Triglyceriden en hart- en vaatziekten: is er een relatie?

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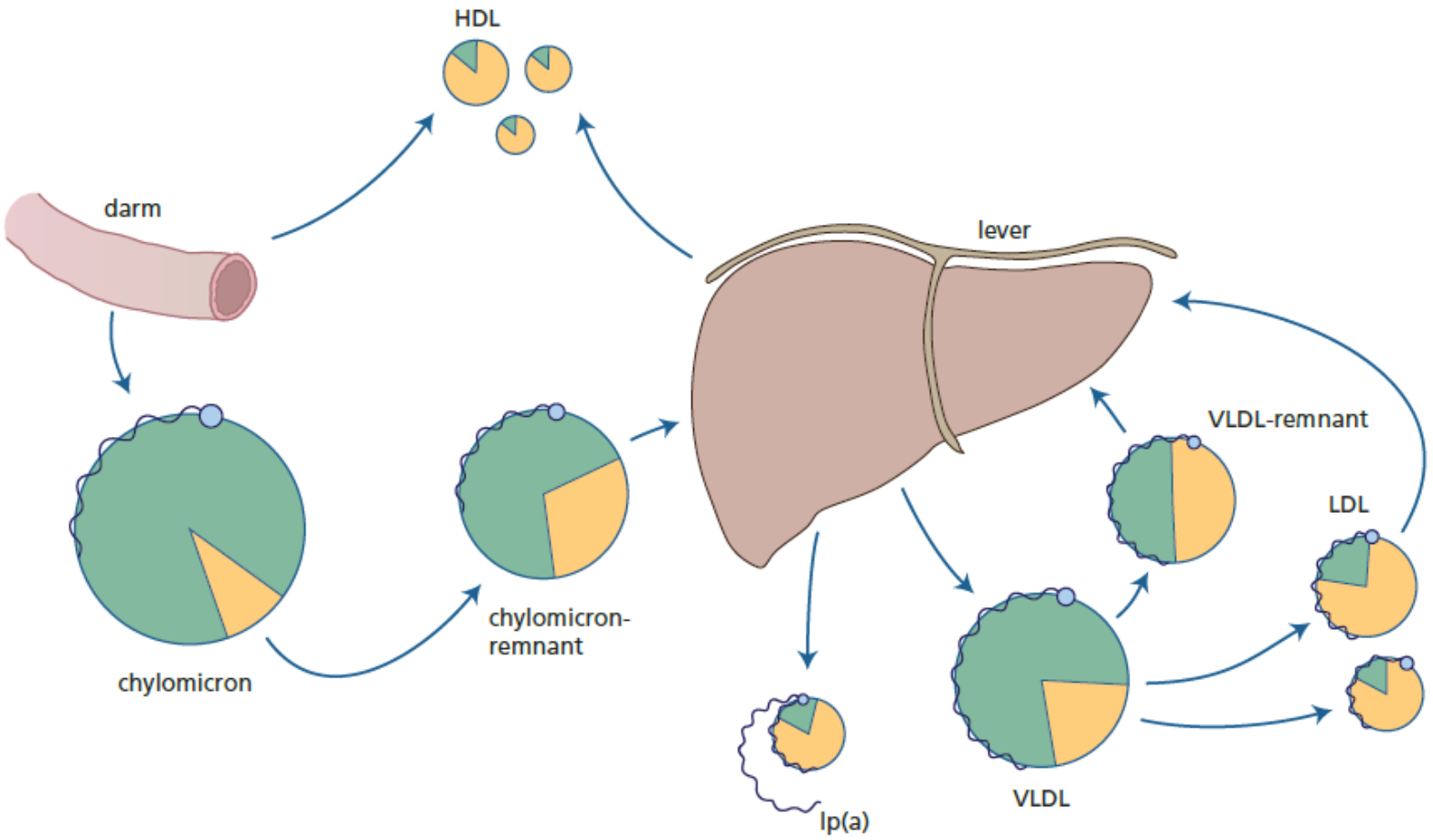
Disclosure potential conflicts of interest

Geen (potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties aan instituut	**Bedrijfsnamen**
Sponsoring of onderzoeksgeld	• **Amryt**
Honorarium of andere (financiële) vergoeding	• **Amgen (zorginnovatie)**
Aandeelhouder	•
Andere relatie, namelijk …	

Lipiden metabolisme voor dummies (1)



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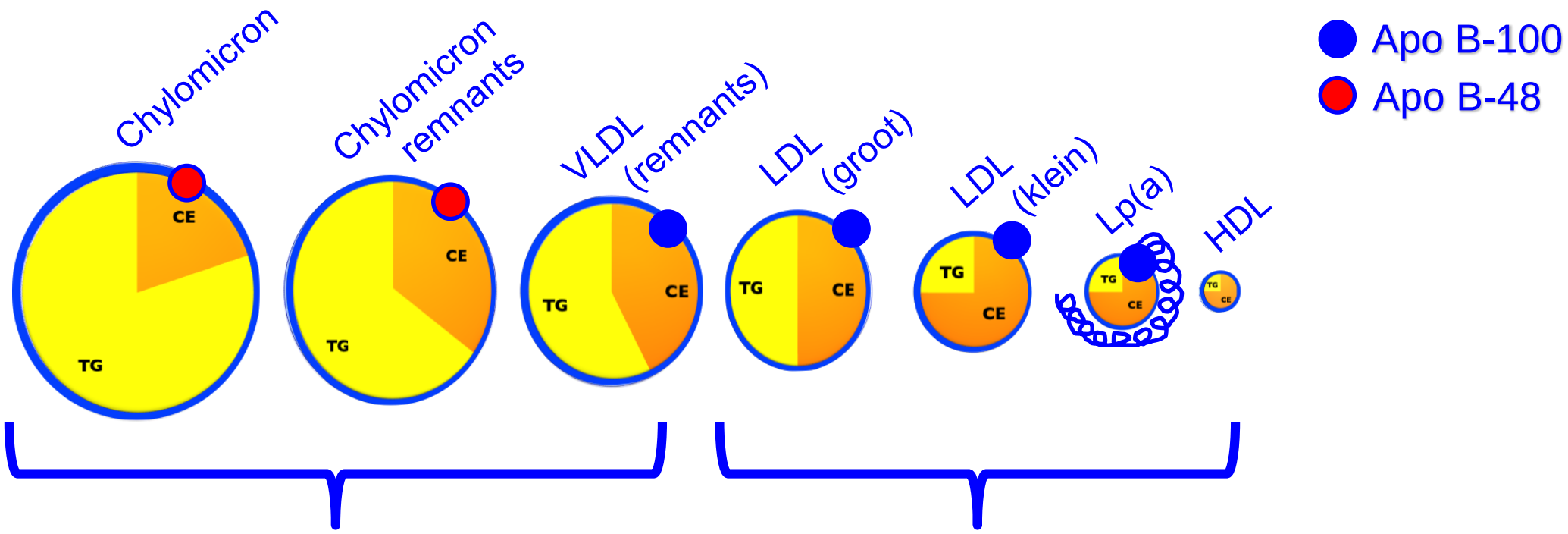
Lipiden metabolisme voor dummies (2)



TG-rijke deeltjes:
- Chylomicronen (remnants)
- VLDL (remnants)

Chol-rijke deeltjes:
- LDL
- Lipoproteine (a)
- HDL

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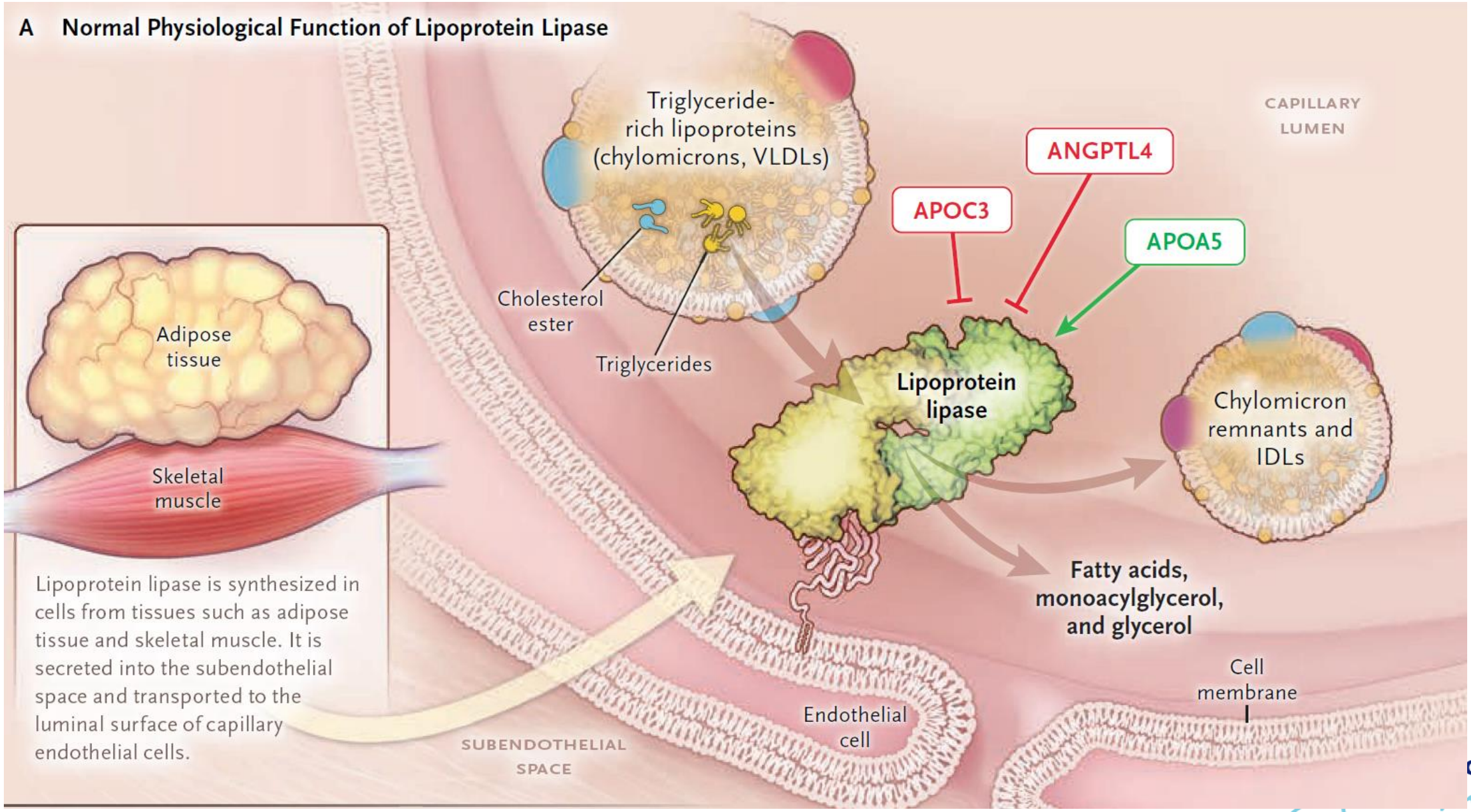
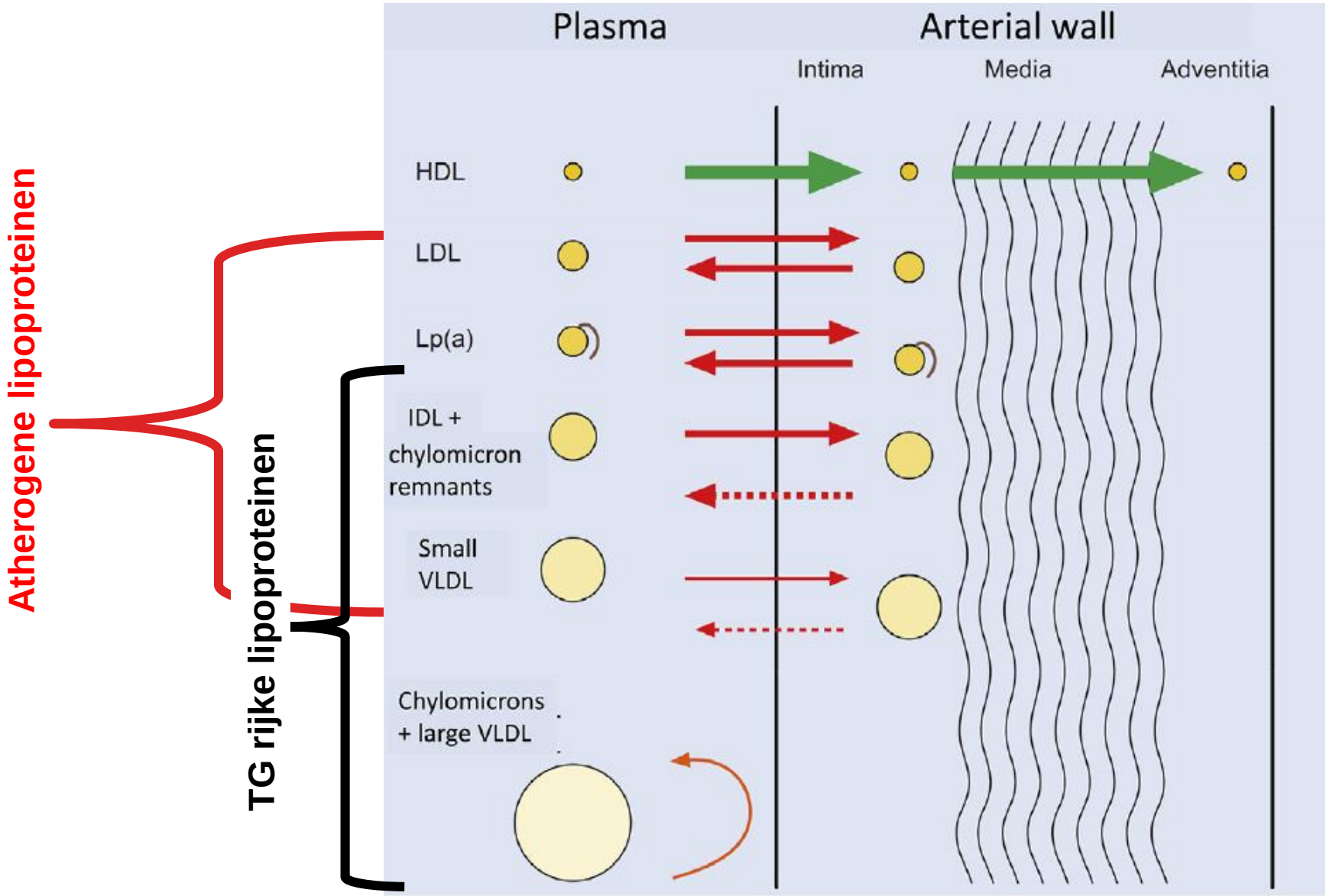


N Engl J Med 2016;374:1134-44.

Welke lipoproteinen zijn atherogeen?



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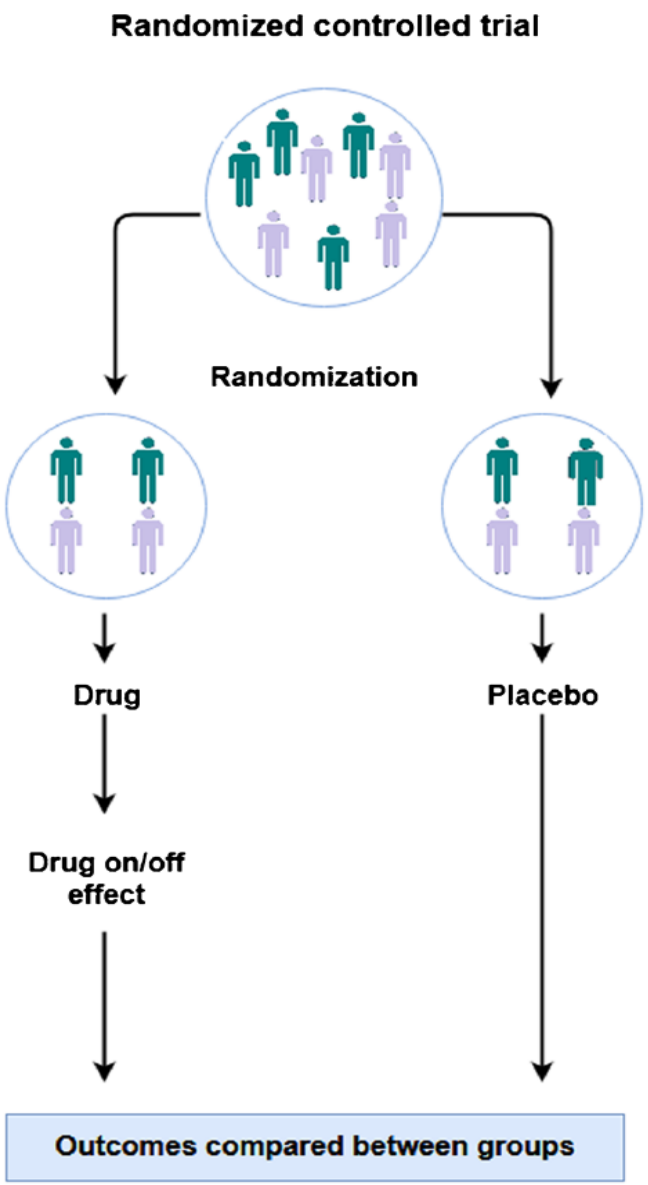
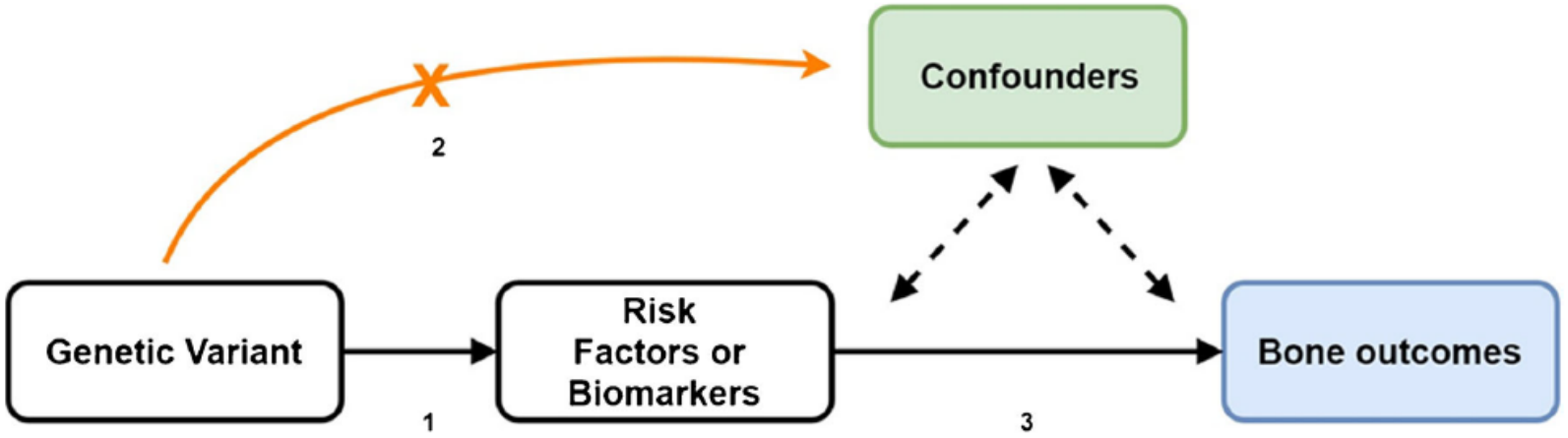
Langsted, Pathology 2018

Mendelian Randomization



Trajanoska Current Osteoporosis Reports 2018

Mendelian Randomization



Assumptions of Mendelian Randomization Study:

Trajanoska Current Osteoporosis Reports 2018

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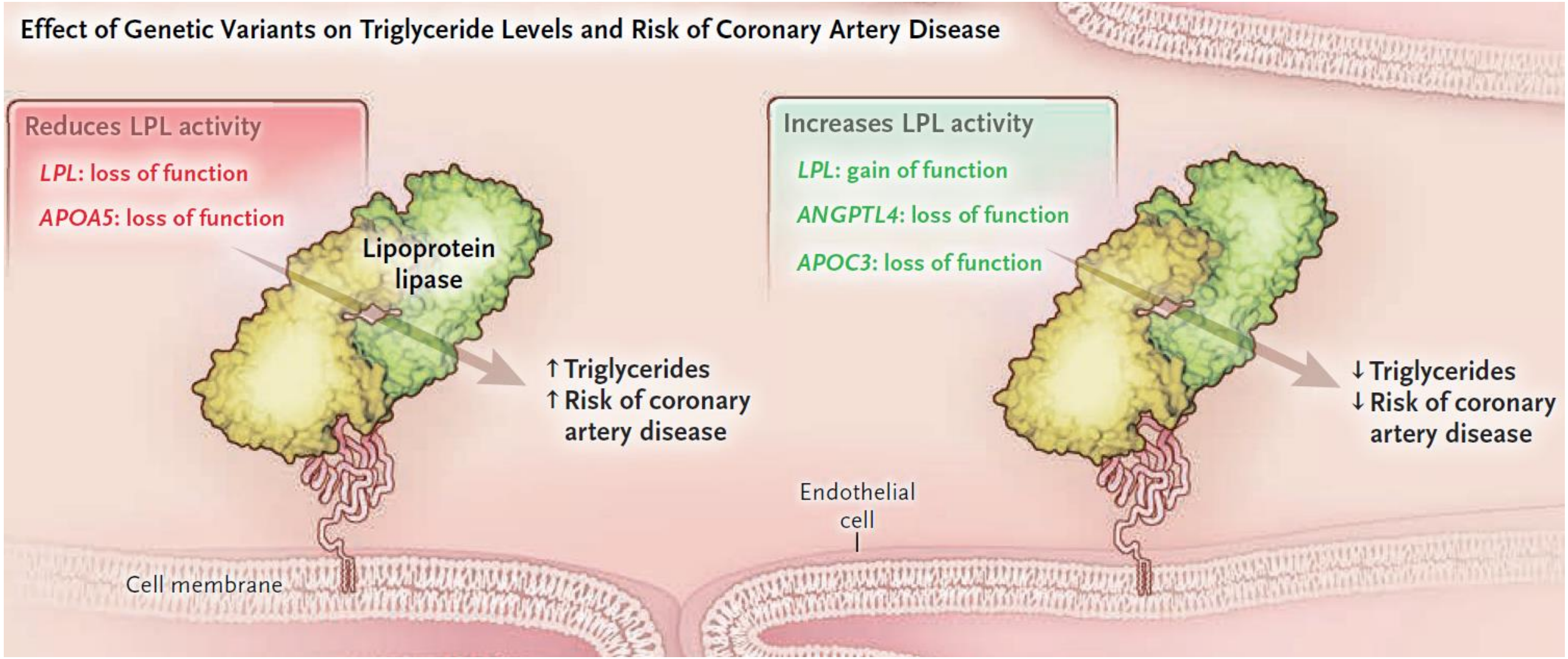
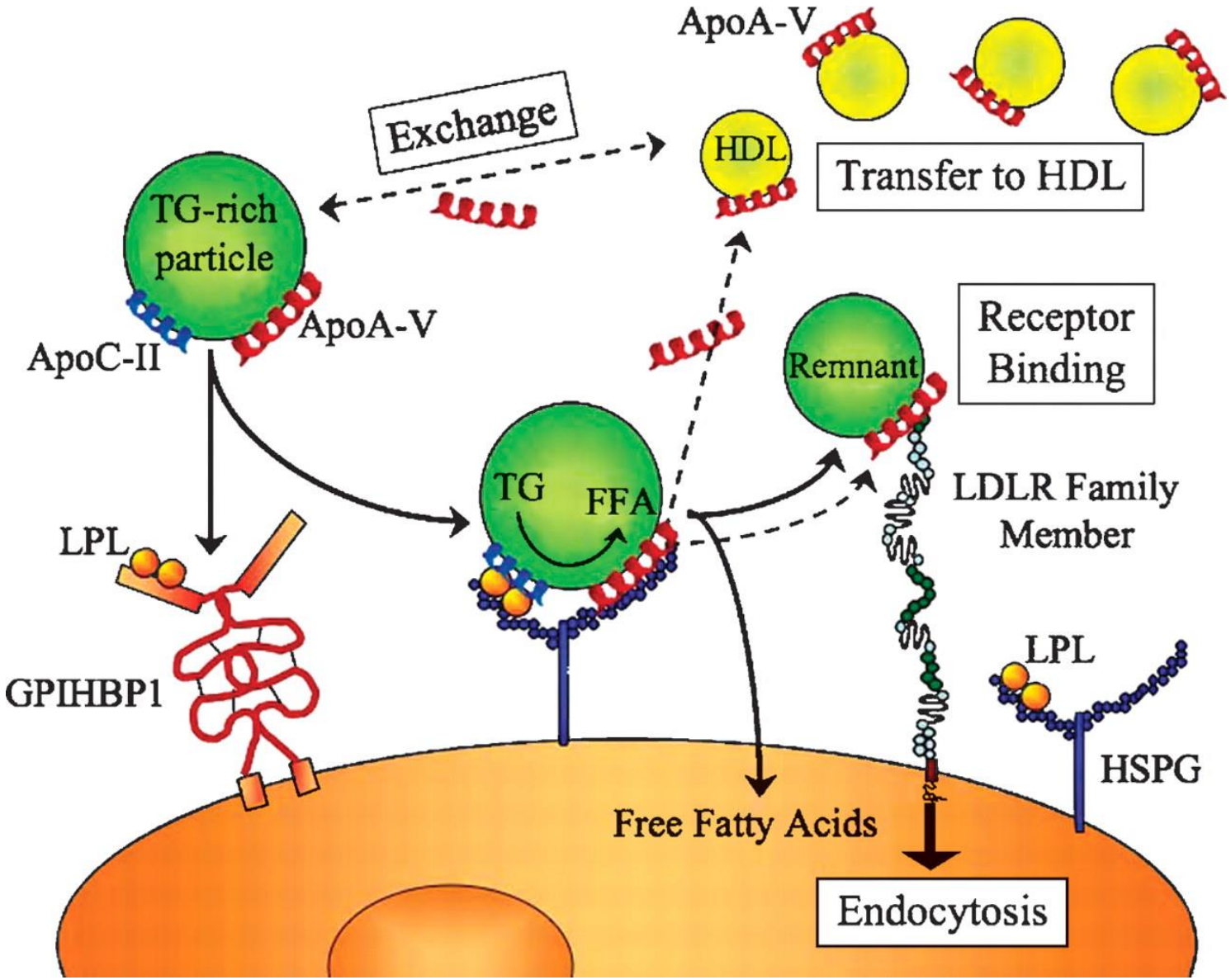


N Engl J Med 2016;374:1134-44.

APOA-V


ApoA-V
Exchange
HDL
Transfer to HDL
TG-rich particle
ApoA-V
ApoC-II
Receptor Binding
Remnant
TG
FFA
LDLR Family Member
LPL
GPIHBP1
LPL
HSPG
Free Fatty Acids
Endocytosis

APOA-V

European Heart Journal (2013) **34**, 1826–1833
doi:10.1093/eurheartj/ehs431

CLINICAL RESEARCH
Genetics/lipids

Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction

Anders Berg Jørgensen[1], Ruth Frikke-Schmidt[1,2], Anders Sode West[1], Peer Grande[3], Børge G. Nordestgaard[2,4,5], and Anne Tybjærg-Hansen[1,2,5*]

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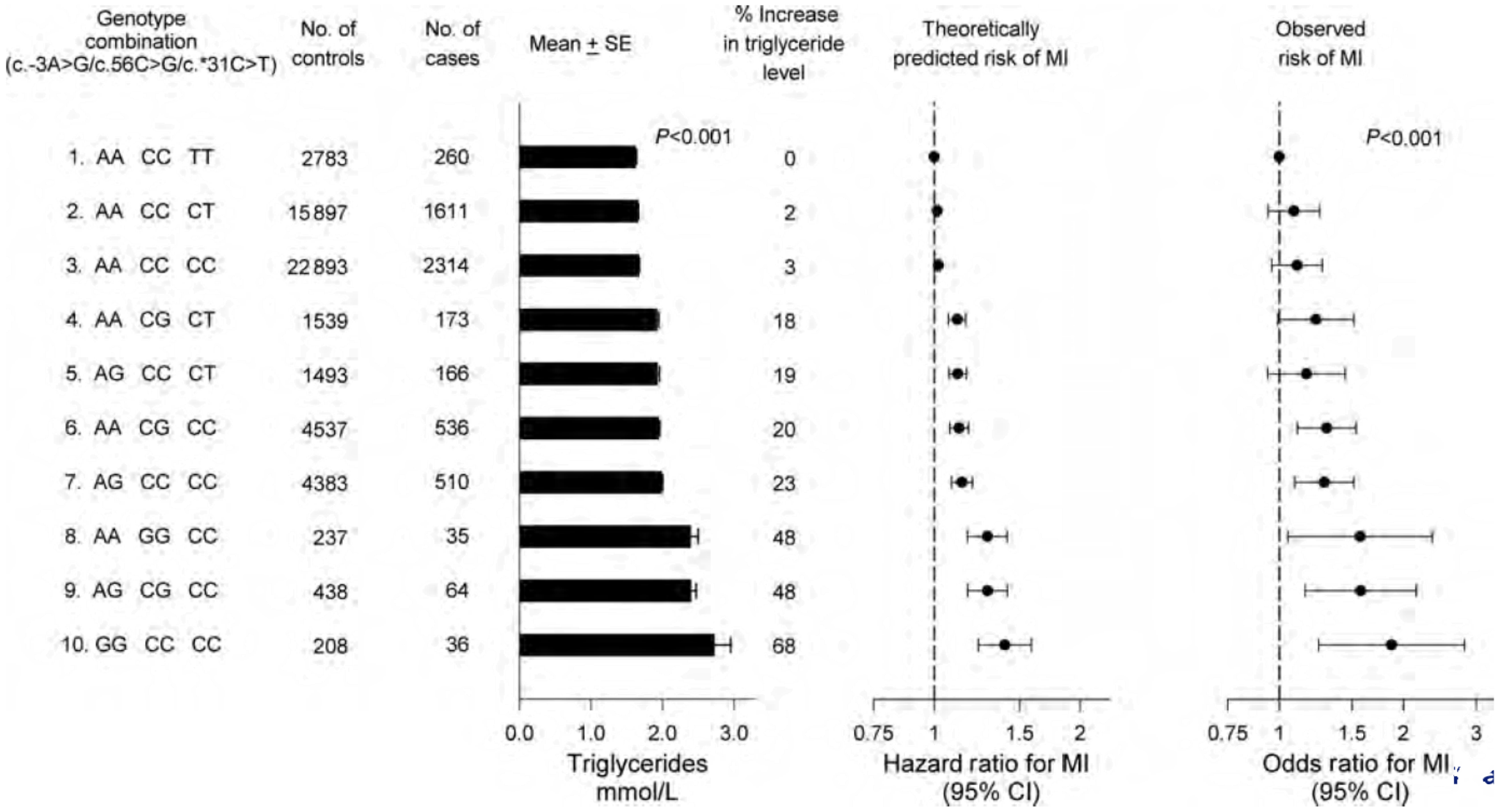
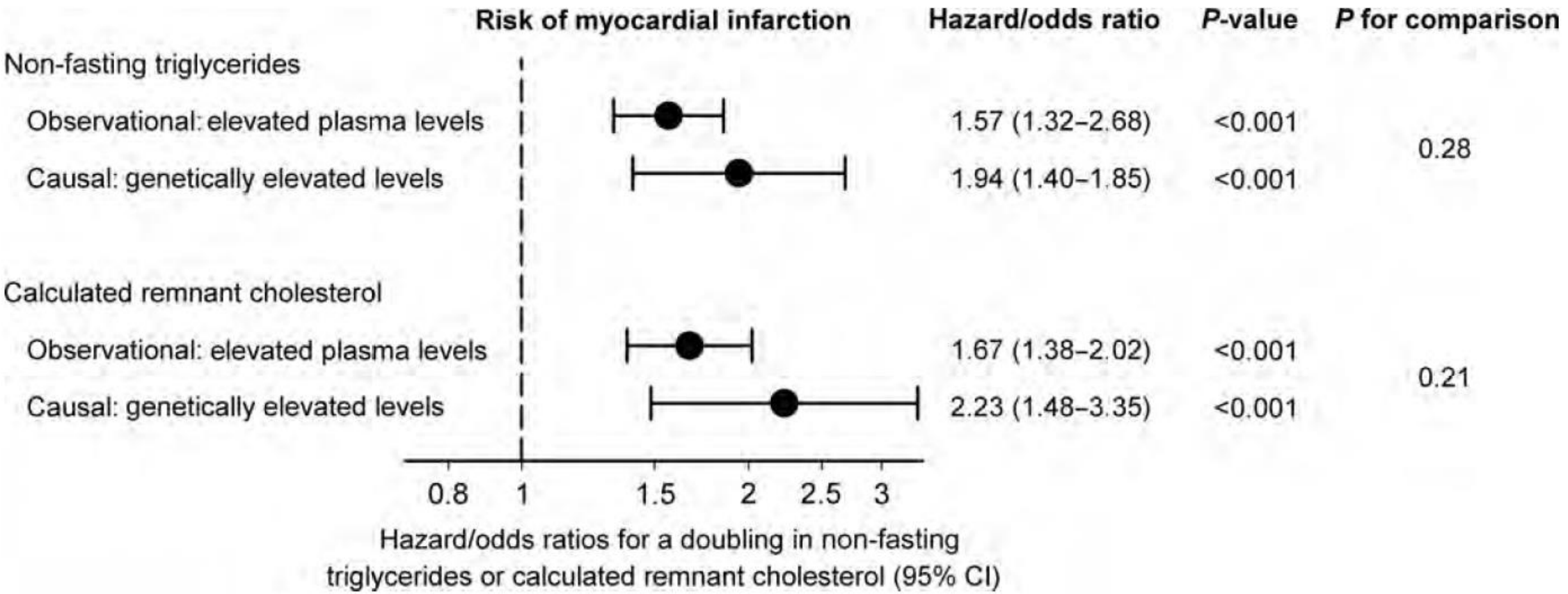
APOA-V



Jorgensen Eur Heart J 2013

APOA-V



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APOA-V

glyceridaemia on risk of MI in our study. Therefore, future studies of yet other genetic variants affecting triglycerides and remnant cholesterol in *LPL*, *APOC2*, and *APOC3*, with or without effects on HDL cholesterol, small dense LDL, HDL functionality, and other lipoprotein parameters, are needed. Such studies to-

Jorgensen Eur Heart J 2013

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APOA-C3

ORIGINAL ARTICLE

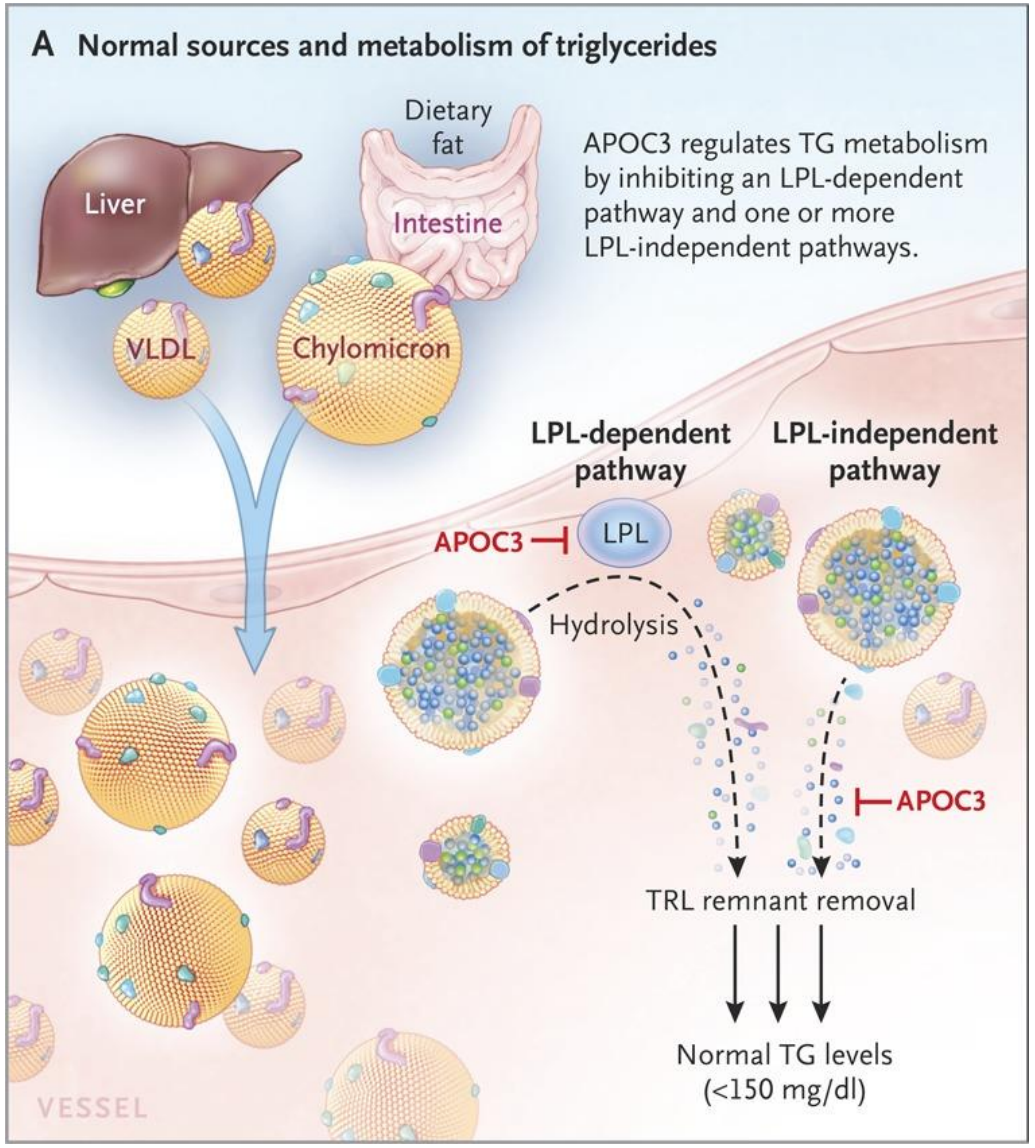
Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

Anders Berg Jørgensen, M.D., Ph.D., Ruth Frikke-Schmidt, M.D., D.M.Sc., Børge G. Nordestgaard, M.D., D.M.Sc., and Anne Tybjærg-Hansen, M.D., D.M.Sc.

ABSTRACT

Jorgensen Eur Heart J 2013

APOA-C3

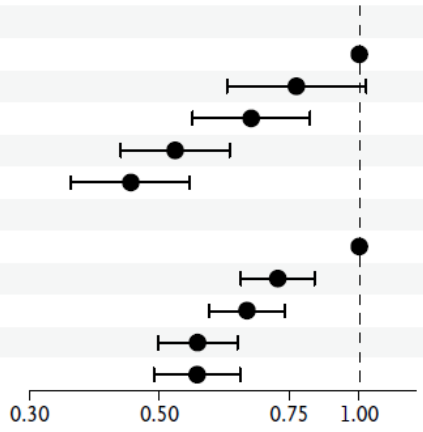


Gaudet NEJM 2014

APOA-C3

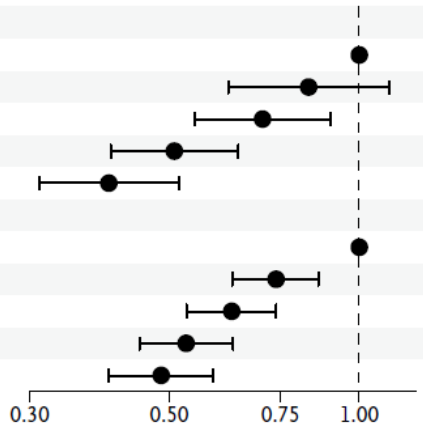
A Risk of Ischemic Vascular Disease

	No. of Participants	No. of Events	Hazard Ratio (95% CI)	P Value
Triglyceride level — mmol/liter				
≥4.00	3,245	331	1.00	<0.001
3.00–3.99	4,026	397	0.80 (0.62–1.02)	
2.00–2.99	11,606	1082	0.67 (0.54–0.83)	
1.00–1.99	32,578	2562	0.51 (0.42–0.63)	
<1.00	18,871	1038	0.43 (0.35–0.54)	
Triglyceride level in quintiles — mmol/liter				
≥2.30	13,730	1373	1.00	<0.001
1.62–2.29	13,788	1193	0.74 (0.65–0.85)	
1.22–1.61	13,841	1101	0.66 (0.58–0.76)	
0.91–1.21	14,239	975	0.55 (0.48–0.64)	
<0.91	14,728	768	0.55 (0.47–0.65)	



B Risk of Ischemic Heart Disease

	No. of Participants	No. of Events	Hazard Ratio (95% CI)	P Value
Triglyceride level — mmol/liter				
≥4.00	3,325	245	1.00	<0.001
3.00–3.99	4,127	292	0.83 (0.62–1.11)	
2.00–2.99	11,918	798	0.70 (0.55–0.90)	
1.00–1.99	33,366	1799	0.51 (0.40–0.64)	
<1.00	19,241	687	0.40 (0.31–0.52)	
Triglyceride level in quintiles — mmol/liter				
≥2.30	14,081	1015	1.00	<0.001
1.62–2.29	14,160	862	0.74 (0.63–0.86)	
1.22–1.61	14,194	768	0.63 (0.53–0.74)	
0.91–1.21	14,550	674	0.53 (0.45–0.63)	
<0.91	14,992	502	0.49 (0.40–0.59)	



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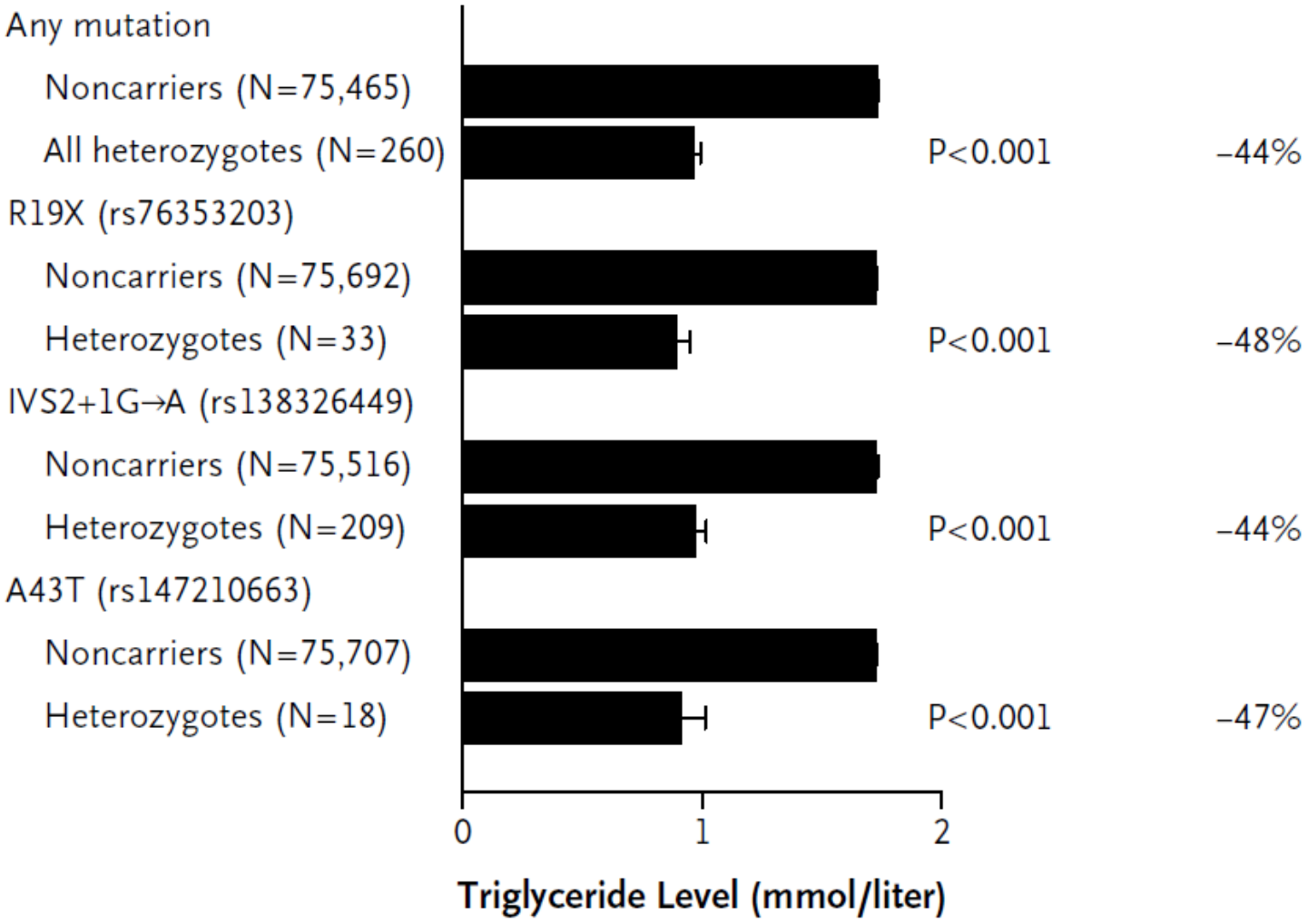
APOA-C3



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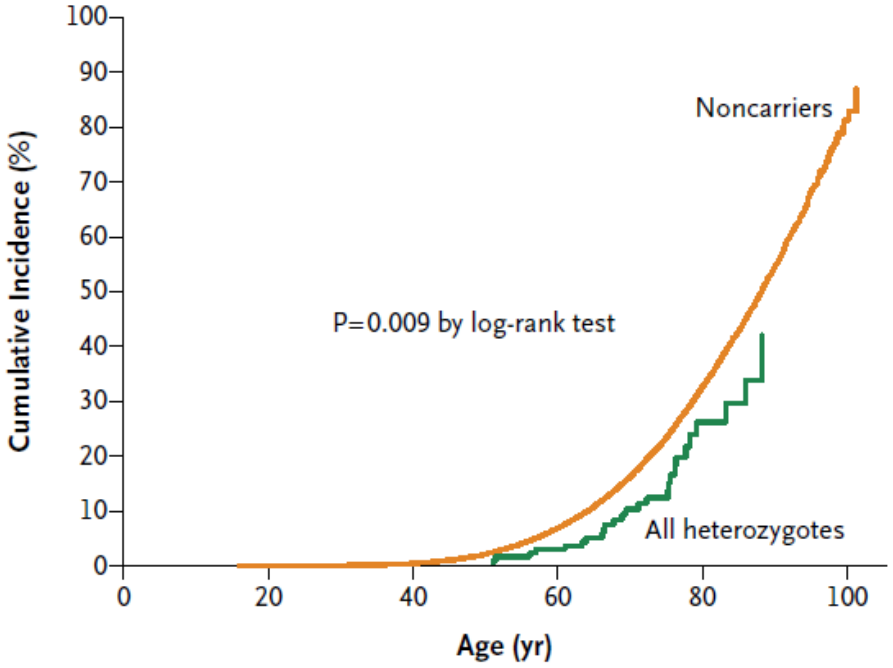
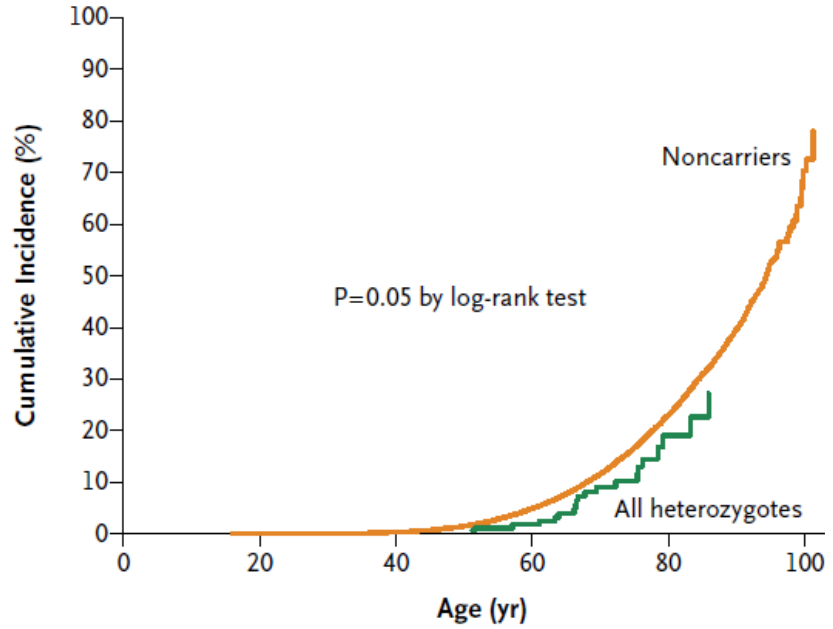
APOA-C3

A Ischemic Vascular Disease



No. at Risk				
Noncarriers	22,347	53,734	40,115	7264
All heterozygotes	69	181	143	29

B Ischemic Heart Disease



No. at Risk				
Noncarriers	22,347	53,734	40,664	7876
All heterozygotes	69	181	145	31

Jorgensen Eur Heart J 2013

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Coding Variation in *ANGPTL4*, *LPL*, and *SVEP1* and the Risk of Coronary Disease

Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators*

ABSTRACT

N Engl J Med 2016;374:1134-44.

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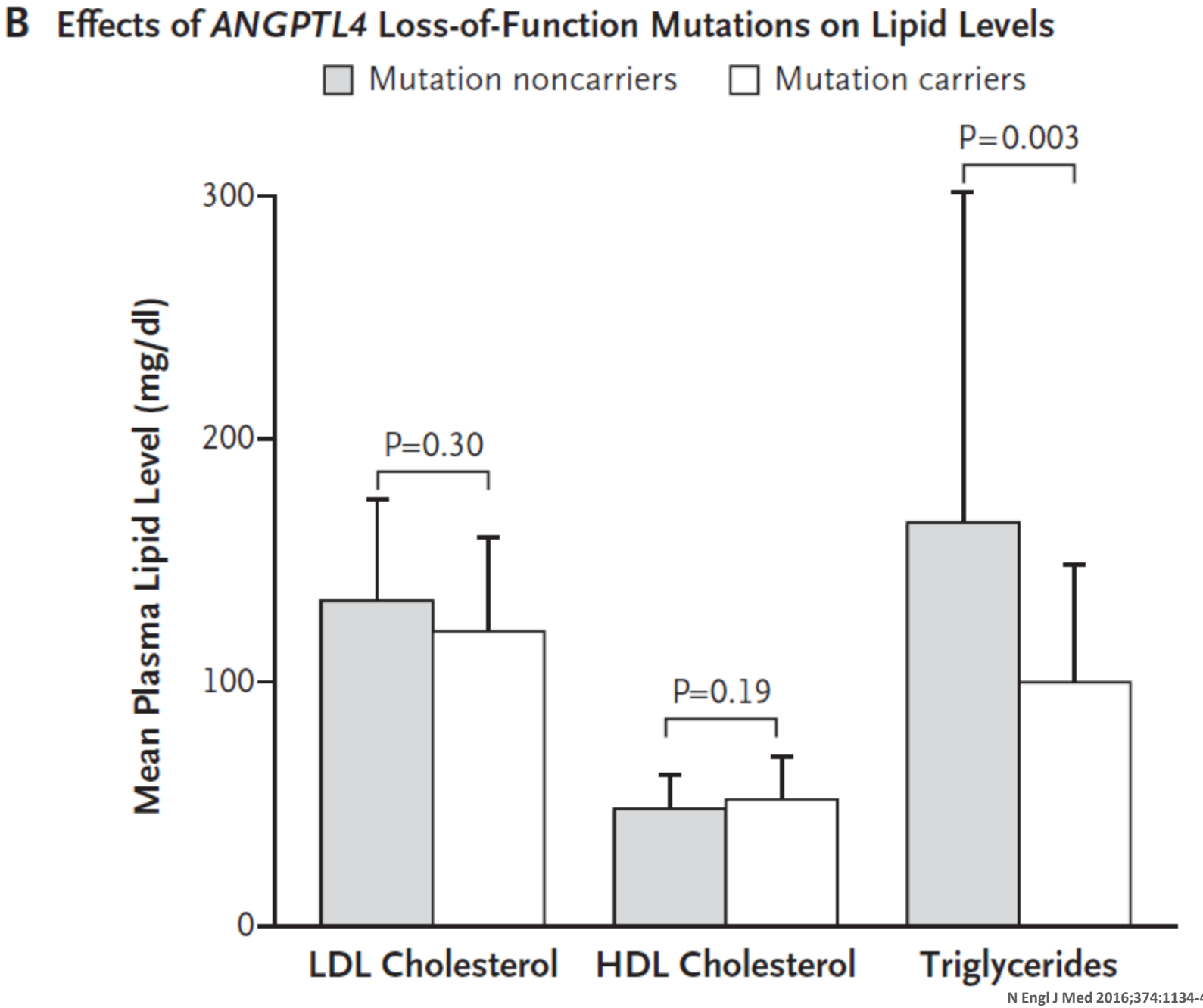

N Engl J Med 2016;374:1134-44.

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Table 2. Novel Low-Frequency Coding Variations Showing Significant Association with Coronary Artery Disease.

Locus and SNP	Chromosome and Nucleotide Position*	Allele 1/ Allele 2	Frequency of Allele 1	Functional Effect	Stage	Odds Ratio†	P Value
			%				
ANGPTL4 rs116843064	19: 8429323	A/G	2.01	p.E40K	Discovery	0.87	3.0×10^{-5}
					Replication	0.86	3.4×10^{-4}
					Combined‡	0.86	4.0×10^{-8}

Table S12. Association between *LPL* variation and risk for CAD

rsID	Chromosome : Position	Allele1/ Allele2	Frequency (Allele1)	Functional effect	Stage	OR	P
rs328	8:19819724	G/C	9.94%	p.S447* GOF	Discovery	0.93	5.0×10^{-6}
					Replication	0.95	8.8×10^{-3}
					Combined	0.94	2.5×10^{-7}
rs1801177	8:19805708	A/G	1.9%	p.D36N LOF	Discovery	1.12	1.6×10^{-3}
					Replication	1.16	0.04
					Combined	1.13	2.0×10^{-4}

Jorgensen Eur Heart J 2013

N Engl J Med 2016;374:1134-44.

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ORIGINAL ARTICLE

Inactivating Variants in *ANGPTL4* and Risk of Coronary Artery Disease

Frederick E. Dewey, M.D., Viktoria Gusarova, Ph.D., Colm O'Dushlaine, Ph.D., Omri Gottesman, M.D., Jesus Trejos, M.S., Charleen Hunt, Ph.D., Cristopher V. Van Hout, Ph.D., Lukas Habegger, Ph.D., David Buckler, Ph.D., Ka-Man V. Lai, Ph.D., Joseph B. Leader, Ph.D., Michael F. Murray, M.D., Marylyn D. Ritchie, Ph.D., H. Lester Kirchner, Ph.D., David H. Ledbetter, Ph.D., John Penn, M.S., Alexander Lopez, M.S., Ingrid B. Borecki, Ph.D., John D. Overton, Ph.D., Jeffrey G. Reid, Ph.D., David J. Carey, Ph.D., Andrew J. Murphy, Ph.D., George D. Yancopoulos, M.D., Ph.D., Aris Baras, M.D., Jesper Gromada, Ph.D., D.M.Sc., and Alan R. Shuldiner, M.D.

N Engl J Med 2016;374:1123-33.
DOI: 10.1056/NEJMoa1510926

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Table 2. Association between *ANGPTL4* E40K or Other Inactivating Mutations and Lipid Levels.*

Lipid	Noncarriers (N=41,177)	E40K Heterozygotes (N=1661)	E40K Homozygotes (N=17)	P Value†	Heterozygotes with Other Inactivating Mutation (N=75)	P Value‡
		median (IQR)			median (IQR)	
Triglycerides — mg/dl	132 (95–182)	115 (85–157)	81 (61–122)	2.0×10^{-23}	115 (78–162)	0.02
HDL cholesterol — mg/dl	48 (40–59)	52 (43–63)	67 (54–72)	1.6×10^{-17}	54 (44–62)	0.009
LDL cholesterol — mg/dl	114 (94–135)	116 (96–138)	107 (89–132)	0.20	119 (101–136)	0.60
Total cholesterol — mg/dl	195 (172–218)	196 (173–219)	182 (168–209)	0.90	193 (179–208)	0.80

Table 3. Association between *ANGPTL4* E40K or Other Inactivating Mutations and Coronary Artery Disease.*

Variants	Allele Frequency		Odds Ratio (95% CI)	P Value
	CAD Cases	CAD Controls		
E40K mutation in 1661 heterozygotes and 17 homozygotes	1.71	2.10	0.81 (0.70–0.92)	0.002
Heterozygous inactivating mutations in 75 participants	0.06	0.10	0.56 (0.32–1.00)	0.05

N Engl J Med 2016;374:1123-33.
DOI: 10.1056/NEJMoa1510926

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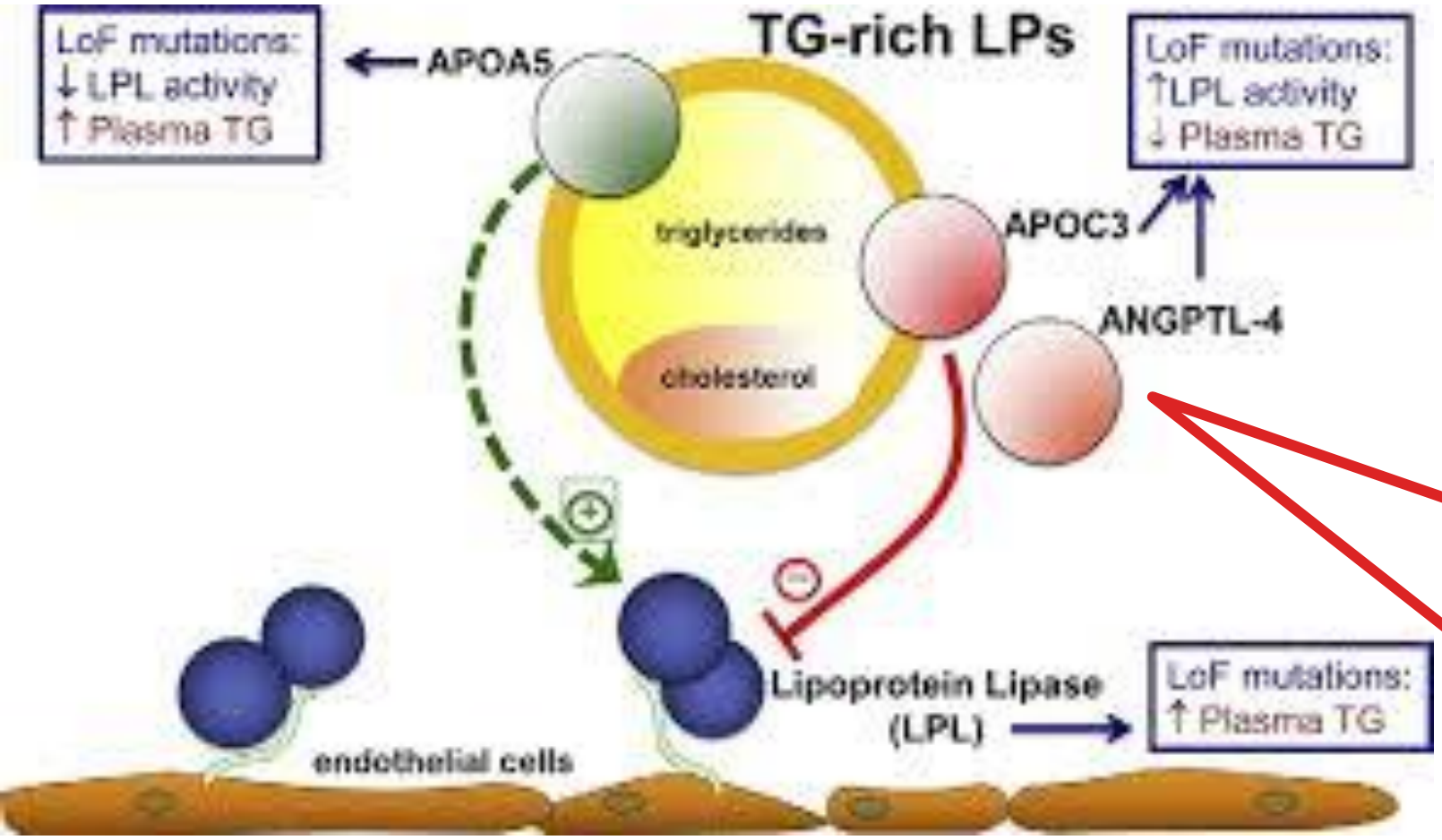
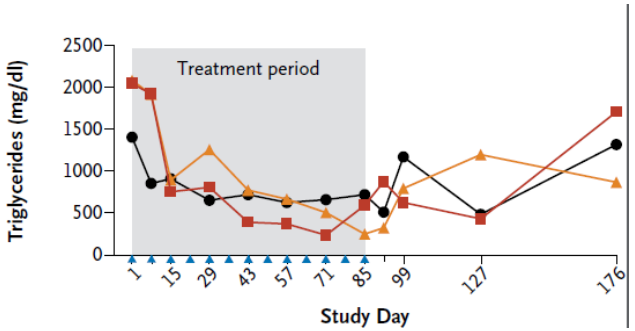
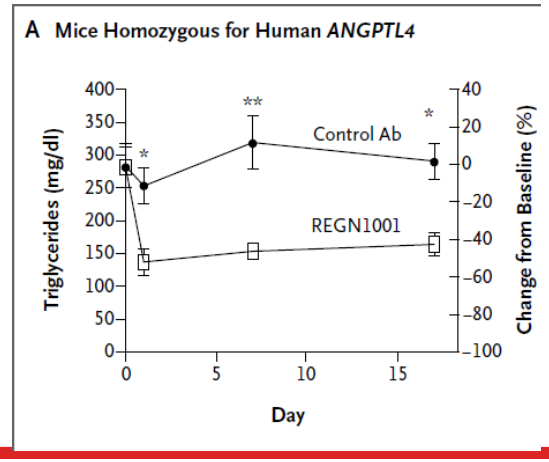
Drug targets



Antisense APOC3



Antilichamen ANGPTL4



Triglyceriden verlagen in de praktijk

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 3, 2019 VOL. 380 NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

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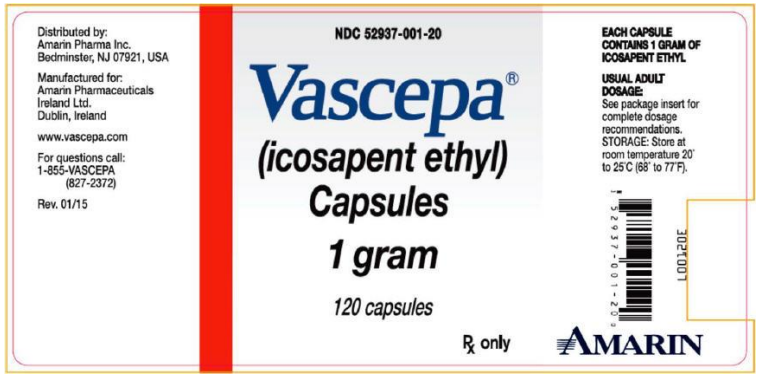
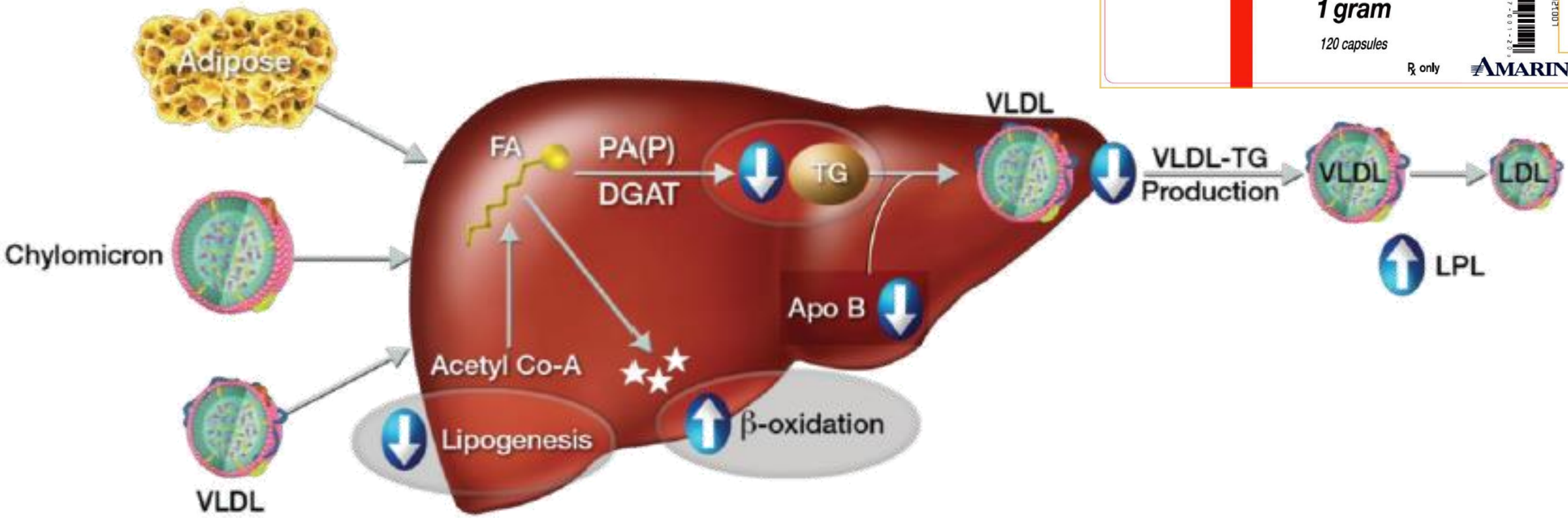
Wat is icosapent ethyl?





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Triglyceriden verlagen in de praktijk: Reduce-it

Gerandomiseerde dubbelblinde trial
8179 patienten met hoog risico HVZ (HVZ, DM of andere RF)
EN statine
EN nuchter TG 1.52-5.63 mmol/L
EN LDL-C 1.06-2.59 mmol/L

Gerandomiseerd naar:
4g (2x2g) icosapent ethyl of placebo

Primair eindpunt:
Cardiovasculair mortaliteit, niet-fataal myocard infarct of CVA, coronaire revascularizatie of instabiele AP

Secundair eindpunt:
Cardiovasculair mortaliteit, niet-fataal myocard infarct of CVA

Follow-up:
mediaan 4.9 jr, max 6,2 jr

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Triglyceriden verlagen in de praktijk: Reduce-it

	icosapent ethyl			Placebo			Tussen groepen
Last visit	**Mediaan**	**Mediane Δ**	**P**	**mediaan**	**Mediane Δ**	**P**	**P**
Triglycerides	170	-45	<0.001	202	-13	<0.001	<0.001
Non-HDLC	112	-5	<0.001	124	6	<0.001	<0.001
HDL-C	41	-1	<0,001	42	2	<0,001	<0,001
LDL-C	84	-1	0.14	92.1	5.7	<0.001	<0.001
Log hsCRP	0,6	-0,1	<0,001	1,0	0,3	0,0481	<0.001

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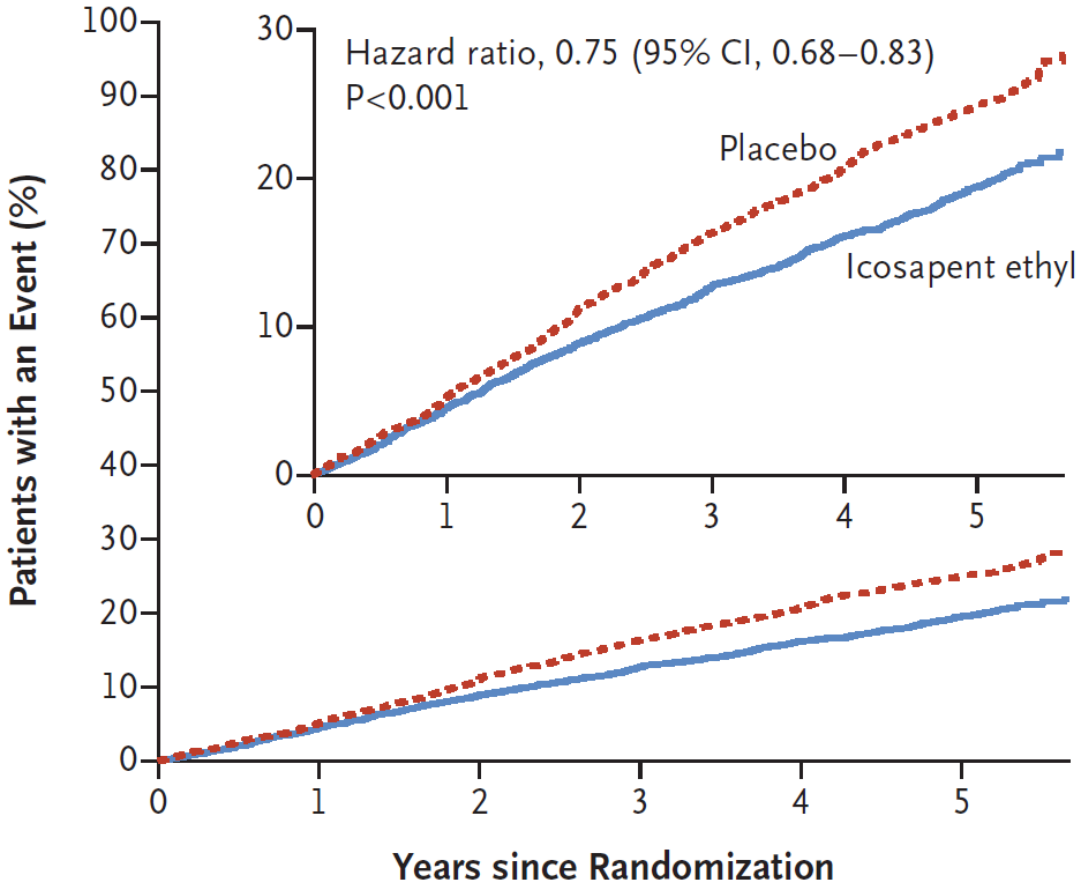
Triglyceriden verlagen in de praktijk: Reduce-it

A Primary End Point*



No. at Risk						
Placebo	4090	3743	3327	2807	2347	1358
Icosapent ethyl	4089	3787	3431	2951	2503	1430

22%

17.2%

- 4.8%
NNT 21

* Cardiovasculair mortaliteit, nonfatal myocard infarct of CVA, coronaire revascularizatie of instabiele AP

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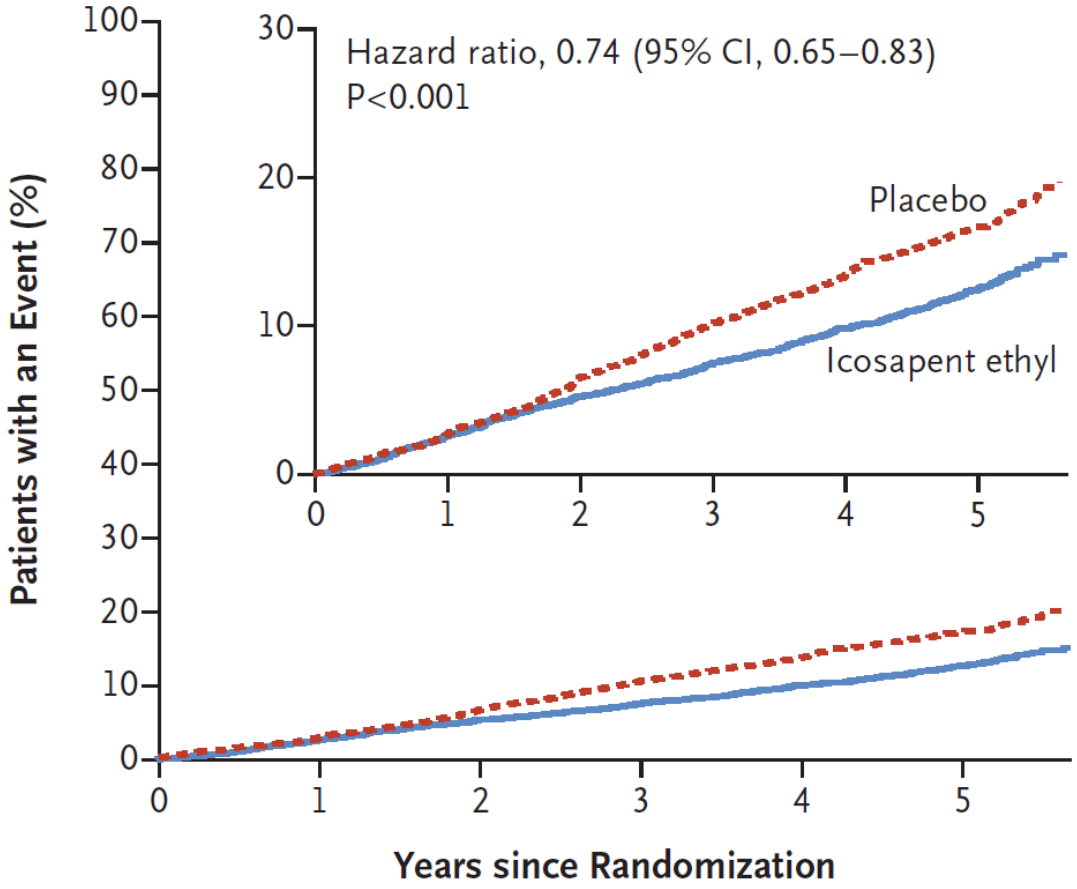
Triglyceriden verlagen in de praktijk: Reduce-it

B Key Secondary End Point *



14.8%
11.2%

- 3.6%
NNT 28

No. at Risk

Placebo	4090	3837	3500	3002	2542	1487
Icosapent ethyl	4089	3861	3565	3115	2681	1562

* Cardiovasculair mortaliteit, nonfatal myocard infarct of CVA,

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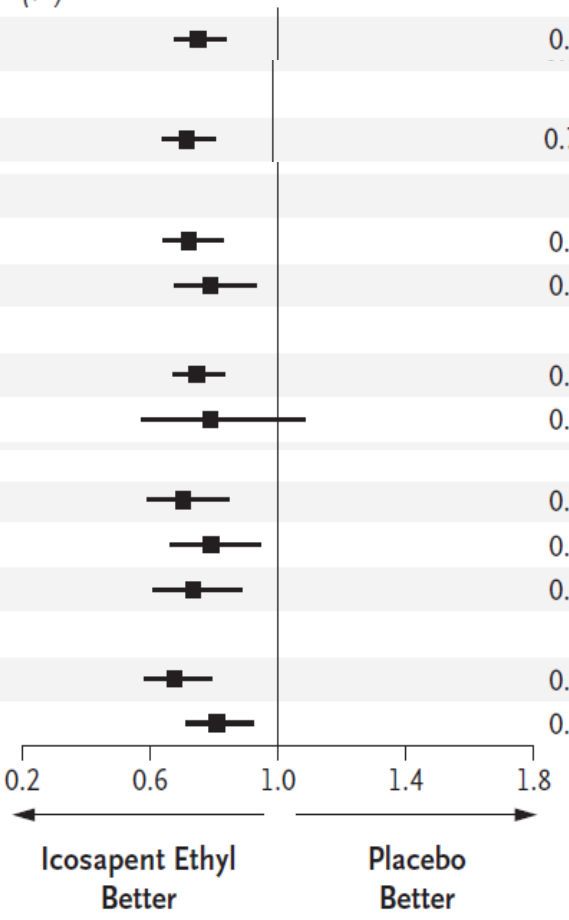
Triglyceriden verlagen in de praktijk: Reduce-it

Subgroup	Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
All patients	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68–0.83)	
Sex				0.33
Male	551/2927 (18.8)	715/2895 (24.7)	0.73 (0.65–0.82)	
Baseline triglycerides				0.45
≥200 mg/dl	430/2481 (17.3)	559/2469 (22.6)	0.73 (0.64–0.83)	
<200 mg/dl	275/1605 (17.1)	342/1620 (21.1)	0.79 (0.67–0.93)	
Baseline triglycerides				0.83
≥150 mg/dl	640/3674 (17.4)	811/3660 (22.2)	0.75 (0.68–0.83)	
<150 mg/dl	65/412 (15.8)	90/429 (21.0)	0.79 (0.57–1.09)	
In thirds				
≤67 mg/dl	244/1481 (16.5)	302/1386 (21.8)	0.72 (0.61–0.85)	
>67 to ≤84 mg/dl	248/1347 (18.4)	307/1364 (22.5)	0.81 (0.68–0.96)	
>84 mg/dl	213/1258 (16.9)	292/1339 (21.8)	0.74 (0.62–0.89)	
Baseline high-sensitivity CRP				0.07
≤2 mg/liter	288/1919 (15.0)	407/1942 (21.0)	0.68 (0.58–0.79)	
>2 mg/liter	417/2167 (19.2)	494/2147 (23.0)	0.81 (0.71–0.93)	



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Reduce-it

- Eerste moderne trial die aantoont dat TG verlaging HVZ reduceert
- Verschil huidige visolie producten 1) dosis (4 gr vs 1 gr) 2) EPA vs DHA
- Mogelijk ook andere mechanismen? (CRP, membraan stabilisatie)
- Meer studies in aantocht:
  - RESPECT-EPA, sec prev trial Japanse populatie
  - EVAPORATE, effect op coronaire plaques
  - STRENGTH, effect MACE 4gr Epanova icm statine

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Take home

- **Triglyceriden (triglyceride-rijke deeltjes) oorzakelijk verband met HVZ**
- **Nieuwe generatie TG verlagende medicatie verlagen HVZ**
- **Kortom:**

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