“THE LOWER THE BETTER”

Rationale, Results and Implications

IMPROVE-IT TRIAL

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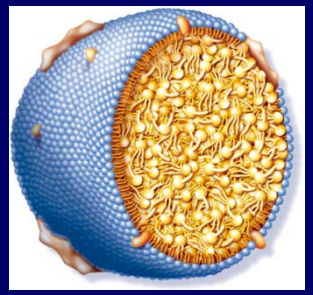
LDL lowering
Looking back, facing forward



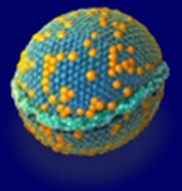
- Current lipid regulating therapeutic strategies.
- IMPROVE-IT rationale and results.
- Implications of IMPROVE-IT for treatment.

Addressing residual risk through lipid regulation

Paradigms of benefit

Lower LDL further

Raise HDL



Increase statin dose
More potent statins

Reduce residual risk

PPAR regulation
Fibrates, glitazones

Cholesterol absorption inhibitors
ezetimibe

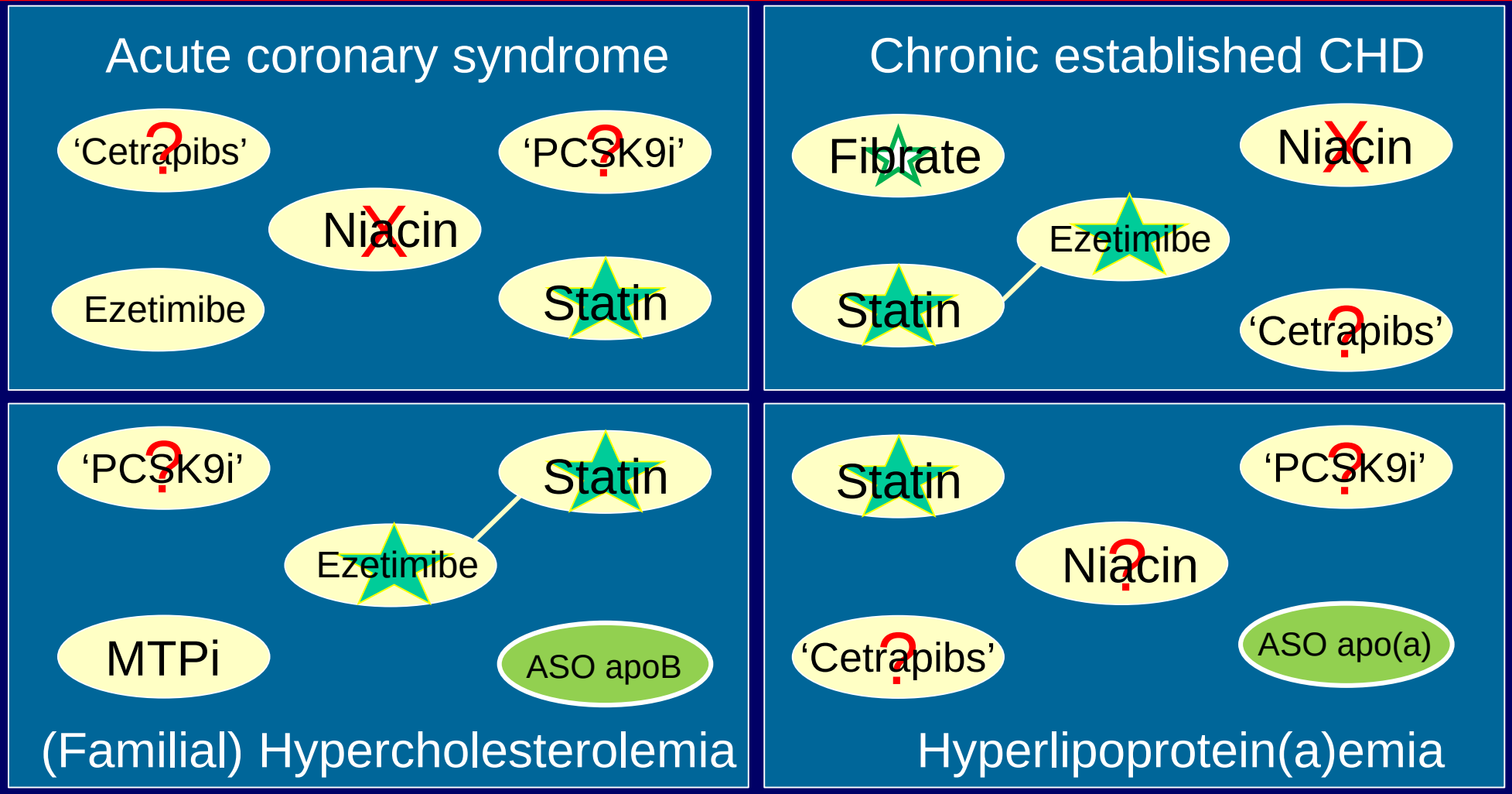
CETP inhibitors
'cetrapibs'

PCSK9 inhibitors

Niacin

Therapeutic agents

Emerging (and retreating) treatment options in dyslipidemia and CVD



ASO review - Visser EHJ (2012) 33;1451-8 Lomitapide - Cuchel et al Lancet (2013) 381:40-46 PCSK9ab - Stein et al NEJM (2012) 366:1108-18

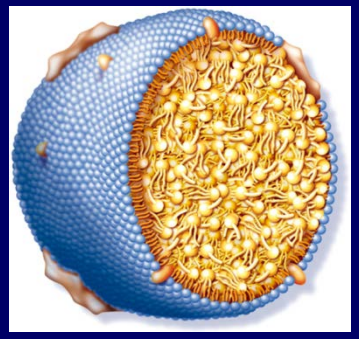
Role of LDL in atherogenesis

Cellular remodelling

Release of bio-active lipids

Extracellular pathology

Lipoprotein retention
Deposits early micro- and later macro-cholesterol crystals.



Innate immunity

Initiates localised inflammation.
Macrophage recruitment.
Intracellular cholesterol accumulation.
Necrosis

Auto-immunity (apoB)
Adaptive immunity

See Libby, Ridker, Hansson. Nature (2011); 473:317-325

Relatie LDLc en plaque

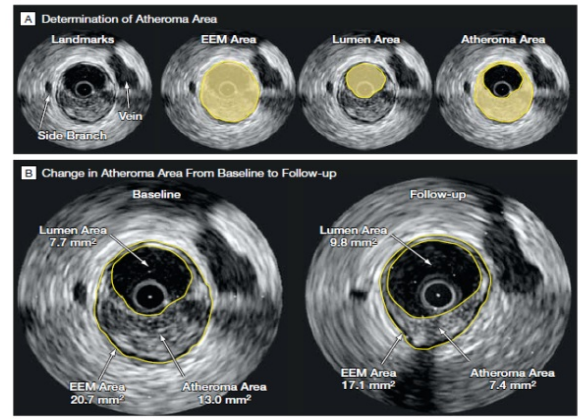
2004 REVERSAL:

Studie opzet

- Dubbel-blinde, gerandomiseerde studie met 654 patiënten die coronaire angiographie moeten ondergaan.
- Atorvastatine 40 mg VS pravastatine 80 mg
- Primair eindpunt: percentage verandering in atheroma volume (follow up – baseline) gemeten door middel van Intravasculair Ultrasound (IVUS)

Resultaten

- Sterkere LDLc daling in de atorvastatine groep
  LDLc 2.85 mmol/L VS 2.05 mmol/L
- **Significante regressie van de plaque in de atorvastatine groep** (P= 0.02)



Nissen, JAMA 2004;291:1071-80

Relatie LDLc en plaque

- **2006 ASTEROID**

Studie opzet

- Open Label, blinded end-ploint trial in 507 patienten
- Rosuvastatine 40 mg
- Primair eindpunt; verandering in PAV en verandering in nominaal atheroma volume gemeten dmv IVUS

Resultaten

- Na 24 mnd LDLc daling naar 1.6 mmol/L
- **Intensieve statine therapie zorgt voor regressie van de plaque**

Nissen JAMA 2006;295:1156-1565

Relatie LDLc en plaqueregressie statines

- **2011 SATURN:**

Studie opzet

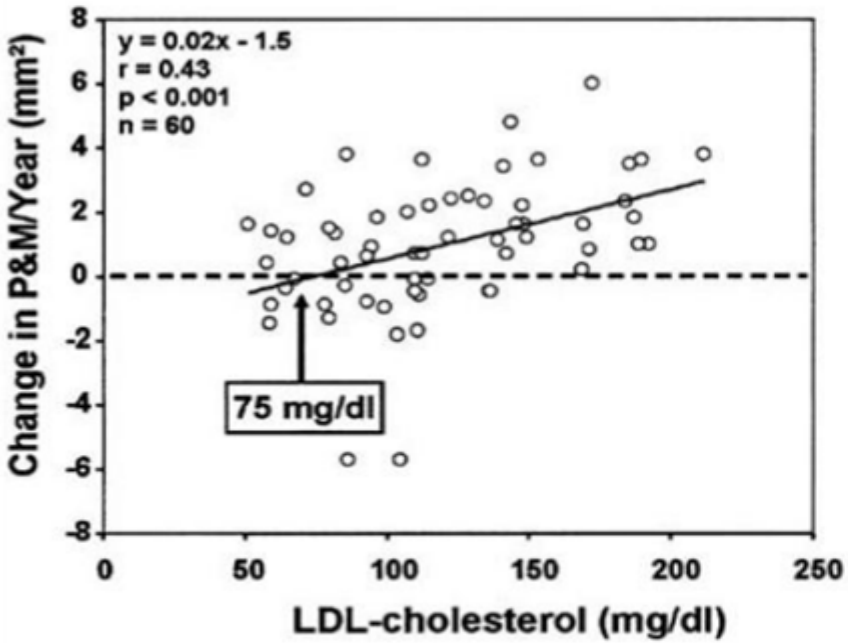
- Prospectieve, gerandomiseerde, multicenter, dubbel-blinde, clinical trial in 1039 patienten met HVZ
- Atorvastatine 80 mg VS rosuvastatine 40 mg
- Primair eindpunt; verandering in PAV en TAV gemeten dmv IVUS

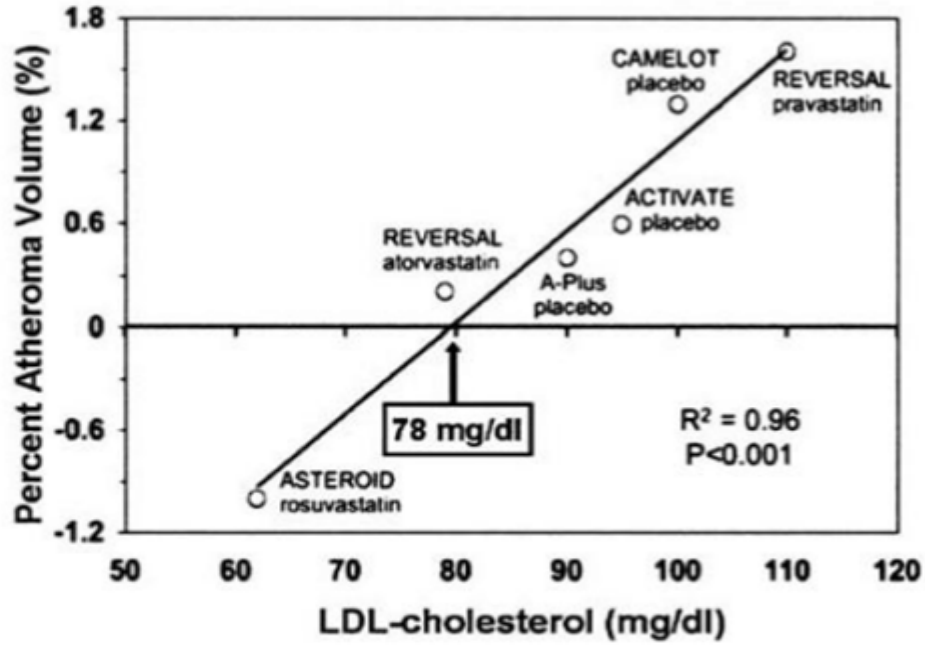
Resultaten

- Na 104 wkn sterke LDLc daling in rosuvastatine groep
  - LDLc 1.62 mmol/L vs 1.82 mmol/L ($P < 0.001$)
- In beide groepen regressie van de plaque
- Verandering in PAV; afname met 0.99% (95% confidence interval [CI], −1.19 to −0.63) met atorvastatine en 1.22% (95% CI, −1.52 to −0.90) met rosuvastatine (P=0.17).

Nicholls et al, n engl j med 365;22; 2011

Relatie LDLc en plaqueregressie/progressie





Er is een **relatie tussen LDLc, statines en plaque/regressie progressie**

- **Lager LDLc is beter**
- Bij een **LDLc < 2.0 mmol/L sprake van regressie (afname) en daarboven progressie (toename) de plaque**
- Tot nu toe bewezen voor statines, geldt dit ook voor **niet-statines?**

Nissen JAMA 2006;295:1156-1565

Plaque regressie en ezetimibe?

- **2015 PRECISE IVUS studie**

Studie opzet

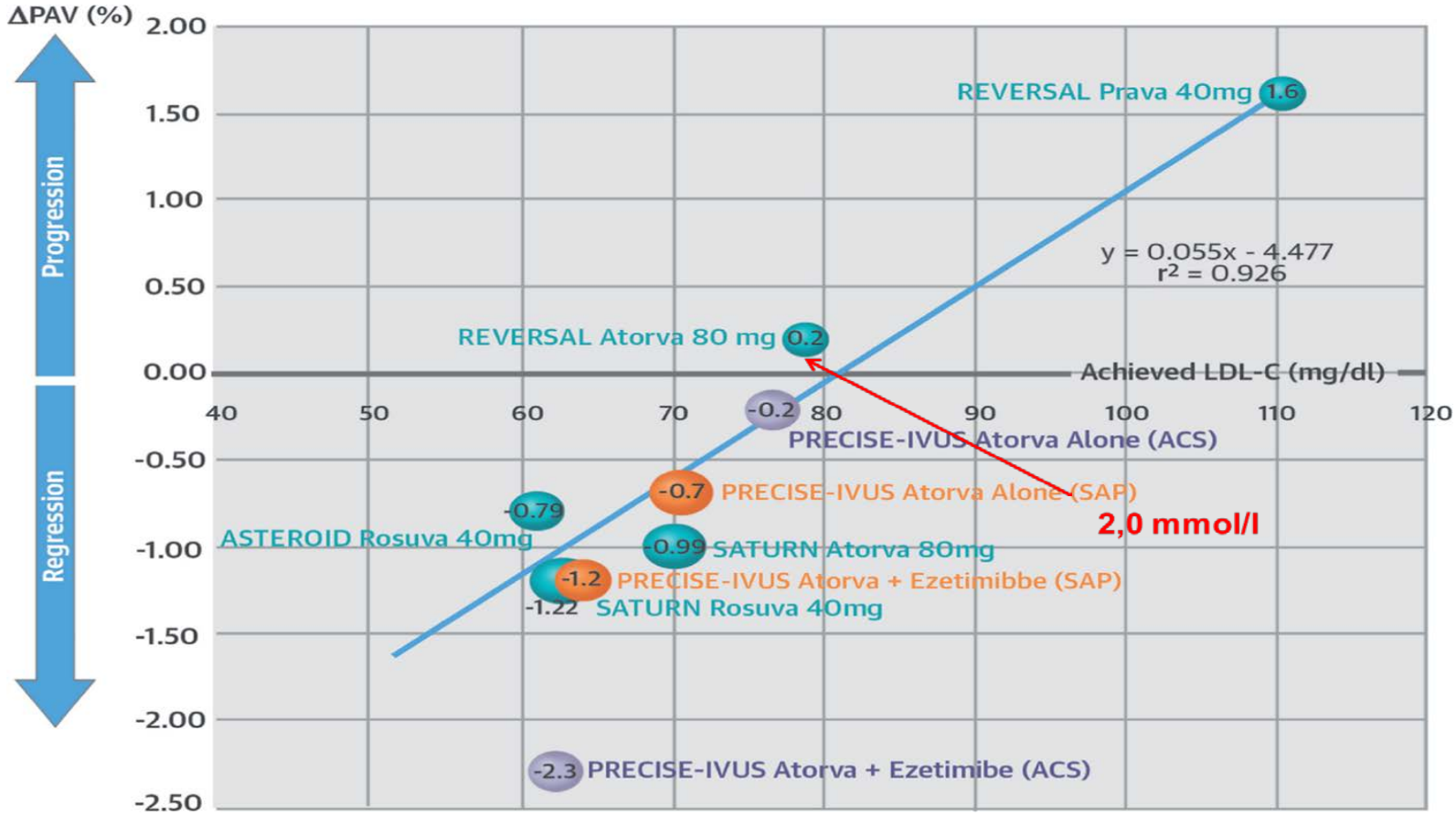
- Multicenter, prospectieve, gerandomiseerde studie in 202 patiënten met ACS/SAP na PCI,
- Atorvastatine VS atorvastatine+ ezetimibe
- Primair eindpunt; verandering in PAV (non-inferiority, hierna test op superioriteit) IVUS

Resultaten

- Voor combinatiegroep non-inferiority aangetoond, maar ook superioriteit op regressie van de plaque
- Verandering in PAV -1.4 in atorva/eze VS -0.3 in atorvastatine groep (P= 0.001)
- Naast statines heeft **ezetimibe** ook invloed op de plaqueregressie

Tsujita JACC 2015;66:495-507

Relatie LDLc en plaque regressie/progressie statines en ezetimibe

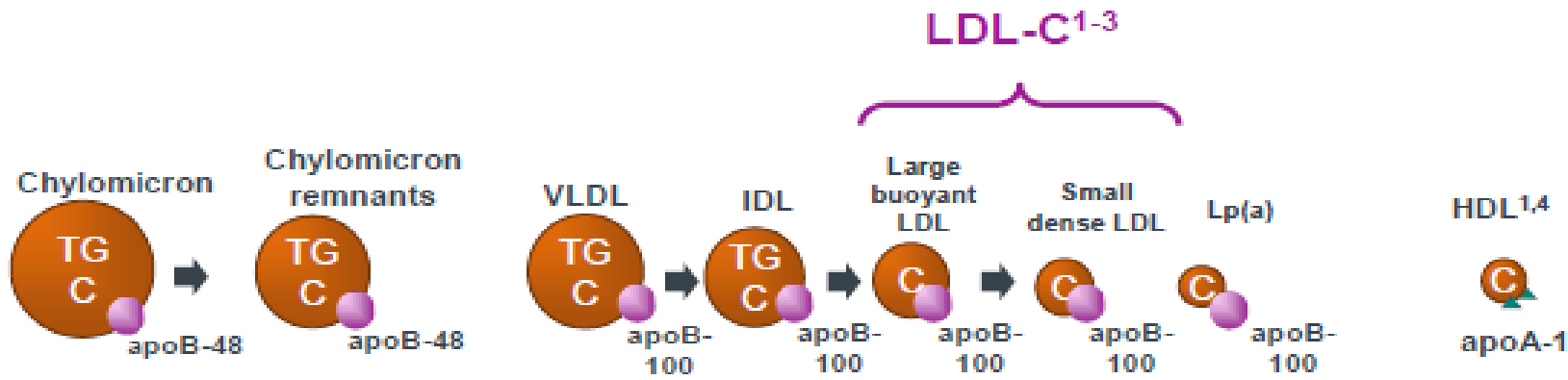


Meer regressie van de plaque bij LDLc < 1.9 mmol/L

Tsujita JACC 2015;66:495-507

Relatie LDL-c en CHD

- Multiple lines of evidence (animal studies, laboratory investigations, epidemiology, genetic forms of hypercholesterolemia, and controlled trials) indicate a strong causal association between elevated LDL-C and CHD[1]



Adapted with permission from Walldius G et al.[5]

CHD = coronary heart disease; TG = triglyceride; Apo = apolipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein; Lp(a) = lipoprotein (a); C = cholesterol.

1. NCEP ATP III Expert Panel. *Circulation*. 2002;106:3143–3421. 2. Rana JS et al. *Curr Opin Cardiol*. 2010;25:622–626. 3. Chapman MJ et al. *Eur Heart J Suppl*. 2004;6(suppl A):A43–A48. 4. Barter P. In: Ballantyne CM. *Clinical Lipidology: A Companion to Braunwald's Heart Disease*. Saunders, an imprint of Elsevier Inc; 2009:387–395. 5. Walldius G et al. *J Intern Med*. 2004;255:188–205.

LDL-c: 4,9 mmol/L versus 3,2 mmol/L

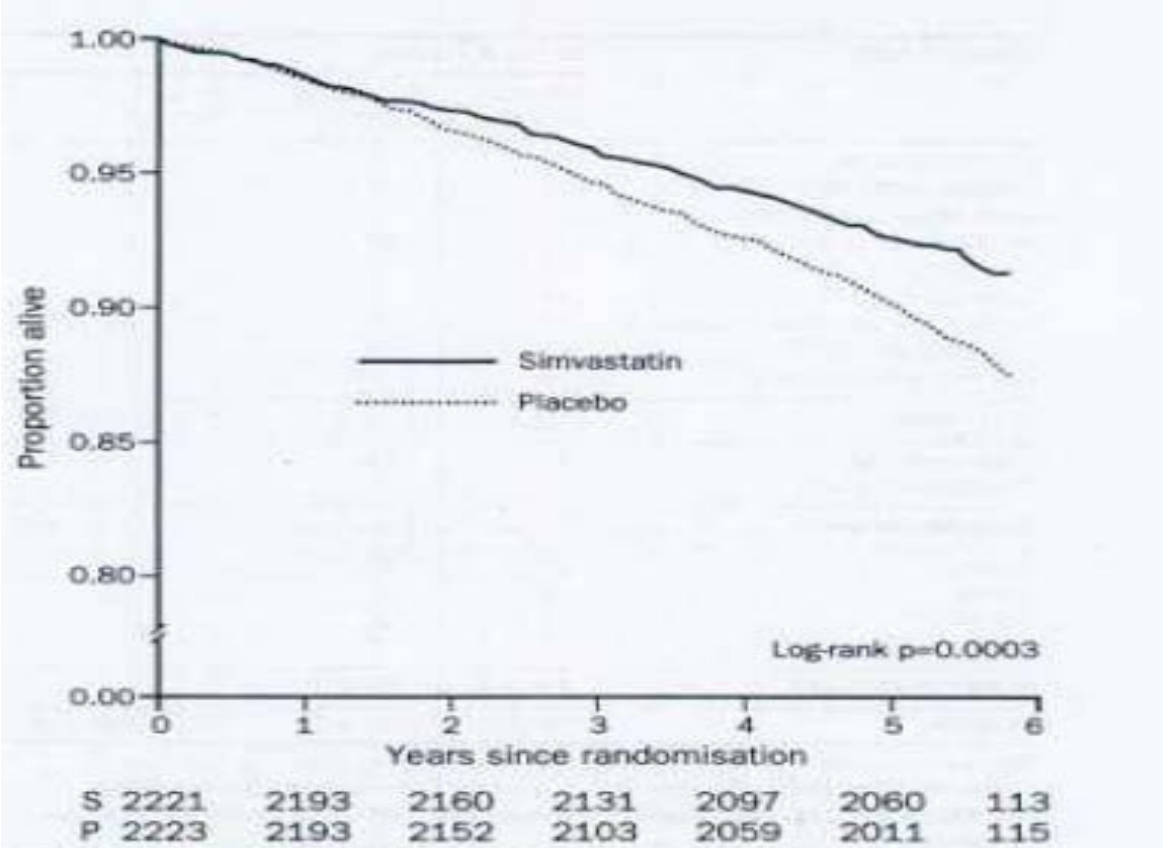


Figure 1: **Kaplan-Meier curves for all-cause mortality**
Number of patients at risk at the beginning of each year is shown below the horizontal axis.

4S - 1994: 30% minder kans op een CV-event

Terje R Pedersen et al *The Lancet* 1994; **34:** 1383–1389

LDL-c: 3.5 mmol/L versus 2.5 mmol/L

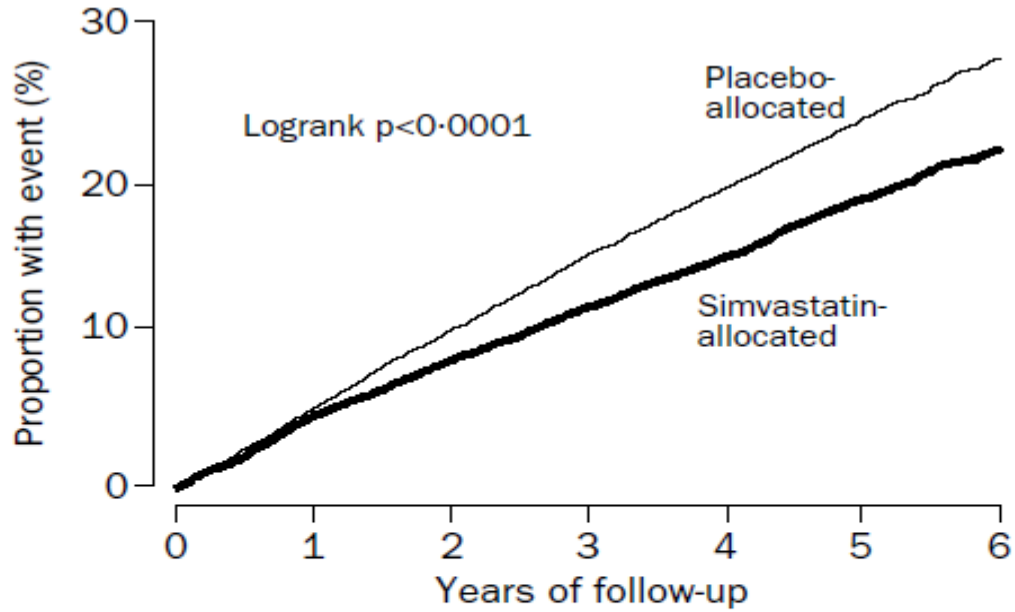


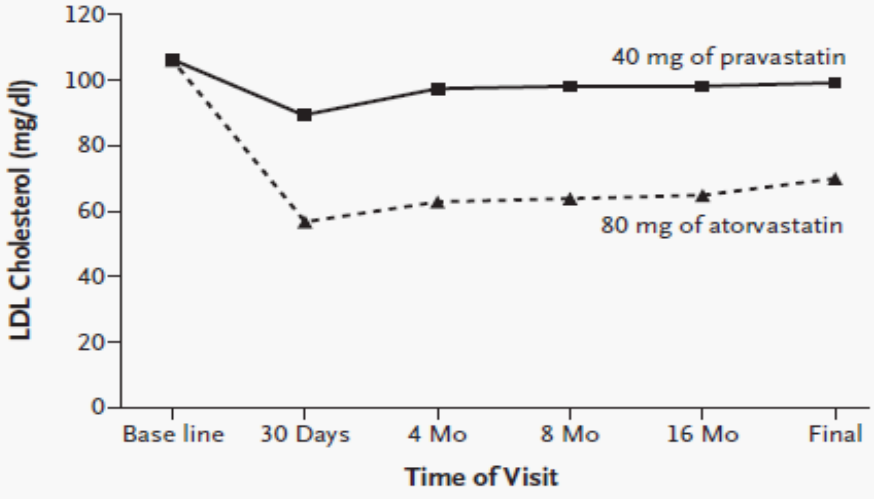
Figure 6: **Life-table plot of effects of simvastatin allocation on percentages having major vascular events**

See figure 5 for numbers of participants having a first event during each year of follow-up.

HPS - 2002: 24% minder kans op een CV-event

Pedersen TR et al *Am J Cardiol* 2000;86;257-262

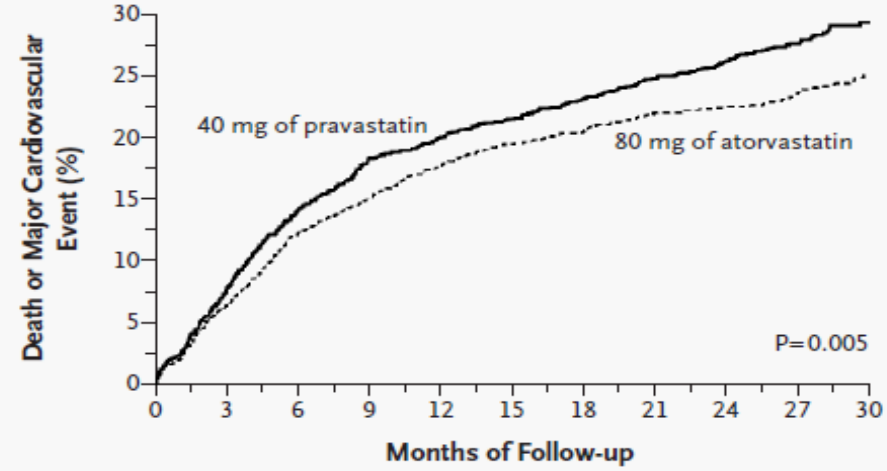
LDL-c 2,5 mmol/L versus 1,8 mmol/L



No. of Patients						
Pravastatin	1973	1844	1761	1647	1445	1883
Atorvastatin	2003	1856	1758	1645	1461	1910

Figure 1. Median Low-Density Lipoprotein (LDL) Cholesterol Levels during the Study.

To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.



No. at Risk						
Pravastatin	2063	1688	1536	1423	810	138
Atorvastatin	2099	1736	1591	1485	842	133

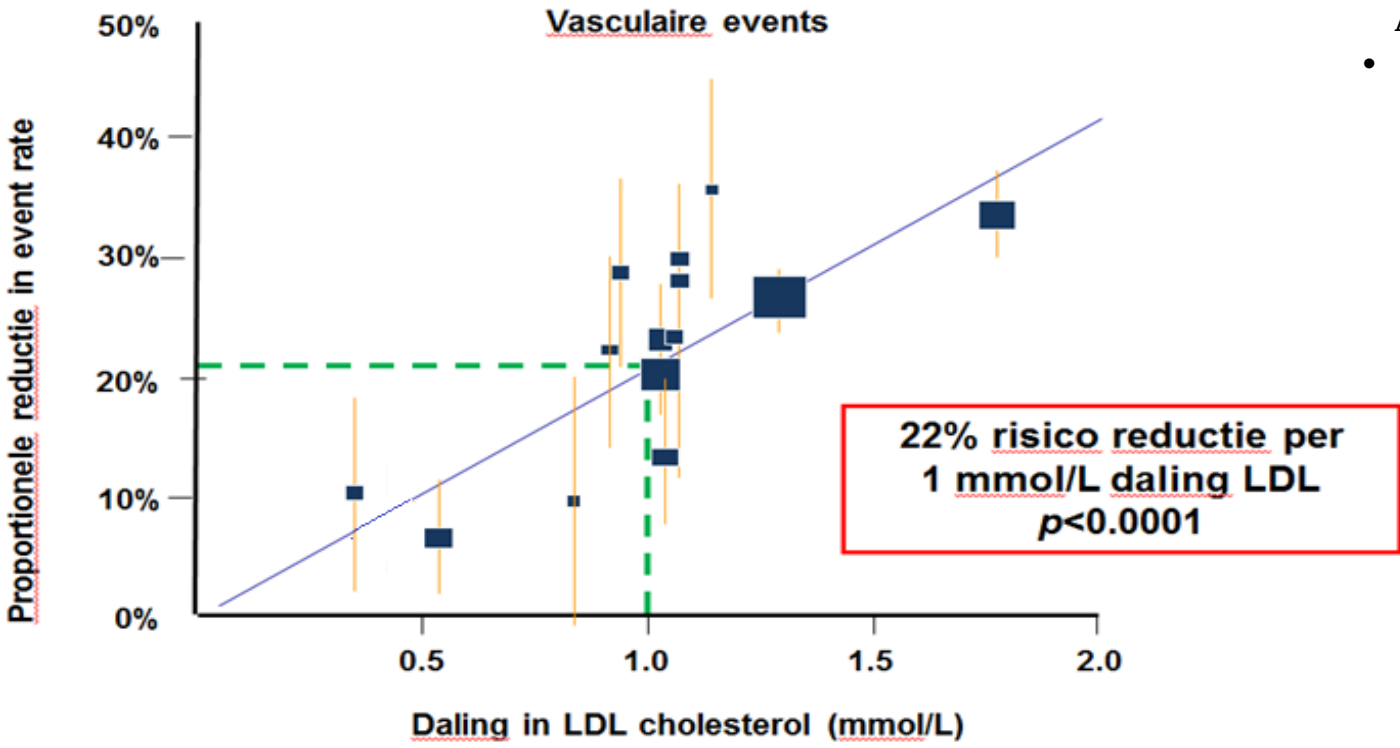
Figure 2. Kaplan–Meier Estimates of the Incidence of the Primary End Point of Death from Any Cause or a Major Cardiovascular Event.

Intensive lipid lowering with the 80-mg dose of atorvastatin, as compared with moderate lipid lowering with the 40-mg dose of pravastatin, reduced the hazard ratio for death or a major cardiovascular event by 16 percent.

Prove IT – 2004: 16% minder kans op een CV-event

Cannon et al *NEJM* 2004; 350:1495-1504

Relatie tussen LDL-c daling en risico op cardiovasculaire events

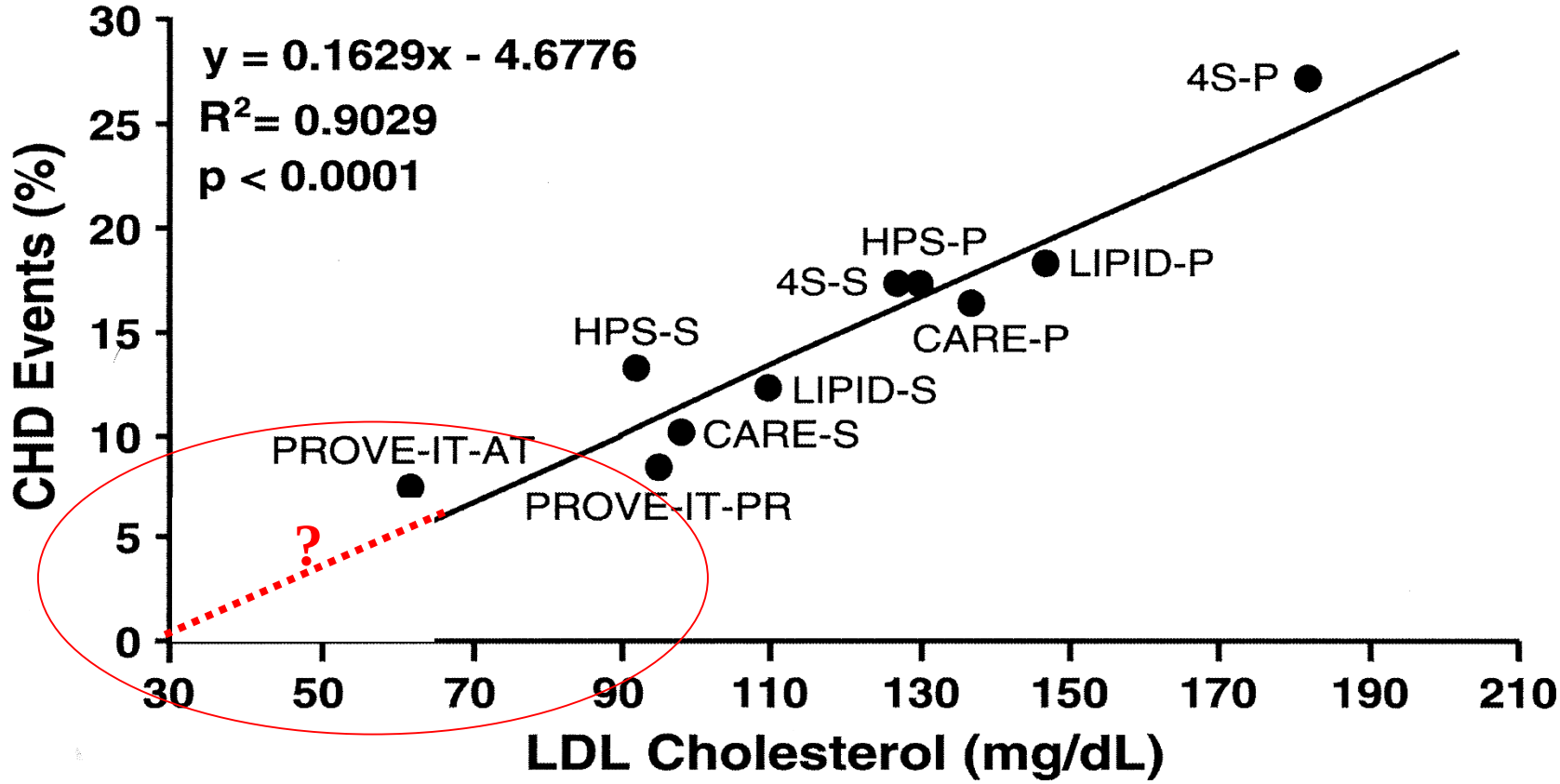


Analyse van CTT Collaborators:

- 14 grote gerandomiseerde trials met statines (oa. 4S, WOSCOPS,CARE, LIPID, HPS, PROSPER, CARDS ALERT)

CTT Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90.056 participants in 14 randomised trials of statins.*Lancet,* 2005; (366):1267-78

Tot welk LDLc wordt voordeel gezien?

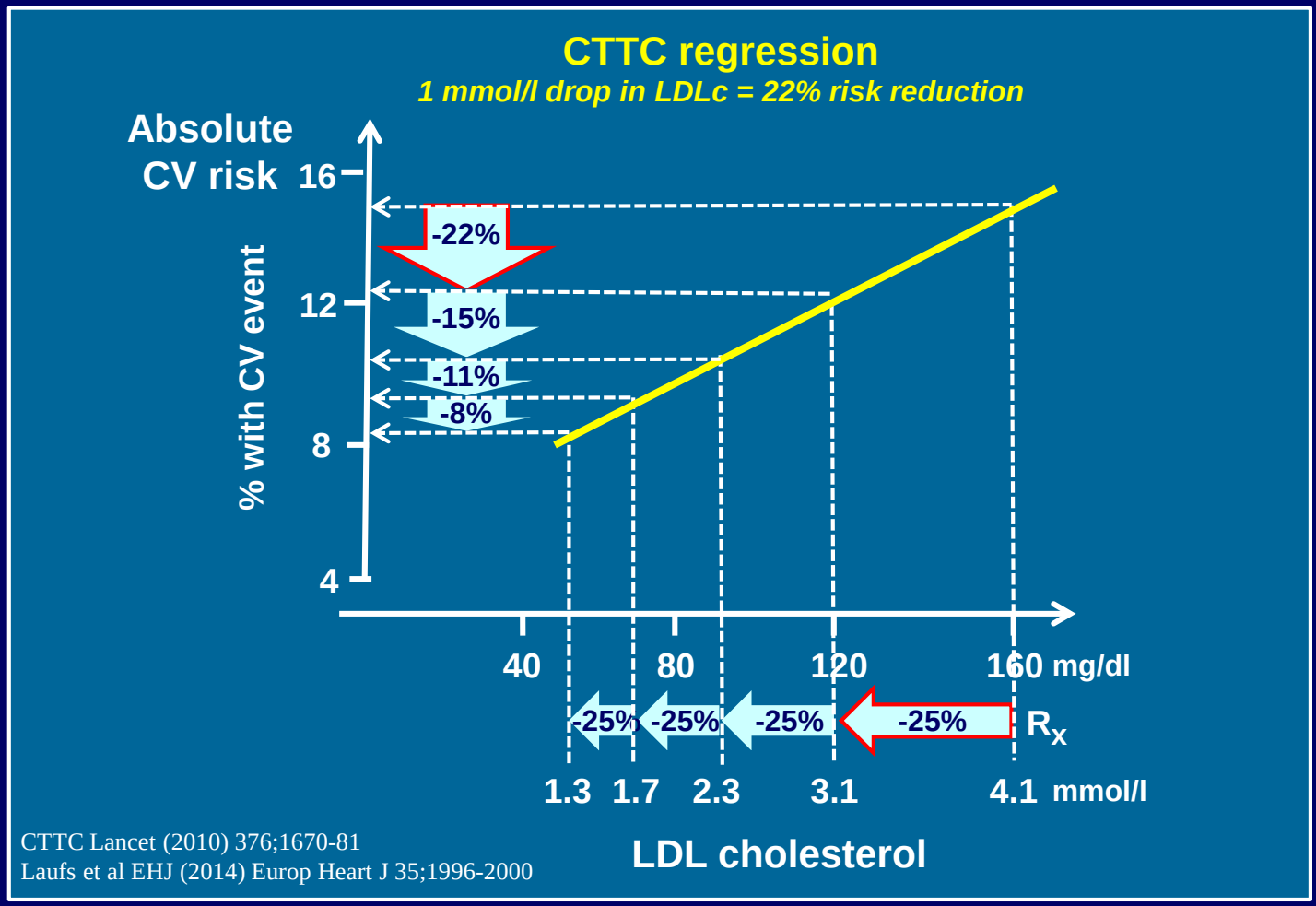


References:
•PROVE-IT: Cannon CP et al. N Engl J Med 2004; 350:1496-1504.
•IMPROVE-IT Background: Cannon CP et al. *Am Heart J*. 2008;156:826-832. 2. Califf RM, et al. *Am Heart J*. 2010;159:705-709
•HPS: Lancet. 2003 Jun 14;361(9374):2005-16.
•CARE: N Engl J Med, 335 (1996), pp. 1001–1009
•LIPID: *N Engl J Med. 1998; 339:1349-1357*
•4s: Lancet. 1994 Nov 19;344(8934):1383-9.

Adapted from O'Keefe JH et al. *JACC* 2004;43:2142-6

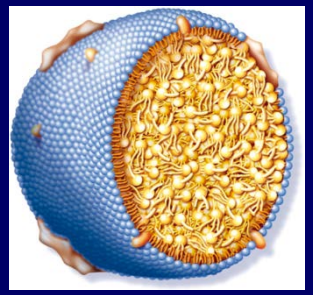
Clinical context for use of add-in / alternate LDL lowering agents

‘Law of diminishing returns’



CTTC Lancet (2010) 376;1670-81
Laufs et al EHJ (2014) Europ Heart J 35;1996-2000

LDL lowering
Looking back, facing forward



- Insights into major trials of LDL reduction
- IMPROVE-IT rationale and results.
- Implications for treatment.

IMPROVE-IT

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome

Ezetimibe: Background

IMPROVE-IT

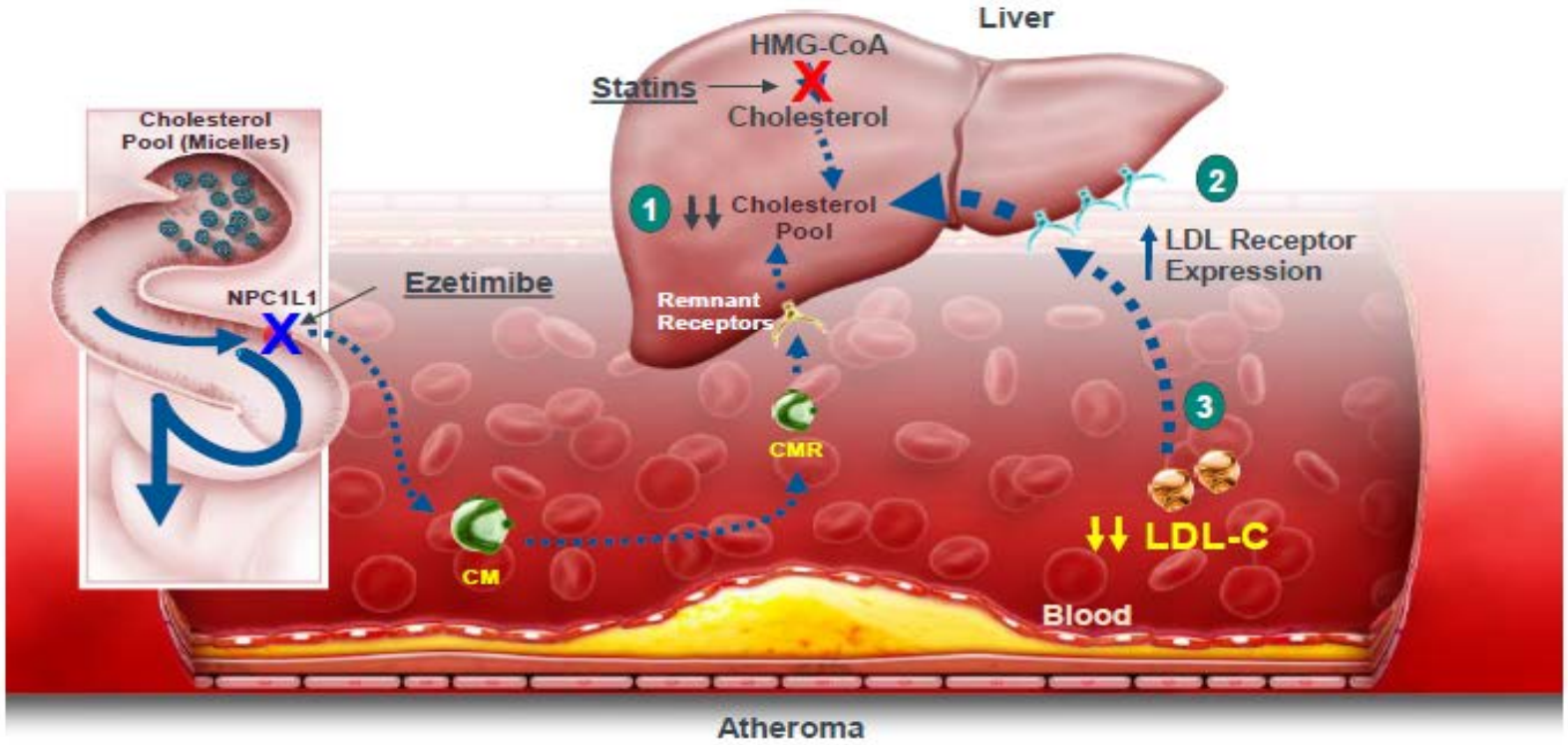
- Ezetimibe inhibits Niemann-Pick C_1-like 1 (NPC_1L_1) protein
  - located primarily on the epithelial brush border of the GI tract
  - resulting in **reduced cholesterol absorption**
- When added to statin, produces ~20% further reduction in LDL-C
- Two recent human genetic analyses have correlated polymorphisms in NPC_1L_1 with lower levels of LDL-C and lower risk of CV events*

**MI Genetics Consortium Investigators NEJM 2014; online Nov 12; Ference BA et al AHA 2014*

Werkingsmechanisme ezetimibe

Together, ezetimibe in combination with a statin provides:

1. Reduction of hepatic cholesterol
2. Increased LDL receptor expression
3. Increased clearance of plasma LDL-C

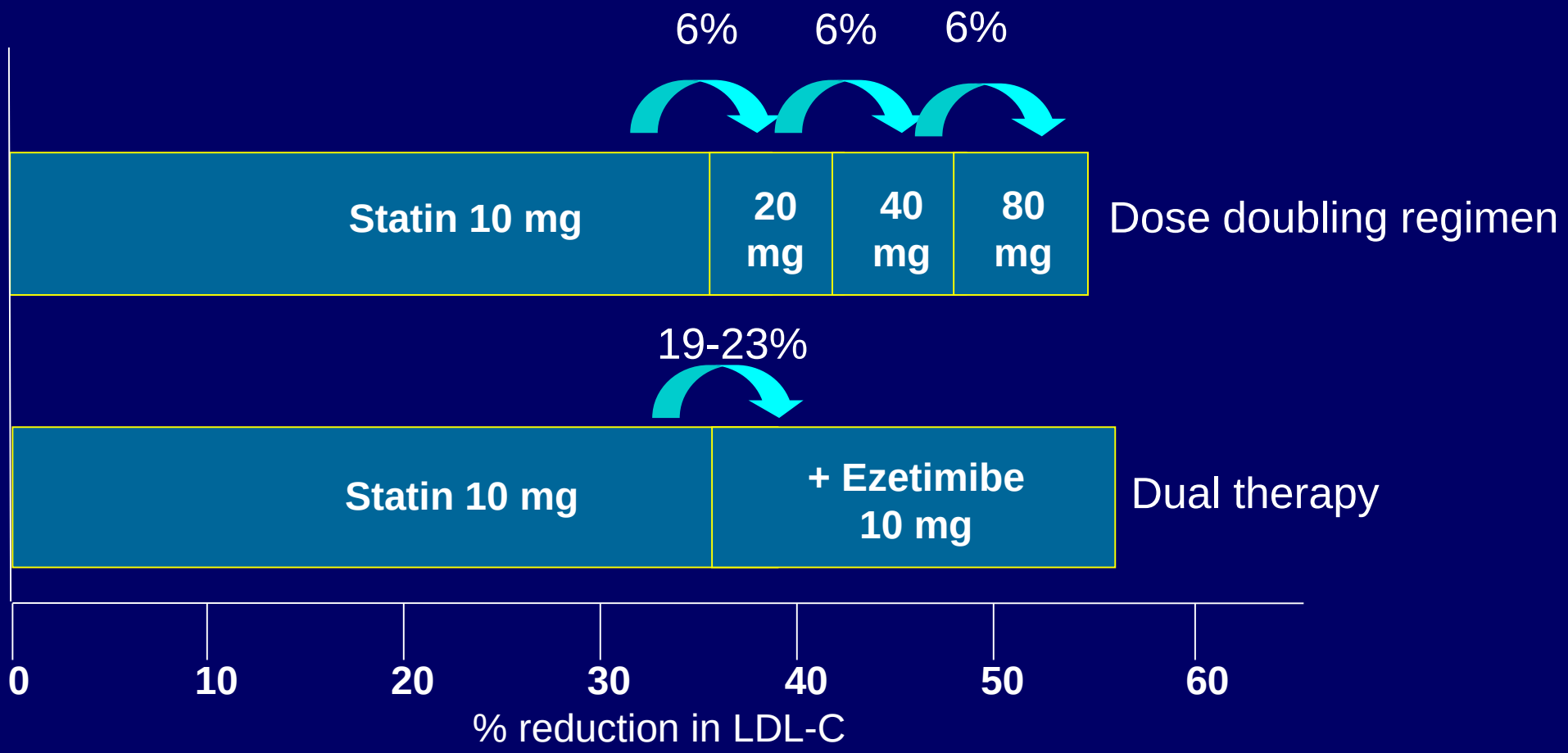


NPC1L1 = Niemann-Pick C1-like 1; HMG-CoA = 3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR = chylomicron remnant.

1. Grigore L et al. *Vas Health Risk Manag*. 2008;4:267–278.

Business Confidential use only

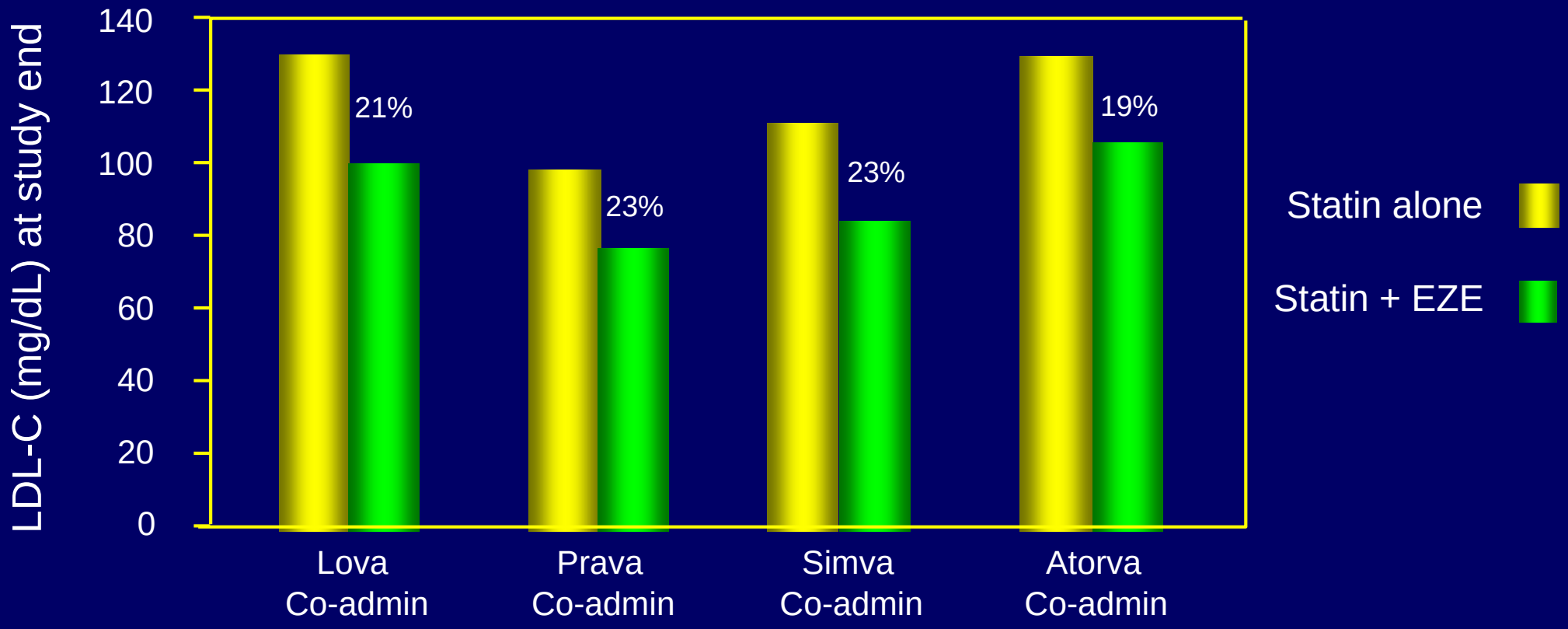
Rationale for combination ezetimibe + statin



Lipka L, et al. *J Am Coll Cardiol (*Suppl). 2002. Melani L, et al. *J Am Coll Cardiol* (Suppl). 2002. Davidson M, et al. *J Am Coll Cardiol* (Suppl). 2002. Ballantyne C, et al. *J Am Coll Cardiol* (Suppl). 2002. Bays H, et al. *J Am Coll Cardiol* (Suppl). 2002.

Effects of adding ezetimibe to a statin

Addition of ezetimibe to statin lowers LDL-C an additional 19%-23%.



Lipka L, et al. *J Am Coll Cardiol (*Suppl). 2002. Melani L, et al. *J Am Coll Cardiol* (Suppl). 2002. Davidson M, et al. *J Am Coll Cardiol* (Suppl). 2002. Ballantyne C, et al. *J Am Coll Cardiol* (Suppl). 2002. Bays H, et al. *J Am Coll Cardiol* (Suppl). 2002.

Goals

IMPROVE-IT: First large trial evaluating clinical efficacy of combination EZ/Simva vs. simvastatin
(i.e., the addition of ezetimibe to statin therapy):

- Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?
- "Is (Even) Lower (Even) Better?"
  (estimated mean LDL-C ~50 vs. 65mg/dL)
- Safety of ezetimibe

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

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

Patient Population

IMPROVE-IT

Inclusion Criteria:

- Hospitalization for STEMI, NSTEMI/UA < 10 days
- Age ≥ 50 years, and ≥ 1 high-risk feature:
  - New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc, prior CABG > 3 years, multivessel CAD
- LDL-C 1,3-3,2 mmol/L (1,3–2,6 mmol/L if prior lipid-lowering Rx)

Major Exclusion Criteria:

- CABG for treatment of qualifying ACS
- Current statin Rx more potent than simva 40mg
- Creat Cl < 30mL/min, active liver disease

Baseline Characteristics

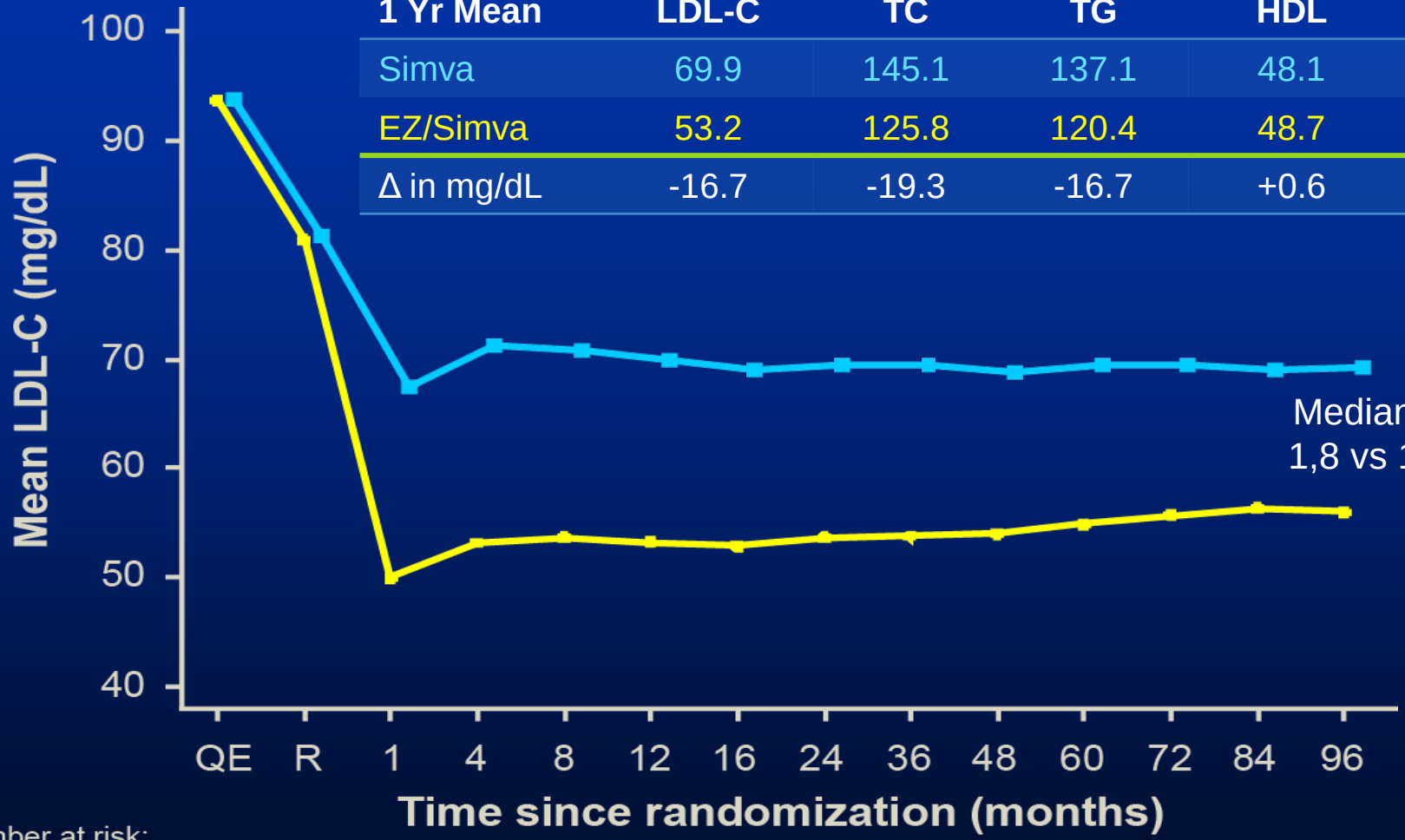
IMPROVE-IT

	Simvastatin (N=9077) %	EZ/Simva (N=9067) %
Age (years)	64	64
Female	24	25
Diabetes	27	27
MI prior to index ACS	21	21
STEMI / NSTEMI / UA	29 / 47 / 24	29 / 47 / 24
Days post ACS to rand (IQR)	5 (3, 8)	5 (3, 8)
Cath / PCI for ACS event	88 / 70	88 / 70
Prior lipid Rx	35	36
LDL-C at ACS event (mg/dL, IQR)	95 (79, 110)	95 (79,110)

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



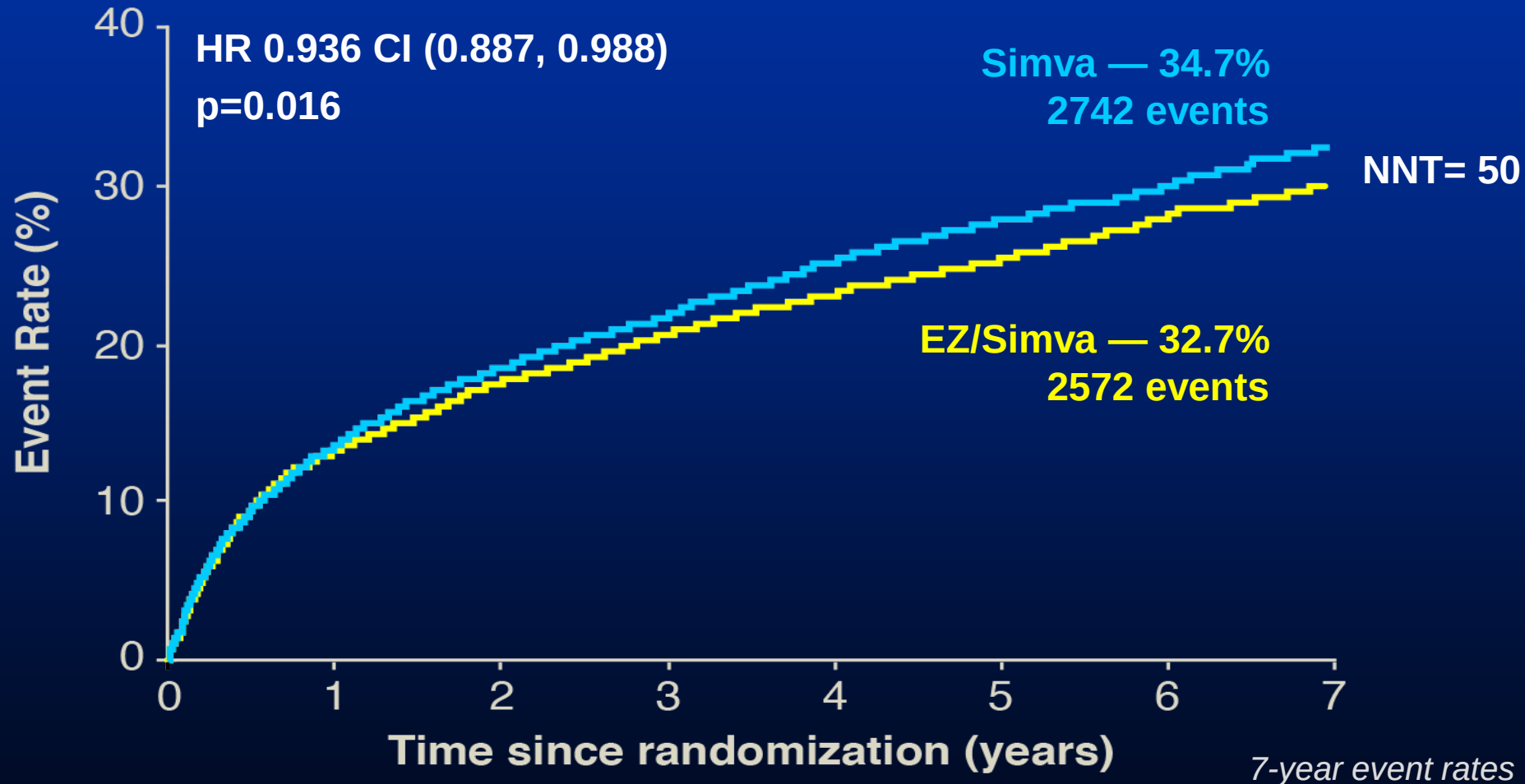
Median Time avg
1,8 vs 1,4 mmol/l

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

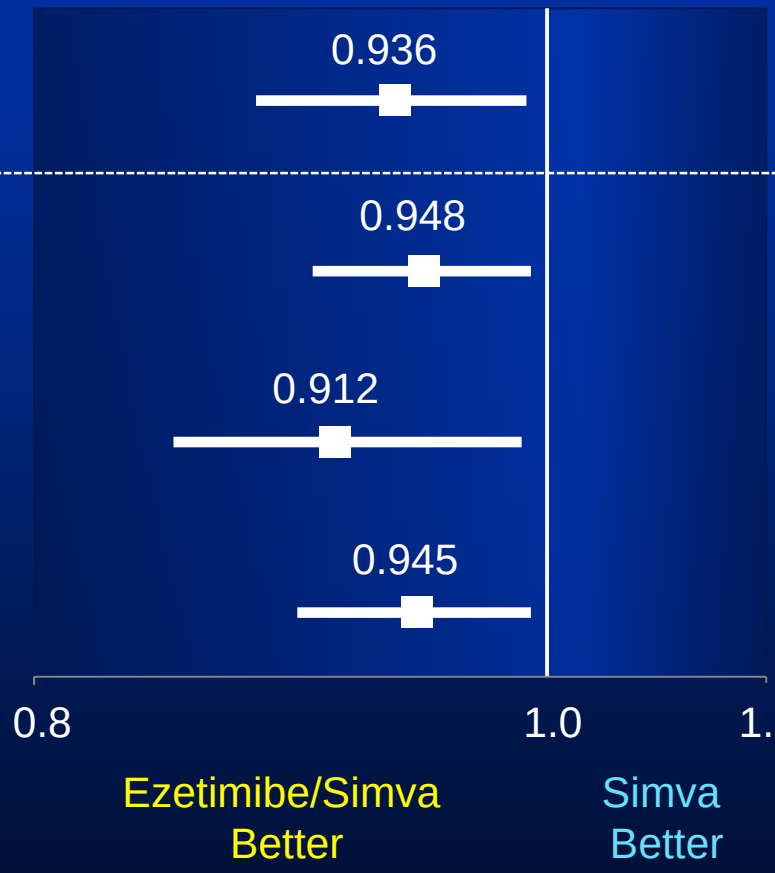
Primary Endpoint — ITT

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



7-year event rates

Primary and 3 Prespecified Secondary Endpoints — ITT



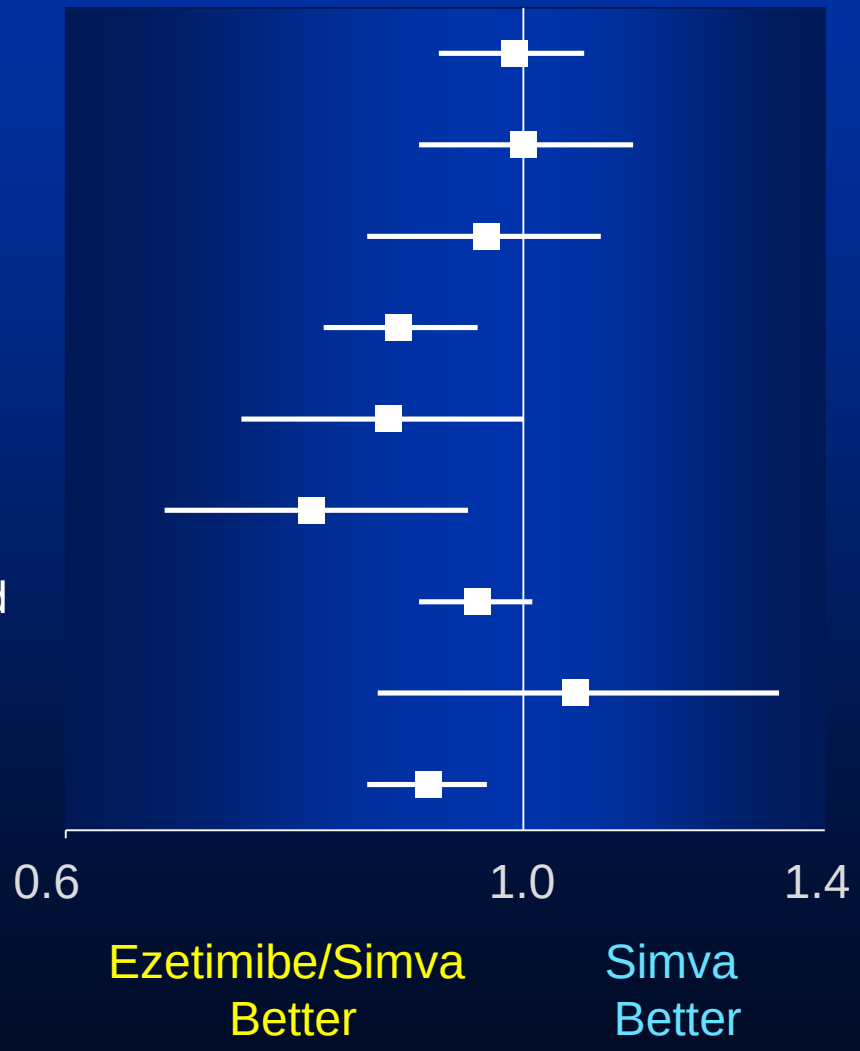
	Simva*	EZ/Simva*	p-value
Primary CVD/MI/UA/Cor Revasc/CVA	34.7	32.7	0.016
Secondary #1 All D/MI/UA/Cor Revasc/CVA	40.3	38.7	0.034
Secondary #2 CHD/MI/Urgent Cor Revasc	18.9	17.5	0.016
Secondary #3 CVD/MI/UA/All Revasc/CVA	36.2	34.5	0.035

**7-year event rates (%)*

UA, documented unstable angina requiring rehospitalization; Cor Revasc, coronary revascularization (≥30 days after randomization); All D, all-cause death; CHD, coronary heart disease death; All Revasc, coronary and non-coronary revascularization (≥30 days)

Individual Cardiovascular Endpoints and CVD / MI / Stroke

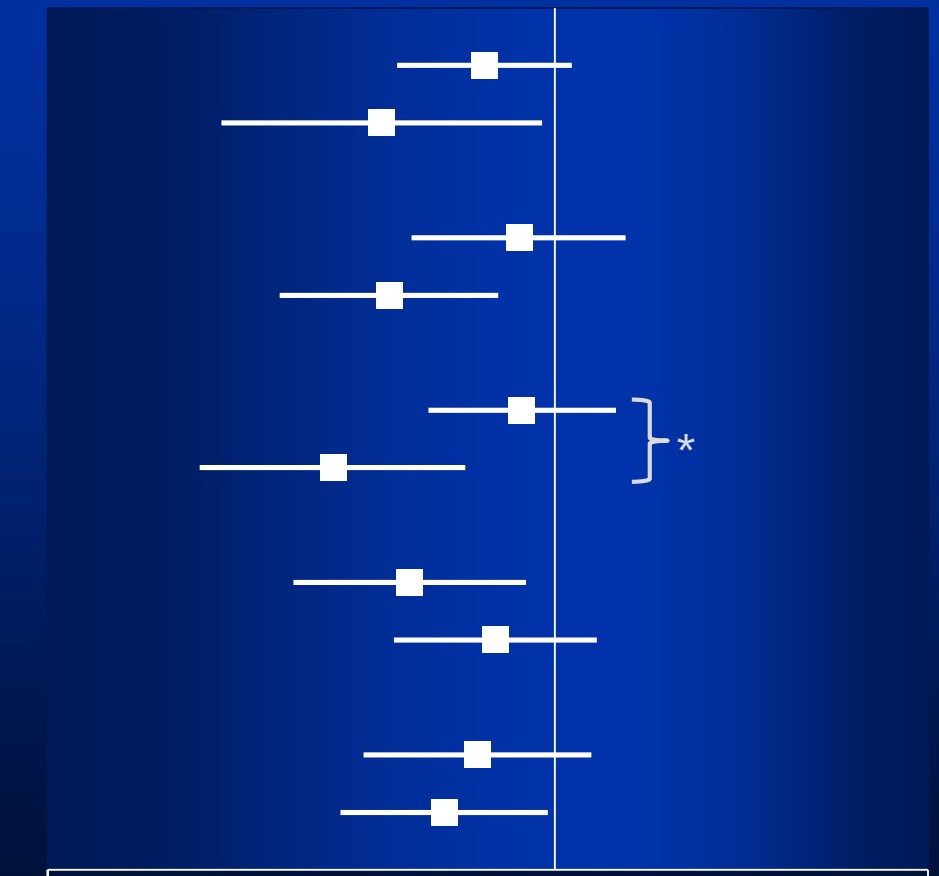
IMPROVE-IT



	HR	Simva*	EZ/Simva*	p-value
All-cause death	0.99	15.3	15.4	0.782
CVD	1.00	6.8	6.9	0.997
CHD	0.96	5.8	5.7	0.499
MI	0.87	14.8	13.1	0.002
Stroke	0.86	4.8	4.2	0.052
Ischemic stroke	0.79	4.1	3.4	0.008
Cor revasc ≥ 30d	0.95	23.4	21.8	0.107
UA	1.06	1.9	2.1	0.618
CVD/MI/stroke	0.90	22.2	20.4	0.003

**7-year event rates (%)*

Major Pre-specified Subgroups



	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
Age < 65 years	30.8	29.9
Age ≥ 65 years	39.9	36.4
No diabetes	30.8	30.2
Diabetes	45.5	40.0
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
LDL-C > 95 mg/dl	31.2	29.6
LDL-C ≤ 95 mg/dl	38.4	36.0

†*7-year event rates*

**p-interaction = 0.023, otherwise > 0.05*

Safety — ITT

No statistically significant differences in cancer or muscle- or gallbladder-related events

	Simva n=9077 %	EZ/Simva n=9067 %	p
ALT and/or AST≥3x ULN	2.3	2.5	0.43
Cholecystectomy	1.5	1.5	0.96
Gallbladder-related AEs	3.5	3.1	0.10
Rhabdomyolysis*	0.2	0.1	0.37
Myopathy*	0.1	0.2	0.32
Rhabdo, myopathy, myalgia with CK elevation*	0.6	0.6	0.64
Cancer* (7-yr KM %)	10.2	10.2	0.57

** Adjudicated by Clinical Events Committee*

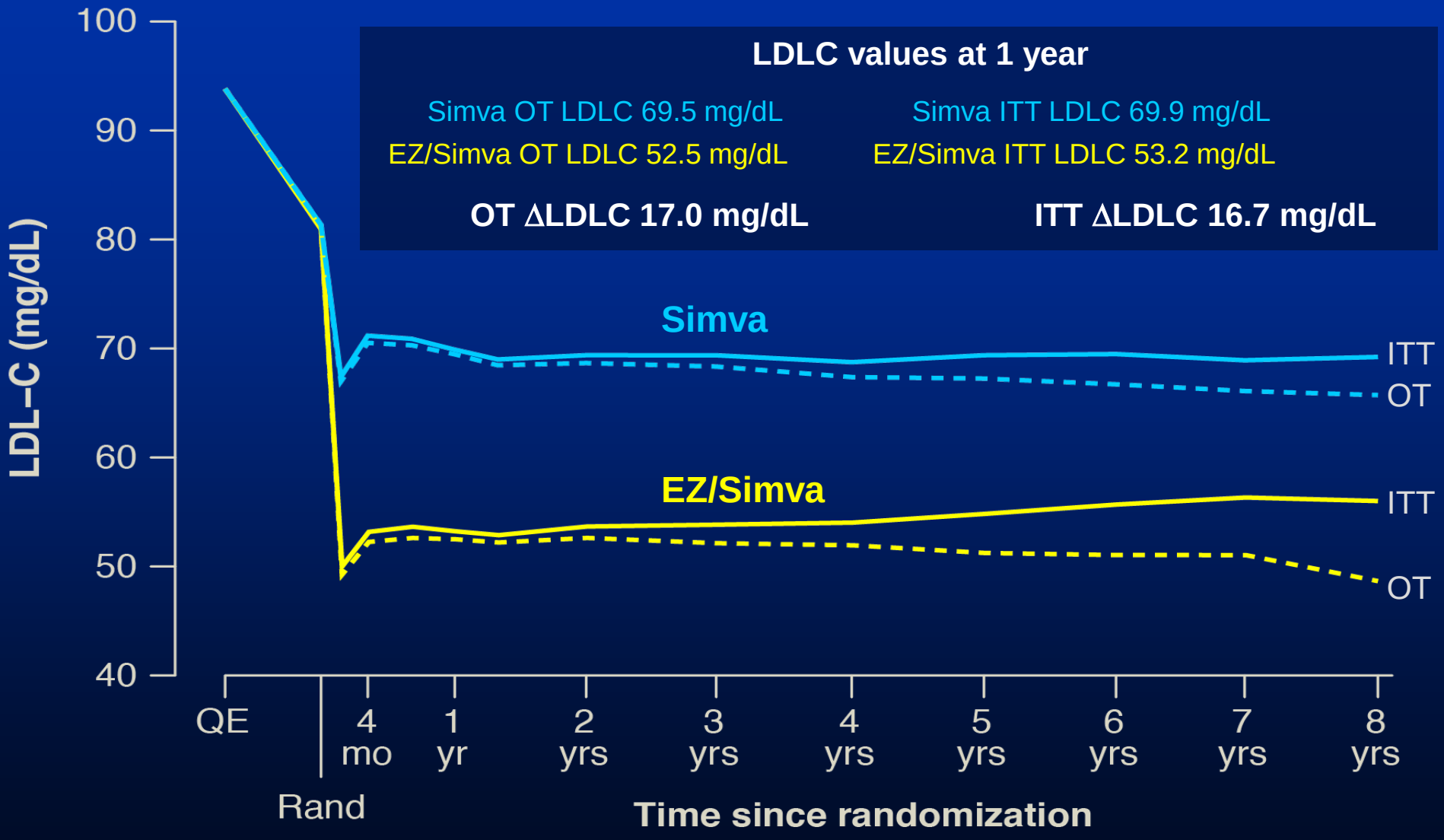
% = n/N for the trial duration

Study Metrics

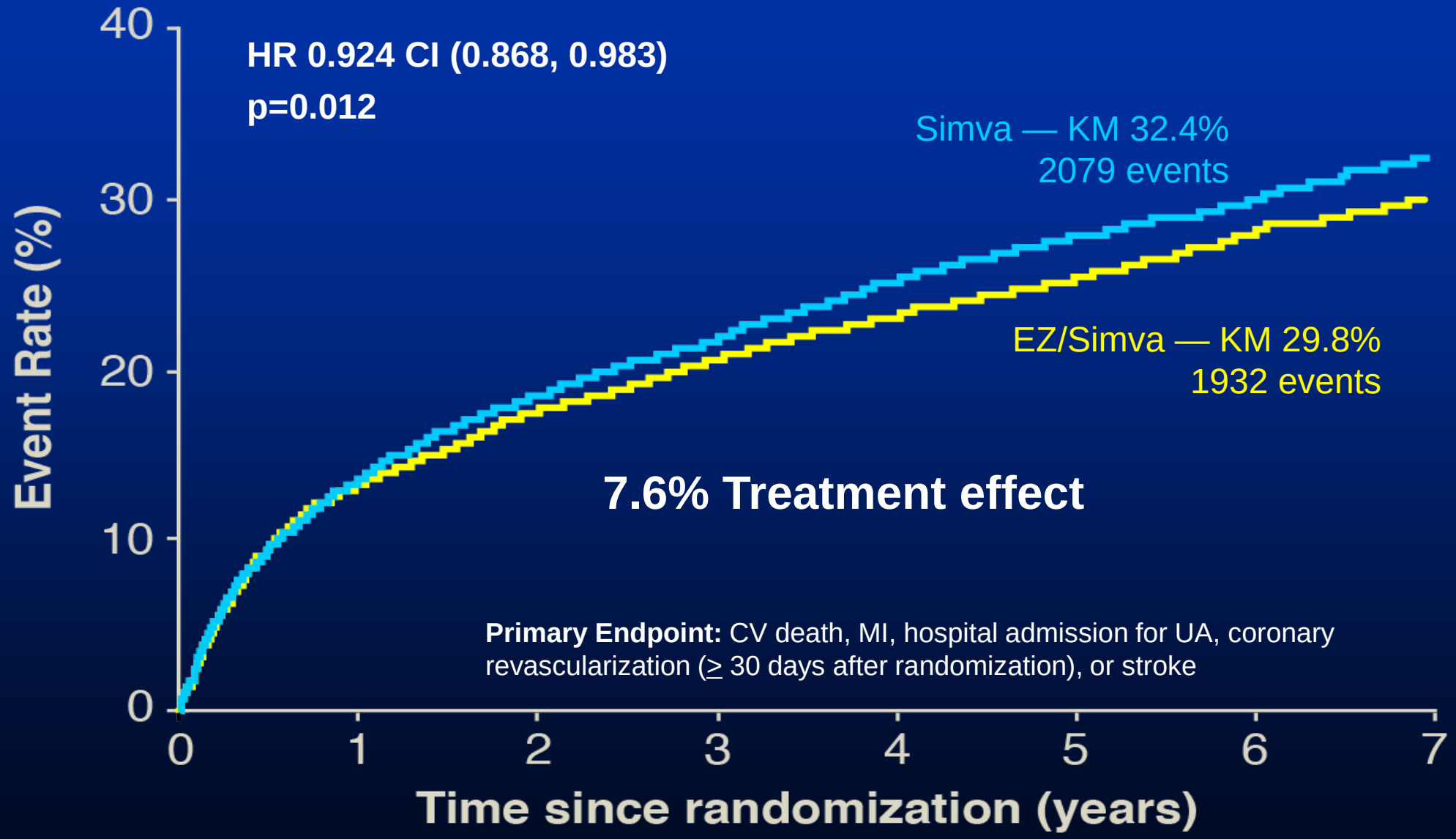
	Simva (N=9077)	EZ/Simva (N=9067)
Uptitration to Simva 80mg, %	27	6
Premature study drug D/C, %	42	42
Median follow-up, yrs	6.0	5.9
Withdraw consent w/o vital status, %/yr	0.6	0.6
Lost to follow-up, %/yr	0.10	0.09
Follow up for primary endpoint, %	91	91
Follow up for survival, %	97	97

Total primary endpoint events = 5314
Total patient-years clinical follow-up = 97,822
Total patient-years follow-up for survival = 104,135

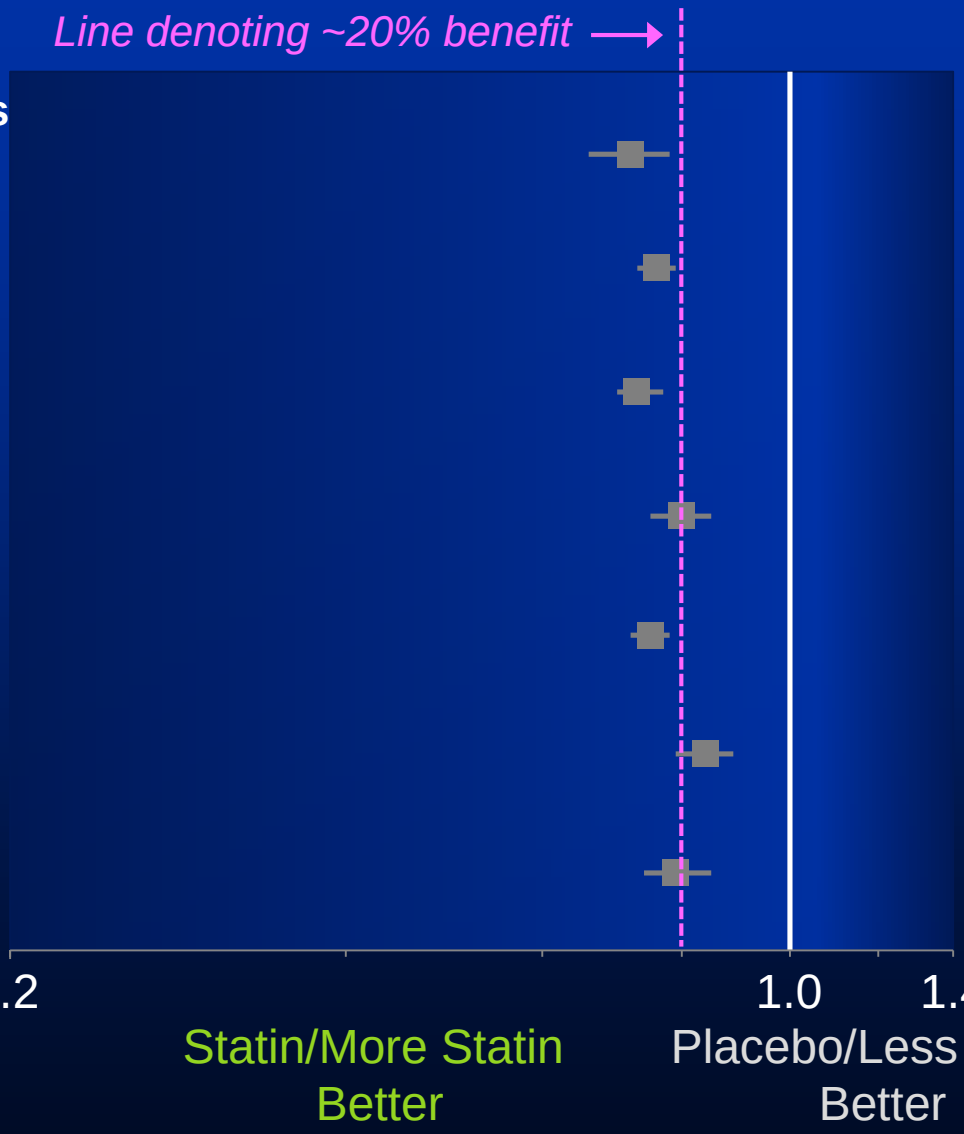
Mean LDL-C at 1 Year
OT & ITT



Primary Endpoint On-Treatment



CTT HR per 1mM LDL-C Reduction for 26 Statin Trials

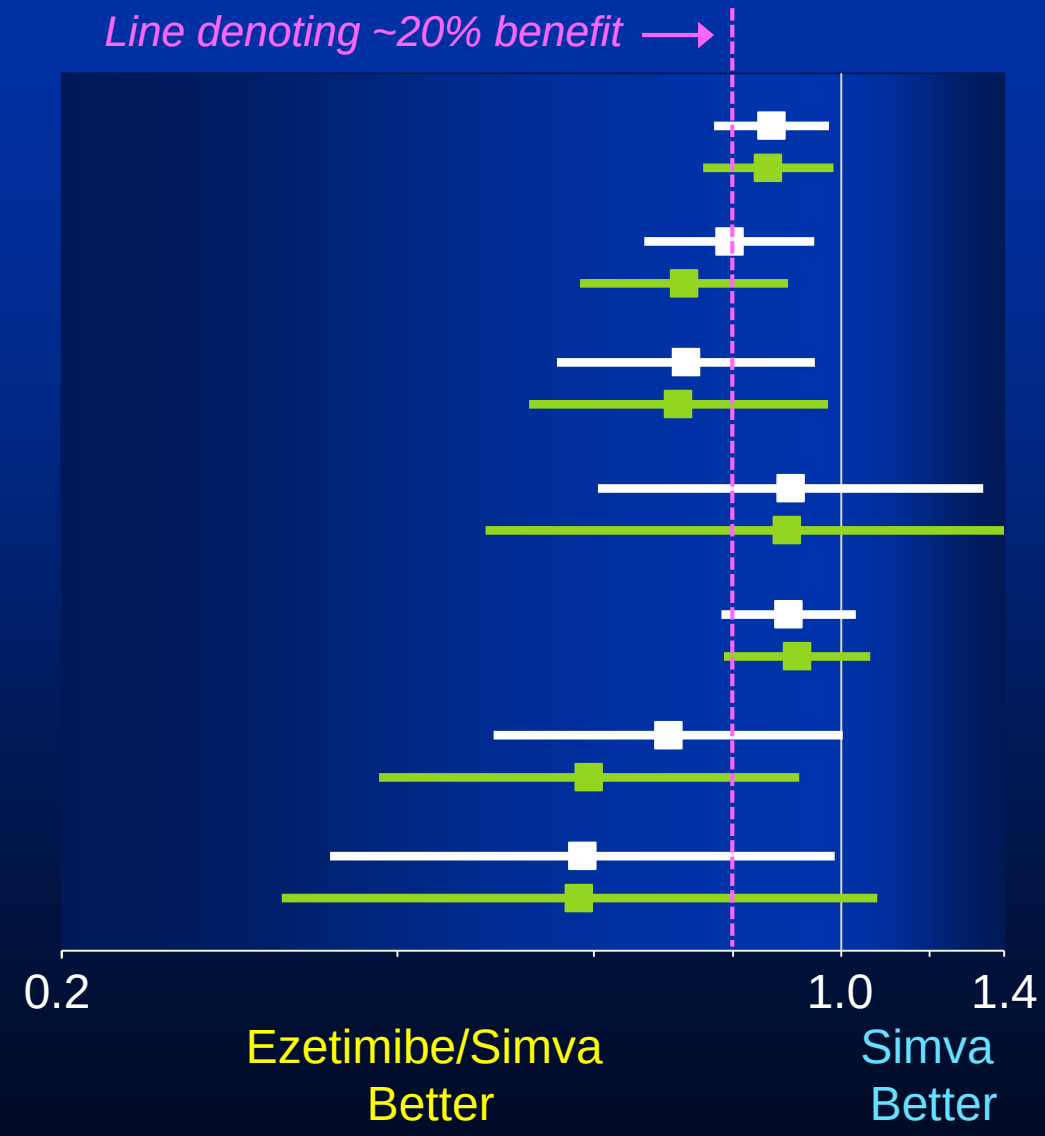


CTT Conclusion:

"…each 1.0 mmol/L reduction reducing the annual rate of (these) major vascular events by just over a fifth"

CTT Collaboration Lancet 2010. & Web Supplement

HR per 1mM LDLC reduction IMPROVE-IT ITT vs OT



	Simva*	EZ/Simva*	HR
Major vascular events (MCE+ CR+ stroke)	37.4	35.3	0.866
	35.4	32.7	0.860
Major coronary events (nfMI+CHD)	18.4	17.0	0.794
	15.8	13.8	0.723
Non-fatal MI	14.4	12.8	0.726
	13.5	11.6	0.714
CHD death (coronary death)	5.8	5.7	0.901
	3.1	3.1	0.894
Coronary revasc.	27.7	26.1	0.897
	27.4	25.3	0.913
Any stroke	4.8	4.2	0.700
	4.5	3.7	0.594
Ischemic stroke	4.1	3.4	0.586
	3.9	3.2	0.582

**7-year event rates*

CTT Collaboration. Lancet 2010

Conclusions

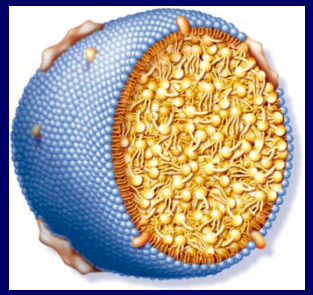
IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:

- **YES:** *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
- **YES:** Even Lower is Even Better (achieved mean LDL-C 1,4 vs.1,8 mmol/L at 1 year)
- **YES:** Confirms ezetimibe safety profile

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

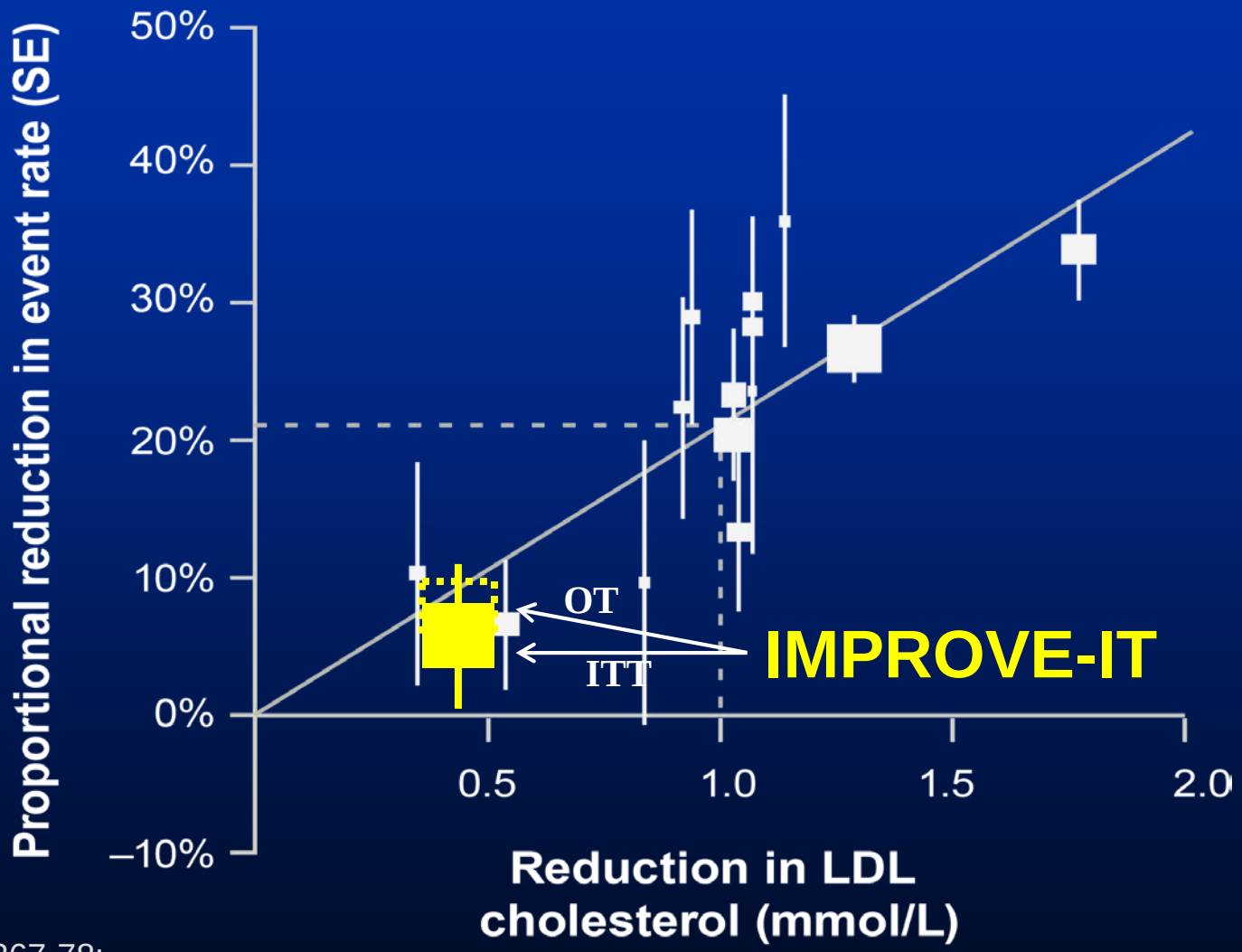
➡ **Results could be considered for future guidelines**

LDL lowering
Looking back, facing forward



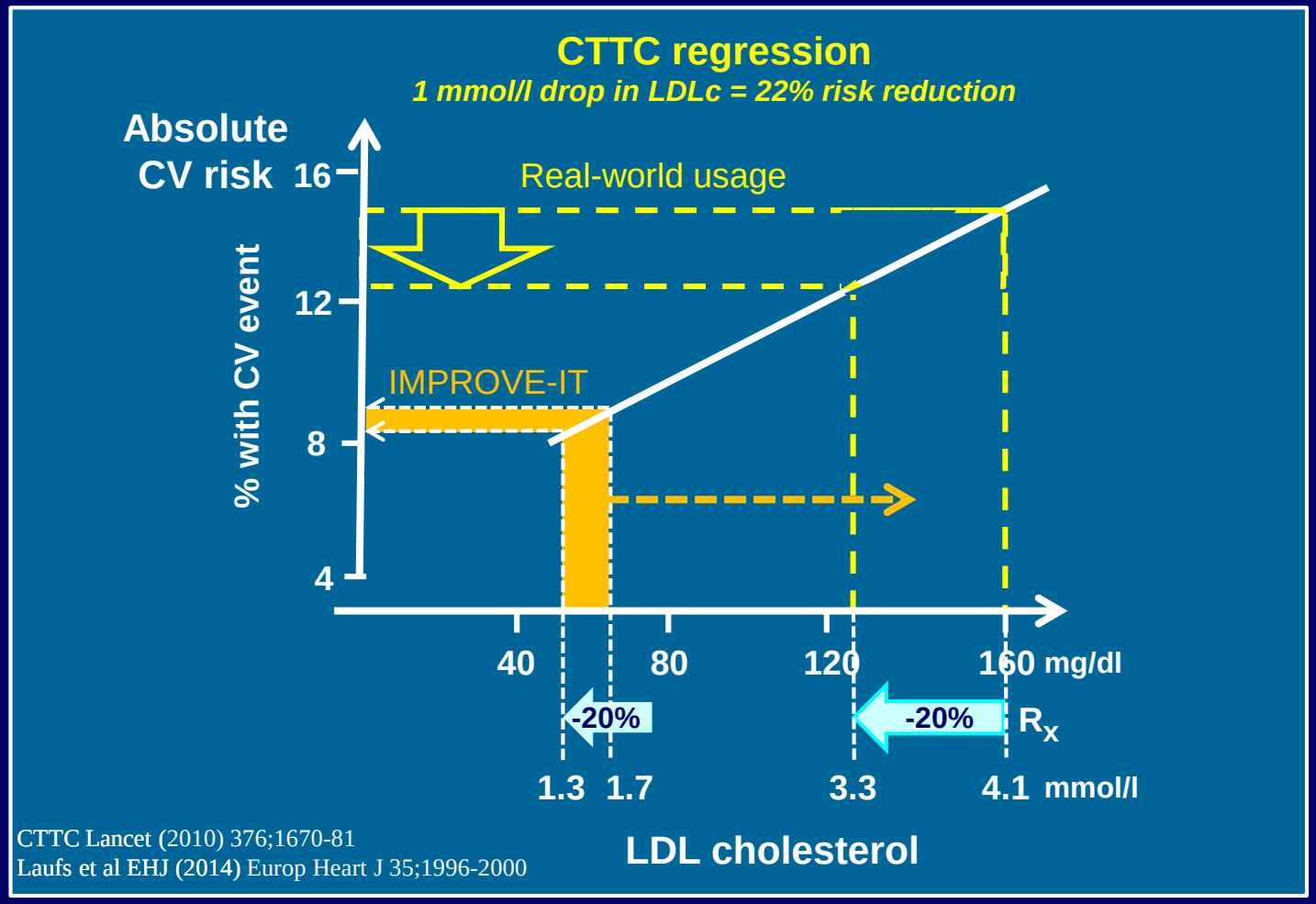
- Insights into major trials of LDL reduction
- IMPROVE-IT rationale and results.
- Implications for treatment.

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



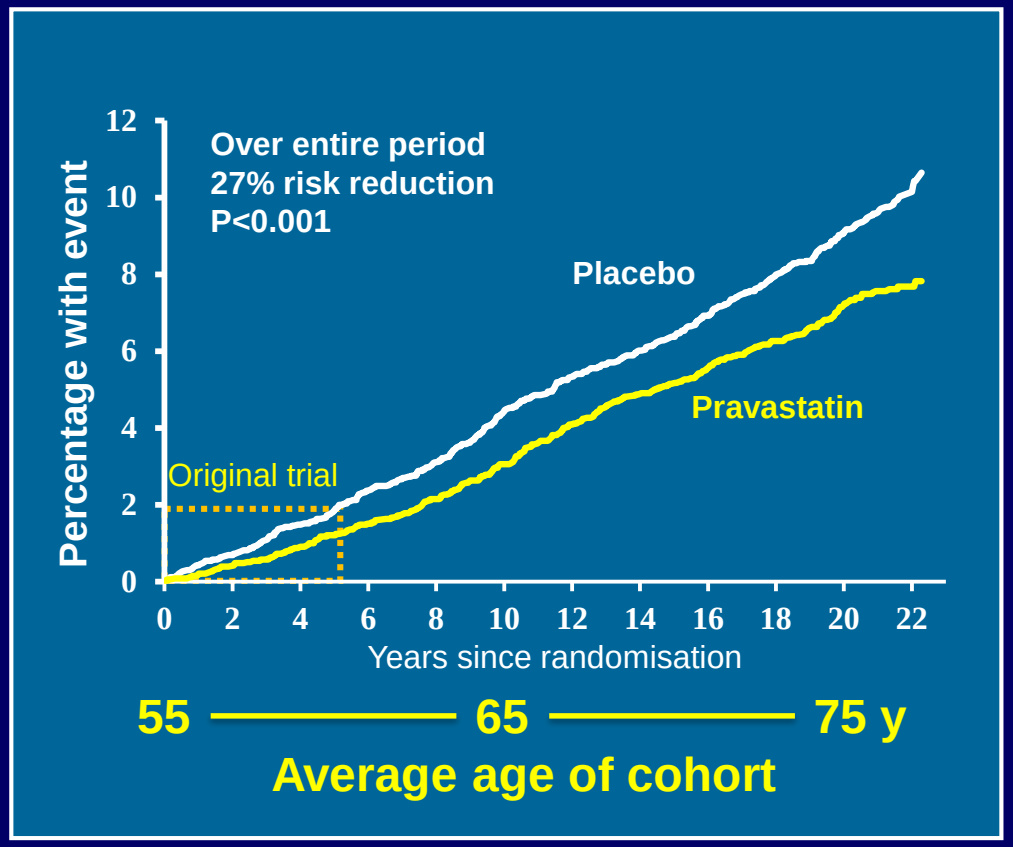
CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376:1670-81.

Understanding the broader impact of LDL lowering in IMPROVE-IT

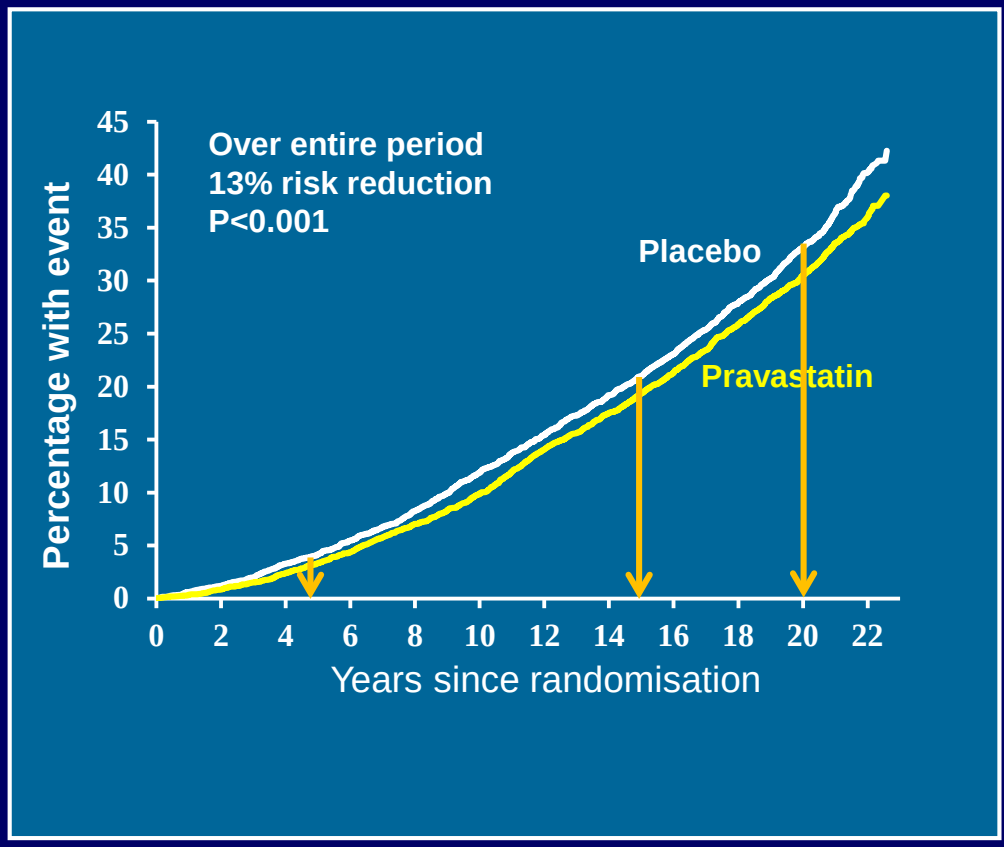


Long term follow up in statin studies
WOSCOPS experience

CHD mortality



All-cause mortality

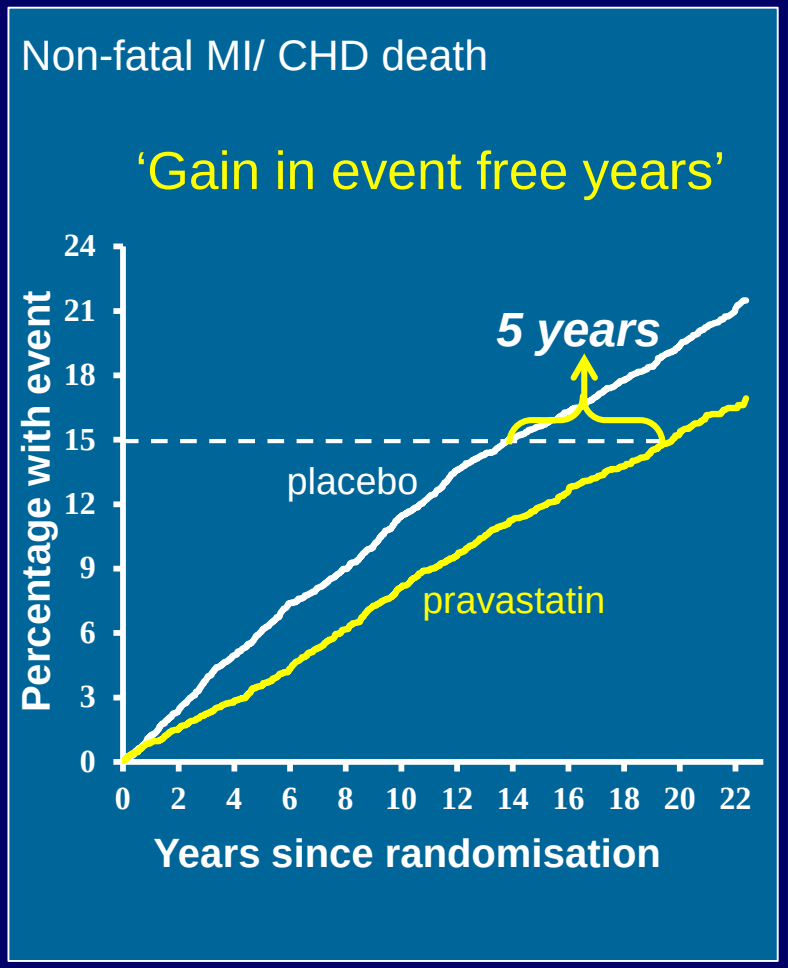


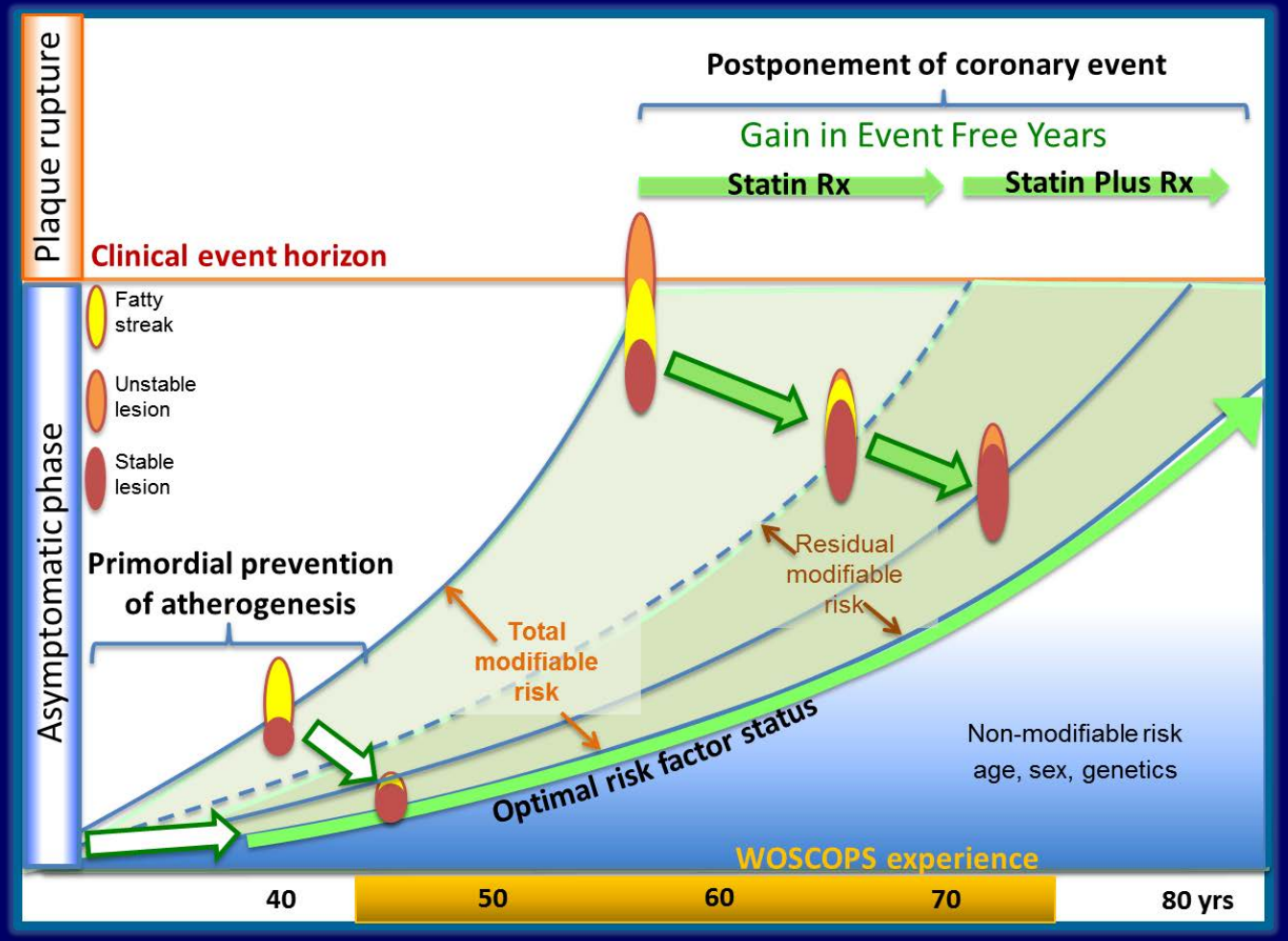
Assessing the long term (lifetime) economic benefits of LDL lowering

Statin therapy is 'cost-saving' over long term in primary prevention

	Placebo			Pravastatin			
Event type	**number of subjects affected**	**number of events**	**Total LOS (days)**	**number of subjects affected**	**number of events**	**Total LOS (days)**	P
Any CV	1209	3007	30342	1044	2457	24038	<0.0001
1: Stroke	353	589	14727	338	562	12410	0.53
2: MI	454	523	4984	343	401	3462	<0.0001
3: HF	116	196	2857	89	129	1708	0.060
4: Other CHD	689	1699	7774	616	1365	6458	0.019
5: Non CV	3193	19362	88229	3210	19966	87989	0.81

Defining disease trajectories in CHD prevention





Options in LDL lowering
High dose statin vs. Dual therapy

21st March 2014

theguardian

• Statins for all: do the benefits outweigh the risks?

society

Doctors' fears over statins may cost lives, says top medical researcher

'I suffered terrible aching limbs'

AE profile
High vs moderate dose statin

Event	Odds ratio(CI)
Any AE	1.44(1.33-1.55)
LFT abnormalities	4.48(3.27-6.16)
CK>10	9.97(1.28-77.9)
Rhabdomyolysis	1.66(0.60-4.57)

Silva et al (2007) Clin. Therap. 29:253-260

Summary

- LDL is the principal causative factor in genesis of atherosclerotic plaque.
- Statins are the cornerstone of treatment but there is an unmet clinical need where patients cannot tolerate any/optimum statin doses, or where goals are not met.
- IMPROVE-IT shows ezetimibe is safe and efficacious, and that even lower LDL is better. It confirms that LDL lowering is the primary goal of lipid regulating pharmacotherapy.
- Important to understand the context of LDL lowering with mono- or combined therapy to deliver optimal benefit.

RICHTLIJNEN

CVRM richtlijn 2012

1. Patiënten mét HVZ

LDL ≤ 2.5 mmol/l

2. Patiënten zonder HVZ
   - Met een 10-jaarsrisico op HVZ ≥20%
   - Met een 10-jaarsrisico van 10-20% én risicofactoren
   - DM of RA (risicotabel + 15 jaar)

LDL ≤ 2.5 mmol/l

ESC/EAS richtlijn 2011

1. Zeer hoog risico
   - Patiënten met HVZ
   - DM
   - CKD patiënt (GFR < 60)
   - 10-jaarsrisico ≥ 10% (scoretabel)

LDL < 1.8 mmol/l

2. Hoog risico
   - Familiaire dyslipidemieën
   - Ernstige hypertensie
   - 10-jaarsrisico ≥ 5% en < 10% (scoretabel)

LDL < 2.5 mmol/l

NHG-Standaard Cardiovasculair risicomanagement (Tweede herziening), Huisarts Wet 2012;55(1):14-28
ESC/EAS Guidelines for the management of dyslipidaemias, European Heart Journal (2011) 32, 1769–1818

NSTEMI ACS richtlijn 2015

Recommendations for long-term management after non-ST-elevation acute coronary syndromes

Recommendations (for the recommendations on antithrombotic treatment, see sections 5.2.9 and 5.3.3)	Class[a]	Level[b]	Ref.[c]
Participation in a well-structured cardiac rehabilitation programme to modify lifestyle habits and increase adherence to treatment should be considered.	IIa	A	535, 541–546
In patients with LDL cholesterol ≥70 mg/dL (≥1.8 mmol/L) despite a maximally tolerated statin dose, further reduction in LDL cholesterol with a non-statin agent[e] should be considered.	IIa	B	529
A systolic blood pressure goal of <140 mmHg should be considered.	IIa	B	547–549

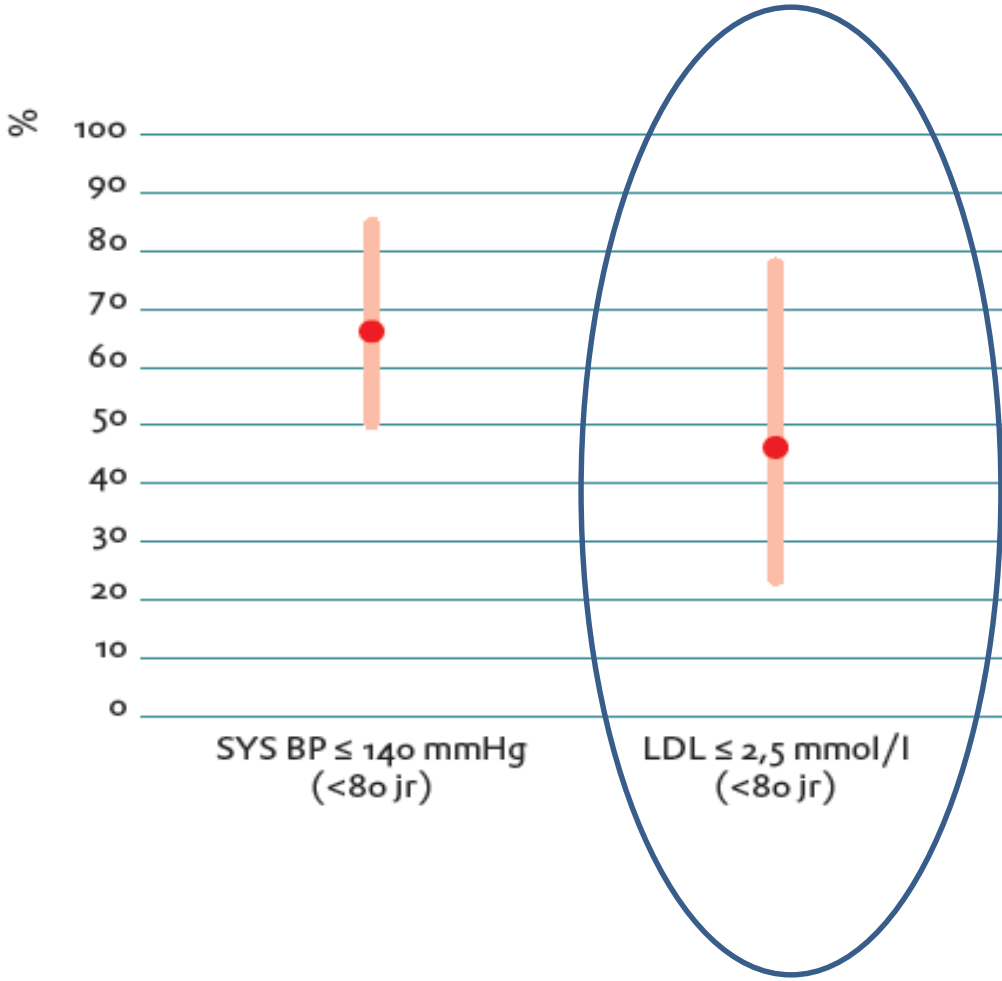
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; NSTE-ACS = non-ST-elevation acute coronary syndromes.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.
[d]Serum creatinine <221 μmol/L (2.5 mg/dL) for men and <177 μmol/L (2.0 mg/dL) for women; serum potassium concentration <5.0 mmol/L.
[e]At the time of finalizing the guidelines, this recommendation applies only to ezetimibe.

- ACS patiënten zijn hoog risico patienten
- LDLc streefwaarde < 1.8 mmol/L

* Op basis van IMPROVE-IT studie; Cannon CP et al, Ezetimibe added to statin therapy after acute coronary syndromes, *N Eng J Med* 2015;**372**:2387-97

European Heart Journal, doi/10.1093/eurheartj/ehv320, 2015

% HVZ-patiënten in CVRM-zorgprogramma (inclusief spreiding tussen zorggroepen) bij wie uitkomst indicatoren CVRM zijn vastgelegd in 2013, naar indicator[13]



Circa 50% van de patiënten in CVRM zorgprogramma is dus niet op streefwaarde!

Vijf jaar cardiovasculair risicomanagement in Nederland:

the state of the art. Nederlandse hartstichting 2013