IMPERIAL

The Remaining Challenges in Lowering LDL-C in Patients at Increased CV Risk

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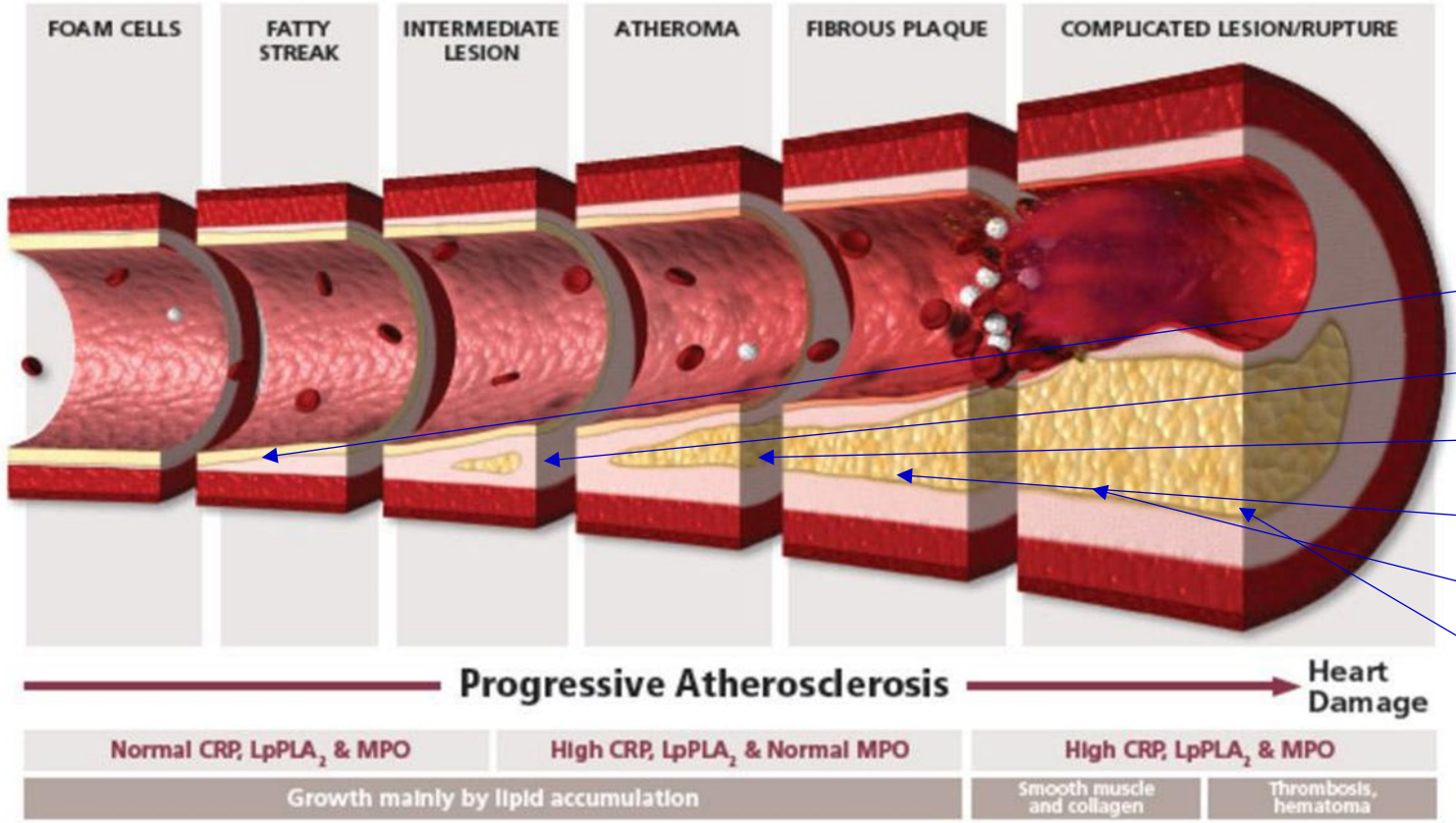
Disclosures: KK Ray

Disclosure of speaker's interests	
Relations that could be relevant for the meeting:	**Company names**
• Sponsorship or research funds • Payment or other (financial) renumeration	• Amgen, Sanofi, Regeneron, MSD, Pfizer, Daiichi Sankyo, Ultragenix • Consultancy: Amgen, Sanofi, Regeneron, Pfizer, Viatris, Abbott, AstraZeneca, Lilly, Kowa Pharmaceutics, Novo Nordisk, Boehringer Ingelheim, Esperion, Cargene Therapeutics, Resverlogix, Novartis, Silence Therapeutics, NewAmsterdam Pharma, Scribe Therapeutics, CRISPR Therapeutics, VAXXINITY, Amarin, CSL Behring, Bayer, Cleerly Health, Emendobio • Stock Options PEMI31, SCRIBE, New Amsterdam Pharma

Atherosclerosis- results from the accumulation of cholesterol in the arterial wall throughout the life-course –genes, risk factors and time



Age Group	Number of People (2020)	% of Global Population
<20 years	2.6 billion	33.2%
20-39 years	2.3 billion	29.9%
40-59 years	1.8 billion	23.1%
60-79 years	918 million	11.8%
80-99 years	147 million	1.9%
100+ years	0.6 million	0.01%

Ray KK et al 2022 WHF Cholesterol Roadmap- Global Heart Journal DOI: https://doi. org/10.5334/gh.1154

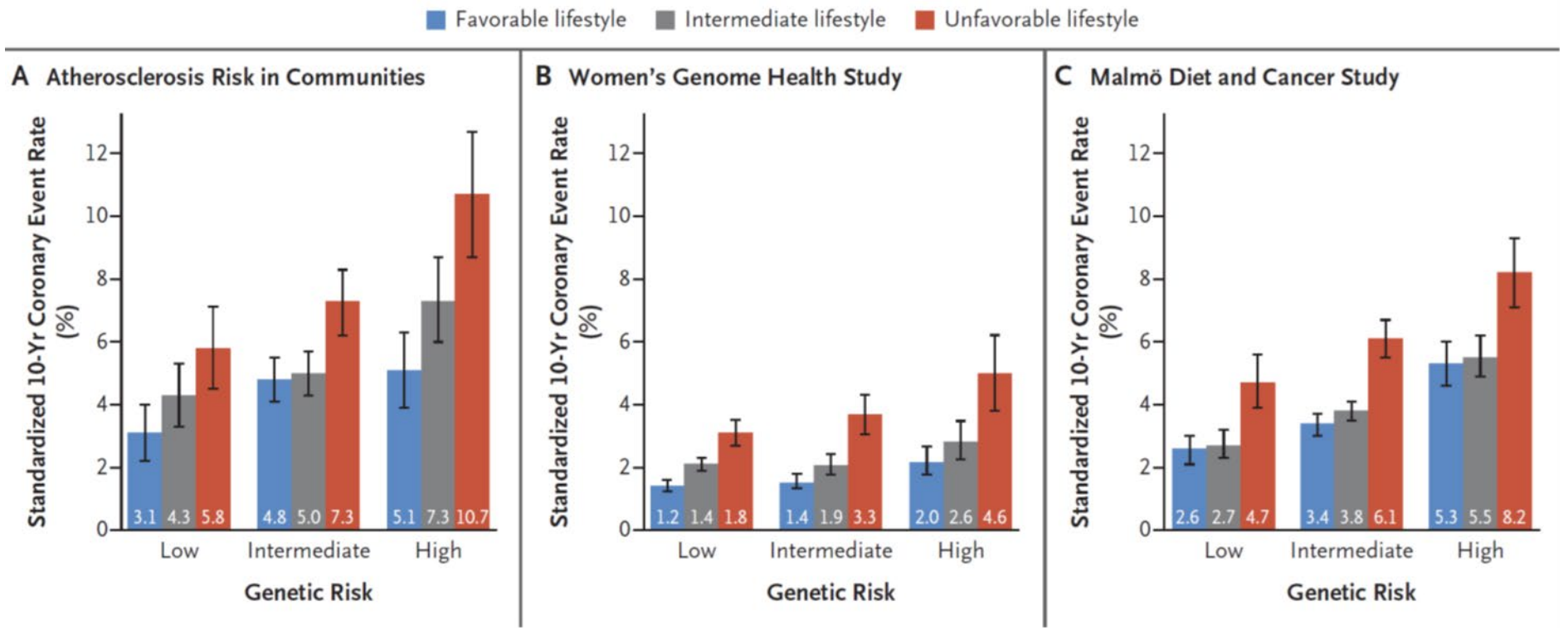
Genetic vulnerability to risk factors (environment) means there is no such thing as normal levels of risk factors

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

Amit V. Khera, M.D., Connor A. Emdin, D.Phil., Isabel Drake, Ph.D., Pradeep Natarajan, M.D., Alexander G. Bick, M.D., Ph.D., Nancy R. Cook, Ph.D., Daniel I. Chasman, Ph.D., Usman Baber, M.D., Roxana Mehran, M.D., Daniel J. Rader, M.D., Valentin Fuster, M.D., Ph.D., Eric Boerwinkle, Ph.D., Olle Melander, M.D., Ph.D., Marju Orho-Melander, Ph.D., Paul M Ridker, M.D., and Sekar Kathiresan, M.D.



This means most CV events will occur, in people without very high levels of risk factors - risk factors age 50s

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality

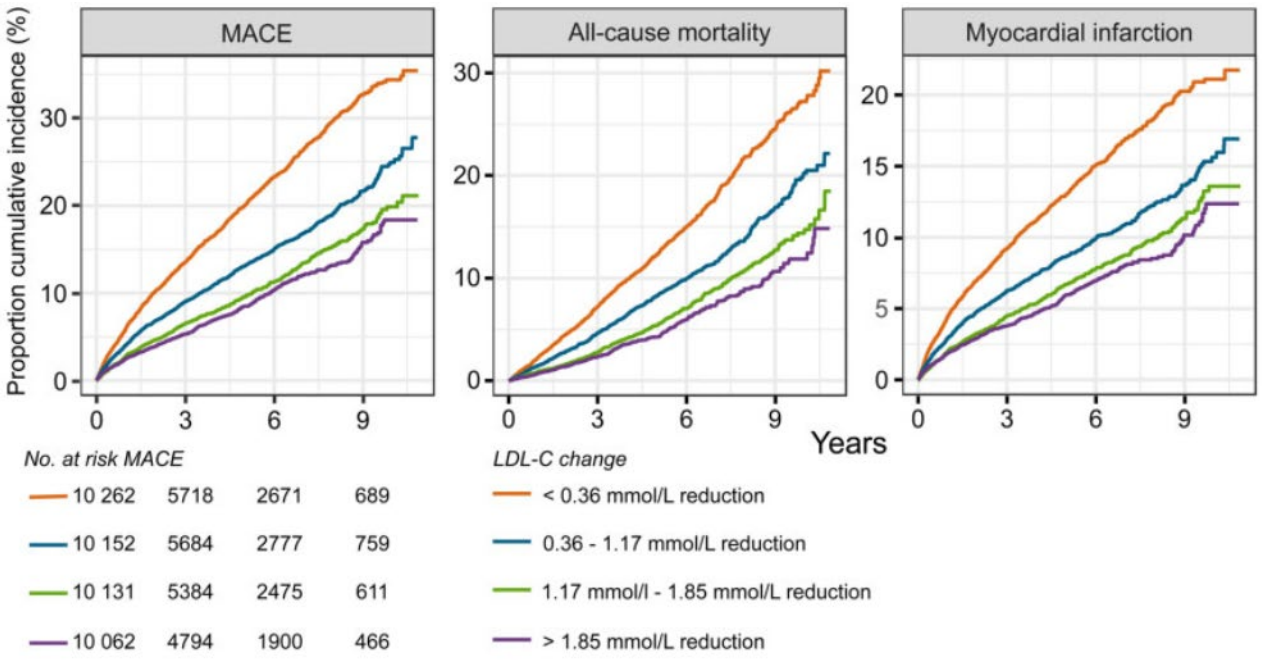
The Global Cardiovascular Risk Consortium

Table 1. Characteristics of the Cohort Studies and Age- and Sex-Standardized Characteristics of the Participants at Baseline According to Geographic Region.*

Characteristic	Global	North America	Latin America	Western Europe	Eastern Europe and Russia	North Africa and the Middle East	Sub-Saharan Africa	Asia	Australia
Cohort studies									
Cohort studies — no.	112	11	10	58	16	5	2	4	6
Participants — no.	1,518,028	65,182	191,244	907,760	51,133	185,608	10,390	59,802	46,909
Range of survey years†	1963–2020	1971–2011	1990–2013	1970–2015	1983–2014	1963–2020	2011–2017	1988–2015	1983–2007
Participants									
Median age (IQR) — yr‡	54.4 (4.2–63.0)	54.0 (45.0–63.0)	54.0 (45.0–63.0)	54.6 (45.5–63.0)	54.1 (45.5–63.0)	54.0 (45.0–62.6)	54.0 (45.0–63.0)	54.0 (45.0–63.0)	54.6 (45.5–63.0)
Male sex — %‡	45.9	45.9	45.9	45.9	45.9	45.9	45.9	45.9	45.9
Median BMI (IQR)	26.4	27.2	28.2	26.1	27.2	27.0	21.0	22.8	26.4
Median SBP (IQR) — mm Hg	130.0 (118.0–144.0)	122.0 (111.0–136.0)	126.7 (118.0–138.7)	134.0 (122.0–148.0)	132.0 (120.0–148.0)	115.0 (105.0–130.0)	125.0 (113.0–140.0)	123.5 (112.0–136.0)	127.0 (116.5–139.0)
Median DBP (IQR) — mm Hg	80.0 (72.0–87.5)	74.0 (67.0–81.0)	82.7 (76.7–90.0)	81.0 (74.0–89.0)	82.0 (75.0–91.0)	75.0 (67.5–80.0)	75.0 (69.0–83.0)	76.0 (68.0–84.0)	72.5 (64.5–80.5)
Median non-HDL cholesterol (IQR) — mg/dl	156.9 (128.8–187.9)	150.0 (123.0–179.4)	156.2 (131.1–185.2)	162.8 (134.8–193.8)	162.4 (135.0–191.8)	140.1 (115.3–167.8)	116.0 (77.3–154.7)	140.0 (117.6–167.0)	151.2 (124.5–181.0)
Current smoking — %	21.6	22.5	30.8	20.9	29.2	14.2	18.6	23.5	14.3
Diabetes — %	8.3	13.0	15.3	4.8	9.0	18.3	2.0	5.1	4.8
Antihypertensive medications — %	19.4	27.5	19.3	17.9	28.8	24.7	18.5	11.6	13.7
Lipid-lowering medications — %	9.6	8.0	2.3	11.5	8.8	11.6	NA	4.4	4.1
History of CVD — %	5.6	7.2	3.6	5.6	11.2	5.6	0	6.3	7.2

Poor ability to predict risk - delays prevention and its optimisation (implementation)

75% of MIs were not on prior LLTs- age 62-64 (half had LDL-C between 2.3-3.8 at time of MI)



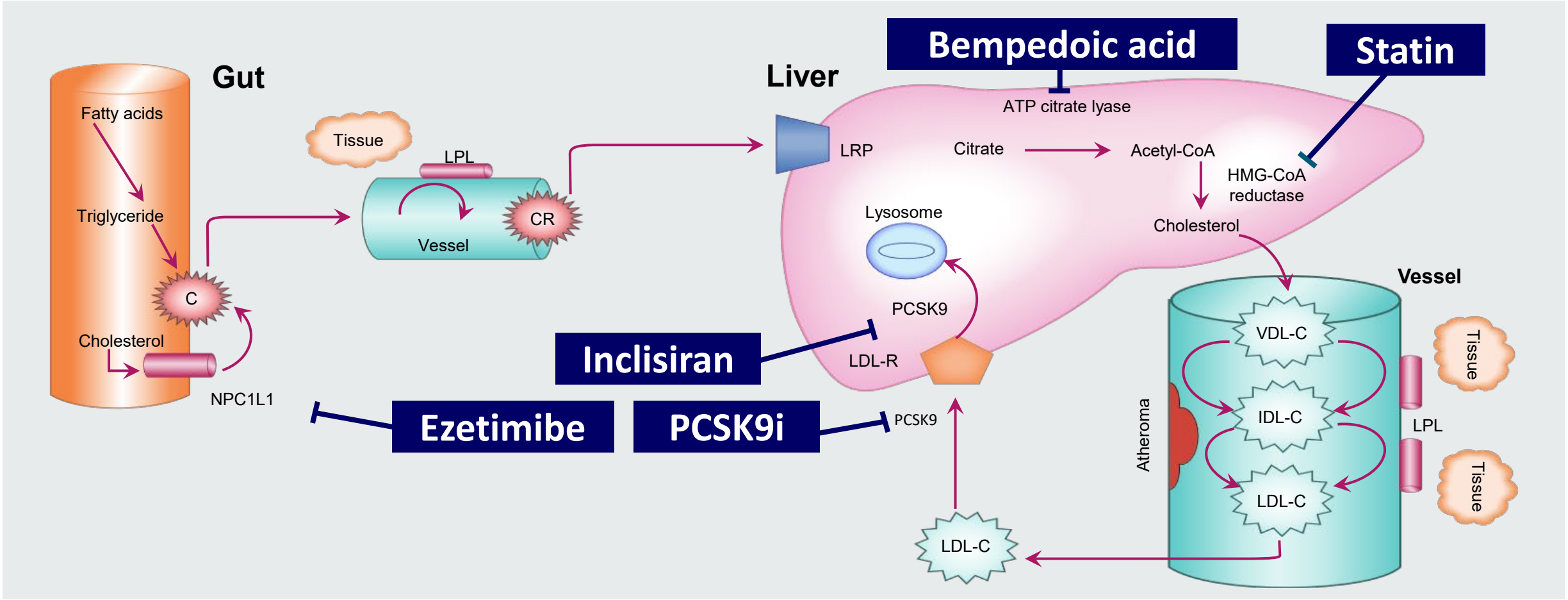
	LDL-C Reduction from index event to CR visit (mmol/L)			
	<0.36	0.36–1.17	1.17–1.85	>1.85
Age (years)	66 (59–71)	64 (57–69)	63 (56–69)	62 (55–68)
Hypertension	54%	43%	37%	34%
Diabetes mellitus	32%	20%	13%	12%
Prior MI	27%	12%	6%	4%
LDL-C at admission (mmol/L)	2.1 (1.7–2.7)	2.8 (2.3–3.2)	3.4 (3.0–3.8)	4.3 (3.8–4.8)
Statin at admission				
No statin	42%	76%	94%	96%
Low intensity	4%	2%	1%	<1%
Medium intensity	45%	19%	5%	3%
High intensity	9%	3%	1%	1%
LDL-C at CR visits (mmol/L)	2.3 (1.8-2.9)	1.9 (1.5-2.4)	1.9 (1.5-2.2)	1.8 (1.5-2.2)

Patients in quartile 1 appear to have more comorbidities, to be at higher risk of CV events and to have highest rates of prior statin treatment (58%).

LLT remained the same, but LDL-C levels changed

Schubert, Jessica, et al. *European heart journal* 42.3 (2021): 243-252.

Numerous targets have been explored to lower LDL-C, with several LLTs now available[1,2]

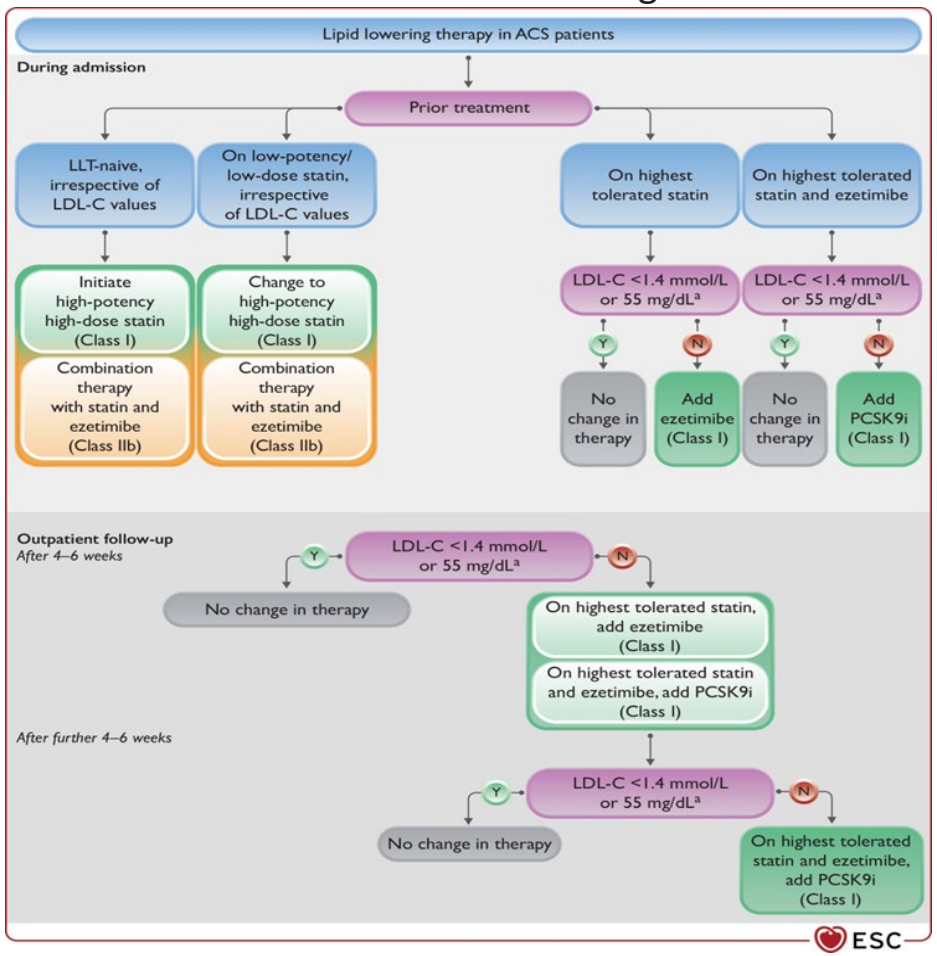


C, chylomicron; **CR,** chylomicron remnant; **HMG-CoA**, 3-hydroxy-3-methylglutaryl coenzyme A; **IDL-C,** intermediate-density lipoprotein cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **LDL-R**, LDL receptor; **LPL**, lipoprotein lipase; **LRP**, LDL relation protein receptor; **LTT**, lipid-lowering therapy; **NPC1L1**, Niemann-Pick C1-like 1; **PCSK9i**, proprotein convertase subtilisin/kexin type 9 inhibitor; **VDL-C**, very low-density lipoprotein cholesterol

1. Adapted from Ryan A, et al. BMJ. 2018;360:k946; **2.** Pinkosky SL, et al. Nat Commun. 2016;7:13457; **3.** NILEMDO®. Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/11743 (accessed July 2024); **4.** NUSTENDI® Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/11744 (accessed July 2024)

Current approaches follow a step by step approach driven by LDL-C levels (response to previous step) – Problem is there a big difference between goal achievement and risk reduction

2023 ESC Guidelines for the management of ACS



Byrne RA, et al. *Eur Heart J. 2023;44(38):3720-3826.*

10y event rate of 40% and an LDL-C of 1.8 mmol/L on HI statins

Add on Tx

LDL-C reduction 25%
New LDL-C is 1.35mmol/L

Relative risk reduction~10%

Residual 10y risk is 36%

Add on Tx

LDL-C reduction 50%
New LDL-C is 0.9 mmol/L

Relative risk reduction~21%

Residual 10y risk is 31.6%

LDL-C, low-density lipoprotein cholesterol; RRR, relative risk reduction.

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ZODIAC Study

OptimiZation Of lipid lowering therapies using a Decision support system In patients with Acute Coronary syndrome (ZODIAC)

Sponsored by Imperial College London

Clinical Trials.gov number:

NCT05844566

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Cluster RCT in ACS Care Pathway

Planned Design

1584 participants across 3 countries.

48 sites randomised to:

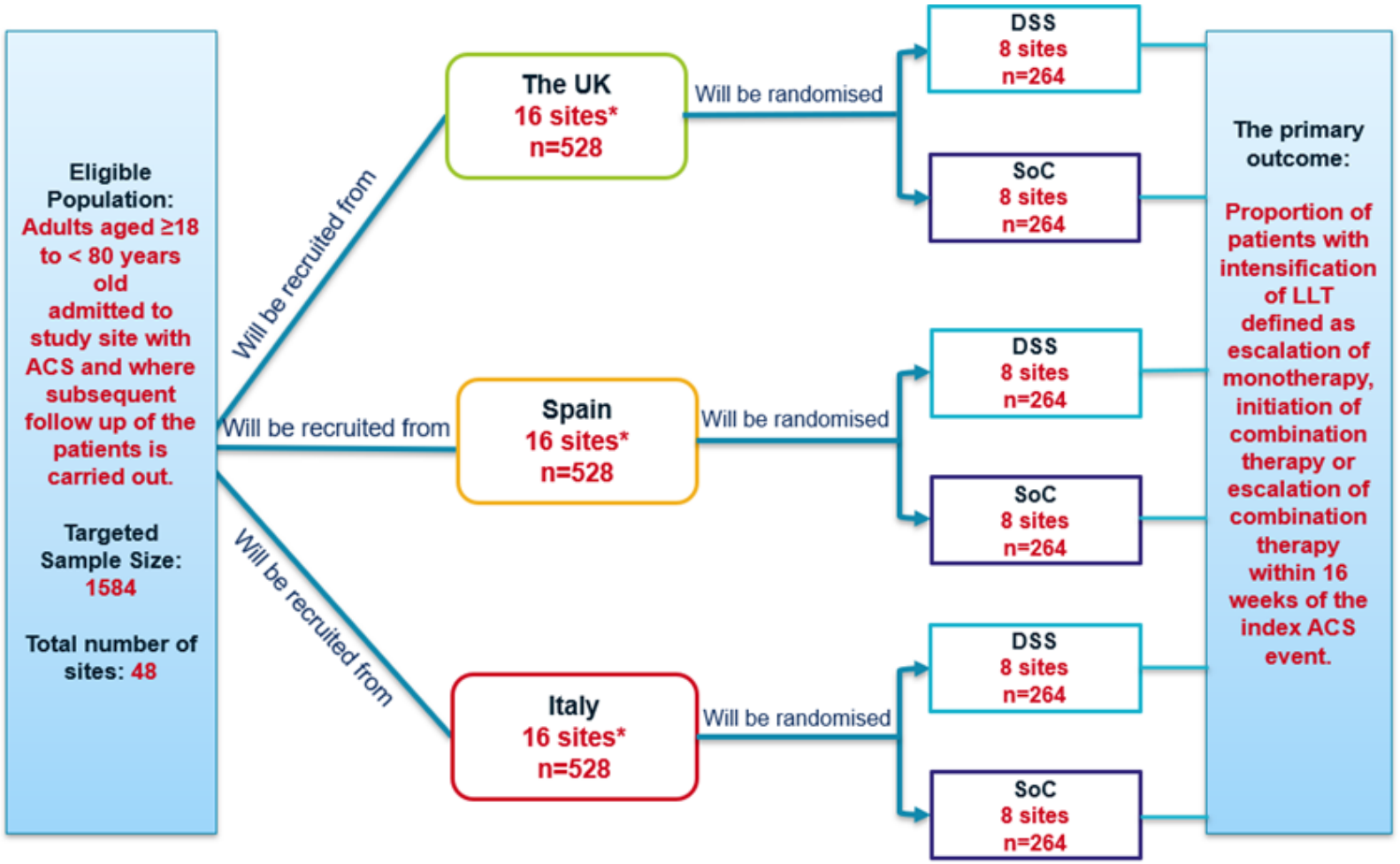
- Standard of Care (SoC) [24 sites] or
- DSS [24 sites] across 3 countries

Each site needs to recruit 33 patients

Study Update

- Recruitment completed

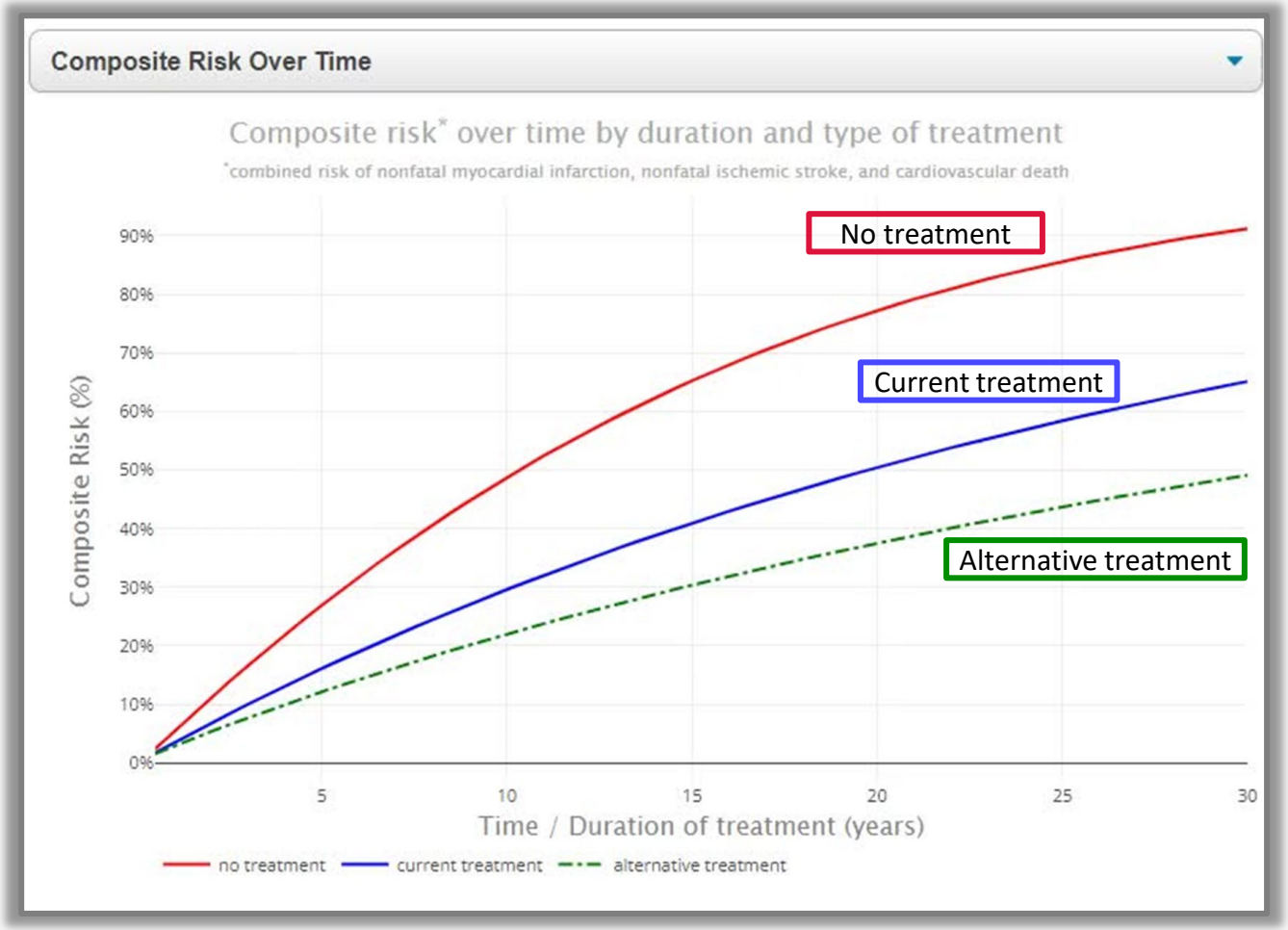
- Currently in the follow-up phase



Usual Care Step by Step LLT up-titration vs availability of a Decision Support System (DSS) that allows the user (HCP) to quantify risk and benefits from combinations of LLT over time

How does it work?

The DSS helps clinicians visualise the combined projected risk of non-fatal MI, non-fatal ischemic stroke, and CV death in ASCVD associated with different treatment options for ACS patients (18-79) hospitalised in the last 72 hours.



An example of one of the four visualisation of risk and benefit when using the DSS.

Conclusion

- The destination is **CV Risk Reduction**
- The journey is through appropriate **LDL-C lowering**
- Problems are **poor perception of risk**, and understanding the **interplay between genes, environment and time**

- Approaches that better help us understand the **benefit** of treatment and not just **risk** might help to **tackle inertia and difficulties** with implementation