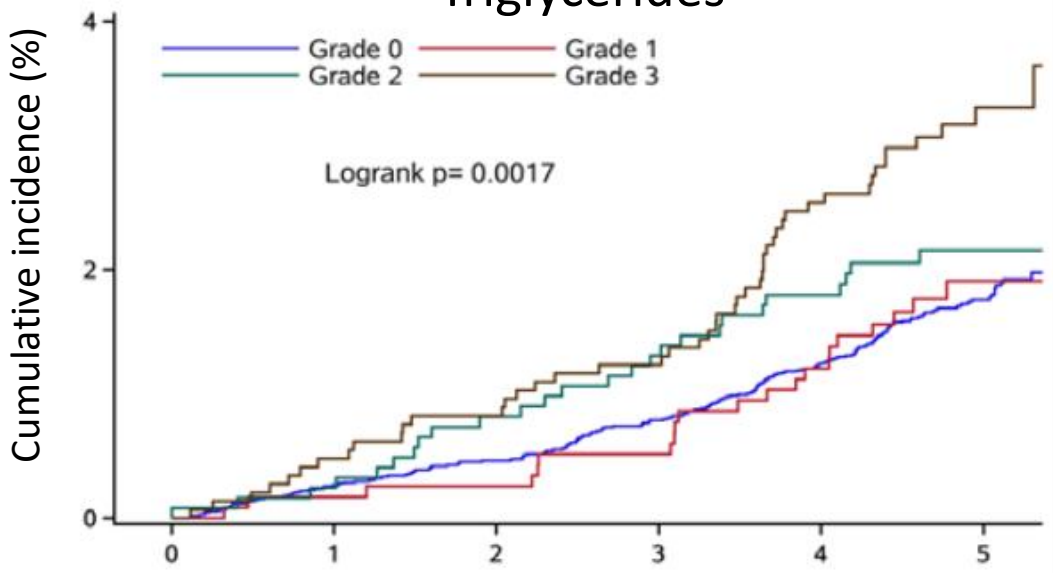
*345 patients with mean LDL-c < 81 mg/dL (2.1 mmol/L)

MIXED DYSLIPIDEMIA

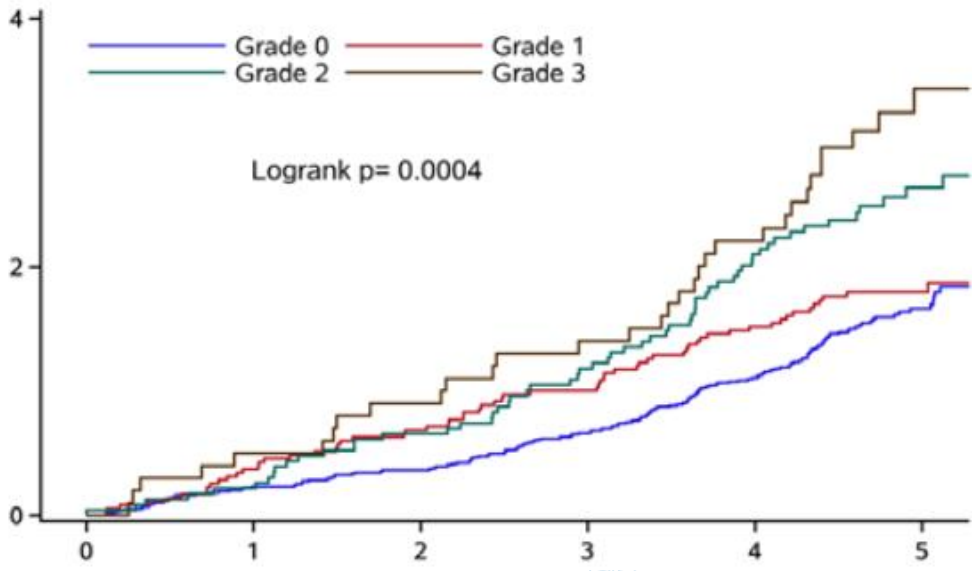
Contribution to excess risk of cardiovascular disease

Higher risk of ischemic stroke

Triglycerides



Non-HDL-cholesterol



Cumulative burden of TG, TC, LDL-c and non-HDL-c was associated with **higher subsequent ischemic stroke risk even with low cumulative burden of LDL-c**

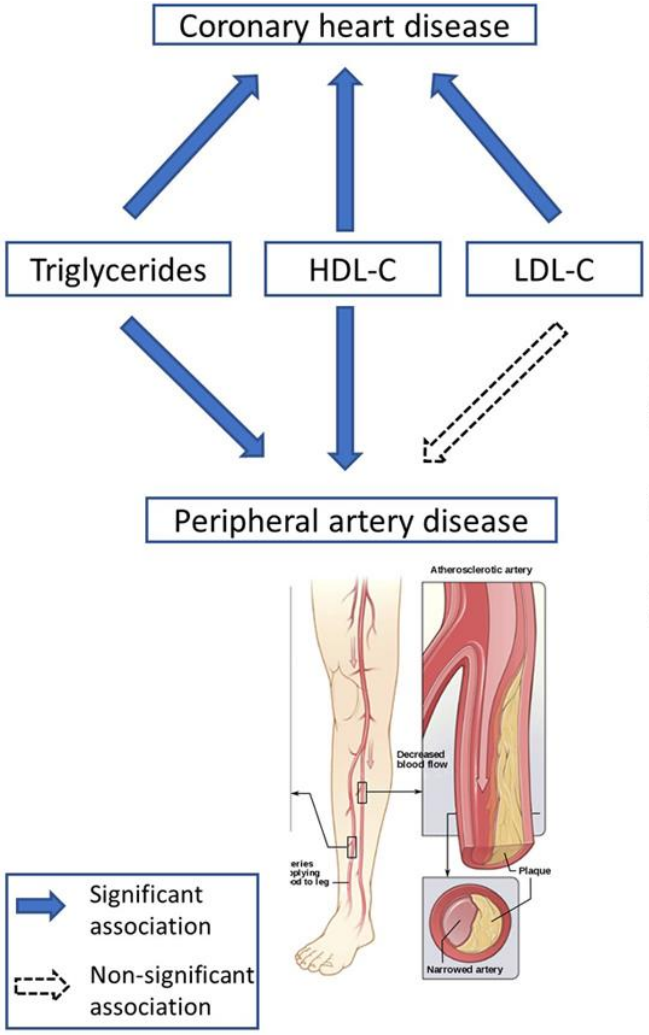
Kailuan General Hospital: 43,836 primary prevention patients participating in 4 surveys from 2006-2013. During follow up (mean 4.67 years), 1023 (2.33%) incident ischemic strokes were recorded. Individual cumulative lipid burden was calculated as number of years (2006–2013) multiplied by the lipid levels.

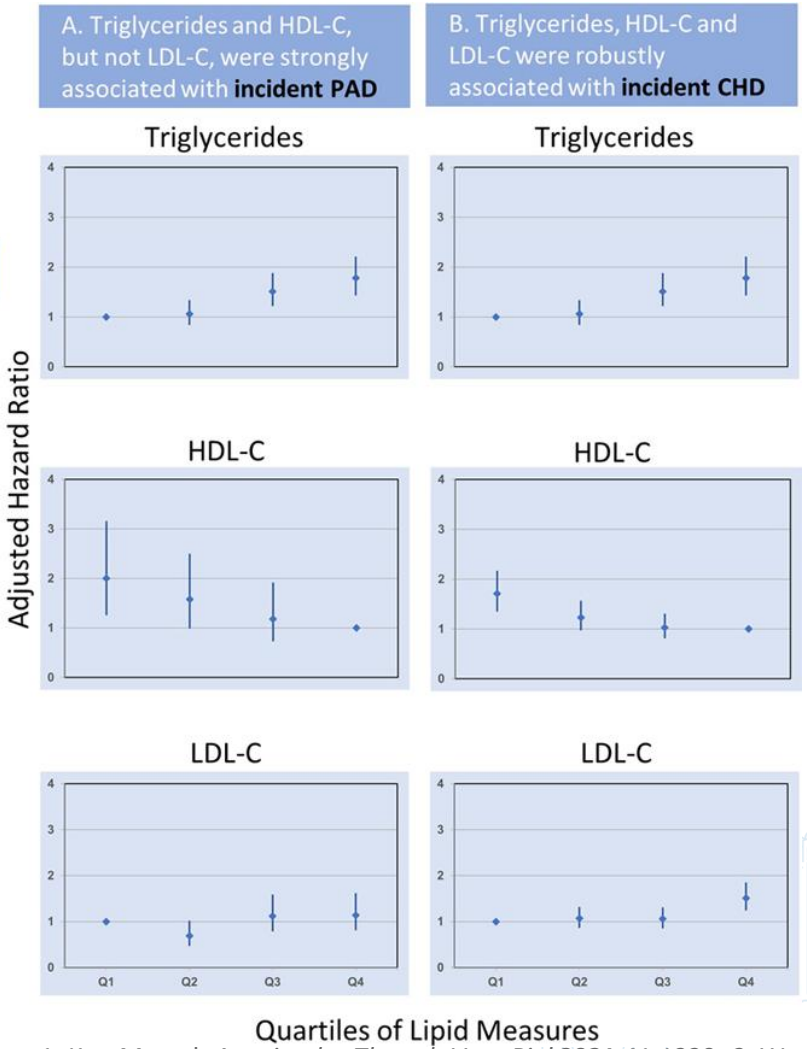
Dai L et al. *Stroke Vasc Neurol* **2021**;6:581

MIXED DYSLIPIDEMIA

Contribution to excess risk of cardiovascular disease

Higher risk of peripheral arterial disease





- Higher baseline levels of TG and lower levels of HDL were independently and robustly associated with incident PAD[1]
- Contribution of LDL-c seems smaller for PAD than CHD[1,2]

Atherosclerosis Risk in Communities (ARIC)[1]: 8,330 participants (mean age 62.8 years) free of PAD at baseline (1996–1998) were followed through 2015. There were 246 incident PAD cases with a median follow-up of 17 years.

PAD, peripheral arterial disease

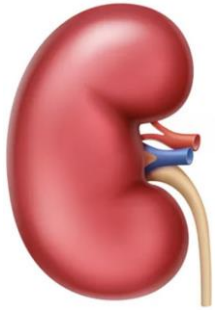
1. Kou M et al. *Arterioscler Thromb Vasc Biol* **2021**;41:1229. 2. Wadstrom BN et al. *Arterioscler Thromb Vasc Biol* **2024** Mar 21. Online ahead of print.

MIXED DYSLIPIDEMIA

Contribution to disease burden

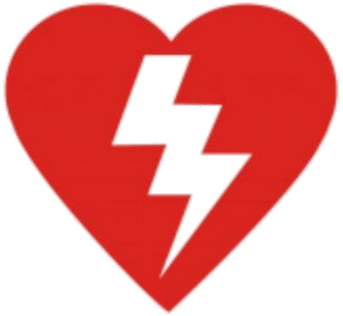
Heart failure

Prospective Population Study of Women in Gothenburg[1]: among 1143 50-year-old women, 155 were diagnosed HF over follow-up of 7-42 years. TG levels independently predicted HF (HR 1.49; 95% CI 1.10-2.03).



Chronic kidney disease

English Clinical Practice Research Datalink[2]: among 911360 subjects age 20-79, 11825 developed stage 3-4 CKD over median follow 7.5 years. Higher TG (HR 1.28; 95% CI 1.15-1.43) and lower HDL-c levels independently predicted CKD (HR 1.27; 95% CI 1.14-1.41).



Sudden cardiac death

SUDDEN[3]: 139 out-of-hospital SCDs and 968 controls age 18-64. Out-of-hospital SCD was predicted by TG/HDL-c ratio in age- and sex-adjusted analysis (OR 1.08 per unit increase in TG/HDL-c ratio; 95% CI 1.03-1.12).

All-cause mortality

BIP[3]: among 15355 patients age 45-74 with CAD, multivariable adjusted mortality over a median follow up of 22.8 years was associated with TG (HR 1.06 per unit increase in log TG; 95% CI 1.01-1.12).

HF, heart failure. HR, hazard ratio. OR, odds ratio.

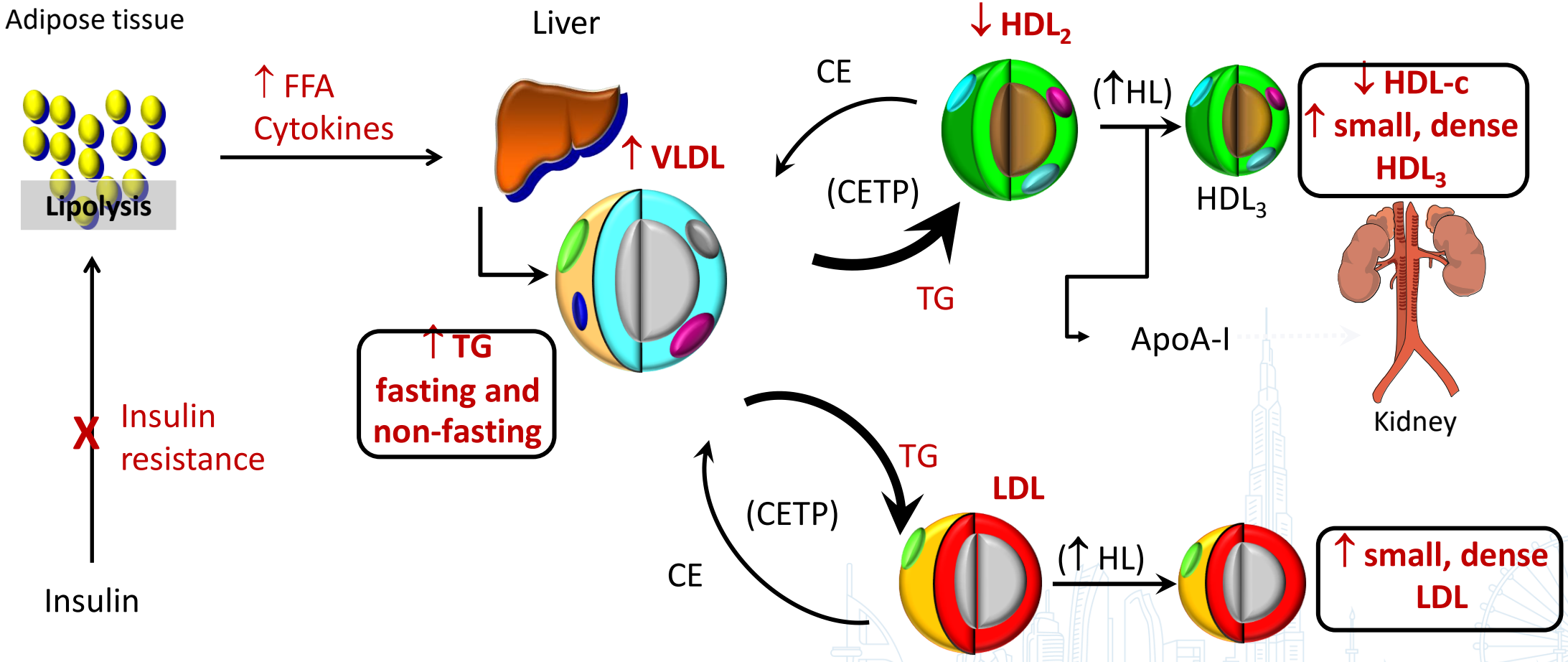
1. Halldin AK et al. *BMJ Open* **2020**;10:e036709. 2. Weldegiorgis M et al. *BMC Nephrology* **2022**;23:312.
3. Hosadurg N et al. *Mayo Clin Proc Inn Qual Out* **2018**;2:257. 4. Klempfner R et al. *Circ Cardiovasc Qual Outcomes* **2016**;9:100.

KEY MESSAGE #3

When TG are >1.7 mmol/L, LDL is no longer the only atherogenic lipoprotein particle … **TG-rich lipoprotein particles also become atherogenic**, and accelerate the accumulation of cholesterol and exacerbate inflammation in the arterial wall

ROLE OF TRIGLYCERIDE-RICH REMNANTS

Pathophysiology of atherogenic dyslipidemia

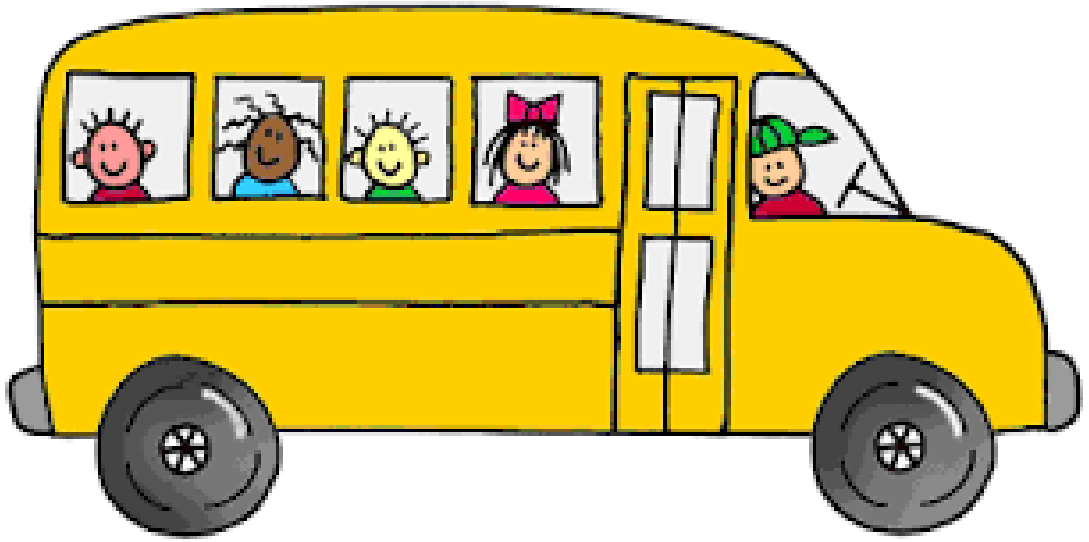


Apo, apolipoprotein. CE, cholesteryl ester. CETP, cholesteryl ester transfer protein. FFA, free fatty acid. HL, hepatic lipase.

ROLE OF TRIGLYCERIDE-RICH REMNANTS

Very simply perspective

- Atherosclerosis is about cholesterol
- Cholesterol is cholesterol
- Lipids are transported in lipoprotein particles



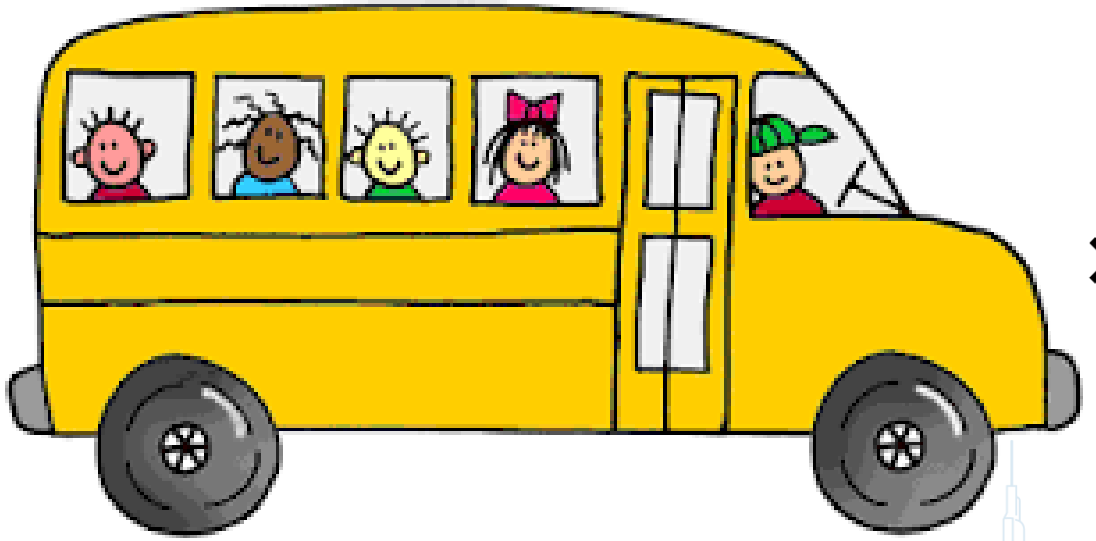
Arterial Wall

- Some particles deliver cholesterol from liver to peripheral tissue, but particle size is critical
- Others deliver cholesterol from tissues back to liver

ATHEROGENIC LIPOPROTEINS

If TG levels are normal

VLDL: TG Chol



Arterial Wall

Statins

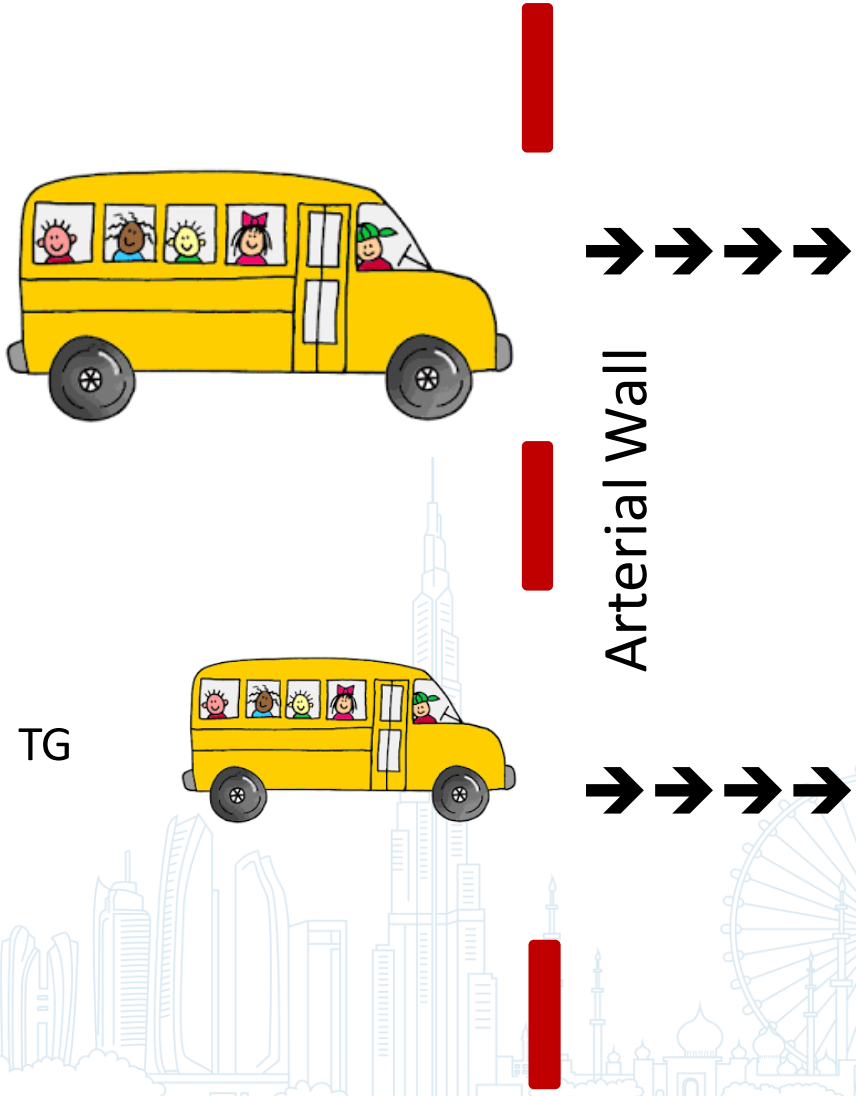
LDL: Chol TG

ATHEROGENIC LIPOPROTEINS

If TG levels are 150-500 mg/dL (1.7-5.7 mmol/L)[1]

Other apoB-containing lipoproteins, beyond LDL, acquire atherogenic activity

Remnant VLDL: TG Chol



Statins

sdLDL: Chol TG

Statins will have less cholesterol-lowering effects because they have a smaller effect on VLDL than on LDL[2]

Chol, cholesterol. sd, small dense.

1. Aguiar C. *Clin Invest Arterioscl* **2017**;29(Supl 2):2. 2. Chapman MJ et al. *Clin Cardiol* **2003**;26(Supl I):I-7.

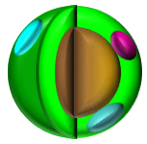
KEY MESSAGE #4

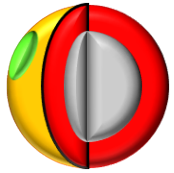
Non-HDL is a better measure of all the cholesterol that is potentially atherogenic … and **guidelines have made it a fundamental target to control CVD risk**

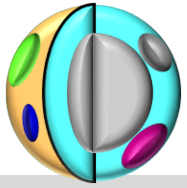
NON-HDL CHOLESTEROL

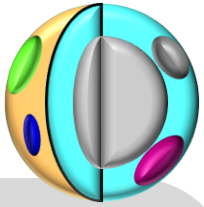
Better treatment target … going beyond LDL-c

Anti-atherogenic lipoprotein	**Atherogenic lipoproteins (=non-HDL)**

HDL-c 

LDL-c 

IDL 

VLDL 

How to calculate non-HDL-c:

non-HDL-c = TC – HDL-c

Non-HDL cholesterol[1,2]

- Non-HDL-c may be a better marker of CVD risk than LDL-c in patients with high TGs and diabetes, metabolic syndrome or chronic kidney disease
- Laboratories should automatically calculate and report non-HDL-c[3]
- EAS/ESC guidelines[2]: non-HDL-c should be considered a secondary target
  – Maximum recommended level = LDL-c goal + 30 mg/dL (0.8 mmol/L)

Total cholesterol in humans is distributed primarily among 3 major lipoprotein classes: VLDL, LDL, and HDL. Smaller amounts of cholesterol are also contained in two minor lipoprotein classes: IDL and Lp(a).

EAS, European Atherosclerosis Society. ESC, European Society of Cardiology.

1. Aguiar C et al. *Atheroscler Suppl* **2015**;19:1 . 2. Mach F et al. *Eur Heart J* **2020**;41:111. 3. Nordestgaard BG et al. *Atherosclerosis* **2020**;294:46.

NON-HDL CHOLESTEROL

American Association of Clinical Endocrinology Guidelines

Non-HDL-c and LDL-c are Co-Primary Targets of Therapy

Risk category	LDL-c	Non-HDL-c	TG	Apo B
Extreme T2DM or T1DM with established ASCVD or severe TOD: eGFR <45 mL/min/1.73m^2; UACR >300 mg/g; ABI <0.9; LV systolic or diastolic dysfunction	<55 mg/dL (1.4 mmol/L)	<80 mg/dL (2.0 mmol/L)	<150 mg/dL (1.7 mmol/L)	<70 mg/dL
Very high T2DM duration >10 y or T1DM >20 y and age >40 y without ASCVD or severe TOD; ≥2 additional traditional ASCVD risk factors	<70 mg/dL (1.8 mmol/L)	<100 mg/dL (2.6 mmol/L)	<150 mg/dL (1.7 mmol/L)	<80 mg/dL
High T2DM duration <10 y, T1DM duration <20 y with <2 additional ASCVD risk factors; no TOD	<100 mg/dl (2.6 mmol/L)	<130 mg/dL (3.4 mmol/L)	<150 mg/dL (1.7 mmol/L)	<90 mg/dL

Management of hyperTG is important with a goal of <150 mg/dL in T2D. In persons with fasting TG >200 mg/dL despite a maximally tolerated statin, optimal glucose control, tight adherence to a healthy diet, fenofibrate and/or high-dose prescription grade omega-3 fatty acid may help to achieve goals for TG levels and nonHDL-C.

UACR, urinary albumin/creatinine ratio.

NON-HDL CHOLESTEROL

Middle East Consensus 2021

Atherosclerosis
Volume 343, February 2022, Pages 28-50

Consensus clinical recommendations for the management of plasma lipid disorders in the Middle East: 2021 update

Nasreen Alsayed [a], Wael Almahmeed [b], Fahad Alnouri [c, 1], Khalid Al-Waili [d], Hani Sabbour [e], Kadhim Sulaiman [f], Mohammad Zubaid [g], Kausik K. Ray [h, 1], Khalid Al-Rasadi [i, 1]

7.3.6. Fibrates

The addition of a fibrate to a statin may benefit some patients with type 2 diabetes with both high TG and low HDL-C dyslipidaemia pattern, particularly those with microvascular complications. When used as an add-on therapy to statins, fibrates are associated with greater reductions in TG levels, and a greater increase in HDL-C (compared with either used as a monotherapy) [132]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study demonstrated that fibrates decrease ASCVD events in subjects with type 2 diabetes with elevated levels of plasma TG and low levels of HDL-C [133]. Furthermore, in the ACCORD-Lipid trial, participants with the combination of significant hypertriglyceridaemia and low HDL-C experienced a 31% lower CVD event rate with statin-fibrate combined treatment [134]. Fibrates are safe and generally well tolerated.

[136]. The use of fibrates in addition to statins in patients with metabolic dyslipidaemia may lower TG levels, increase HDL-C, and lower the risk of ASCVD events [132–134]. Fibrates are generally well tolerated.

NON-HDL CHOLESTEROL

American Heart Association Scientific Advisory

N-3 fatty acids for management of hypertriglyceridemia

n-3 FAs (**4 g/day**) for **improving ASCVD risk in patients with hypertriglyceridemia** is supported by a ↓25% in major adverse cardiovascular endpoints in REDUCE- IT

TG 200-499 mg/dL	4 g/day n-3 FA: ↓TG by 20-30% and no ↑LDL-c
TG ≥500 mg/dL	4 g/day n-3 FA: ↓TG by ≥30%; DHA-containing agents ↑LDL-c
Children/adolescents	Apparently safe; more research needed to further evaluate efficacy
Use with other lipid therapy	Safe and apparently additive ↓TG with statin therapy; apparently safe with fibrates but more research needed to evaluate efficacy
Prescription n-3 FA agent	All prescription agents appear comparably effective, but head-to-head comparisons are lacking Safe and additive TG reduction on top of statins and fibrates

KEY MESSAGE #5

To reduce the exacerbated risk of CVD in individuals with high TG (non-HDL >0.8 mmol/L above the LDL-C), **add fenofibrate and/or n-3 FA to the LDL-C lowering treatment**

FENOFIBRATE

Optimizing cardiovascular disease outcomes in type 2 diabetes

Trial	Patient population	Outcomes	
FIELD[1,2]	9795 patients with T2DM • 22% patients with CVD	**All patients** Baseline median TG levels of 1.7 mmol/L **Non-fatal MI + CHD death** **RRR 11% (p=0.16)**	**Patients with TG ≥2.30 mmol/L and HDL <1.30/1.29 mmol/L men/women**[a] **Total CV events (CV deaths, MI, stroke, revascularisation)** **RRR 27% (p=0.005)** **NNT_5=23**
ACCORD Lipid[3,4]	5518 patients with T2DM • 37% patients with CVD	**All patients** Baseline median TG levels of 1.8 mmol/L **CVD death, non-fatal MI + non-fatal stroke** **RRR 8% (p=0.32)**	**Patients with TG ≥2.3 mmol/L and HDL-c ≤0.9 mmol/L**[b] **CVD death, non-fatal MI + non-fatal stroke** **RRR 31% (p=0.032)** **NNT_5=20**

[a]Post-hoc analysis of data from the FIELD trial[2]; [b]Pre-specified subgroup analysis for ACCORD Lipid trial

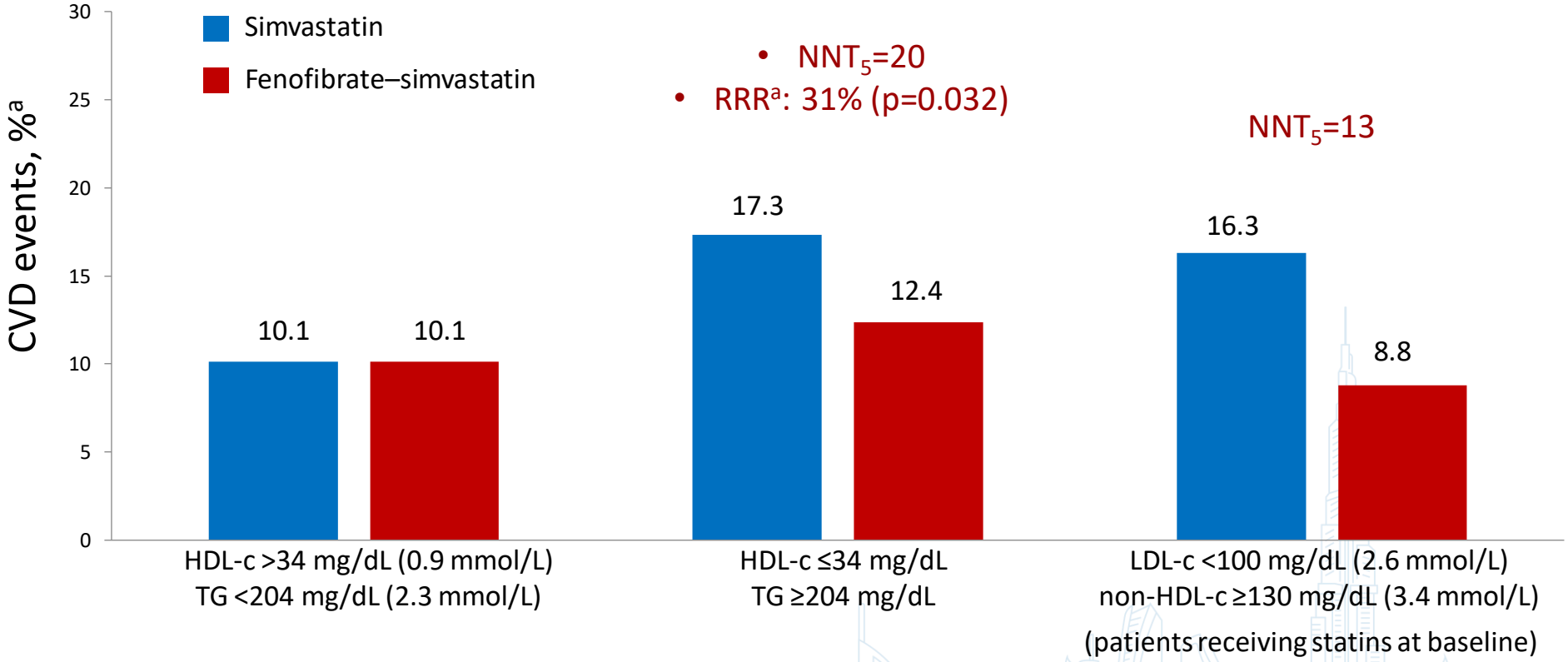
NNT_5, number needed to treat for 5 years. T2DM, type 2 diabetes mellitus.

1. Keech A et al. *Lancet* **2005**;366:1849.
2. Scott R et al. *Diabetes Care* **2009**;32:493. 3. Ginsberg HN et al. *N Engl J Med* **2010**;362:1563.
4. FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting. 19 May 2011.

FENOFIBRATE + STATIN

Combination improves cardiovascular disease outcomes in type 2 diabetes

Reduction in the number of CVD events in the ACCORD Lipid trial according to lipid profile[1,2]



ACCORD-LIPID: 5518 T2DM patients at high CVD risk received open-label simvastatin plus either fenofibrate or placebo

[a]CVD events (1º outcome): first occurrence of non-fatal MI, non-fatal stroke or death from CVD causes

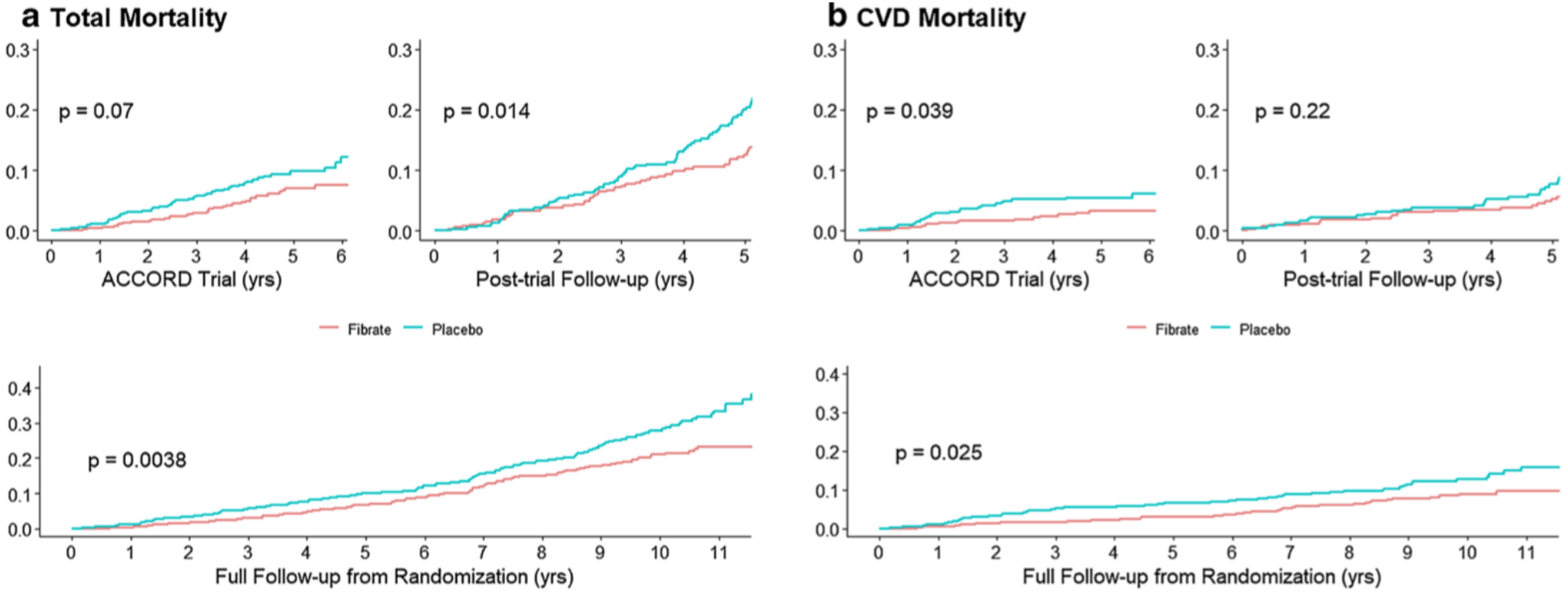
RRR, relative risk reduction.

1. Ginsberg HN et al. *N Engl J Med* **2010**;362:1563.
2. FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting. 19 May 2011.

FENOFIBRATE + STATIN

Combination improves cardiovascular disease outcomes in type 2 diabetes

Legacy effect in ACCORDION study

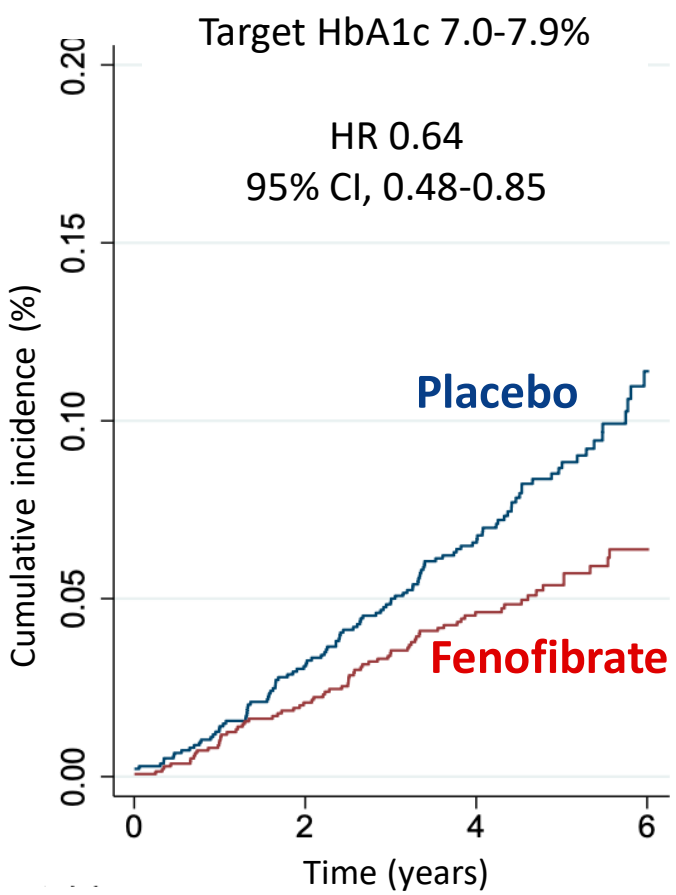


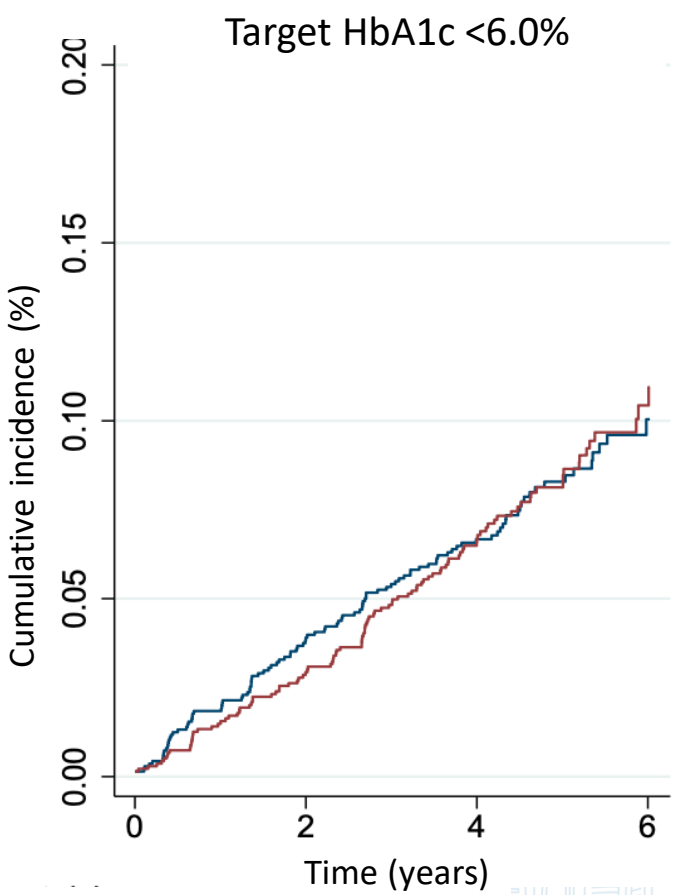
ACCORDION: 853 atherogenic dyslipidemia survivors of ACCORD consented to an additional 5 years nontreatment, observation-only study (mean total follow-up 9.7 years). Minimal differences between randomized groups for any of the lipid parameters during the post-trial period.

FENOFIBRATE + STATIN

Combination improves cardiovascular disease outcomes in type 2 diabetes

Reduction in risk of CV death or heart failure hospitalization in ACCORD-LIPID





ACCORD-LIPID: 5518 T2DM patients at high CVD risk received open-label simvastatin plus either fenofibrate or placebo

Endpoint for this analysis: CV death or heart failure hospitalization.

Fenofibrate reduced the endpoint (6.9%) vs placebo (8.3%): HR 0.82 (95% CI, 0.68-1.00; p=0.048). This result was independent of baseline lipid levels.

Fenofibrate significantly reduced heart failure hospitalizations among patients receiving the standard glucose-lowering treatment: HR 0.60 (95% CI 0.42-0.85)

FENOFIBRATE + STATIN

Safety and tolerability of combination therapy

- **Fenofibrate does not influence the metabolism or pharmacokinetics of statins**[1]
  - Another fibrate, gemfibrozil, inhibits statin glucuronidation-mediated lactonisation[1]
  - When used in combination with simvastatin in the ACCORD Lipid trial, fenofibrate treatment did not increase statin concentration and the risk of myositis or rhabdomyolysis[2]

- **Fenofibrate–statin combination therapy showed glucose-mitigating effects** in patients with mixed dyslipidemia[3,4]

1. Prueksaritanont T et al. *Drug Metab Dispos* **2002**;30:1280. 2. Ginsberg HN et al. *N Engl J Med* **2010**;362:1563. 3. Krysiak R et al. *Pharmacol Rep* **2010**;62:120. 4. Wysocki J et al. *Int J Clin Pharmacol Ther* **2004**;42:212.

FENOFIBRATE + STATIN

Safety and tolerability of combination therapy

Kidney	Liver	Pancreas
• Reversible,[1,2] increases in creatinine production[3,4] • Reduction in urine albumin concentration[3,4] and rate and progression of micro- and macroalbuminuria[1] • Lower loss of eGFR[3,4,5] • No long-term impact on renal function or ESRD observed[1]	• Increases in ALT observed in a small number of patients[1]	• Non-significant increases in pancreatitis following long-term treatment[3] • No association between fibrate and pancreatitis according to a recent meta-analysis[6]

ALT, alanine aminotransferase. eGFR, estimated glomerular filtration rate. ESRD, end-stage renal disease.

1. Ginsberg HN et al. *N Engl J Med* **2010**;362:1563.
2. Mychaleckyj JC et al. *Diabetes Care* **2012**;35:1008. 3. Keech A et al. *Lancet* **2005**;366:1849.
4. Davis TM et al. *Diabetologia* **2011**;54:280. 5. Frazier R et al. *Kidney Int Rep* **2018**;4:94. 6. Preiss D et al. *JAMA* **2012**;308:804.

KEY MESSAGES

1. LDL-C goal attainment is a fundamental intervention to reduce mortality and morbidity in high risk individuals … **but CVD risk can remain high even when LDL-C is at goal**

2. A common feature of individuals who have a persistently high residual risk of CVD events, despite taking LDL-C lowering treatments … is a **TG level >1.7 mmol/L**

3. When TG are >1.7 mmol/L, LDL is no longer the only atherogenic lipoprotein particle … **TG-rich lipoprotein particles also become atherogenic**

KEY MESSAGES

4. **Non-HDL** is a better measure of all the cholesterol that is potentially atherogenic … and **guidelines have made it a fundamental target to control CVD risk, beyond LDL-C**

5. To reduce the exacerbated risk of CVD in individuals with high TG (non-HDL >0.8 mmol/L above the LDL-C), **add fenofibrate and/or n-3 FA to the LDL-C lowering treatment**

KEEP IN MIND

Atherosclerosis is the **most common preventable chronic disease** … but it remains #1 cause of death worldwide

'Residual risk' is a **euphemism for failed prevention**

- ✓ Up to 95% of all MI can be prevented
- ✓ Almost as much of other atherosclerotic complications can be prevented
- ✓ Failure should be a rare event

Let's transform atherosclerosis into a rare disease …

We know how and we have what is needed