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Cholesterol and Cardiovascular Disease- From genetics, risk prediction to novel therapies and implementation research

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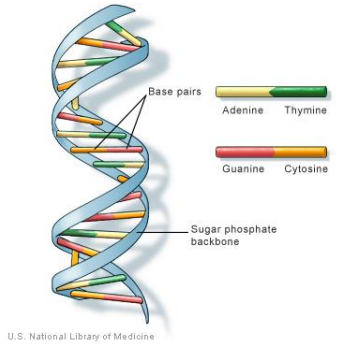
Lifetime trajectory of gene-environment interactions towards vascular disease and death

Genetic Vulnerability

Adaptive Or Maladaptive

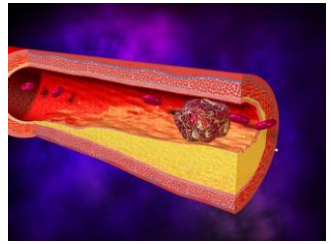


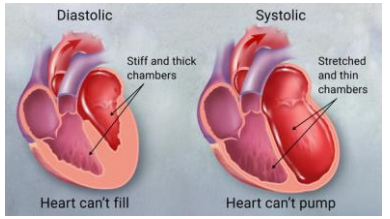
Exposures (causal factors or enhancers)

Magnitude x Duration

Cumulative Burden

Disease





Lifetime trajectory of gene-environment interactions towards vascular disease and death

Genetic Vulnerability

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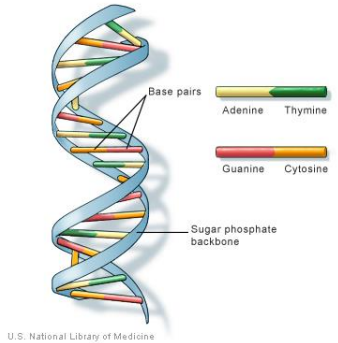

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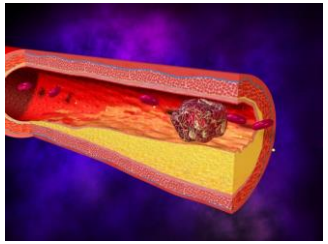
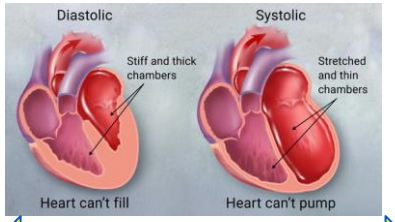
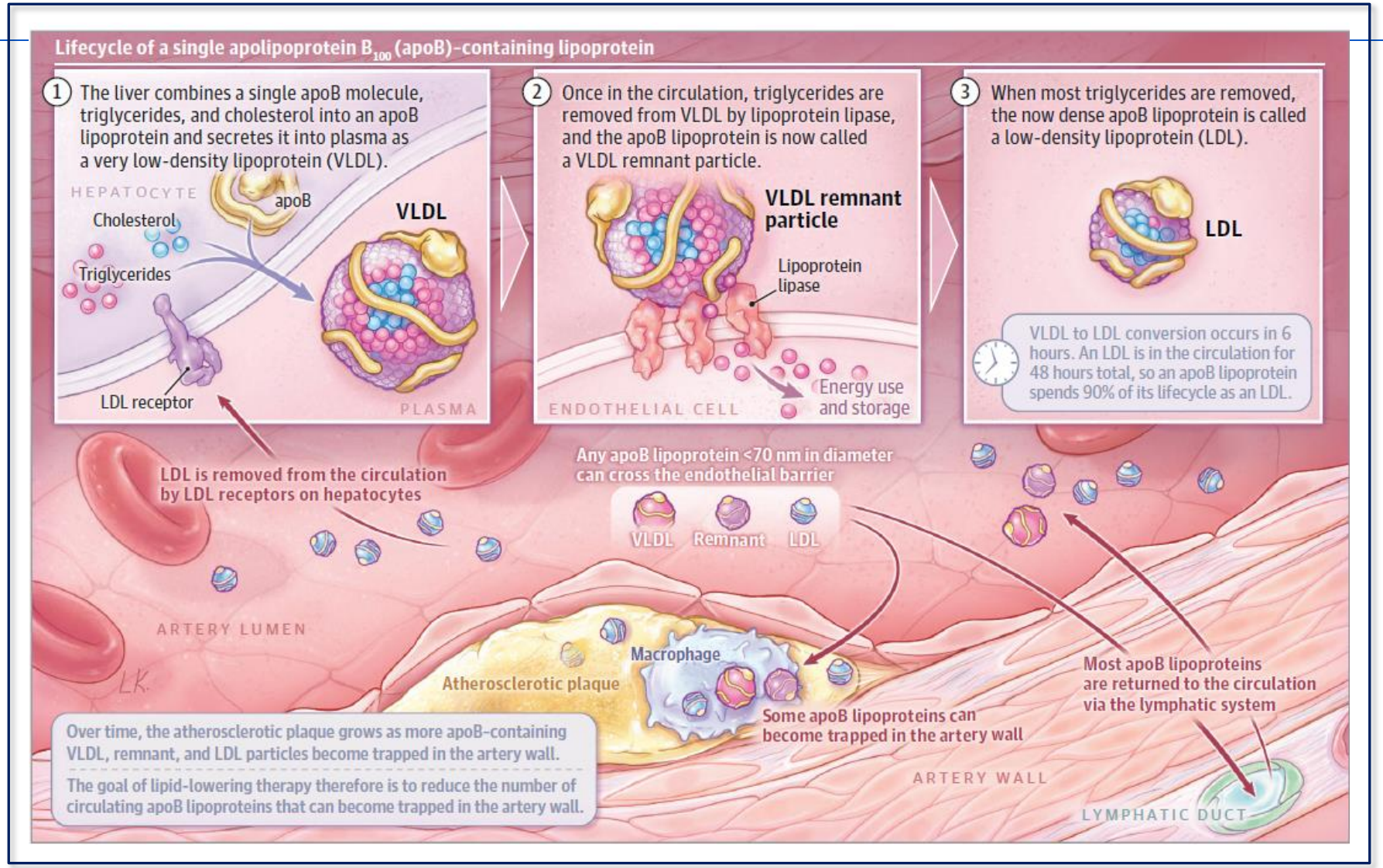




PRESERVE HEALTH

PALLIATION / QOL

Central role of LDL in atherosclerotic cardiovascular disease



Ference BA, Kastelein JPP, Catapano AL. JAMA, 2020: doi:10.1001/jama.2020.5685

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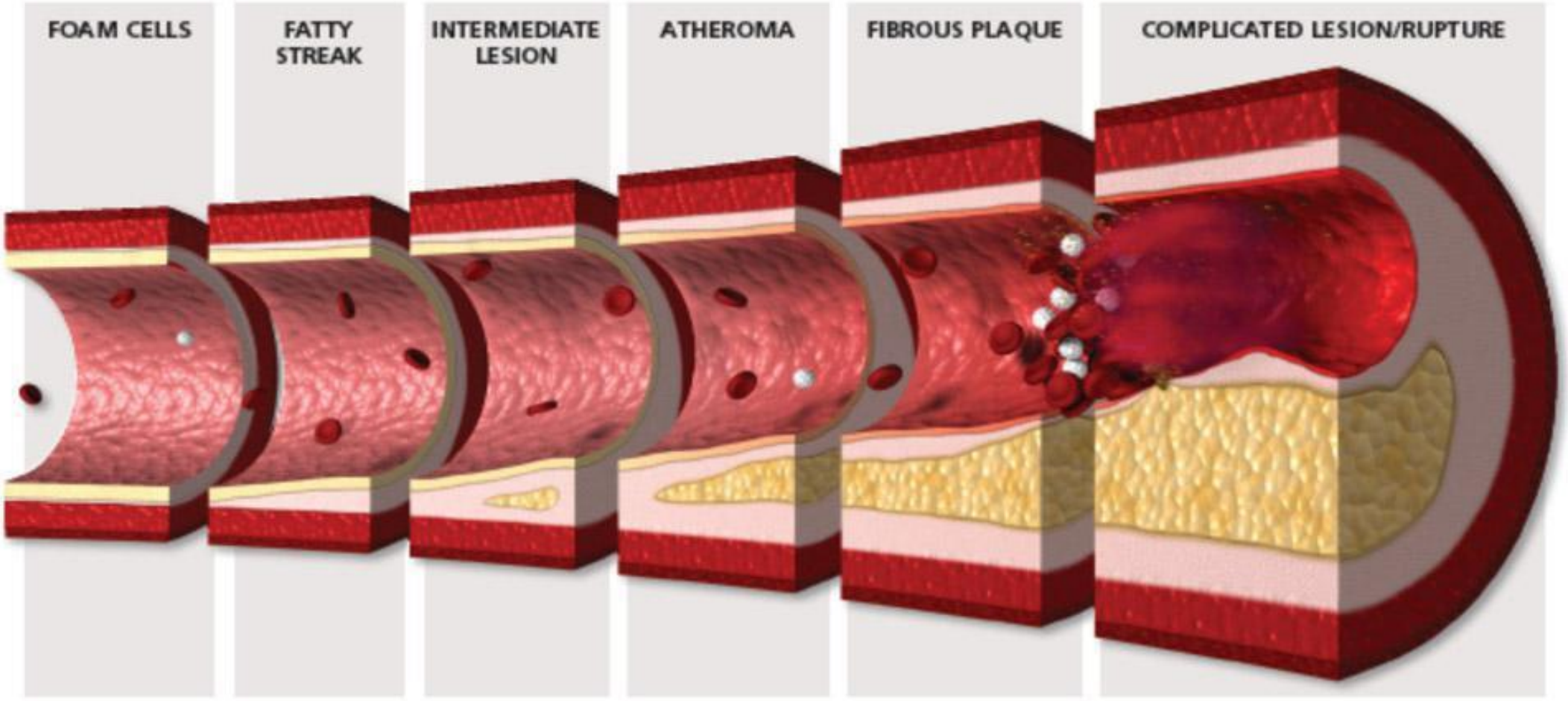
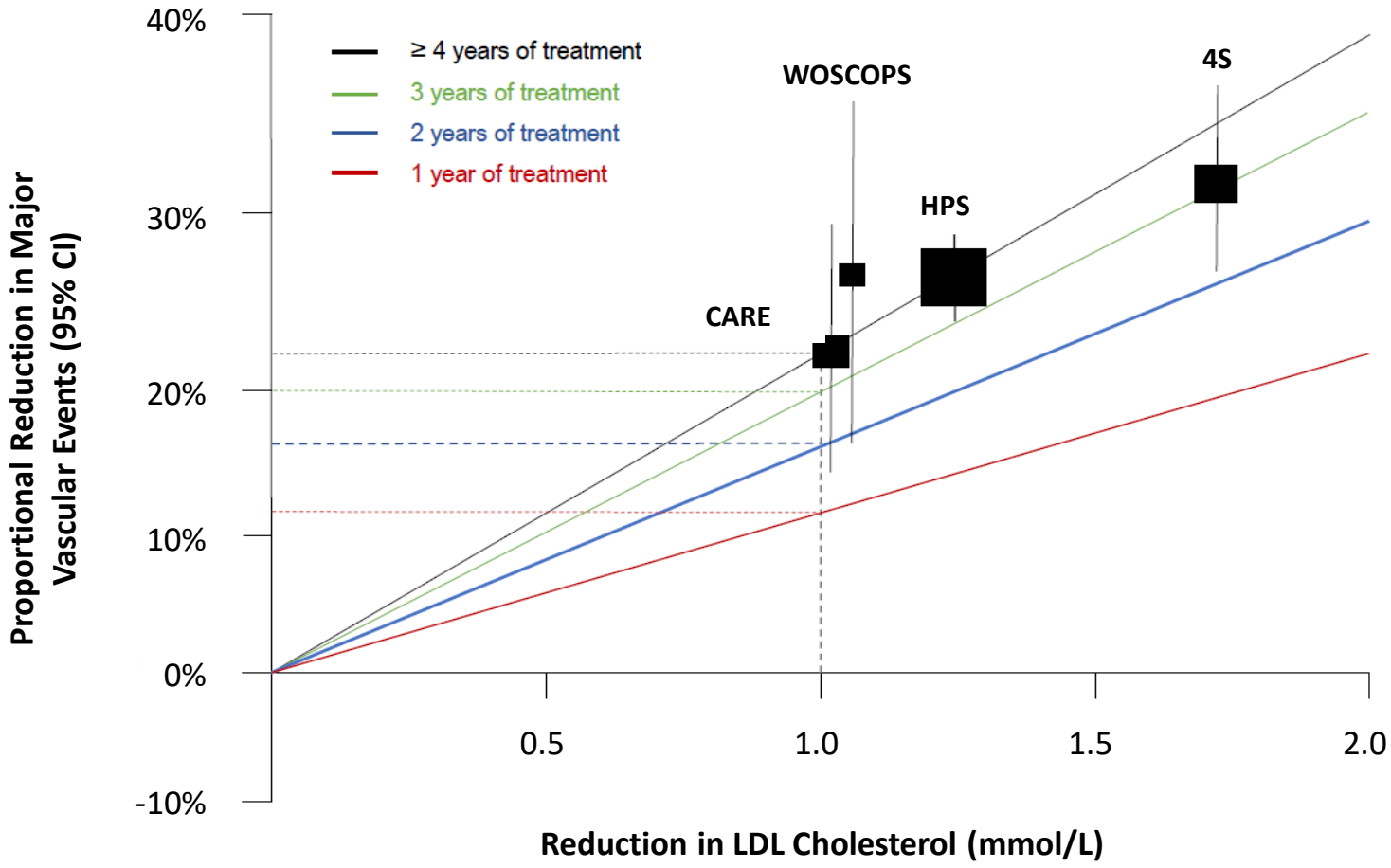
Coronary Atherosclerosis Timeline



We know that benefit is related to absolute reductions in LDL-C and the duration of that absolute reduction



Ference BA, et al. *Eur Heart J*. 2017; doi: 10.1093/eurheartj/ehx450.
CI = confidence interval; LDL = low-density lipoprotein.

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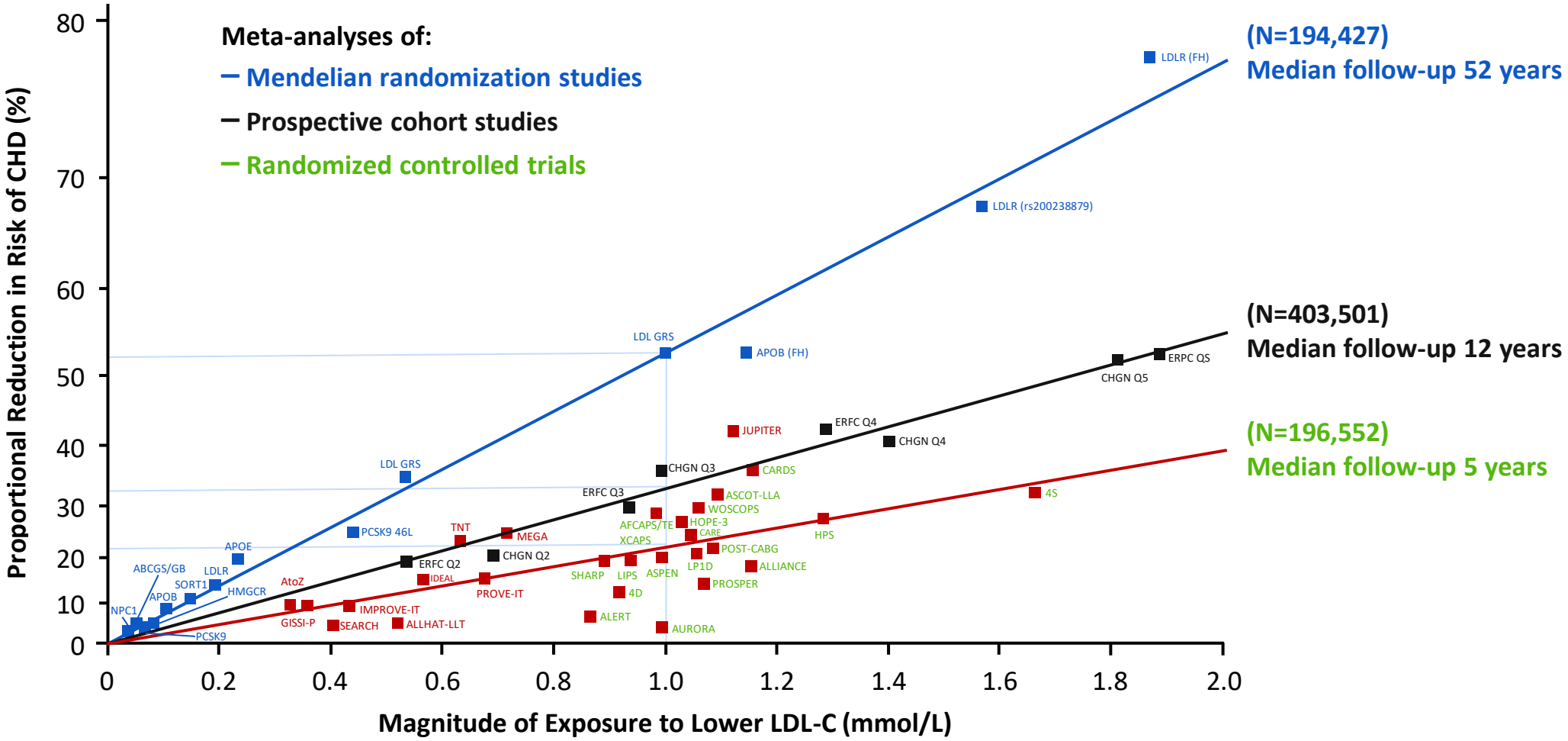
The Benefits of Lowering LDL-C are cumulative

Small reduction maintained over 52 y provide the same benefits as larger reductions in LDL-C over a short exposure



Ference BA, et al. EAS Consensus Statement on LDL Causality. *Eur Heart J.* 2017;doi:10.1093/eurheartj/ehx144.
CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol.

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Age at which a patient encounters a physician

LATE

MISSED YEARS

MORE ADVANCED DISEASE

Lifetime exposure to BP and LDL-C and CV outcomes

JAMA | Original Investigation

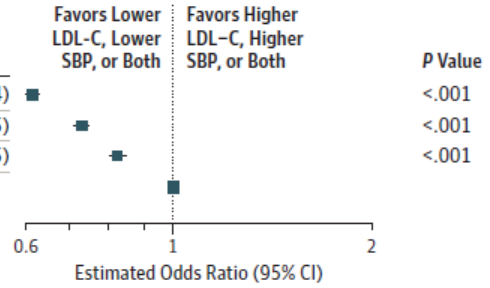
Association of Genetic Variants Related to Combined Exposure to Lower Low-Density Lipoproteins and Lower Systolic Blood Pressure With Lifetime Risk of Cardiovascular Disease

Brian A. Ference, MD, MPhil, MSc; Deepak L. Bhatt, MD, MPH; Alberico L. Catapano, PhD; Chris J. Packard, DSc; Ian Graham, MD; Stephen Kaptoge, PhD; Thatcher B. Ference; Qi Guo, PhD; Ulrich Laufs, MD, PhD; Christian T. Ruff, MD, MPH; Arjen Cupido; G. Kees Hovingh, MD, PhD; John Danesh, DPhil; Michael V. Holmes, MBBS, PhD; George Davey Smith, MD, DSc; Kausik K. Ray, MD, MPhil; Stephen J. Nicholls, MBBS, PhD; Marc S. Sabatine, MD, MPH

Figure 3. Associations of Exposure to Lower LDL-C, Lower SBP, or Both With Risk of Major Coronary Events

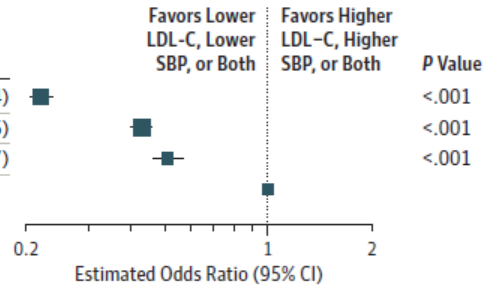
A Associations for the observed difference in LDL-C and SBP vs reference group

	No. of Participants	No. of Events	Difference in LDL-C Score, mg/dL	Difference in SBP, mm Hg	Odds Ratio (95% CI)	*P* Value
Lower LDL-C and lower SBP	105 528	4832	-13.9	-3.1	0.61 (0.59-0.64)	<.001
Lower LDL-C	109 027	5784	-14.7	-0.1	0.73 (0.70-0.75)	<.001
Lower SBP	111 097	6515	1.6	-2.9	0.82 (0.80-0.85)	<.001
Reference	113 300	7849				



B Associations scaled for a 38.67-mg/dL lower LDL-C, 10-mm Hg lower SBP, or both vs the reference group

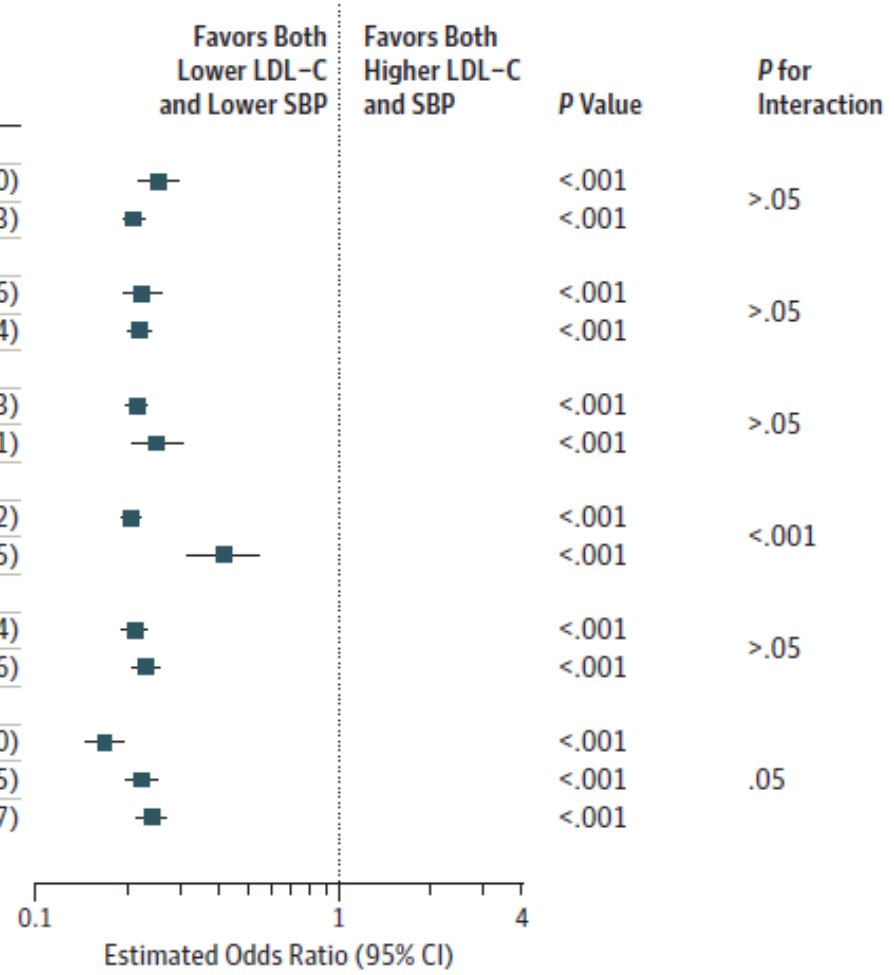
	No. of Participants	No. of Events	Difference in LDL-C Score, mg/dL	Difference in SBP, mm Hg	Odds Ratio (95% CI)	*P* Value
Lower LDL-C and lower SBP	105 528	4832	-38.67	-10.0	0.22 (0.21-0.24)	<.001
Lower LDL-C	109 027	5784	-38.67	0	0.43 (0.40-0.46)	<.001
Lower SBP	111 097	6515	0	-10.0	0.51 (0.46-0.57)	<.001
Reference	113 300	7849				



Benefits across major subgroups

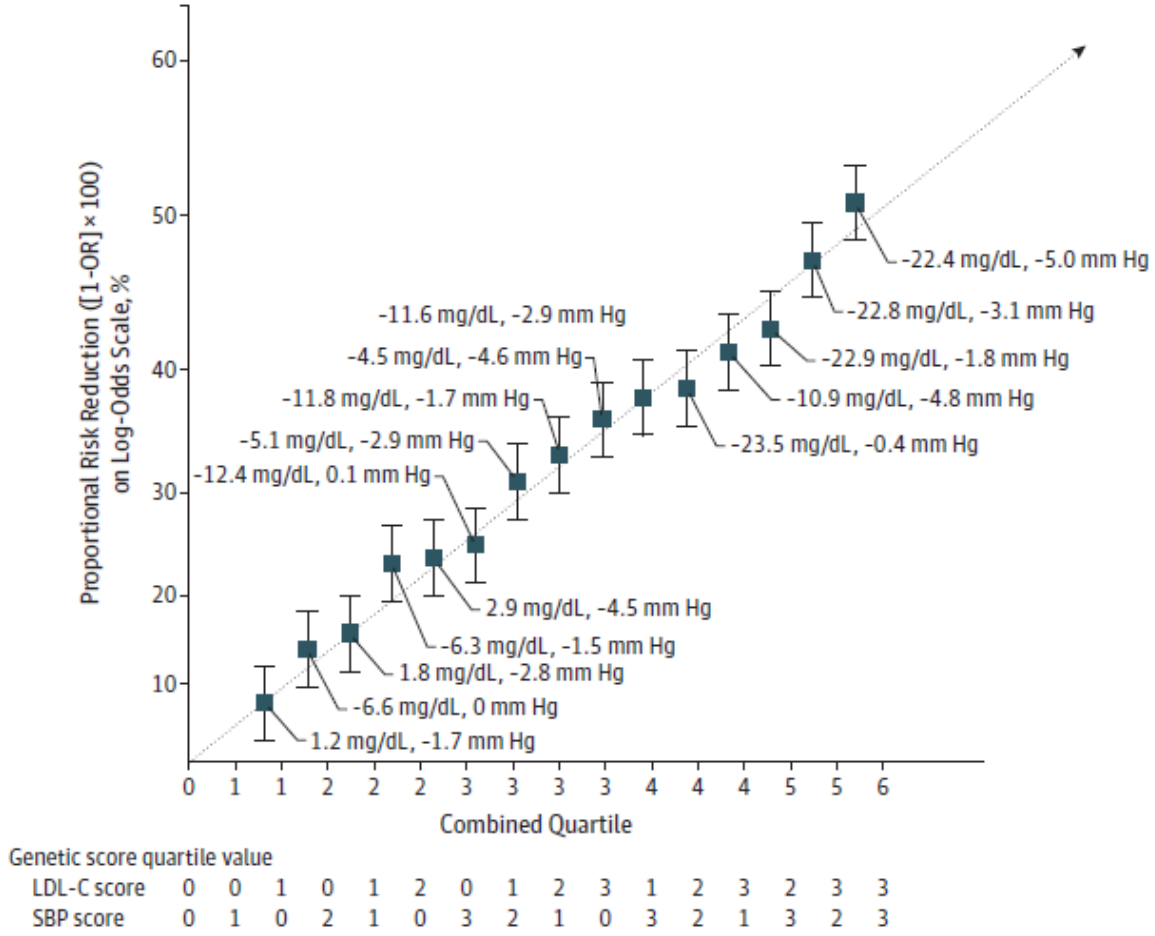
B Associations scaled for 38.67-mg/dL lower LDL-C and 10-mm Hg lower SBP vs the reference group

	No. of Participants	Difference in LDL-C Score, mg/dL	Difference in SBP, mm Hg	Odds Ratio (95% CI)	*P* Value	*P* for Interaction
Sex						
Women	238004	-38.67	-10	0.25 (0.22-0.30)	<.001	>.05
Men	200948	-38.67	-10	0.21 (0.19-0.23)	<.001	
Age, y						
≤65	214350	-38.67	-10	0.23 (0.20-0.26)	<.001	>.05
>65	224602	-38.67	-10	0.22 (0.20-0.24)	<.001	
Diabetes						
No	368728	-38.67	-10	0.22 (0.20-0.23)	<.001	>.05
Yes	70224	-38.67	-10	0.25 (0.21-0.31)	<.001	
Current smoker						
No	407380	-38.67	-10	0.21 (0.19-0.22)	<.001	<.001
Yes	31572	-38.67	-10	0.42 (0.32-0.55)	<.001	
Ever smoker						
No	301463	-38.67	-10	0.21 (0.19-0.24)	<.001	>.05
Yes	137489	-38.67	-10	0.23 (0.21-0.26)	<.001	
BMI, tertile						
1	147346	-38.67	-10	0.17 (0.15-0.20)	<.001	
2	146467	-38.67	-10	0.23 (0.20-0.25)	<.001	.05
3	145139	-38.67	-10	0.24 (0.22-0.27)	<.001	



CV risk could be avoided by BP and LDL-C control

Figure 6. Dose-Dependent Associations and Meta-Regression Analysis for Combinations of Increasingly Lower LDL-C and Lower SBP on the Risk of Major Coronary Events



Comparative clinical benefit: earlier v. later LDL lowering

Timing of LDL-C Lowering	Source of Point Estimate	Size (N)	Adjusted per 38.7 mg/dl (1 mmol/L) Lower LDL-C: OR_{CHD} (95% CI)	RRR (95% CI)	p (difference)
Early in life	Meta-Analysis of Mend Rand	826,443	0.46 (0.43-0.49)	54% (51-57)	$p = 8.4x10^{-54}$
Later in life	Meta-Analysis of Statin trials	169,138	0.78 (0.76-0.80)	22% (20-24)	

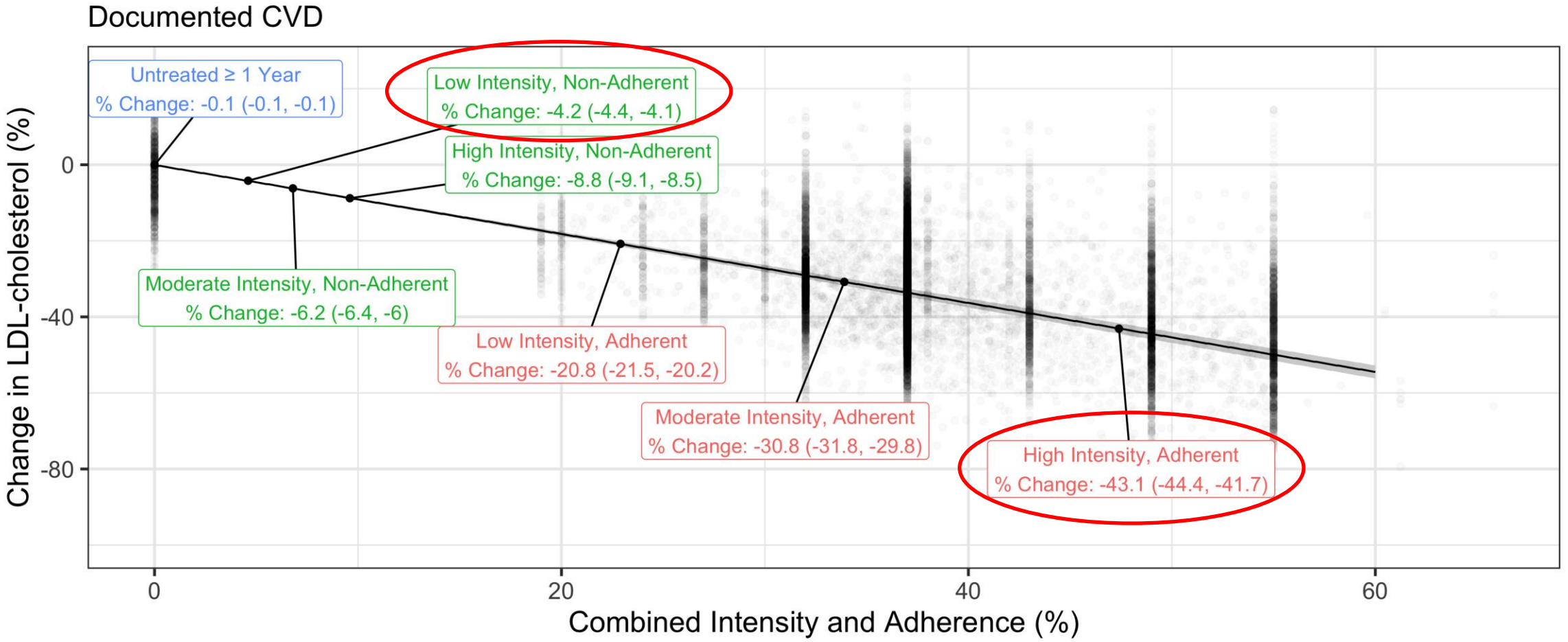
Early in life: *38.7 mg/dl (1 mmol/L)* *lower LDL-C* → *~ 55% RRR* *(OR: 0.46)*

Later in life: *116 mg/dl (3 mmol/L)* *lower LDL-C* → *~ 55% RRR* *(OR: 0.44 ~ 0.78*0.78*0.78)*

- Prolonged exposure to lower LDL-C beginning early in life is associated with 3-fold greater clinical benefit for each unit lower LDL than treatment with a statin started later in life
- ***May explain much of the residual risk among persons treated with a statin***

Ference, BA et al. J Am Coll Cardiol 2012;60:2631-9.

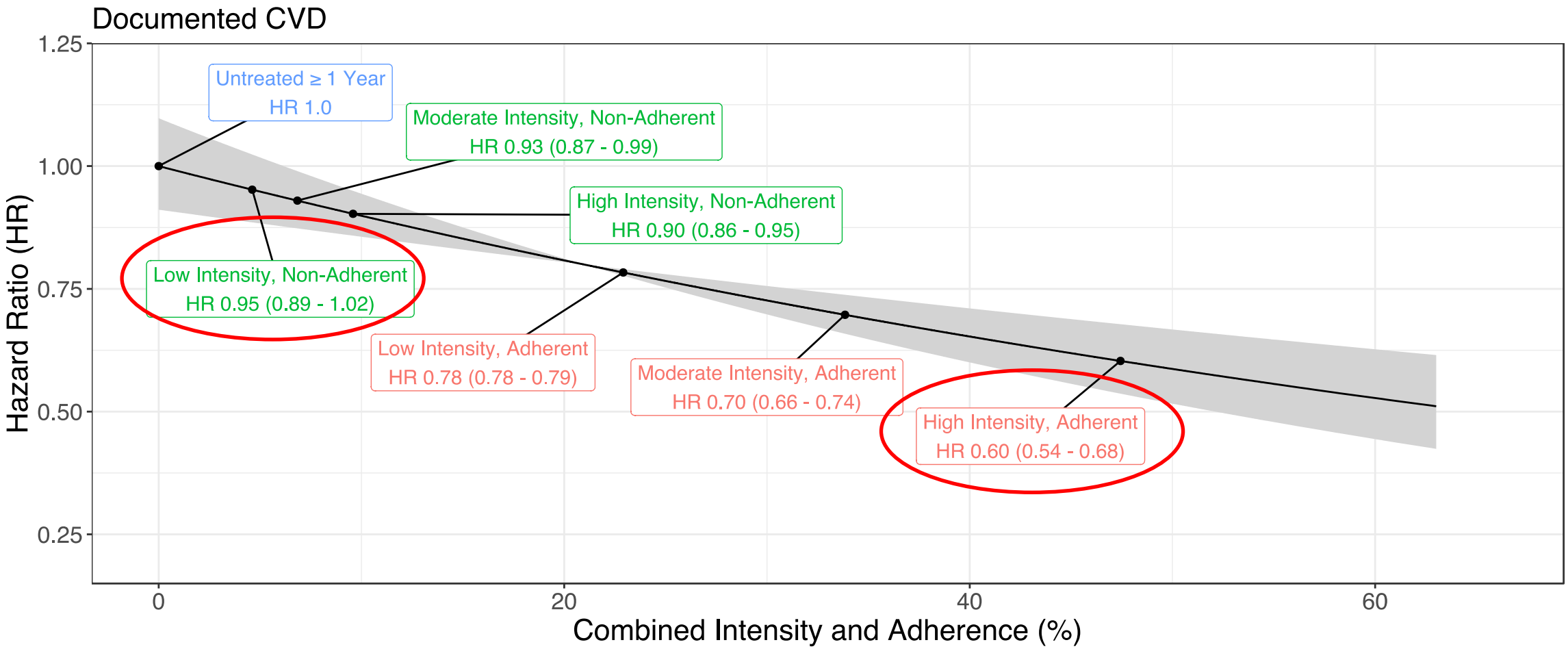
Effect of the Combined Measure of *Adherence x Intensity* on LDL-C Reduction



Results for diabetes and CKD cohorts were similar

***Khunti K , Ray KK JAMA Network Open Dec 7th 2018* 1(8):e185554.**
doi:10.1001/jamanetworkopen.2018.5554

Effect of the Combined Measure of *Adherence x Intensity* on Cardiovascular Risk



Results for diabetes and CKD cohorts were similar

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Estimate of the Benefit from Optimal Adherence and Intensity on Cardiovascular Events

Documented CVD population

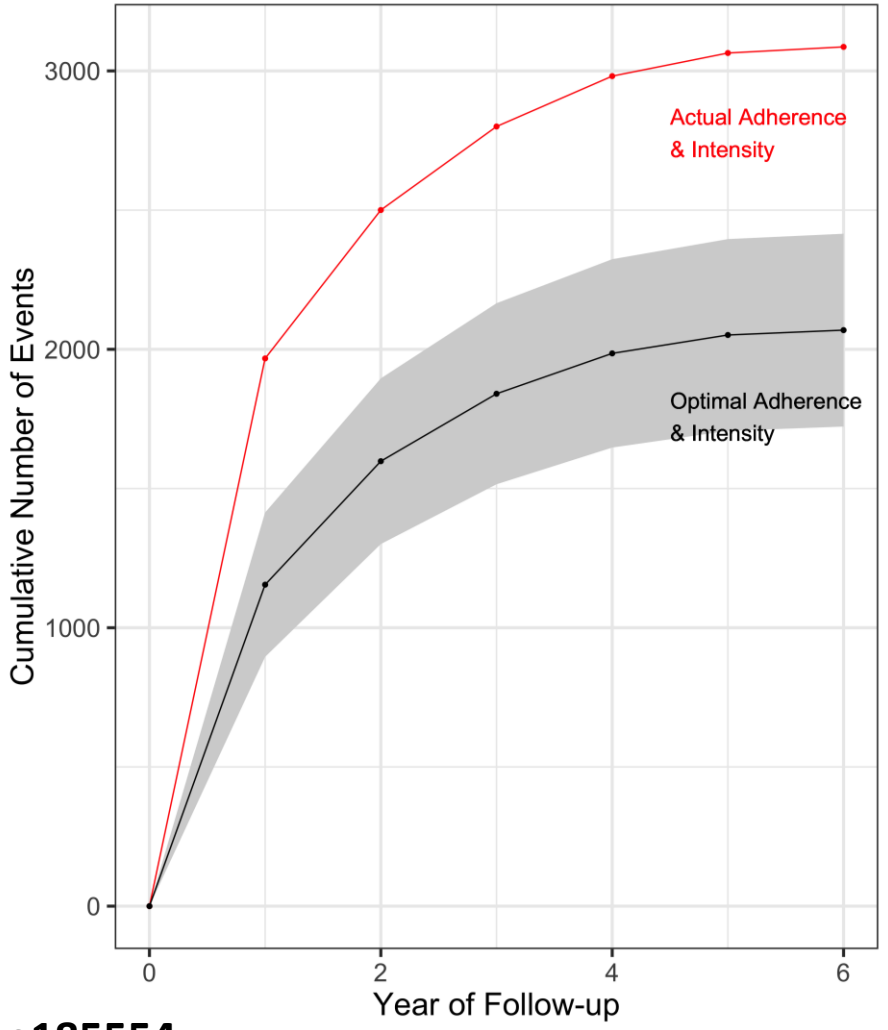
With an actual combined adherence x intensity measure of 21%, the mean event rate was

- 72 per 1,000 person-years

With an optimal (hypothetical) combined measure of 50% for everyone, the mean event rate was

- 48 per 1,000 person-years

In a population of 500,000, this translates to 12,000 events prevented per year



Khunti K , Ray KK JAMA Network Open Dec 7th 2018 1(8):e185554.
doi:10.1001/jamanetworkopen.2018.5554

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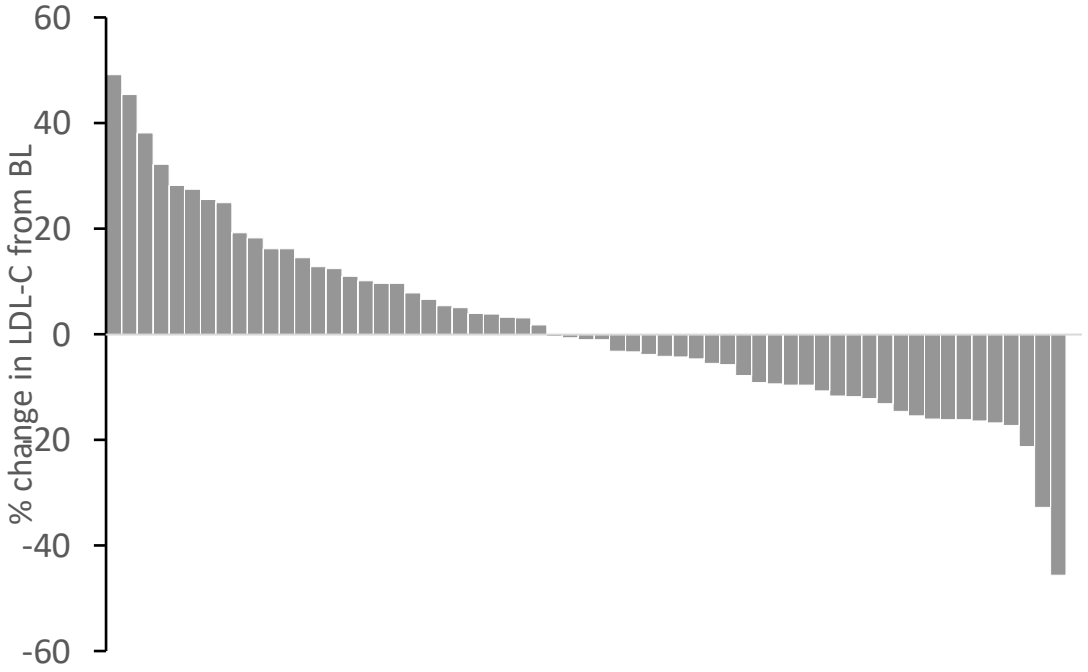
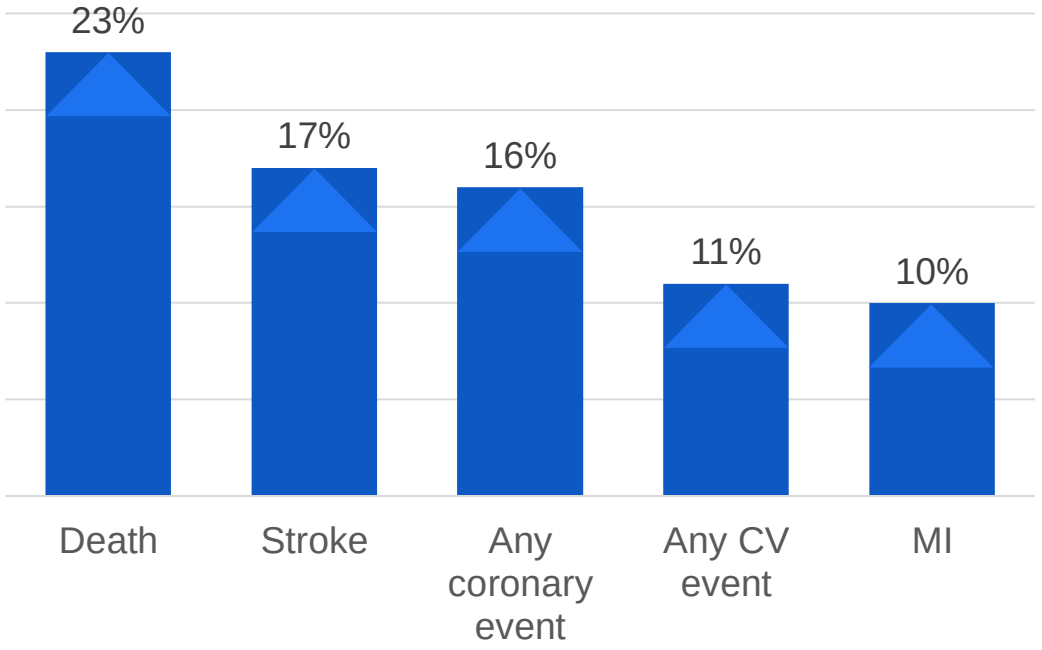
Challenge is to achieve chronic sustained LDL reductions

LDL-C variability common, associated with worse outcomes

Six month percent change in LDL-C among statin users from starting level[1]



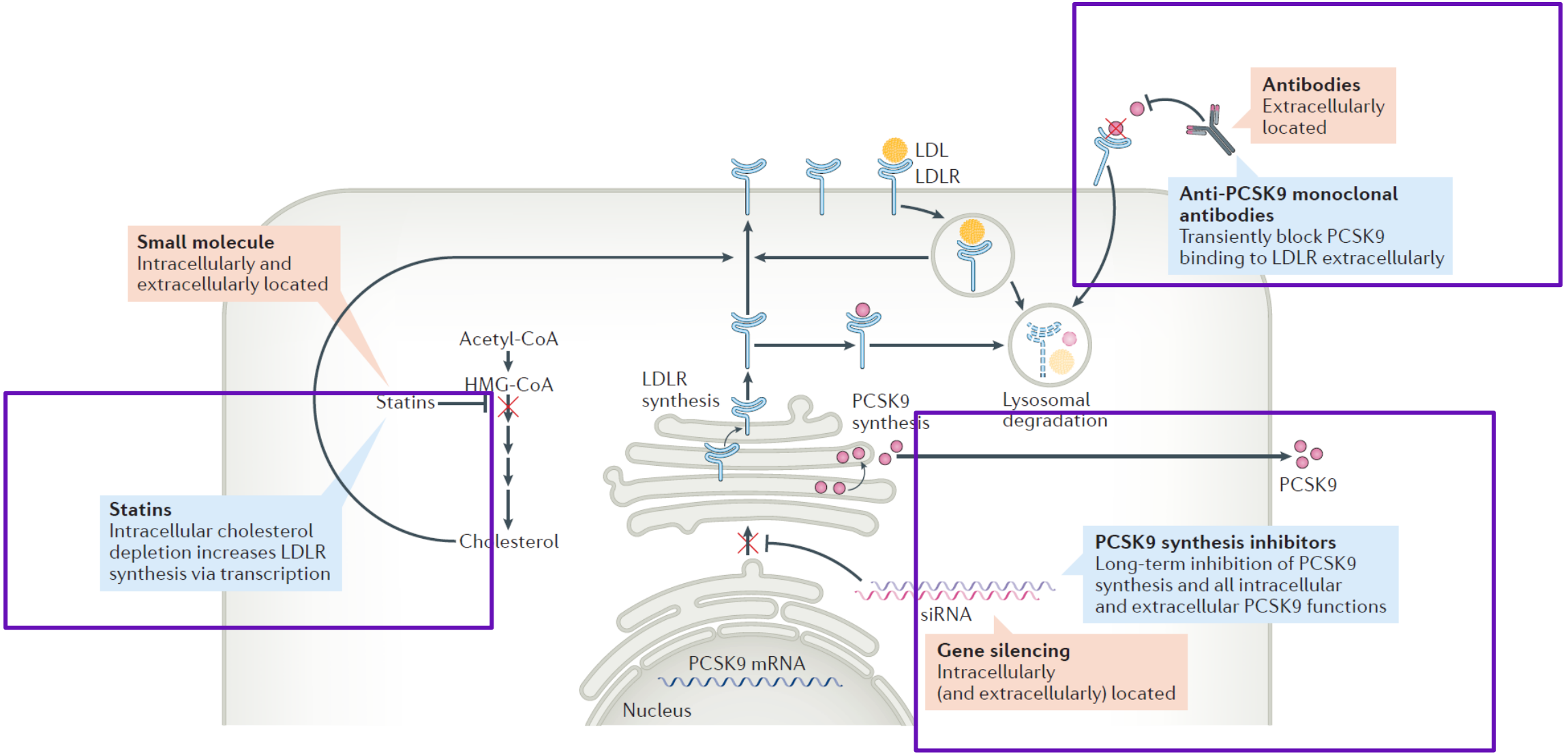
Increase in death, CV outcomes with each 1 standard deviation of LDL-C variability[2]



1. Ray KK et al. N Engl J Med 2017; 376:1430-1440
2. Bangalore S et al. JACC 2015; 65: 1539-1548

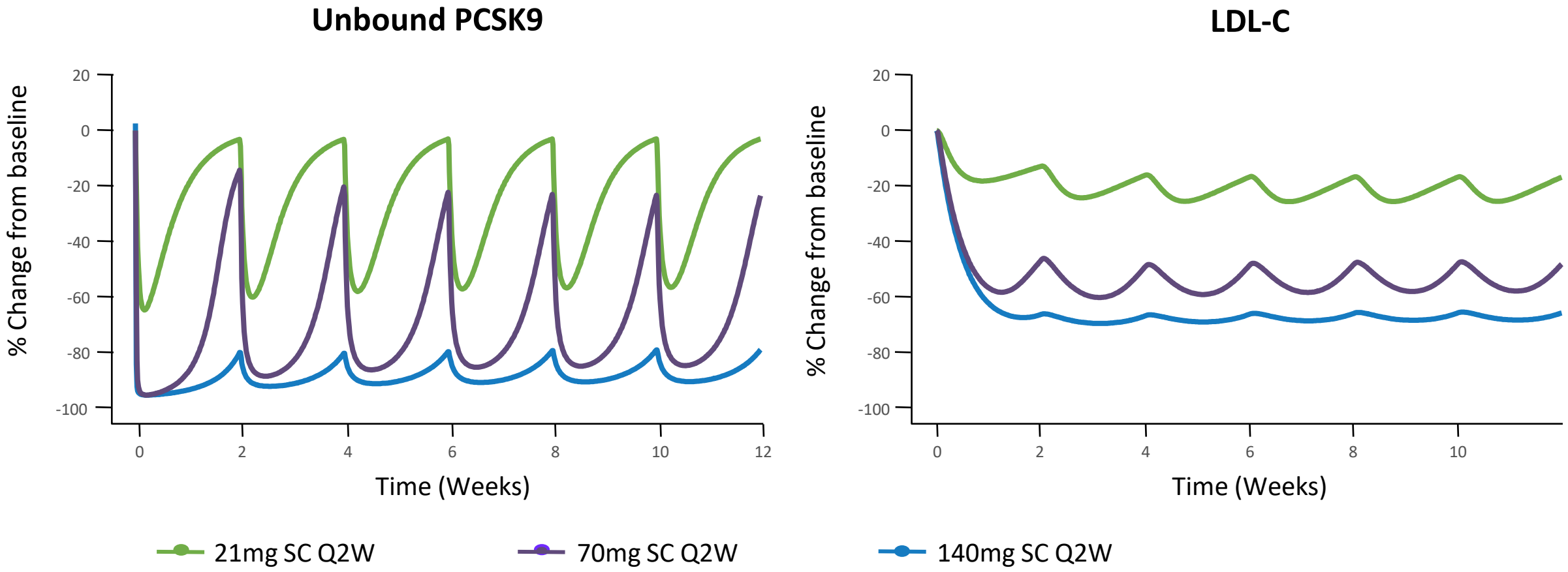
Therapeutic approaches to reducing LDL-C via the LDL recptor

Small Molecules, Mabs, siRNA



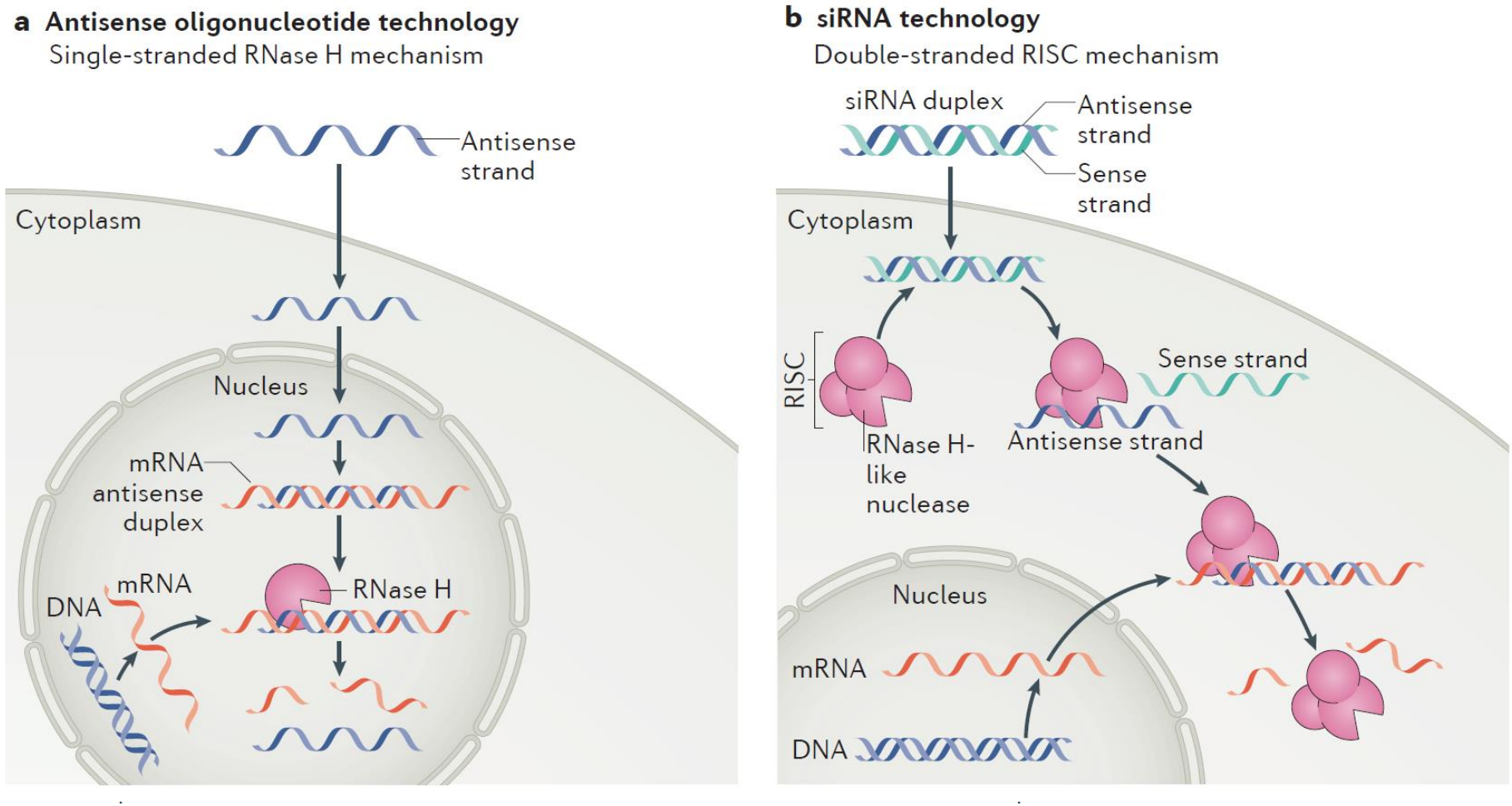
1. Nordestegaard B, Ray KK Nature Reviews Cardiology Jan 2018

Sustained PCSK9 inhibition with 140 mg Q2W evolocumab leads to effective, stable LDL-C reduction



*http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/*EndocrinologicandMetabolicDrugsAdvisoryCommittee*/UCM452354.pdf. Accessed 25 Feb 2016.*

RNA based approaches

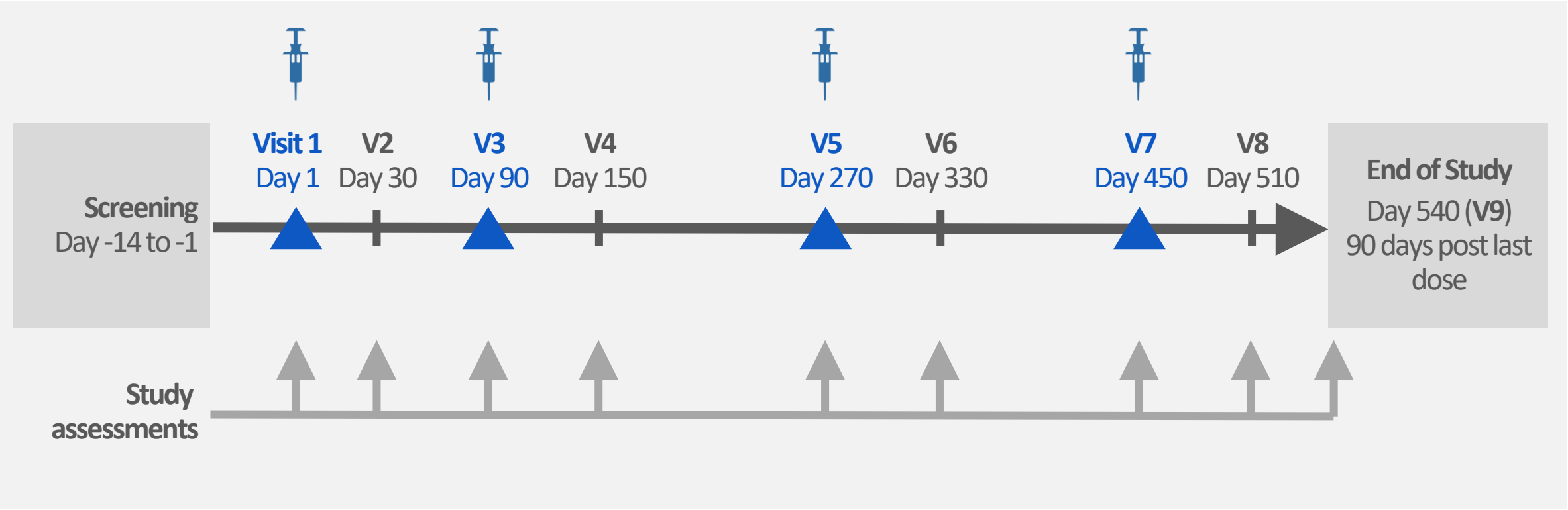


1. Nordestegaard B, Ray KK Nature Reviews Cardiology Jan 2018

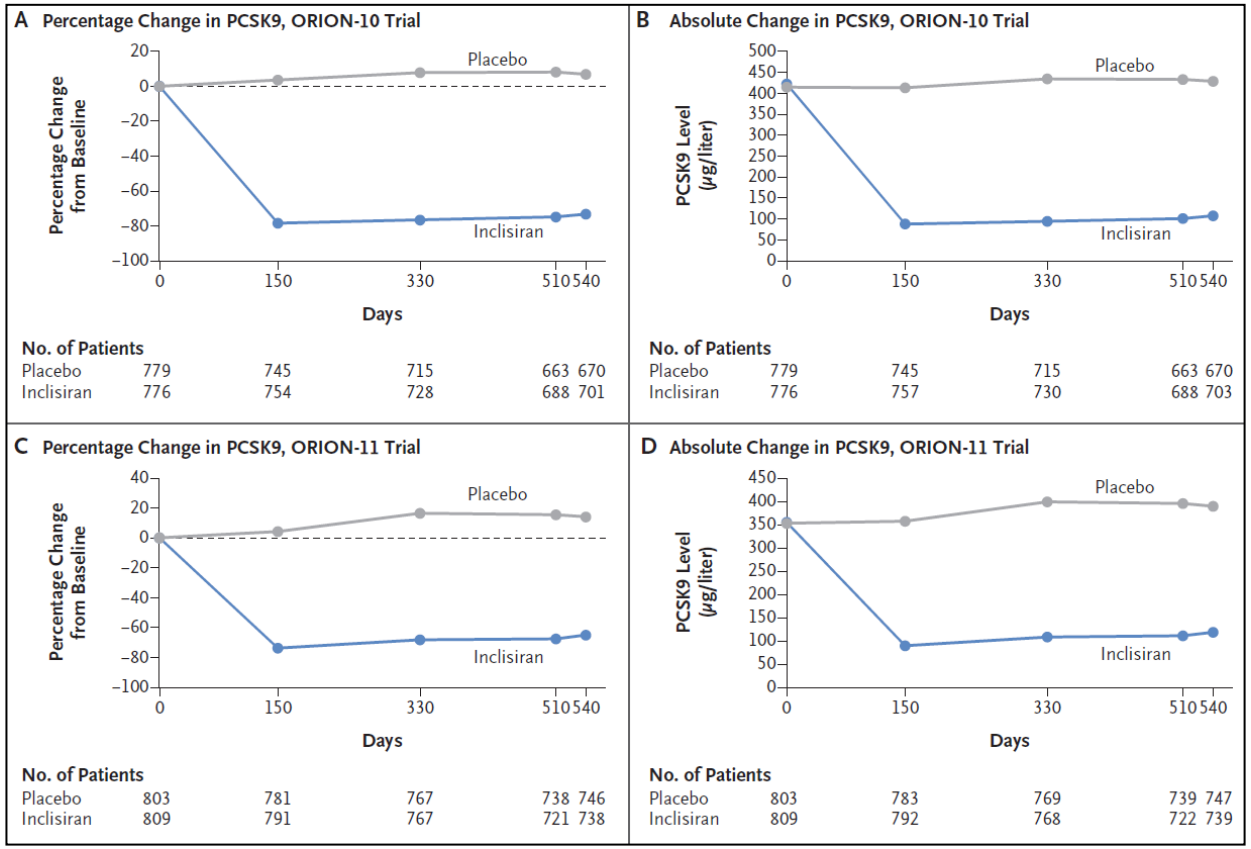
ORION-9,10,11: Study design

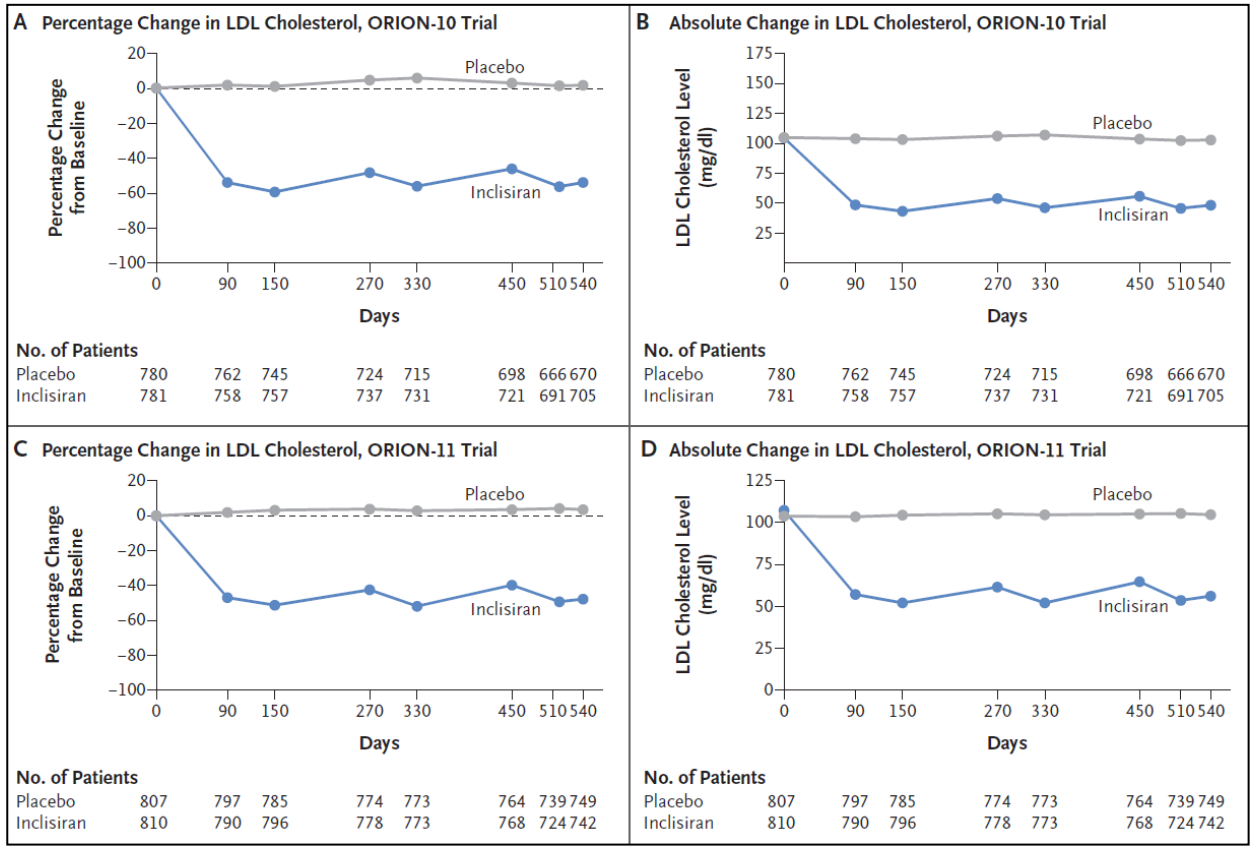
Eighteen months treatment and observation

- Randomized 1:1 inclisiran 300 mg *vs.* placebo – with maximally tolerated statins



Efficacy and safety of inclisiran in ORION 10 and 11





Ray KK et al. N Engl J Med 2020;382:1507–1519

ORION 9 Efficacy in HeFH

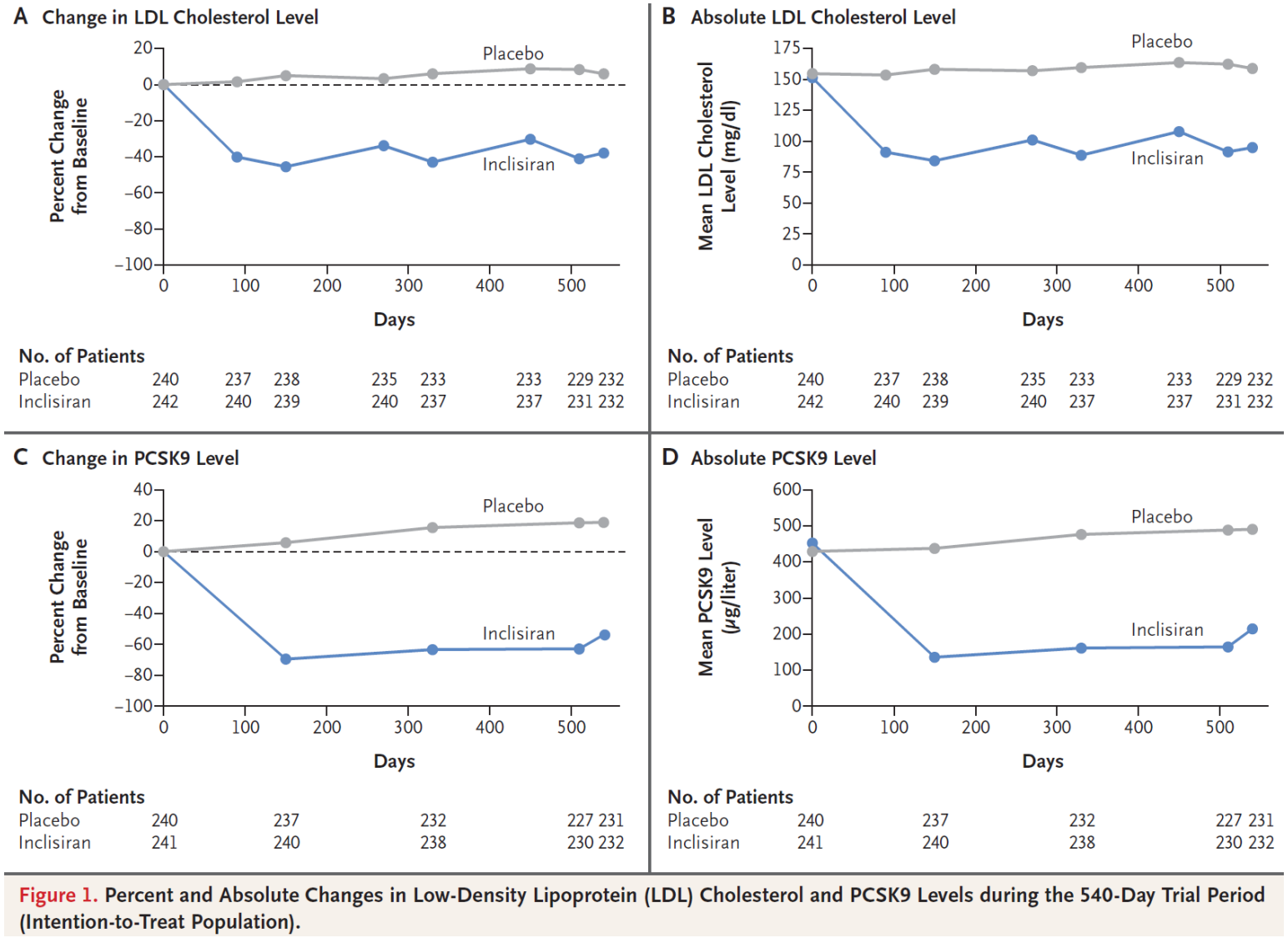
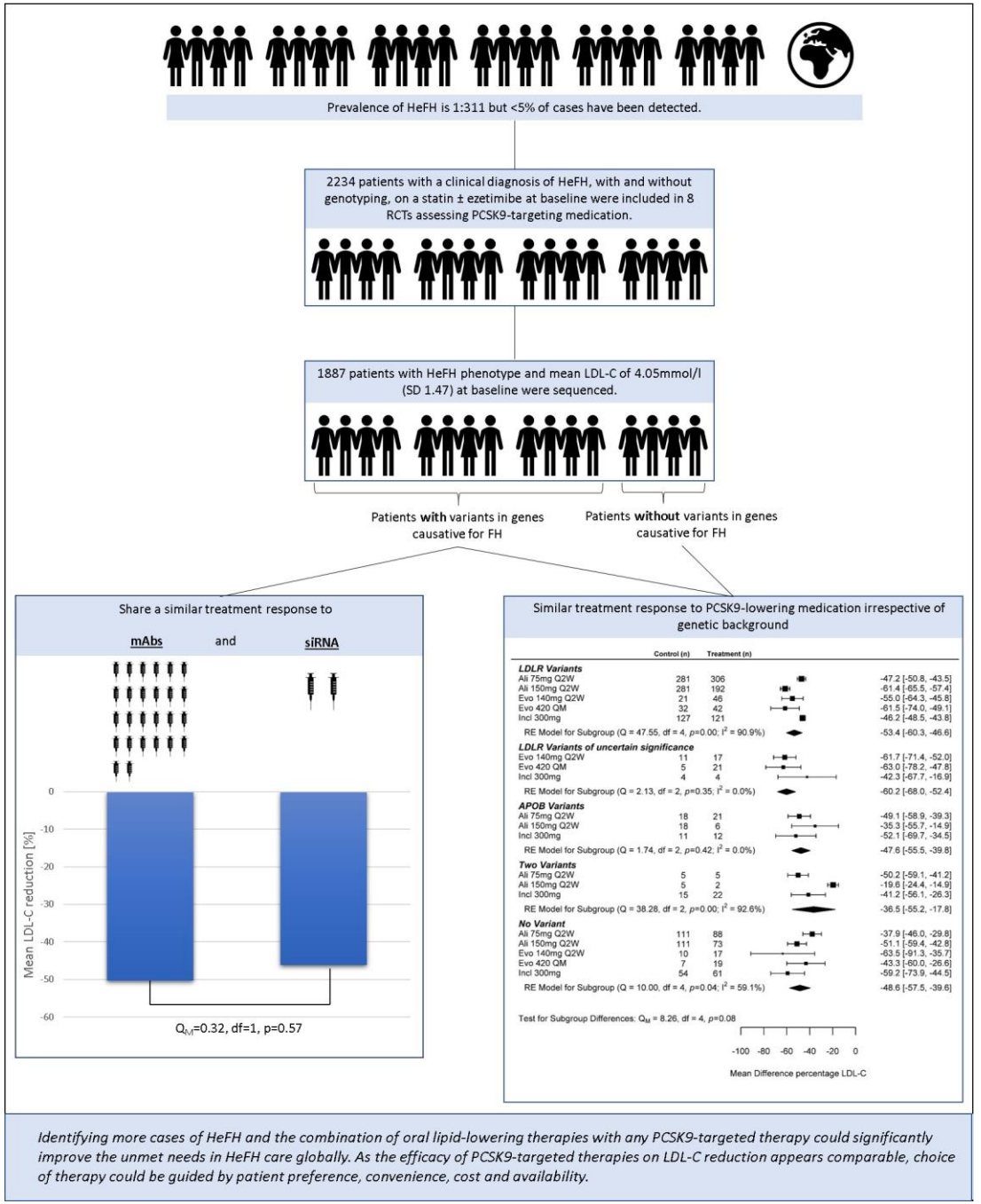


Figure 1. Percent and Absolute Changes in Low-Density Lipoprotein (LDL) Cholesterol and PCSK9 Levels during the 540-Day Trial Period (Intention-to-Treat Population).

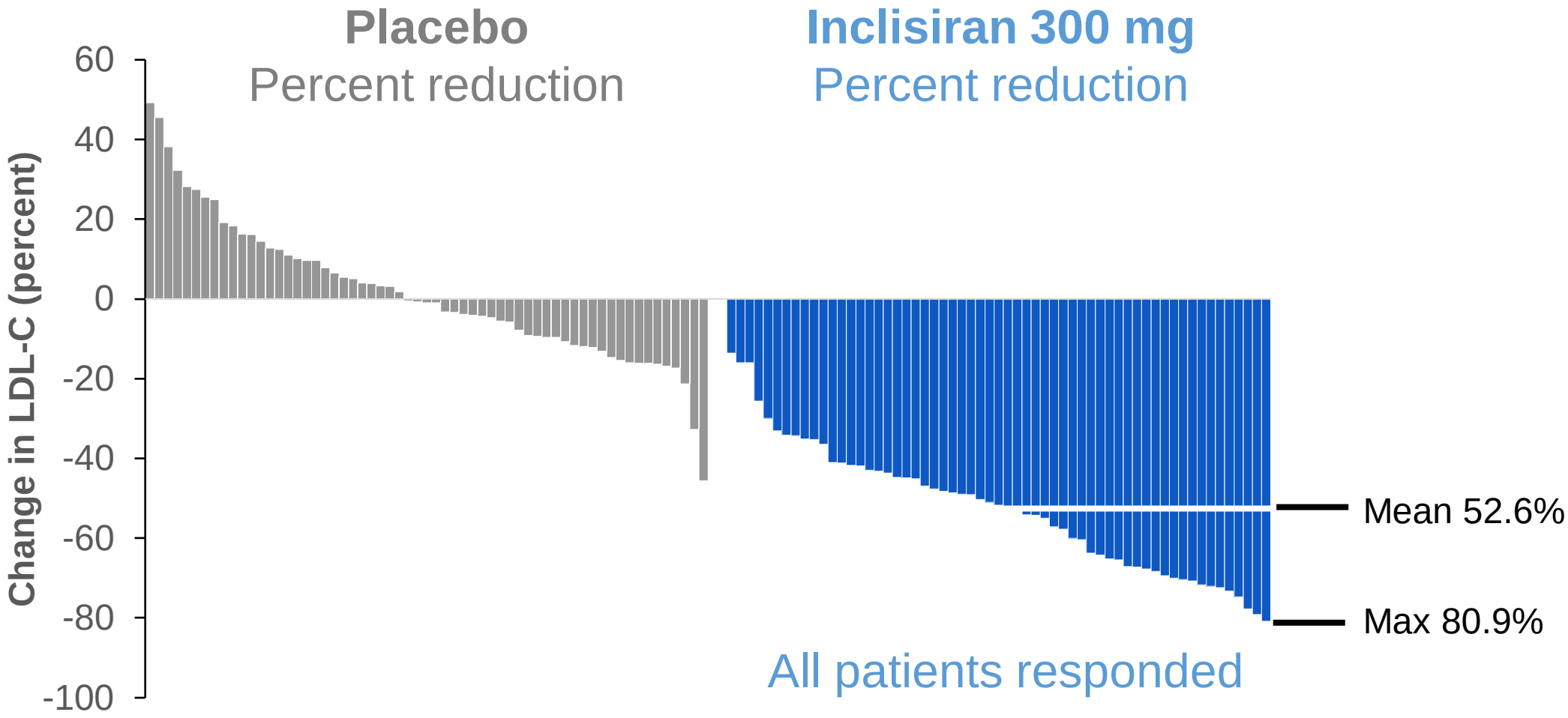
Raal D, Ray KK et al. N Engl J Med 2020;382:



Brandts J , Ray KK Atherosclerosis 2021

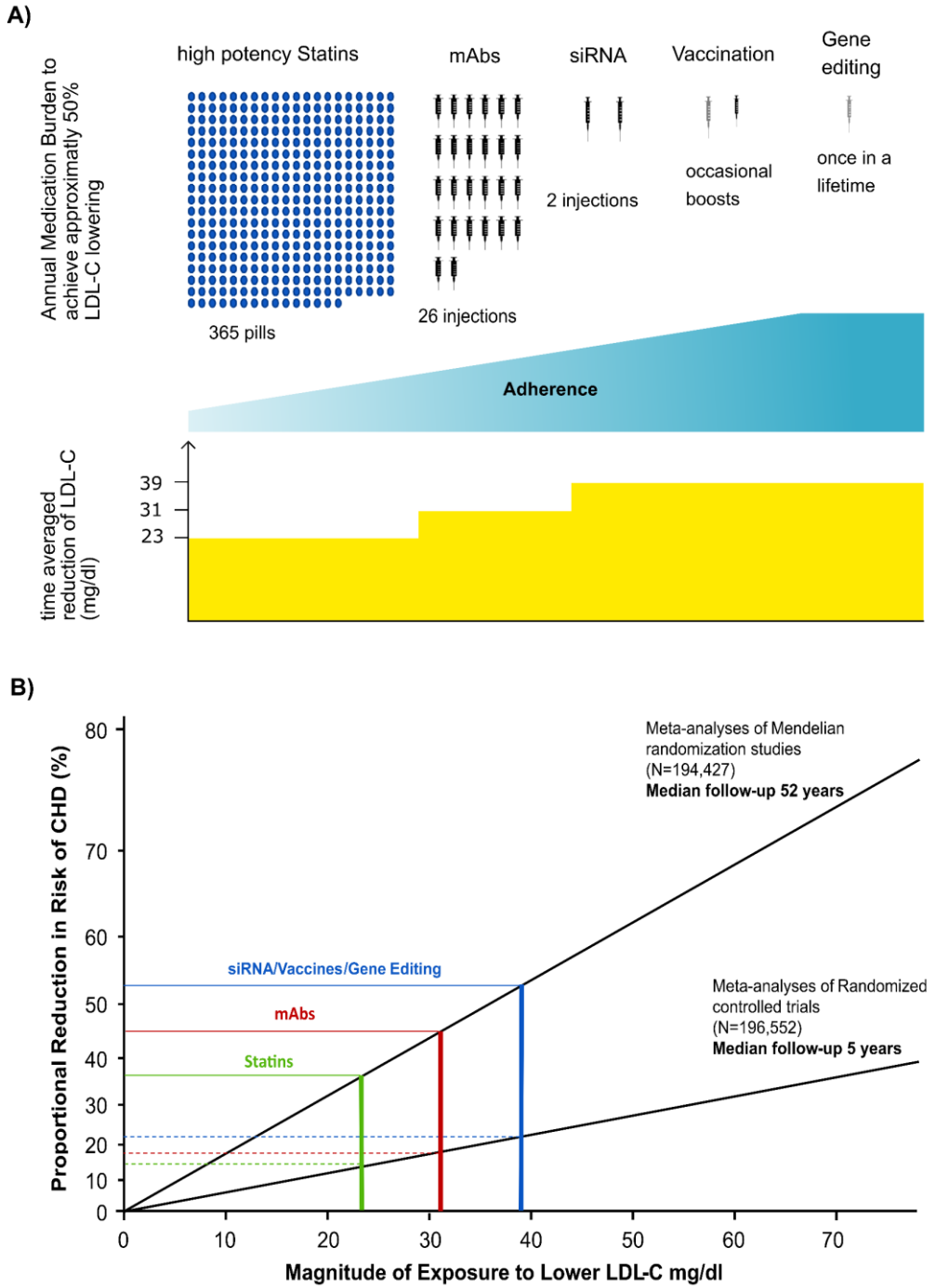
Efficacy: Two dose starting regimen

Individual patient responses (%) at day 180



1. Ray KK et al. N Engl J Med 2017; 376:1430-144

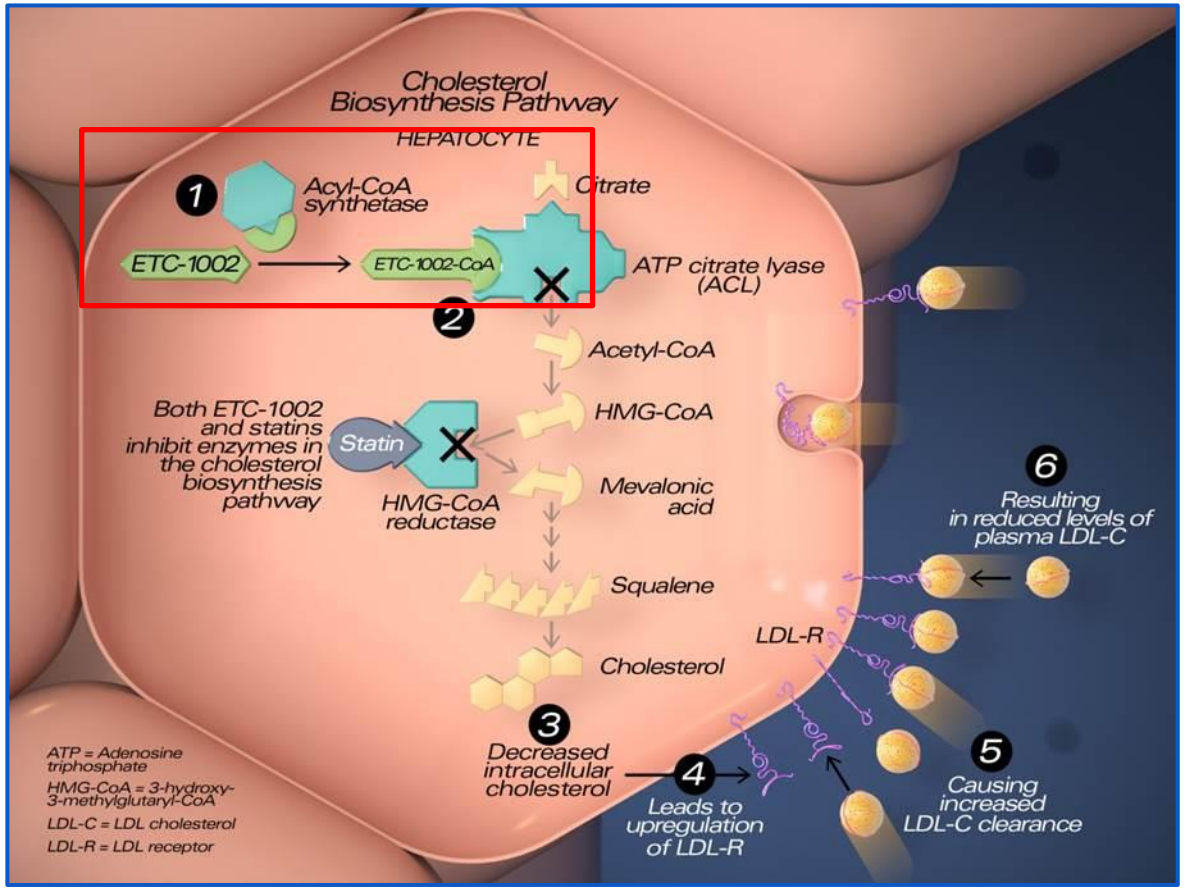
Moving to a cumulative Exposure Model for Population Health



Brandts J, Ray KK Circulation 2020

Bempedoic Acid Mechanism of Action

Converted to ETC-1002-CoA, the Active Form, only in Liver



- Bempedoic acid (BA) acts in the same cholesterol biosynthesis pathway as statins
- BA targets ATP-Citrate Lyase (ACL), an enzyme upstream of HMG-CoA reductase
- Up-regulates LDL receptors and lowers LDL-C
- The specific isozyme (ACSVL1) which converts BA into an active drug is not present in skeletal muscle

Adapted from Pinkosky et al. Nature Communications. 2016 Nov 28; DOI: 10.1038/ncomms13457

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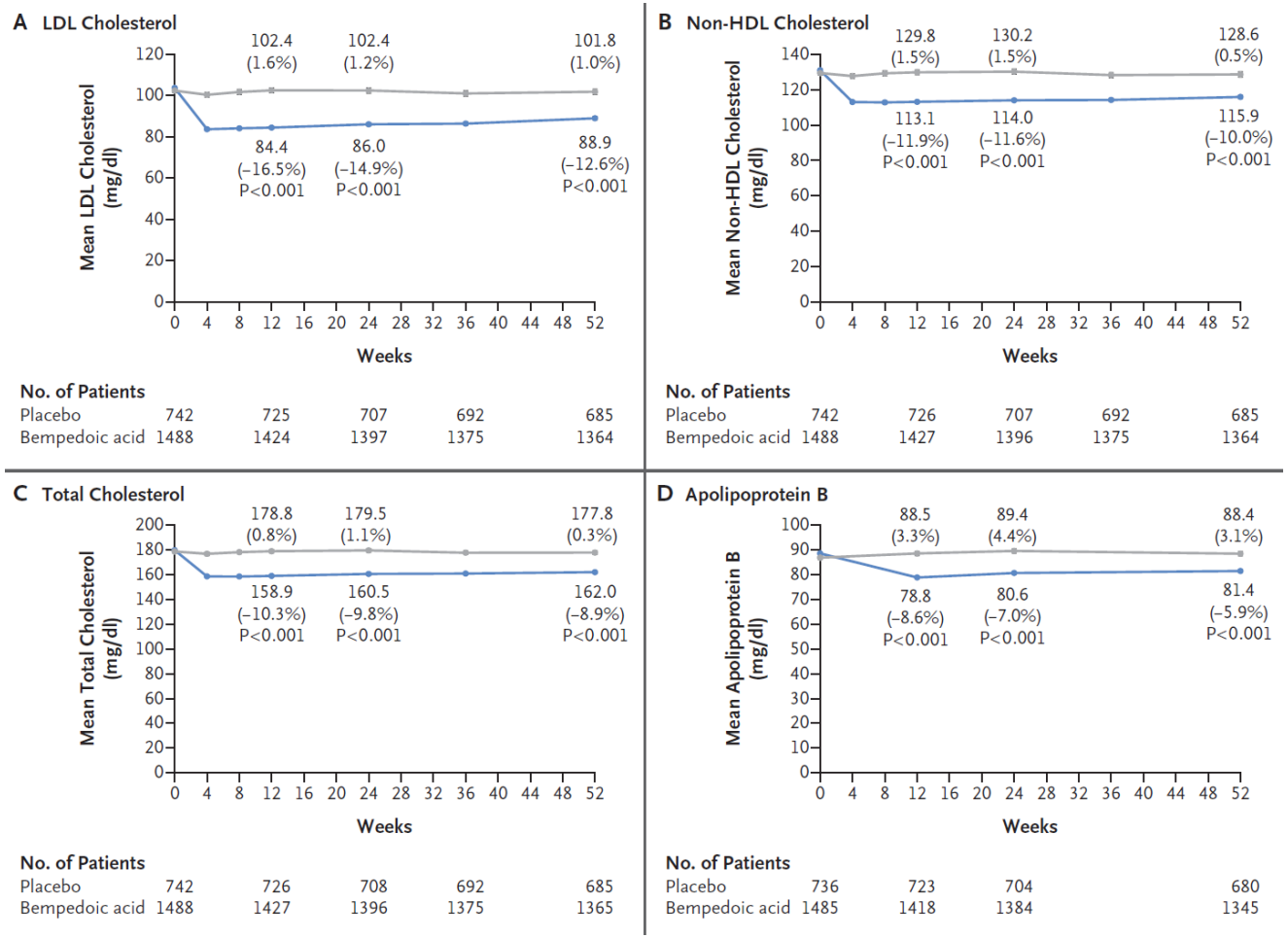
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., Harold E. Bays, M.D., Alberico L. Catapano, Ph.D., Narendra D. Lalwani, Ph.D., M.B.A., LeAnne T. Bloedon, M.S., R.D., Lulu R. Sterling, Ph.D., Paula L. Robinson, M.S., and Christie M. Ballantyne, M.D., for the CLEAR Harmony Trial*

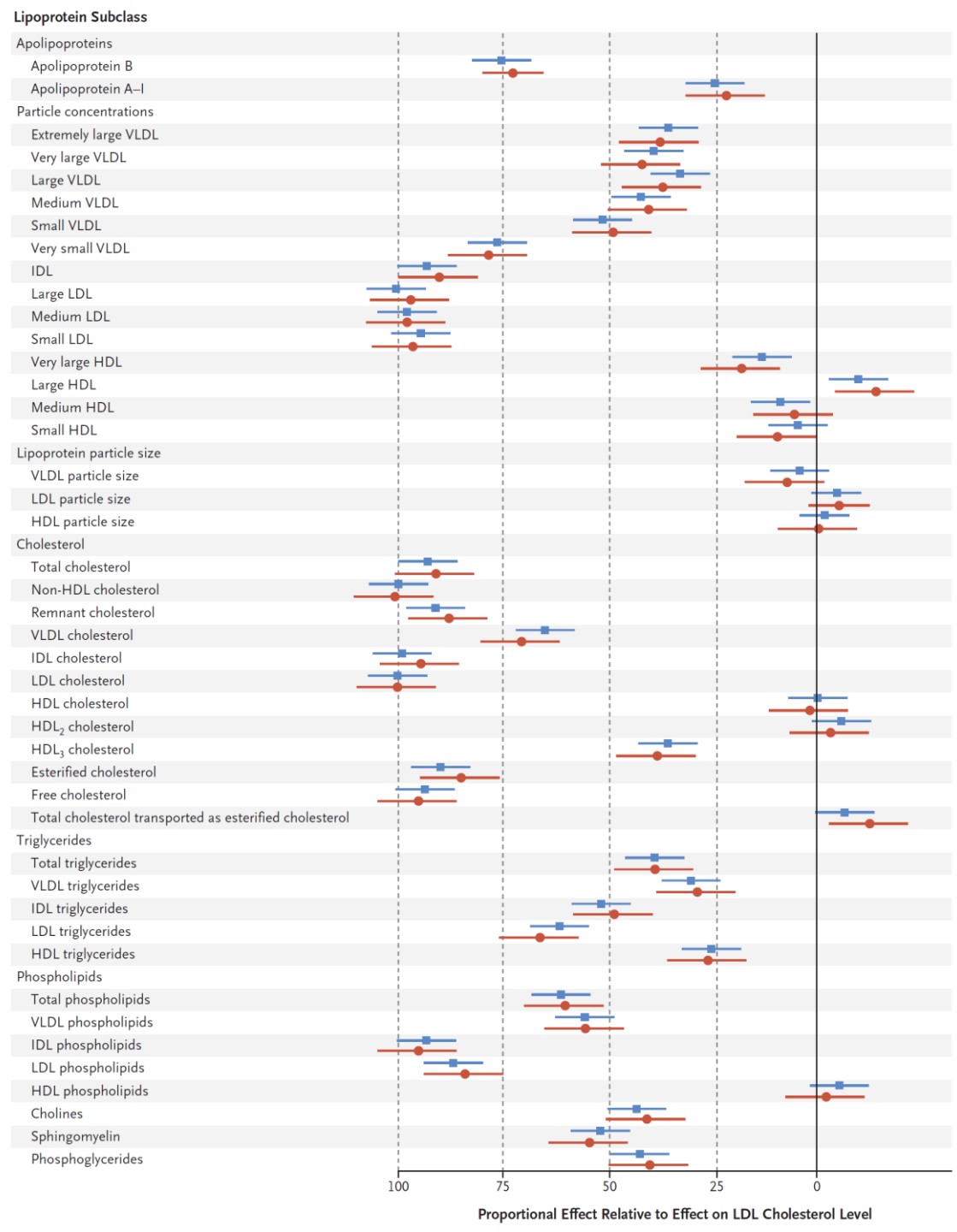


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

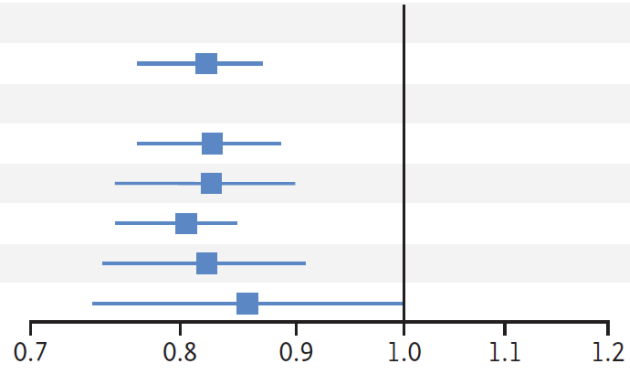
Mendelian Randomization Study of *ACLY* and Cardiovascular Disease

Brian A. Ference, M.D., Kausik K. Ray, M.D., Alberico L. Catapano, Ph.D., Thatcher B. Ference, Stephen Burgess, Ph.D., David R. Neff, D.O., Clare Oliver-Williams, Ph.D., Angela M. Wood, Ph.D., Adam S. Butterworth, Ph.D., Emanuele Di Angelantonio, M.D., John Danesh, D.Phil., John J.P. Kastelein, M.D., Ph.D., and Stephen J. Nicholls, M.B., B.S., Ph.D.



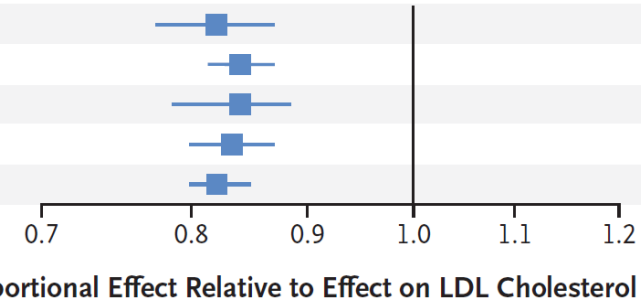
A ***ACLY* Score**

Outcome	No. of Participants	Odds Ratio for Cardiovascular Events per Decrease of 10 mg/dl in LDL Cholesterol Level (95% CI)
Primary outcome		
Major cardiovascular event	105,429	0.82 (0.78–0.87)
Secondary outcomes		
Major coronary event	28,591	0.83 (0.78–0.89)
Coronary heart disease	23,995	0.83 (0.76–0.90)
Myocardial infarction	65,145	0.81 (0.76–0.86)
Coronary revascularization	11,426	0.82 (0.75–0.91)
Death from coronary heart disease	4,348	0.86 (0.74–1.00)

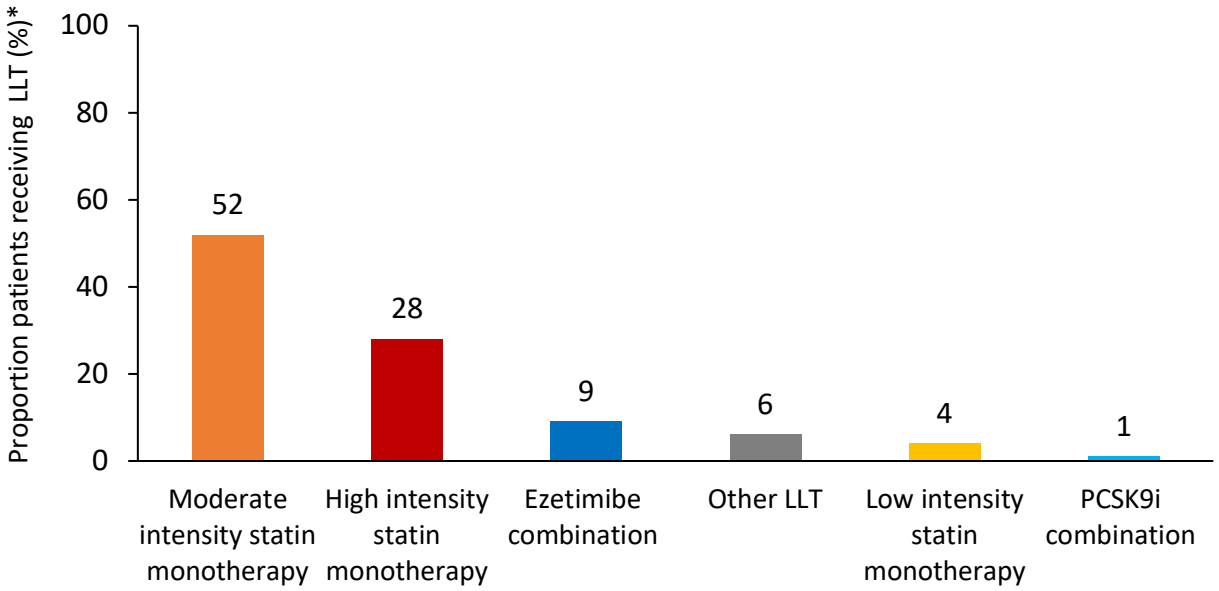


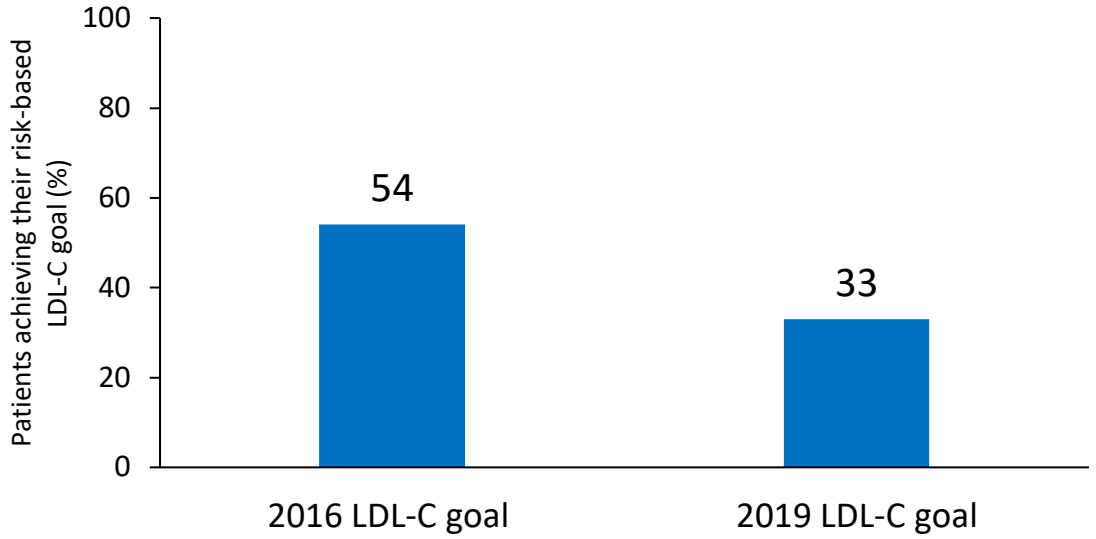
B **All Scores**

Genetic Score	Odds Ratio for Cardiovascular Events per Decrease of 10 mg/dl in LDL Cholesterol Level (95% CI)
ACLY	0.82 (0.78–0.87)
HMGCR	0.84 (0.82–0.87)
NPC1L1	0.84 (0.79–0.89)
PCSK9	0.83 (0.80–0.87)
LDLR	0.82 (0.80–0.85)



Overall LLT use & risk-based LDL-C goal attainment





- **The majority of patients were receiving moderate intensity statin monotherapy**
- **Only 28% of patients were receiving high intensity statin monotherapy**
- **Few patients (9%) were receiving ezetimibe combo**
- **A small number of patients (1%) received PCSK9i combo**

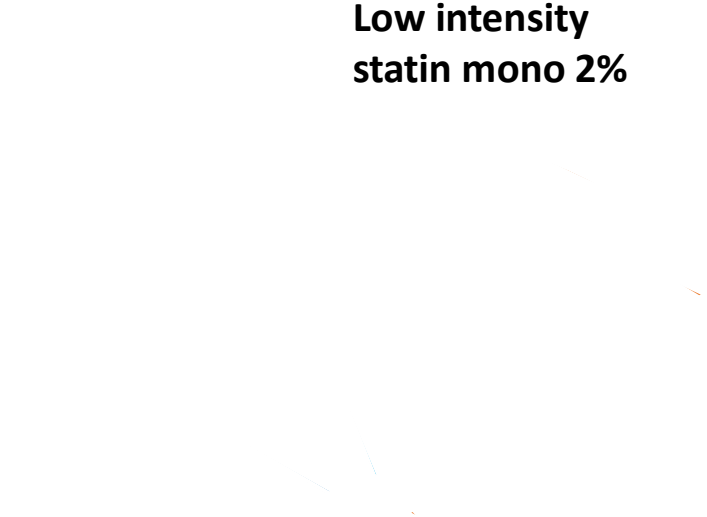
- **Approximately half of all patients did not achieve their 2016 risk-based LDL-C goal**
- **Only one-third achieved their 2019 risk-based LDL-C goal**

Ray KK Da Vinci study EJPC 2020

*Stabilised LLT at time of LDL-C measurement. combo, combination; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; PCSK9i; proprotein convertase subtilisin/kexin type 9 inhibitor

LDL-C goal attainment by LLT in patients with established ASCVD

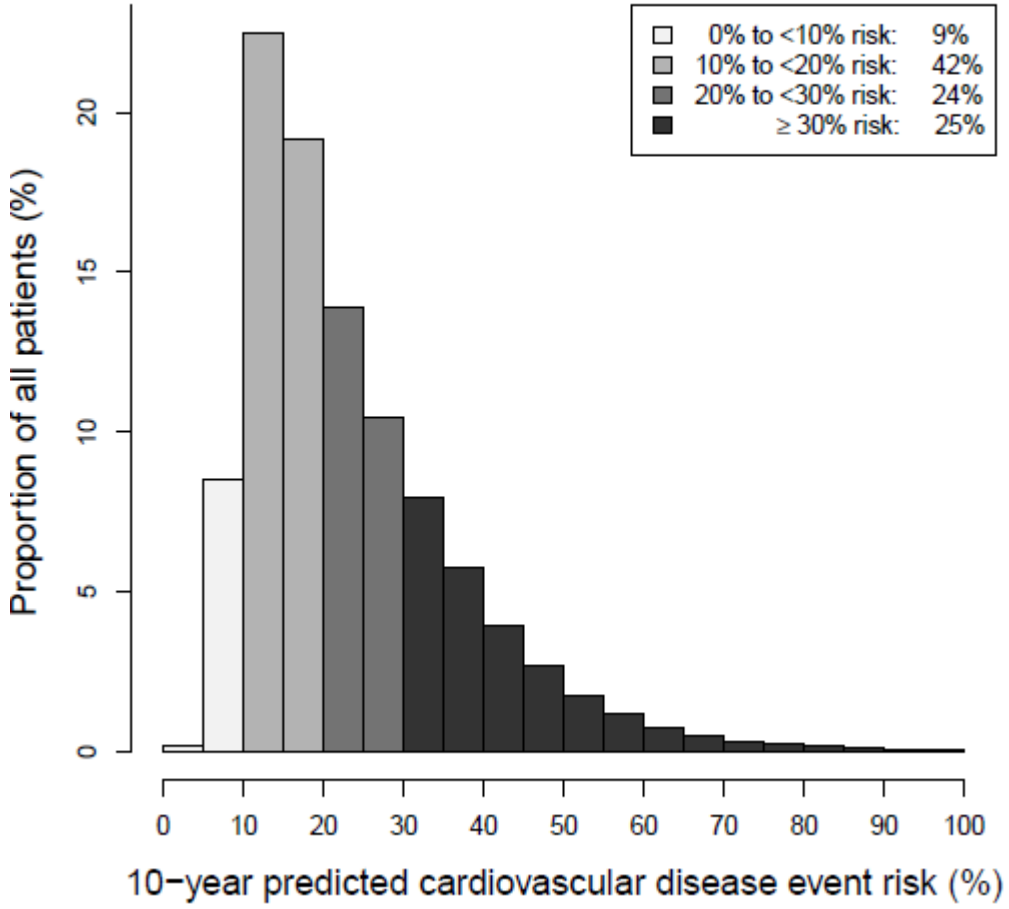
LLT use among patients with established ASCVD

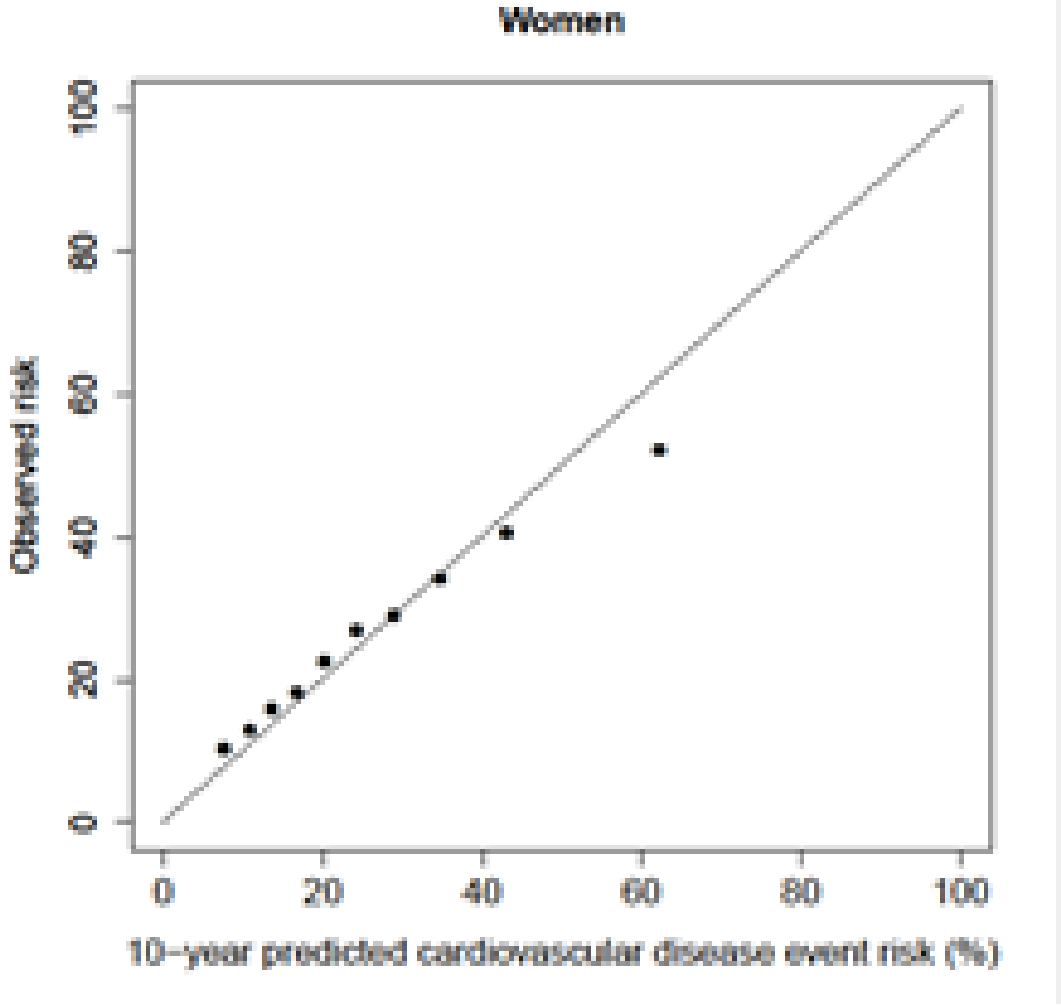


2016/2019 goal attainment in patients with established ASCVD

Pie chart shows % of patients receiving each LLT at LDL-C measurement. Bar chart shows % of patients achieving 2016 (solid bars) and 2019 (hashed bars) LDL-C goals. mono, monotherapy.

The SMART model performs well in EHR records in 244 000 UK ASCVD patients with a risk profile





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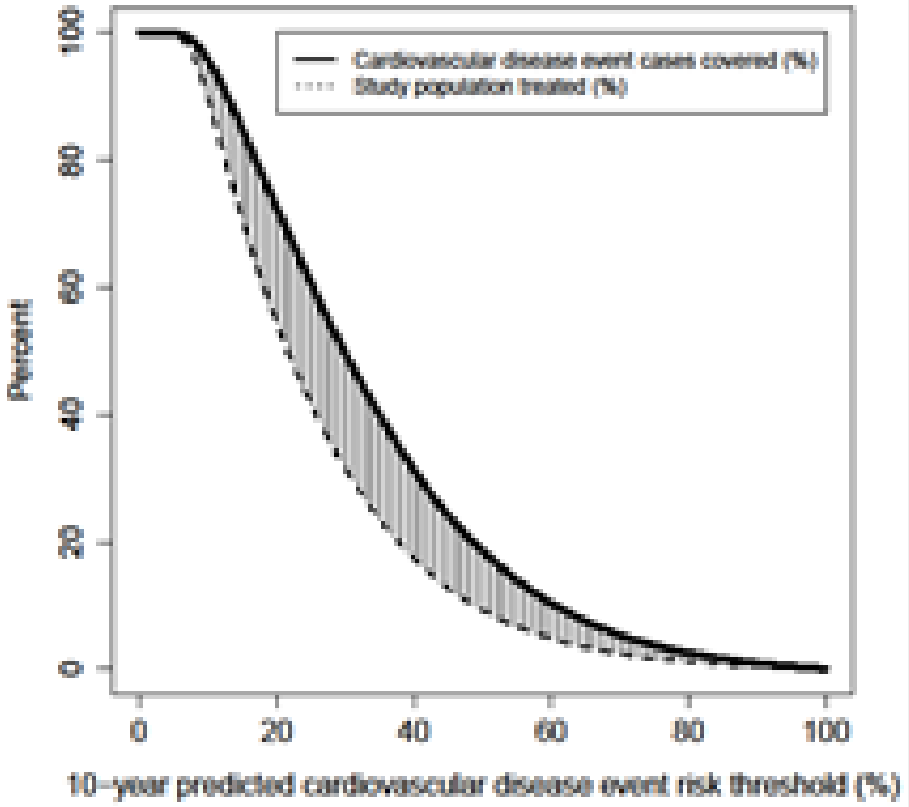
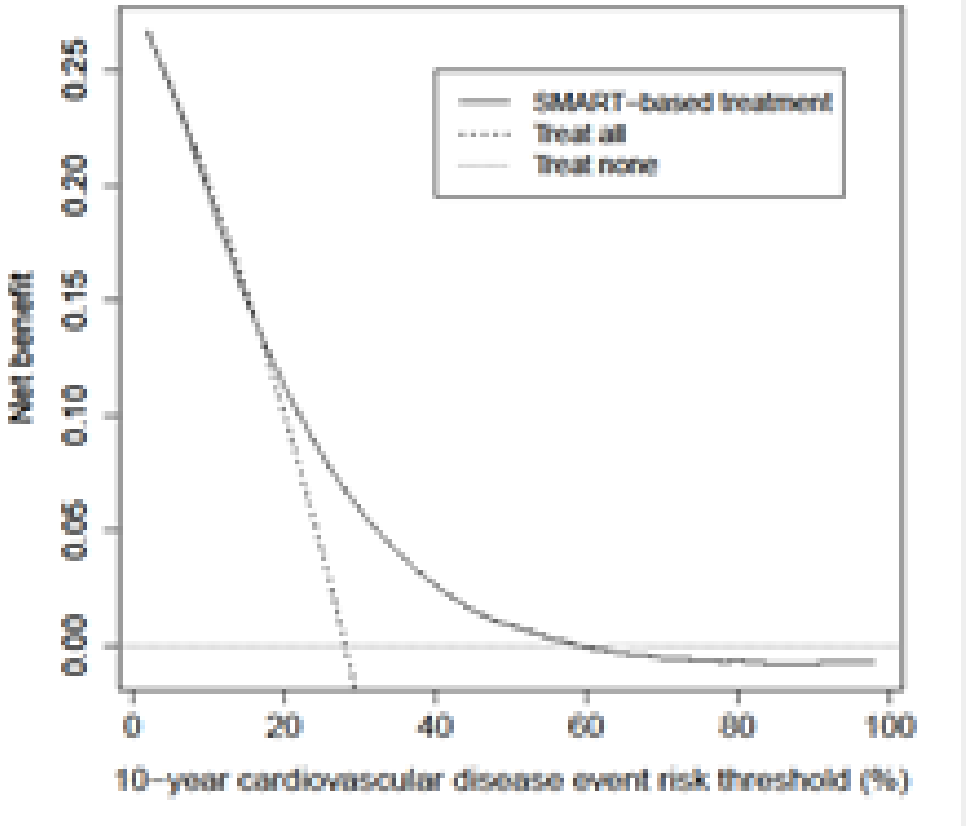
Decision Curves To set risk thresholds and how many of the population would be treated





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Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
non-HDL cholesterol (mmol/L)	2.79	3.26	2.95	3.07	2.89	2.61	2.79	3.20	3.49	3.49	3.49	3.49	3.49
HDL cholesterol (mmol/L)	0.517	0.517	0.491	0.698	0.646	0.698	0.698	0.517	0.749	0.646	0.465	0.517	0.646
Total cholesterol (mmol/L)	3.31	3.77	3.44	3.77	3.54	3.31	3.49	3.72	4.24	4.13	3.95	4.01	4.13
Age (years)	63.6	57.0	62.6	46.1	74.7	71.0	72.1	72.0	73.4	62.3	69.0	57.1	77.0
Sex	M	M	F	M	F	F	F	M	F	M	M	F	M
Current smoking status	No	Yes	No	Yes	No	Yes	Yes	No	No	No	No	No	No
Systolic BP (mm Hg)	114	150	140	130	165	148	150	160	170	156	160	145	110
Diabetes Mellitus	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Coronary Heart Disease	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes
Cerebrovascular Disease	No	No	No	Yes	No	No	No	No	No	Yes	No	No	Yes
Abdominal Aortic Aneurysm	No	No	No	Yes	No	No	No	No	No	No	No	No	No
Peripheral Vascular Disease	No	No	No	No	Yes	Yes	No	No	No	No	Yes	No	No
Years since ASCVD	-	-	2.2	-	11.8	-	12.6	14.5	23.9	4.5	7.5	-	21.5
eGFR (ml/min/1.73m)	67.7	71.0	54.1	71.5	78.6	48.4	59.9	75.3	30.9	85.7	54.2	53.1	91.1
hsCRP (mg/L) imputed	2.0	2.3	2.1	4.5	3.4	3.4	2.7	2.5	2.7	2.0	2.4	2.5	2.5
SMART 10-year predicted baseline risk (%)	20.0	20.0	20.0	20.0	40.0	40.0	40.0	40.0	75.7	23.8	45.4	18.1	61.7
Addition of rivaroxaban													
Predicted 10-year risk and 95 % CI	15.2 (13.2-17.2)	15.2 (13.2-17.2)	15.2 (13.2-17.2)	15.2 (13.2-17.2)	30.4 (26.4-34.4)	30.4 (26.4-34.4)	30.4 (26.4-34.4)	30.4 (26.4-34.4)	57.5 (50.0-65.1)	18.1 (15.7-20.5)	34.5 (30.0-39.0)	13.8 (11.9-15.6)	46.9 (40.7-53.1)
Absolute risk reduction (%)	4.8	4.8	4.8	4.8	9.6	9.6	9.6	9.6	18.2	5.7	10.9	4.3	14.8
Addition of a PCSK9 MAb													
Estimated reduction in non-HDL cholesterol (mmol/L)	1.40	1.63	1.47	1.54	1.45	1.30	1.40	1.60	1.74	1.74	1.74	1.74	1.74
Predicted 10-year risk and 95% CI	15.5 (15.0-15.9)	14.8 (14.3-15.3)	15.2 (14.8-15.7)	15.1 (14.6-15.5)	30.6 (29.7-31.5)	31.4 (30.6-32.2)	30.9 (30.0-31.7)	29.7 (28.8-30.7)	54.8 (52.9-56.7)	17.2 (16.6-17.8)	32.9 (32.7-34.0)	13.1 (12.7-13.6)	44.7 (43.1-46.2)
Absolute risk reduction (%)	4.6	5.2	4.8	5.0	9.4	8.6	9.1	10.3	20.9	6.6	12.5	5.0	17.0

Mackay A, ….Ray KK EJPC in Press

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Total cholesterol (mmol/L)	3.31	3.77	3.44	3.77	3.54	3.31	3.49	3.72	4.24	4.13	3.95	4.01	4.13
Age (years)	63.6	57.0	62.6	46.1	74.7	71.0	72.1	72.0	73.4	62.3	69.0	57.1	77.0
Sex	M	M	F	M	F	F	F	M	F	M	M	F	M
Current smoking status	No	Yes	No	Yes	No	Yes	Yes	No	No	No	No	No	No
Systolic BP (mm Hg)	114	150	140	130	165	148	150	160	170	156	160	145	110
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Years since ASCVD	-	-	2.2	-	11.8	-	12.6	14.5	23.9	4.5	7.5	-	21.5
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Cerebrovascular Disease	No	No	No	Yes	No	No	No	No	No	Yes	No	No	Yes
Abdominal Aortic Aneurysm	No	No	No	Yes	No	No	No	No	No	No	No	No	No
Peripheral Vascular Disease	No	No	No	No	Yes	Yes	No	No	No	No	Yes	No	No
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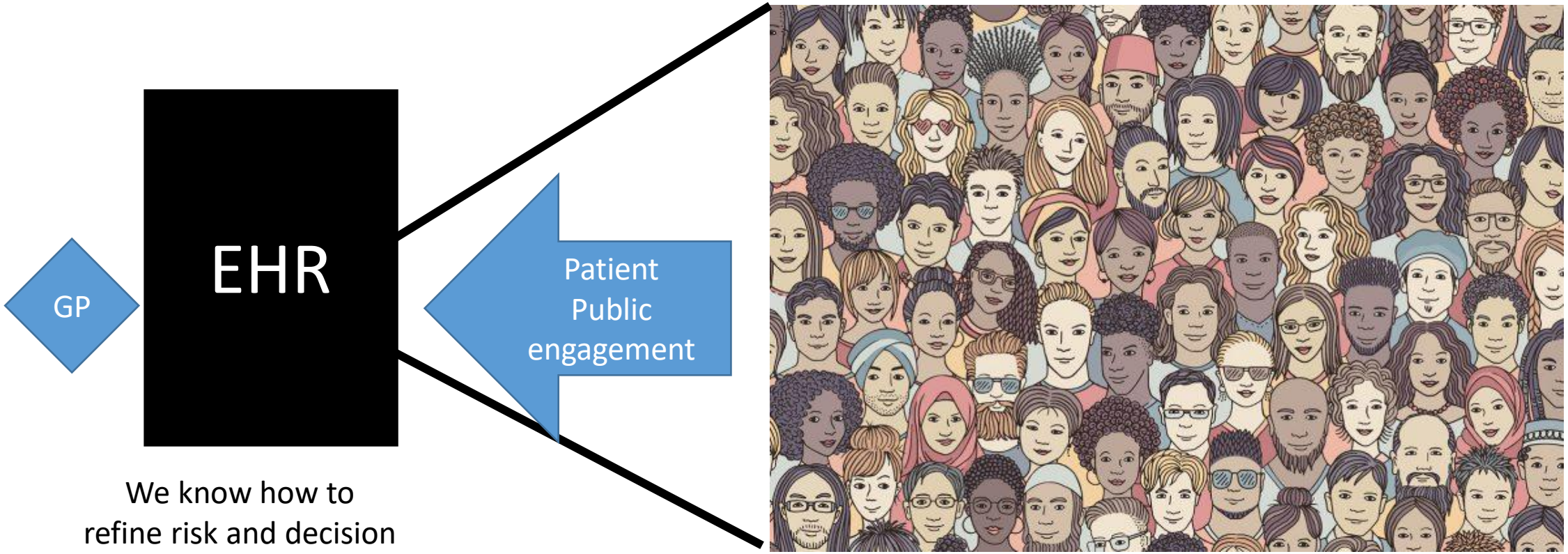
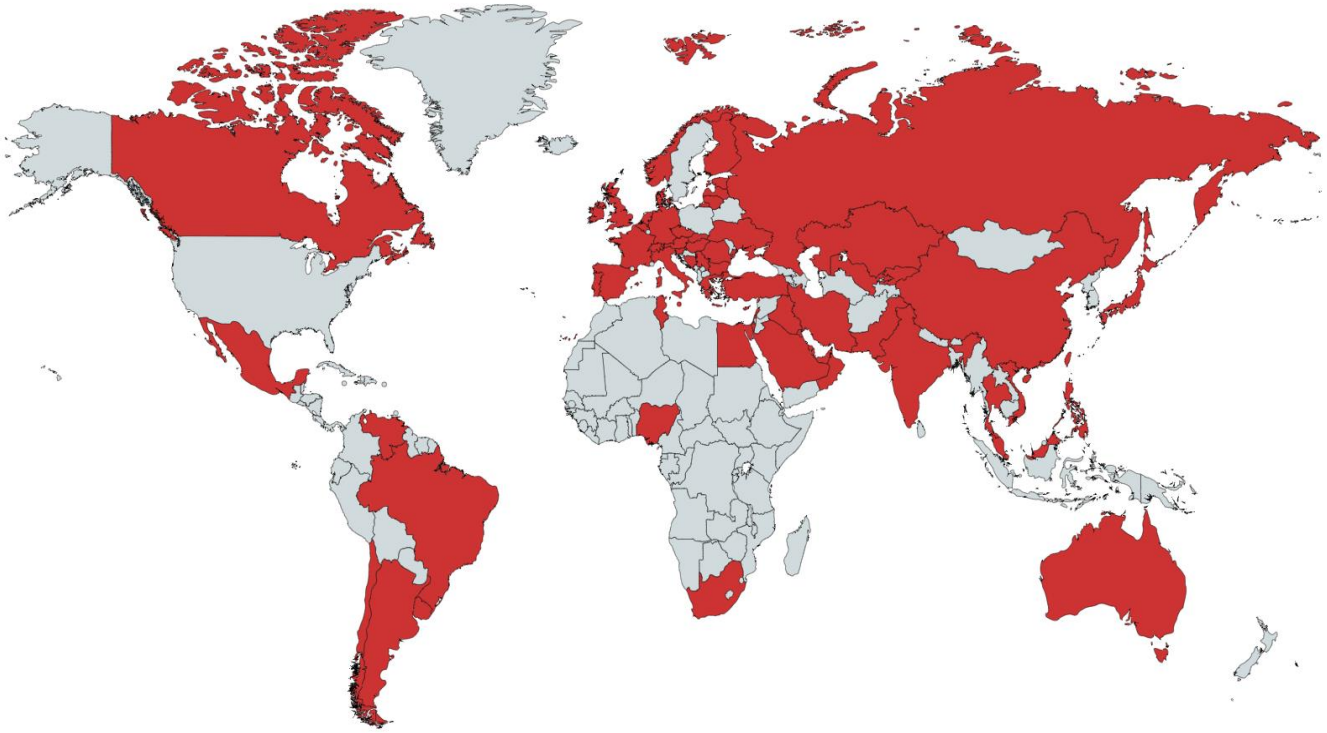
Targeted risk management in primary care



We know how to
refine risk and decision
support systems that help
manage risk
can easily be built

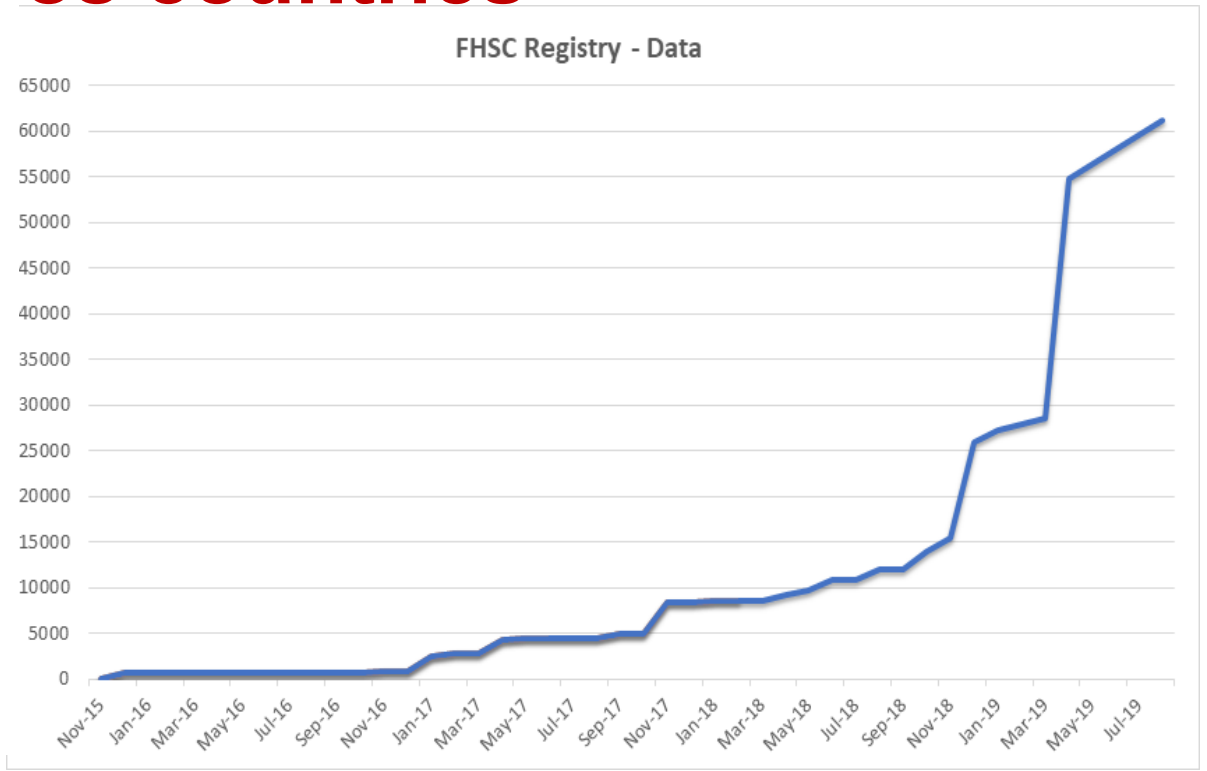
EAS FHSC Network & Registry- Sep 2019

FHSC Network – Investigators from 69 countries worldwide



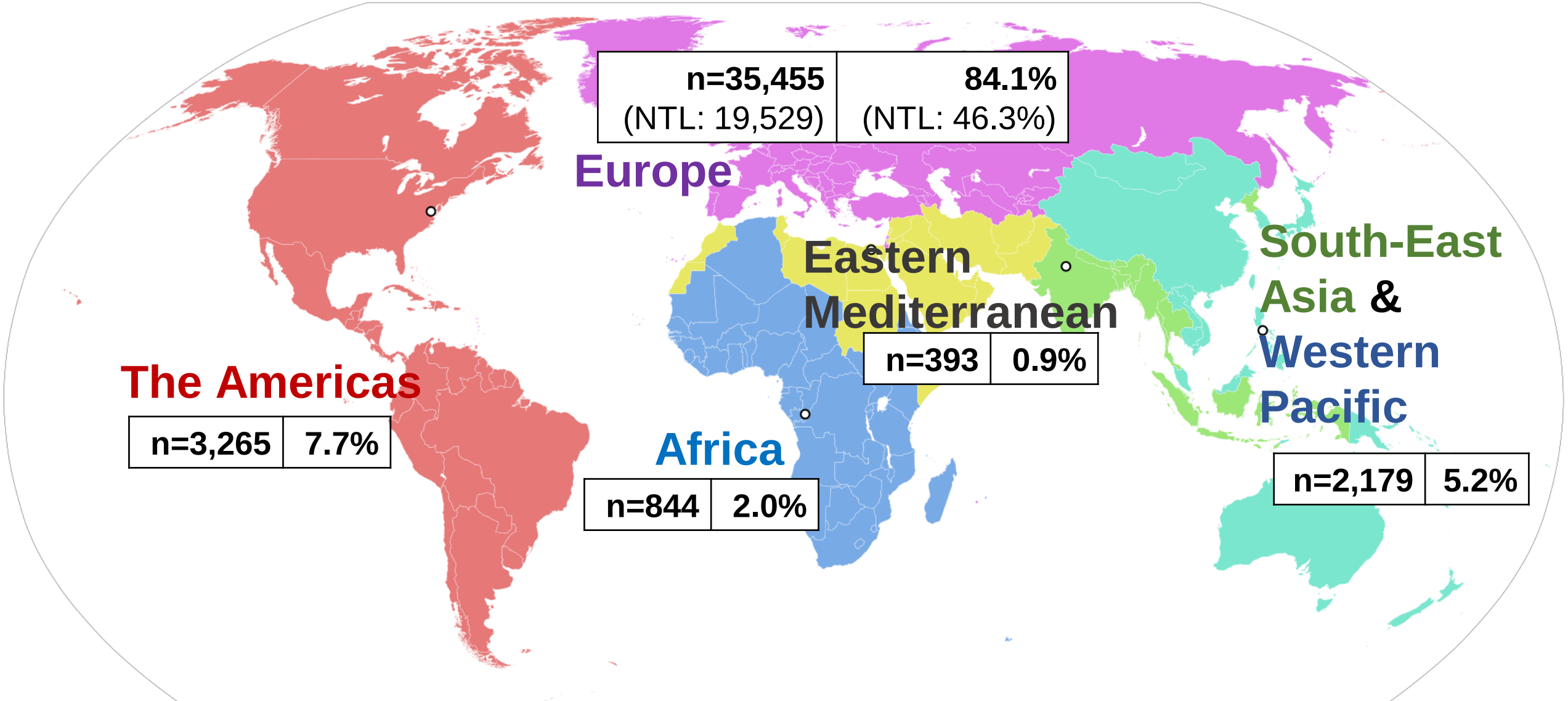
https://www.eas-society.org/fhsc

Data received so far– Over 61,000 participants from 58 countries



FHSC Registry cases by WHO regions

Global burden – Low number of cases identified beyond Western countries

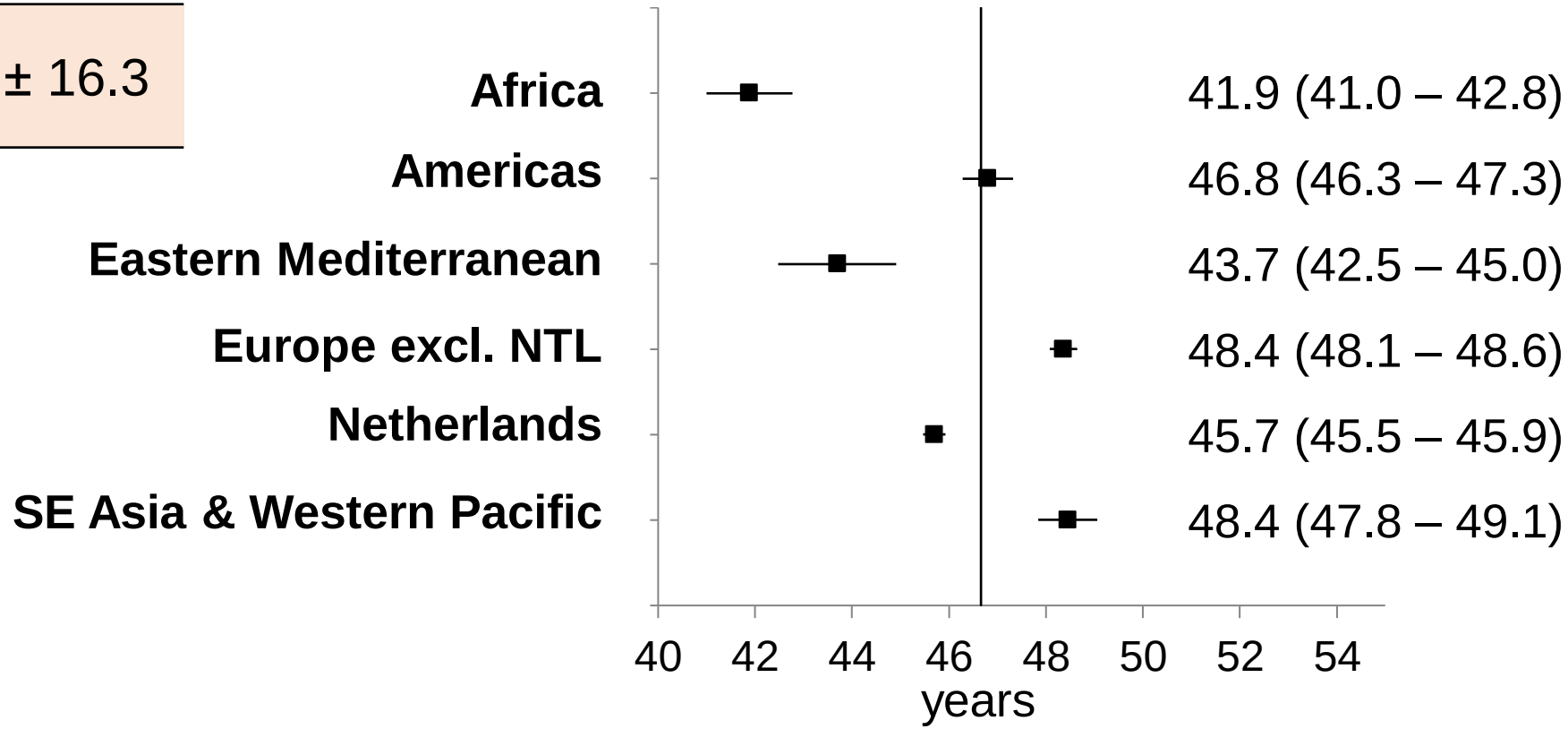


General characteristics HeFH adults

Mean age approx. 47 years

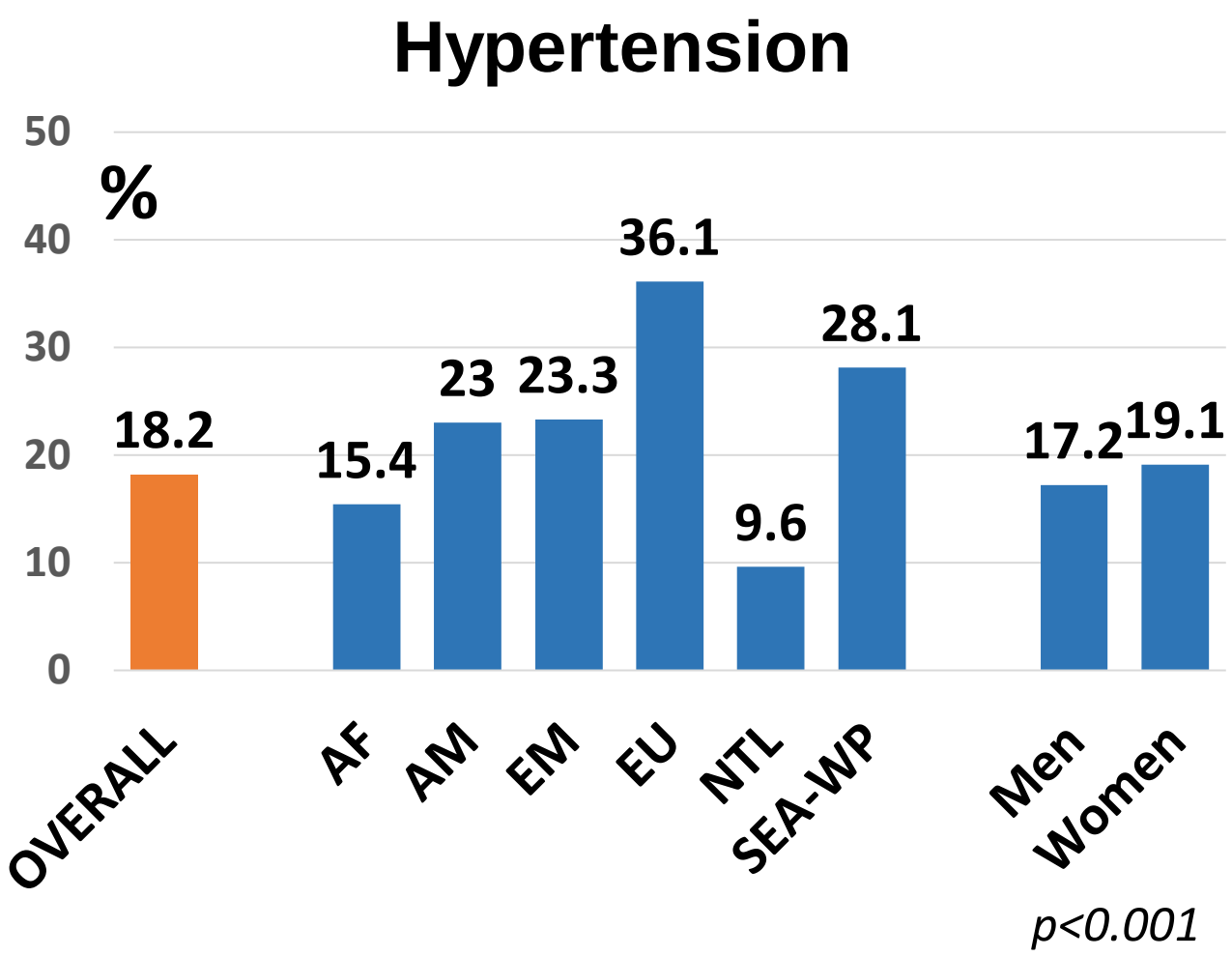
	mean ± SD
Age at Baseline, years	**46.7** ± 15.8
Age at FH Diagnosis, years	**44.9** ± 16.3

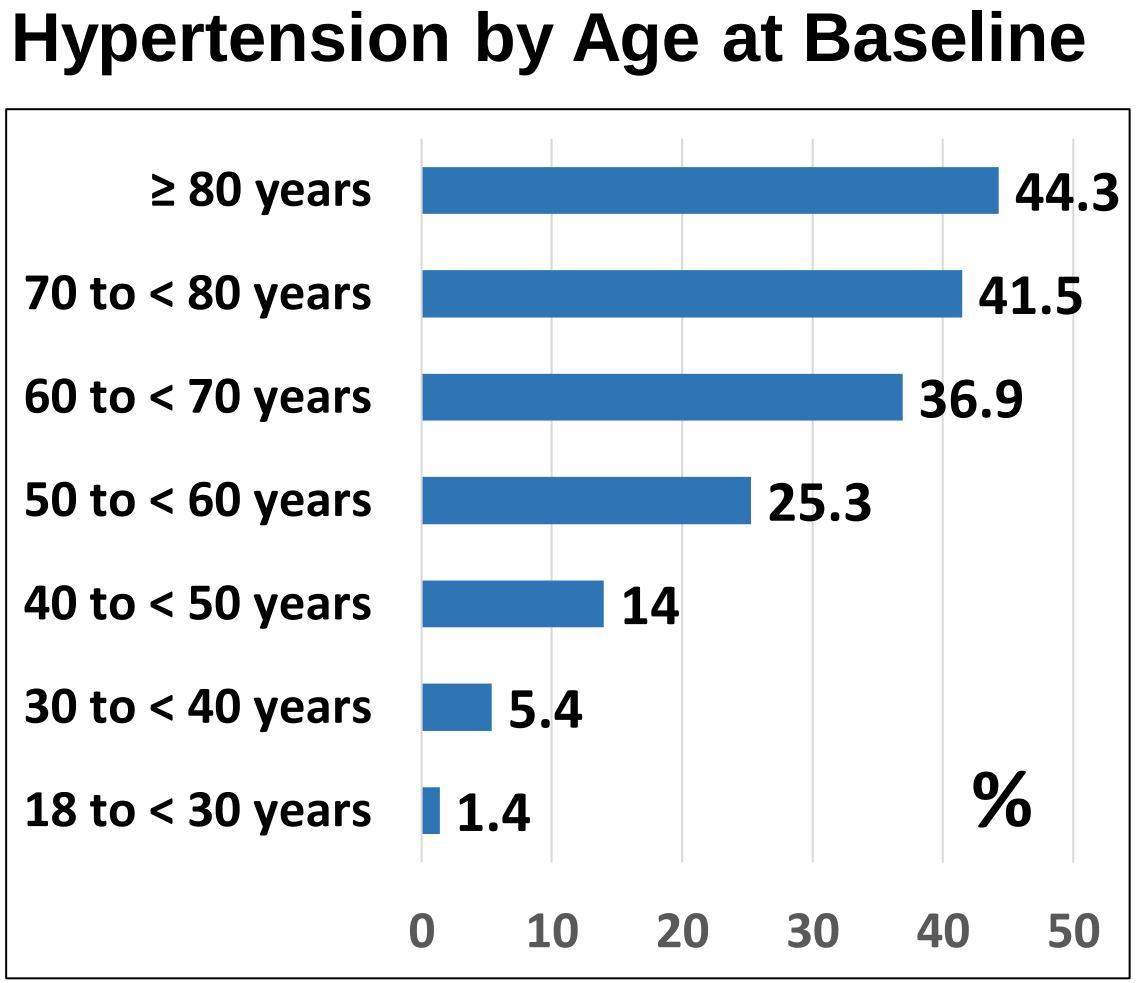
Age (years) at **Baseline** [mean, 95% CI]



Comorbidity in FH

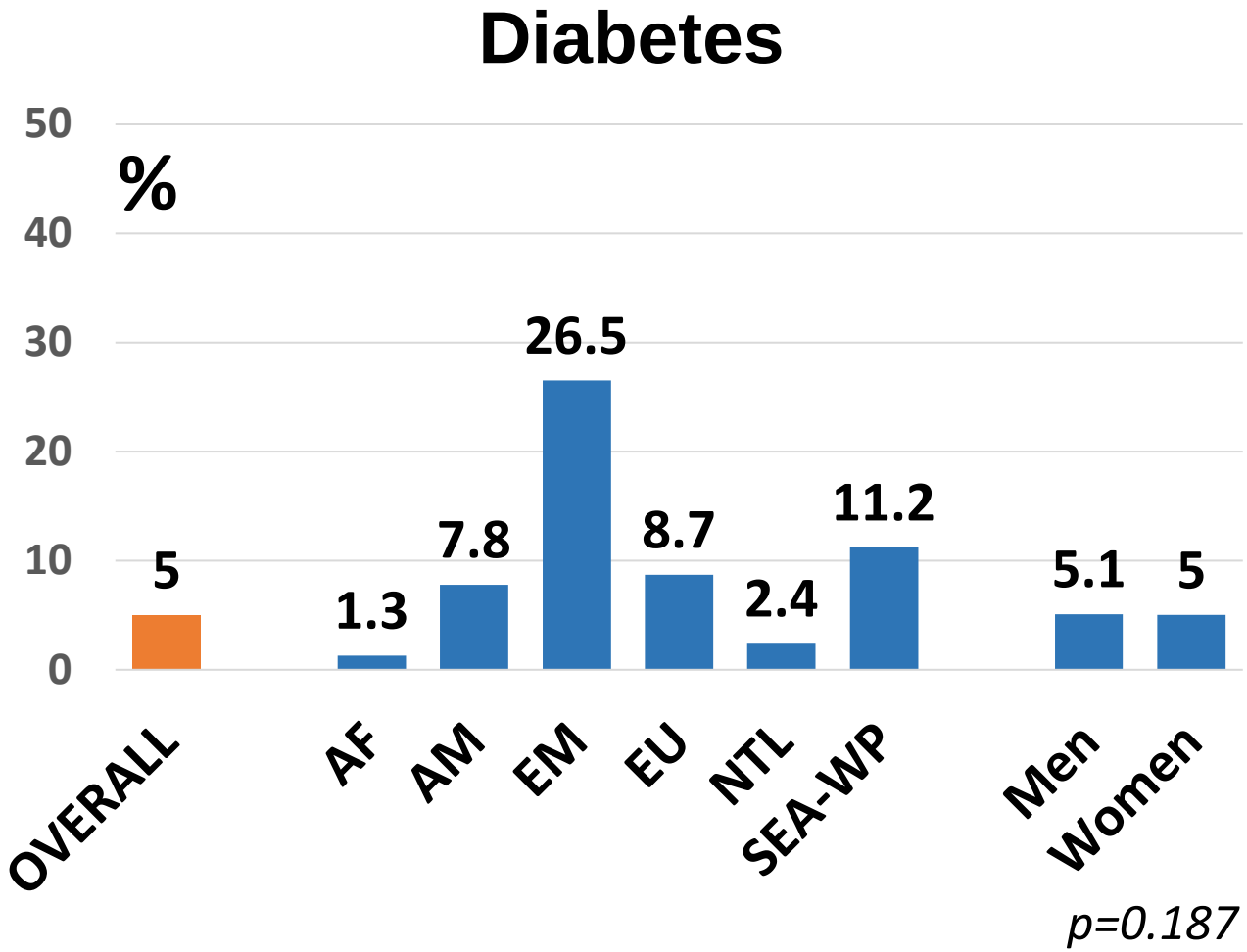
Hypertension prevalence ~18% overall, increases with age

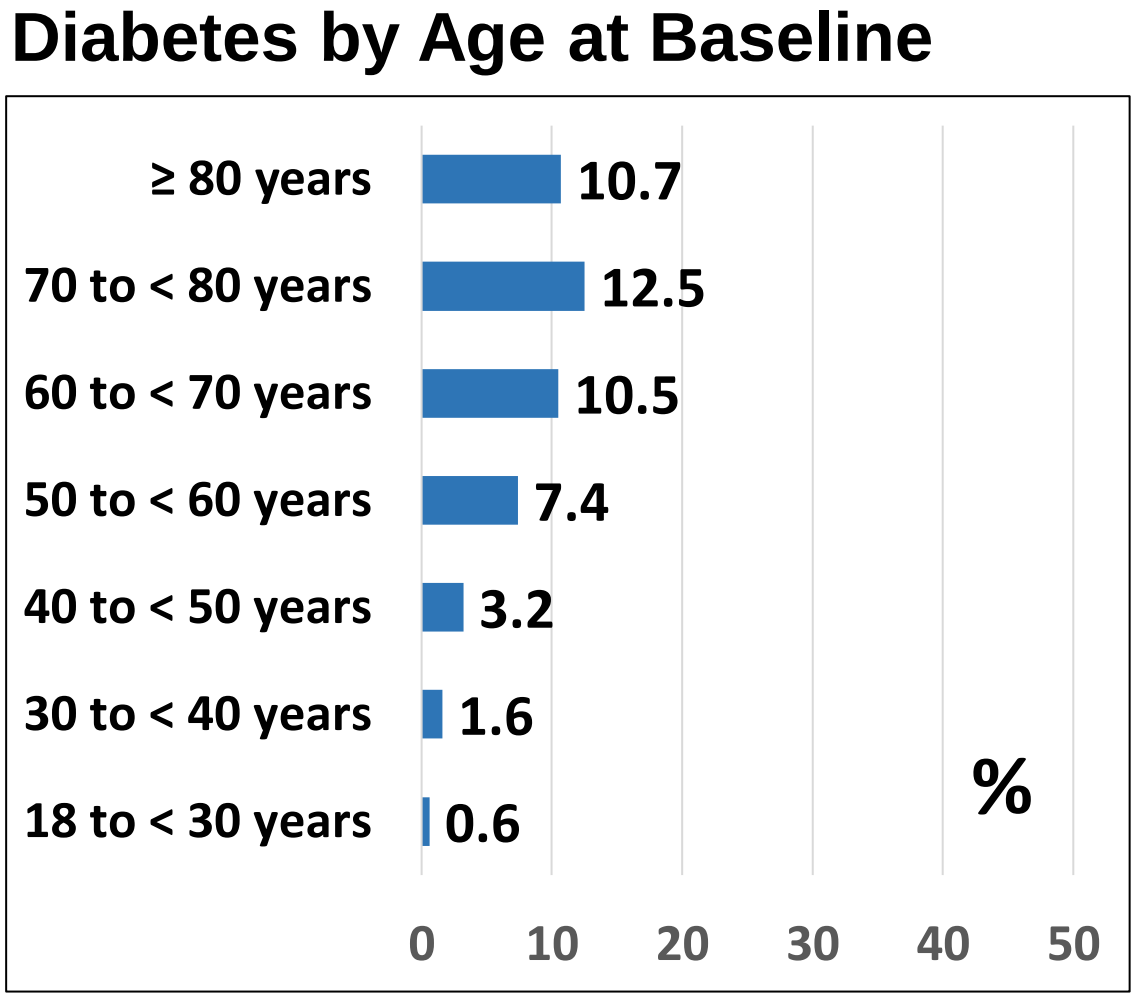




Comorbidity in FH

Low prevalence of Diabetes ~5% overall, regional variation, increases with age





Index Cases vs Non-Index Cases

Non-IC: younger, lower prevalence CV risk factors, lower LDL-C

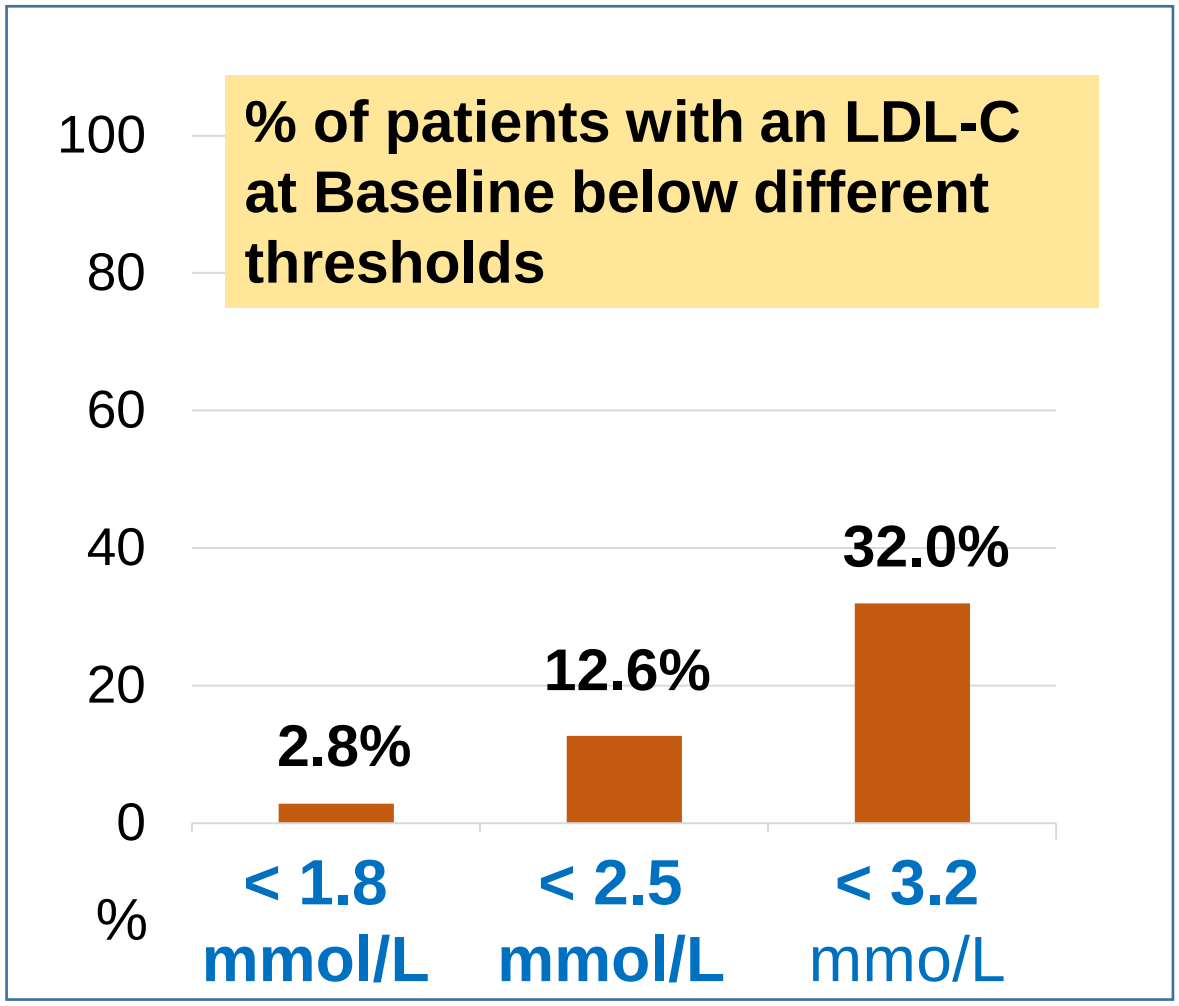
	INDEX CASES	NON INDEX CASES
Age at Baseline (years)	50.0 (39.0 – 59.8)	44.0 (32.1 – 57.7)
Age at FH Diagnosis (years)	47.8 (36.5 – 57.2)	43.6 (31.7 – 57.1)
Hypertension	21.1%	12.8%
Diabetes	5.9%	3.4%
BMI (kg/m^2)	26.4 ± 5.4	25.1 ± 4.3
Obesity (BMI ≥30 kg/m^2)	20.3%	12.0%
LDL-C (mg/dL)	-	-
▪ Among patients not taking LLM	234.3 (195.0 – 286.0)	178.7 (143.5 – 214.2)
▪ Among patients taking LLM	180.9 (124.2 – 235.7)	150.4 (120.6 – 190.6)

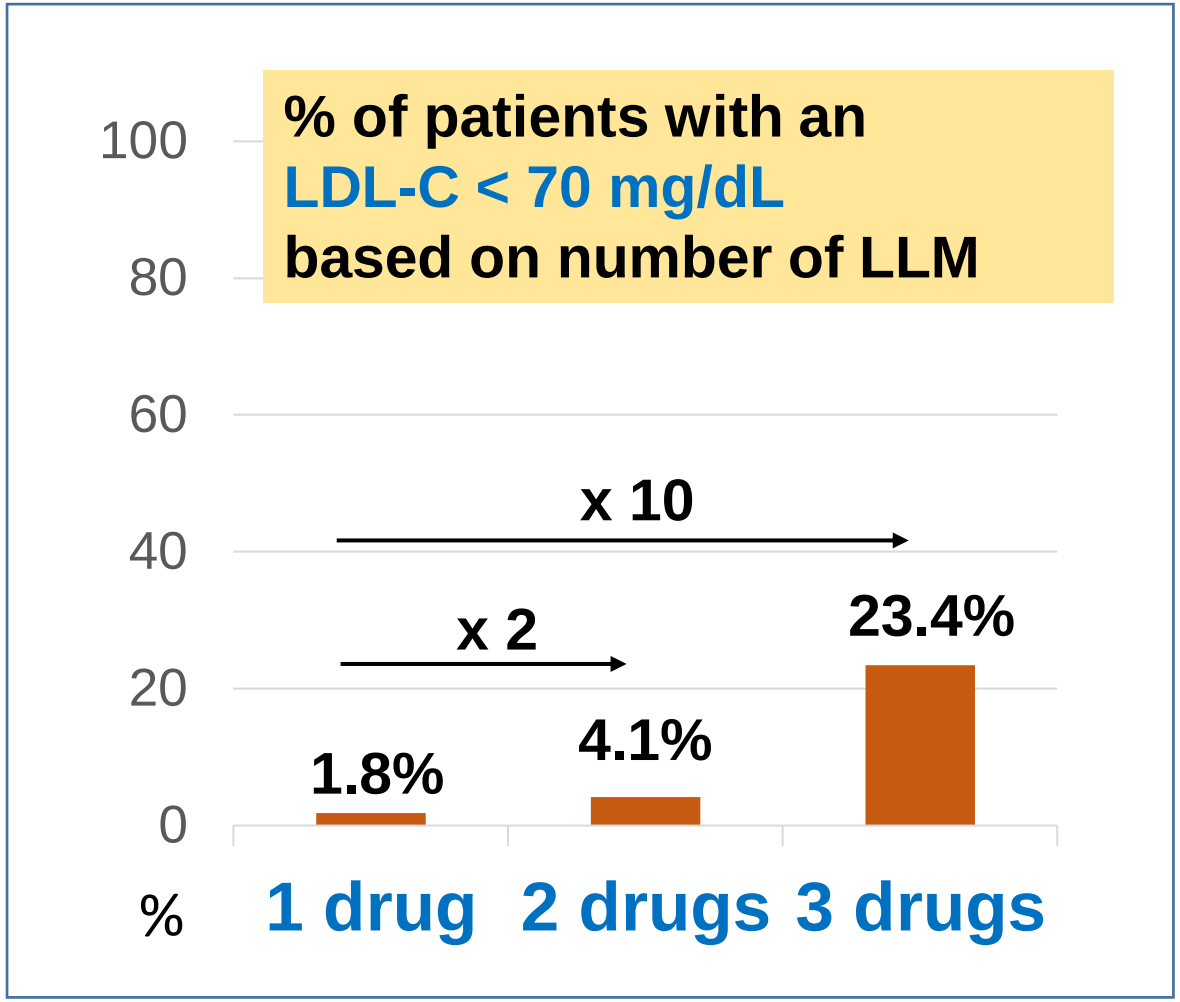
Index Cases vs Non Index Cases, all p<0.001

LDL-C target attainment at entry in the registry

Low % of patients below 2016 recommended thresholds

Patients on LLM (Statins and/or Ezetimibe and/or PCSK9 Inh)





Conclusion

Small / Modest reductions LDL-C maintained over time offer cumulative benefits

This means that much of prevention can be helped by earlier interventions maintained over a longer period of time

For those diagnosed identified later combination therapies are needed

A potential game changer are RNA based approaches which could overcome issues such as adherence.