Understanding the role of triglycerides in the assessment of residual risk

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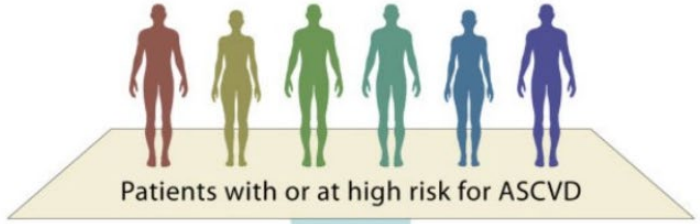
Faculty Disclosure

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Alfasigma	x							
Amgen	x							
Eli Lilly	x							
Fidia	x							
Chiesi	x	x						
Abbott - Mylan	x	x						
Daiichi Sankyo	x							
Servier	x							
Sanofi	x							
Amarin	x	x						
Novartis		x						

UNDERSTANDING THE ROLE OF TRIGLYCERIDES IN THE ASSESSMENT OF RESIDUAL RISK

- Residual Cardiovascular Risk (RCVR): A Complex Clinical Challenge
- RCVR: Triglyceride Rich Lipoproteins: Stars or second Leads
  - *Pathophysiology: TG and Inflammation*
  - *Clinical evidence: TG and CVD Events*
- Reducing TGRL Atherogenicity: more than just TG…..modulation of multiple steps along the atherothrombotic process IS THE KEY

Residual CV Risk: A Multifaceted Clinical Challenge



Optimal LDL-C levels

Biological Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk	Residual Diabetes Risk
Critical Biomarker	LDL-C ≥100 mg/dL	hsCRP ≥2mg/L	No simple biomarker	TG ≥150mg/dL	Lp(a) ≥50mg/dL	HbA1c Fasting glucose
Potential Intervention	Targeted LDL/Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction	SGLT2 Inhibitors GLP-1 Agonists
Randomized Trial Evidence	IMPROVE-IT FOURIER SPIRE ODYSSEY	CANTOS COLCOT *LoDoCo2* *OASIS-9*	PEGASUS COMPASS THEMIS	REDUCE-IT	Planned	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

R3i Residual Risk Reduction initiative

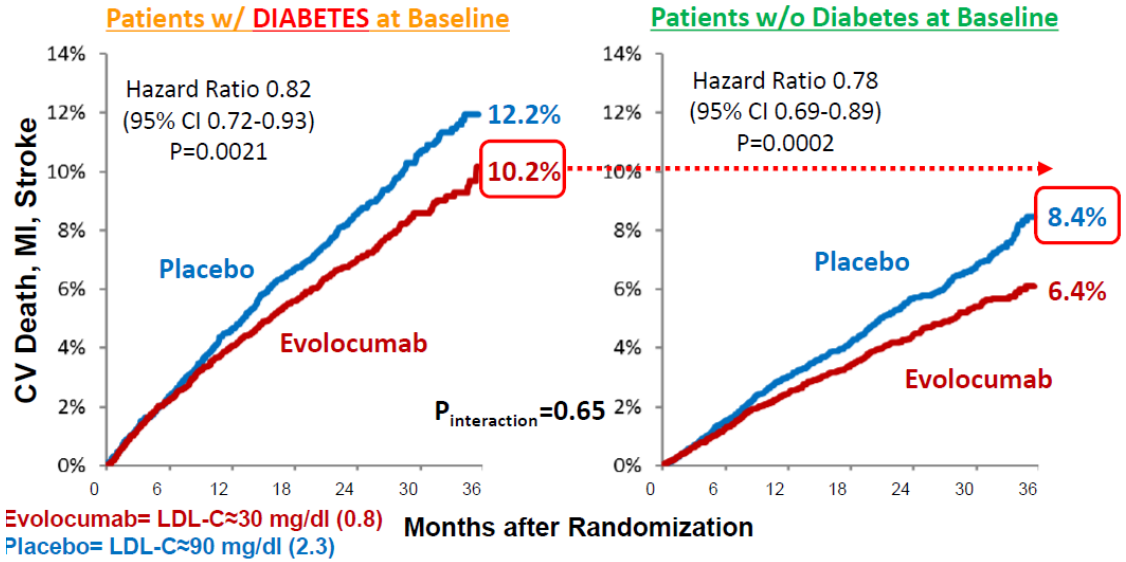
Residual Vascular Risk: DEFINITION

Residual Risk of macro-vascular events, including risk from established (such as unhealthy lifestyles, dyslipidemia, high blood ty) and atients

Residual CV Risk on Optimal LDL-C levels

fourier

Effect of Evolocumab on Key Secondary Endpoint



Evolocumab= LDL-C≈30 mg/dl (0.8)
Placebo= LDL-C≈90 mg/dl (2.3)

Patients with **DIABETES at LDL-C 30 mg/dl** (0.8 mmol/L) have **greater CV risk** than NON DIABETIC SUBJECT at LDL-C 90 mg/dl (2.3 mmol/L)!!!!

Lipid values are expressed in mg/dl (mmol/L)

ESC European Society of Cardiology
European Heart Journal (2022) 43, 807–817
https://doi.org/10.1093/eurheartj/ehab875

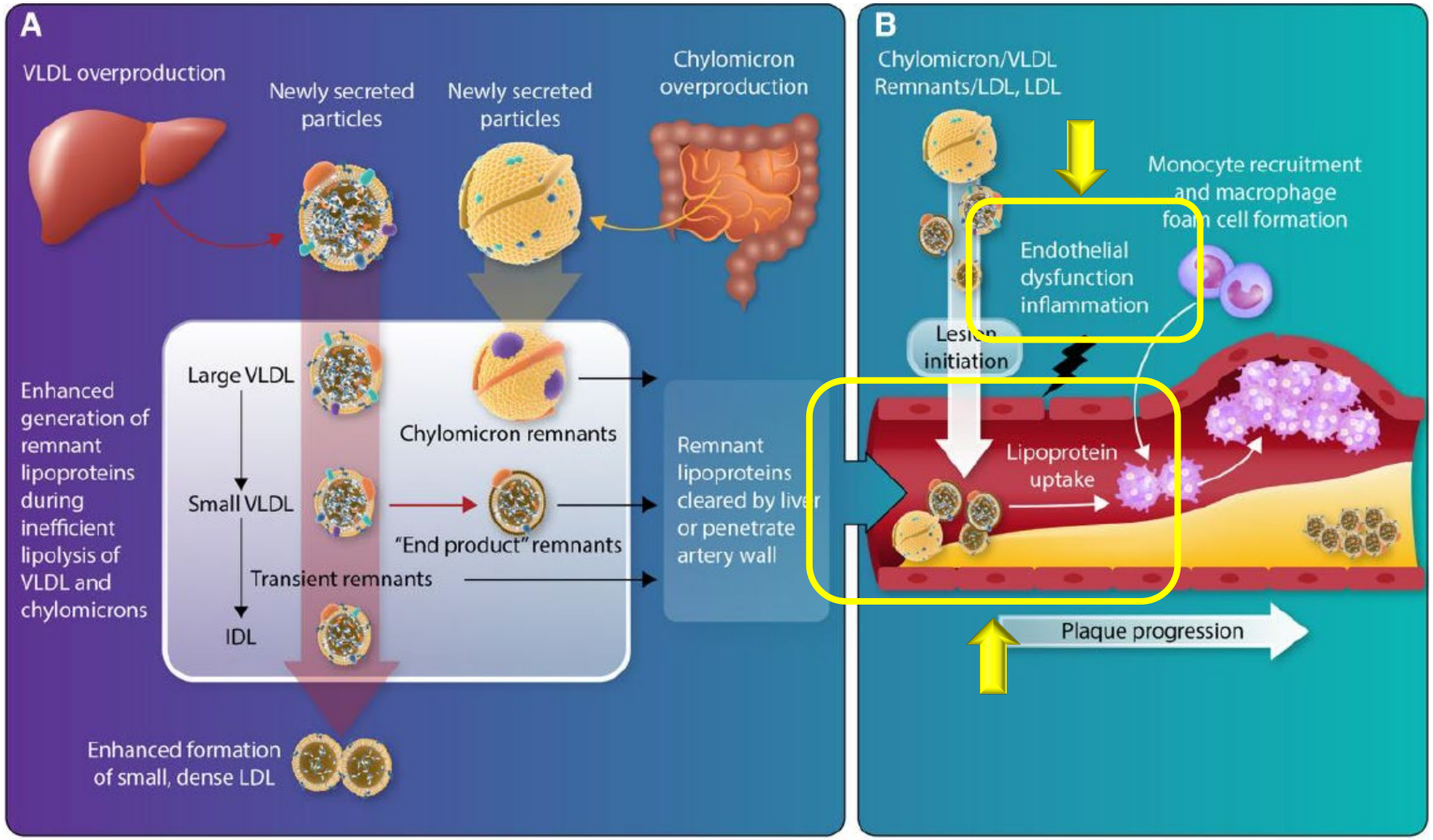
Lale Tokgozoglu [1]*, Carl Orringer [2], Henry N. Ginsberg [3], and Alberico L. Catapano [4]

The year in cardiovascular medicine 2021: dyslipidaemia

Triglyceride-Rich Lipoprotein (TGRL) are CAUSAL in Promoting The Atherothrombotic Process

1 TG-RICH LIPOPROTEIN IS AS ATHEROGENIC AS 1 LDL PARTICLE

ROBUST, RECENT EVIDENCE supports a **CAUSAL association between** triglyceride-rich lipoproteins, and **TRIGLYCERIDE-RICH LIPOPROTEIN REMNANTS WITH CARDIOVASCULAR EVENTS**. Overproduction and inefficient lipolysis, such as in **TYPE 2 DIABETES, mainly in the post-prandial phase**, of both very low-density lipoprotein and chylomicrons lead to increased remnant formation. Triglyceride-rich lipoprotein remnants contribute to the **initiation and progression of atherosclerotic lesions**.



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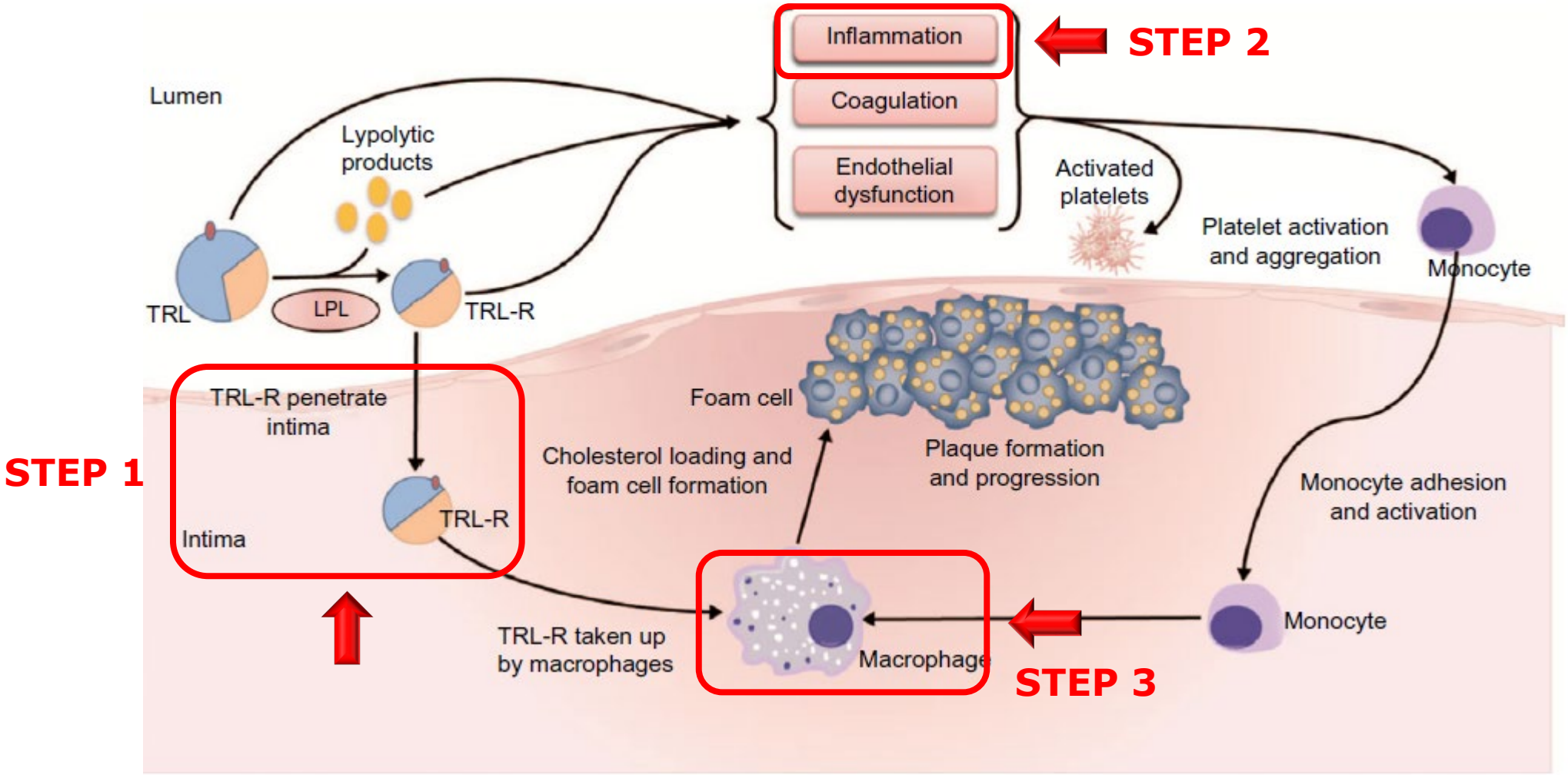
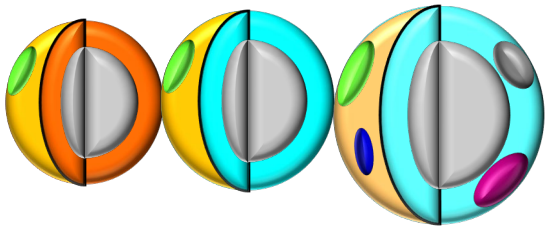
Pathophysiology of TG-rich lipoproteins in the progression of atherosclerosis



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

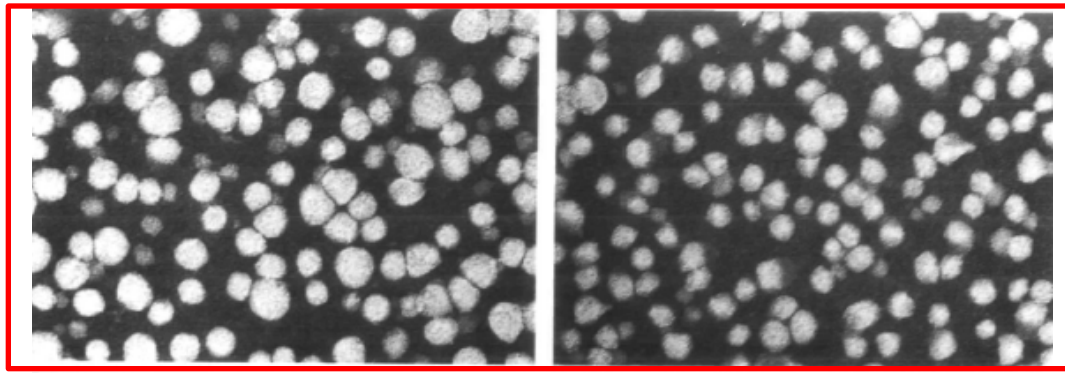
Toth PP et al Vascular Health and Risk Management 2016:12 171–183

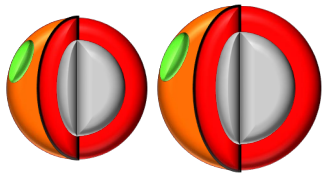
Triglyceride-Rich Lipoproteins Isolated From Human Coronary Atherosclerotic Plaque - EVIDENCE FROM THE PAST - 1994



VLDL + IDL

LDL



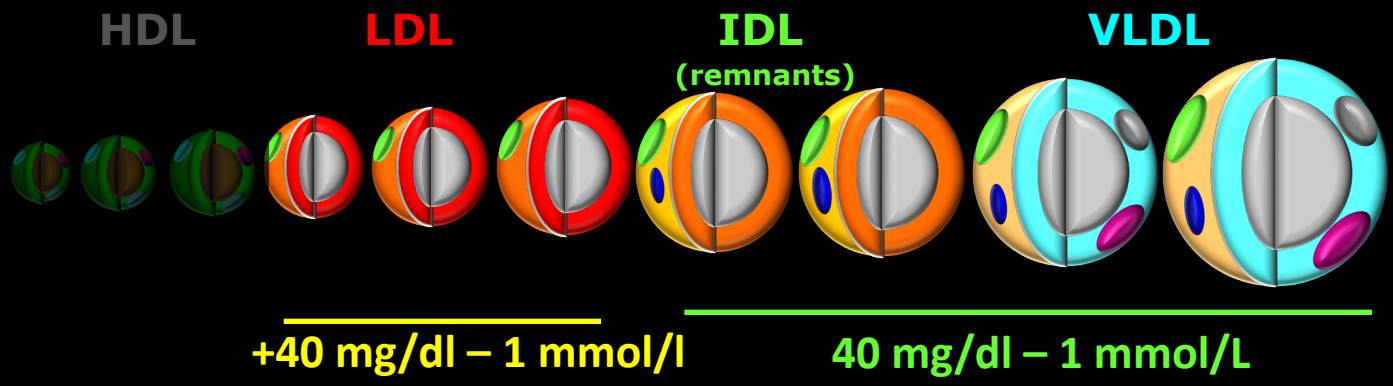


PLASMA

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

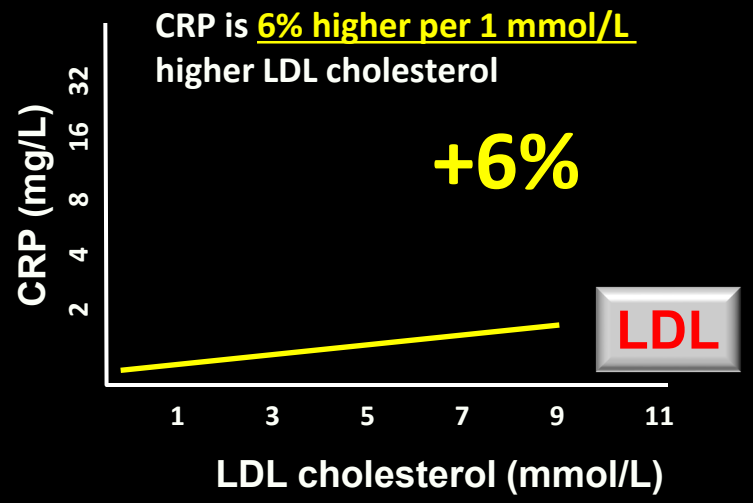
*Havel RJ, Kane JP et al Arterioscler Thromb.*1994;14:1767-1774.

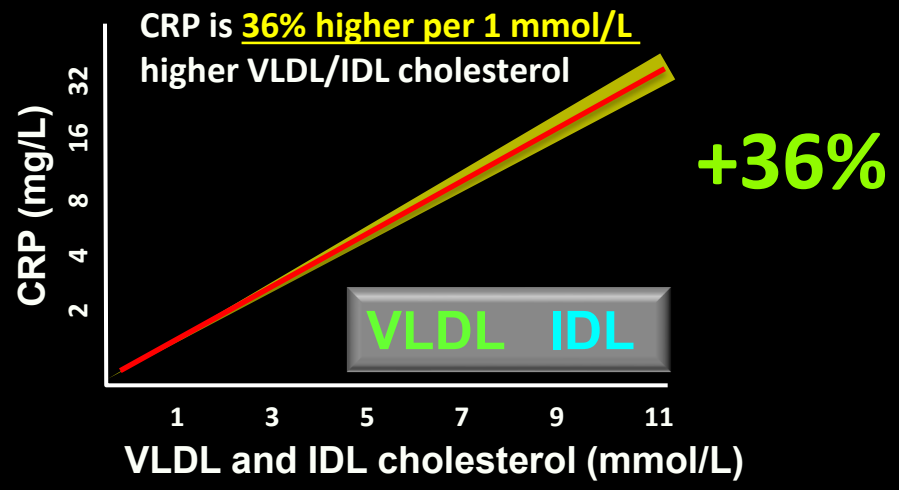
Association of nonfasting IDL and VLDL cholesterol (**right**) and LDL-C (**left**) with C-reactive protein (CRP) in 48 250 participants from the Copenhagen General Population Study.



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

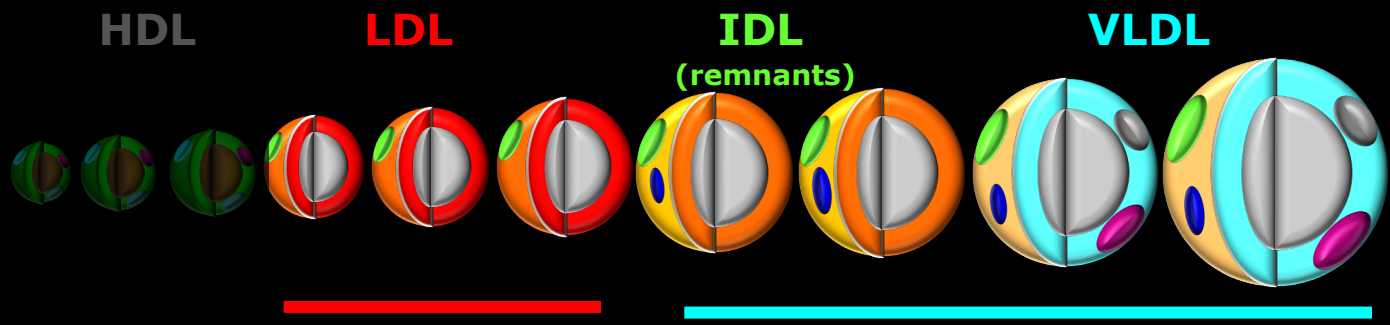
Age,sex, lipid-lowering therapy, smoking, hypertension, diabetes, menopause, and HRT



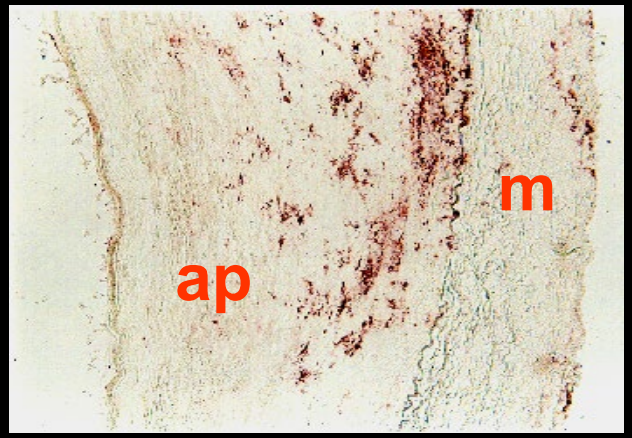


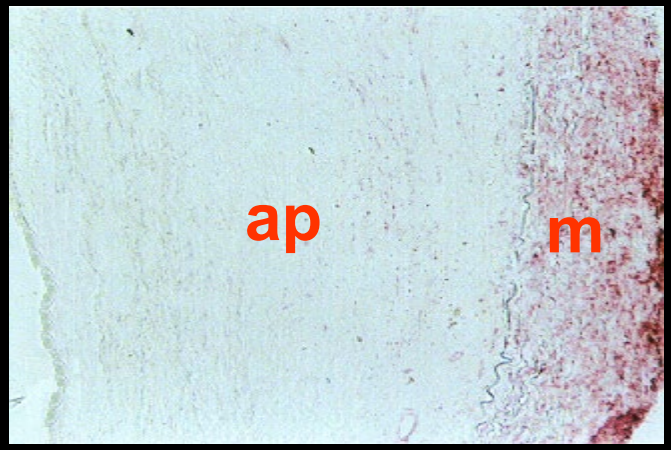
Varbo A et al.Circulation. 2013;128:1298-1309.

Correlation between LDL-C, TG-Rich Lipoproteins Cholesterol and Carotid Plaque Composition



Association between Lipoproteins and Macrophage Plaque Content

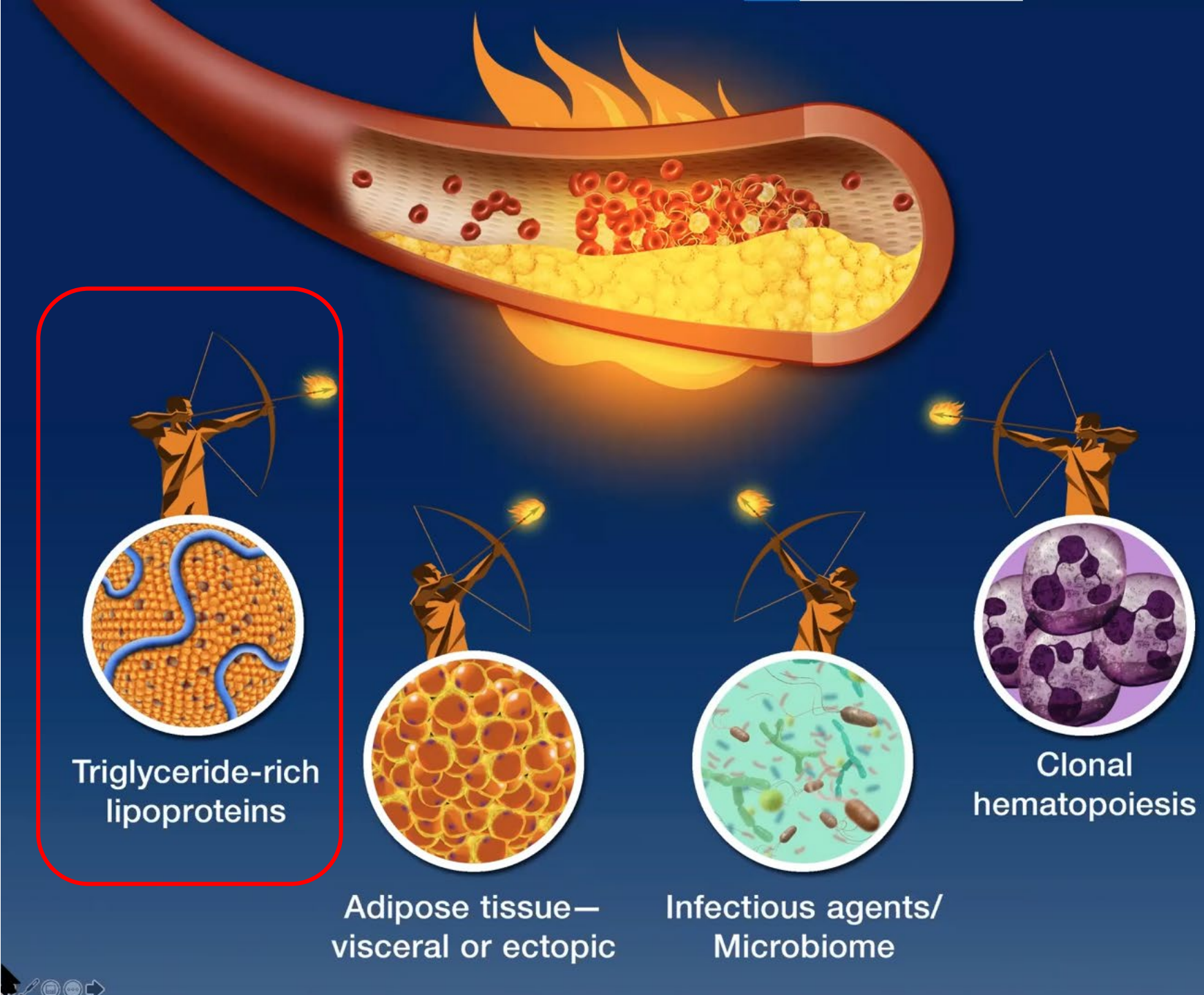




Association between Lipoproteins and Smooth Muscle Cell Plaque Content

LDL-C	r= 0.11, p=ns	r=0.15, p=ns
TG-Rich lipoproteins	r= 0.62, p<0.01	r= -044, p<0.05

Zambon A et al Atherosclerosis 2013 230:106-109



Some non-traditional risk factors drivers of arterial inflammation

Arson in the Artery: Who Set the Atheroma Aflame?

Peter Libby

Trends in Cardiovascular Medicine 29 (2019) 473–475

Journal of the American Heart Association

ORIGINAL RESEARCH

Association of Hypertriglyceridemia with All-Cause Mortality and Atherosclerotic Cardiovascular Events in a Low-Risk Italian Population: The TG-REAL Retrospective Cohort Analysis

Marcello Arca, MD; Chiara Veronesi, PhD; Laura D'Erasmo, MD, PhD; Claudio Borghi, MD; Furio Colivicchi, MD; Gaetano Maria De Ferrari, MD; Giovambattista Desideri, MD; Roberto Pontremoli, MD; Pier Luigi Temporelli, MD; Valentina Perrone, PhD; Luca Degli Esposti, PhD; on the behalf of Local Health Units Group*

CLINICAL PERSPECTIVE

What Are the Clinical Implications?

- The main clinical implication of our findings is that they further support the concept that triglyceride measurement must be considered an important part of the routine evaluation for all patients (including those estimated to be at low risk) to manage cardiovascular risk.

- **n= 158 042 individuals**
- **Normal TG < 150 mg/dl**
- **High TG: 150-500 mg/dl**
- **Very High > 500 mg/dl**

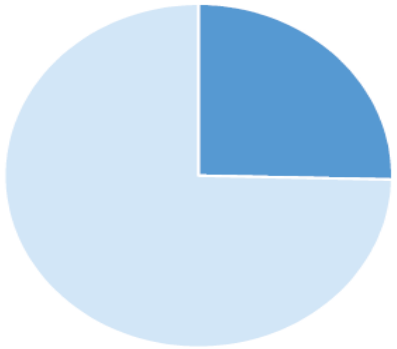
*age, sex, hypertension, diabetes, chronic kidney disease (CKD), previous cardiovascular hospitalizations, antidiabetic medication, statin, antihypertensive, anticoagulants, total cholesterol, and HDL-C.

ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–9
doi:10.1093/eurheartj/ehz767

Real-world risk of cardiovascular outcomes associated with hypertriglyceridaemia among individuals with atherosclerotic cardiovascular disease and potential eligibility for emerging therapies

Patrick R. Lawler, Gynter Kotrri, Maria Koh et al.

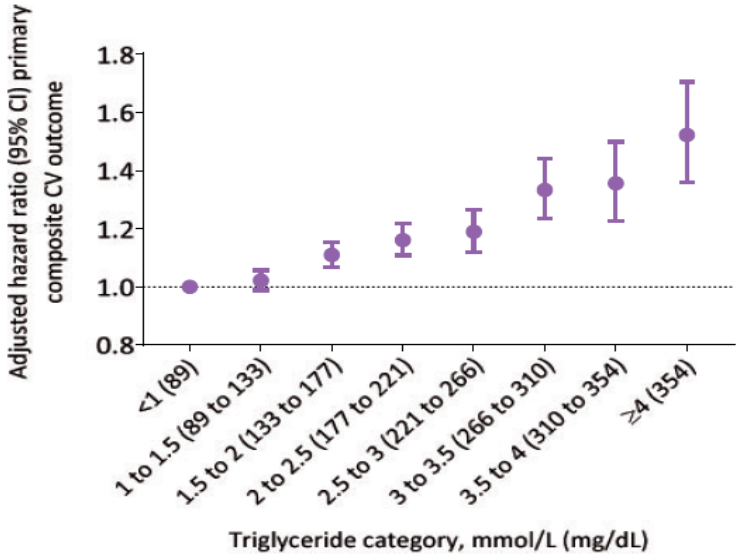
Approximately 1 in 4 patients with ASCVD in the general population may have hypertriglyceridemia and controlled LDLc*



*defined as triglyceride 1.52-5.63 mmol/L (135-499 mg/dL) and LDLc 1.06-2.59 mmol/L (41-100 mg/dL)

Mean LDL-C 68 mg/dl

Risk of ASCVD events associated with triglyceride level among 196,717 patients with prevalent ASCVD in the population



Models were adjusted for age, sex, income, LDL cholesterol, baseline diabetes and hypertension

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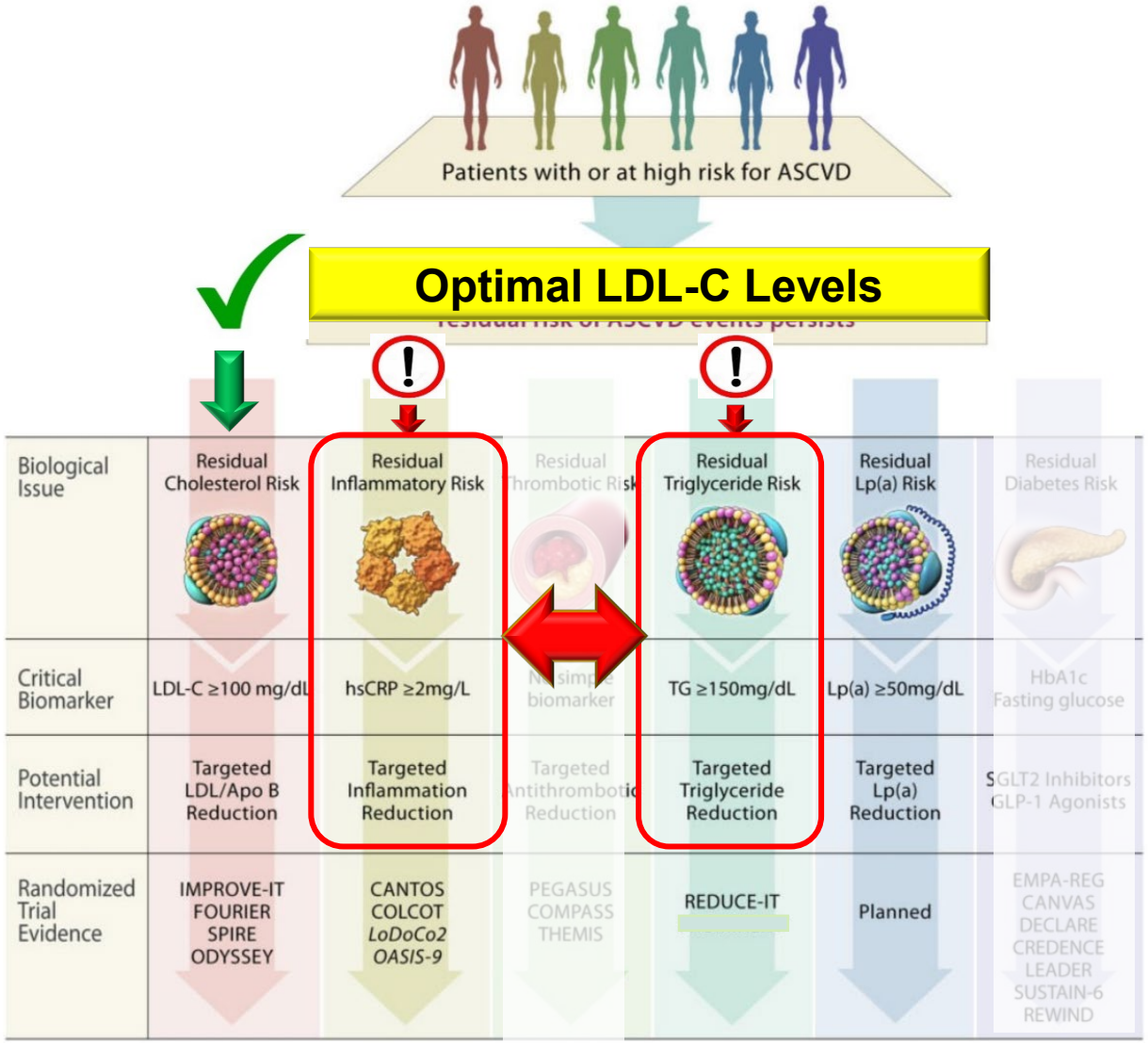
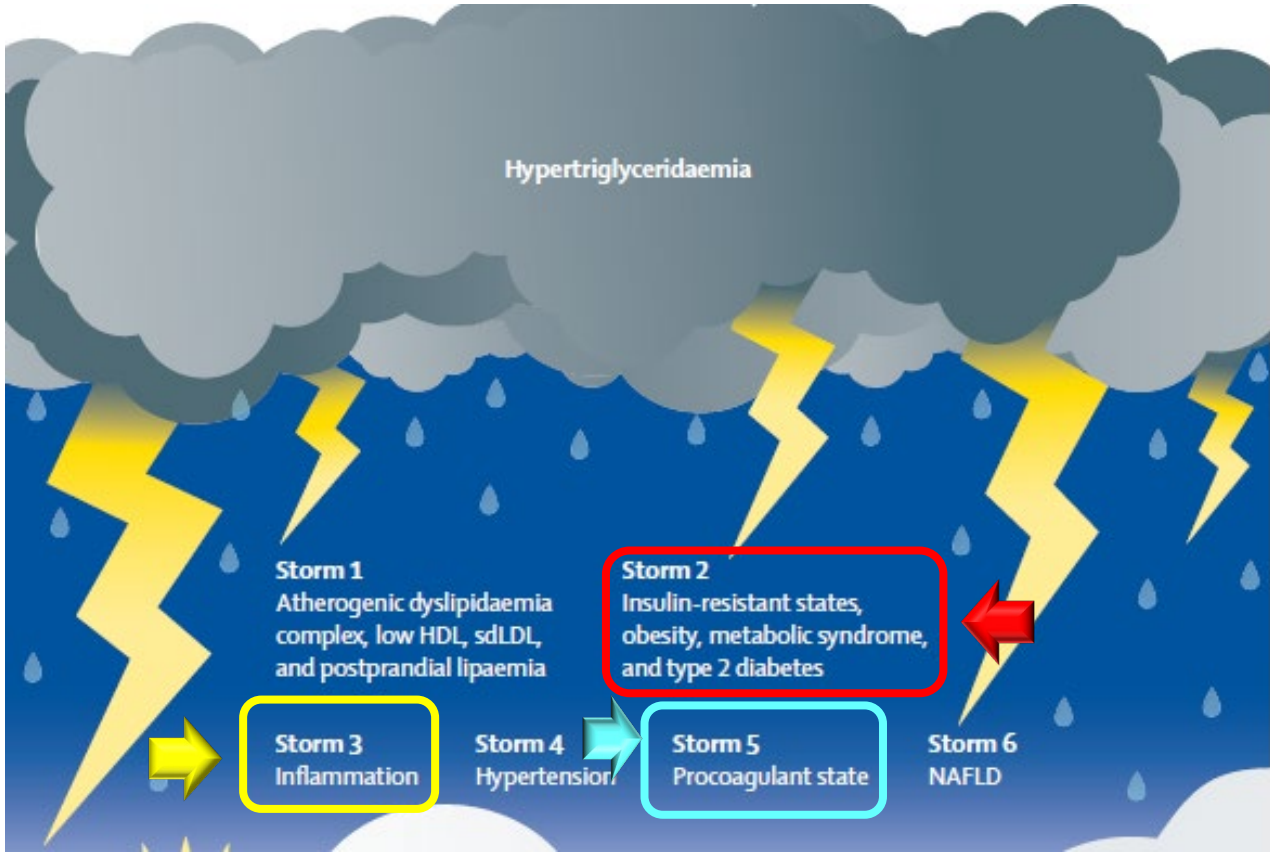


Effective, disease-modifying, clinical approaches to patients with mild-to-moderate hypertriglyceridaemia

HYPERTRIGLYCERIDAEMIA
A COMMON PRESENCE IN
ACUTE AND CHRONIC CLINICAL SETTING



Gary F Lewis, Robert A Hegele Lancet Diabetes Endocrinol 2022; 10: 142–48

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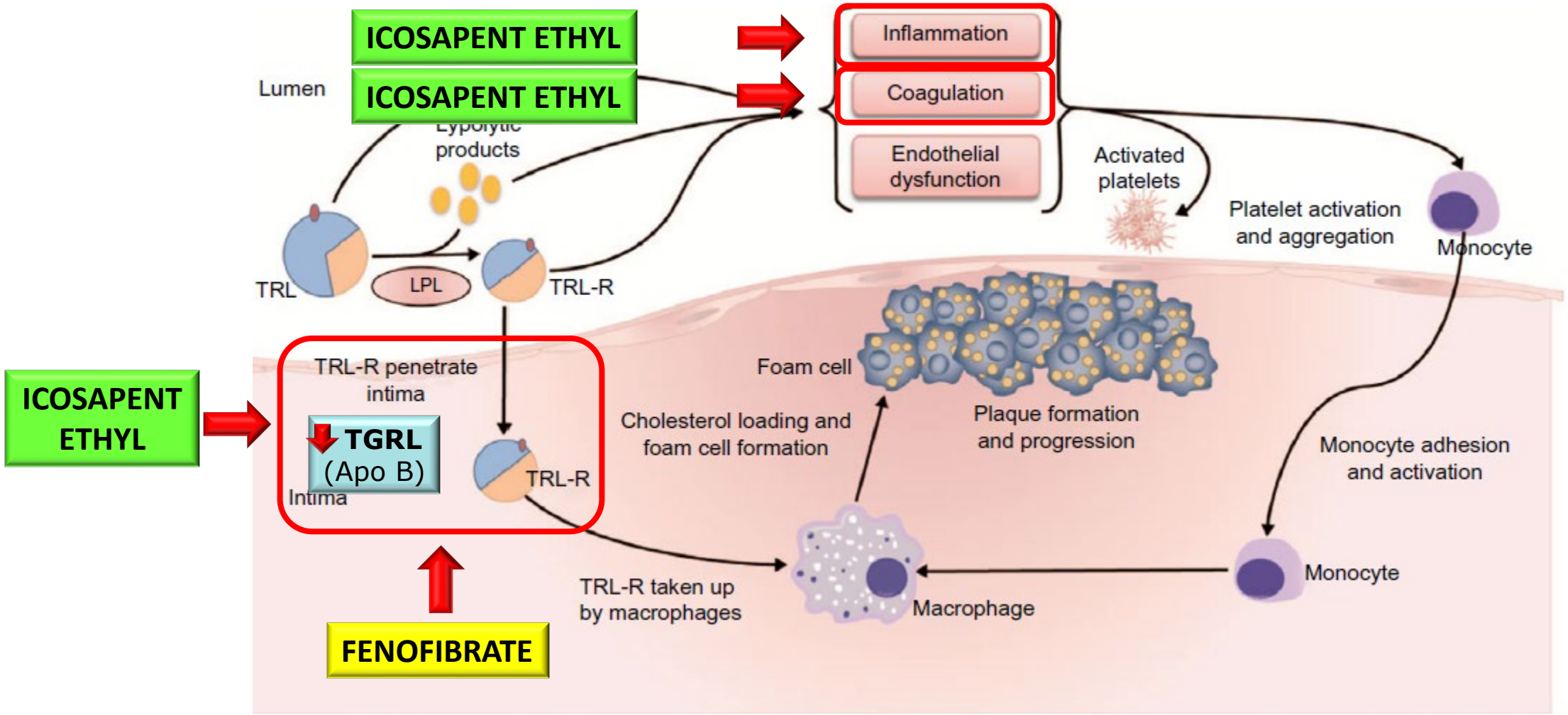
Current Triglyceride Lowering Approaches to reduce CVD Risk: More than Just TG ?



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