Een patiënt met hypertriglyceridemie. Wat zijn de behandelmogelijkheden?

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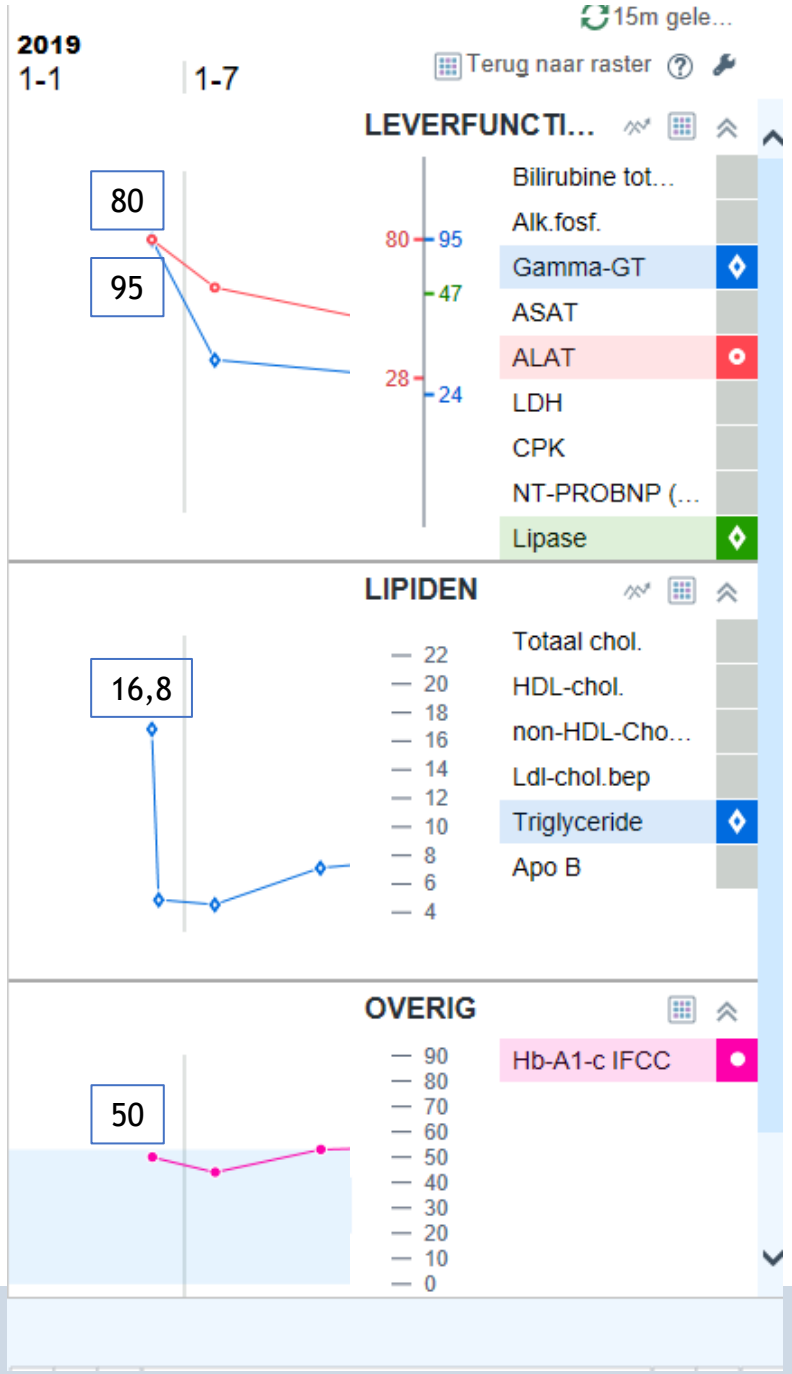
Internist-vasculair geneeskundige, Amsterdam UMC

Nederlandse Lipiden Academie

Casus: Dhr. K 44 jaar

- Reden van komst: hypertriglyceridemie (TG 16,8)

- VG/ 2010 Status na hodgkin-lymfoom,
  - waarvoor ABVD kuren en RT mediastinum. Complete remissie.
- 2010 Diabetes (35 jaar) met microalbuminurie,
  - waarvoor metformine 2 x 500, insuline 50 Eh/24 uur (soms meer)
- 2010 Hypertensie
- 2017 Milde testosterondeficiëntie,
  - waarvoor testosterongel



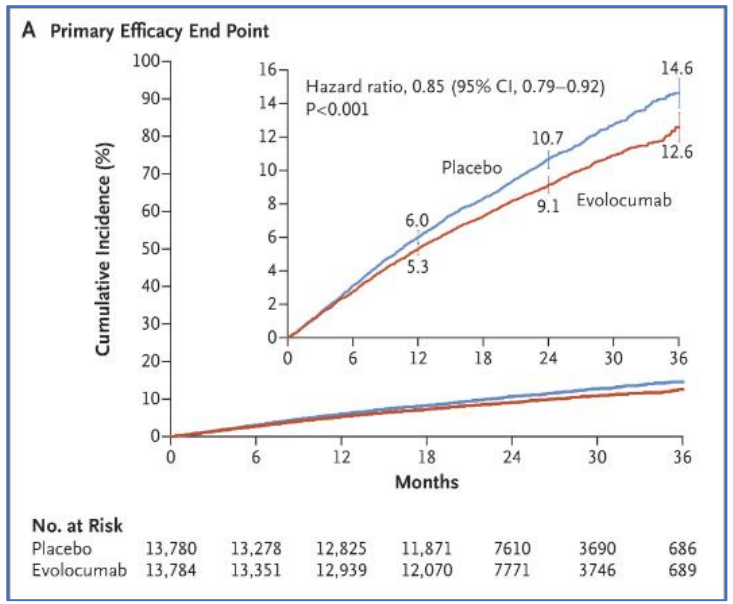
Vraag

Gebruikt u het triglyceridegehalte voor de inschatting van het CV-risico?

A. Ja
B. Nee
C. Alleen voor pancreatitis risico

Data van RCT's

Residuaal asHVZ risico zelfs bij patiënten met optimale LDL-C-behandeling

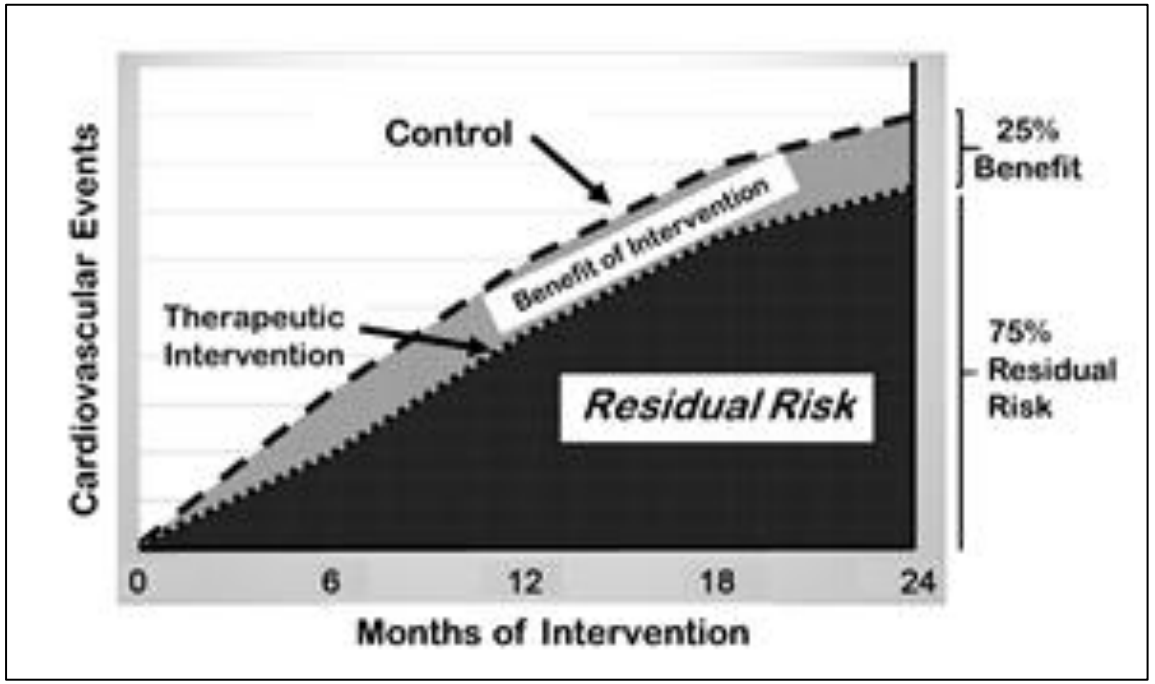


LDL 2.4 mmol/L

LDL ↓ 60% p<0.001

LDL 0.8 mmol/L

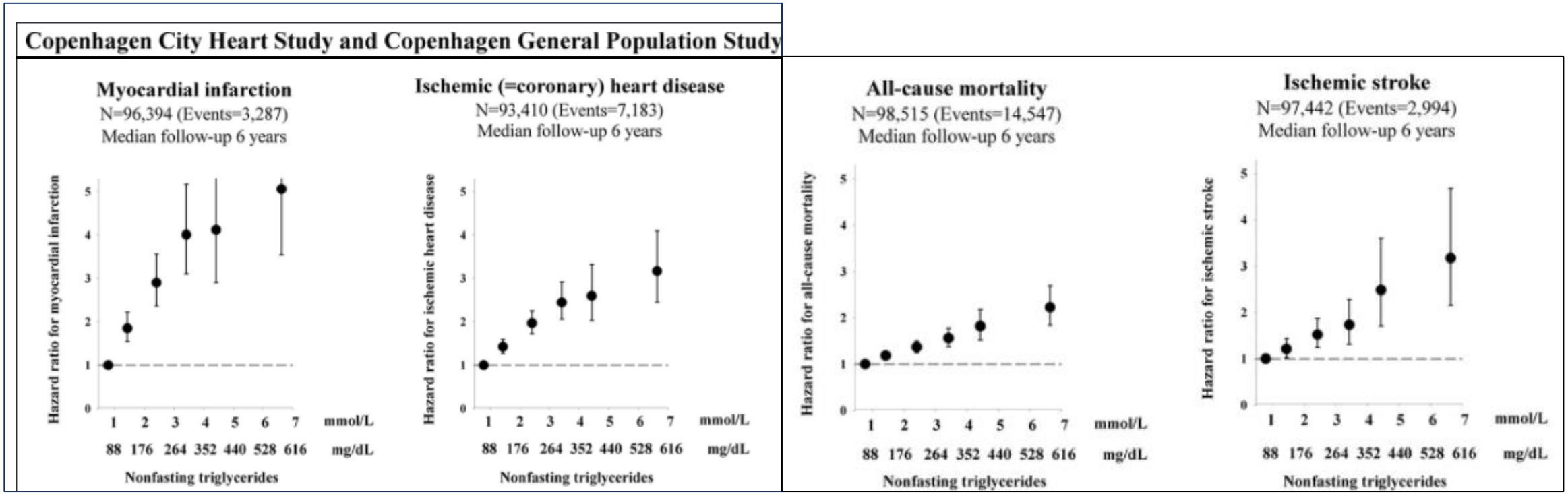
Primaire eindpunt: CV dood, Myocardinfarct, CVA, hospitalisatie voor ACS, coronaire revascularisatie[1]



1. Sabatine et al, Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease, N Engl J Med 2017; 376:1713-1722
2. Schade, D. and Eaton, R. (2018) Residual Cardiovascular Risk—Is Inflammation the Primary Cause?. World Journal of Cardiovascular Diseases, 8, 59-69

Observationele data

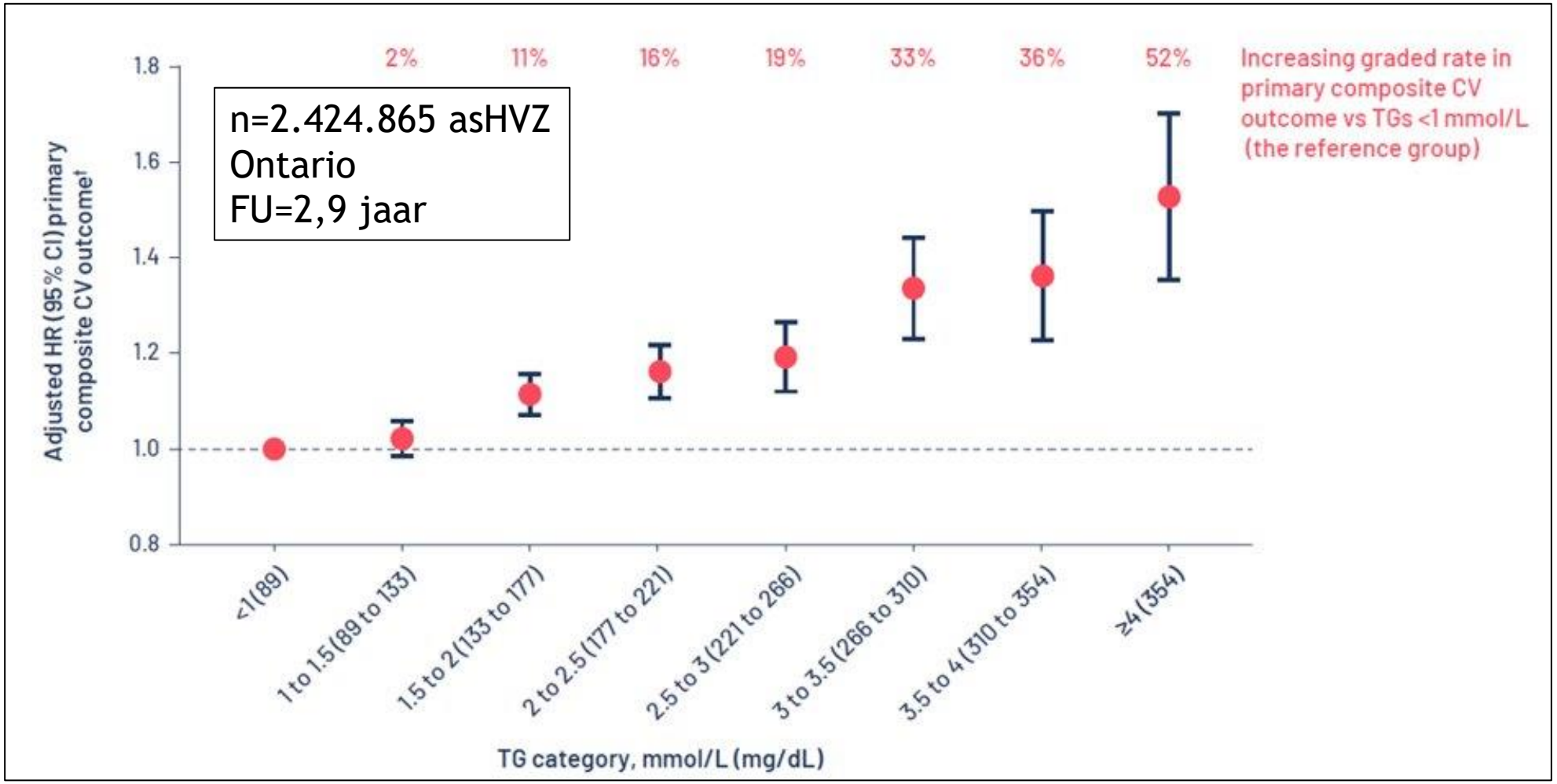
Verhoogde TG-waarden geassocieerd met verhoogd risico op asHVZ



Nordestgaard, Circ Res 2016

Observationele data

Residuaal asHVZ risico bij patiënten op statine met verhoogde TG-levels

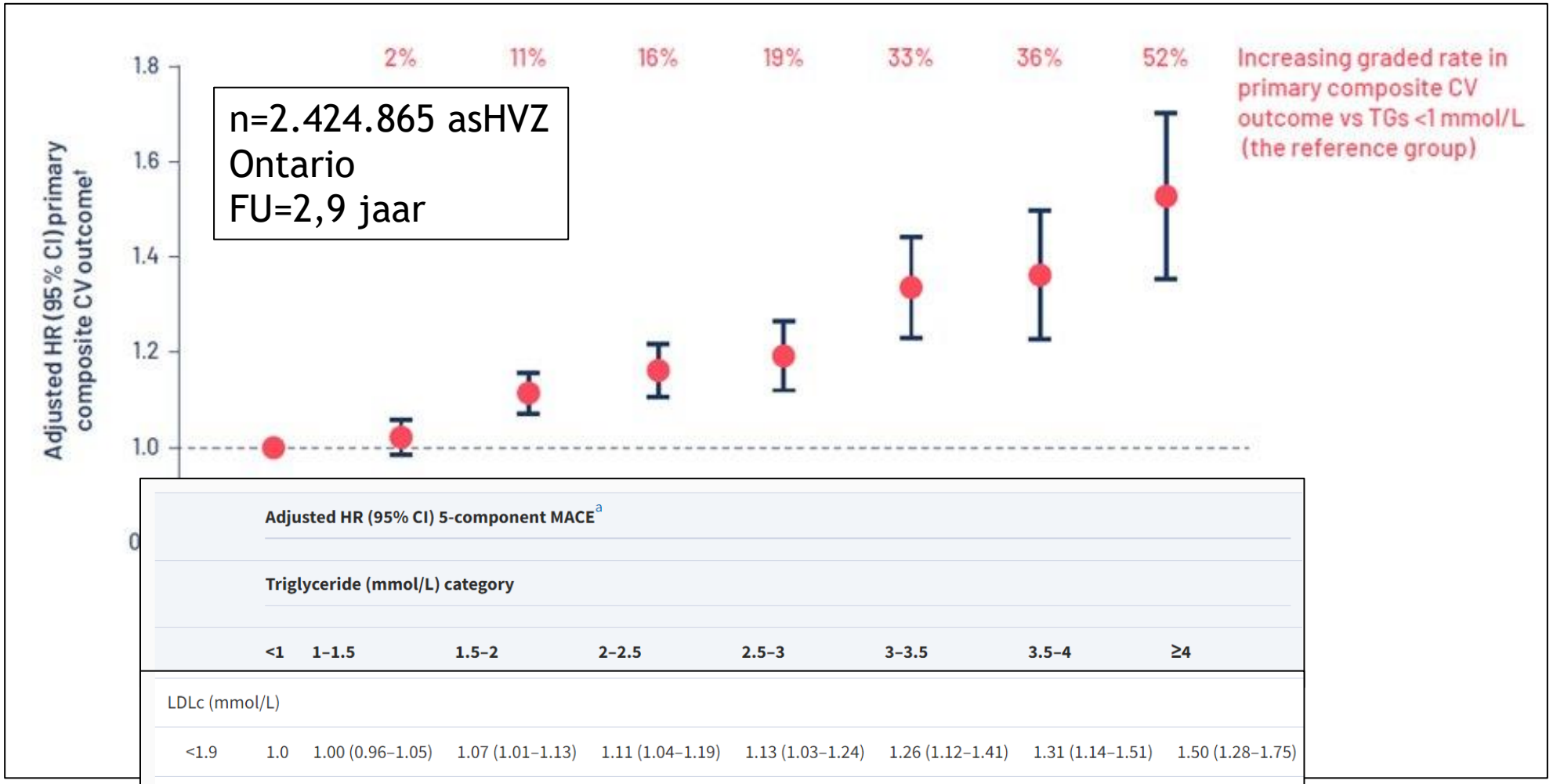


Primaire eindpunt: CV dood, Myocardinfarct, CVA, hospitalisatie voor ACS, coronaire revascularisatie

Lawler PR, Kotrri G, Koh M, et al., 2020

Observationele data

Residuaal asHVZ risico bij patiënten op statine met verhoogde TG-levels



	Adjusted HR (95% CI) 5-component MACE[a]							
	Triglyceride (mmol/L) category							
	<1	1–1.5	1.5–2	2–2.5	2.5–3	3–3.5	3.5–4	≥4
LDLc (mmol/L)								
<1.9	1.0	1.00 (0.96–1.05)	1.07 (1.01–1.13)	1.11 (1.04–1.19)	1.13 (1.03–1.24)	1.26 (1.12–1.41)	1.31 (1.14–1.51)	1.50 (1.28–1.75)
≥1.9	1.0	1.07 (1.02–1.13)	1.20 (1.14–1.27)	1.27 (1.19–1.36)	1.33 (1.22–1.44)	1.50 (1.35–1.67)	1.49 (1.30–1.71)	1.65 (1.40–1.94)

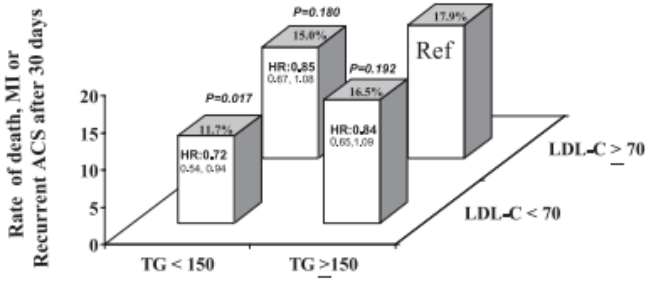
Primaire e ie

Lawler PR, Kotrri G, Koh M, et al., 2020

Data van RCT's

Nuchtere TG-waarden voorspellen recidief ischemische events in asHVZ patiënten met goed behandelende LDL-C-waarden

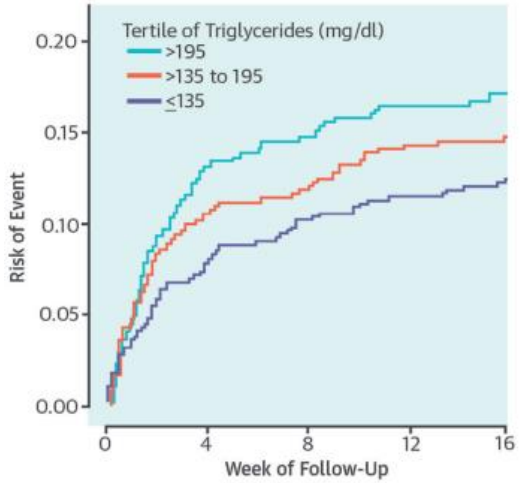
Risk of recurrent events using selected cut-points of LDL-C and TG
mediaan LDL 1,8



PROVE-IT [1]

n= 4.162
Pat: ACS
Atorvastatine 80 vs pravastatine 40
FU=30 dagen

Short term risk after ACS
mediaan LDL 1,6

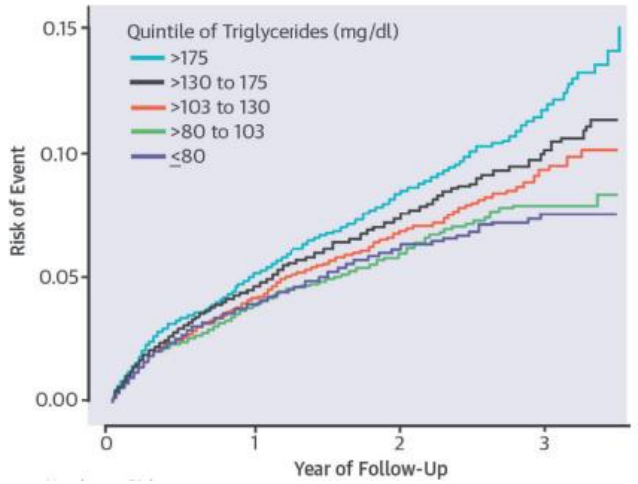


MIRACL[2]

n= 1.501
Pat: ACS

Dalcetrapib vs placebo
FU=31 maanden

Long term risk after ACS
mediaan LDL 1,9

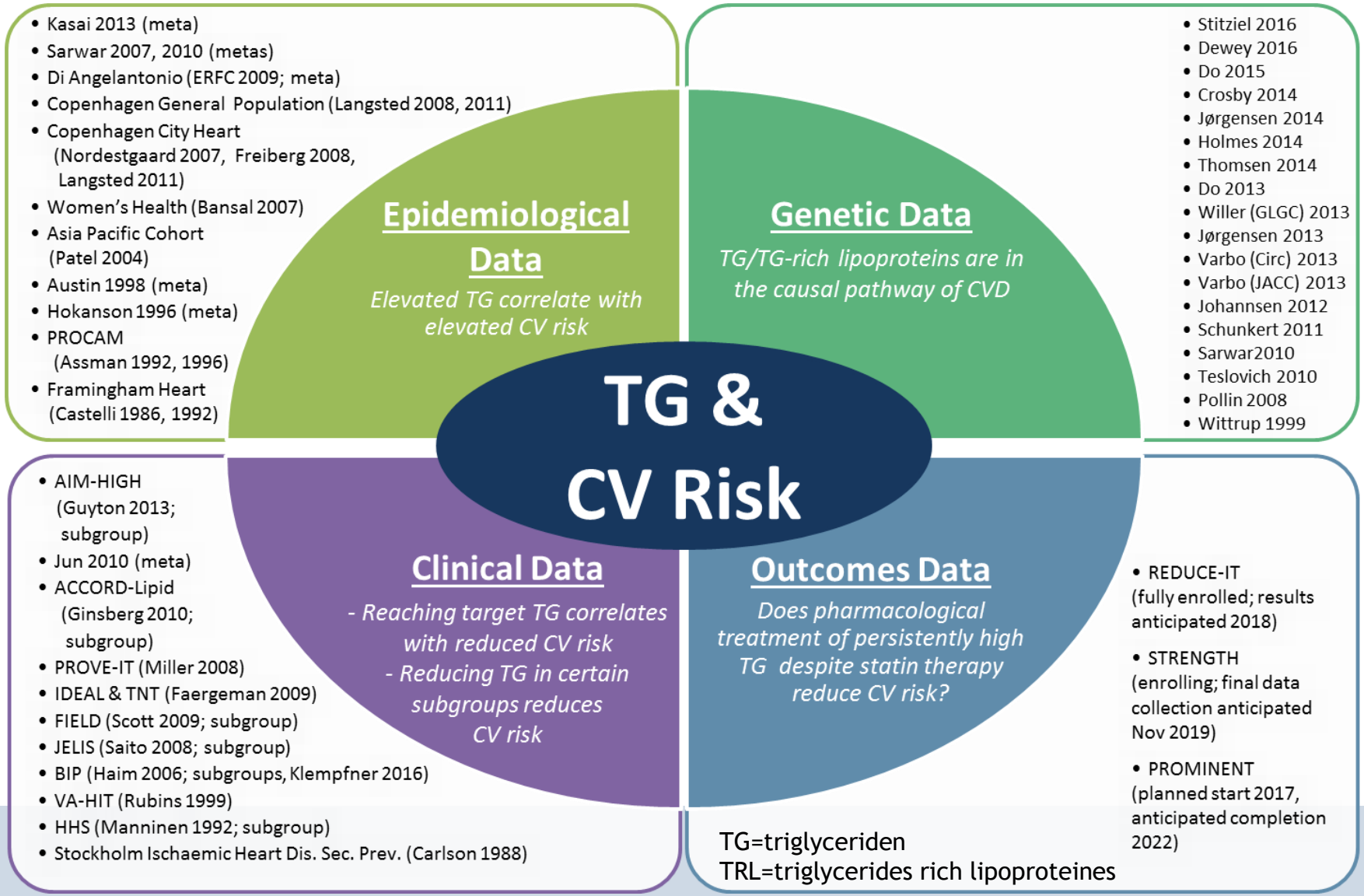


DAL-OUTCOMES [2]

n= 15.817
Pat: ACS
Atorvastatine 80
FU=3,5 jaar

1. Miller M et al. JACC 2008;51(07). 2. Schwartz G et al. JACC 2015;65(21).

TG / TRL mogelijk causaal betrokken bij asHVZ en derhalve belangrijk behandeldoel

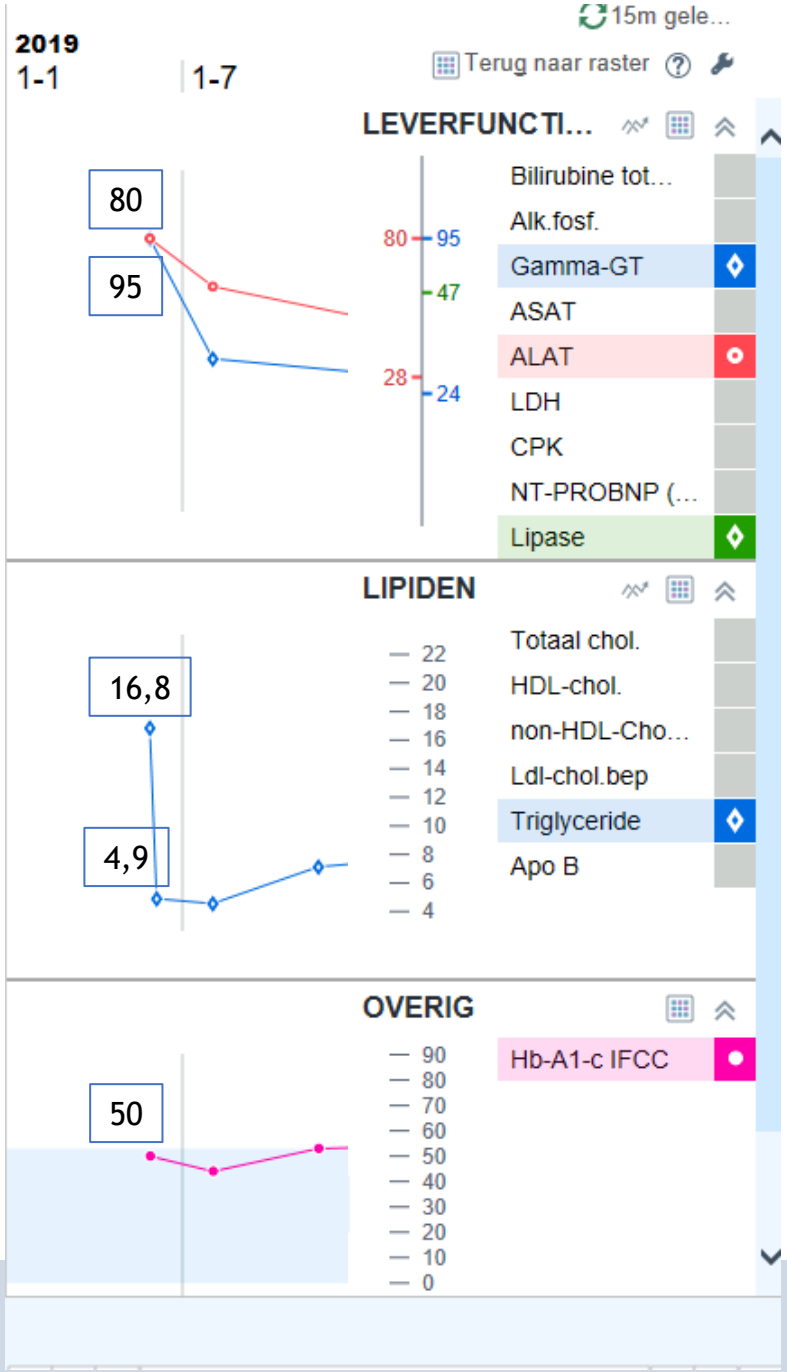


Vraag

Wat gaat u als eerste doen in het geval van de casus van dhr. K?

A. Water en brood
B. Start fibraten
C. Start visolie

Water en brood geeft sterke daling na 1 WEEK



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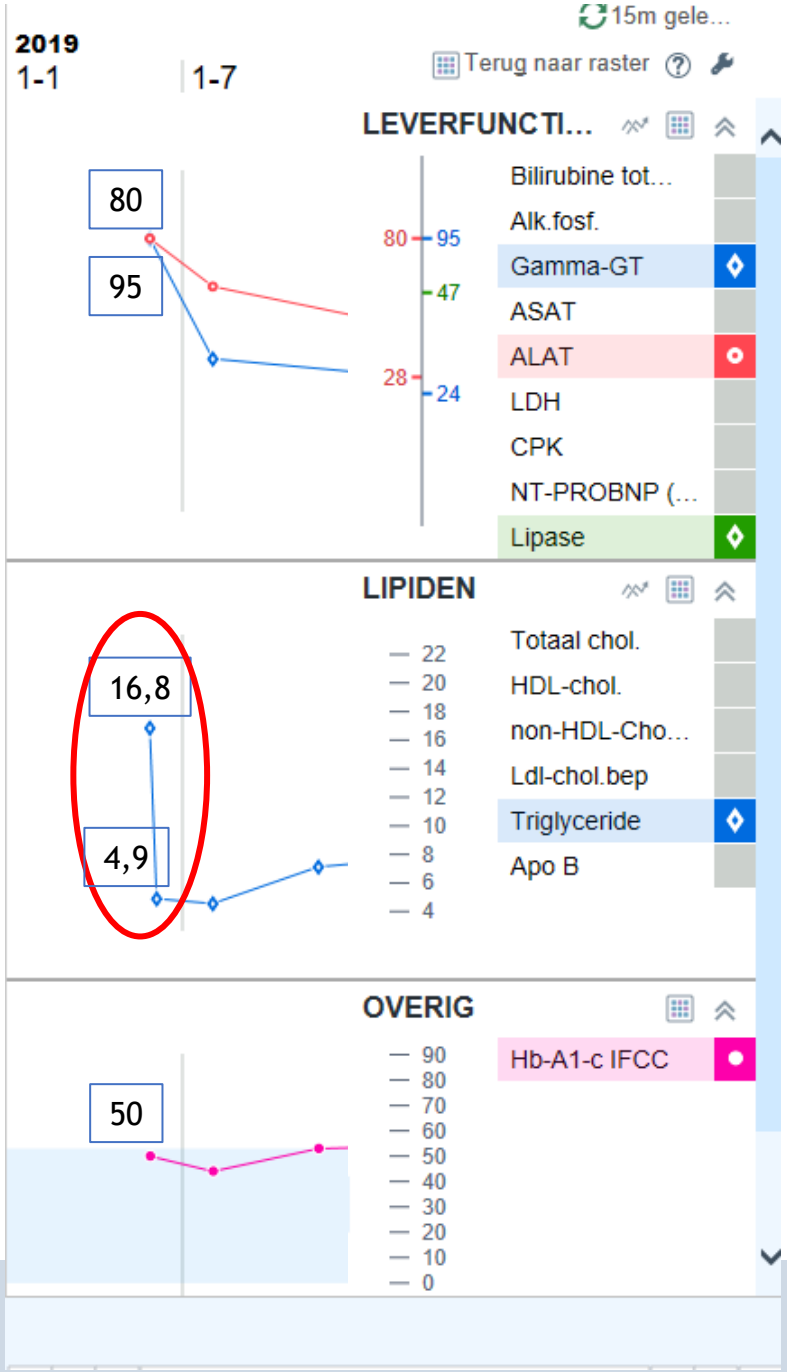


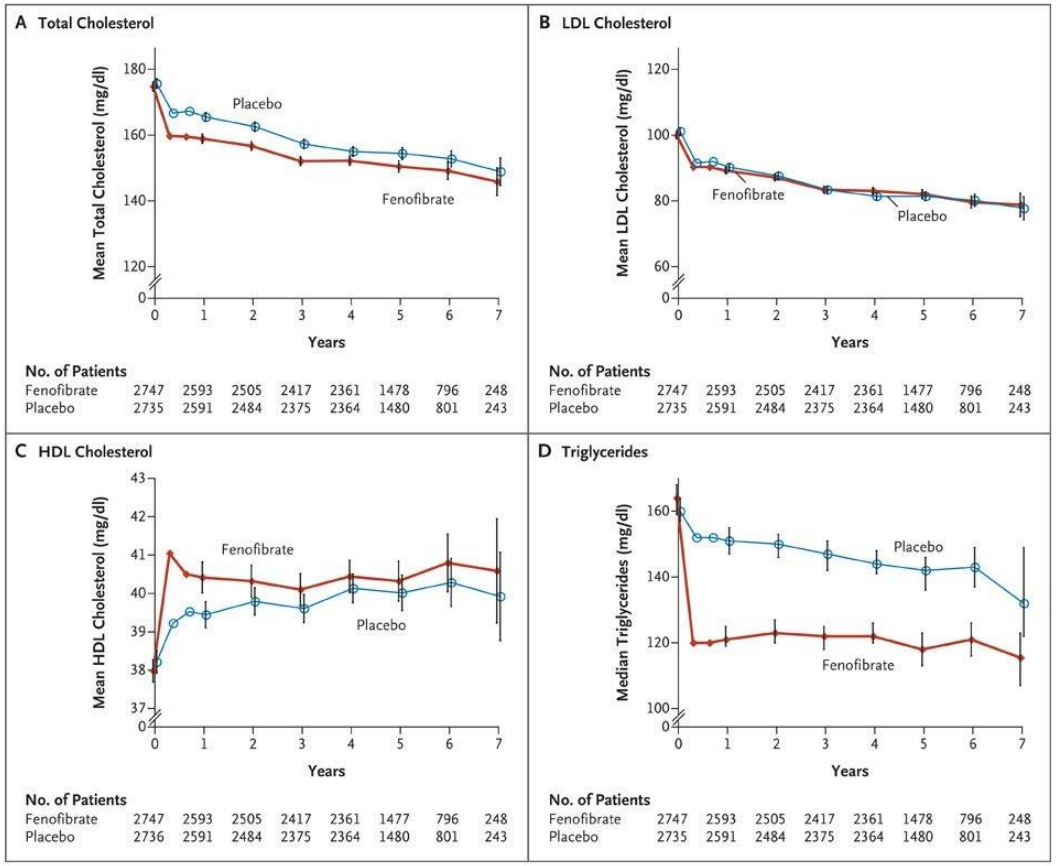
Amsterdam UMC
University Medical Centers

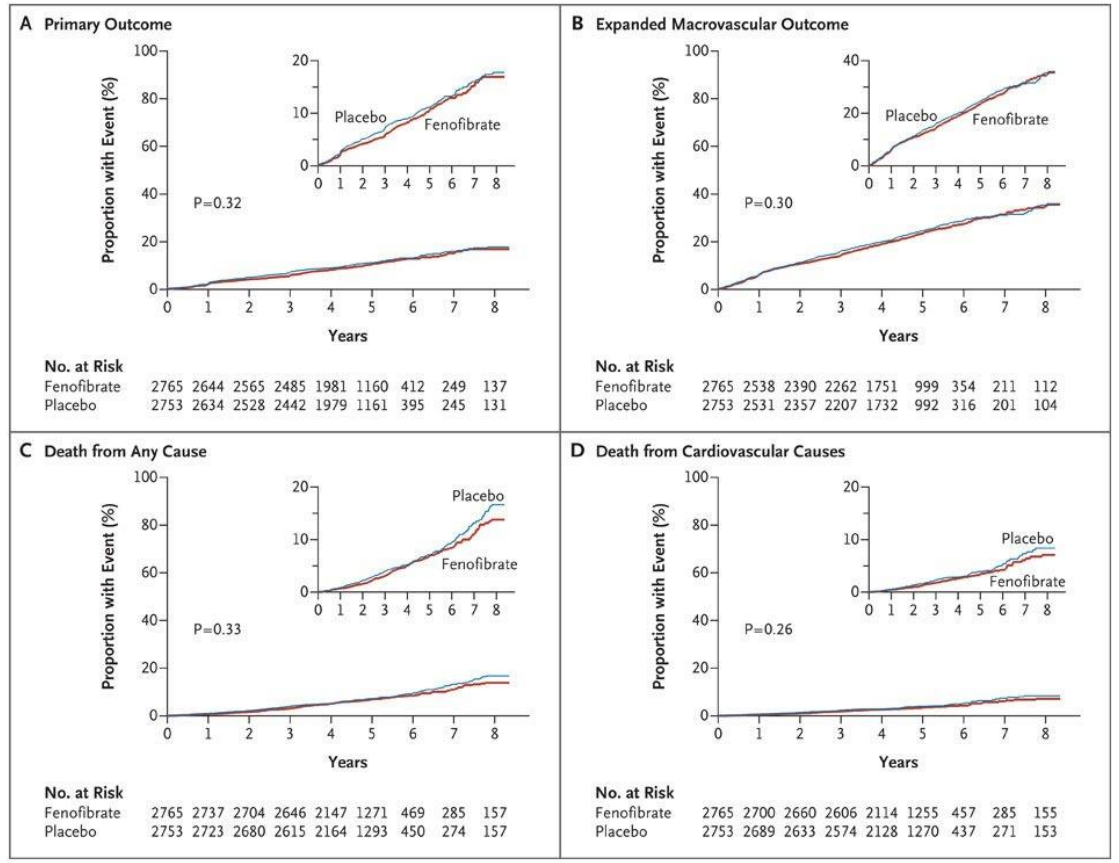
Fibraten

1ste on top of statin OUTCOME trial (ACCORD)

Fenofibrate/placebo in diabetes type 2

n=5518
Fenofibrate vs placebo
achtergrond simvastatine
FU=4,7 jaar





Ginsberg HN. Et al. NEJM 2010

1ste on top of statin OUTCOME trial (ACCORD)

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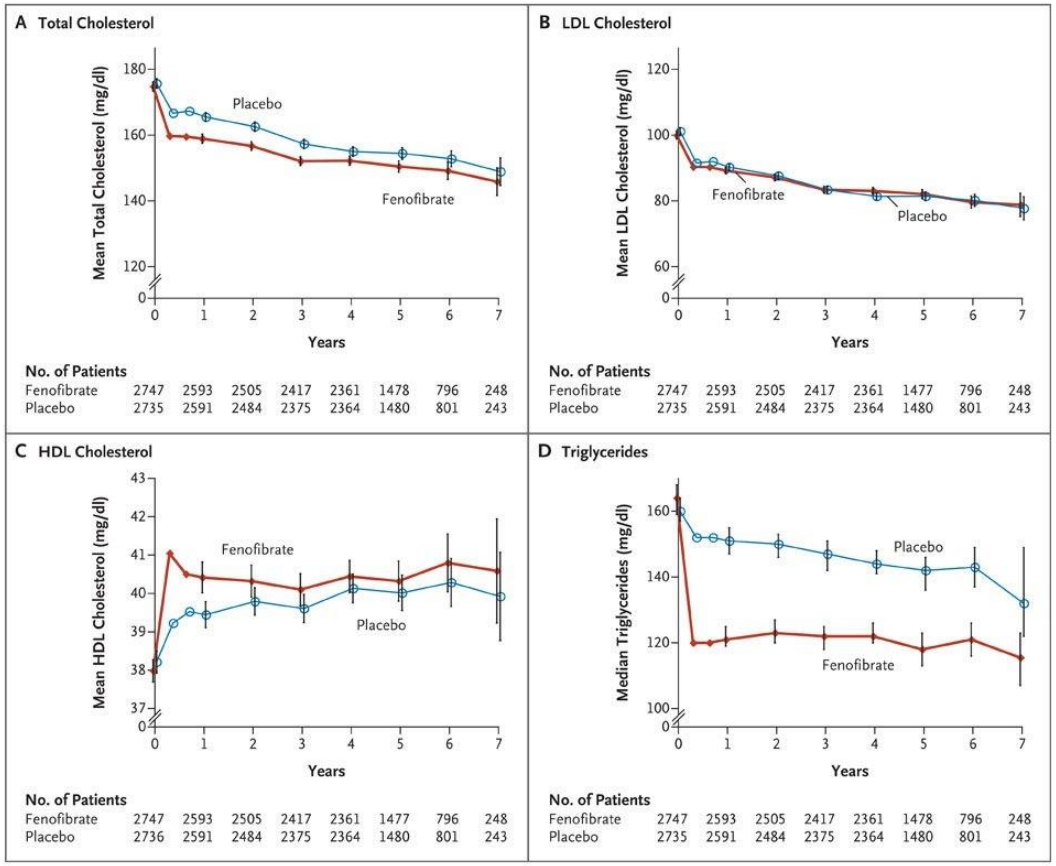
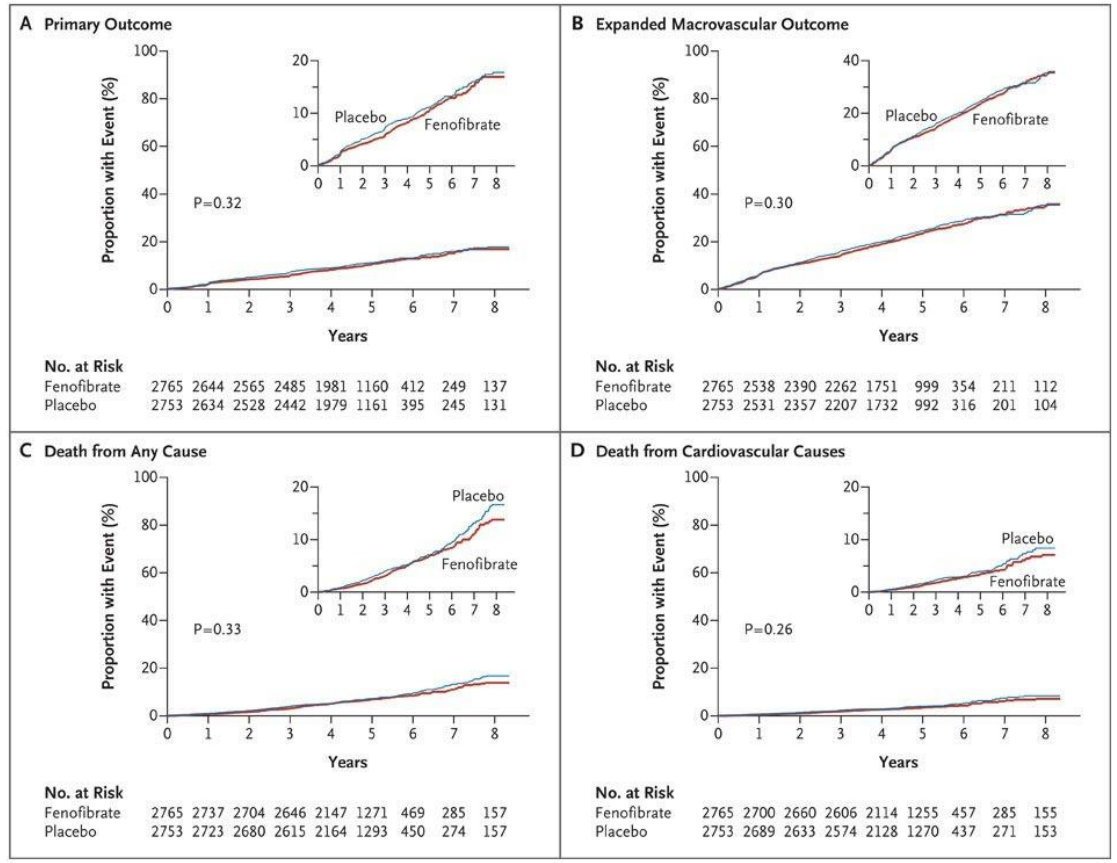
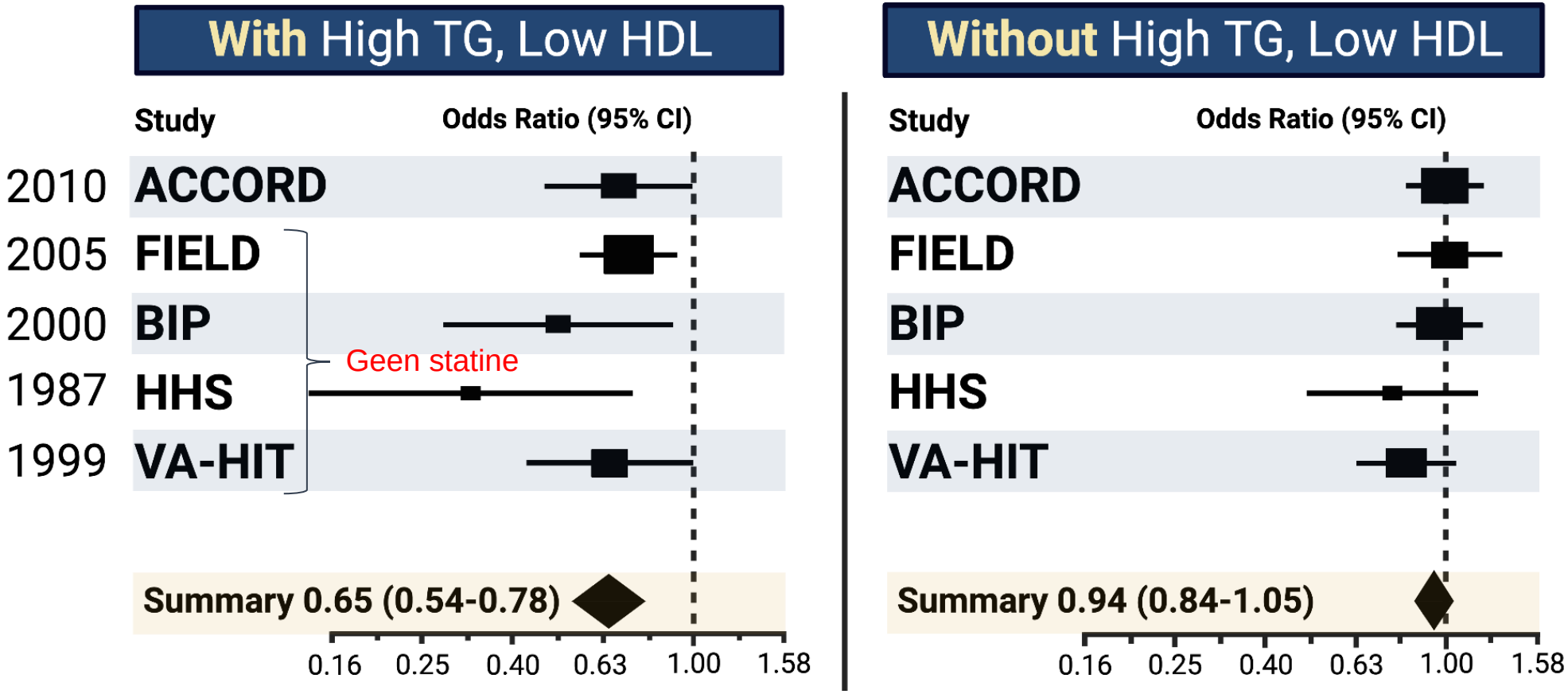




Geen effect van fibraten on top of statine voor CV/all cause dood, niet fataal MI/CVA

Ginsberg HN. Et al. NEJM 2010

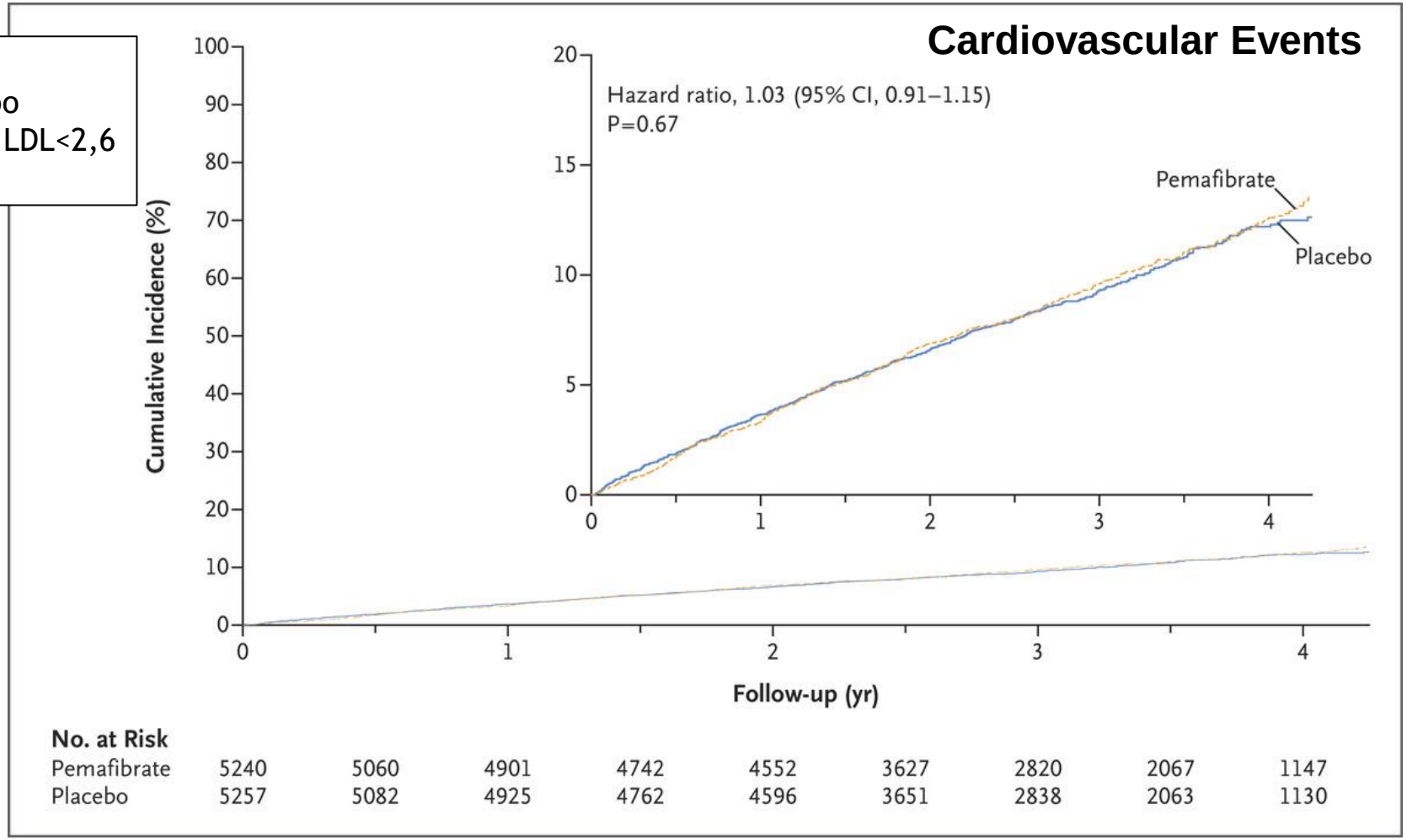
Fibraten on top of statine geen effect, tenzij dyslipidemie?



Sacks FM, NEJM 2010

PROMINENT: fibraat on top of statine in patiënten met dyslipidemie

N=10497 DM2
Pemafibrate vs placebo
Achtergond statine of LDL<2,6
FU=3,4 jaar



A Das Pradhan et al. N Engl J Med 2022;387:1923-1934.

Effect fibraat en intensivering DM medicatie

Amsterdam UMC
University Medical Centers

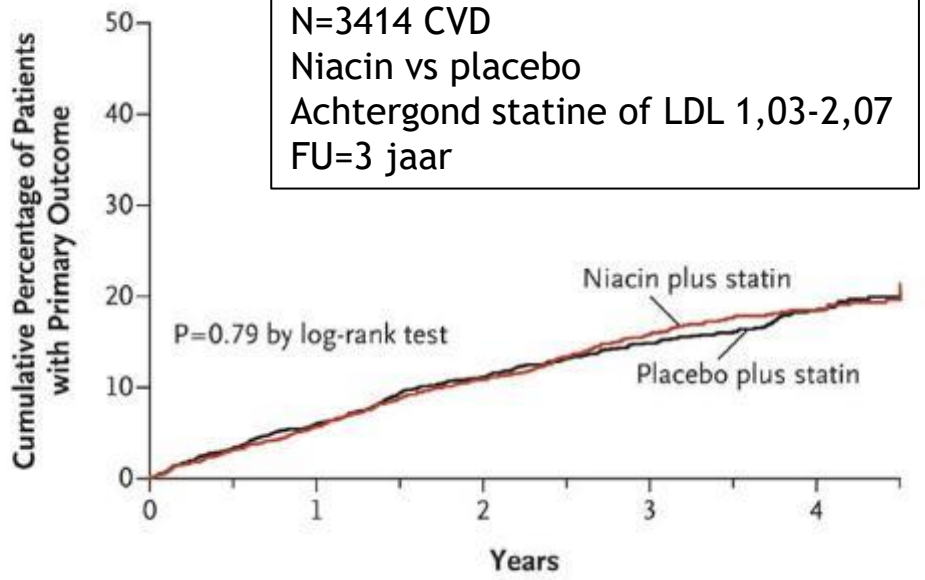
Nicotinezuur

Nicotinezuur RCT's on top of statine

N=25673 CVD
Niacin+laropiprant vs placebo
Achtergond statine
FU=3,9 jaar

Niacine

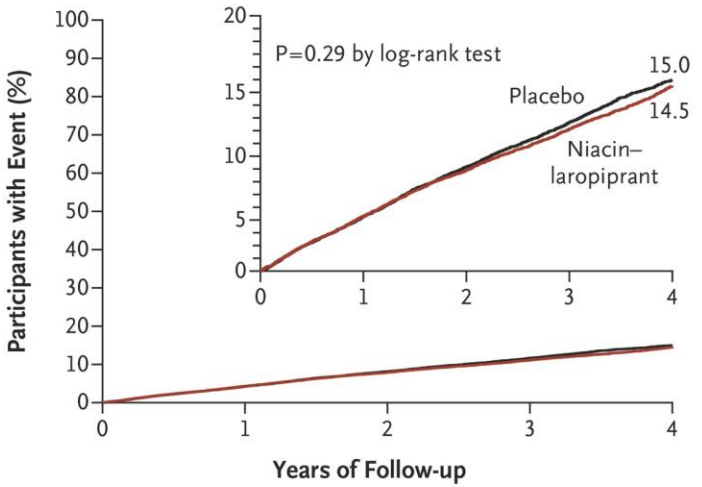
N=3414 CVD
Niacin vs placebo
Achtergond statine of LDL 1,03-2,07
FU=3 jaar



No. at Risk					
Placebo plus statin	1696	1581	1381	910	436
Niacin plus statin	1718	1606	1366	903	428

The AIM-HIGH Investigators. N Engl J Med 2011;365:2255-2267

Niacine/Laropiprant (antagoneert flushes)



No. at Risk					
Niacin–laropiprant	12,838	12,232	11,517	7672	4978
Placebo	12,835	12,247	11,523	7643	5036
Benefit per 1000 participants assigned to niacin–laropiprant		0±3	3±3	5±5	5±7

The HPS2-THRIVE Collaborative Group. N Engl J Med 2014;371:203-212

Vraag

Gebruikt u visolie voor de behandeling van verhoogde triglyceriden?

A. Nee, daar heb ik geen ervaring mee bij patiënten
B. Nee, want studies hebben nog geen overtuigend effect laten zien
C. Ja, maar dan alleen wanneer verschillende vetzuren worden gecombineerd
D. Ja, maar dan alleen indien 1 sterk gezuiverd vetzuur wordt gebruikt

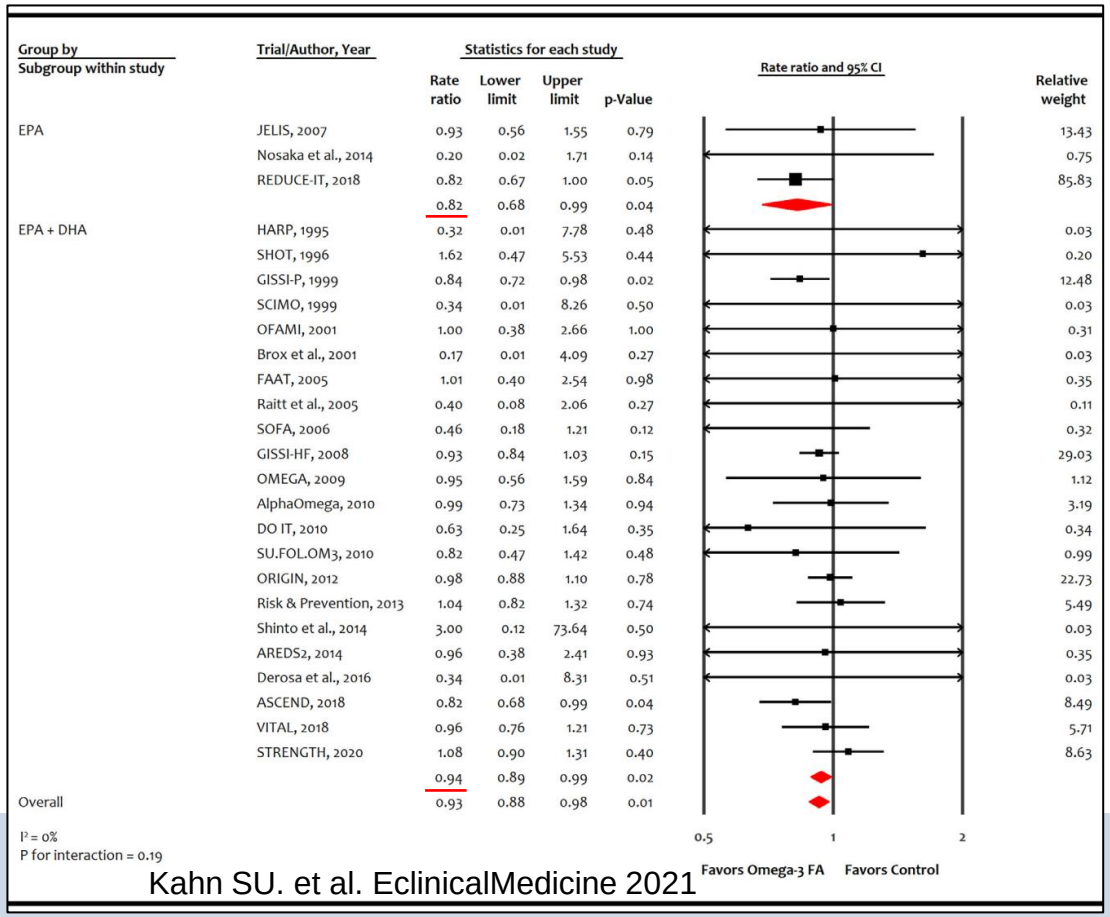
Omga-3-vetzuren

EPA = Eicosapentaenoidezuur → IPE = Icosapent ethyl (gezuiverd ethyl ester van EPA)
DHA = Docosahexaenoidezuur

beide omega-3-vetzuren van vette semi-zoetwatervissen zoals zalm

Omega-3-vetzuren

CVD mortaliteit

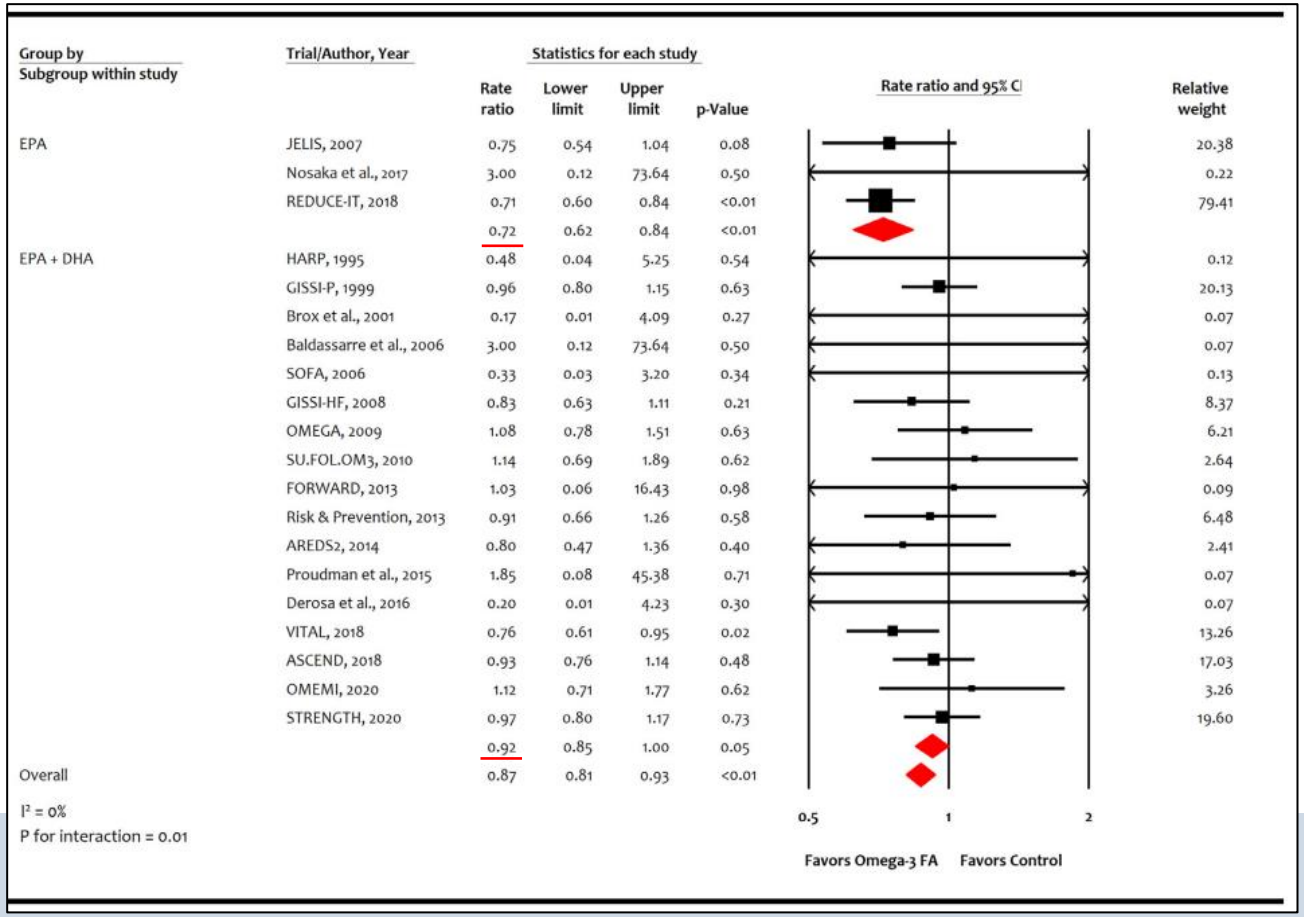


Group by Subgroup within study	Trial/Author, Year	Rate ratio	Lower limit	Upper limit	p-Value	Relative weight
EPA	JELIS, 2007	0.93	0.56	1.55	0.79	13.43
	Nosaka et al., 2014	0.20	0.02	1.71	0.14	0.75
	REDUCE-IT, 2018	0.82	0.67	1.00	0.05	85.83
		0.82	0.68	0.99	0.04	
EPA + DHA	HARP, 1995	0.32	0.01	7.78	0.48	0.03
	SHOT, 1996	1.62	0.47	5.53	0.44	0.20
	GISSI-P, 1999	0.84	0.72	0.98	0.02	12.48
	SCIMO, 1999	0.34	0.01	8.26	0.50	0.03
	OFAMI, 2001	1.00	0.38	2.66	1.00	0.31
	Brox et al., 2001	0.17	0.01	4.09	0.27	0.03
	FAAT, 2005	1.01	0.40	2.54	0.98	0.35
	Raitt et al., 2005	0.40	0.08	2.06	0.27	0.11
	SOFA, 2006	0.46	0.18	1.21	0.12	0.32
	GISSI-HF, 2008	0.93	0.84	1.03	0.15	29.03
	OMEGA, 2009	0.95	0.56	1.59	0.84	1.12
	AlphaOmega, 2010	0.99	0.73	1.34	0.94	3.19
	DO IT, 2010	0.63	0.25	1.64	0.35	0.34
	SU.FOL.OM3, 2010	0.82	0.47	1.42	0.48	0.99
	ORIGIN, 2012	0.98	0.88	1.10	0.78	22.73
	Risk & Prevention, 2013	1.04	0.82	1.32	0.74	5.49
	Shinto et al., 2014	3.00	0.12	73.64	0.50	0.03
	AREDS2, 2014	0.96	0.38	2.41	0.93	0.35
	Derosa et al., 2016	0.34	0.01	8.31	0.51	0.03
	ASCEND, 2018	0.82	0.68	0.99	0.04	8.49
	VITAL, 2018	0.96	0.76	1.21	0.73	5.71
	STRENGTH, 2020	1.08	0.90	1.31	0.40	8.63
		0.94	0.89	0.99	0.02	
Overall		0.93	0.88	0.98	0.01	

I^2 = 0%
P for interaction = 0.19

Kahn SU. et al. EclinicalMedicine 2021

Niet fataal MI

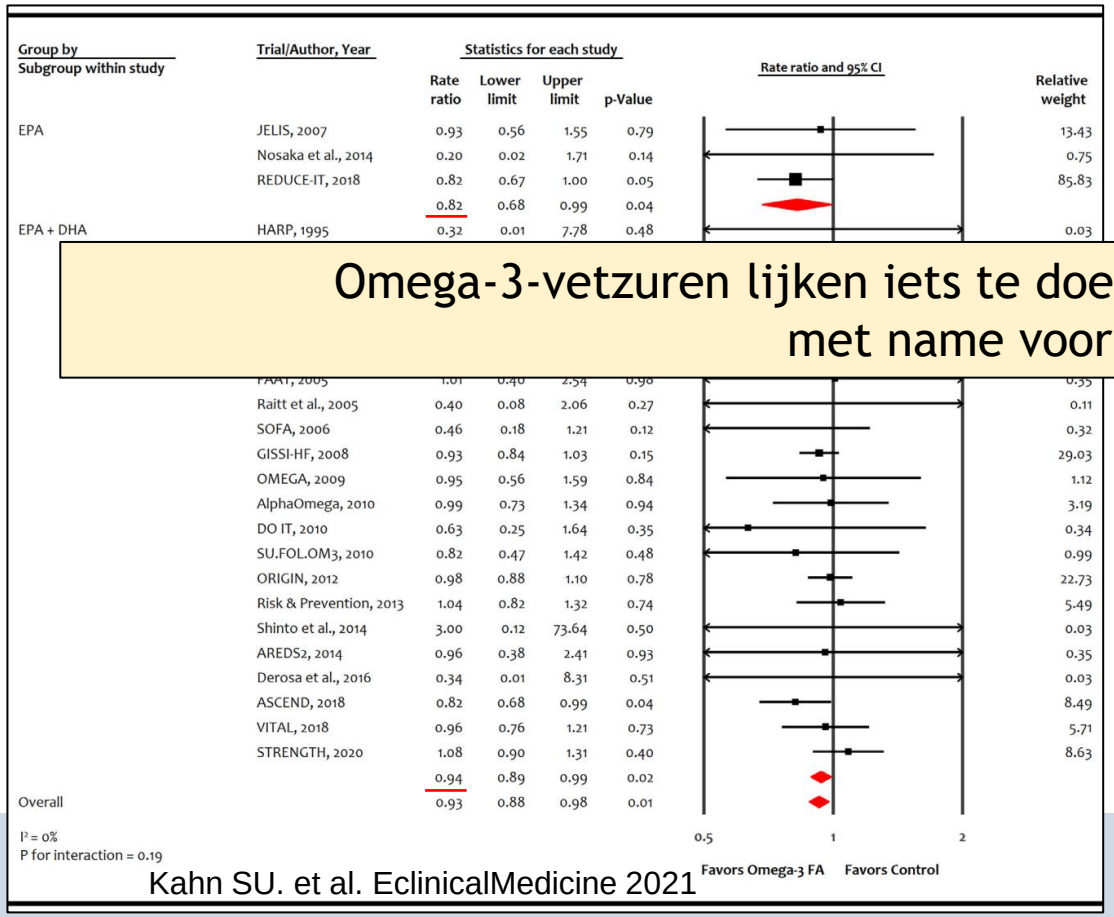


Group by Subgroup within study	Trial/Author, Year	Rate ratio	Lower limit	Upper limit	p-Value	Relative weight
EPA	JELIS, 2007	0.75	0.54	1.04	0.08	20.38
	Nosaka et al., 2017	3.00	0.12	73.64	0.50	0.22
	REDUCE-IT, 2018	0.71	0.60	0.84	<0.01	79.41
		0.72	0.62	0.84	<0.01	
EPA + DHA	HARP, 1995	0.48	0.04	5.25	0.54	0.12
	GISSI-P, 1999	0.96	0.80	1.15	0.63	20.13
	Brox et al., 2001	0.17	0.01	4.09	0.27	0.07
	Baldassarre et al., 2006	3.00	0.12	73.64	0.50	0.07
	SOFA, 2006	0.33	0.03	3.20	0.34	0.13
	GISSI-HF, 2008	0.83	0.63	1.11	0.21	8.37
	OMEGA, 2009	1.08	0.78	1.51	0.63	6.21
	SU.FOL.OM3, 2010	1.14	0.69	1.89	0.62	2.64
	FORWARD, 2013	1.03	0.06	16.43	0.98	0.09
	Risk & Prevention, 2013	0.91	0.66	1.26	0.58	6.48
	AREDS2, 2014	0.80	0.47	1.36	0.40	2.41
	Proudman et al., 2015	1.85	0.08	45.38	0.71	0.07
	Derosa et al., 2016	0.20	0.01	4.23	0.30	0.07
	VITAL, 2018	0.76	0.61	0.95	0.02	13.26
	ASCEND, 2018	0.93	0.76	1.14	0.48	17.03
	OMEMI, 2020	1.12	0.71	1.77	0.62	3.26
	STRENGTH, 2020	0.97	0.80	1.17	0.73	19.60
		0.92	0.85	1.00	0.05	
Overall		0.87	0.81	0.93	<0.01	

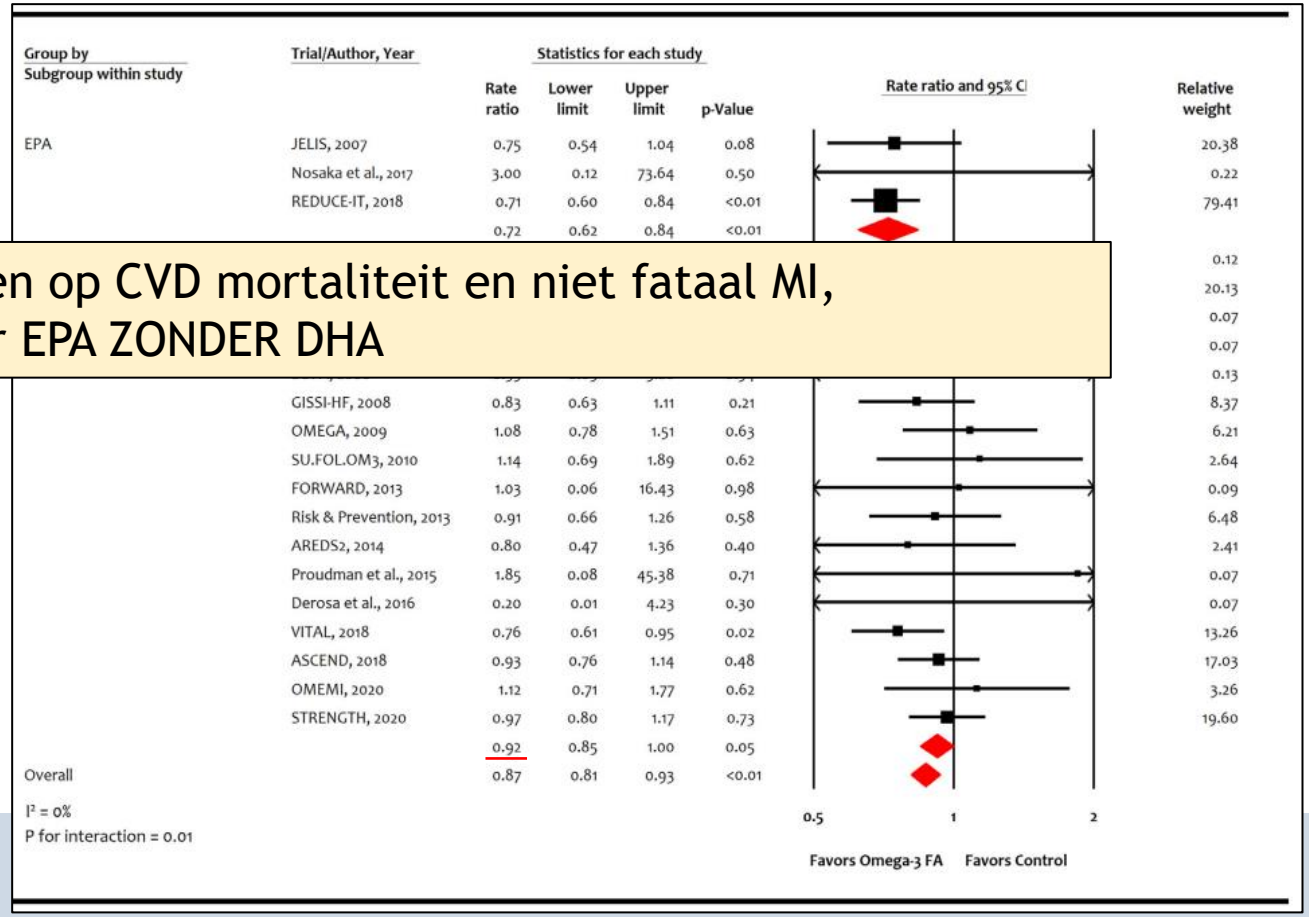
I^2 = 0%
P for interaction = 0.01

Omega-3-vetzuren

CVD mortaliteit



Niet fataal MI



Omega-3-vetzuren lijken iets te doen op CVD mortaliteit en niet fataal MI, met name voor EPA ZONDER DHA

Kahn SU. et al. EclinicalMedicine 2021

RCT CVOTs met omega-3 on top of statine in patiënten met *dyslipidemie*

CVOT	REDUCE-IT[1]	STRENGTH[2]
TEST THERAPY	EPA (EE)	EPA+DHA (FFA)
Dose	4 g/day	4 g/day
N	8,175	~13,000
POPULATION	CVD (70%) High CVD risk; DM+ (30%)	CVD (≥ 50%) High CVD risk (≤ 50%) • DM+ • Age+
Age (years)	≥ 45	≥ 18
TG (mmol/L) ***HDL-C (mmol/L)***	≥ 2,26 and < 5,65 none	≥ 2,03 and < 5,65 < 1,09 (men) / < 1,22 (women)
~ Follow-up (years)	4–6	3-5
Statin Use ***LDL-C (mmol/L)***	100% *and* >1,03 and ≤2,59	100% *and* < 2,59
PRIMARY EP	CVD†, nfMI, nfCVA, revasc, hACS	CVD†, nfMI, nfCVA, revasc, hACS
outcome	25% reduction	No benefit

[1]REDUCE-IT (REDUction of Cardiovascular Events with icosapent ethyl Intervention Trial), NEJM 2019;
[2]STRENGTH (Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia), JAMA 2020

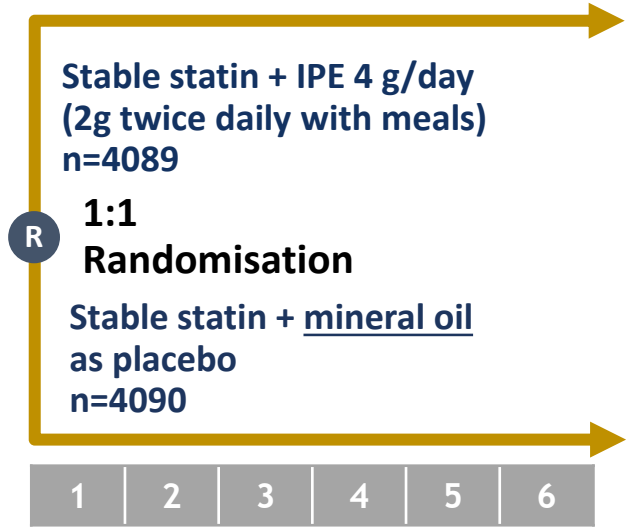
TG-verlagende therapieën hebben geen asHVZ voordeel aangetoond on top of statine

TG-Lowering Agent	Key Trials*	Met 1° MACE Endpoint?
Fibrates	ACCORD[1] FIELD[2] PROMINENT[3]	✕
Niacin	AIM-HIGH[4] HPS2-THRIVE[5]	✕
Prescription and supplement, EPA + DHA mixtures [DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid]	RISK & PREVENTION,[6] ORIGIN,[7] OMEGA,[8] ASCEND,[9] VITAL,[10] STRENGTH[11]	✕

1. ACCORD NEJM 2010; 2. FIELD Lancet 2005; 3. PROMINENT NEJM 2022; 4. AIM-HIGH NEJM 2011; 5. HPS2-THRIVE NEJM 2014; 6. Risk and Prevention Study Collaborative Group, NEJM 2013; 7. ORIGIN effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction), Circulation 2010; 9. ASCEND (A Study of Cardiovascular Events in Diabetes), NEJM 2018; 10. VITAL (Vitamin D and Omega-3 Trial), NEJM 2019; 11. STRENGTH (Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia), JAMA 2020

REDUCE-IT: Een multicenter, gerandomiseerde, dubbelblinde, placebo-gecontroleerde, CVOT

- 473 study centres
- 11 countries



Median trial follow-up: 4.9 years

IPE: icosapent ethyl

Primary Endpoint

Time to first 5-point composite MACE:

- CV death
- Non-fatal MI
- Non-fatal stroke
- Coronary revascularisation
- Hospitalisation for unstable angina

Key Secondary Endpoint

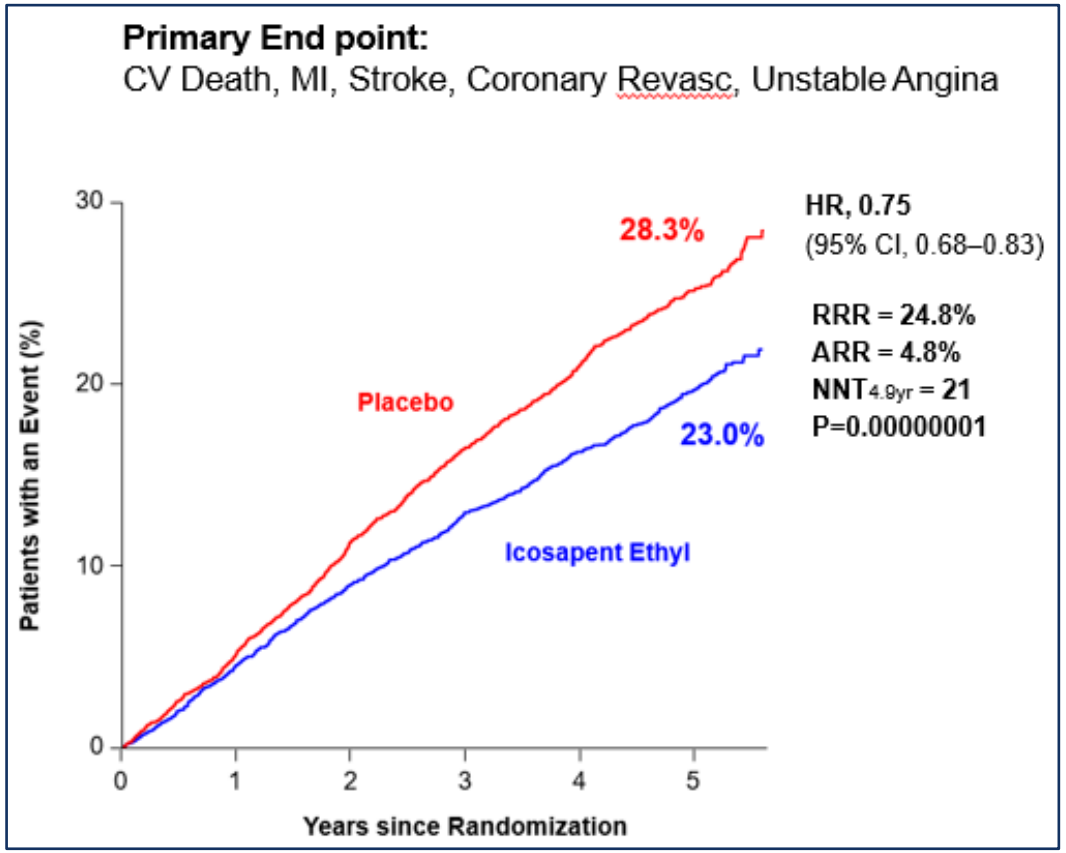
Time to first 3-point composite MACE:

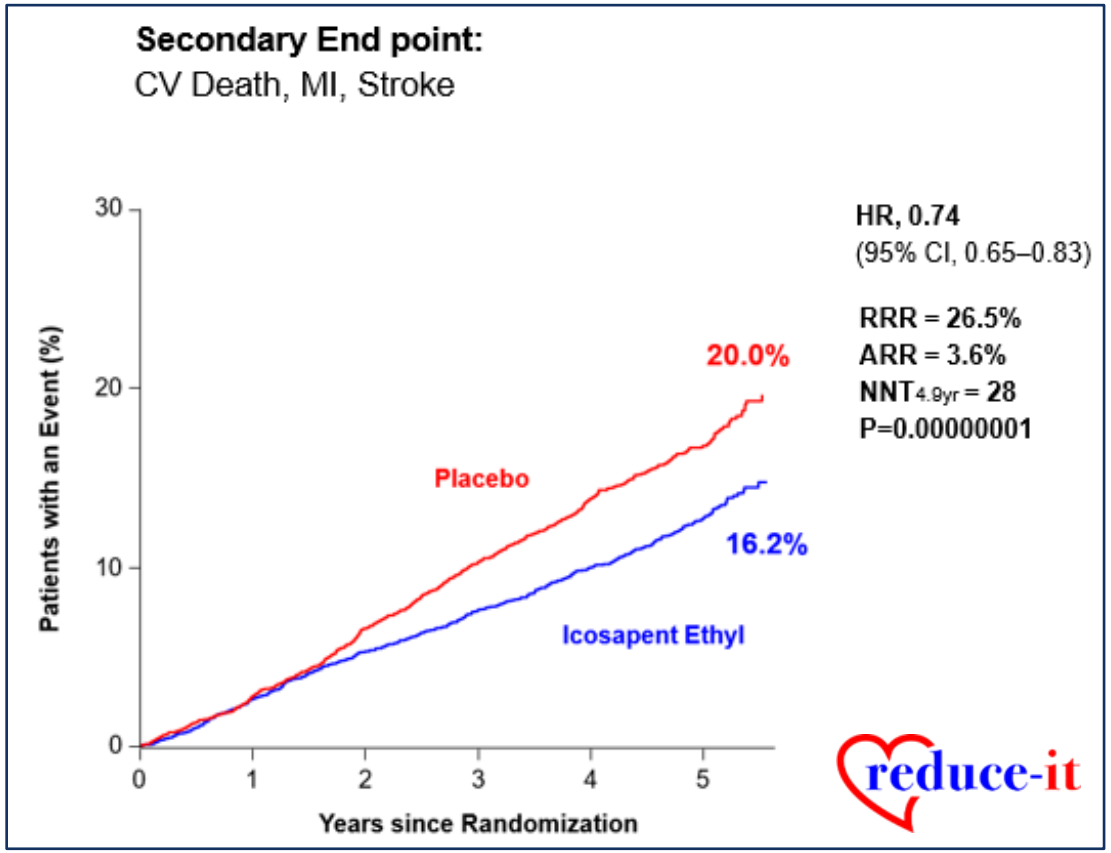
- CV death
- Non-fatal MI
- Non-fatal stroke

reduce-it

Bhatt, Clin Cardiol 2017; Bhatt, NEJM 2019

Primaire en secondaire eindpunten



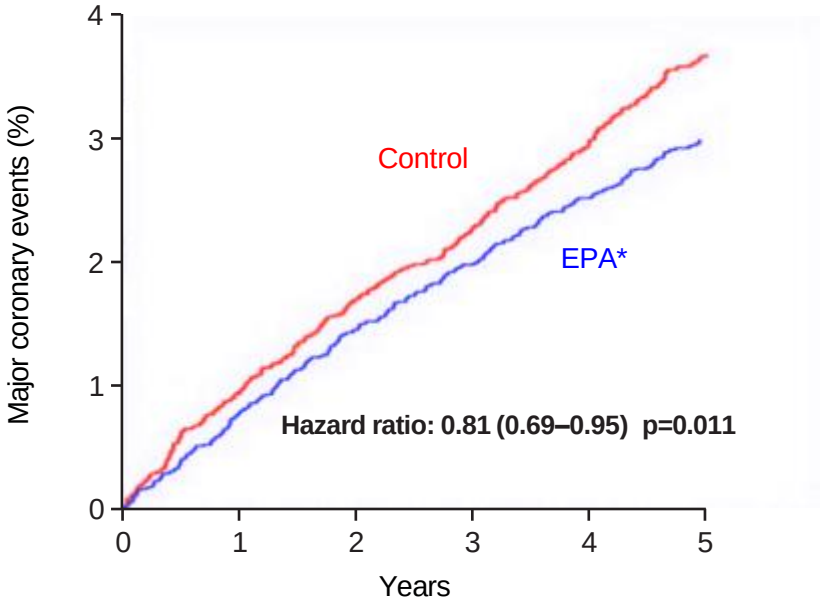


Kaplan–Meier event curves for the primary and key secondary efficacy endpoint in a time-to-event analysis

Bhatt, Clin Cardiol 2017; Bhatt, NEJM 2019

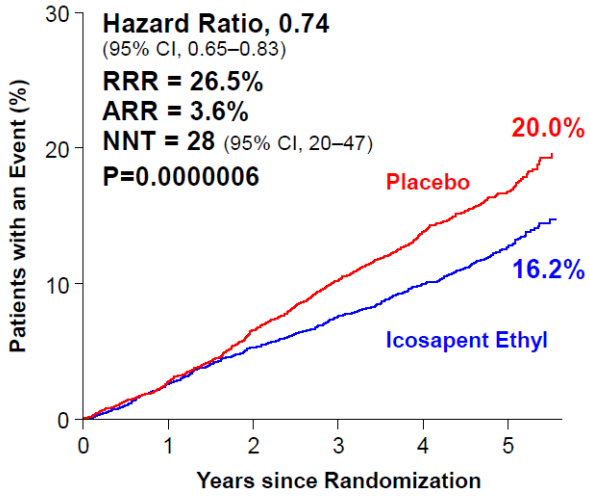
Hoe verklaren we de discrepanties in uitkomsten tussen de 3 grote studies met omega-3-vetzuren?

JELIS[1]



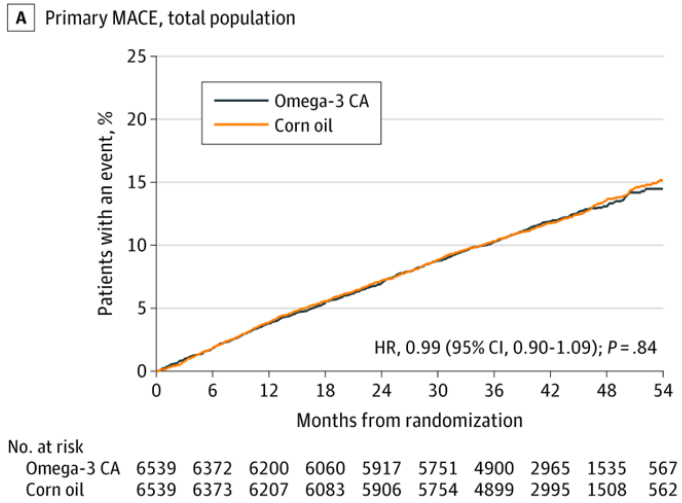
1.8 g EPA
No placebo

REDUCE IT[2]



4 g EPA
Mineral oil placebo

STRENGTH[3]



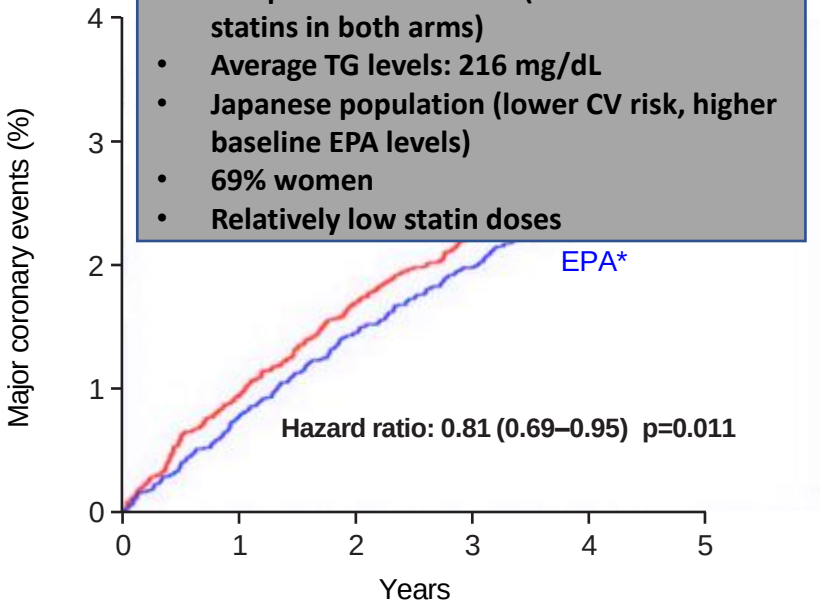
4 g EPA and DHA
Corn oil placebo

1. Yokoyama, Lancet 2007; 2. Bhatt, NEJM 2019; 3. Nicholls, JAMA 2020

Hoe verklaren we de discrepanties in uitkomsten tussen de 3 grote studies met omega-3-vetzuren?

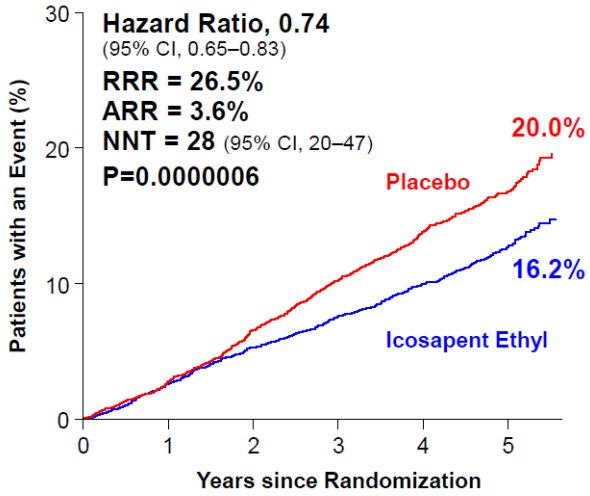
JELIS[1]

- Open label trial
- Not placebo controlled (usual care with statins in both arms)
- Average TG levels: 216 mg/dL
- Japanese population (lower CV risk, higher baseline EPA levels)
- 69% women
- Relatively low statin doses



1.8 g EPA
No placebo

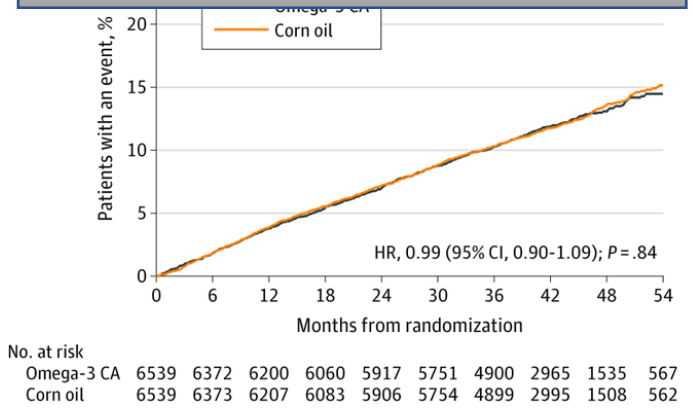
REDUCE IT[2]



4 g EPA
Mineral oil placebo

STRENGTH[3]

- Mineral oil as placebo bad for CV-risk?
- Less high EPA-levels?
- EPA in combination with DHA less effective?



4 g EPA and DHA
Corn oil placebo

1. Yokoyama, Lancet 2007; 2. Bhatt, NEJM 2019; 3. Nicholls, JAMA 2020

asHVZ voordeel van IPE is onafhankelijk van *baseline* TG-waarden

Primary endpoint in subgroups*	Icosapent ethyl n/N (%)	Placebo n/N (%)	HR (95%CI)	Int P value
Baseline TGs				
• ≥2.3 mmol/L (200 mg/dL)	430/2481 (17.3%)	559/2469 (22.6%)	0.73 (0.64-0.83)	0.45
• <2.3 mmol/L (200 mg/dL)	275/1605 (17.1%)	342/1620 (21.1%)	0.79 (0.67-0.93)	
Baseline TGs				
• ≥1.7 mmol/L (150 mg/dL)	640/3674 (17.4%)	811/3660 (22.2%)	0.75 (0.68-0.83)	0.83
• <1.7 mmol/L (150 mg/dL)	65/412 (15.8%)	90/429 (21.0%)	0.79 (0.57-1.09)	
Baseline TGs ≥2.3 mmol/L (200 mg/dL) and HDL ≤0.9 mmol/l (35mg/dl)				
• Yes	149/823 (18.1%)	214/794 (27.0%)	0.62 (0.51-0.77)	0.04
• No	554/3258 (17.0%)	687/3293 (20.9%)	0.79 (0.71-0.88)	

* Prespecified subgroups

Bhatt, NEJM 2019

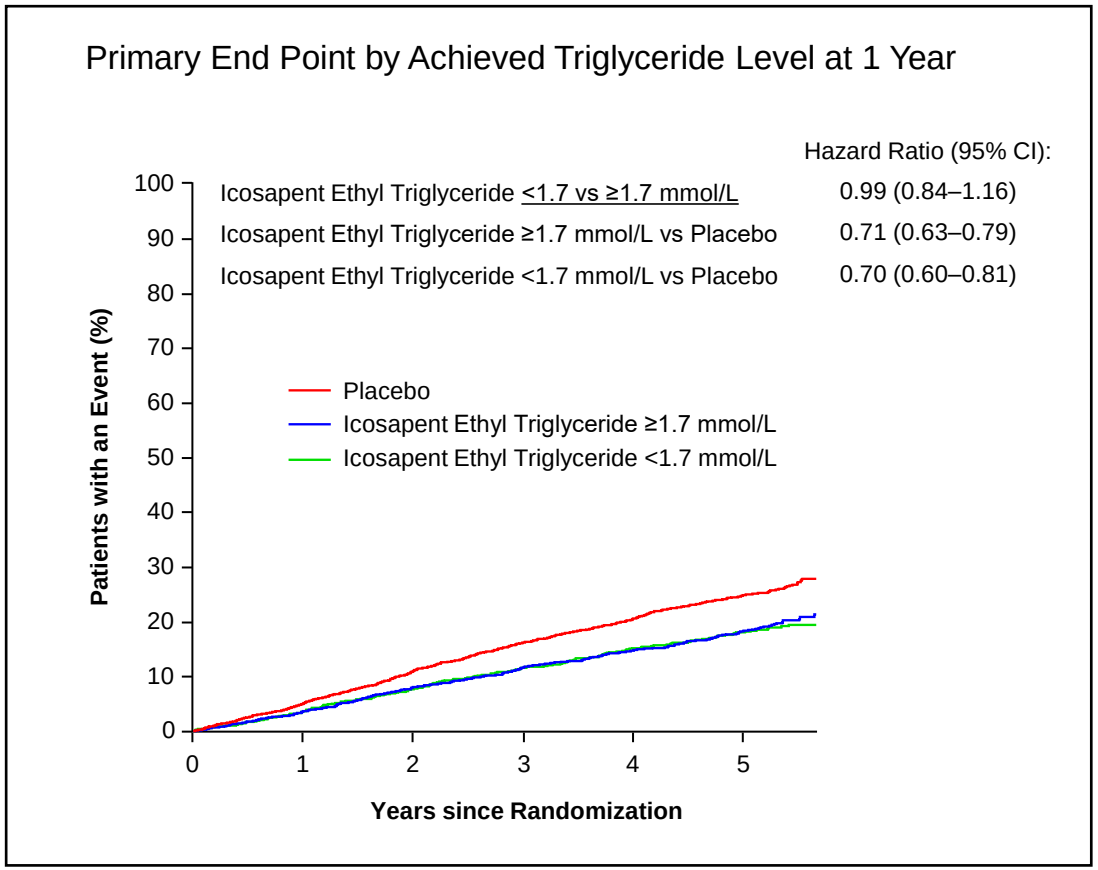
asHVZ voordeel van IPE is onafhankelijk van *baseline* TG-waarden

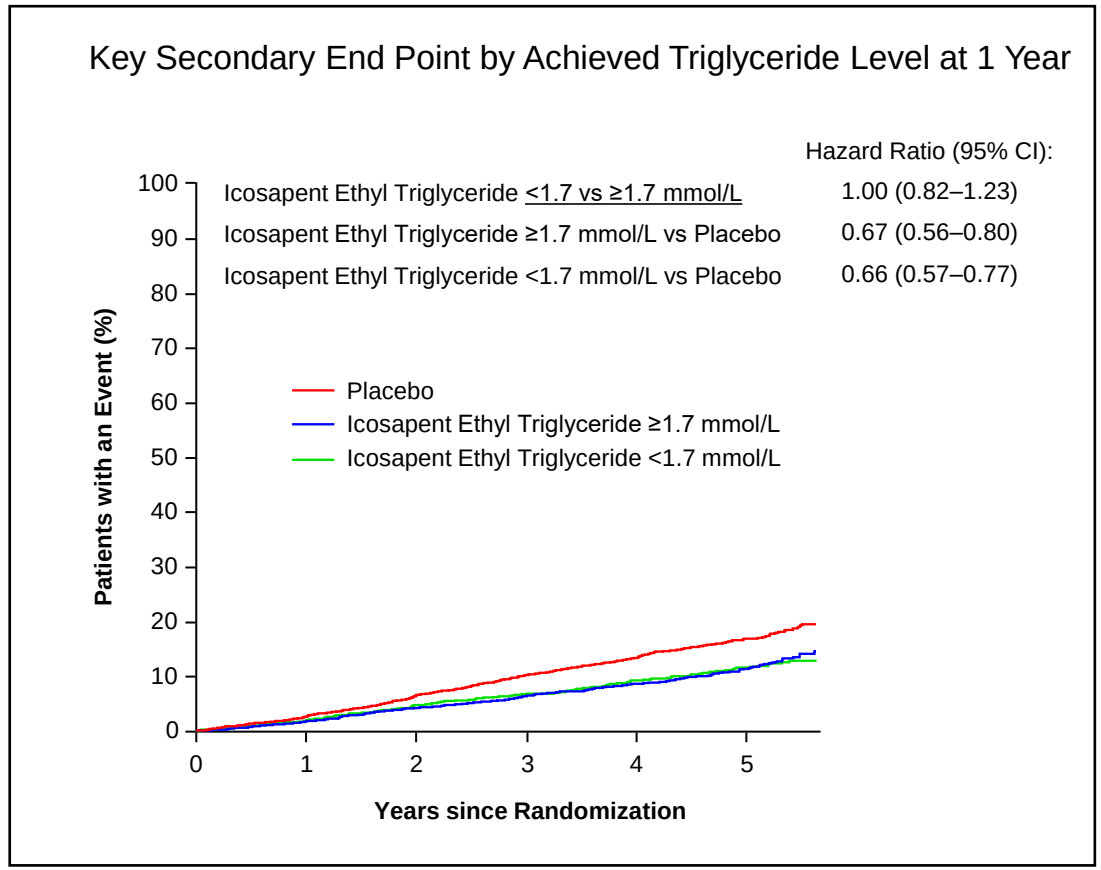
Primary endpoint in subgroups*	Icosapent ethyl n/N (%)	Placebo n/N (%)	HR (95%CI)	Int P value
Baseline LDL-C				
• ≤1.73 mmol/L (67 mg/dL)	244/1481 (16.5%)	302/1386 (21.8%)	0.72 (0.61-0.85)	0.62
• >1.73 and ≤2.17 mmol/L (>67 and ≤84 mg/dL)	248/1347 (18.4%)	307/1364 (22.5%)	0.81 (0.68-0.96)	
• >2.17 mmol/L (> 84 mg/dL)	213/1258 (16.9%)	292/1339 (21.8%)	0.74 (0.62-0.89)	

* Prespecified subgroups

Bhatt, NEJM 2019

EN… onafhankelijk van behaalde TG-waarden

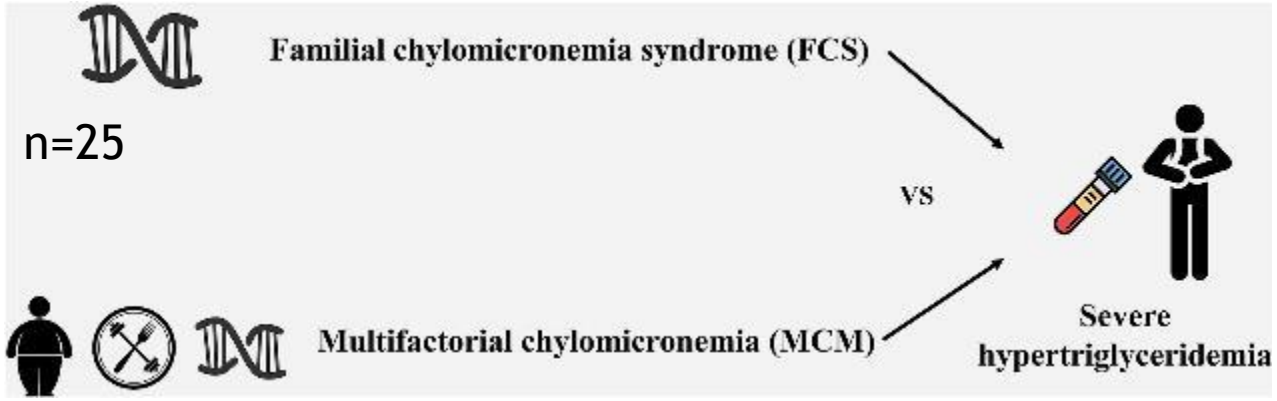


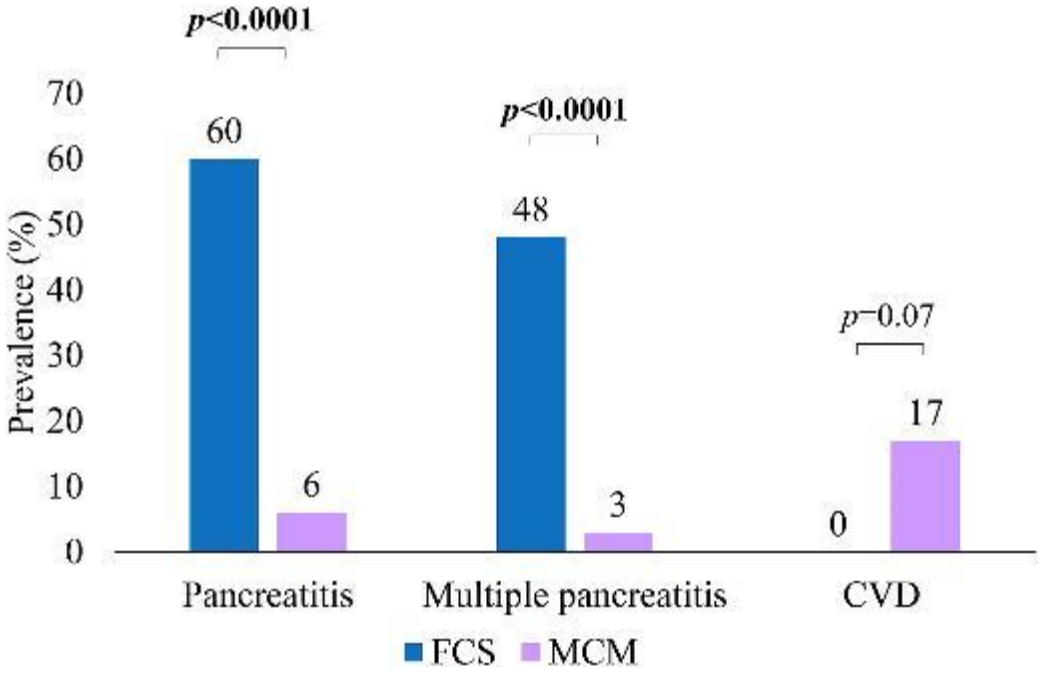


Bhatt, NEJM 2019

Nature vs nurture

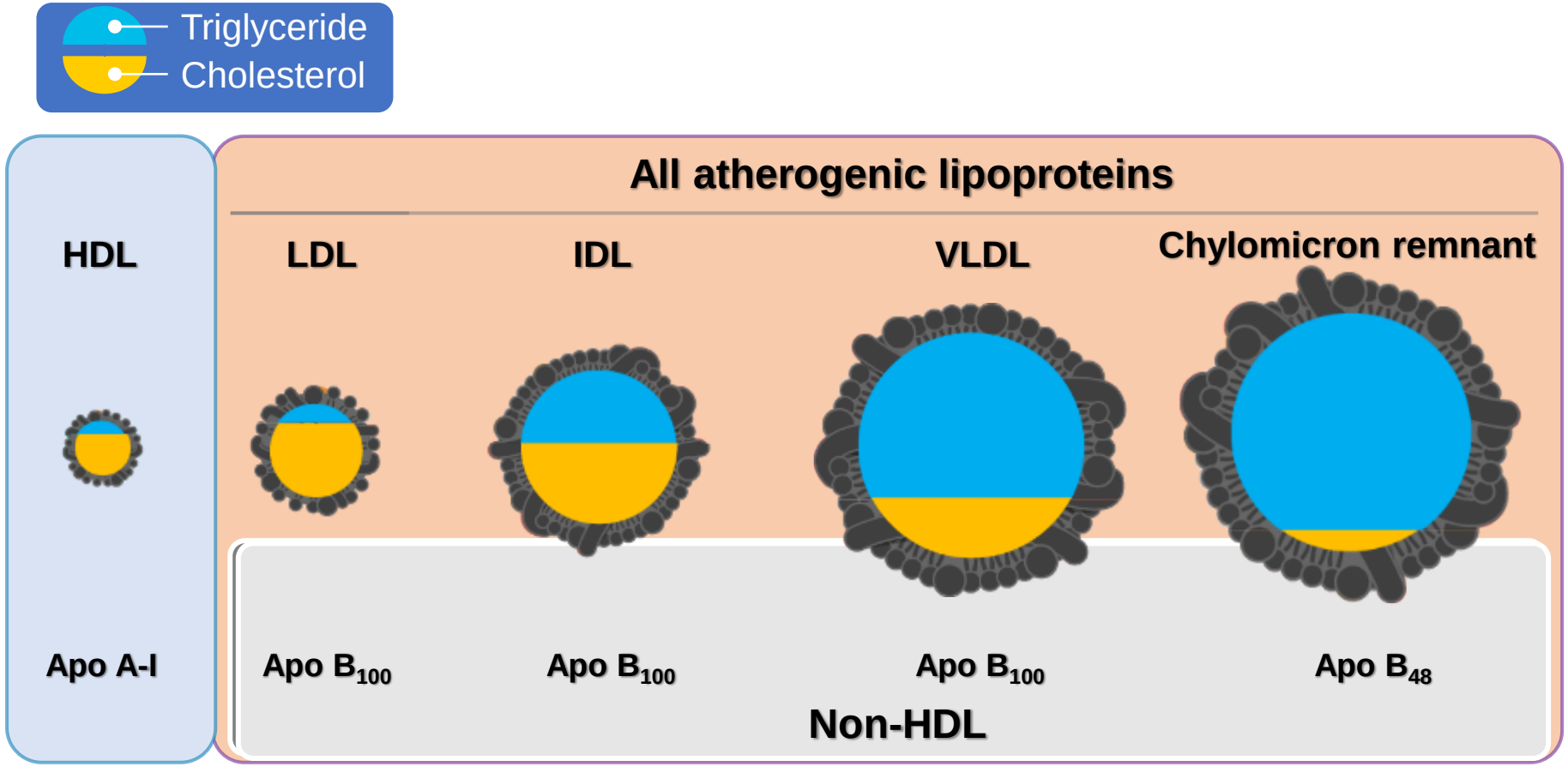
Retrospectieve studie





Paquette M. et al. Atherosclerosis 2019

Lipoproteïne classificatie en inhoud

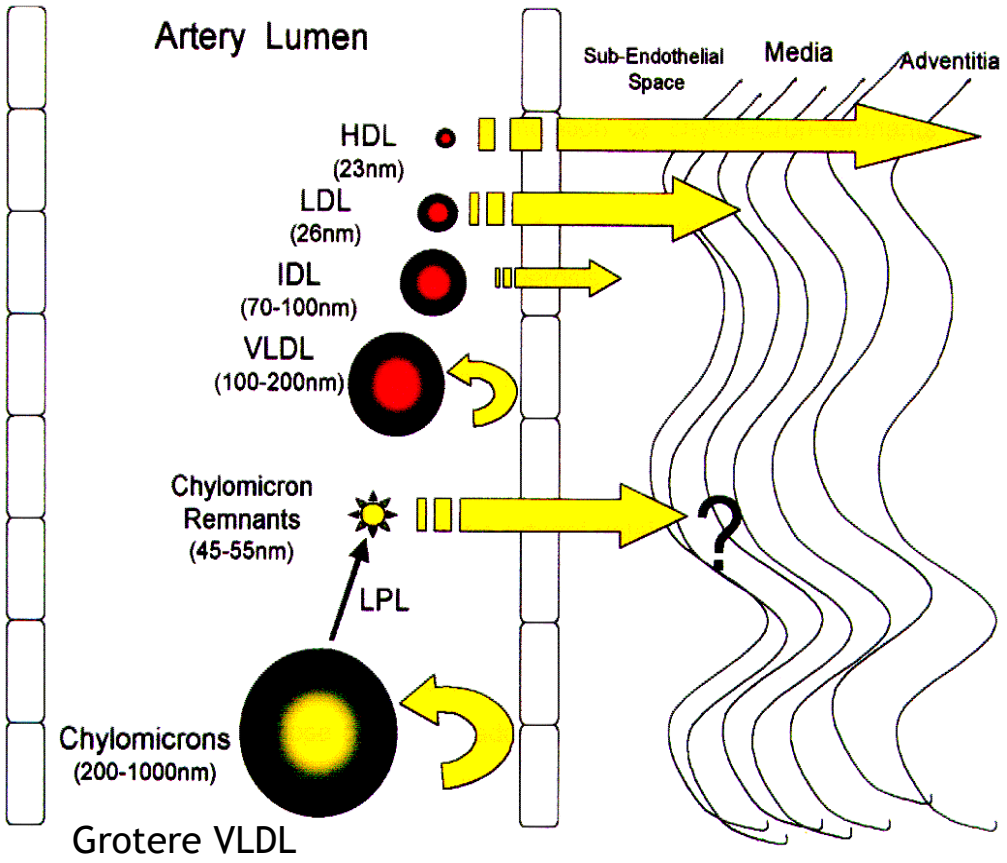


Non–HDL-C = Total cholesterol – HDL-C

Jones, Am J Med 2011

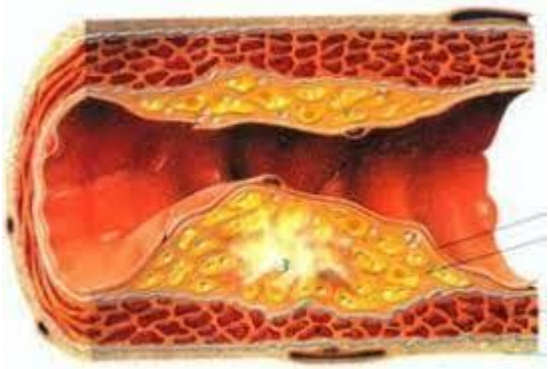
Wat is atherogeen

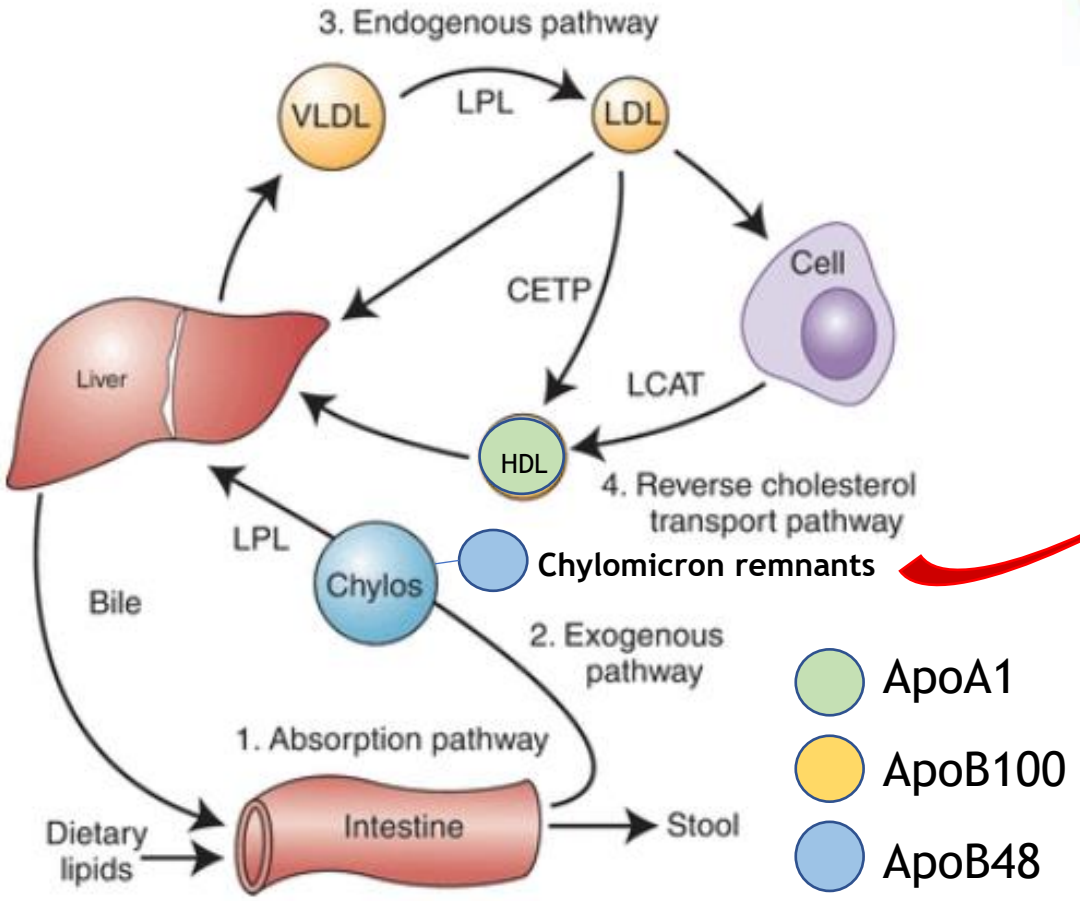
- Kleine deeltjes penetreren intima
- Bevatten minder triglyceriden
- Maar vele kleine deeltjes = hogere TG
- Vele kleine deeltjes = hoger ApoB100



Lipidenmetabolisme

ApoB100





ApoB48 remnants

ApoA1

ApoB100

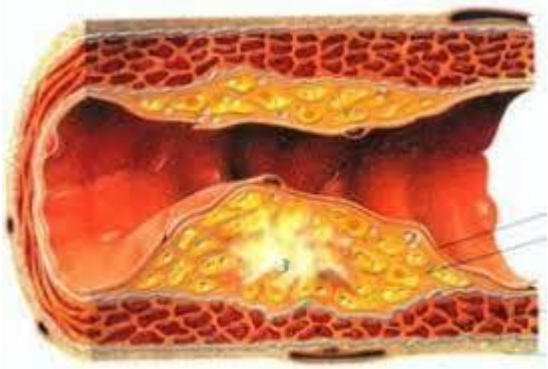
ApoB48

ApoB48 geklaard door heparine sulfaat proteoglycanen (HSPG) → geremd door hoge glucose waarde (IR/DM)

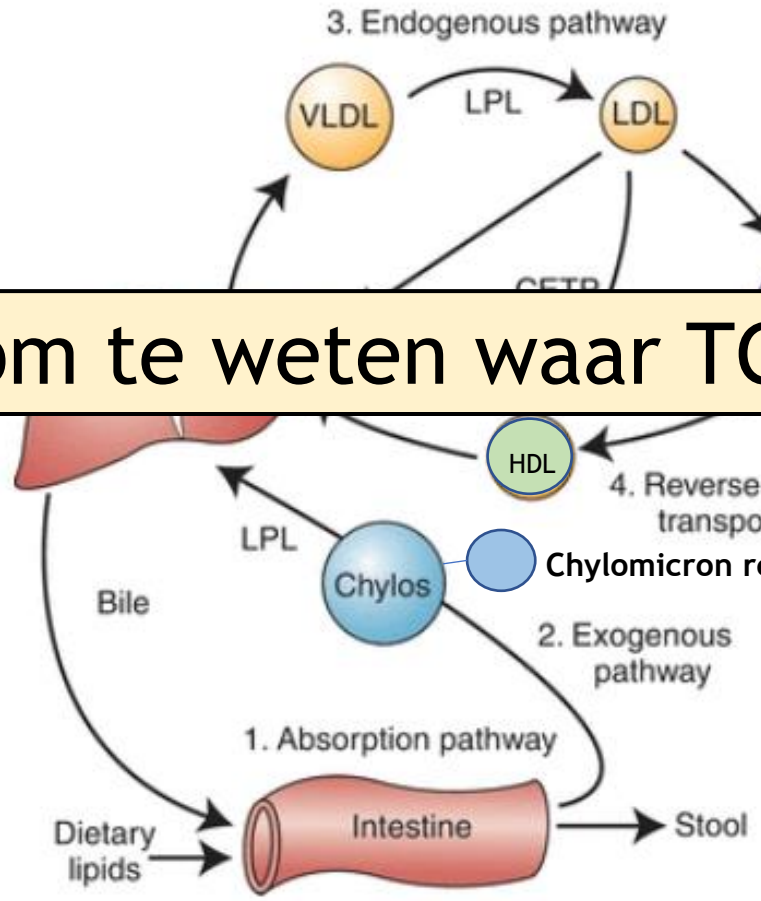
https://basicmedicalkey.com/lipids-and-lipoproteins/

Lipidenmetabolisme

ApoB100



ApoB48 remnants



Belangrijk om te weten waar TG's vandaan komen

ApoA1

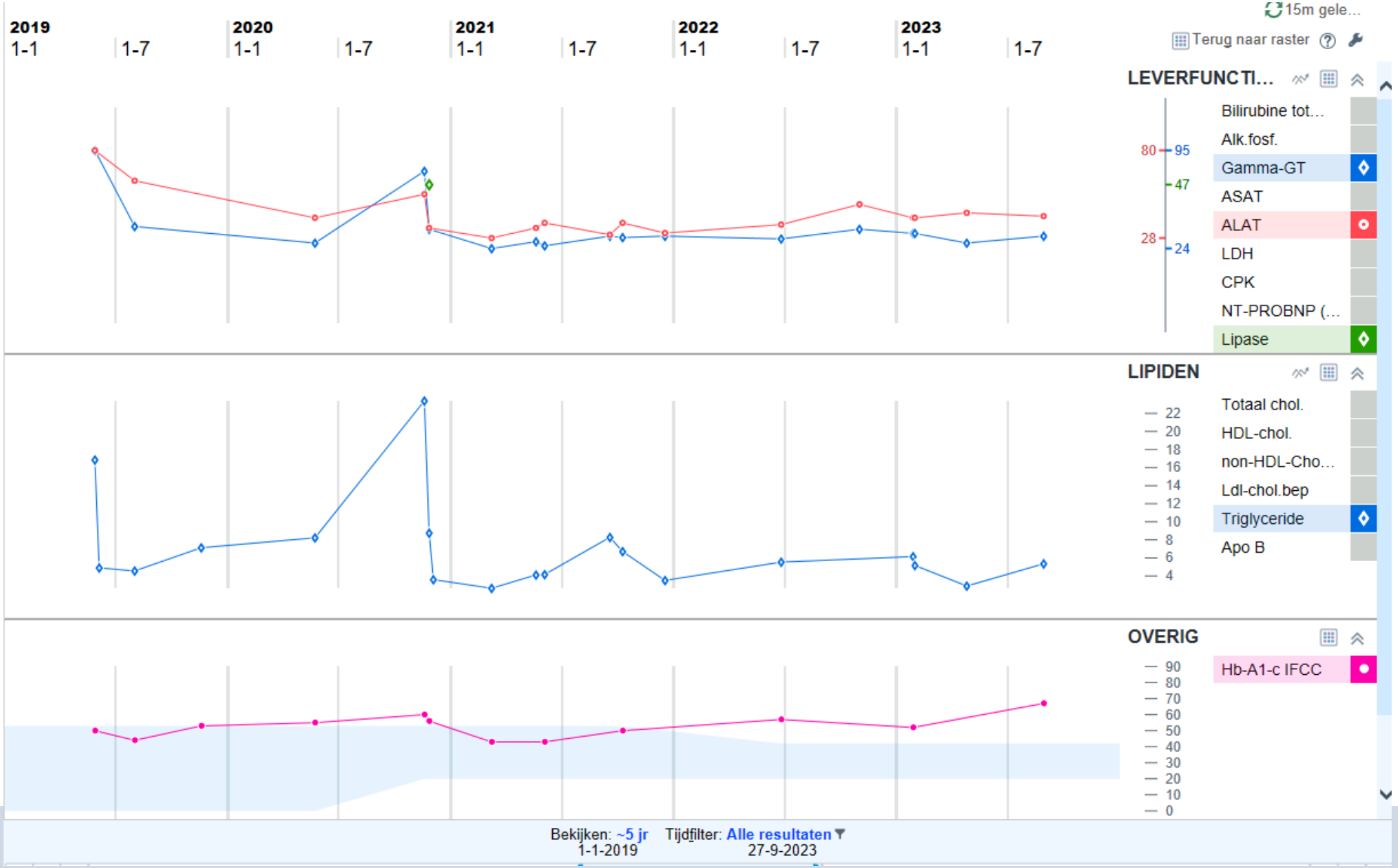
ApoB100

ApoB48

ApoB48 geklaard door heparine sulfaat proteoglycanen (HSPG) → geremd door hoge glucose waarde (IR/DM)

https://basicmedicalkey.com/lipids-and-lipoproteins/

Hoe is het met Dhr. K afgelopen?



Samenvatting

- Verhoogde TG-waarden identificeert een patiëntengroep met residuaal asHVZ risico, ondanks optimale statinetherapie
- Alleen wanneer deze TG-waarden van ApoB100-deeltjes (en minder van ApoB48) komt is het atherogeen
- Alleen visolie met EPA (en niet in combinatie met DHA) geeft reductie van dit risico
- Behandeling met icosapent ethyl (gezuiverd EPA) geeft een 25% reductie van dit risico, onafhankelijk van baseline/behaalde TG-waarde en LDL-C-waarde

Discussie

Nederlandse Lipiden Academie

PANORAMA

Personalized Algorithms, based on Novel Outcomes
Reshaping cArdiovascular Management Approaches

CVGK