Hoe hypertriglyceridemie aanpakken ?

Ann Mertens, MD, PhD
Endocrinologie, UZ Leuven

BSA
BLC
Belgian Society of Atherosclerosis/ Belgian Lipid Club

UZ Leuven | Herestraat 49 B - 3000 Leuven | www.uzleuven.be tel. +32 16 33 22 11

Definitie van Hypertriglyceridemie

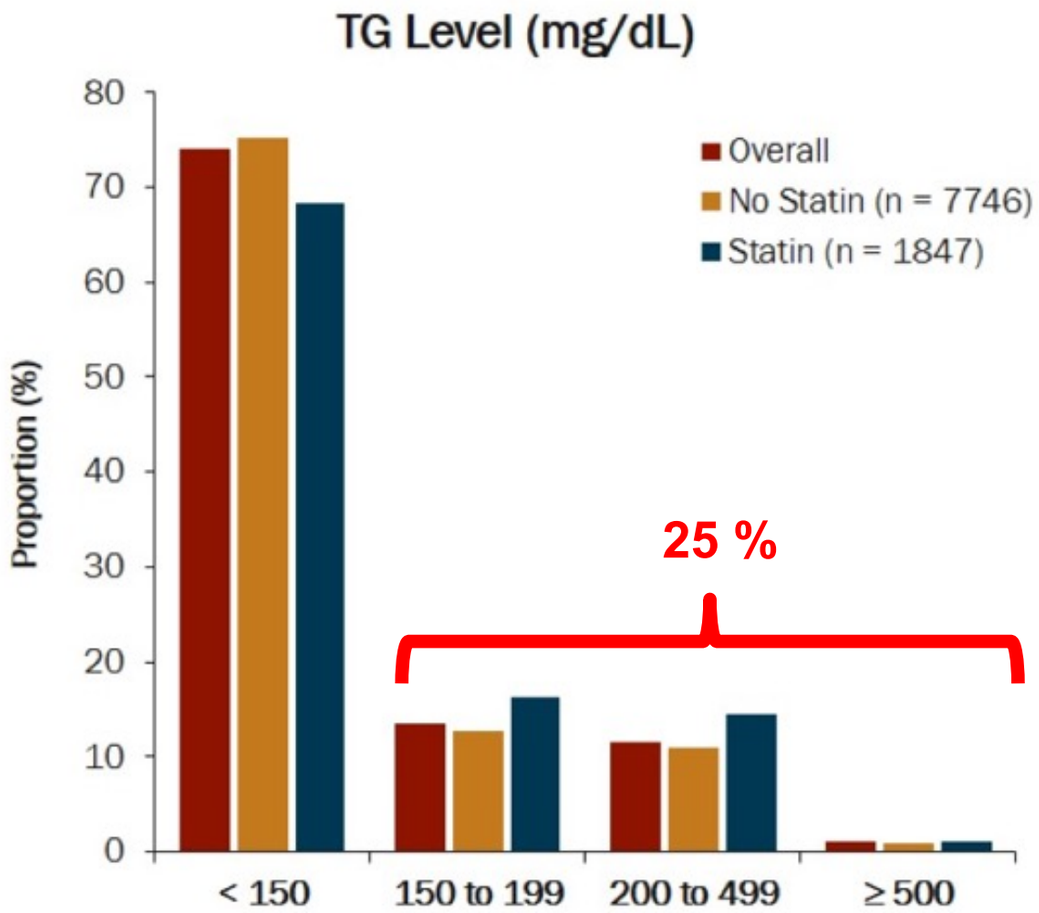
	Plasma triglyceride concentration mg/dL
2011 ESC/EAS guidelines[47]	
Normal	< 150
Hypertriglyceridaemia	150 – 885
Severe hypertriglyceridaemia	> 885
2001 NCEP ATP III guidelines[5] / AHA	
Normal	< 150
Hypertriglyceridaemia	
Borderline high	150 – 200
High	200 – 500
Very high	> 500
2012 Endocrine Society guidelines[1]	
Normal	< 150
Hypertriglyceridaemia	
Mild	150 – 200
Moderate	200 – 1000
Severe hypertriglyceridaemia	
Severe	1000 – 2000
Very severe	> 2000

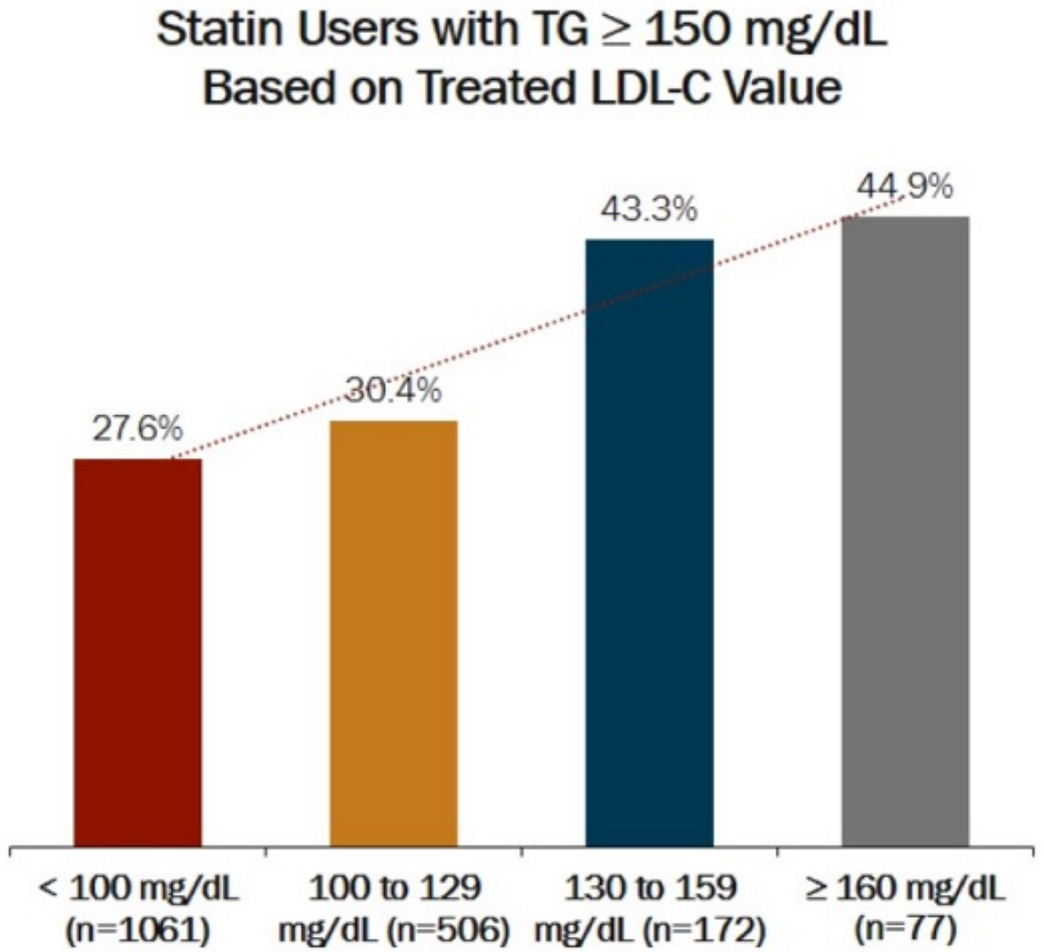
ESC=European Society of Cardiology. EAS=European Atherosclerosis Society. NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III.

Table 1: Clinical definitions for hypertriglyceridaemia

Lancet Diabetes Endocrinol 2014; 2: 655–66

Prevalentie van Hypertriglyceridemie
NHANES populatie (2007-2014), nuchtere TG

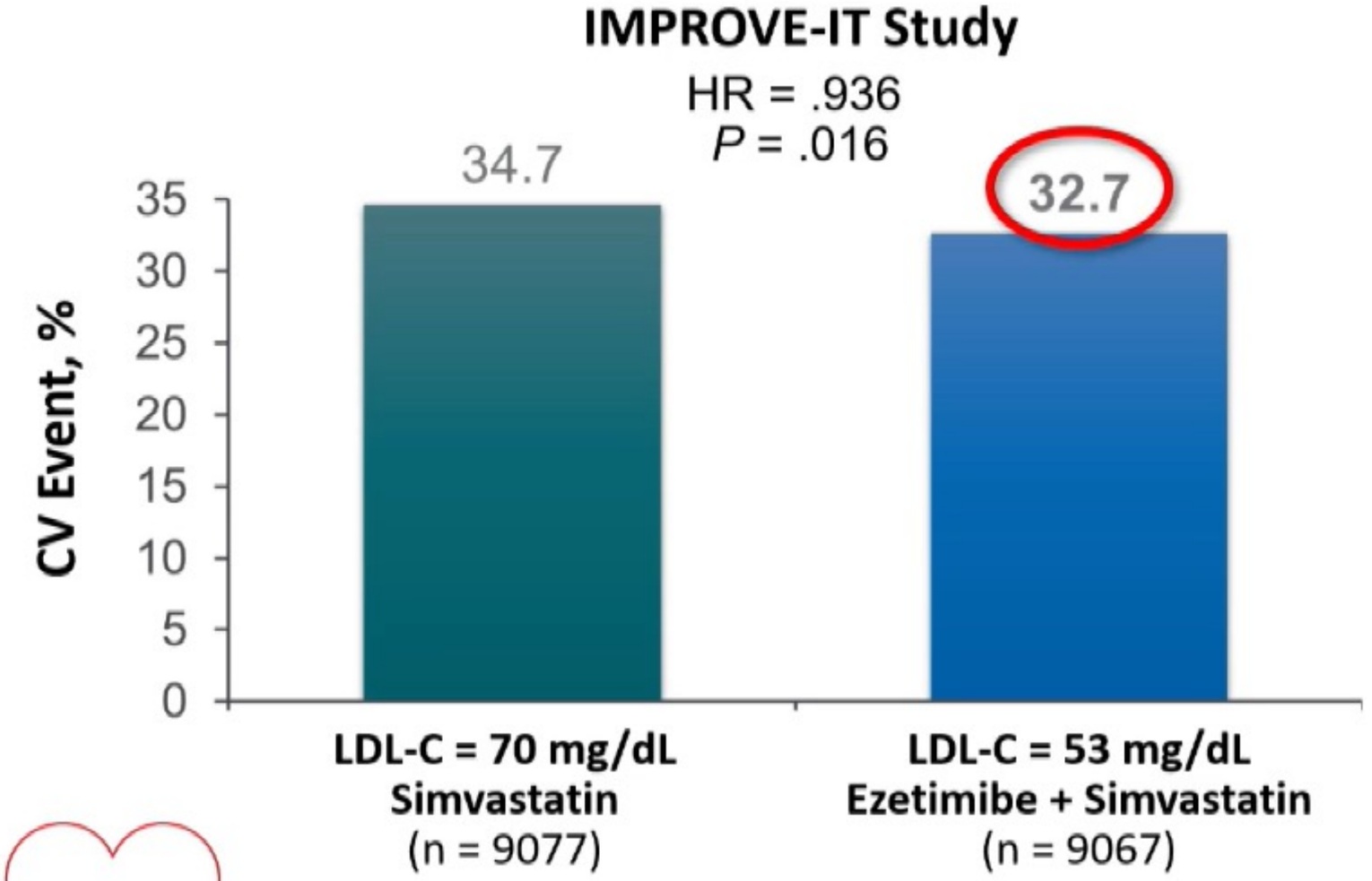




NHANES, National Health and Nutrition Examination Survey.
Fan W, et al. J Clin Lipidology. 2019;13:100-108.

Aggressive LDL-C Lowering Does Not Eliminate ASCVD Risk

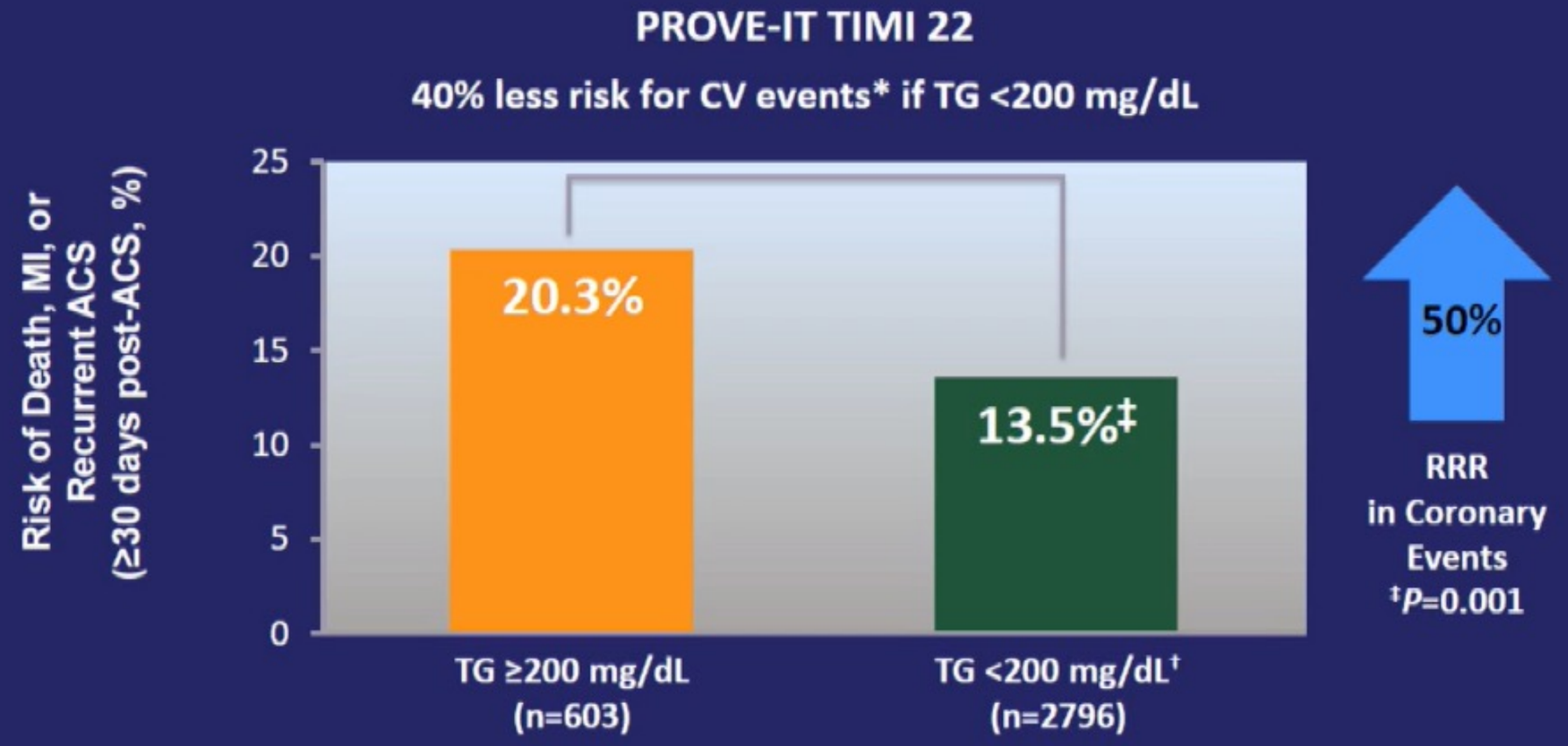
Significant Residual Risk Remains Untreated



Residual risk due to increased triglycerides, elevated Lp(a), non – HDL, hyperglycemia and/or other untreated risk factors

Cannon CP, et al. *NEJM.* 2015;372(25)2387-97.

High TG Is a *"Red Flag" for ↑Residual Risk* Despite *Statin MonoRx*, Even with LDL-C <70 mg/dL



RRR=relative risk reduction.

*Death, myocardial infarction, or recurrent acute coronary syndrome.

†From adjusted hazard ratio of TG <200 mg/dL (95% CI) = 0.60 (0.45–0.81).

Miller M et al. *J Am Coll Cardiol*. 2008;51(7):724-730.

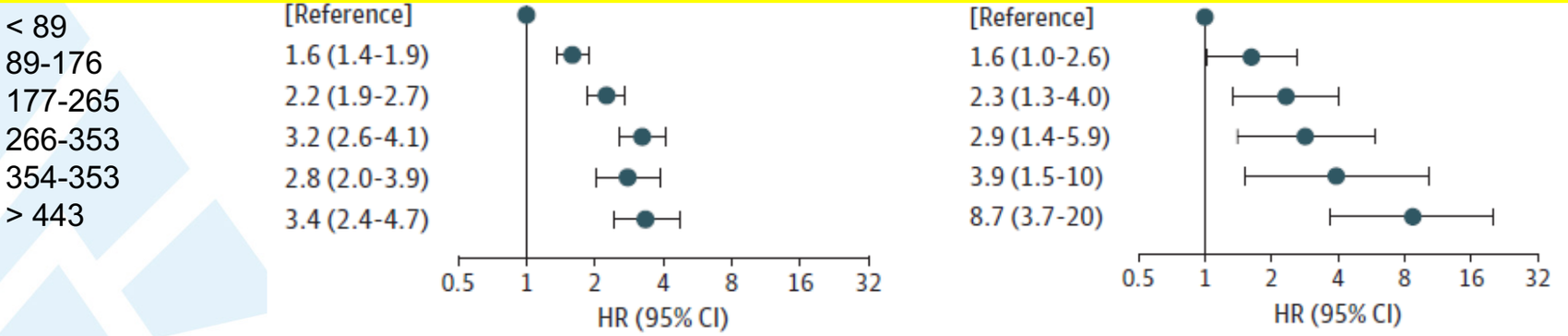
JAMA Internal Medicine | Original Investigation

Nonfasting Mild-to-Moderate Hypertriglyceridemia and Risk of Acute Pancreatitis

Simon B. Pedersen, BMSc; Anne Langsted, MD, PhD; Børge G. Nordestgaard, MD, DMSc

116,550 individuals from general population

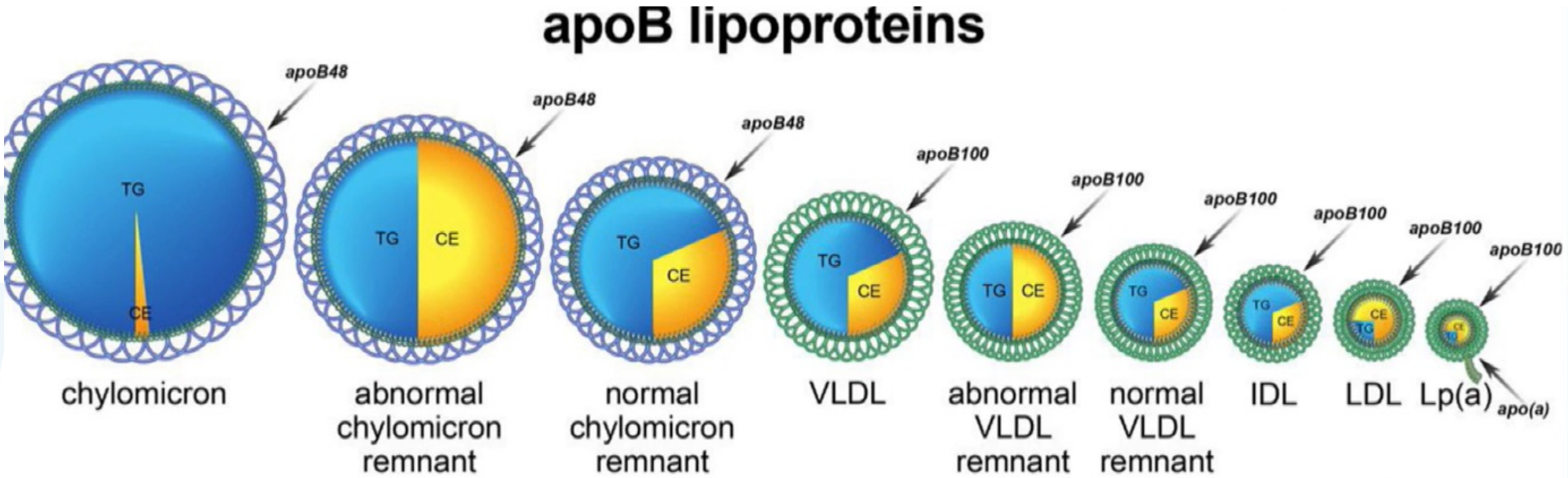
Triglyceriden	Myocardinfarct	Acute pancreatitis
> 150 mg/dL	x2	x2
> 250 mg/dL	x3	x3
> 400 mg/dL	x3.5	x8

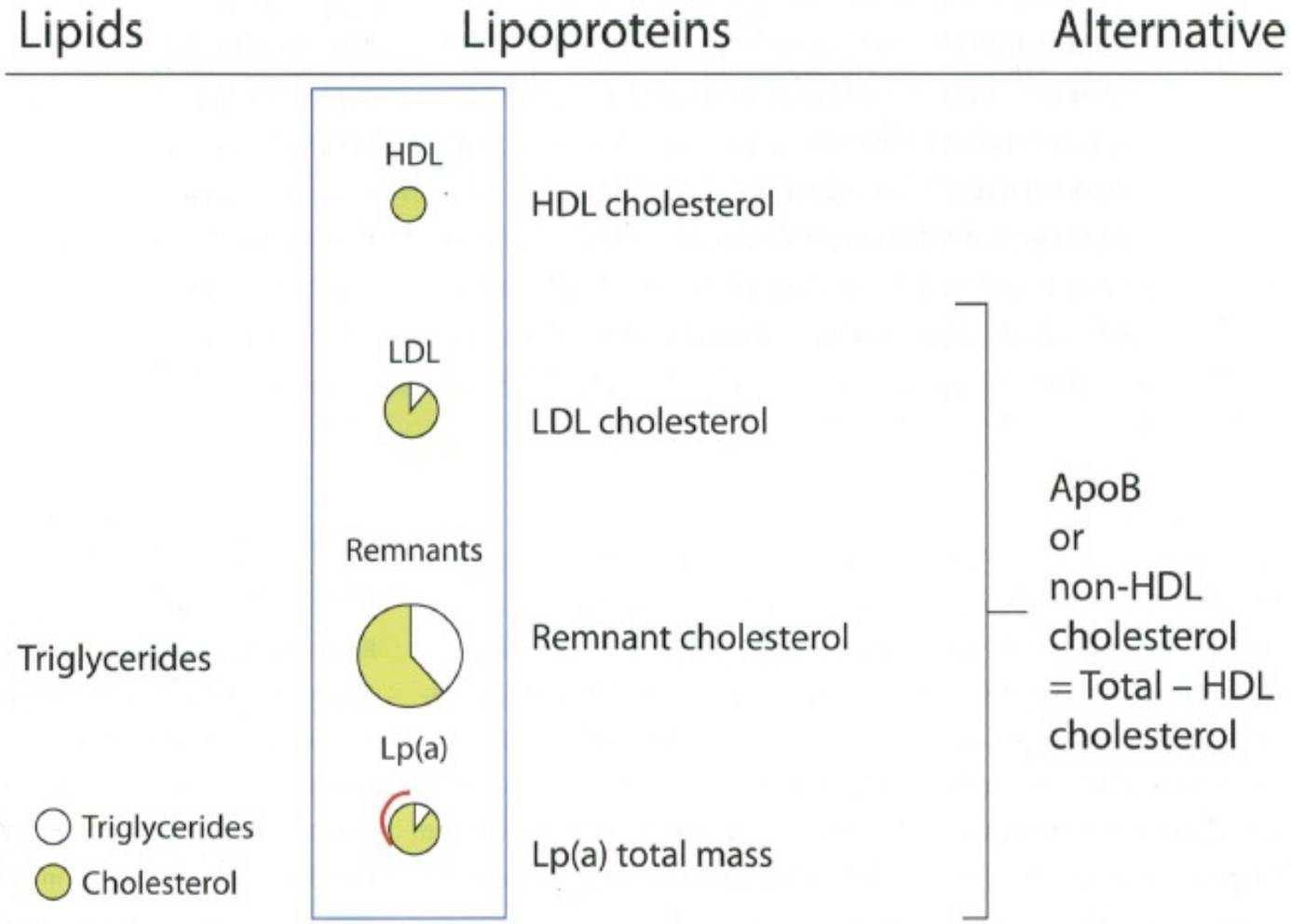


Multivariable adjusted for age, sex, education, smoking, hypertension, statin use, birth year, study cohort

JAMA Intern Med. 2016;176(12):1834-1842. doi:10.1001/jamainternmed.2016.6875
Published online November 7, 2016.

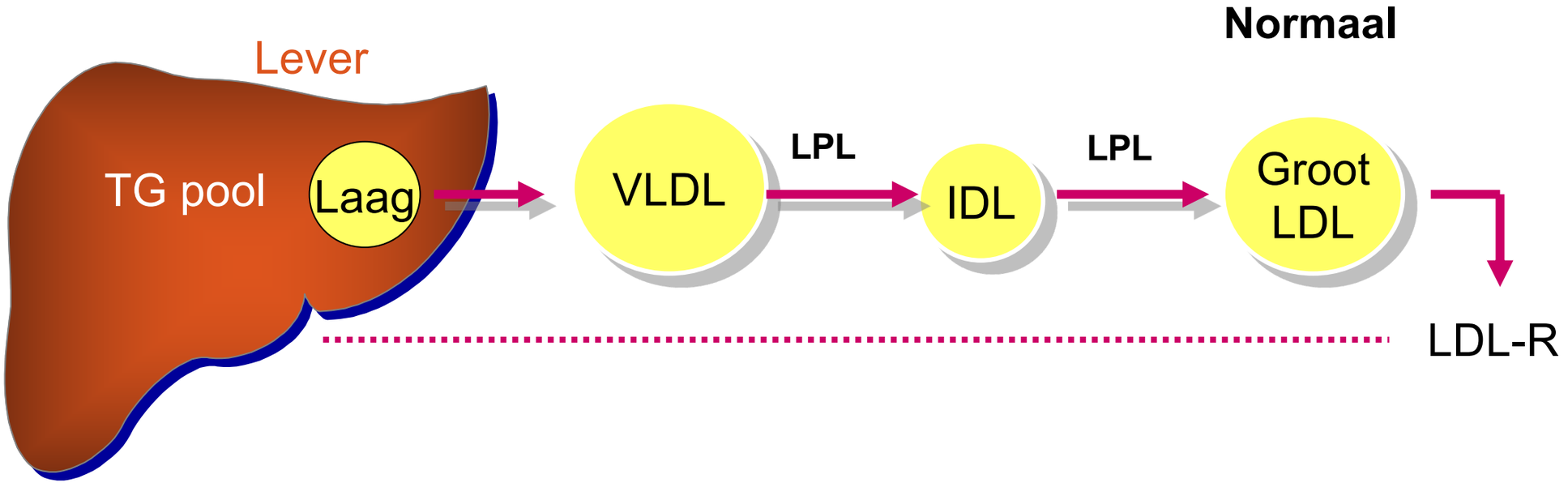
Triglyceriden zijn een biomarker van triglyceridenrijke lipoproteïnen

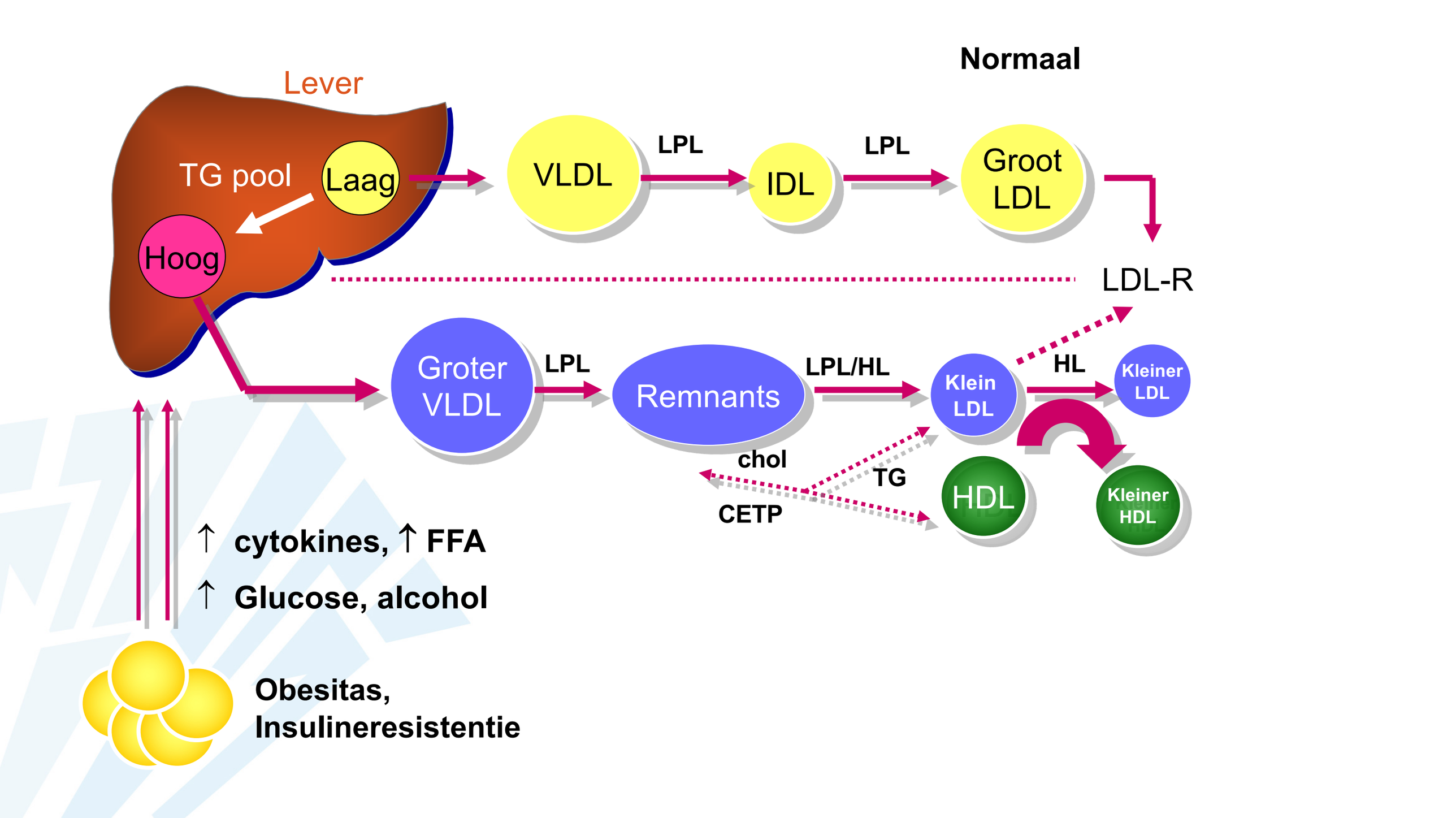


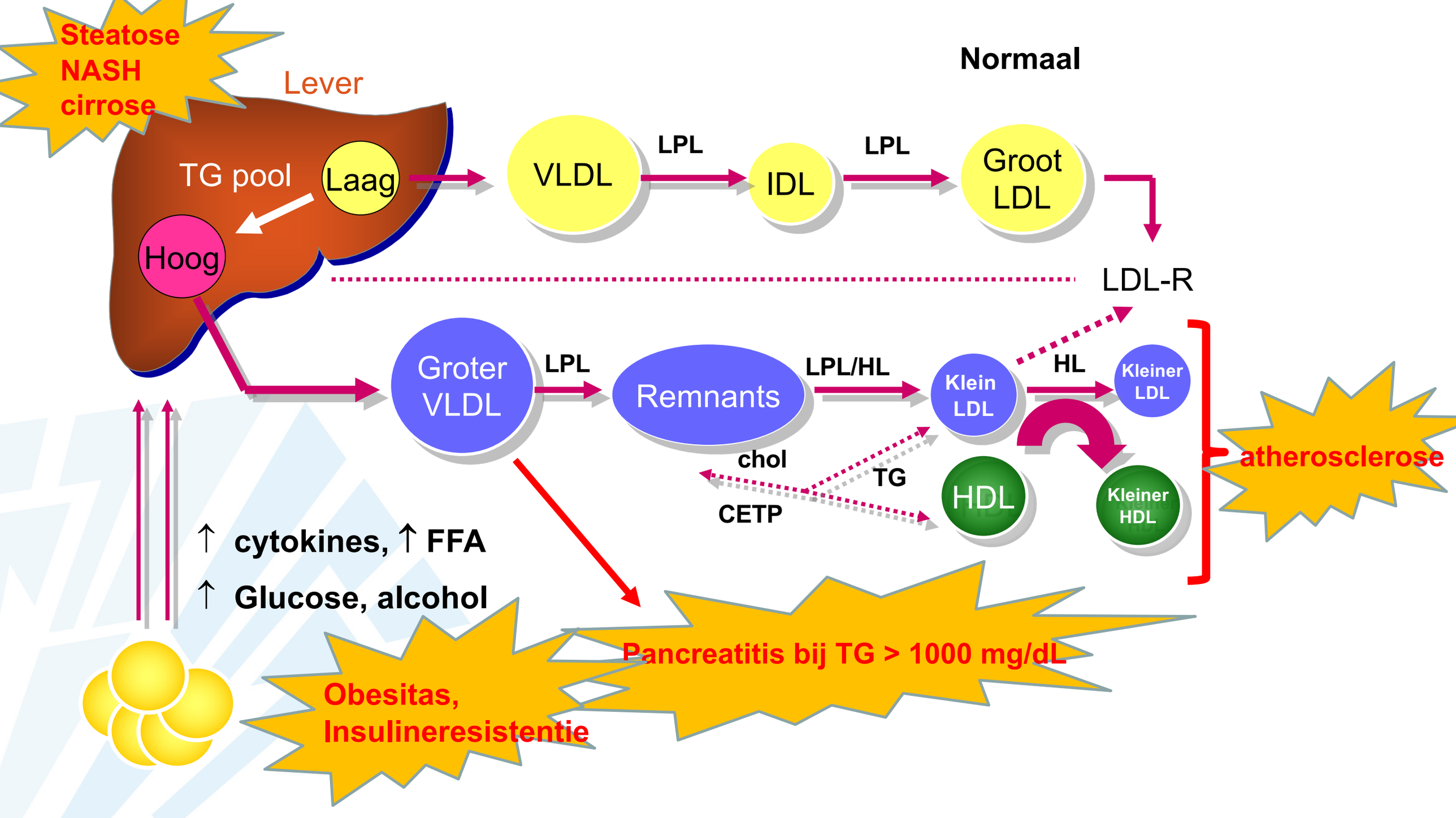


Non-HDL-cholesterol = totaal cholesterol – HDLcholesterol
= alle atherogene cholesterolfracties

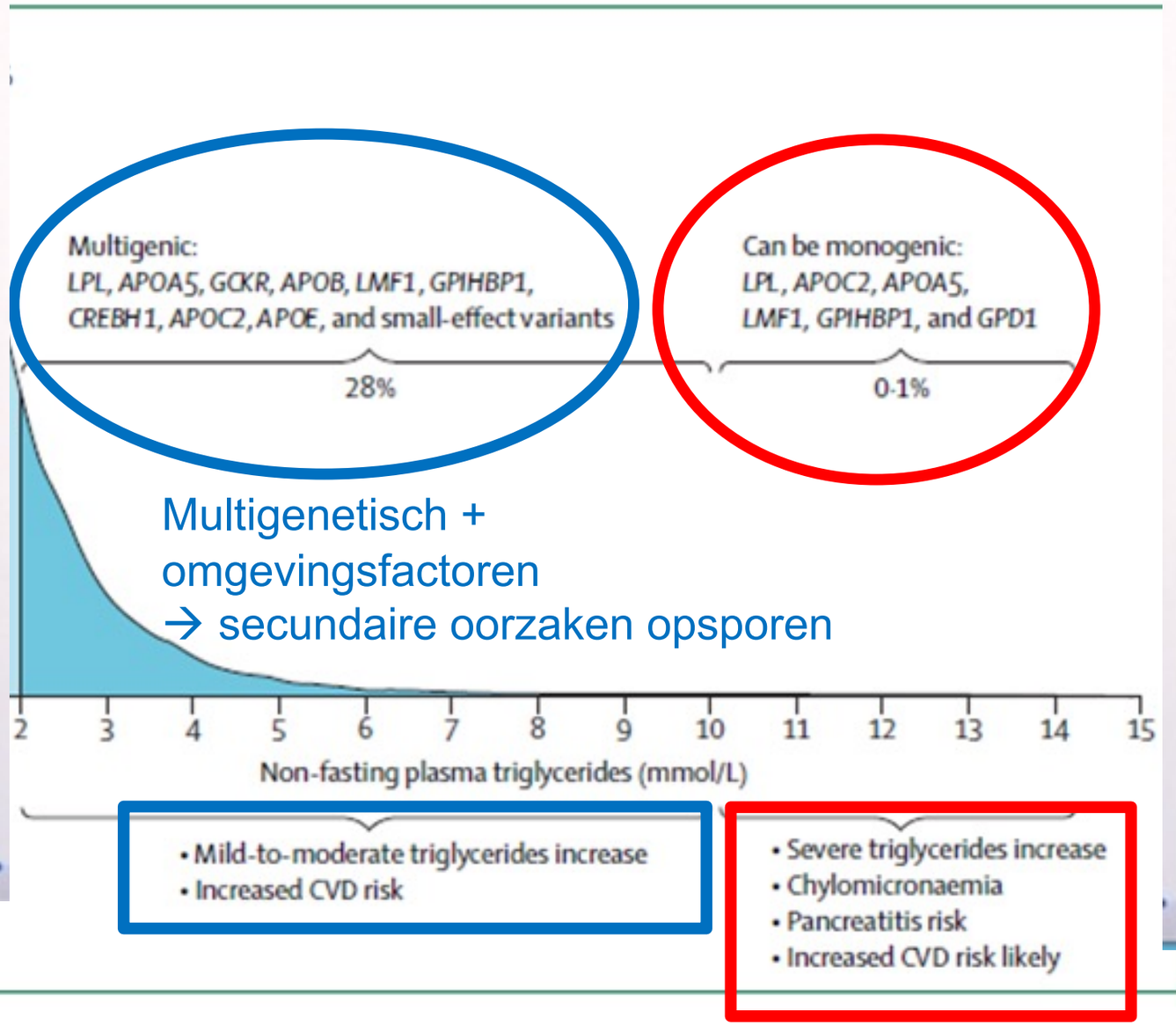
→ is niet afhankelijk van postprandiale variaties in triglyceriden


Normaal
Lever
TG pool
Laag
VLDL
LPL
IDL
LPL
Groot
LDL
LDL-R


Normaal
Lever
TG pool
Laag
Hoog
VLDL
LPL
IDL
LPL
Groot LDL
LDL-R
Groter VLDL
LPL
Remnants
LPL/HL
Klein LDL
HL
Kleiner LDL
chol
TG
CETP
HDL
Kleiner HDL
↑ cytokines, ↑ FFA
↑ Glucose, alcohol
Obesitas,
Insulineresistentie


Steatose
NASH
cirrose
Lever
TG pool
Laag
Hoog
Normaal
VLDL
LPL
IDL
LPL
Groot
LDL
LDL-R
Groter
VLDL
LPL
Remnants
LPL/HL
Klein
LDL
HL
Kleiner
LDL
chol
TG
CETP
HDL
Kleiner
HDL
atherosclerose
↑ cytokines, ↑ FFA
↑ Glucose, alcohol
Pancreatitis bij TG > 1000 mg/dL
Obesitas,
Insulineresistentie

Complexe Genetische Basis bij Hypertriglyceridemie



Lancet Diabetes Endocrinol
2014; 2: 655–66

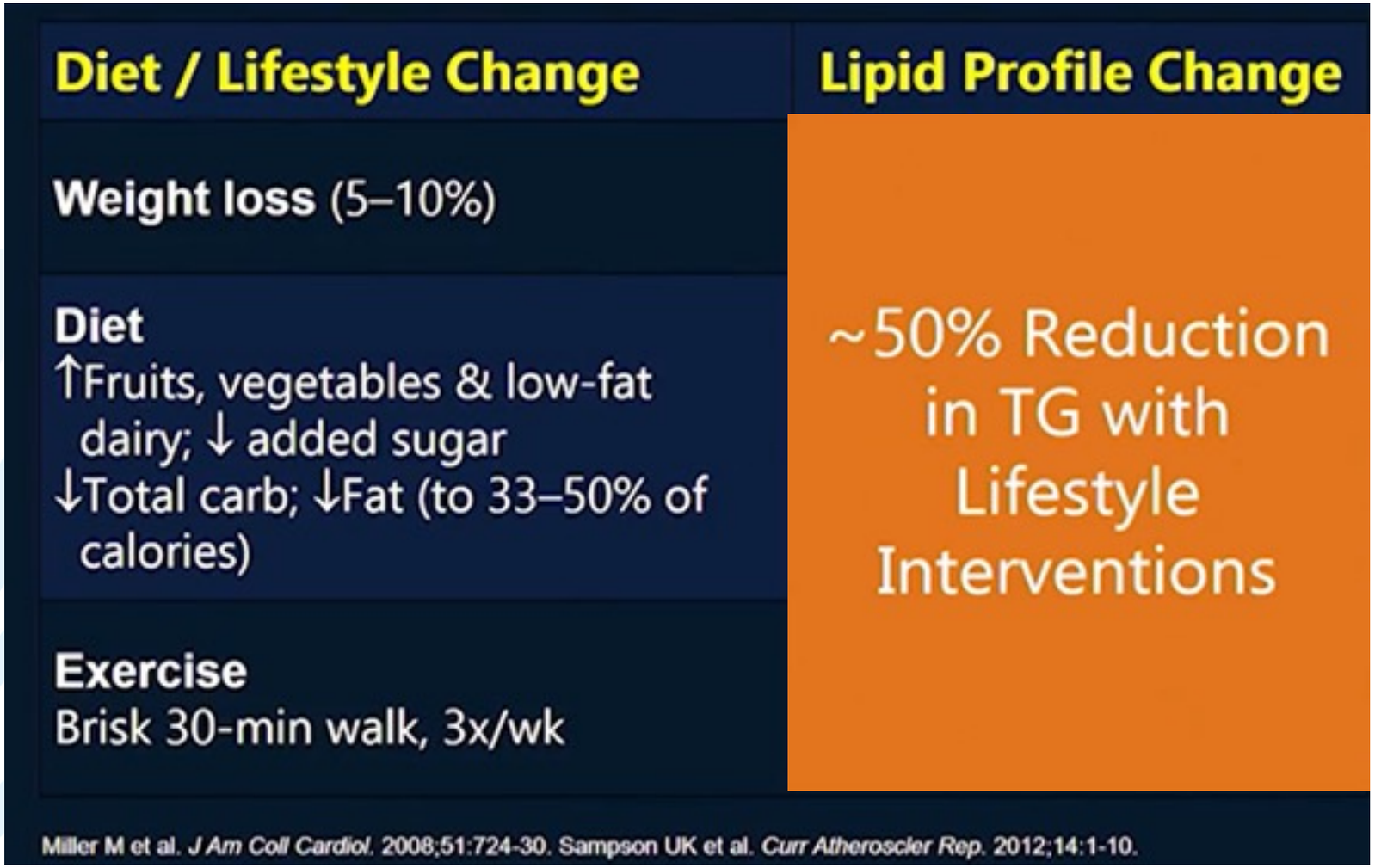
Secundaire Oorzaken van Hypertriglyceridemie

- Obesitas
- Metabool syndroom
- Hoog calorisch dieet (vetrijk, hoge glycemische index)
- Slecht geregelde diabetes (meestal type 2)
- Overmatig alcoholgebruik
- Hypothyroïdie
- Nierlijden (proteïnurie, uremie, glomerulonefritis)
- Zwangerschap (vooral derde trimester)
- Paraproteïnemie
- Systeem lupus erythematosus
- Geneesmiddelen: corticosteroïden
  orale oestrogenen
  tamoxifen
  thiaziden
  niet-cardioselectieve betablokkers
  protease-inhibitoren
  tweede generatie antipsychotica (olanzapine, clozapine)

Lancet Diabetes Endocrinol
2014; 2: 655-66

BEHANDELING van HYPERTRIGLYCERIDEMIE

Belangrijkste aanbeveling: lifestyle !!!!



Statins and Triglycerides

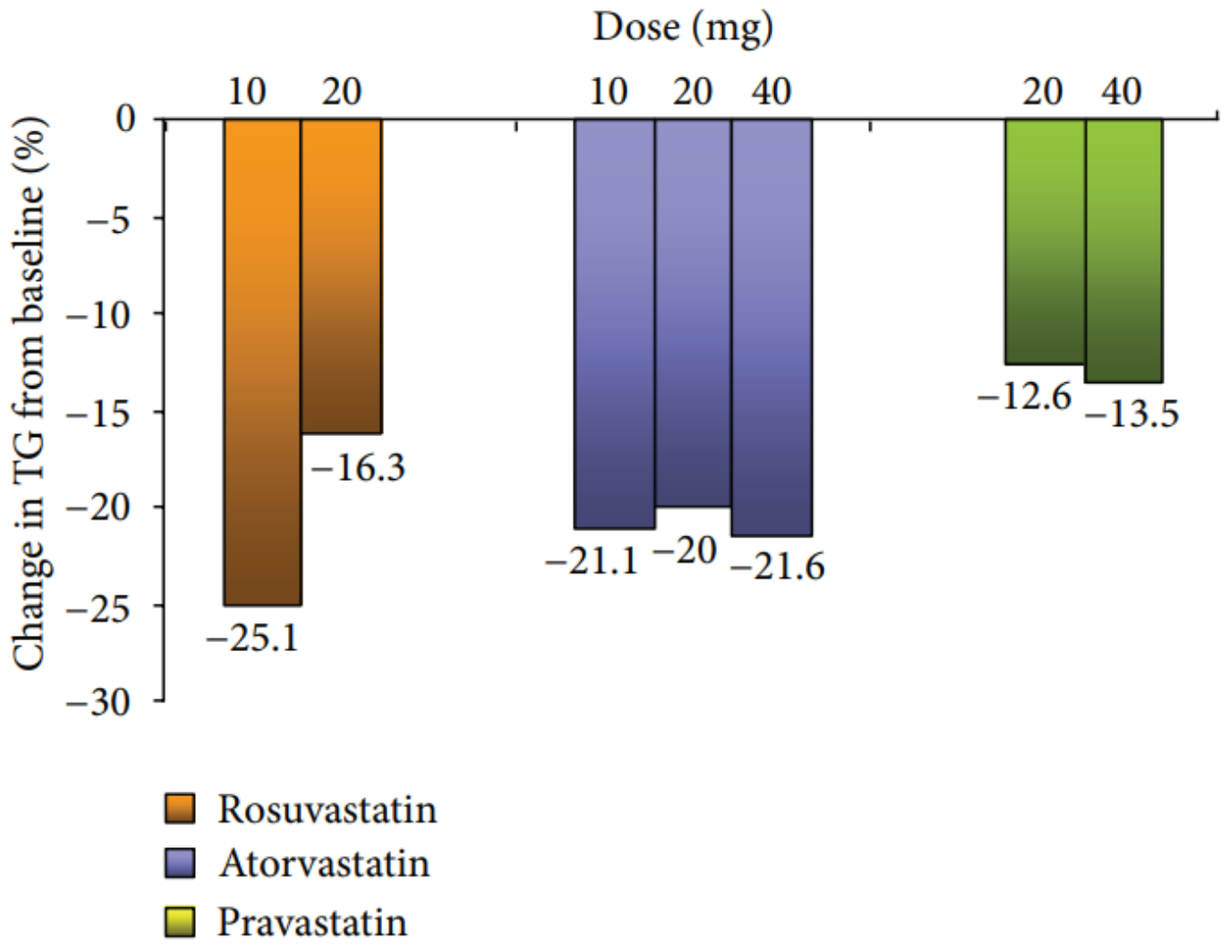
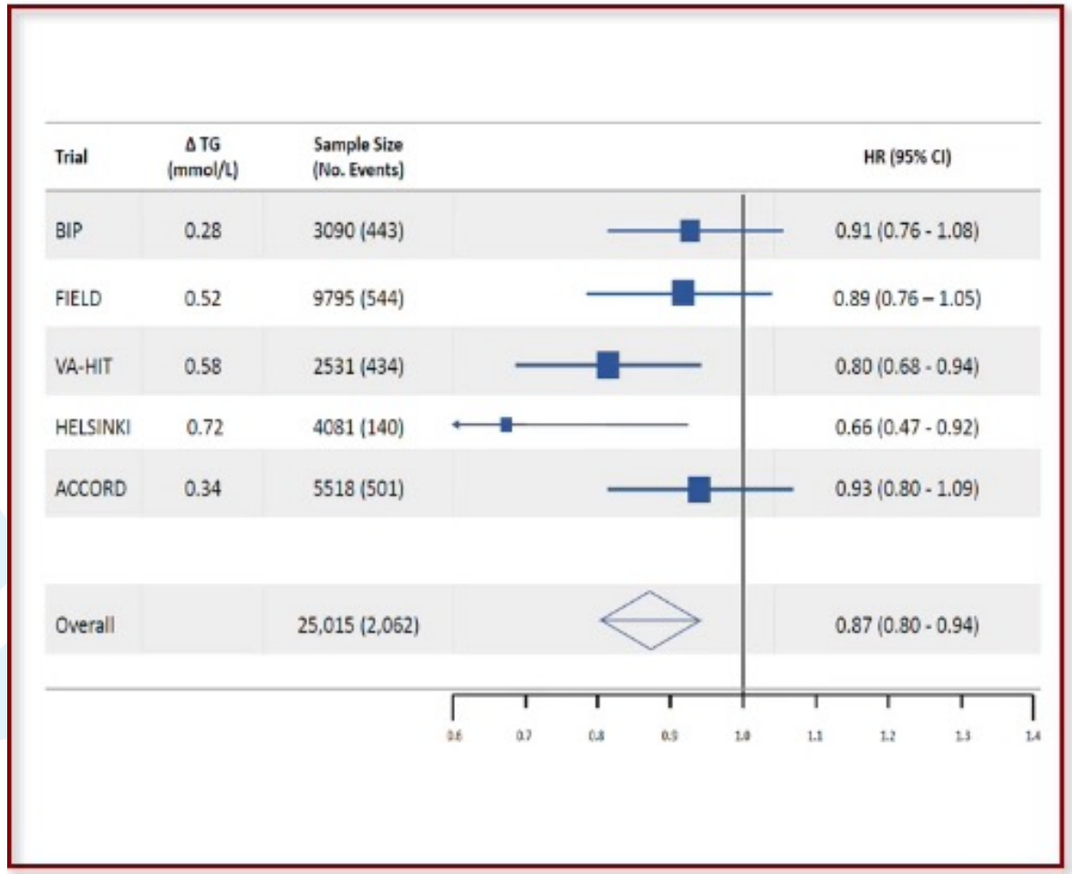


FIGURE 2: Rosuvastatin versus other statins, change in triglycerides.

Barakat et al. Pharmacology 2013

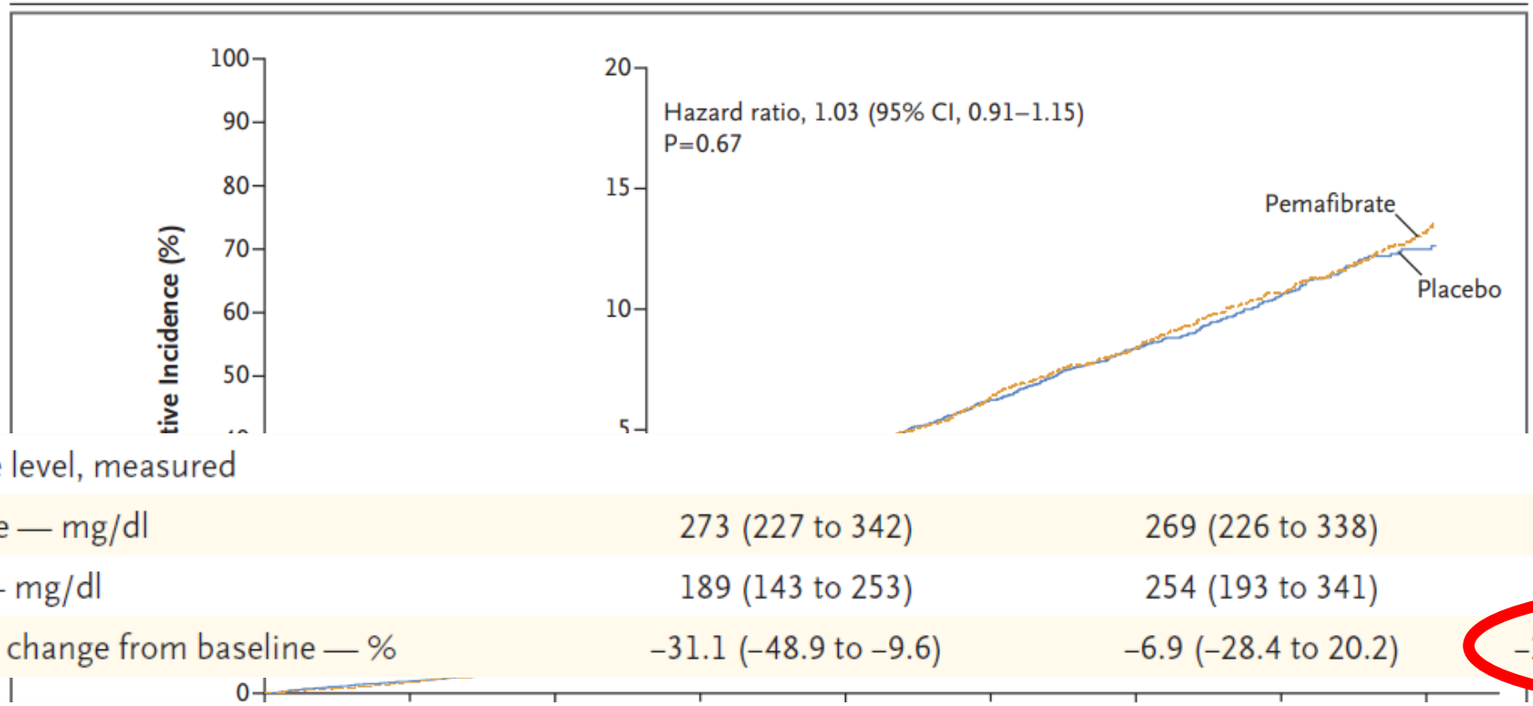
Fibrates and Triglycerides

Fibrate randomized trials



BIP: Circulation. 2000;102:21-27; Field: Lancet 2005; 366: 1849–61; VA-HIT: N Engl J Med 1999;341:410-8; Helsinki: N Engl J Med 1987;317:1237-45; ACCORD: N Engl J Med 2010;362:1563-74.

PROMINENT-trial (pemafibraat)



Triglyceride level, measured			
Baseline — mg/dl	273 (227 to 342)	269 (226 to 338)	
4 Mo — mg/dl	189 (143 to 253)	254 (193 to 341)	
Median change from baseline — %	−31.1 (−48.9 to −9.6)	−6.9 (−28.4 to 20.2)	−26.2 (−28.4 to −24.10)

Table 2. (Continued.)

Variable	Pemafibrate (N=5240)	Placebo (N=5257)	Treatment Effect†
	Median Value (IQR)		Mean % Change (95% CI)
Apolipoprotein B level, measured			
Baseline — mg/dl	90 (75 to 108)	89 (74 to 107)	
4 Mo — mg/dl	93 (77 to 111)	87 (73 to 105)	
Median change from baseline — %	3.2 (−12.0 to 19.7)	−1.6 (−13.4 to 11.8)	4.8 (3.8 to 5.8)

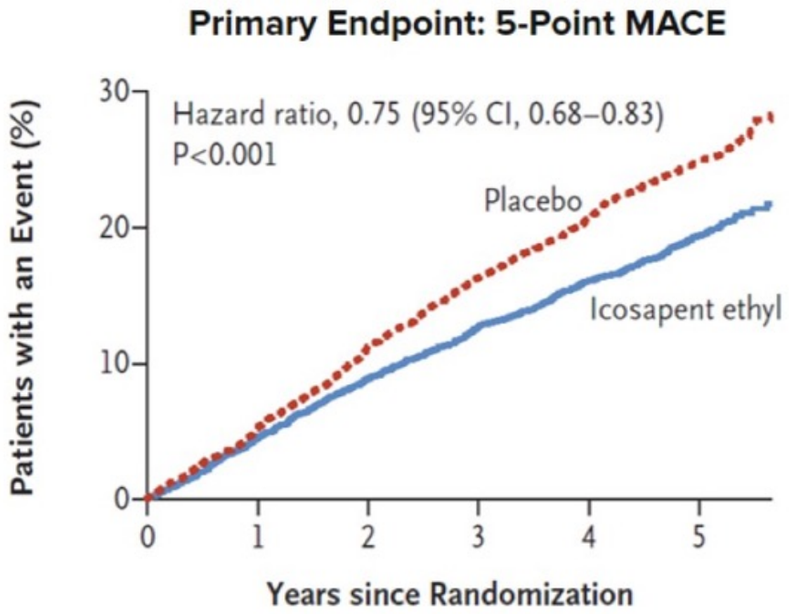
NEJM nov 2022

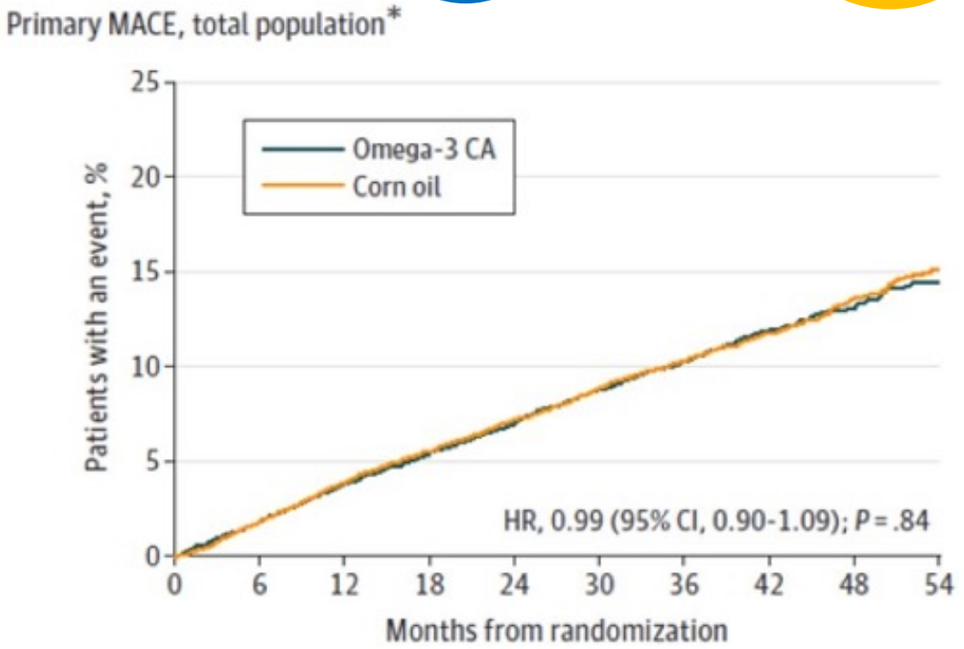
Omega-3 and Triglycerides

REDUCE-IT Trial
Efficacy of EPA (4 g/d)

STRENGTH Trial
Efficacy of EPA+DHA (4 g/d)

Biomarker	LDL-C	TG	nonHDL	apoB	LDL-C	TG	nonHDL	apoB
Change with R/	-7.0	-46.1	-17.2	-8.9	+1.0	-44.3	-8.2	-0.4





*Composite of CV death, nonfatal MI, or nonfatal stroke.

Bhatt DL, et al. N Engl J Med. 2019;380:11-22.

Nicholls SJ, et al. JAMA. 2020;324:2268-2280.

A proprietary purification process of Icosapent ethyl

Majority of Fish Oil Supplements*
EPA 18%
DHA 12%

EPA 26%
DHA 16%

EPA 65%
DHA <5%

Icosapent-Ethyl
≥EPA 96%
DHA Not Detected

IPE PURITY

**Based on fish oil capsules containing 18% EPA, 12% DHA, and 70% other undisclosed fatty acids*

DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; IPE: icosapent ethyl.
Data on file (VAS-01751).

BEHANDELING van HYPERTRIGLYCERIDEMIE

Recommendations	Class	Level
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia (TG >2.3 mmol/L (>200 mg/dL)).	I	B
In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2 g/day) should be considered in combination with statin.	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

Catapano A, *et al. Eur Heart J*. 2016; 37, 2999-3058 - Mach F, *et al. Eur Heart J*. 2019; 0:1-78

Besluit

Hypertriglyceridemie

- Komt voor bij 25% van de patiënten (nuchter)

- Genetische oorzaken: weinig voorkomend, maar denk eraan bij familiaal voorkomen op jonge leeftijd en indien pancreatitis op jonge leeftijd

- Secundaire oorzaken: zeer frequent, verband met metabole problemen en geneesmiddelen

- Leefstijl interventie is essentieel en vormt de basis van de behandeling
  - Gewicht: -5 à 10 % (zelfs -15 %) → daling TG met 50 %
  - Diabetes: metformine, GLP1-analogen, SGLT2i
  - Fysieke activiteit: 5x 30 min per week

- Geneesmiddelen: **apoB is the target** !!
  - statine is ALTIJD eerste keuze (+ ezetimibe)
  - fibraat (vooral ter preventie van acute pancreatitis)
  - in de toekomst omega-3 (4g EPA/d) ?