Ezetimibe:

- ***Ook hiermee reductie van events van een niet-statine middels LDL daling***
- ***Improve-It***
- ***Ook ondersteuning door Mendelian Randomization studies***

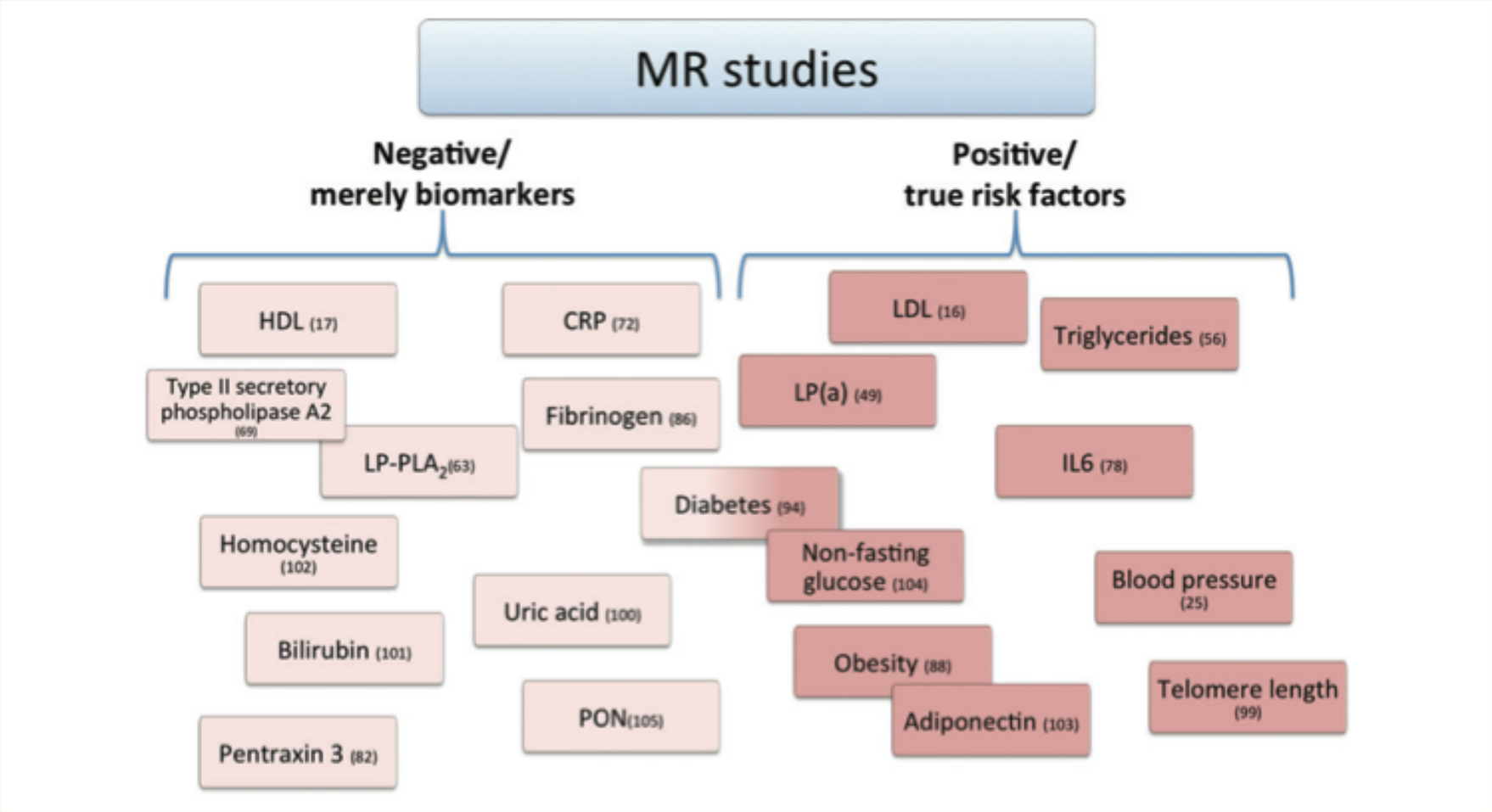


Figure 4 Brief overview about candidates tested in Mendelian randomization settings. While many biomarkers suggested a causal role in coronary artery disease in Mendelian randomization studies, others disappointed by negative results. The effect of diabetes mellitus single nucleotide polymorphisms was by far smaller than expected and barely significant. Numbers refer to the references in which the Mendelian randomization data have been reported. [100–105]

Inactivating Mutations in *NPC1L1* and Protection from Coronary Heart Disease

The Myocardial Infarction Genetics Consortium Investigators

ABSTRACT

BACKGROUND

Ezetimibe lowers plasma levels of low-density lipoprotein (LDL) cholesterol by inhibiting the activity of the Niemann–Pick C1-like 1 (NPC1L1) protein. However, whether such inhibition reduces the risk of coronary heart disease is not known. Human mutations that inactivate a gene encoding a drug target can mimic the action of an inhibitory drug and thus can be used to infer potential effects of that drug.

NEJM 2015

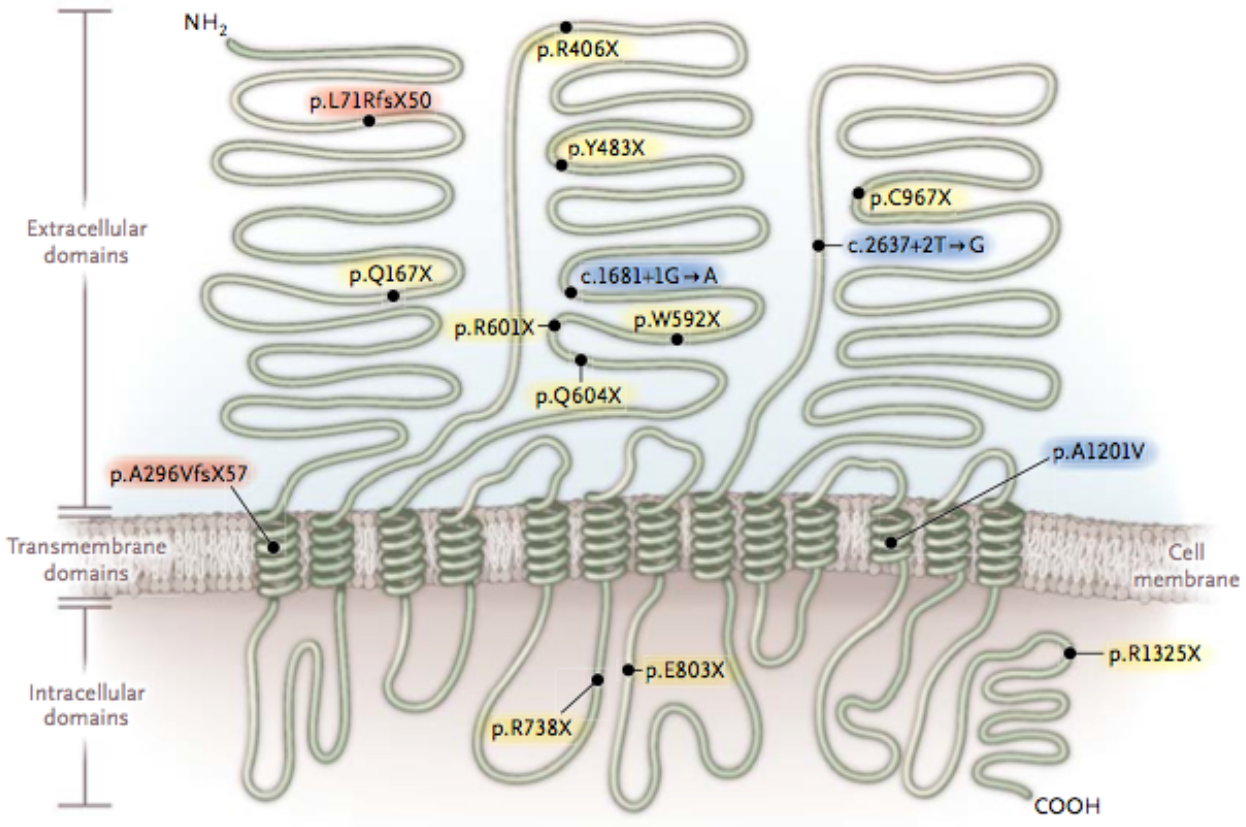


Figure 1. Inactivating Mutations in *NPC1L1* Identified in the Study.

Black circles indicate individual mutations along with the effect expected to lead to NPC1L1 inactivation. Mutations p.L71RfsX50 and p.A296VfsX57 (red shading) are indels that shift the open reading frame and induce a premature termination codon after an additional 50 and 57 amino acids, respectively. Mutations c.1681+1G→A, c.2637+2T→G, and p.A1201V (c.3602C→T) (blue shading) alter the splicing process at sites of modification of the nascent pre–messenger RNA transcript (splice-site mutations). All other mutations (yellow shading) are single-nucleotide variants that introduce a termination codon. The locations of the three main extracellular domains, 13 transmembrane domains, and intracellular domains are based on data from Betters and Yu.[27] NH_2 denotes the N-terminal at which protein translation is initiated, and COOH the C-terminal at which translation terminates.

RESULTS

With sequencing, we identified 15 distinct *NPC1L1* inactivating mutations; approximately 1 in every 650 persons was a heterozygous carrier for 1 of these mutations. Heterozygous carriers of *NPC1L1* inactivating mutations had a mean LDL cholesterol level that was 12 mg per deciliter (0.31 mmol per liter) lower than that in noncarriers (P=0.04). Carrier status was associated with a relative reduction of 53% in the risk of coronary heart disease (odds ratio for carriers, 0.47; 95% confidence interval, 0.25 to 0.87; P=0.008). In total, only 11 of 29,954 patients with coronary heart disease had an inactivating mutation (carrier frequency, 0.04%) in contrast to 71 of 83,140 controls (carrier frequency, 0.09%).

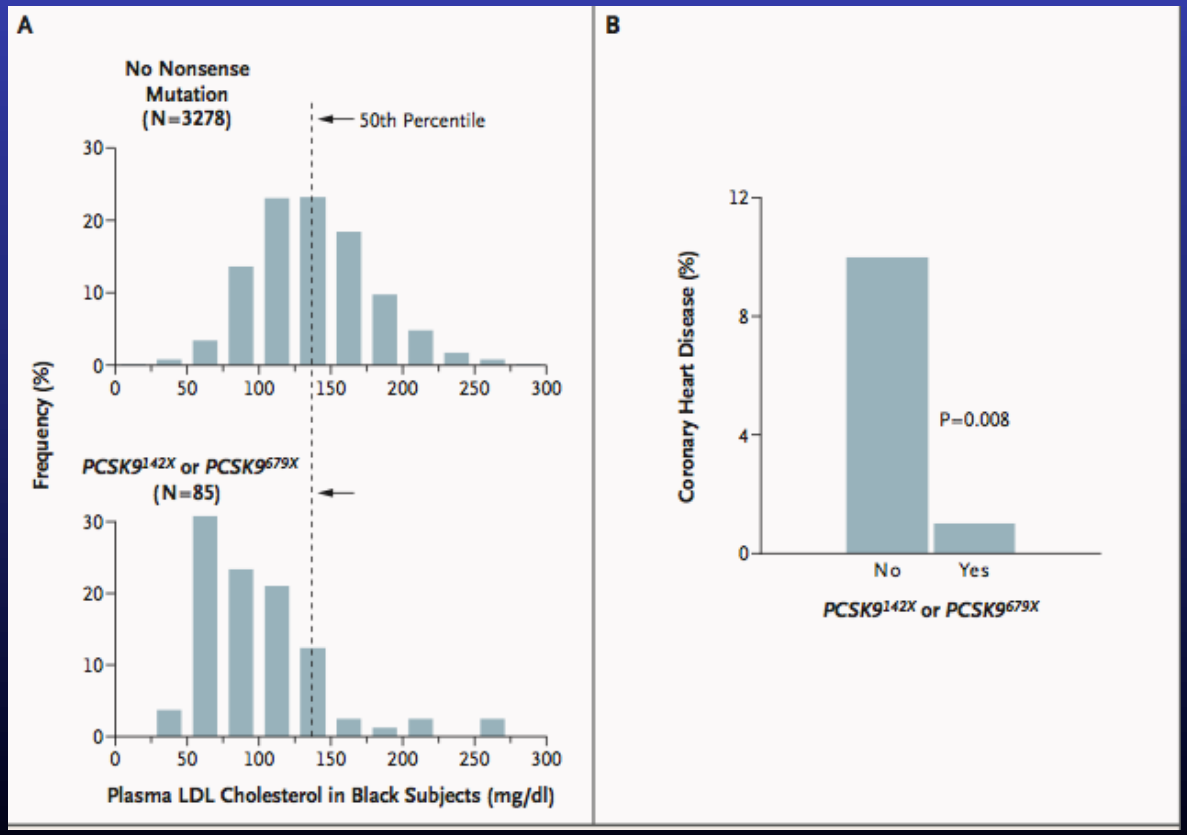
CONCLUSIONS

Naturally occurring mutations that disrupt NPC1L1 function were found to be associated with reduced plasma LDL cholesterol levels and a reduced risk of coronary heart disease. (Funded by the National Institutes of Health and others.)

ORIGINAL ARTICLE

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.



NEJM 2006

LDL 100 mg/dl = 2.5 mmol/l

Study Design

IMPROVE-IT

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

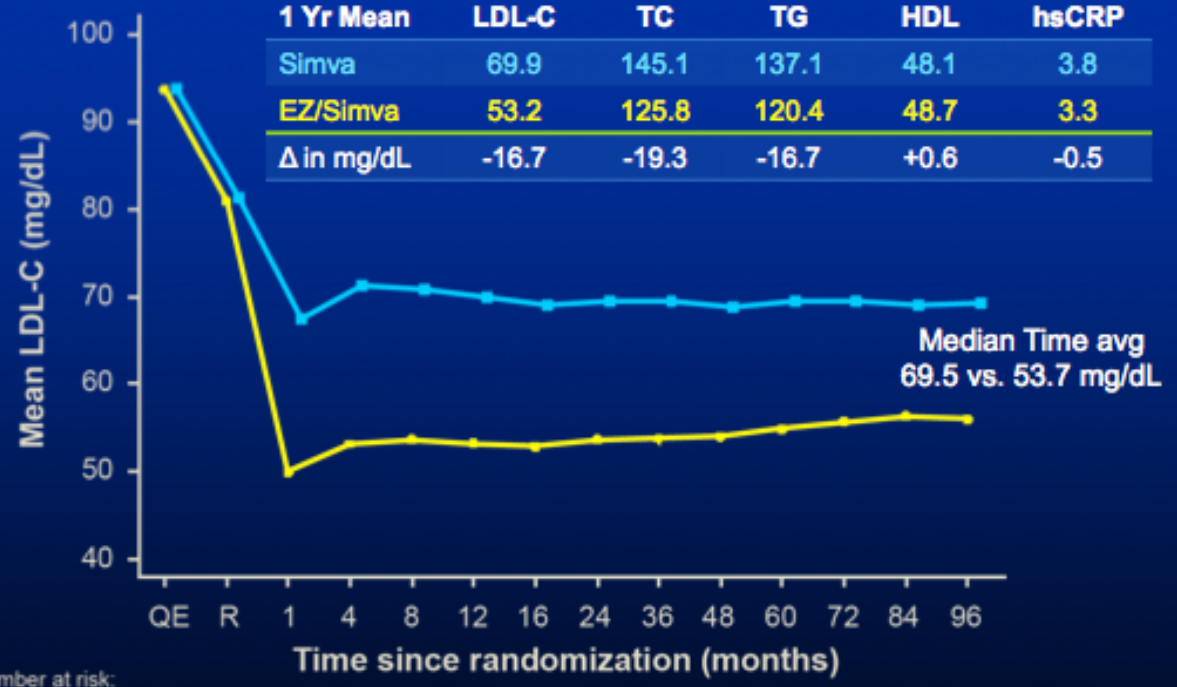
Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

LDL-C and Lipid Changes

IMPROVE-IT

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5

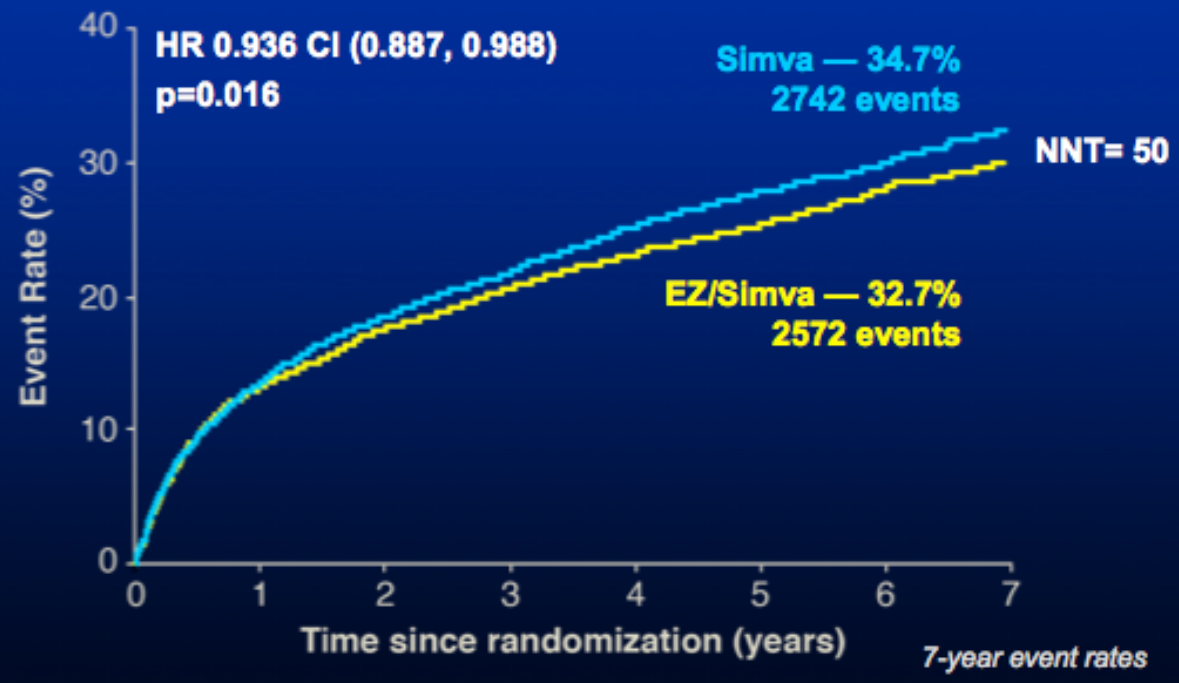


Number at risk:

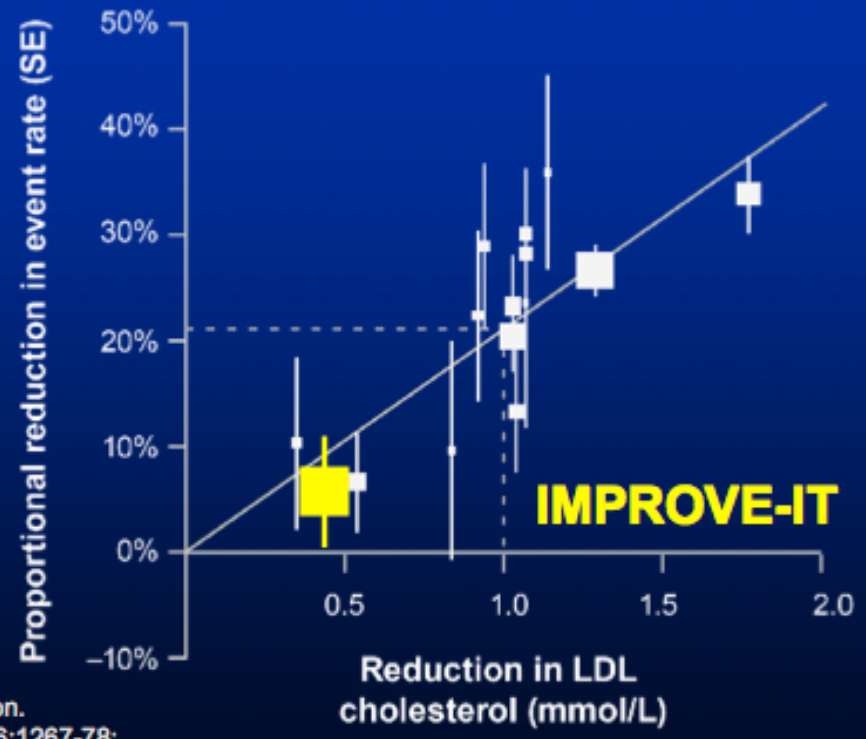
EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit



CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376:1670-81.

Conclusions

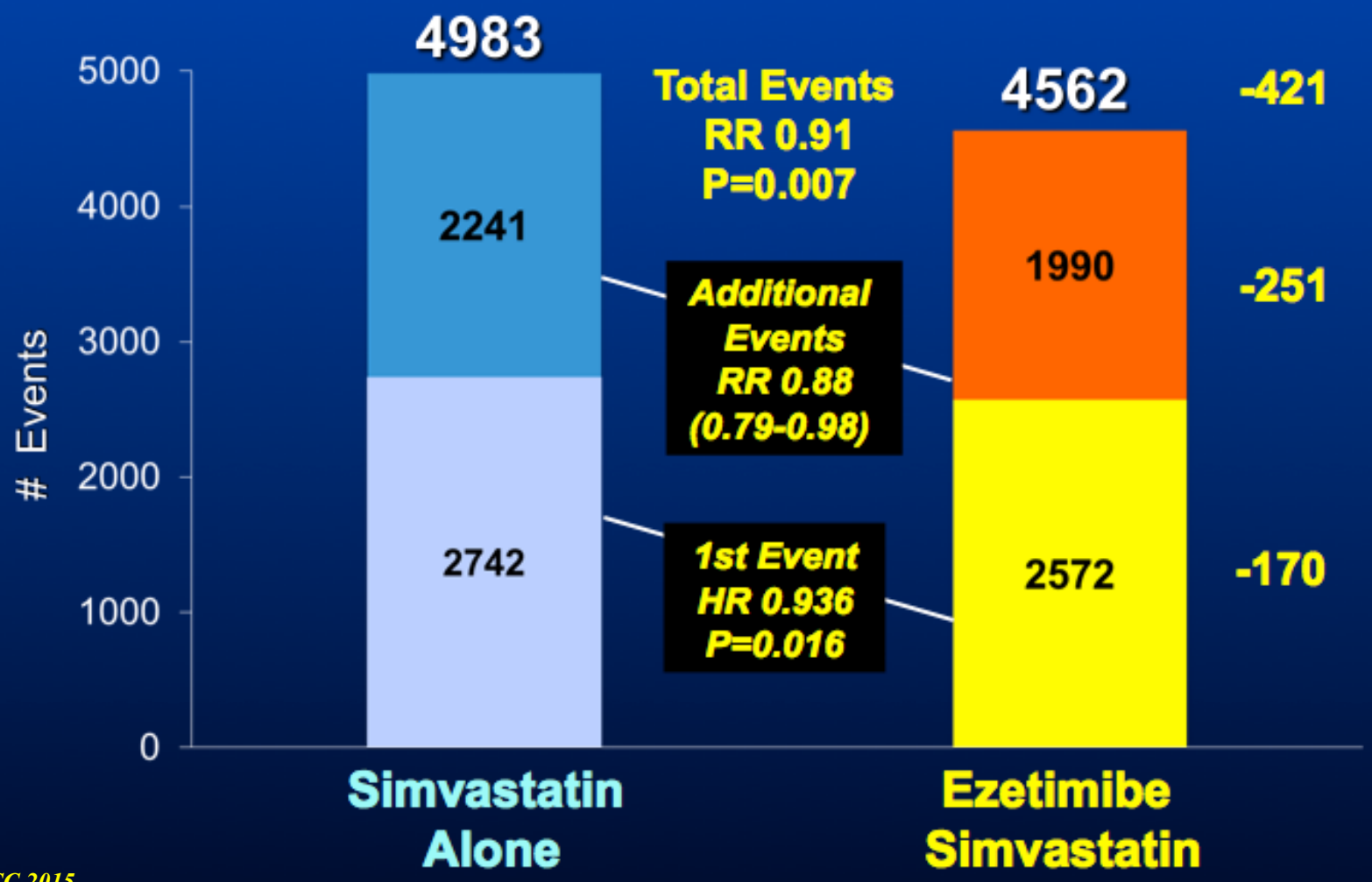
IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:

- **YES:** *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
- **YES:** Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
- **YES:** Confirms ezetimibe safety profile

➡ **Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events**

➡ **Results could be considered for future guidelines**

Total Primary Endpoint Events



ACC 2015

Improve-It: externe validiteit

- ***Middel is effectief en veilig ….***
- ***Enge interpretatie: alleen tbv streven naar zeer lage LDL waarden post ACS..***
- ***Ruime interpretatie: te gebruiken naast max getolereerde statine therapie bij streven naar voldoende LDL daling cq streven naar LDL doelwaarde ..***
- ***Immers: rosuva ook te gebruiken buiten prim preventie populatie met licht verhoogd CRP ….***

Dus visie tav ezetimibe:

- ***Genetisch gevalideerd***
- ***Externe validiteit***
- ***Ook incorporatie in toekomstige adviezen tav PCSK9***

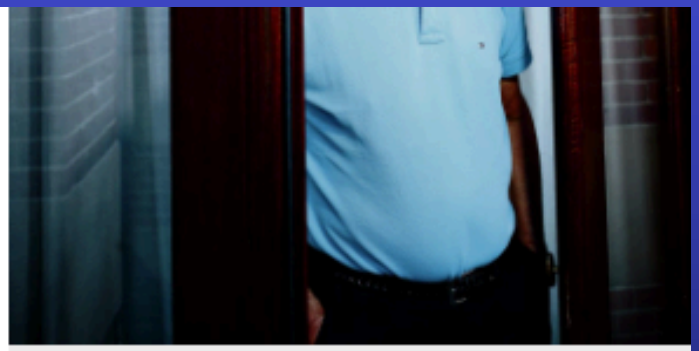
Geneesmiddelen zijn gevaarlijk

Peter Gøtzsche „Het wordt tijd dat mensen in opstand komen tegen de farmaceutische industrie."

Sander Voormolen 16 november 2015

Gooi alle medicijnen maar het raam uit. „Dat zou niet eens zo'n gek idee zijn", zegt Peter Gøtzsche op een hotelkamer in Amsterdam. „We zouden veel minder pillen moeten slikken dan we op dit moment doen. Als je je bedenkt dat medicijnen, na kanker en hart- en vaatziekten, de op twee na grootste doodsoorzaak zijn, dan is het duidelijk dat we er een hoop uit het raam zouden moeten gooien."

Gøtzsche is hoogleraar opzet en analyse van klinisch onderzoek in Kopenhagen. Dit weekend verscheen zijn boek *Dodelijke medicijnen en georganiseerde misdaad* in Nederlandse vertaling. De oorspronkelijke uitgave in het Deens en Engels deed al veel stof opwaaien in de medische wereld. Gøtzsche beschuldigt de farmaceutische industrie onomwonden van 'maffiapraktijken', en daarmee gaat hij veel verder dan andere schrijvers die de farmaceutische industrie bekritiseerden.



Peter Gøtzsche: „De hele gezondheidszorg is corrupt. De industrie koopt iedereen om die in de weg staat."

Er is weinig verschil met de georganiseerde misdaad, zegt Gøtzsche, want de farmaceutische industrie gaat letterlijk over lijken om zijn doel te bereiken: woekerwinsten maken. „Geneesmiddelen zijn veel gevaarlijker dan mensen beseffen, daarom heb ik dit boek geschreven", zegt Gøtzsche.

Nb: LDL daling .. het hoe is ook van belang !!

Selected Clinical Trials of Medications for Lowering LDL Cholesterol Levels Other Than Statins Alone and Their Effects on Cardiovascular Events.*

Trial	Study Drug	Comparison	Primary End Point	% Difference in LDL Cholesterol Levels†	Cardiovascular Outcome	
					Hazard Ratio (95% CI)	P Value
HERS	Estrogen (alone or in combination with medroxyprogesterone)	Placebo	Nonfatal myocardial infarction or death due to coronary heart disease	–11	0.99 (0.80–1.22)	0.91
FIELD	Fenofibrate	Placebo	Nonfatal myocardial infarction or death due to coronary heart disease	–12	0.89 (0.75–1.05)	0.16
ILLUMINATE	Torcetrapib–atorvastatin	Placebo plus atorvastatin	Nonfatal myocardial infarction, stroke, hospitalization for unstable angina, or death due to coronary heart disease	–27	1.25 (1.09–1.44)	0.001
HPS-2 THRIVE	Niacin–laropiprant	Placebo	Nonfatal myocardial infarction, death from coronary causes, stroke, or arterial revascularization	–16	0.96 (0.90–1.03)	0.29
IMPROVE-IT	Ezetimibe–simvastatin	Placebo plus simvastatin	Death due to cardiovascular causes, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke	–24	0.94 (0.89–0.99)	0.02

Veiligheid
Zijn we te bang?

Politiek
Is democratie echt *overrated*?

Werk
Werken we straks allemaal flexibel?

Privacy
Wie kan nog een geheim bewaren?

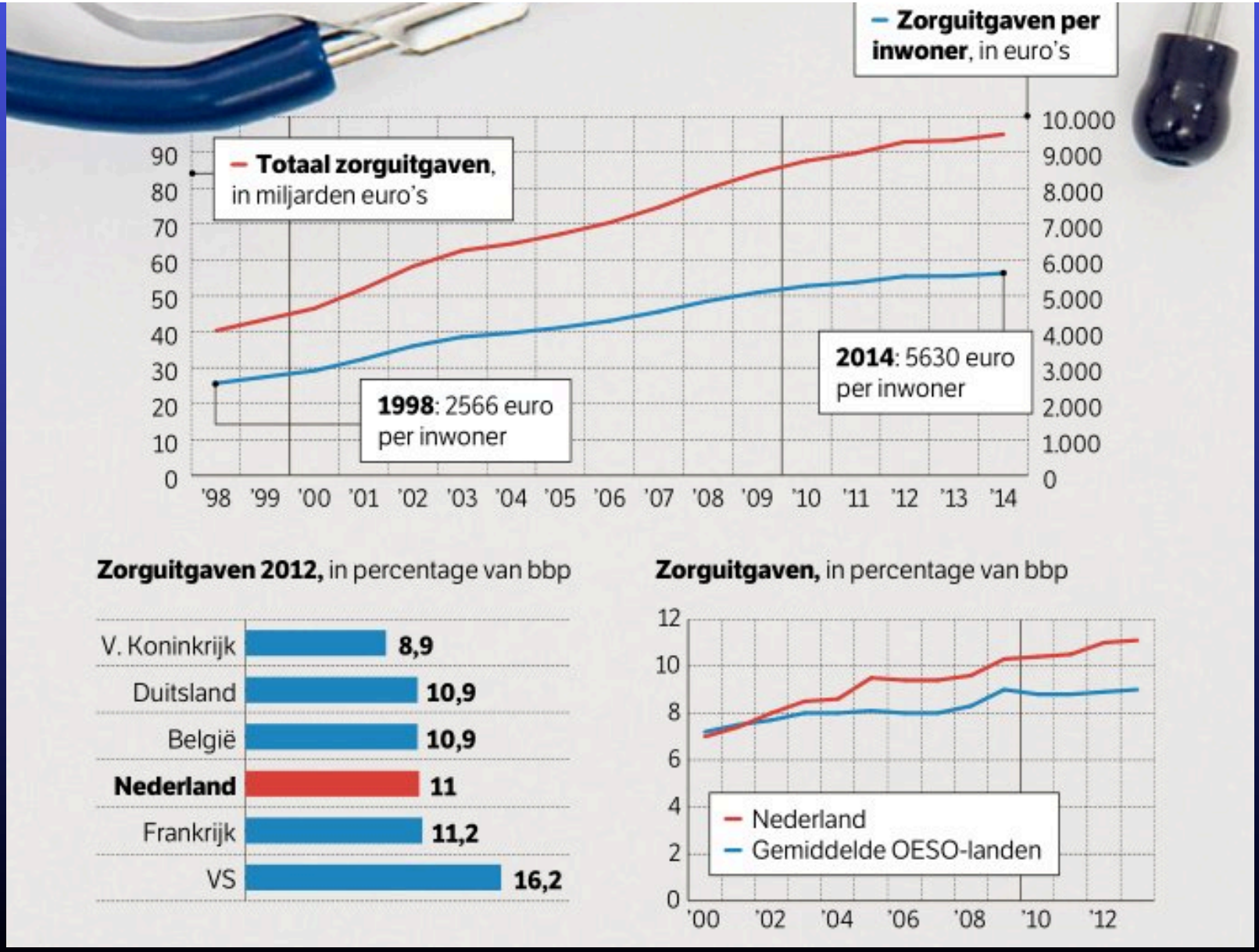
Onderwijs
Leren we het goede?

Zorg
Hoe veel mag een mensenleven kosten?

Economie
Hoe blijven we zo rijk?

Hoeveel mag een **mensenleven** kosten?

Gezondheidszorg Minister Schippers voelde zich niet thuis bij de vraag naar een bovengrens voor dure behandelingen. Niet spreken over wat een gezond jaar mag kosten is ook niet ethisch, menen sommigen. En besteden we het geld wel goed?


Zorguitgaven per inwoner, in euro's
Totaal zorguitgaven, in miljarden euro's
1998: 2566 euro per inwoner
2014: 5630 euro per inwoner
90
80
70
60
50
40
30
20
10
0
10.000
9.000
8.000
7.000
6.000
5.000
4.000
3.000
2.000
1.000
0
'98 '99 '00 '01 '02 '03 '04 '05 '06 '07 '08 '09 '10 '11 '12 '13 '14
Zorguitgaven 2012, in percentage van bbp
V. Koninkrijk 8,9
Duitsland 10,9
België 10,9
Nederland 11
Frankrijk 11,2
VS 16,2
Zorguitgaven, in percentage van bbp
12
10
8
6
4
2
0
'00 '02 '04 '06 '08 '10 '12
Nederland
Gemiddelde OESO-landen

Nature Reviews Drug Discovery | AOP, published online 17 October 2014; doi:10.1038/nrd4475

NEWS & ANALYSIS

FROM THE ANALYST'S COUCH

The dyslipidaemia market

Victoria Hudson

Yellow sofa, image from iStock.

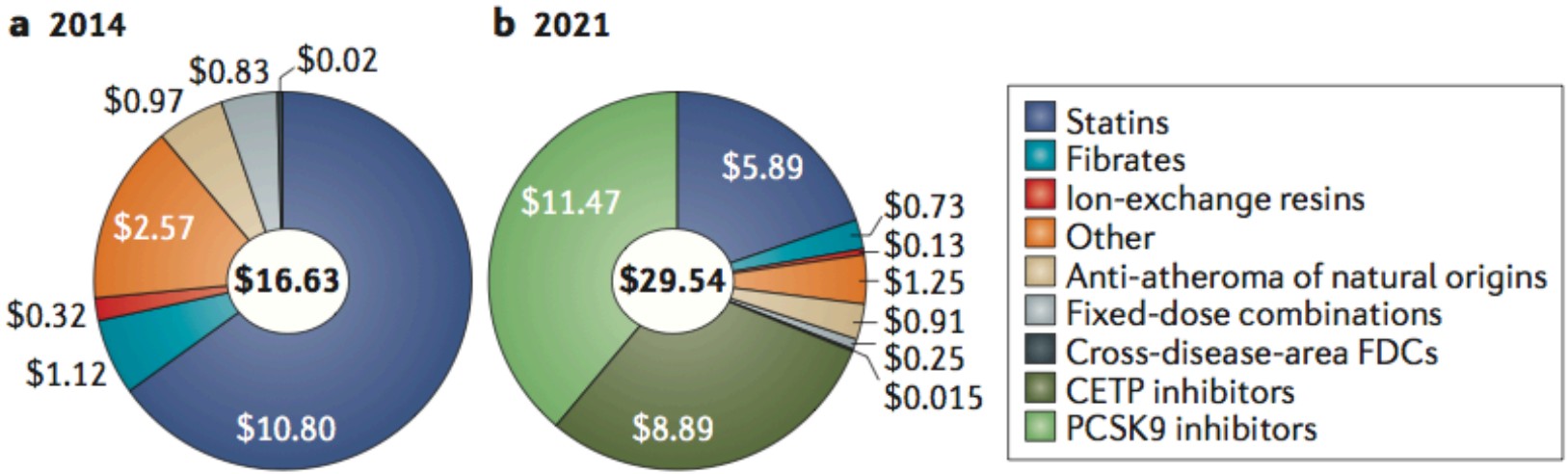


Figure 1 | **Shifting composition of the dyslipidaemia market.** Data are for the United States, Japan, and five major European Union markets (namely, France, Germany, Italy, Spain and the United Kingdom). The dyslipidaemia market is forecast to grow from US$16.6 billion in 2014 to $29.5 billion in 2021. 'Other' refers to the compounds in Merck & Co.'s ezetimibe franchise: Zetia, Vytorin, and Liptruzet, as well as to the niacin class. All values are in US$ billions. CETP, cholesteryl ester transport protein; FDC, fixed-dose combination; PCSK9, proprotein convertase subtilisin kexin type 9.

PCSK9:

- ***Alles wijst op een succesvolle uitkomst van de studies***
- ***Genetisch gevalideerd***
- ***Safety zal zelden in een RCT goed tot uiting komen***
- ***Primair inzetten bij patiënten met een zeer hoog residueel risico (maar denk tegelijkertijd aan andere medicatie .. langer geven van DAPT etc)..***
- ***Game-changer: vergelijkbaar met introductie van NOACs bij AF***