S.I.Te.C.S.
SOCIETÀ ITALIANA DI TERAPIA CLINICA E SPERIMENTALE

DYSLIPIDAEMIAS: PRESENT AND FUTURE APPROACHES TO PHARMACOLOGICAL INTERVENTION

November 9th-10th, Sorrento (NA) - Italy

Chairs: Alberico L. Catapano, Pasquale Perrone Filardi and Lale Tokgözoğlu

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November 9th, 2019

LIPOPROTEINS AND ATHEROSCLEROSIS

TG Lowering Benefits: Clinical Evidence

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Faculty Disclosure

	No, nothing to disclose
X	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
AMGEN	x							
Eli Lilly	x							
MSD	x							
Abbott - Mylan	x							
Servier	x							
SANOFI	x							
Chiesi	x							

Triglyceride Lowering Benefits: Clinical Evidence

- ✓ **What plasma TG range should we be focusing on?**
- ✓ What if it's again cholesterol (in TG-rich lipoproteins + their remnants)
- ✓ Why are TG-rich lipoproteins and their remnants atherogenic? A glance on pathophysiology
- ✓ Are TGs still associated with risk of CV events at low LDL-C?
- ✓ TG lowering approaches (supported by ESC/EAS 2019 Guidelines) and their clinical benefits

Hypertriglyceridemia: a simplified classification

TG plasma levels: #1 driver for clinical management

Normal	<175 mg/dL (<2,0 mmol/L)
Mild-moderate	175-885 mg/dL (2,0–10,0 mmol/L)
Severe	>885 mg/dL (>10,0 mmol/L)

GENETIC BACKGROUND

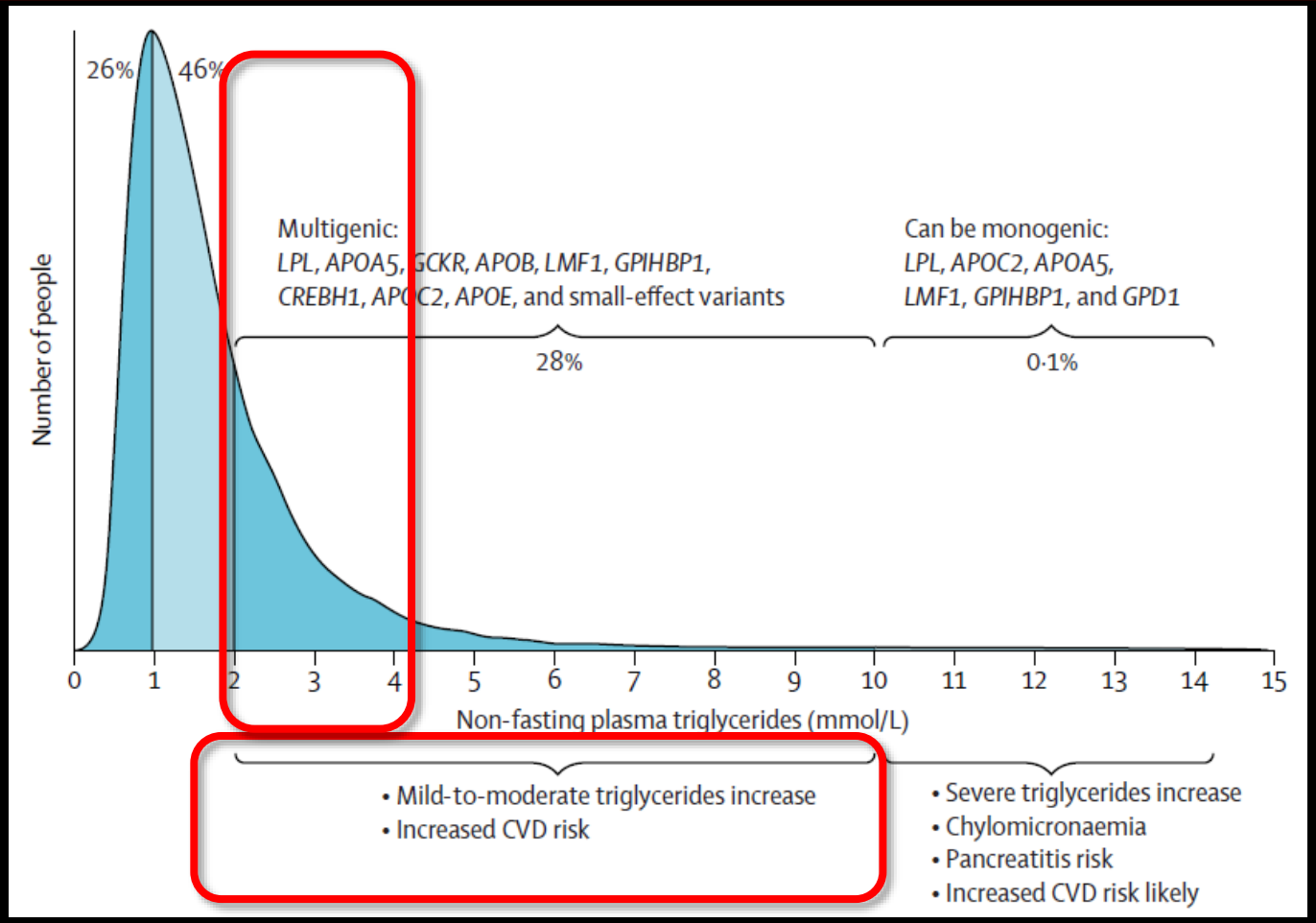
- **HTG mild-moderate** (common) usually **polygenic**
- HTG severe (rare) usually monogenic

CLINICAL IMPLICATIONS

- **HTG mild-moderate** (common): **increased CV risk**
- HTG severe (rare): risk factor for acute pancreatitis

Source: The Lancet Diabetes & Endocrinology (DOI:10.1016/S2213-8587(13)70191-8)

Redefinition of hypertriglyceridaemia (HTG) based on genetic data



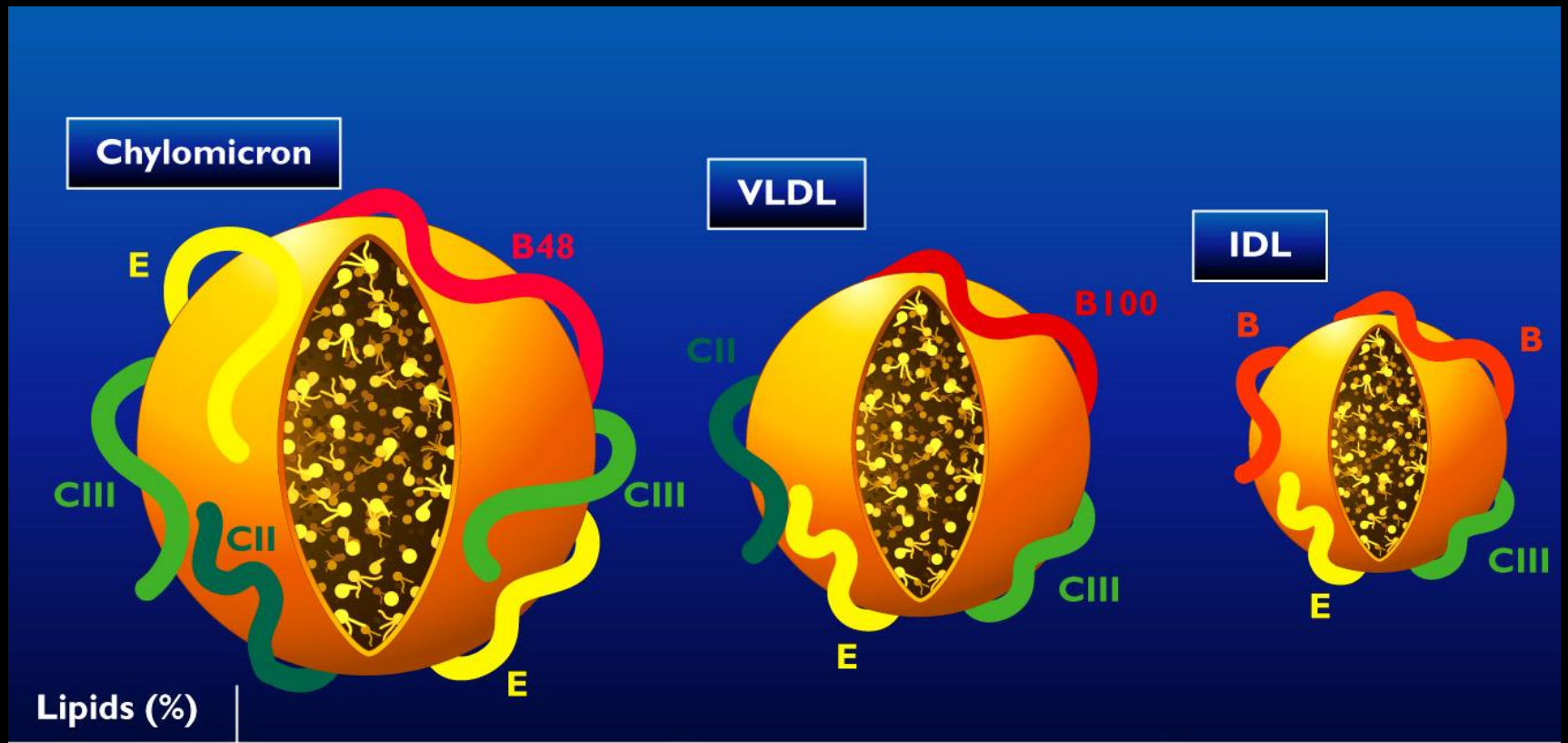
- >95% of adult patients with HTG have a genetic component (polygenic)
- Plasma triglyceride concentrations and approximate population percentages are based on data for more than 70 000 adults (>20 years of age) from the Copenhagen General Population Study

Source: The Lancet Diabetes & Endocrinology (DOI:10.1016/S2213-8587(13)70191-8)

Triglyceride Lowering Benefits: Clinical Evidence

- ✓ What plasma TG range should we be focusing on?
- ✓ **What if it's again cholesterol (in TG-rich lipoproteins + their remnants)?**

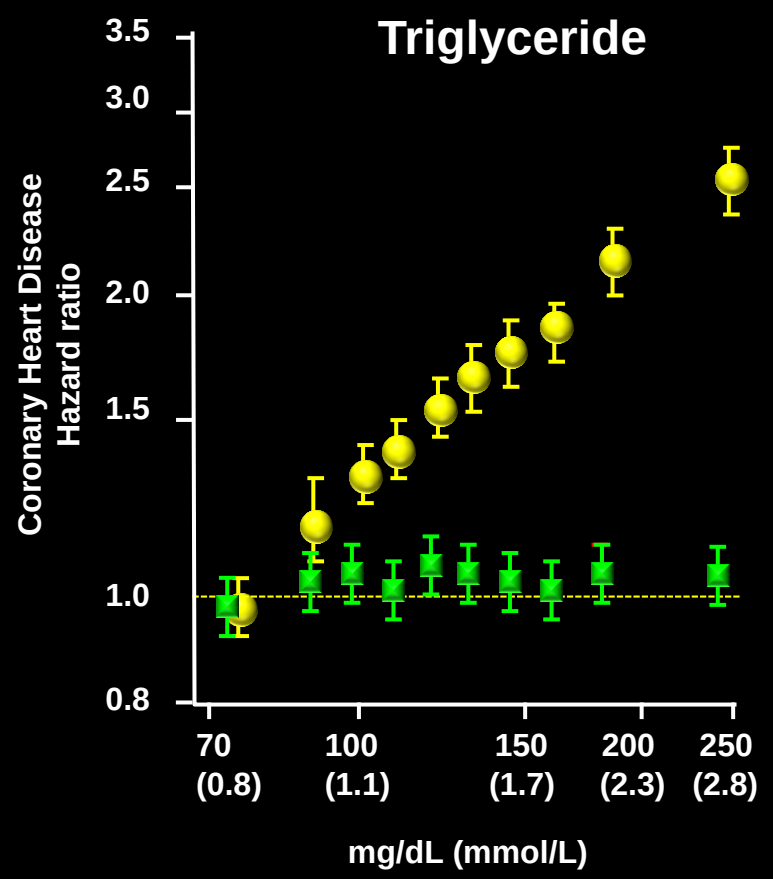
TRIGLYCERIDE-RICH LIPOPROTEINS



Lipids (%)			
TG	85–90	50–60	18–25
Cholesterol	2–6	14–22	30–38
Phospholipid	6–9	12–20	20–28
Size (Å)	800–5000	300–800	200–350

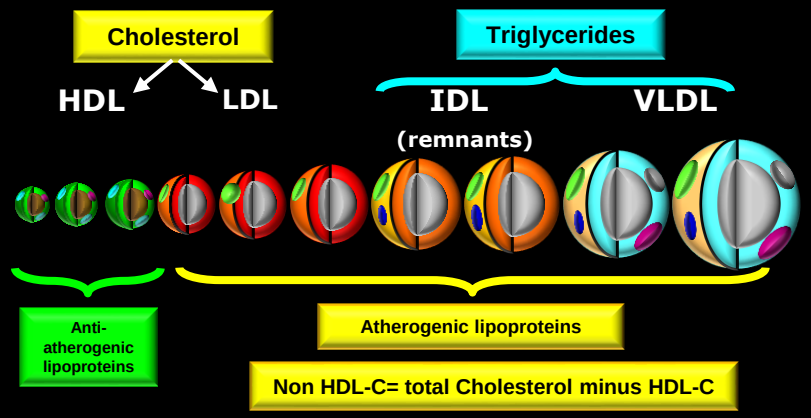
Hazard ratios for coronary heart disease across quantiles of usual concentrations of triglycerides, HDL

The Emerging Risk Factors Collaboration



Adjusted for age and sex only

Further adjusted for several risk factors (including LDL-c and Non-HDL-C*!)

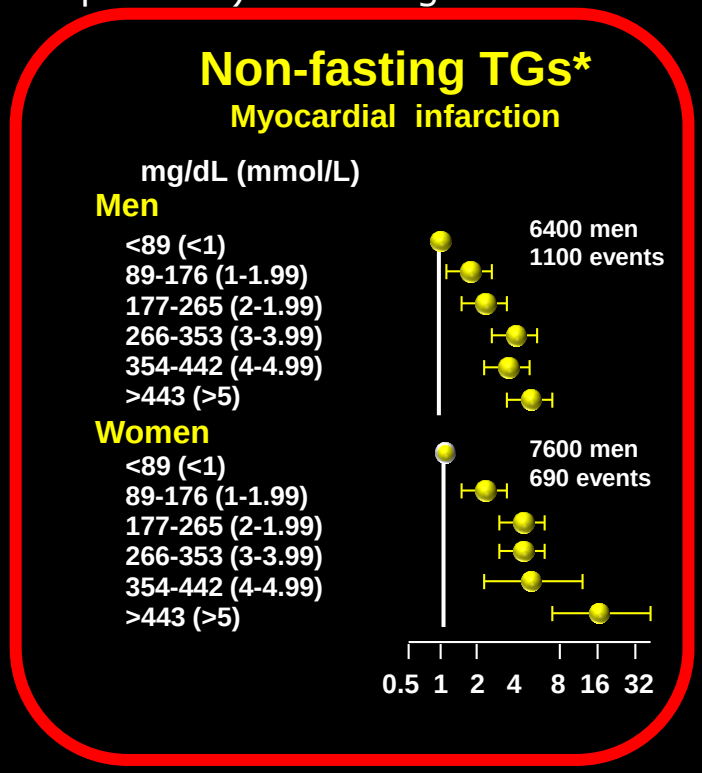


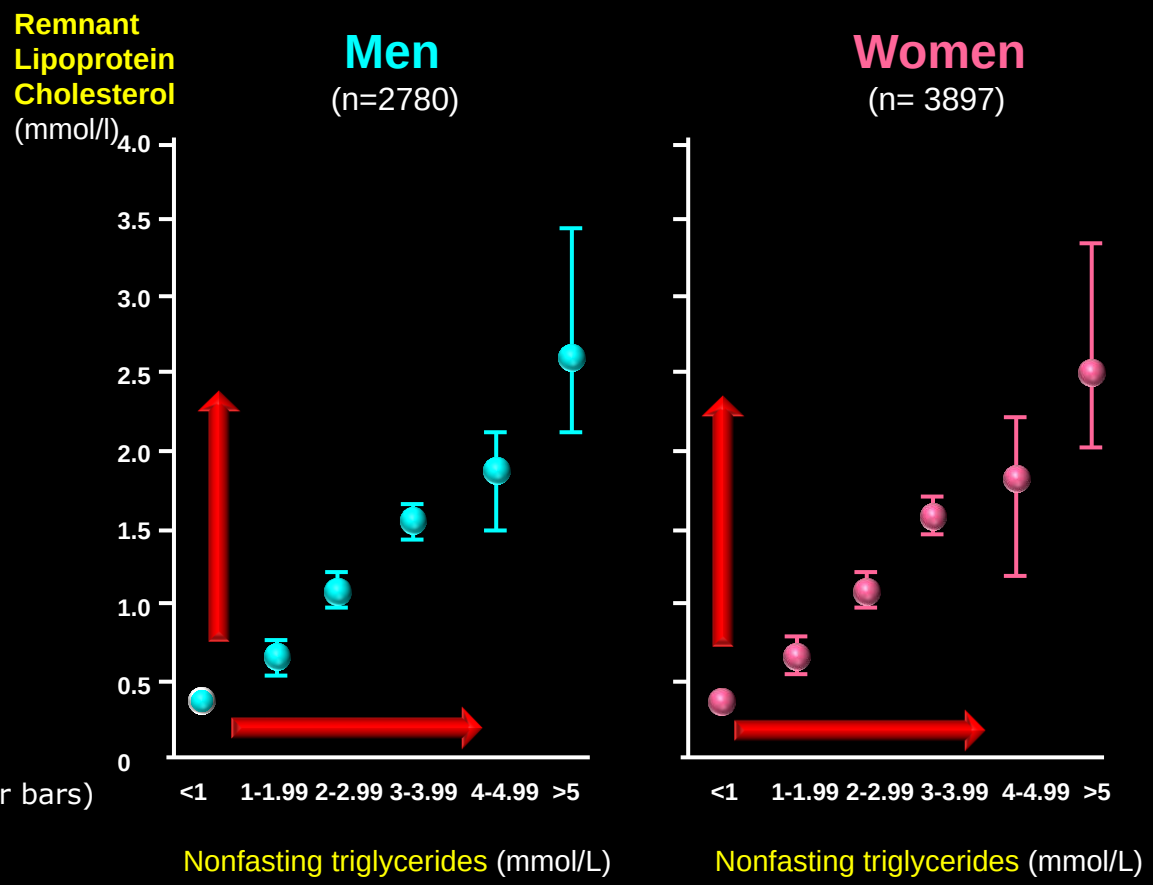
*Association is abrogated after additional adjustment for non-HDL cholesterol (cholesterol in LDL and remnants combined), in accordance with the idea that the cause of ischaemic heart disease is the cholesterol content in TG-rich lipoprotein particles, rather than raised triglycerides.

Di Angelantonio E et al. JAMA 2009;302:1993–2000

Nonfasting Triglycerides and Risk of Myocardial Infarction, Ischemic Heart Disease, and Death in Men and Women:
The Copenhagen City Heart study

Large long-term prospective cohort study (mean follow-up 26 years of almost 14 000 patients) assessing the risk of nonfasting triglyceride levels in the general population.





*Values are median and interquartile range (error bars)
Triglycerides 1 mmol/l= 88.5 mg/dl

- Elevated nonfasting triglyceride levels are associated with increased risk of myocardial infarction, IHD and death in men and women.
- Remnant lipoprotein cholesterol is a function of serum triglycerides, which may explain the increased risk of CVD events

Nordestgaard BG et al. JAMA 2007; 298:299–308

Triglyceride Lowering Benefits: Clinical Evidence

- ✓ **What plasma TG range should we be focusing on?**
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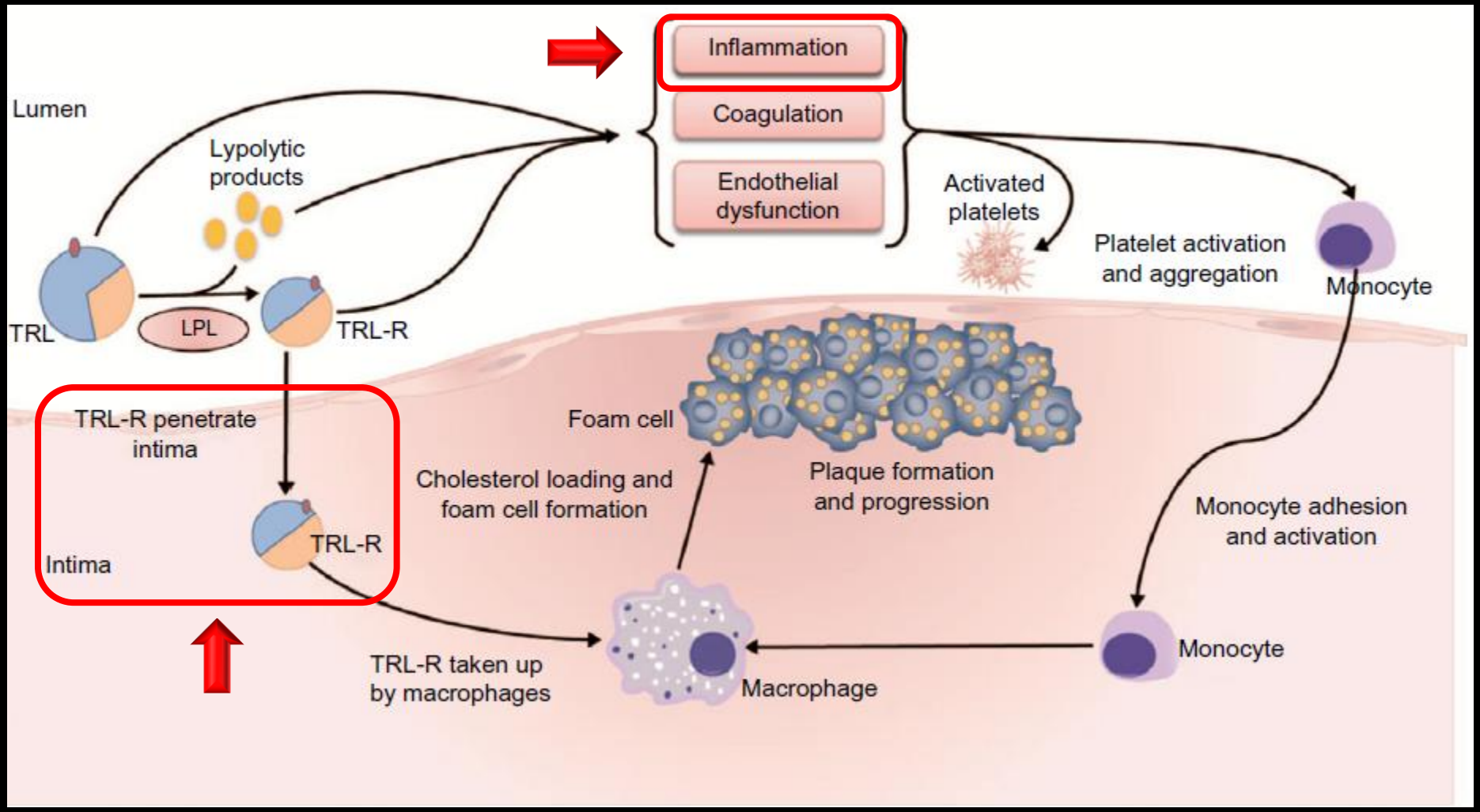
Pathophysiology of TG-rich lipoproteins in the progression of atherosclerosis

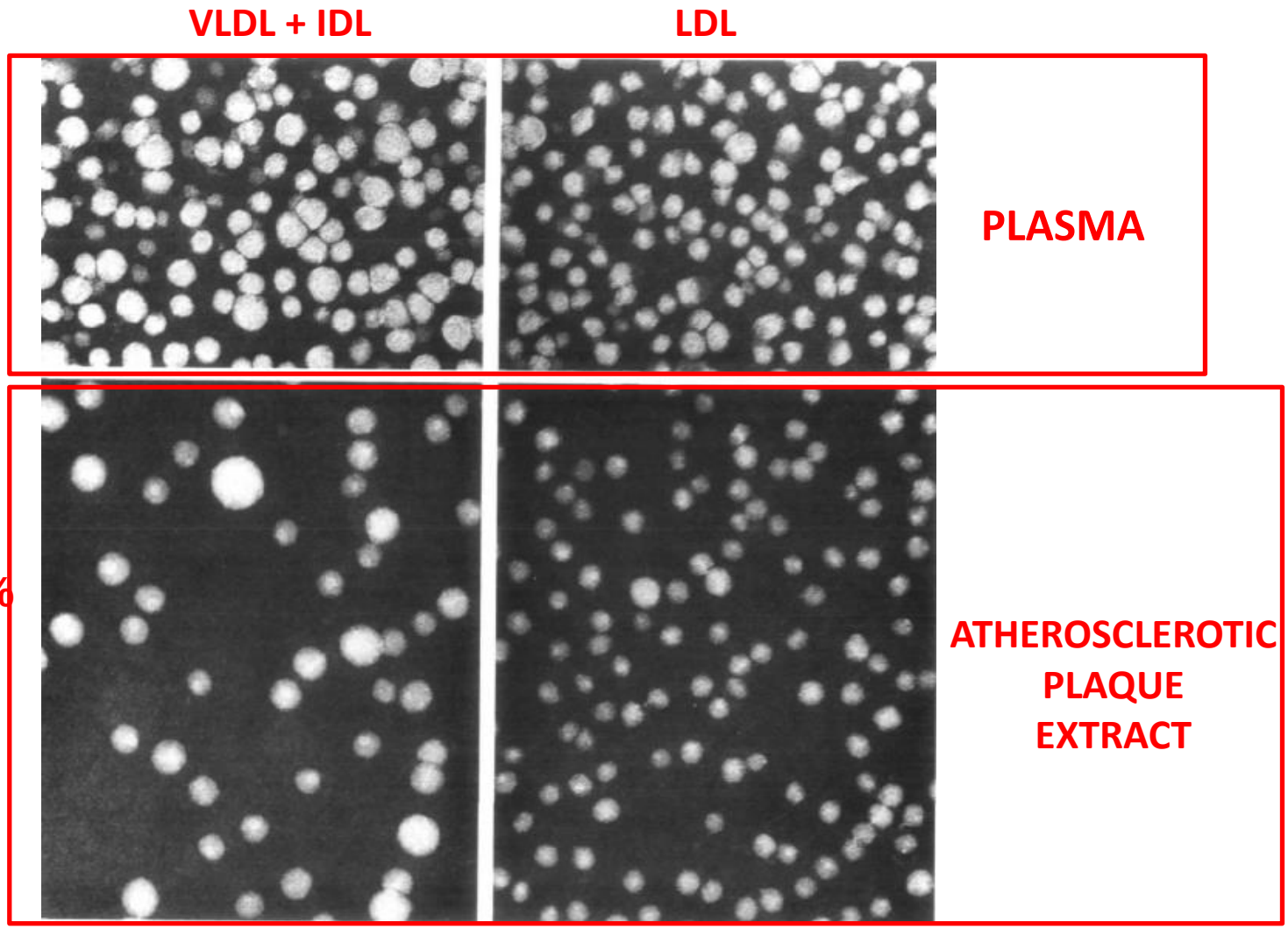


LPL, lipoprotein lipase; TRL, triglyceride-rich lipoproteins; TRL-R, triglyceride-rich lipoprotein remnants.

Toth PP et al Vascular Health and Risk Management 2016:12 171–183

Triglyceride-Rich Lipoproteins Isolated by Selected-Affinity Anti-Apolipoprotein B Immunosorption From Human Atherosclerotic Plaque

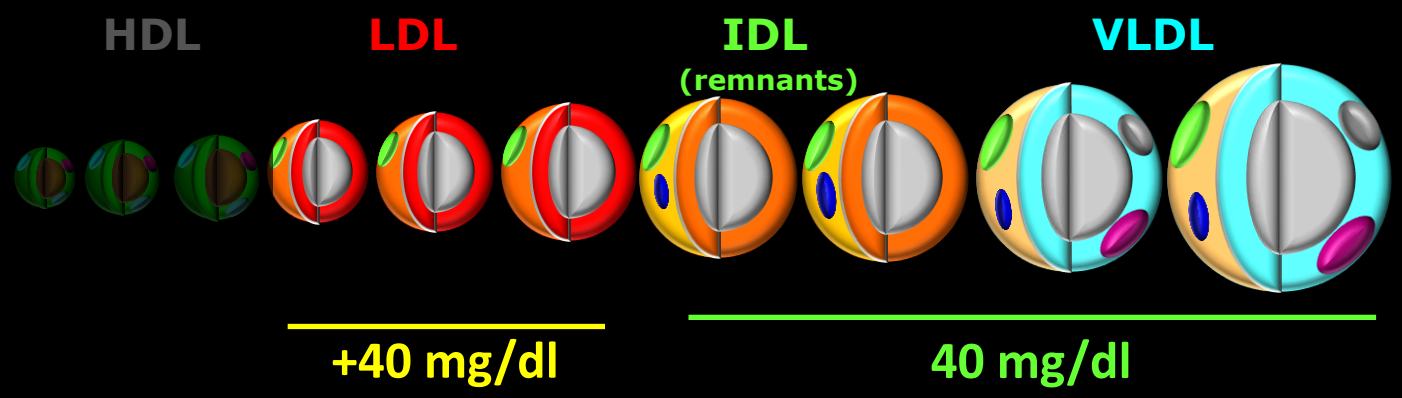
….**VLDL+IDL** accounting for **36%** of the lipoprotein **cholesterol** from the atherosclerotic plaque extracts….



Photomicrographs show negatively stained lipoproteins from a single patient:
Left pictures show very-low-density lipoprotein+ intermediate-density lipoprotein;
Right pictures, low-density lipoprotein. Top, Serum; middle, plaque extract

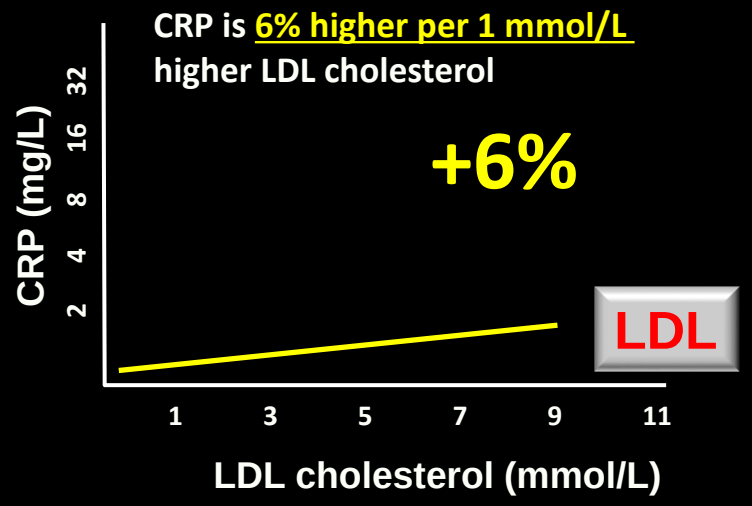
Havel RJ, Kane JP et al Arterioscler Thromb. 1994;14:1767-1774.

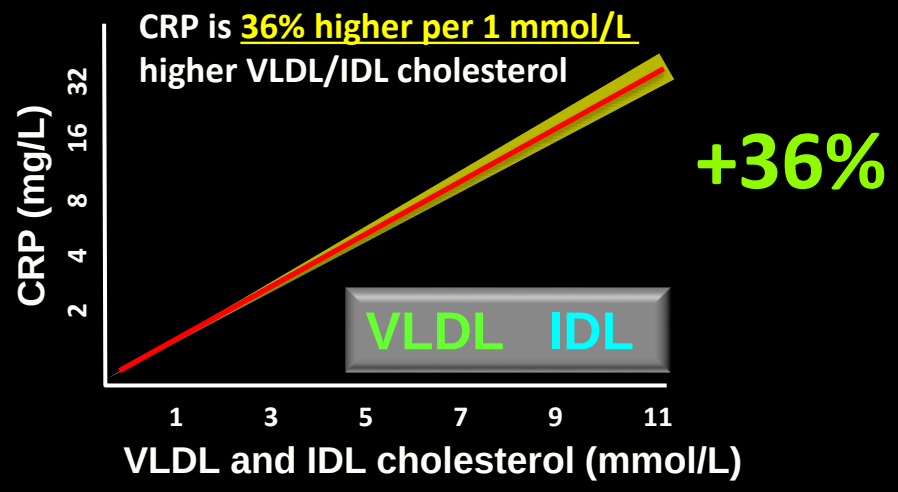
Association of nonfasting IDL and VLDL cholesterol (**right**) and LDL-C (**left**) with C-reactive protein (CRP) in 48 250 participants from the Copenhagen General Population Study.



Multivariable adjusted association CRP and LDL-C and IDL/VLDL-C

Age,sex, lipid-lowering therapy, smoking, hypertension, diabetes, menopause, and HRT





Varbo A et al.Circulation. 2013;128:1298-1309.

Zambon A et al Atherosclerosis 2013 230:106-109

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ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–78
doi:10.1093/eurheartj/ehz455

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

ESC/EAS GUIDELINES

RECOMMENDATIONS FOR DRUG TREATMENT OF PATIENTS WITH HYPERTRIGLYCERIDAEMIA

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].[355]	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.[194]	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	C

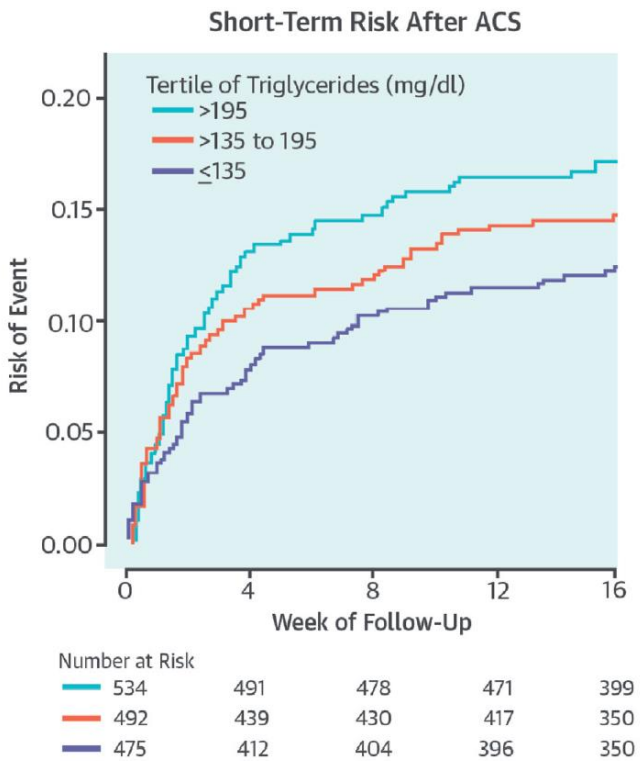
CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acids; TG = triglyceride.

Adapted from: Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455. Epub ahead of print.

Fasting Triglycerides Predict Recurrent Ischemic Events in Patients With Acute Coronary Syndrome Treated With StatinS

Kaplan-Meier Analysis of Coronary Heart Disease Death, Nonfatal Myocardial Infarction, Ischemic Stroke, Cardiac Arrest With Resuscitation, or Hospitalization for Unstable Angina After ACS

The MIRACL Trial (n=1501)



- Short-term cumulative incidence of events according to tertile of triglycerides at initial random assignment in the **atorvastatin 80 mg** group of the MIRACL trial.
- Time 0 corresponds to a mean of 63 h after index ACS;
- p = 0.03 for trend across tertiles

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Pharmacological Therapy of Atherogenic Dyslipidemias

Class	Main Lipid Target	Outcome data on CVD events	Incident Diabetes	Other Adverse Events
Statins	LDL-C	YES (regardless of baseline lipid profile or clinical phenotype)	YES	Muscle-related intolerance 7-8% (Myalgia, Myopathy), Rabdomyolisis (extremely uncommon), elevation liver enzymes
Ezetimibe	LDL-C	YES (in combination with statin therapy, SHARP, IMPROVE-IT)	NO	Elevation liver enzymes, myalgia, myopathy (very rare)
PCSK9i Evolocumab Alirocumab	LDL-C	YES (FOURIER Evolocumab)	NO	No serious adverse events as monotherapy when combined with best available therapy
FIBRATES	↓TG 25-50%	SUBGROUPS (low HDL-C- high TG) ACCORD, FIELD, VA-HIT, BIP, HHS)	NO	Gastrointestinal complaints most common Myopathy (Gemfibrozil), increased serum creatinine
Omega-n-3	↓TG Up to 45%	YES REDUCE-IT	NO	No major safety concerns Eructation, dyspepsia and disrupted ability to taste (dysgeusia) are most common

Chapman MJ et al for the EASociety Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J 2011; 32: 1345–1361 and Brunzell J. N Engl J Med 2007;357:1009-1017

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–78
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Primary Prevention

FIBRATE+STATIN

High-Risk Patients

- On statin
- At LDL-C goal
- High TG

- On statin
- At LDL-C goal
- High TG

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acids; TG = triglyceride.

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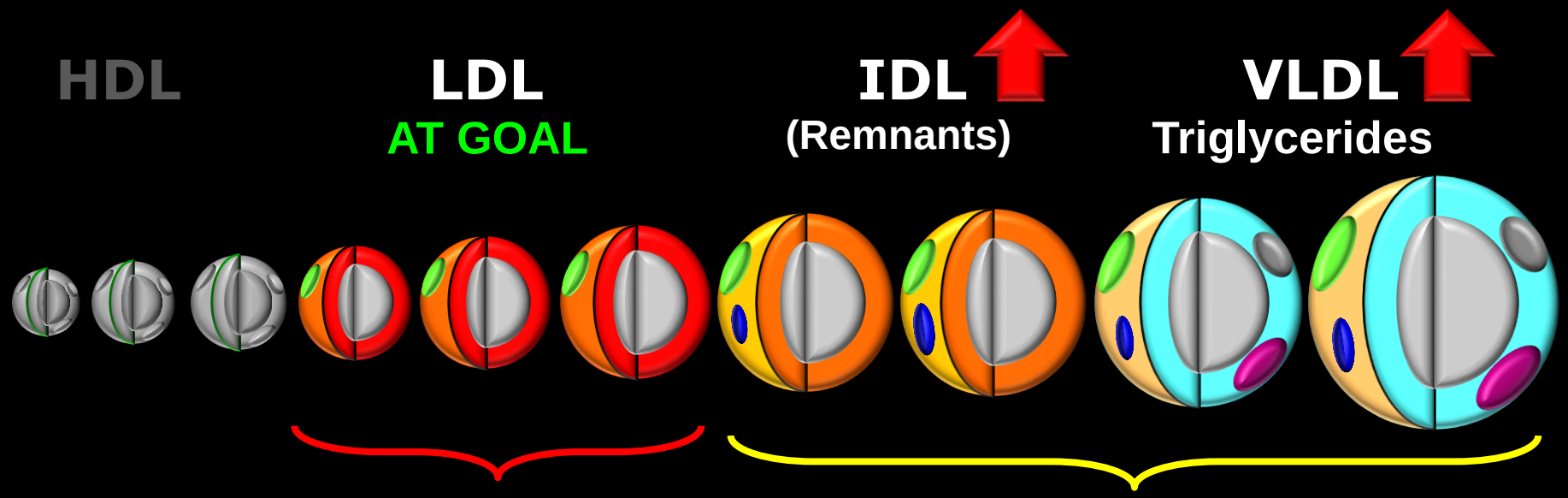
LDL-C at goal and elevated TG

(How to target Non-HDL Cholesterol)

HIGH TG (Non HDL-C NOT AT GOAL)

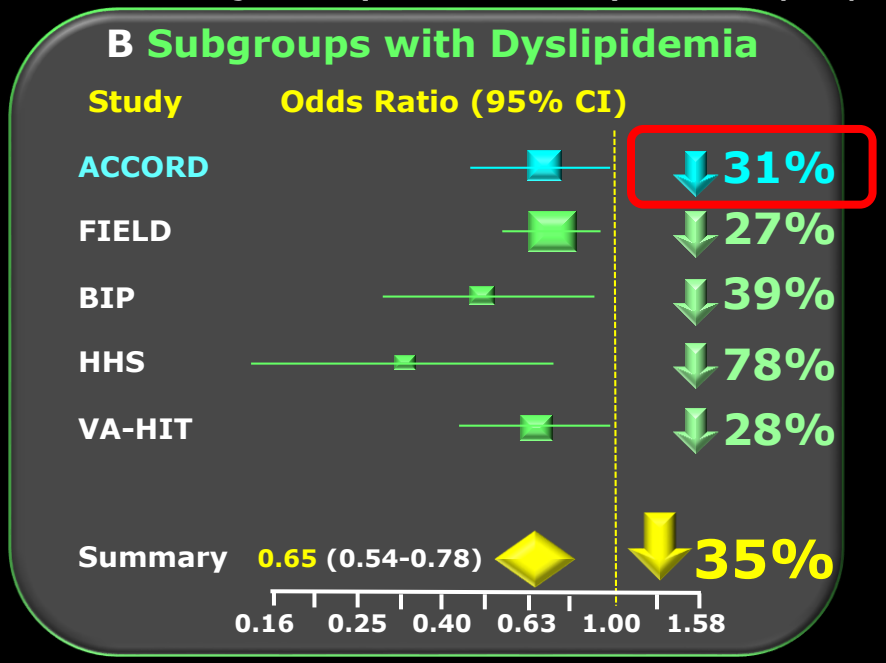


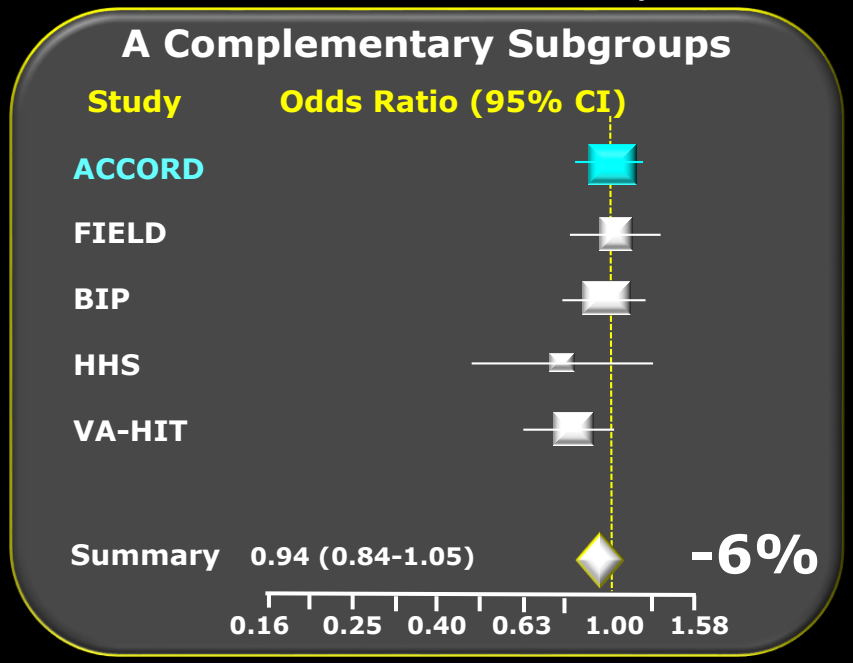
STATINS (±Ezetimibe PCSK9i) + ↓ ↓ ? ↓ ↓

Fibrates

Effect of fibrates in subgroups without (A) and with (B) dyslipidemia

A total of 2428 fibrate-treated subjects (302 events) and 2298 placebo-treated subjects (408 events) with dyslipidemia were included in the analysis





LIPID CRITERIA FOR DYSLIPIDEMIA

Trial	Triglycerides cut-off (mg/dL)	HDL cholesterol cut-off (mg/dL)
FIELD	≥204 (2.2 mmol/L)	<40 in men (1.0) ; <50 in women (1.3)
BIP	≥200	<35
Helsinki Heart Study	>204	<42
VA-HIT	>180	<40

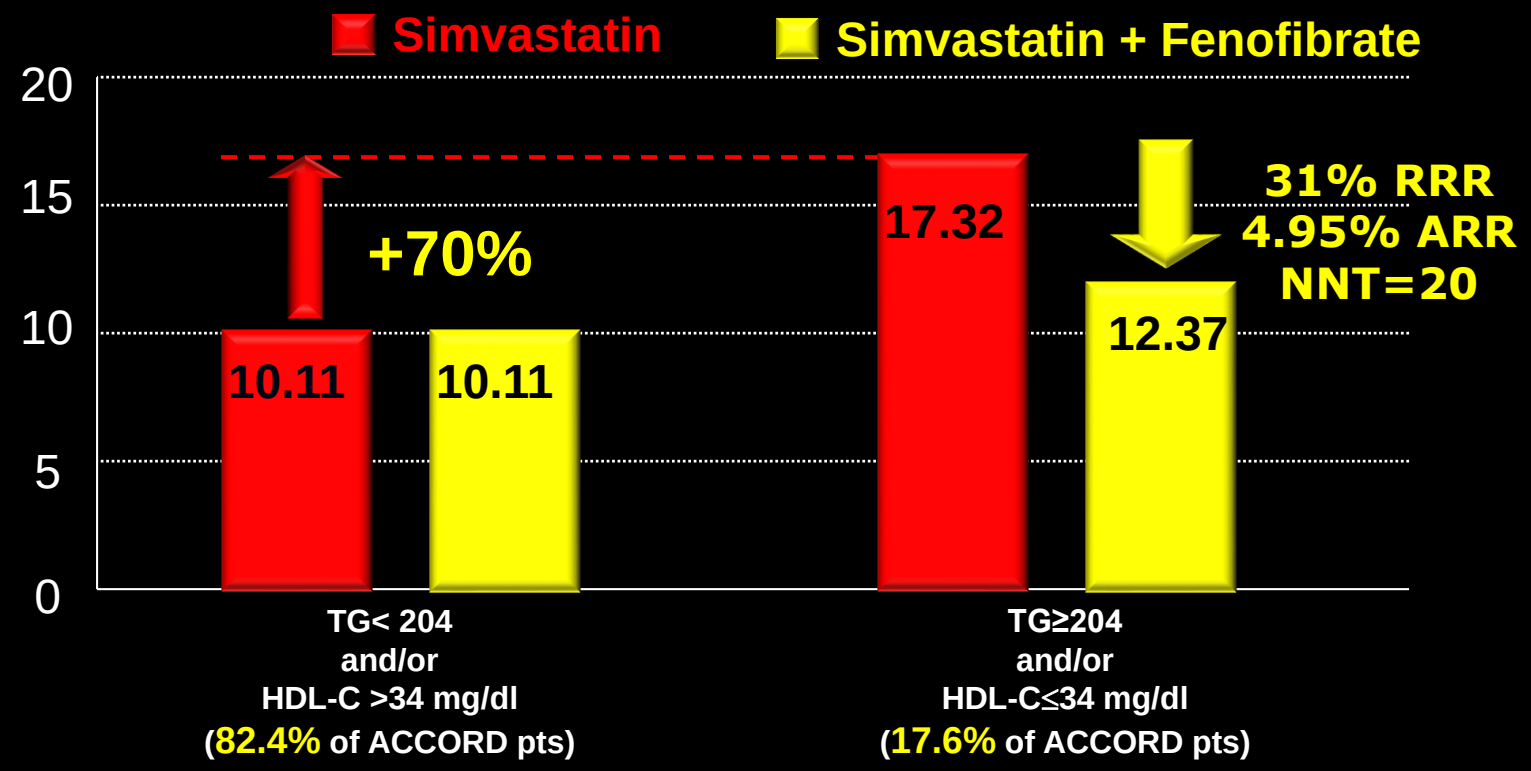
Bruckert E et al J Cardiovasc PharmacolT 57:267, 2011

Lee M et al Atherosclerosis (2011), doi:10.1016/j.atherosclerosis

Sacks FM et al. N Engl J Med 2010

ACCORD Pre-Specified Endpoint
Patients with Elevated TG and Low HDL-C

- Patients with **Atherogenic Dyslipidaemia** had a **70% higher relative risk of major CV events**** compared to those without Atherogenic Dyslipidemia, despite achieving a mean **LDL-C of 80 mg/dl**



Major CV event (1º endpoint): CV death, nonfatal MI or nonfatal stroke

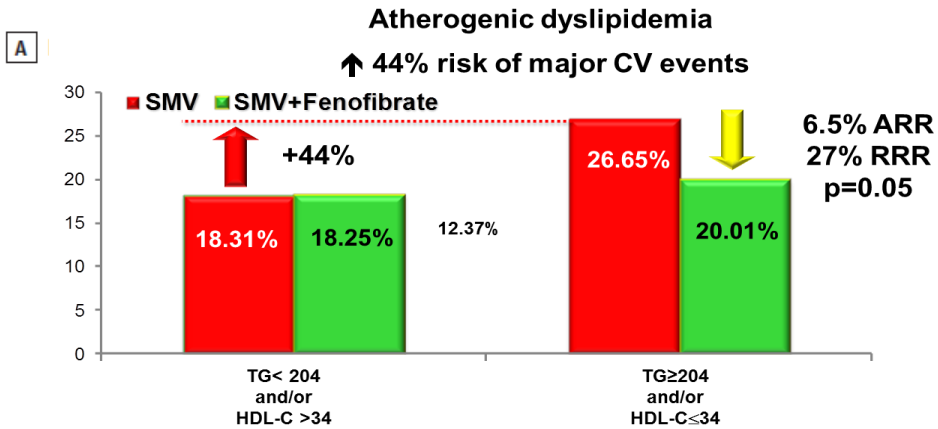
HDL-C<34 mg/dl= 0.88 mmol/L, TG>204 mg/dl= 2.2 mmol/l; All groups LDL-C: 80 mg/dl (2.0 mmol/L)

All groups LDL-C: 80 mg/dl (2.0 mmol/L)

Modified form ACCORD Study Group. *N Engl J Med* **2010**; 362: 1563. FDA EMDAC Meeting 19 May 2011.

JAMA Cardiology | Original Investigation

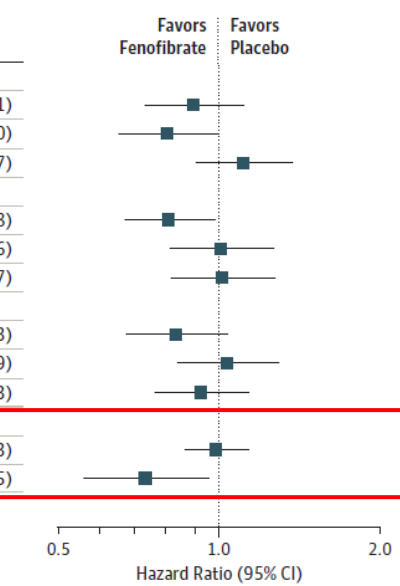
Association of Fenofibrate Therapy With Long-term Cardiovascular Risk in Statin-Treated Patients With Type 2 Diabetes ACCORDION – 9.7 yrs Follow-up



.....despite these overall neutral results, we continued to find evidence that fenofibrate therapy effectively reduced CVD in study participants with dyslipidemia, TG>204mg/dL and HDL_C >34mg/dl (HR, 0.73; 95%CI, 0.56-0.95).....

Figure 3. Hazard Ratios for the Primary Outcome in Prespecified Subgroups

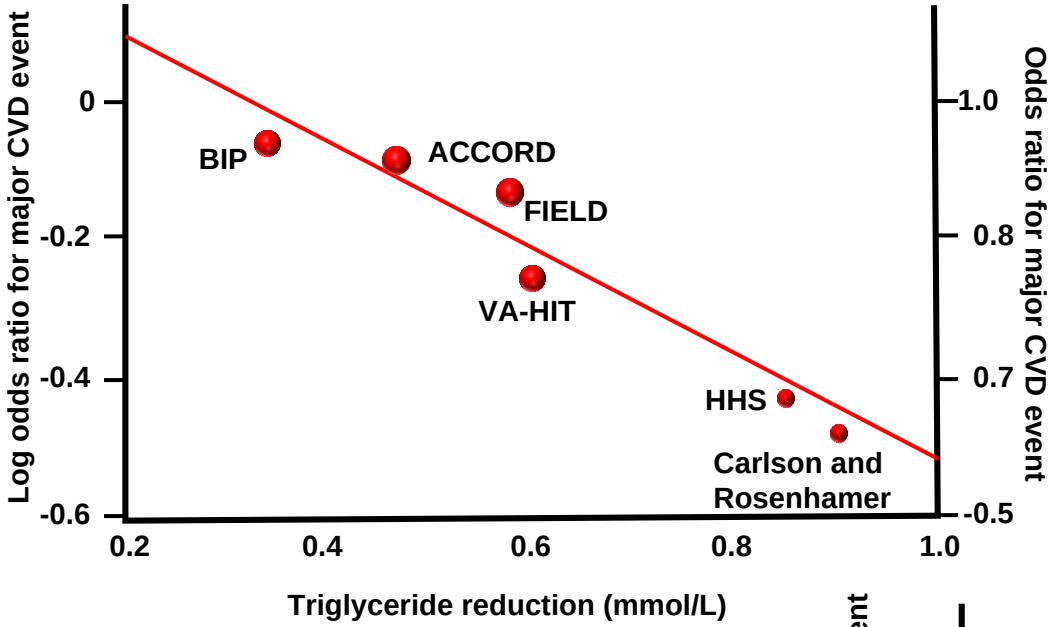
Characteristic	Statin + Fenofibrate Events/No. (%)	Statin + Placebo Events/No. (%)	Hazard Ratio (95% CI)	P Value for Interaction
LDL-C				
<85	169/925 (18.27)	175/885 (19.77)	0.90 (0.73-1.11)	.09
85+111	155/928 (16.70)	182/916 (19.87)	0.80 (0.65-1.00)	
≥112	182/871 (20.90)	179/919 (19.48)	1.11 (0.91-1.37)	
HDL				
<35	197/956 (20.61)	224/903 (24.81)	0.81 (0.67-0.98)	.20
35-40	159/852 (18.66)	157/858 (18.30)	1.01 (0.81-1.26)	
≥41	150/916 (16.38)	155/959 (16.16)	1.02 (0.81-1.27)	
Triglycerides				
<129	146/879 (16.61)	186/930 (20.00)	0.83 (0.67-1.03)	.37
129-203	171/918 (18.63)	160/908 (17.62)	1.04 (0.84-1.29)	
≥204	189/927 (20.39)	190/882 (21.54)	0.93 (0.76-1.13)	
Dyslipidemia				
No	407/2242 (18.15)	415/2266 (18.31)	0.99 (0.86-1.13)	.05
Triglycerides >204 and HDL-C <34	99/482 (20.54)	121/454 (26.65)	0.73 (0.56-0.95)	



Elam MB et al. JAMA Cardiol. doi:10.1001/jamacardio.2016.4828, Published online December 28, 2016.

ASSOCIATION BY META-REGRESSION BETWEEN TRIGLYCERIDE-LOWERING AND REDUCTION IN RISK OF A MAJOR CARDIOVASCULAR EVENT IN LARGE CONTROLLED TRIALS WITH FIBRATES

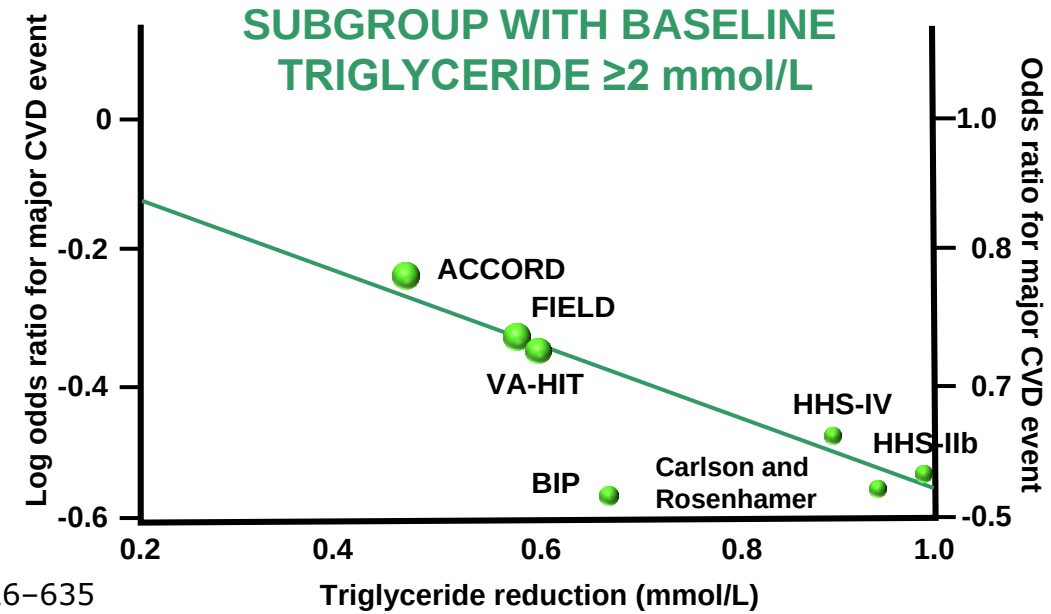
ALL STUDY PARTECIPANTS



Reduction in major CV events
54% per 1 mmol/L TG reduction

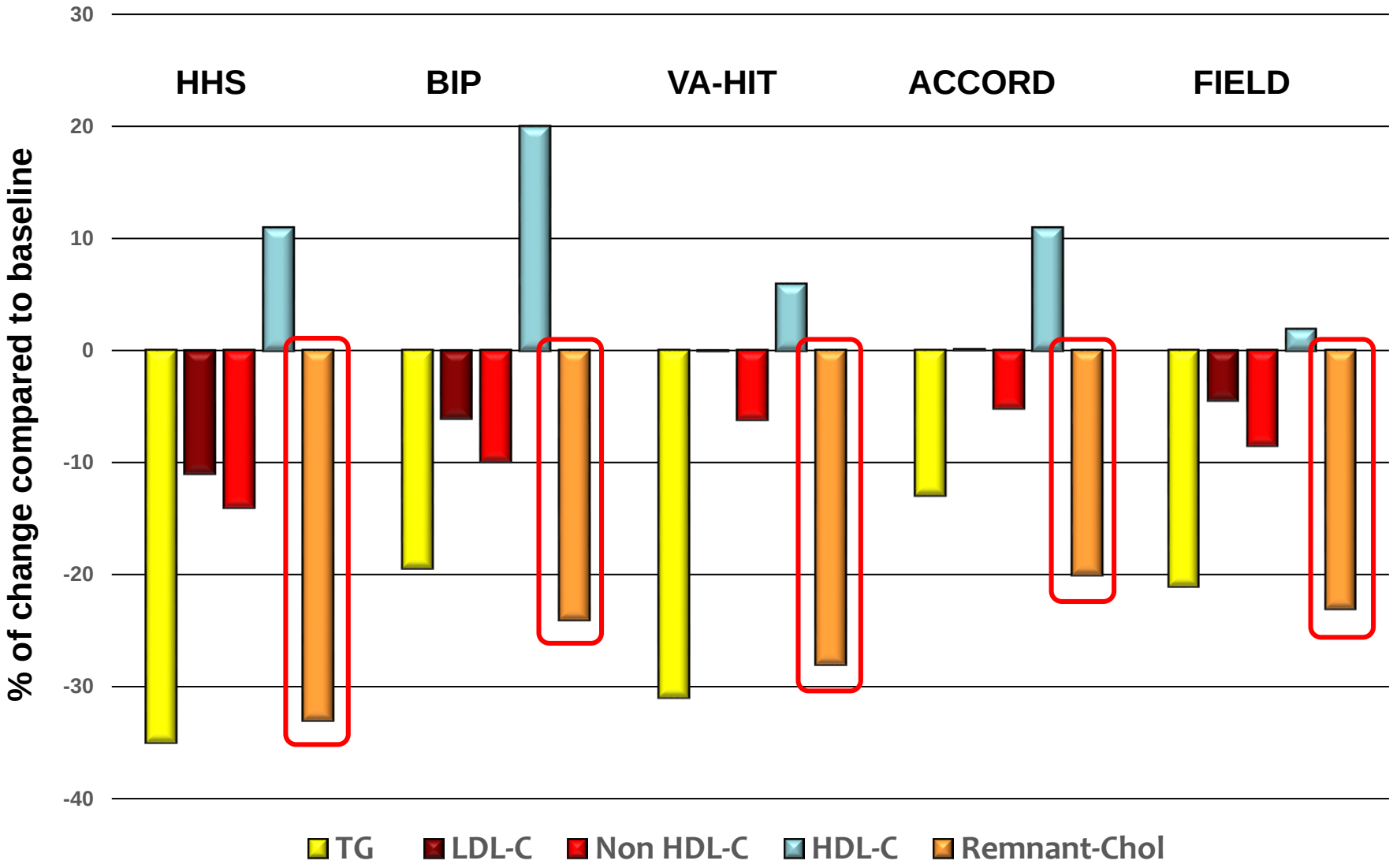
Reduction in major CV events
45% per 1 mmol/L TG reduction

SUBGROUP WITH BASELINE TRIGLYCERIDE ≥2 mmol/L



Børge G Nordestgaard, Anette Varbo Lancet 2014; 384: 626–635

Results from Clinical Trials with Fibrates



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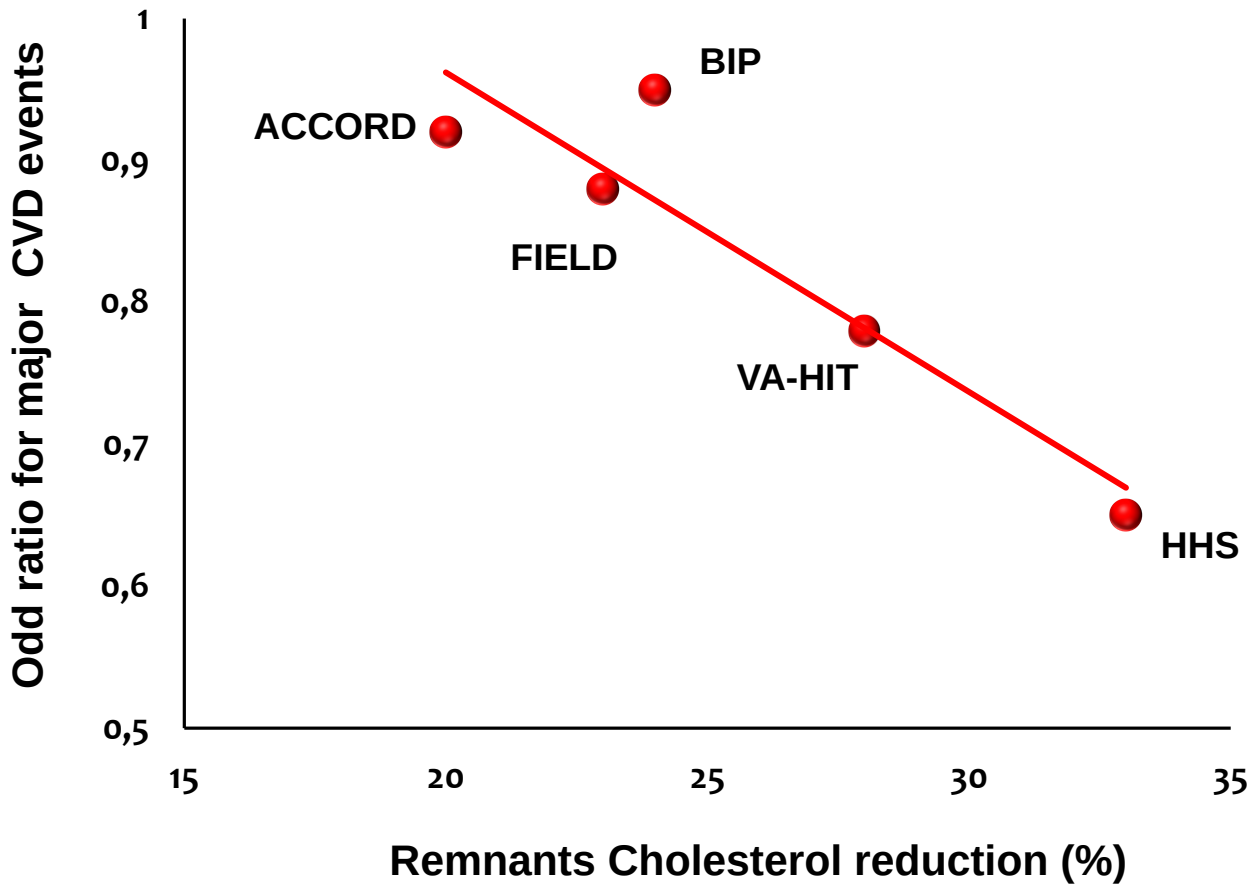
Remnant Cholesterol Reduction with Fibrates and CVD Risk Reduction



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Design of the PROMINENT study with PEMAFIBRATE

PROMINENT Study Design

MEN AND WOMEN WITH TYPE 2 DIABETES

10,000 PARTICIPANTS 24 COUNTRIES

TG 200-499 mg/dL (2.26-5.64 mmol/L) and HDL ≤40 mg/dL (1.03 mmol/L)

Moderate-High Intensity Statin Therapy or LDL-C Control (≤70 mg/dL or ≤100 mg/dL if statin intolerant)

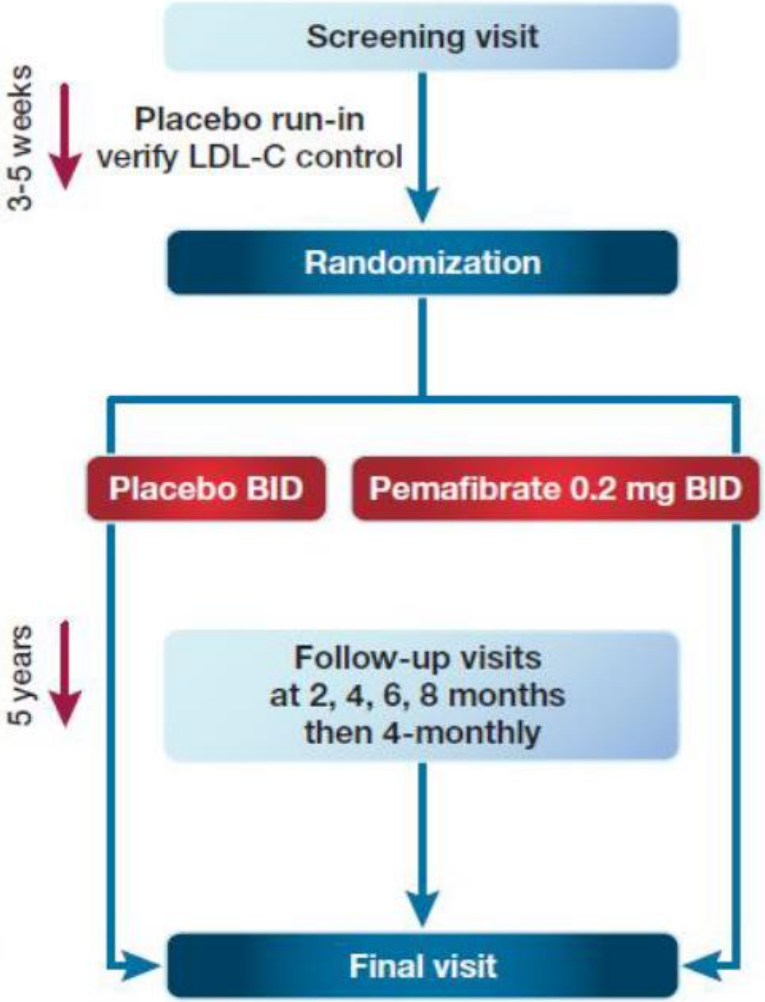
1/3 Primary Prevention, 2/3 Secondary Prevention

ENDPOINTS

Event Driven: 1092 Primary Endpoints, 200 in women

PRIMARY ENDPOINT (MACE): Myocardial infarction, ischemic stroke, or unstable angina requiring unplanned revascularization, cardiovascular death

Secondary/Tertiary Endpoints: all-cause mortality, any coronary revascularization, heart failure, total stroke, retinopathy, nephropathy, glycemic control, PAD, biomarkers, quality of life



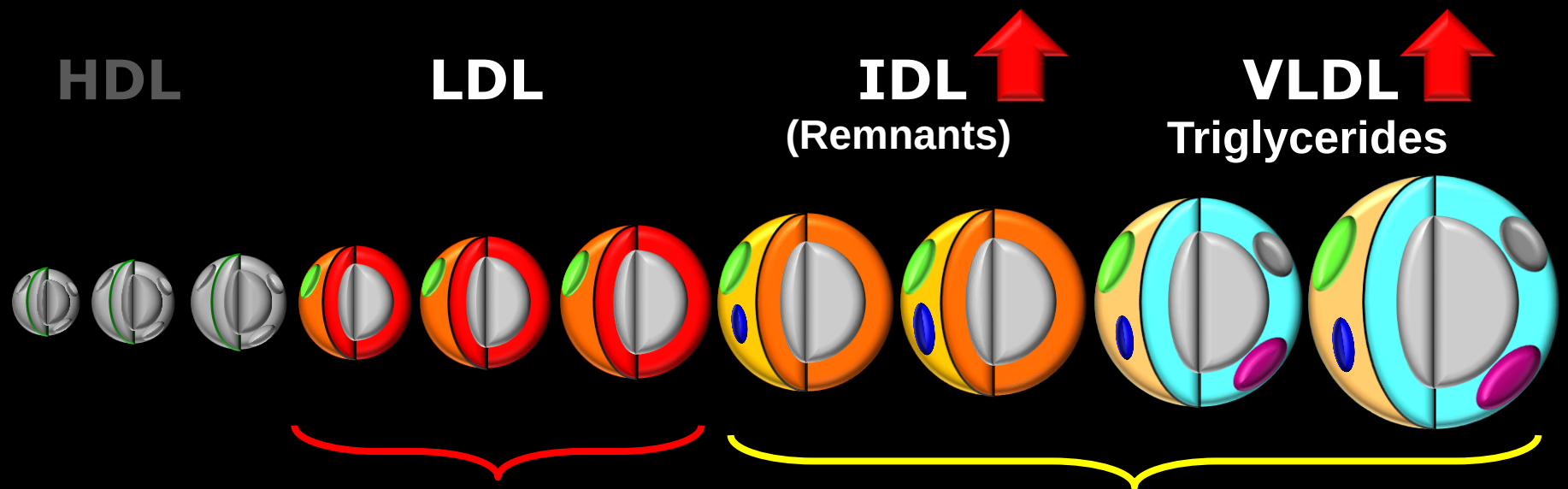
Abbreviations: HDL-C high-density lipoprotein cholesterol; LDL-C low-density lipoprotein cholesterol; PAD peripheral artery disease; TG triglycerides

Fruchart J-C, Santos RD et al Cardiovascular Diabetology 2019

How to target Non-HDL Cholesterol

(When TG are elevated)

HIGH TG (Non HDL-C NOT AT GOAL)



STATINS
(±Ezetimibe
PCSK9i)

+

Omega n-3 Fatty Acids

ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–78
doi:10.1093/eurheartj/ehz455

RECOMMENDATIONS FOR DRUG TREATMENT OF PATIENTS WITH HYPERTRIGLYCERIDAEMIA

High-Risk Patients

N3 PUFA EPA +STATIN

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].[355]	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.[194]	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	C

- **On statin**
- **High TG**

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acids; TG = triglyceride.

Adapted from: Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455. Epub ahead of print.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

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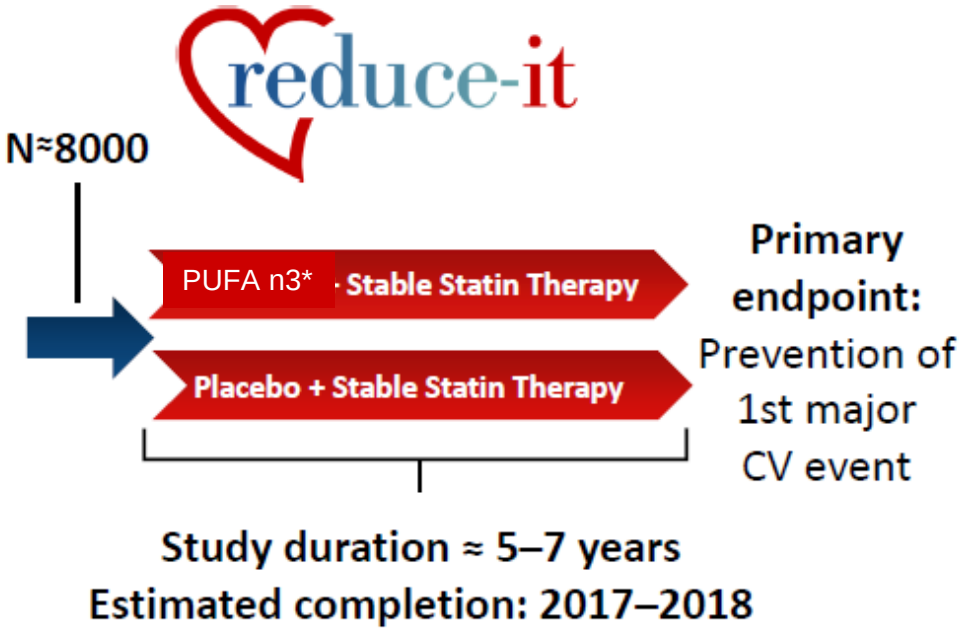
Article available at https://www.nejm.org
Slides available for download at https://professional.heart.org
or at https://www.ACC.org

Reduction of CV Events with Icosapent Ethyl-Intervention Trial

- Men and women ≥45 years of age
- Established CHD or at high risk for CHD (diabetes + ≥1 risk factor)
- Atherogenic dyslipidemia
  - All patients required to be on stable statin therapy for at least 4 weeks
  - LDL-C >40 mg/dL and ≤100 mg/dL prior to randomization into the study
  - TG ≥200 to <500 mg/dL



- Randomized, double-blind, parallel-group design
- International trial; first patient enrolled: November 2011
- Other outcome measures: Incidence of additional CV events, lipid and lipoprotein levels, etc.
- Pre-defined subgroup analyses such as patients with diabetes
- Interim analysis planned for 967th event: Sept–Oct 2016; study expected to continue as planned

Primary Endpoint

Time from randomization to the first occurrence of composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

***96% pure ethyl aster of EPA**
2 X 2gr/day

Bhatt DL, Ballantyne CM et al. Clinical Cardiology. 2017;**40:**138–148.

Effects on Biomarkers from Baseline to Year 1

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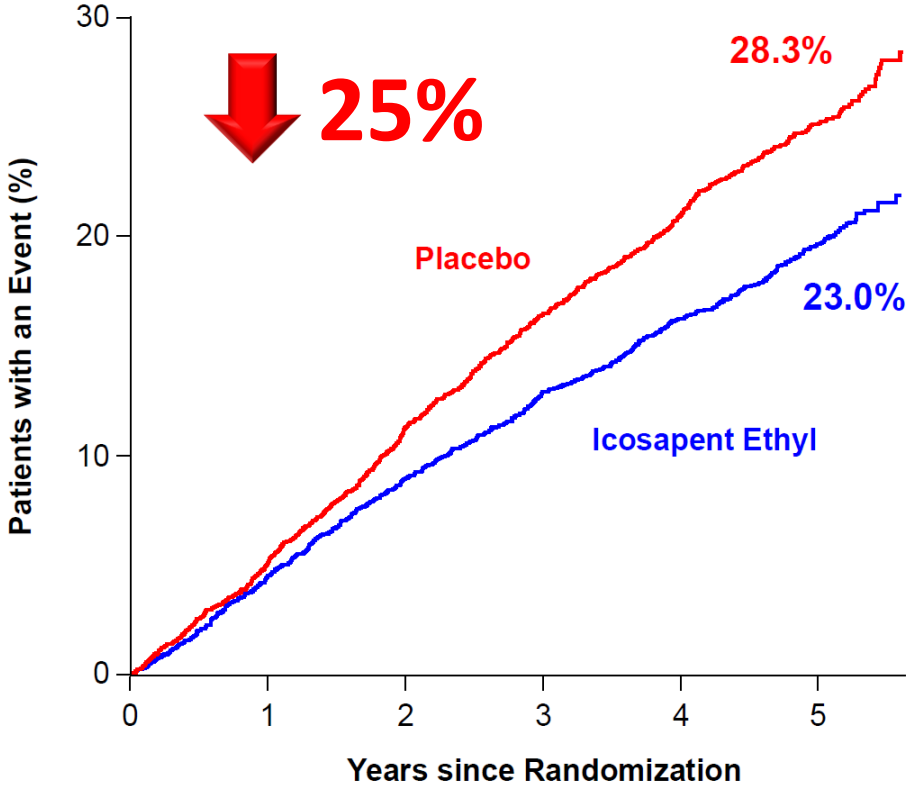
	Biomarker*	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
		Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
2.5	Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
3.1	Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
1.8	LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
	HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
	Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
	hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
	Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
	EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

Prespecified Hierarchical Testing

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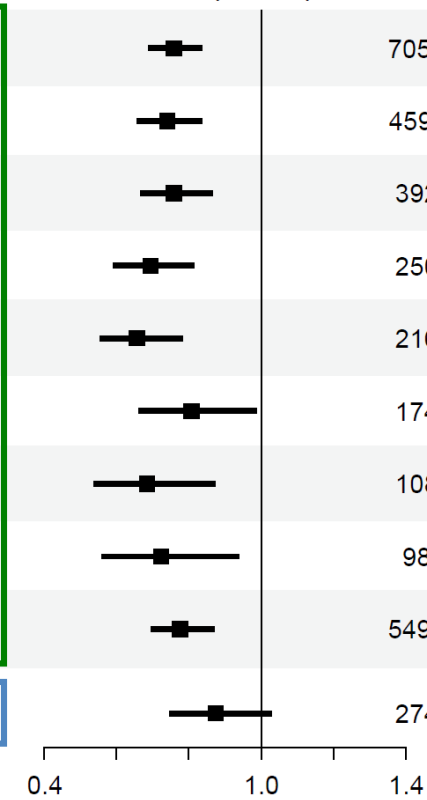
Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09

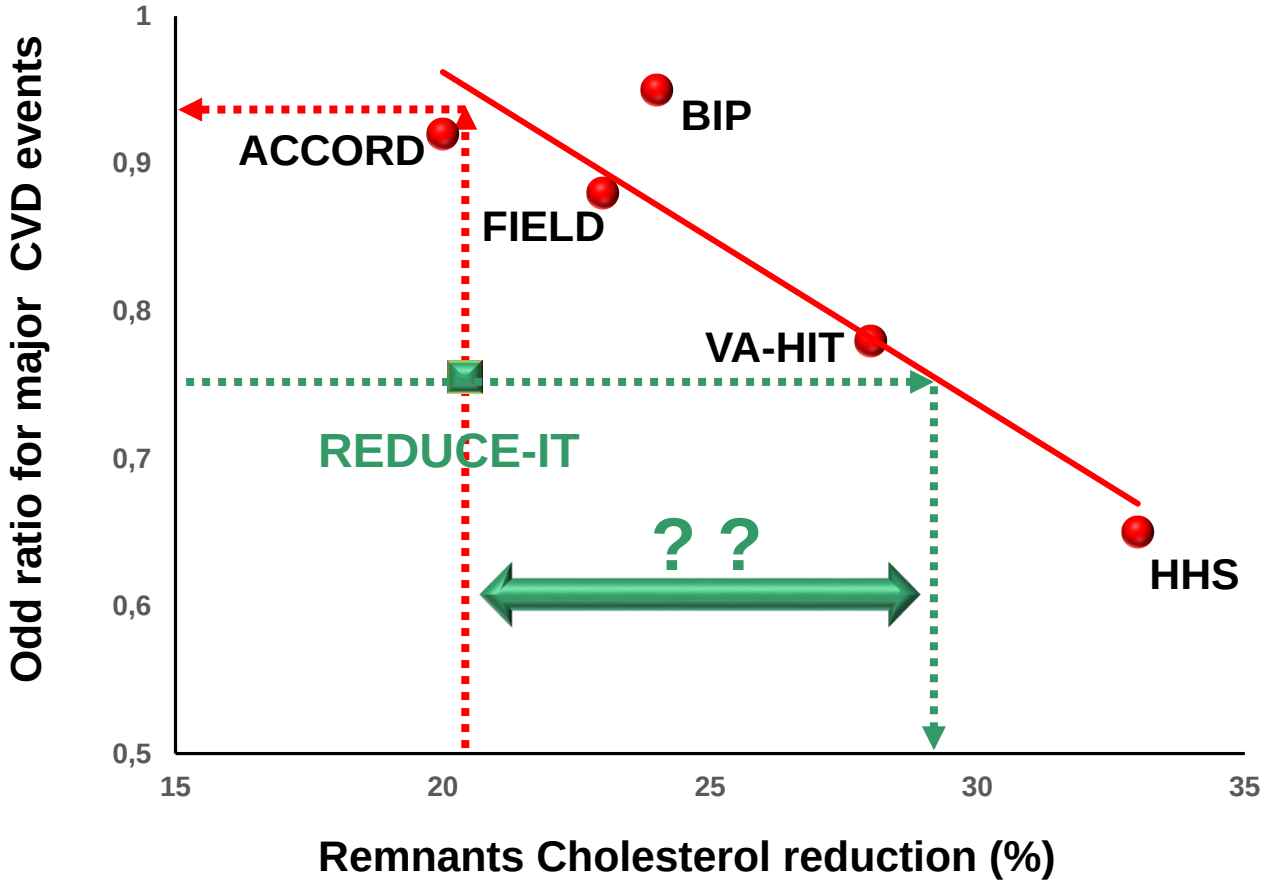


RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Remnant Cholesterol Reduction with Fibrates and EPA and CVD Risk Reduction



Adapted and used with kind permission of Norata GD et al

Treatment-Emergent Adverse Event of Interest: Serious Bleeding

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	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Bleeding related disorders	111 (2.7%)	85 (2.1%)	0.06
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	0.15
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	0.42
Other bleeding	41 (1.0%)	30 (0.7%)	0.19

- No fatal bleeding events in either group
- Adjudicated hemorrhagic stroke - no significant difference between treatments (13 icosapent ethyl versus 10 placebo; P=0.55)

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

WHAT'S BEHIND THE CV BENEFITS in REDUCE-IT?

Reduction CV Death, MI and Stroke by 25%

Lipids Diabetes

- ↓ **TG 19.7% (45 mg/dl)**
- LDL-C 6.6% (5.0 mg/dl)
- ↓ Non HDL-C 13% (15.5 mg/dl)
- Apo B 9.7% (8.0 mg/dl)

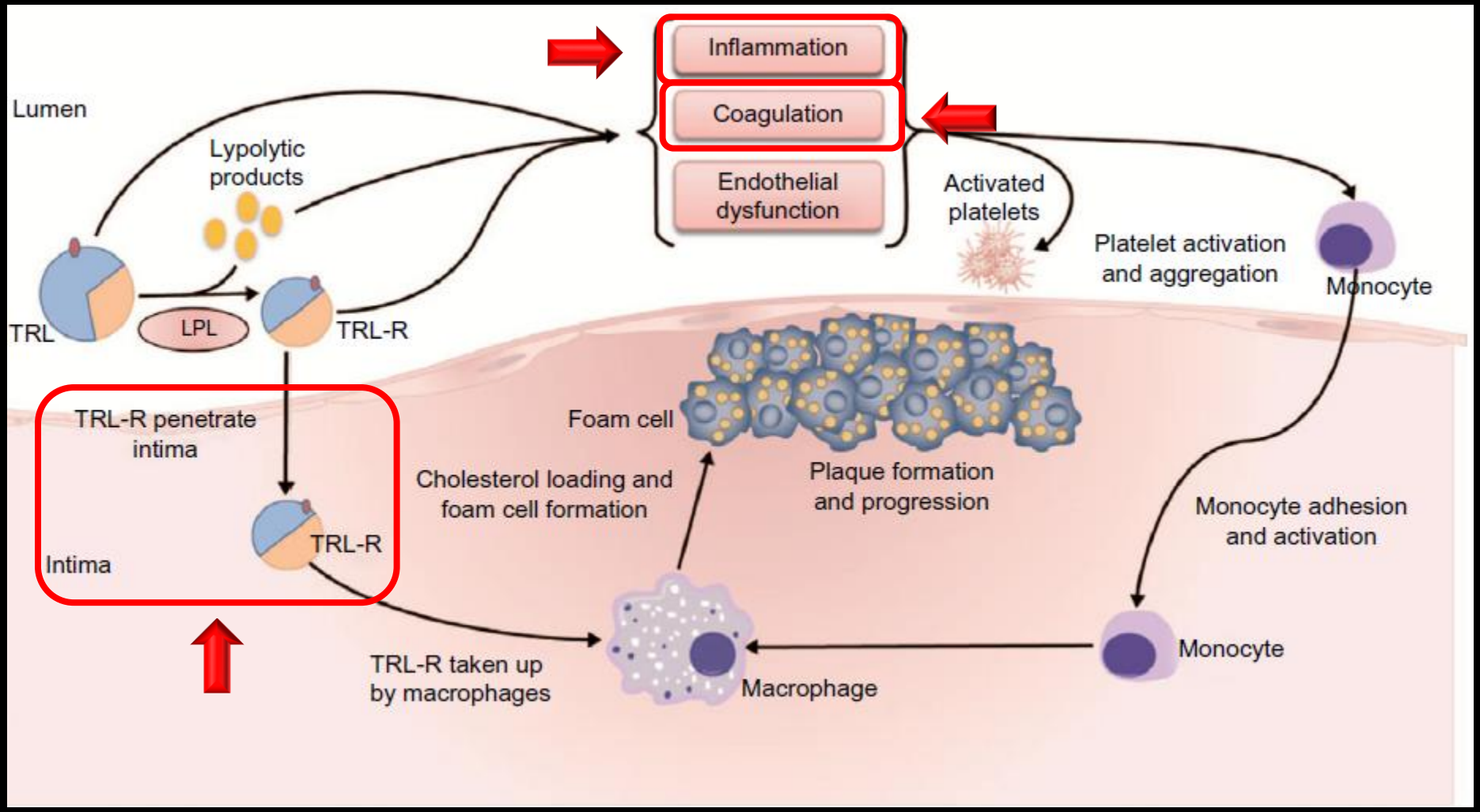
Hemostatic Thrombotic

Antithrombotic
Inhibition of Platelet Aggregation

Inflammatory

Antinflammatory
- ↓ **hsCRP 40% (0.9 mg/L)**

Pathophysiology of TG-rich lipoproteins in the progression of atherosclerosis



LPL, lipoprotein lipase; TRL, triglyceride-rich lipoproteins; TRL-R, triglyceride-rich lipoprotein remnants.

Toth PP et al Vascular Health and Risk Management 2016:12 171–183

MAIN CHARACTERISTICS IN INTERVENTION STUDIES IN HYPERTRIGLYCERIDEMIA

The reduction in clinical events in subjects with elevated TG and reduced HDL-C in FIELD and ACCORD explains the choice of this population in subsequent studies

	FIELD	ACCORD Lipid	REDUCE-IT
No. randomized	9795	5518	8179
Daily dose	Feno 200 mg	Feno 160 mg	EPAEE 4 g
TG mg/dL **Baseline median**	89-443 **154**	<750 **162**	150/200-500 **216**
HDL-C mg/dL **Baseline median**	- 43	<50 in M <55 in F 38	- 40
LDL-C mg/dL **Baseline median**	Total cholesterol 116-251 **119**	60-180 **101**	41-100 **74**
	T2DM	T2DM	Established CVD or T2DM (59%)
On statin	0%	all	all
Primary endpoint	Coronary death, nonfatal MI	CV death, nonfatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke, coronary revascularization, Hospitalized for UA
Results	2005	2010	Nov 2018

MAIN CARDIOVASCULAR OUTCOMES IN INTERVENTION STUDIES IN HYPERTRIGLYCERIDEMIA

	FIELD	ACCORD lipid	REDUCE-IT
No of subjects	9795	5518	8179
Population (lipids in mg/dl)	Overall	Overall	Overall
Coronary death, nonfatal MI	-11% p=0.16		**-31% p<0.001**
CV death, nonfatal MI, nonfatal stroke		-8% p=0.32	**-26% p<0.001**
Coronary death, nonfatal MI, coronary revascularization			
CV death, nonfatal MI, nonfatal stroke, coronary or carotid revascularization	-11% p<0.05		
CV death, nonfatal MI, nonfatal stroke, coronary revascularization, Hospitalized for UA			**-25% p<0.001** **-23% in diabetes** **HR 0.77** **95% CI (0.68-0.87)**

Trigliceride-Rich Lipoproteins (TgRL) and Cardiovascular Disease

Summary of Key Points

- **Raised triglycerides** concentrations, likely as marker of **REMNANT CHOLESTEROL**, are an additional causal risk factor for cardiovascular disease and all-cause mortality

- Available evidence suggests that the inflammatory component of atherosclerosis may be modulated by triglyceride rich lipoproteins

- Clinical trials with conventional/intensive statin therapy suggest that this association is present also at low LDL-C levels

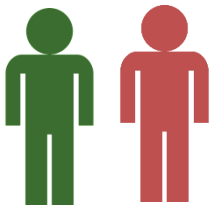
- **PHARMACOLOGICAL APPROACHES TO LOWER TG-RICH LIPOPROTEINS EFFECTIVELY REDUCE CVD in patients with elevated TG**

- Recognized by ESC/EAS 2019 Guidelines (Class IIa-IIb, Level B-C)

Superb Lipid Control To Prevent CVD Events

Known CV Disease,
Diabetes
Total Cholesterol 5.9 ;
LDL-C 4.1 (160)
TG 1.4 (130); HDL-C 1.2

Mr. Green



Mr. Red

Known CV Disease, **Diabetes**
TC 5.5 - **LDL-C 3.3 (128)**
HDL-C 1.1 (43) – **TG 2.4 (212)**

High Intensity **Statin** Therapy*

LDL-C Phenotype

LDL-C and TRIGLYCERIDES Phenotype

Mr. Green

LDL-C >80 mg/dl (>2,0 mmol/l)
TG OK

SUPERB LDL-C CONTROL

STATIN+ EZETIMIBE $
STATIN+EZE+PCSK9i $$$$

CV EVENT REDUCTION
14%-18 CV RRR

Mr. Red

#1

LDL-C

LDL-C <80 mg/dl (<2.0)
TG >150-170 mg/dl (>1.8-2.0)

SUPERB LDL-C CONTROL

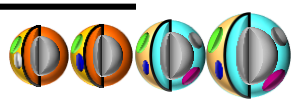
STATIN+ EZETIMIBE $
STATIN+EZE+PCSK9i $$$$

CV EVENT REDUCTION
14%-18 CV RRR

-14%
-18%

Mr. Red

#2



IDL **VLDL**

↑ TG Rich Lipoproteins

LDL-C <80 mg/dl (<2.0)
TG >150-170 mg/dl (>1.8-2.0)

SUPERB TRIGLYCERIDES CONTROL

STATIN+ EPA (omega-3) $$
STATIN+FENOFIBRATE $

CV EVENT REDUCTION
25%-35% CV RRR

Benefits On CVD

-25%
-30%