University Hospitals Sussex
NHS Foundation Trust

Lipid lowering; myth busting, what and why...

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Learning Outcomes

- Myth busting: e.g. role of diet and exercise, dementia, frailty, statin safety and efficacy
- What: choices and indications
- Why: challenge statin hesitancy for patients, reduce/obliterate avoidable atherosclerosis, save lives, reduce morbidity

Myth busting: Role of diet and exercise

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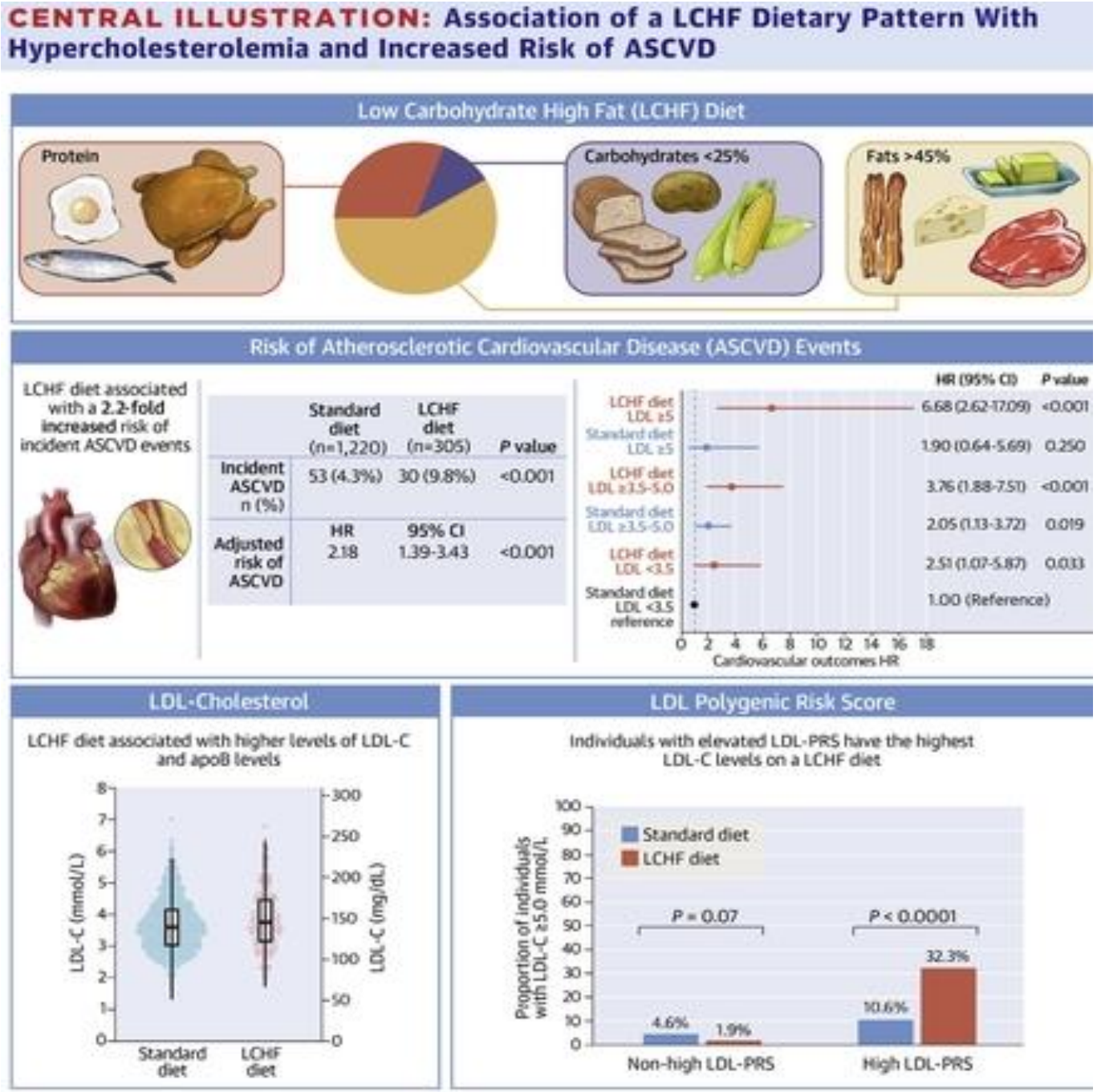
- There is no evidence that giving 5-10 mins of dietary advice in a clinic setting has any benefits (modest evidence only comes from participants receiving ‘programmes’ e.g. food in controlled environments)
- Restricting dietary cholesterol has been shown to have no impact on CVD (dietary cholesterol is not a major source) – eggs are cheap and very nutritious so should not be excluded from diets
- Most people do not want to be fat and would love to enjoy their leisure time with exercise
- Waiting for lifestyle modification delays starting therapy which will have a real impact on patient survival – in essence ‘who’ are we… ultimately doctors

Nutrients. 2018 Jun 16;10(6):780



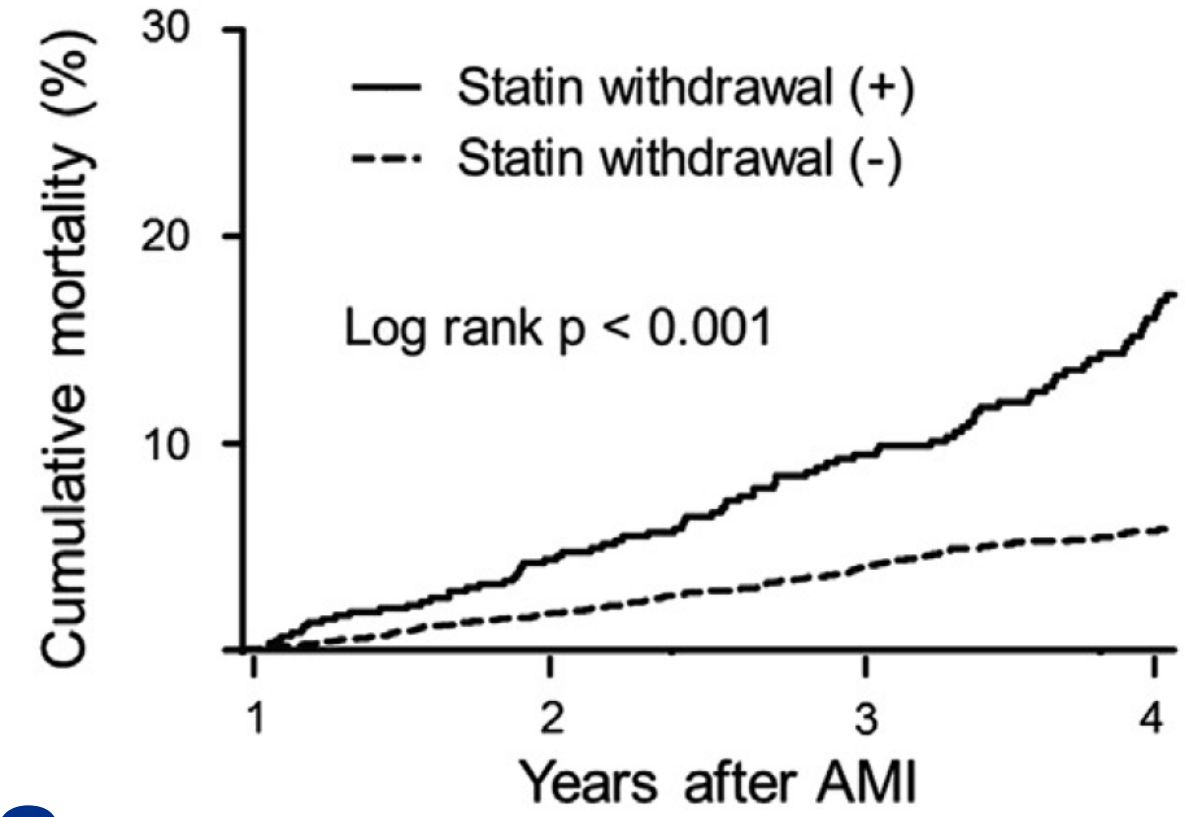
'..305 LCHF and 1220 Standard Diet …completed an enrollment assessment concurrently with lipid collection. In this cohort, LDL-C and apoB were significantly increased in the LCHF vs SD group ($P < 0.001$). 11.1% of LCHF and 6.2% of SD individuals demonstrated severe hyperchol. (LDL-C >5 mmol/L, $P < 0.001$). After 11.8 years, 9.8% of LCHF vs 4.3% of SD … experienced a MACE ($p < 0.001$). This …remained significant after adjustment for CVD RFs (HR: 2.18, 95% CI: 1.39-3.43, $P < 0.001$). Individuals with elevated LDL-C polygenic risk score had the highest conc of LDL-C on a LCHF diet. Similar sig. changes in lipids and MACE …were confirmed in the entire cohort...(2034 LCHF and 8136 SD)'

Iatan I, et al. JACC Adv. 2024;3(6):100924.
JACC Advances An Open Access Journal

Exercise in secondary prevention

- ‘Individuals with preexisting CVD … derive greater benefits from physical activity than their counterparts without CVD…
- The dose-response relationships between the intensity, frequency, duration and volume of physical activity and adverse CV outcomes …are complex… though a general trend suggests that more …activity leads to better outcomes, some evidence suggests an increased risk of adverse CVE at extremely high levels …
- …sedentary individuals stand to gain the most from becoming physically active.
- physical activity …150 min of moderate-intensity … or 75 min of vigorous-intensity …or. combination per week may be a min. requirement for patients with preexisting CVD.
- There were consistent reductions in adverse CV outcomes following exercise-based Cardiac Rehab or structured exercise training in individuals with preexisting CVD.’

Effect of statin withdrawal on mortality post MI



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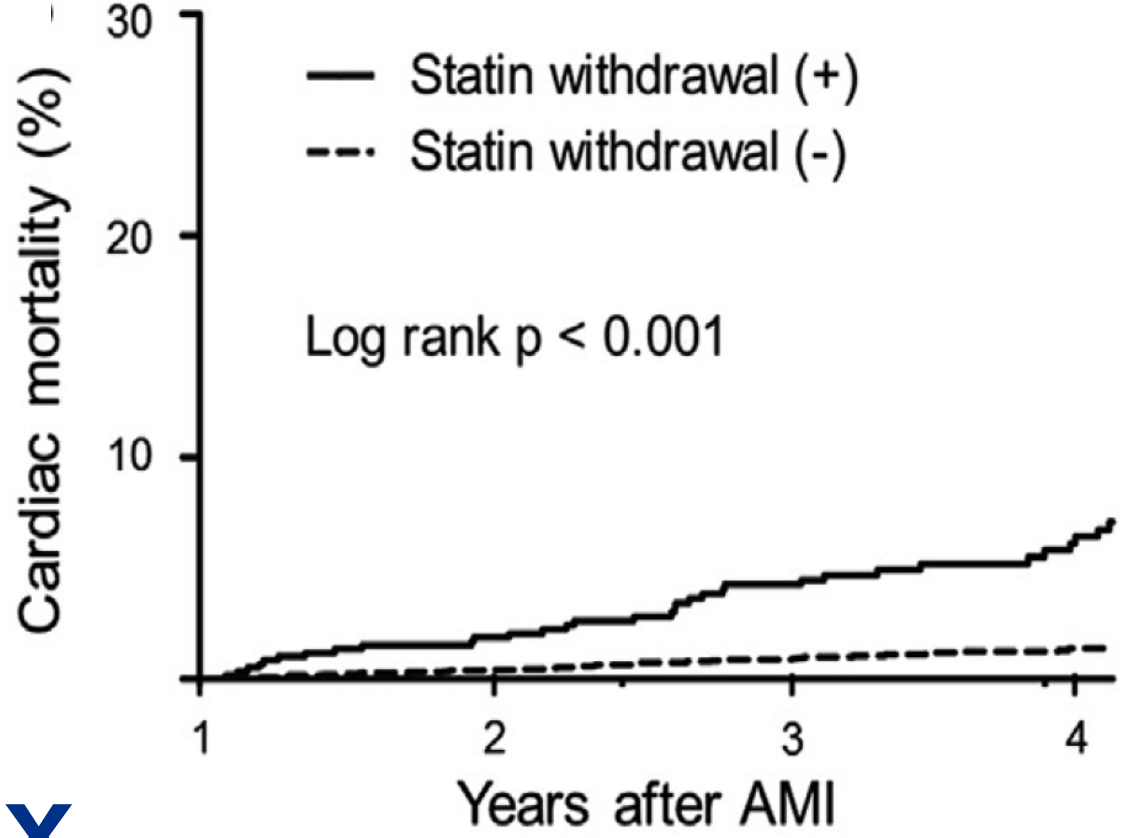
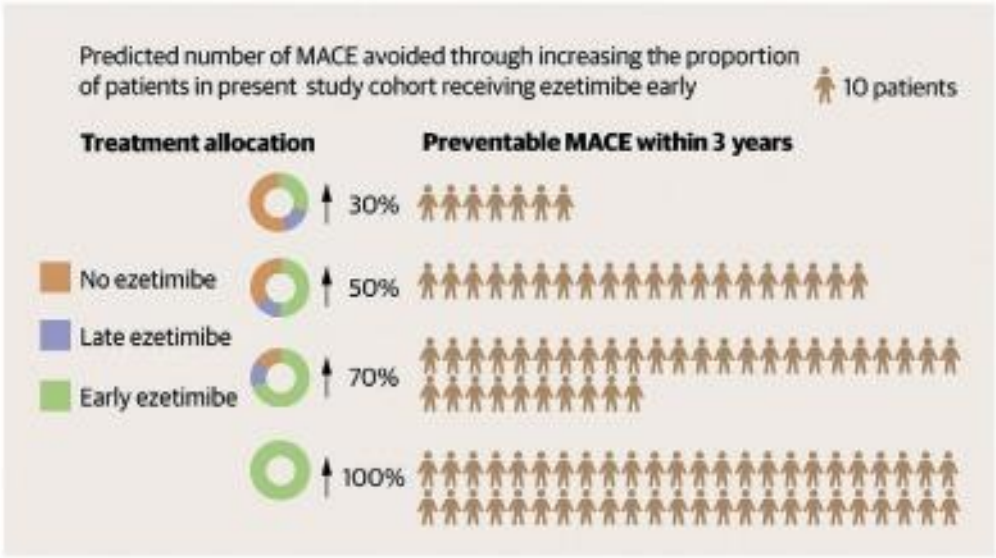


4x

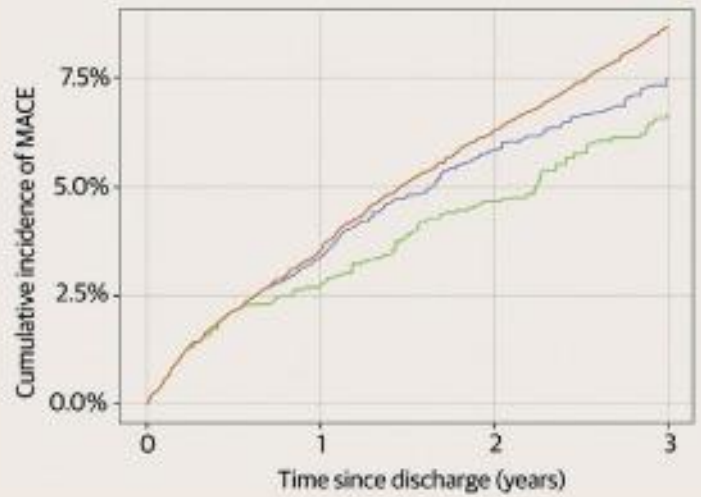
This multi-centre register study assessed 3,807 Korean patients who had survived for >1 year after an MI and were prescribed a statin on discharge; 603 patients withdrew from therapy . MI: Myocardial Infarction; AMI: Acute Myocardial Infarction. Kim, MC et al., *Am J Cardiol* 2015;**115:**1

CENTRAL ILLUSTRATION: Early Ezetimibe Initiation After Myocardial Infarction Protects Against Later Cardiovascular Outcomes

Method **Clone-censor-weight framework**



2,570 MACE events occurring over 3 years



Risk difference (95% CI)

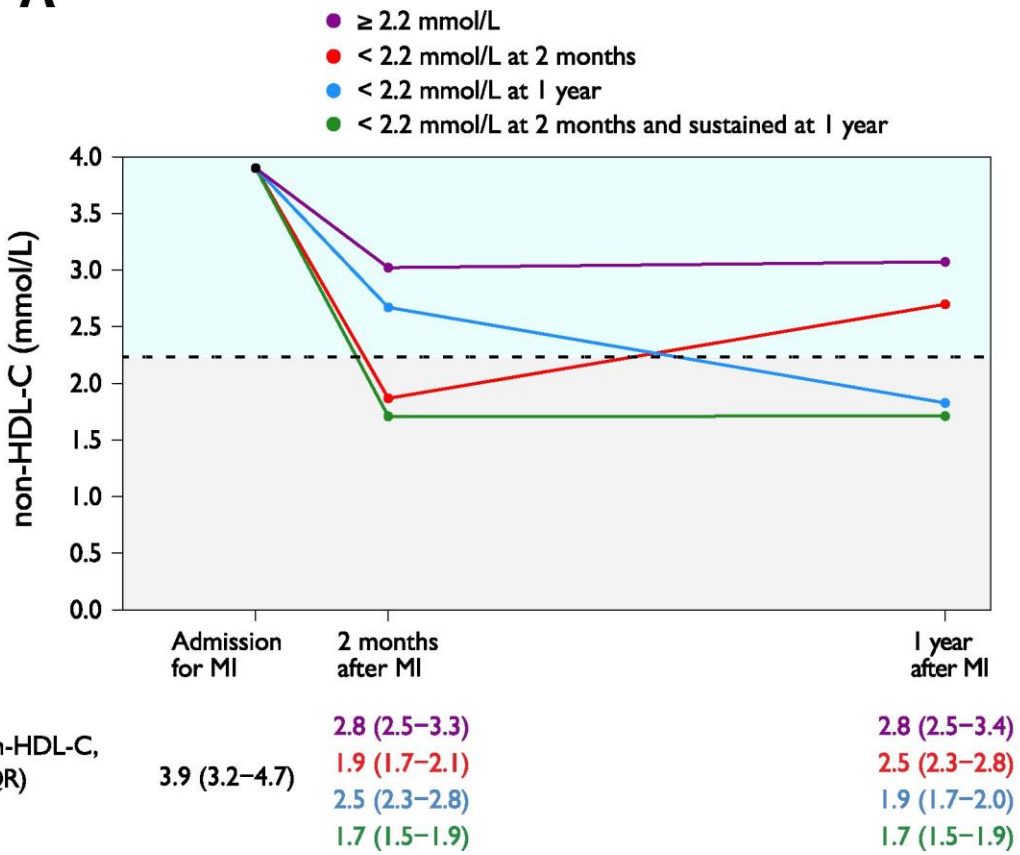
No ezetimibe	0.7% (0.2%-1.3%)*	1.6% (0.8%-2.5%)*	1.9% (0.8%-3.1%)*
Late ezetimibe	0.6% (0.1%-1.1%)*	1.1% (0.3%-2.0%)*	0.7% (-0.6% to 2.3%)
Early ezetimibe	Ref	Ref	Ref

*$P < 0.01$

Leosdottir M, et al. JACC. 2025;85(15):1550-1564.

Figure 4 (A) Non–HDL-C values at myocardial infarction admission and early and late goal achievement. (B) Adjusted Cox ...

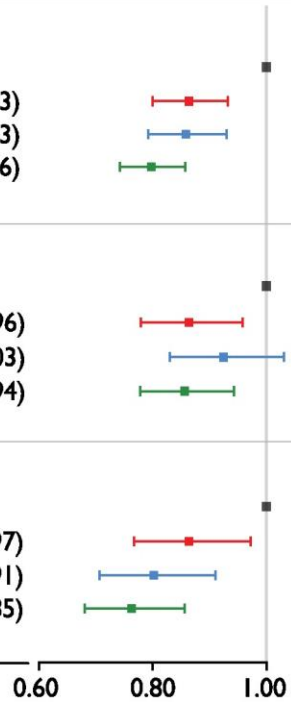
A



Median non-HDL-C, mmol/L (IQR)			
	3.9 (3.2–4.7)	2.8 (2.5–3.3)	2.8 (2.5–3.4)
		1.9 (1.7–2.1)	2.5 (2.3–2.8)
		2.5 (2.3–2.8)	1.9 (1.7–2.0)
		1.7 (1.5–1.9)	1.7 (1.5–1.9)

B

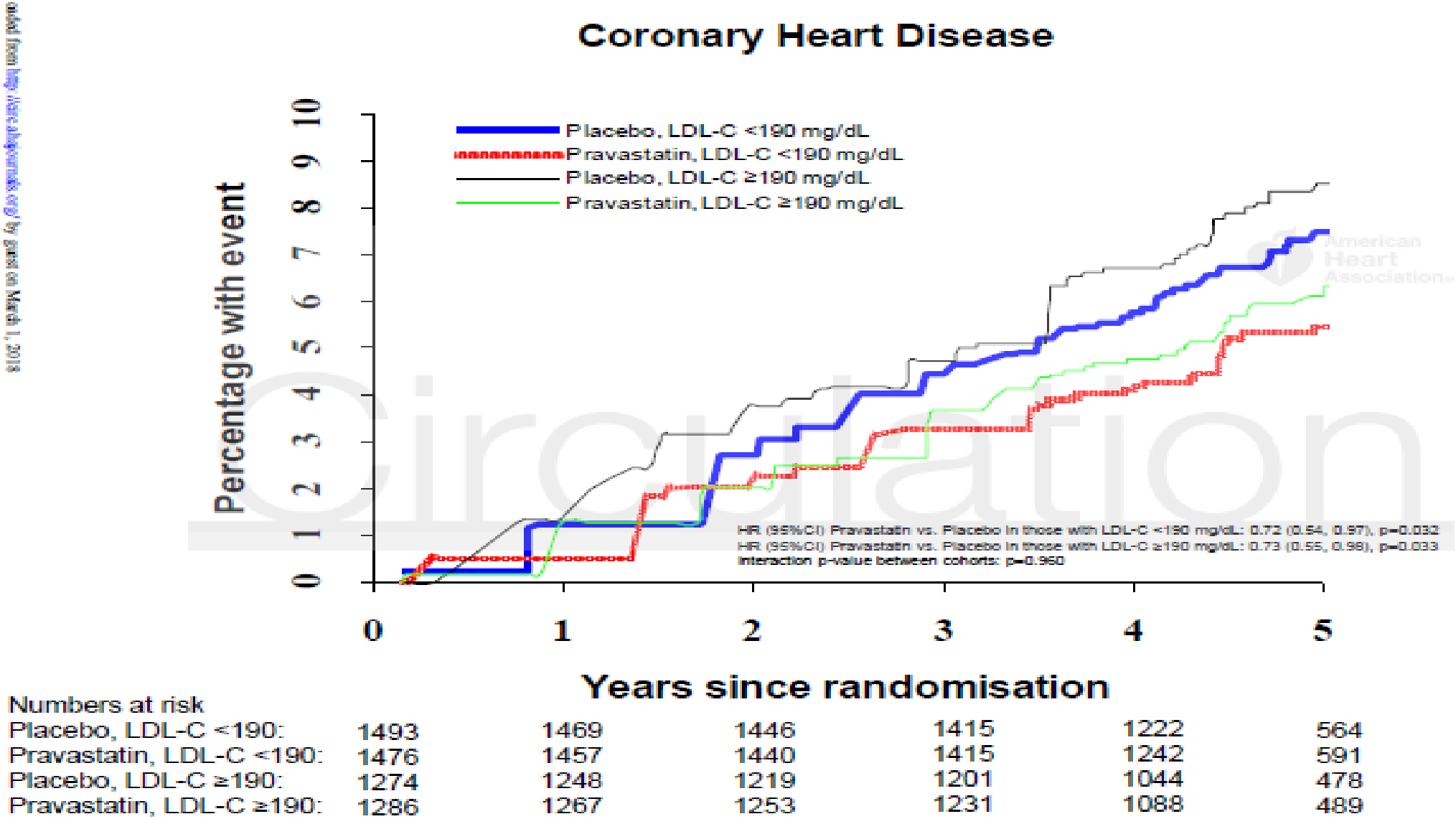
	No. of patients	Event rate (95% CI)	Hazard Ratio (95% CI)	P for trend
MACE				
≥ 2.2 mmol/L	22,005	3.2 (3.1–3.3)	1.00	<0.001
< 2.2 mmol/L at 2 months	5379	2.9 (2.7–3.1)	0.86 (0.80–0.93)	
< 2.2 mmol/L at 1 year	7050	2.6 (2.4–2.8)	0.86 (0.79–0.93)	
< 2.2 mmol/L at 2 months and sustained at 1 year	12,084	2.6 (2.4–2.7)	0.80 (0.74–0.86)	
All-cause mortality				
≥ 2.2 mmol/L	22,005	1.6 (1.6–1.7)	1.00	0.002
< 2.2 mmol/L at 2 months	5379	1.5 (1.4–1.6)	0.86 (0.78–0.96)	
< 2.2 mmol/L at 1 year	7050	1.4 (1.3–1.5)	0.92 (0.83–1.03)	
< 2.2 mmol/L at 2 months and sustained at 1 year	12,084	1.4 (1.3–1.6)	0.85 (0.78–0.94)	
Myocardial infarction				
≥ 2.2 mmol/L	22,005	1.3 (1.3–1.4)	1.00	<0.001
< 2.2 mmol/L at 2 months	5379	1.2 (1.0–1.3)	0.86 (0.76–0.97)	
< 2.2 mmol/L at 1 year	7050	1.0 (0.9–1.1)	0.80 (0.71–0.91)	
< 2.2 mmol/L at 2 months and sustained at 1 year	12,084	1.0 (0.9–1.0)	0.76 (0.68–0.85)	



https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehae576/7744248

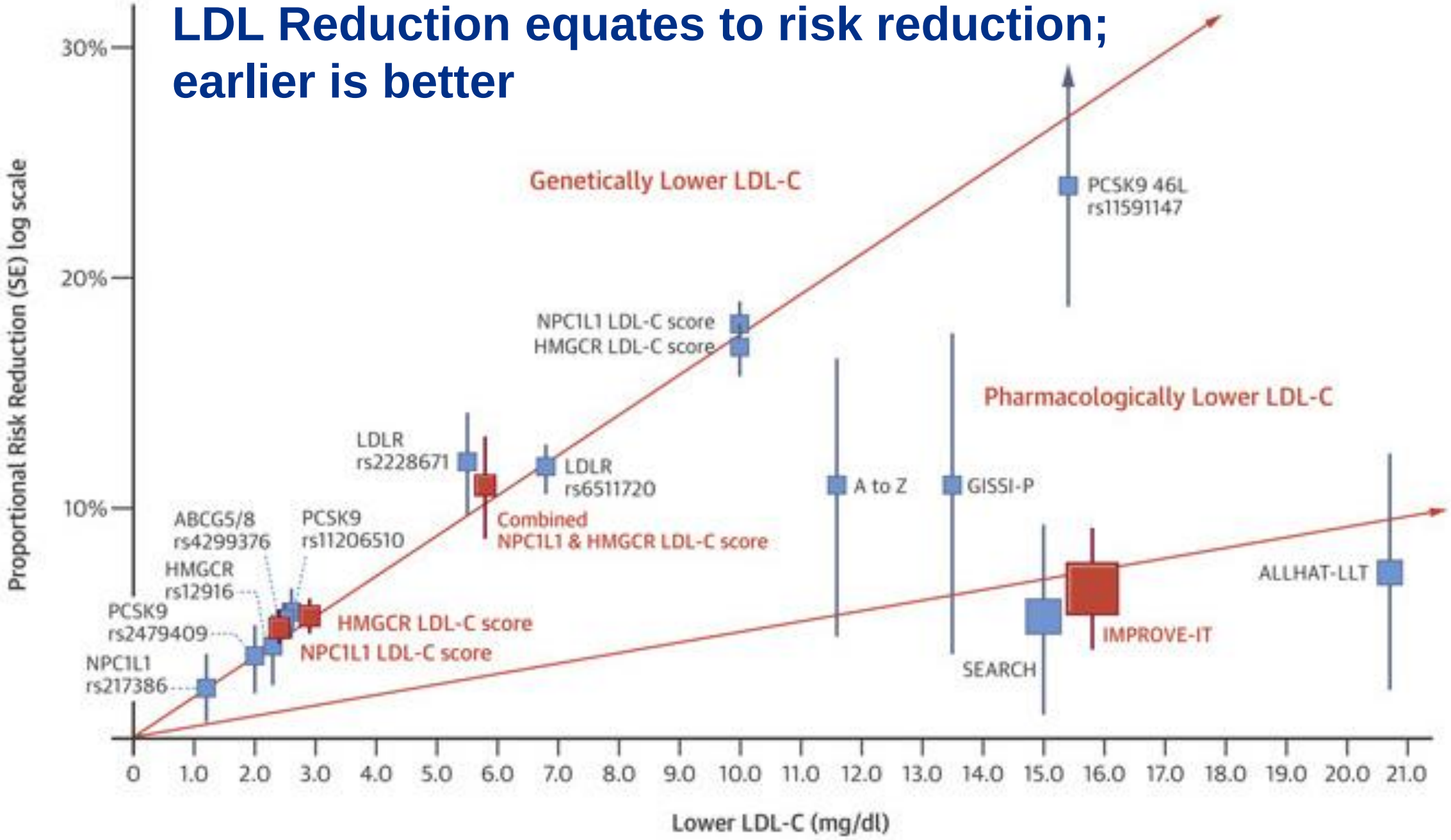
https://doi.org/10.1161/CIRCULATIONAHA.117.027966

20 years later CVD death reduced by 25% overall



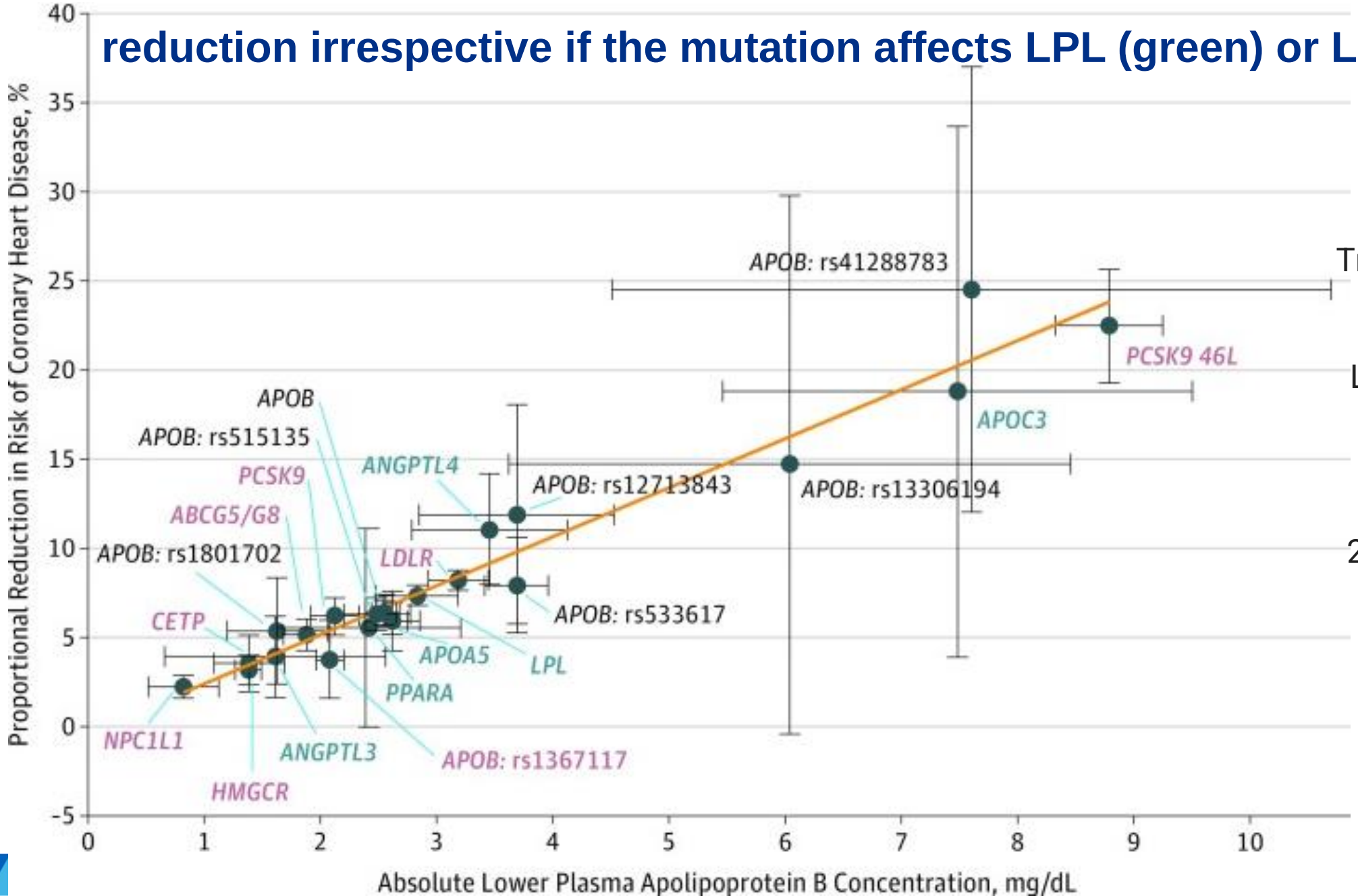
WOSCOPS 20 years on (primary prevention data)

LDL Reduction equates to risk reduction; earlier is better



Ference, B.A. et al. J Am Coll Cardiol. 2015; 65(15):1552-61.

The reduction of risk is proportional to the degree of Apo B reduction irrespective if the mutation affects LPL (green) or LDL



Ference BA et al. Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants With Risk of Coronary Heart Disease. JAMA. 2019 Jan 29;321(4):364-373.

Myth busting: Role of diet and exercise

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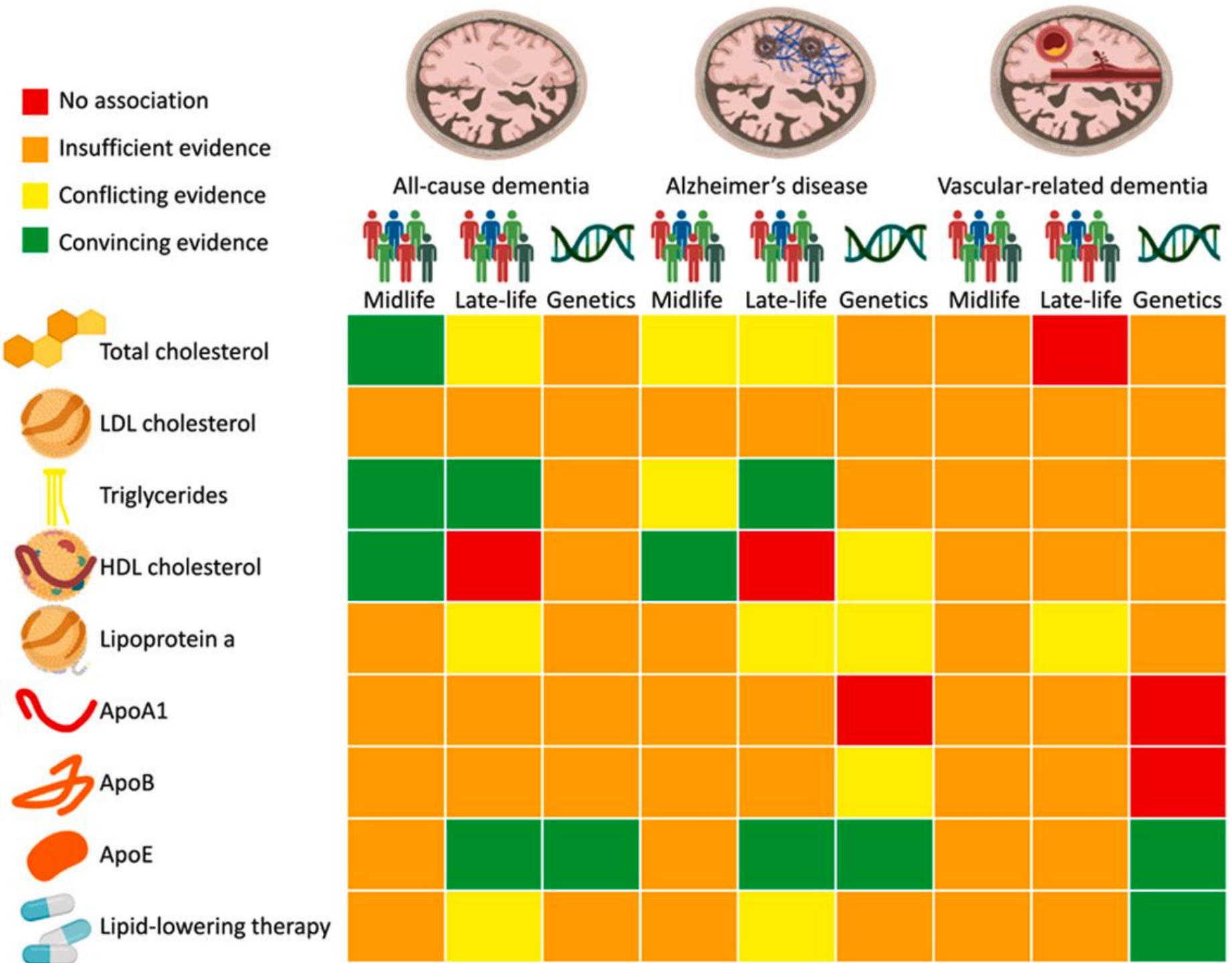
- Summary:
- **Do not delay** indicated lipid lowering therapy (LLT)
- Even short courses of low doses of LLT have tremendous long term legacy benefits
- Diet and exercise has a role (particularly high trigs, low HDL, metabolic syndrome, MASLD, insulin resistance) but this is as well as medication not instead (do not discriminate against this high-risk population by withholding medication)
- No diet is particularly superior (modest evidence for mediterranean and low salt diet programs but note this is not the same as advice…just ‘eat less’, ‘avoid alcohol’, ‘don’t smoke’, ‘avoid high protein high fat or processed food diets’)

Myth busting: dementia



Juul Rasmussen, Ida et al. Atherosclerosis, 2024 Volume 398, 118614

Low-density lipoprotein cholesterol levels and risk of incident dementia: a distributed network analysis using common data models

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- ‘aimed to examine the association between LDL-C and the risk of dementia and assess the influence of statin therapy’
- ‘retrospectively analysed data from 11 university hospitals participating in the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). Participants with a prior diagnosis of dementia or those with <180 days of observation before cohort inclusion, …were excluded. The primary outcome was all-cause dementia, with the secondary outcome being Alzheimer’s disease-related dementia (ADRD). The study utilised 1:1 propensity score matching to compare individuals with LDL-C <1.8 mmol/L against those with >3.4 mmol/L, resulting in a primary analysis cohort of **108 980 matched patients**. Secondary analyses further examined LDL-C thresholds <1.4 mmol/L and the influence of statin use

Low-density lipoprotein cholesterol levels and risk of incident dementia: a distributed network analysis using common data models

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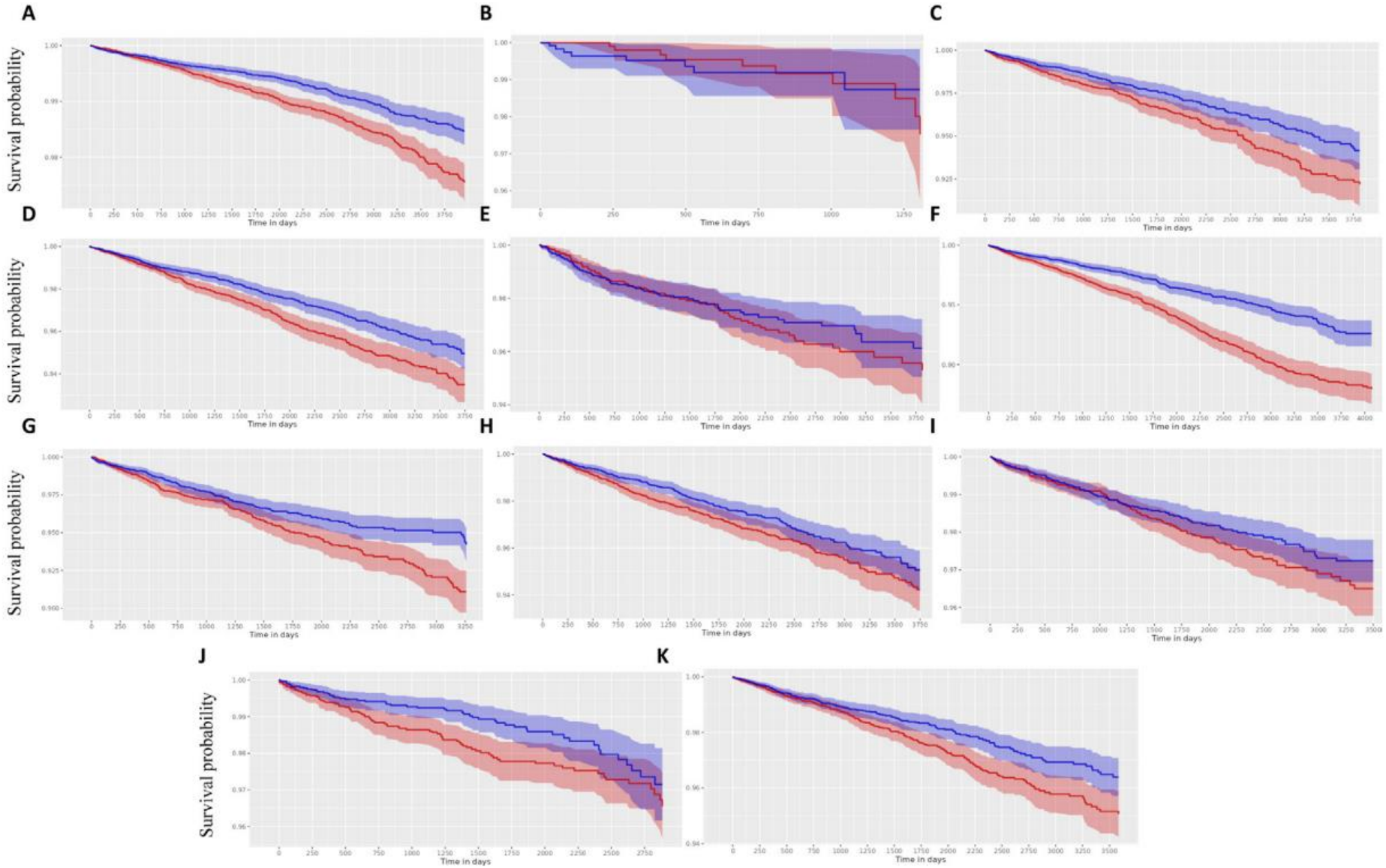
- ‘LDL-C <1.8 mmol/L associated with a 26% reduction in the risk of all-cause dementia and a 28% reduction in the risk of ADRD, compared with >3.4 mmol/L. LDL-C <1.4 mmol/L, there was an 18% risk reduction for both … those with LDL-C <1.8 mmol/L, statin use was associated with a 13% reduction in all cause dementia risk and a 12% decrease in ADRD risk compared with non-users.’
- LDL <1.8 is significantly a/w reduced risk of dementia, including ADRD, with statin therapy providing additional protective effects. These findings support the necessity of targeted lipid management as a preventive strategy against dementia, indicating the importance of personalised treatment approaches.’

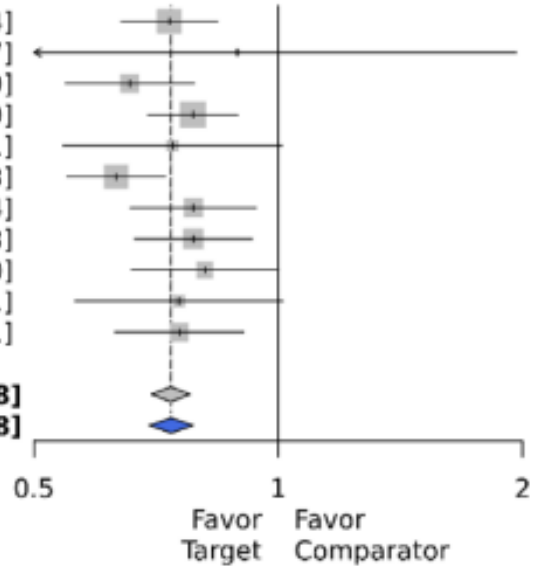


Kaplan-Meier curves for the risk of all-cause dementia between the group with LDL-C <70 mg/dL(<1.8 mmol/L) and LDL-C >130 mg/dL (>3.4 mmol/L). (A) –(K) are different hospital sites. LDL-C, low-density lipoprotein cholesterol.

A

Source	Target Total	Target Event	Comparator Total	Comparator Event	HR	95% CI
AUMC	39,718	366	39,718	473	0.73	[0.64; 0.84]
GNUCH	1,317	11	1,317	15	0.89	[0.40; 1.97]
KDH	6,938	192	6,938	292	0.66	[0.55; 0.79]
KHMC	11,936	431	11,936	530	0.78	[0.69; 0.89]
KHNMC	3,314	69	3,314	95	0.74	[0.54; 1.01]
KWMC	7,204	330	7,204	514	0.63	[0.55; 0.73]
MJH	5,751	219	5,751	269	0.79	[0.66; 0.94]
SCHBC	9,015	251	9,015	305	0.79	[0.67; 0.93]
SCHCA	8,938	166	8,938	193	0.81	[0.66; 1.00]
SCHGM	4,601	76	4,601	107	0.75	[0.56; 1.01]
SCHSU	10,054	207	10,054	262	0.76	[0.63; 0.91]
Common effect model	**108,786**	**2,318**	**108,786**	**3,055**	**0.74**	**[0.70; 0.78]**
Overall					**0.74**	**[0.69; 0.78]**

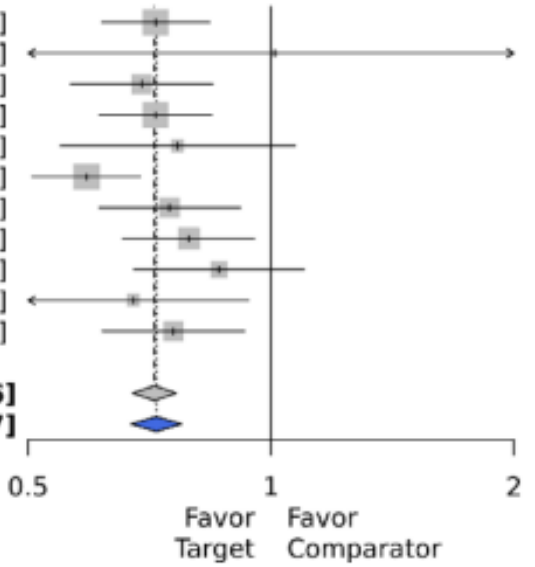
Heterogeneity: I^2 = 0.0%



B

Source	Target Total	Target Event	Comparator Total	Comparator Event	HR	95% CI
AUMC	39,750	287	39,750	377	0.72	[0.62; 0.84]
GNUCH	1,319	9	1,319	11	1.01	[0.41; 2.49]
KDH	6,949	158	6,949	229	0.69	[0.56; 0.85]
KHMC	11,984	264	11,984	356	0.72	[0.61; 0.84]
KHNMC	3,322	60	3,322	80	0.77	[0.55; 1.07]
KWMC	7,227	258	7,227	430	0.59	[0.51; 0.69]
MJH	5,768	168	5,768	217	0.75	[0.61; 0.92]
SCHBC	9,030	199	9,030	241	0.79	[0.66; 0.95]
SCHCA	8,954	125	8,954	137	0.86	[0.68; 1.10]
SCHGM	4,605	59	4,605	92	0.68	[0.49; 0.94]
SCHSU	10,072	167	10,072	211	0.76	[0.62; 0.93]
Common effect model	**108,980**	**1,754**	**108,980**	**2,381**	**0.72**	**[0.67; 0.76]**
Overall					**0.72**	**[0.67; 0.77]**

Heterogeneity: I^2 = 7.0%



Meta-analysis of the impact of LDL-C levels on (A) all-cause dementia and (B) Alzheimer's disease dementia. In the distributed network analysis with 1:1 propensity score matching, the LDL-C >3.4 mmol/L were a/w decreased risk of incident all-cause dementia and Alzheimer's disease dementia. (in the different hospitals)

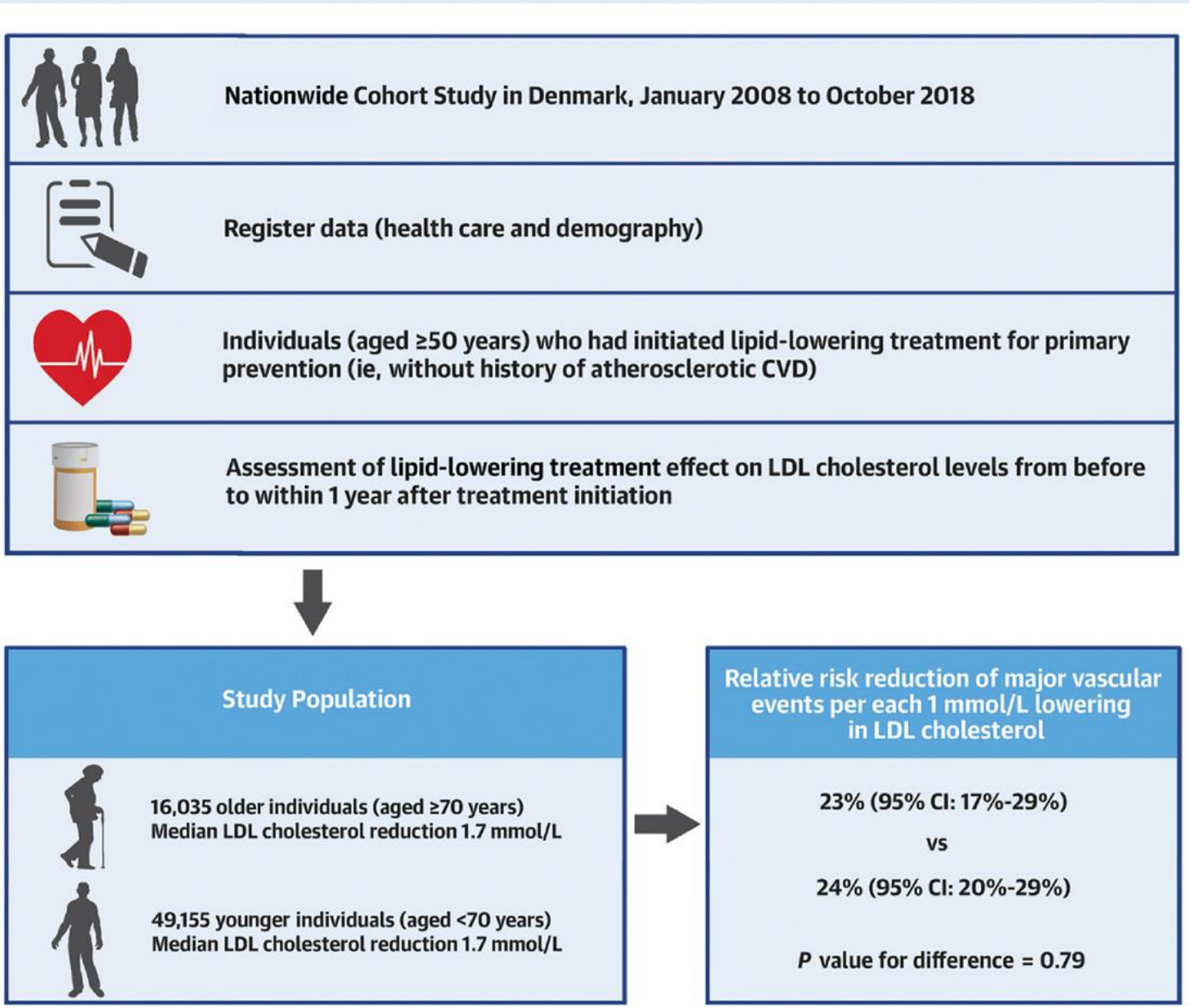
Lee M, et al. J Neurol Neurosurg Psychiatry 2025;0:1–9.

Dementia - CETPi

- Mendelian Randomisation analysis of lower CETP conc. recapitulated the blood lipid effects observed in clinical trials of CETP-inhibitors, as well as protective effects on coronary heart disease (odds ratio (OR) 0.92, 95% confidence interval (CI) 0.89; 0.96), heart failure, abdominal aortic aneurysm, any stroke, ischemic stroke, and small vessel stroke (0.90, 95%CI 0.85; 0.96). Consideration of dementia related traits indicated that lower CETP concentrations were associated with higher total brain volume (0.04 per standard deviation, 95%CI 0.02; 0.06), lower risk of Lewy Body Dementia (OR 0.81, 95%CI 0.74; 0.89) and Parkinson's dementia risk (OR 0.26, 95%CI 0.14; 0.48). *APOE4* stratified analyses suggested the LBD effect was most pronounced in *APOE*-ε4 + participants (OR 0.61 95%CI 0.51; 0.73), compared to *APOE*-ε4- (OR 0.89 95%CI 0.79; 1.01); interaction *p*-value 5.81×10^{-4}.

Myth busting: frailty

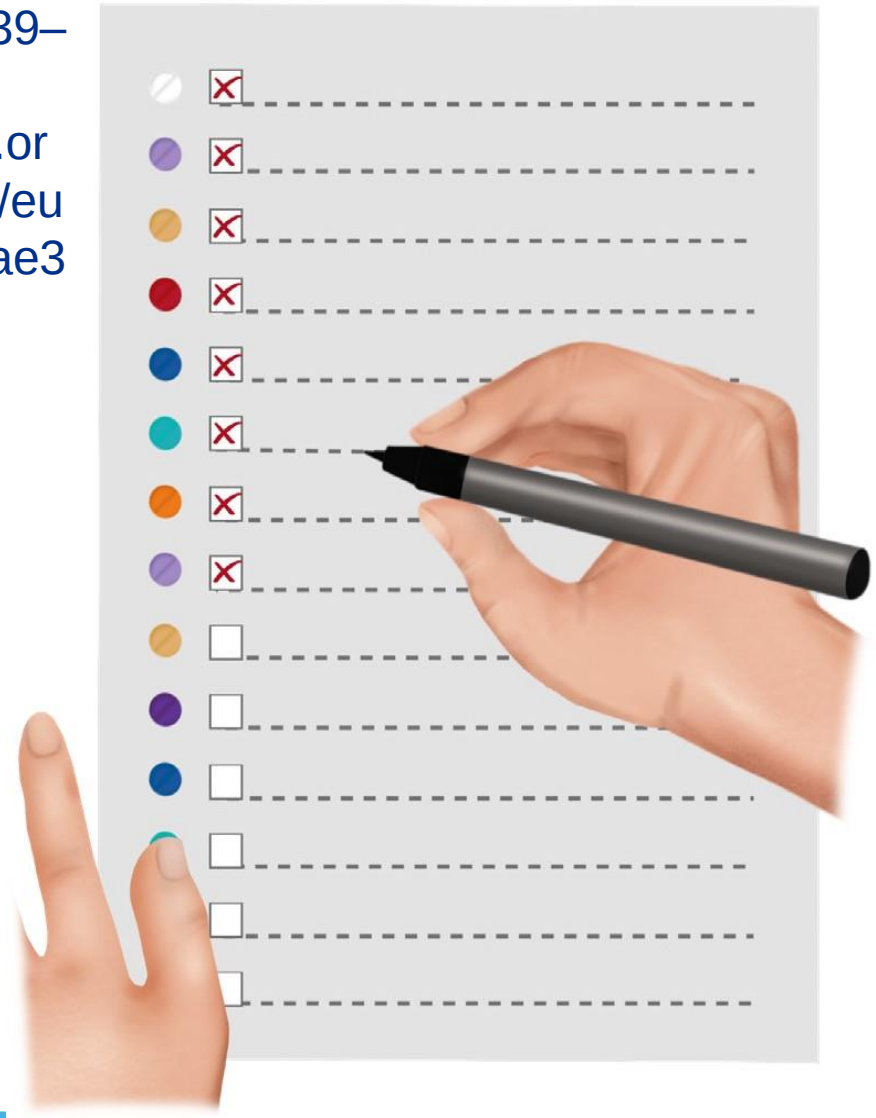
- The evidence for using statins to reduce mortality in frail people is lacking i.e. don't start in frailty
- There is good evidence for benefit irrespective of age



Andersson NW, et al. J Am Coll Cardiol. 2023;82(14):1381-1391.

Eur Heart J, Volume 45, Issue 23, 14 June 2024, Pages 2039–2051, https://doi.org/10.1093/eurheartj/ehae302

When cardiovascular medicines should be stopped



To prevent harm

- Addition of antiplatelets to OAC in patients with AFIB and stable ASCVD
- Aspirin in primary prevention
- Combination of beta-blockers and calcium channel blockers
- Calcium channel blockers in patients with HFrEF
- DPP-4 inhibitors in patients with CVD
- Dobutamine / Milrinone in patients without life-threatening hypoperfusion
- DAPT >3 weeks after stroke
- Niacin
- NSAIDs
- Combining certain RAAS-inhibitors
- Thiazolidinediones for patients with HFrEF

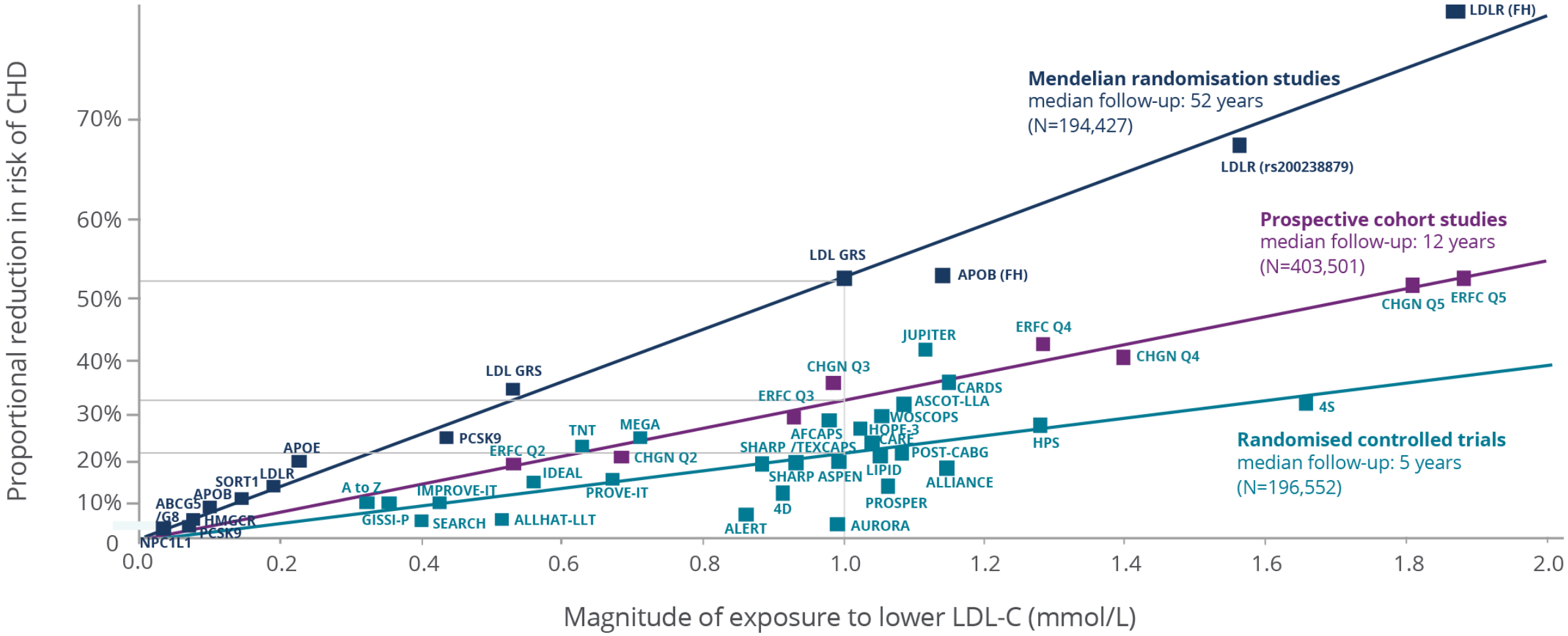
For lack of benefit

- Beta-blockers post MI with normal LV function
- Coenzyme Q10 and vitamin D for SAMS
- Digoxin as first line for rate control in AFIB
- Fibrates
- Fish oil supplements
- Loop diuretics in compensated heart failure
- Long-term DAPT

Better alternatives available

- ACEi/ARBs in HFrEF
- Non-evidence based beta-blockers in HFrEF
- Beta-blockers as first line therapy in hypertension
- Clopidogrel after ACS
- Simvastatin for lipid lowering
- Warfarin in AFIB

Myth busting: safety and efficacy



Ference BA et al. Eur Heart J 2017;38(32):2459-2472

Prevention of Stroke with the Addition of Ezetimibe to Statin Therapy in Patients With Acute Coronary Syndrome in IMPROVE-IT...2017

- ‘The addition of ezetimibe to simvastatin in patients stabilized after acute coronary syndrome reduces the frequency of ischemic stroke, with a particularly large effect seen in patients with a prior stroke.’
- N = 18144. HR Ischaemic stroke 0.76, HR if had prior stroke 0.52 NNT 13

Box 1 | Using cumulative exposure to LDL as a therapeutic target for personalized prevention

- Step 1: estimate the remaining lifetime risk of an individual of developing an acute atherosclerotic cardiovascular event.
- Step 2: choose a remaining lifetime risk goal (for example, 5%).
- Step 3: estimate the proportional reduction in risk needed to achieve the remaining lifetime risk goal.
- Step 4: calculate the absolute reduction in plasma LDL-cholesterol (LDL-C) levels needed to achieve the required proportional risk reduction, taking into account prior cumulative exposure to LDL and other causes of arterial wall injury using a causal artificial intelligence algorithm.
- Step 5: calculate the absolute plasma LDL-C level needed to slow plaque progression enough to keep the cumulative exposure to LDL below the personal plaque threshold of an individual needed to achieve the remaining lifetime risk goal.
- Step 6: calculate the proportional reduction in plasma LDL-C levels needed to achieve the target LDL-C level to guide selection of the intensity of the required LDL-C-lowering therapy.
- Step 7: repeat measurements of plasma LDL-C (and other causes of arterial wall injury) annually to update the calculation of the remaining lifetime risk based on achieved reductions in cumulative exposure to LDL and changing values of other causes of arterial wall injury using a causal artificial intelligence algorithm.
- Step 8: iteratively adjust the intensity of LDL-C lowering needed over time to keep the accruing cumulative exposure to LDL below the personal plaque threshold required to achieve the selected remaining lifetime risk goal.

Safety: N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects

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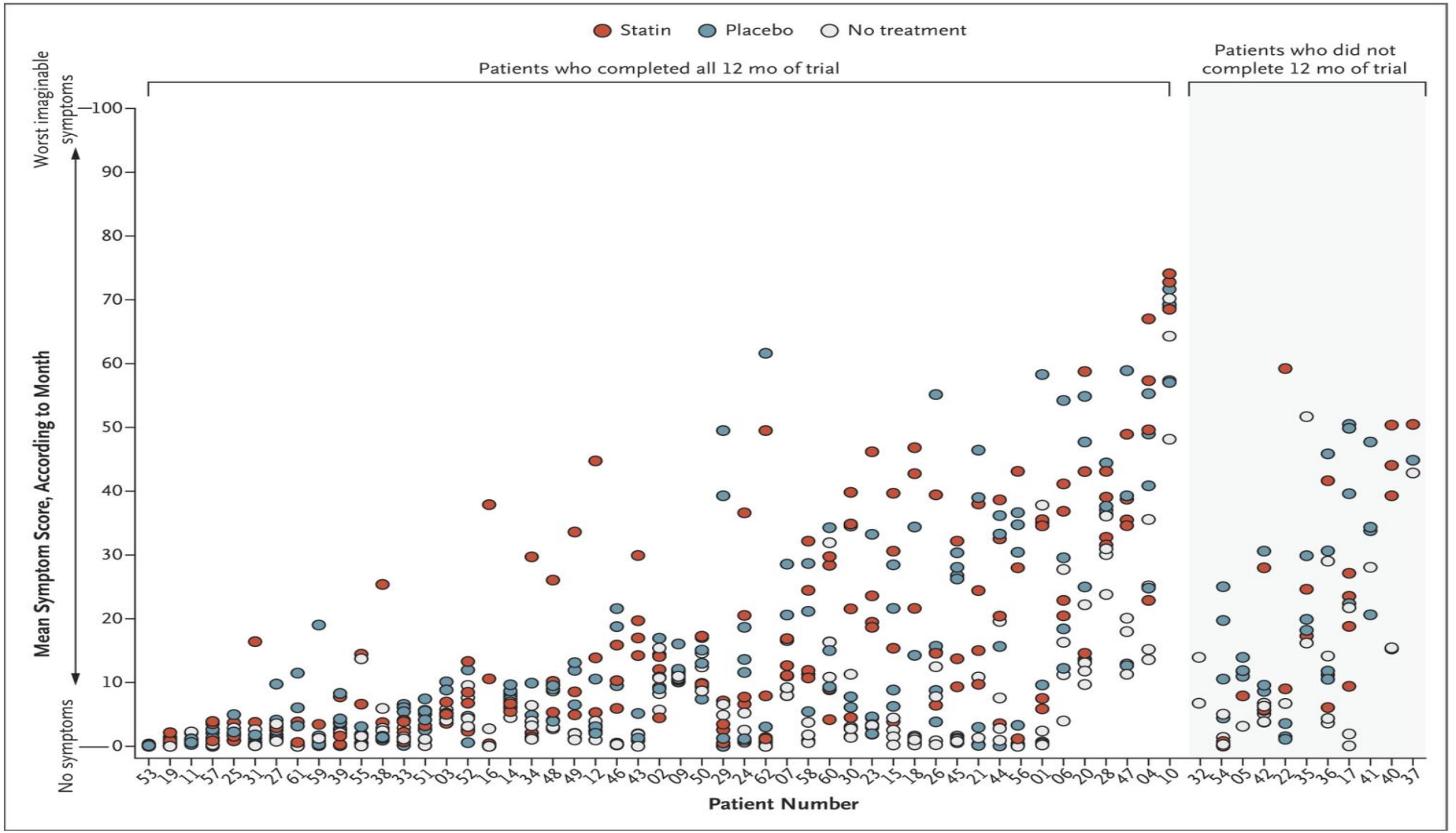

N Engl J Med 2020; 383:2182-2184

N-of-1 Trial of a Statin, Placebo, or No Treatment

- Pts discontinued statins because of side effects that occurred within 2 weeks
- Double-blind, three-group, n-of-1 trial (n=60)
- Four bottles containing atorvastatin 20 mg, four bottles containing placebo, and four empty bottles; each bottle was to be used for a 1-month period according to a random sequence.
- Symptom scores ranged from 0 (no symptoms) to 100 (worst imaginable symptoms).

N-of-1 Trial of a Statin, Placebo, or No Treatment

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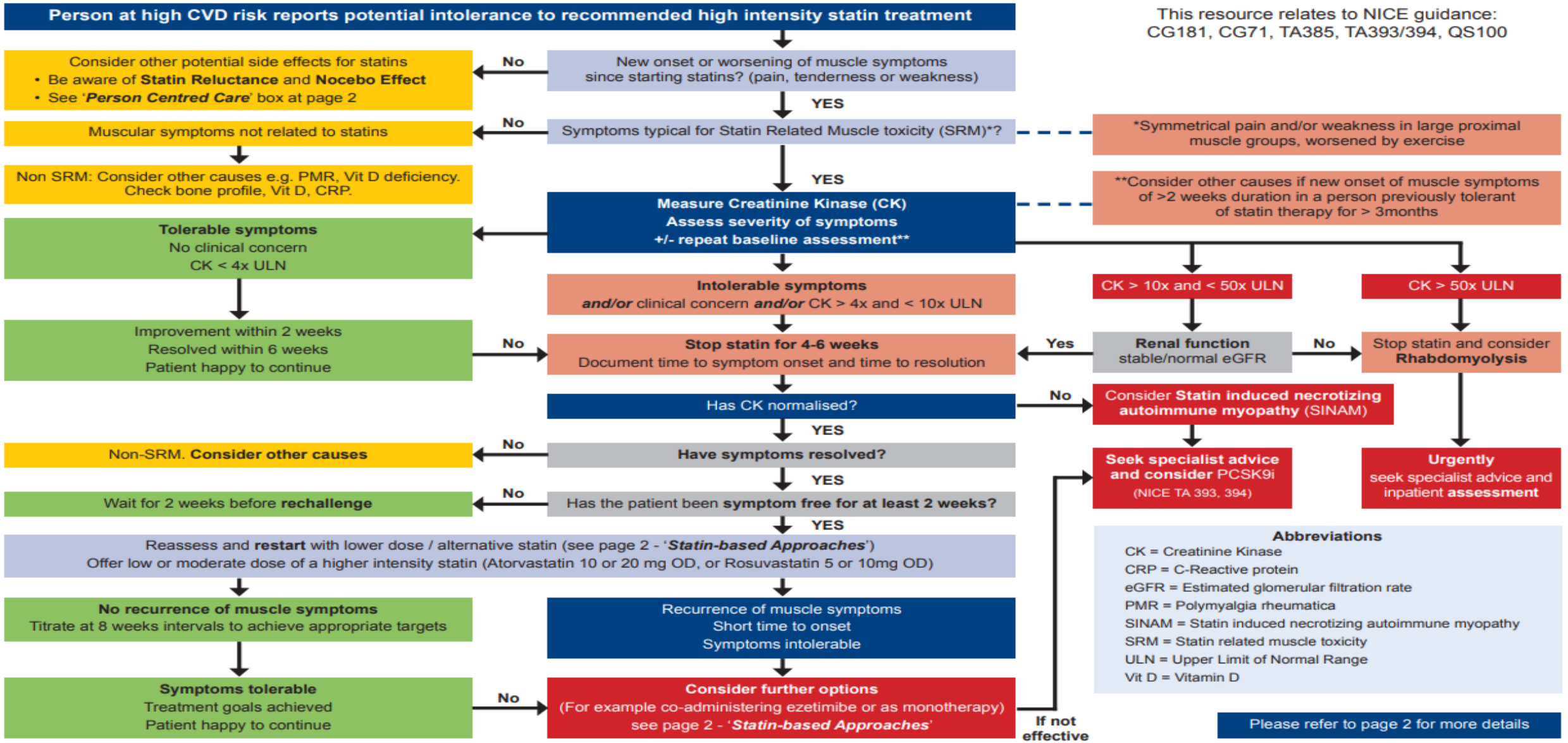
- 90% of the symptom burden elicited by a statin challenge was also elicited by placebo.
- 6 mnths after completing the trial, 30 (50%) had restarted statins, 4 planned to do so, 1 was uncontactable.
- 25 would not restart due to: side effects (18), chol. improved in 4 (no longer believed statins causing SE), a recollection that their cholesterol had not been reduced by statins (1), new dx of progressive neurodegenerative dis. 1, and feeling themself to be “too old” in 1

Statin Intolerance Pathway

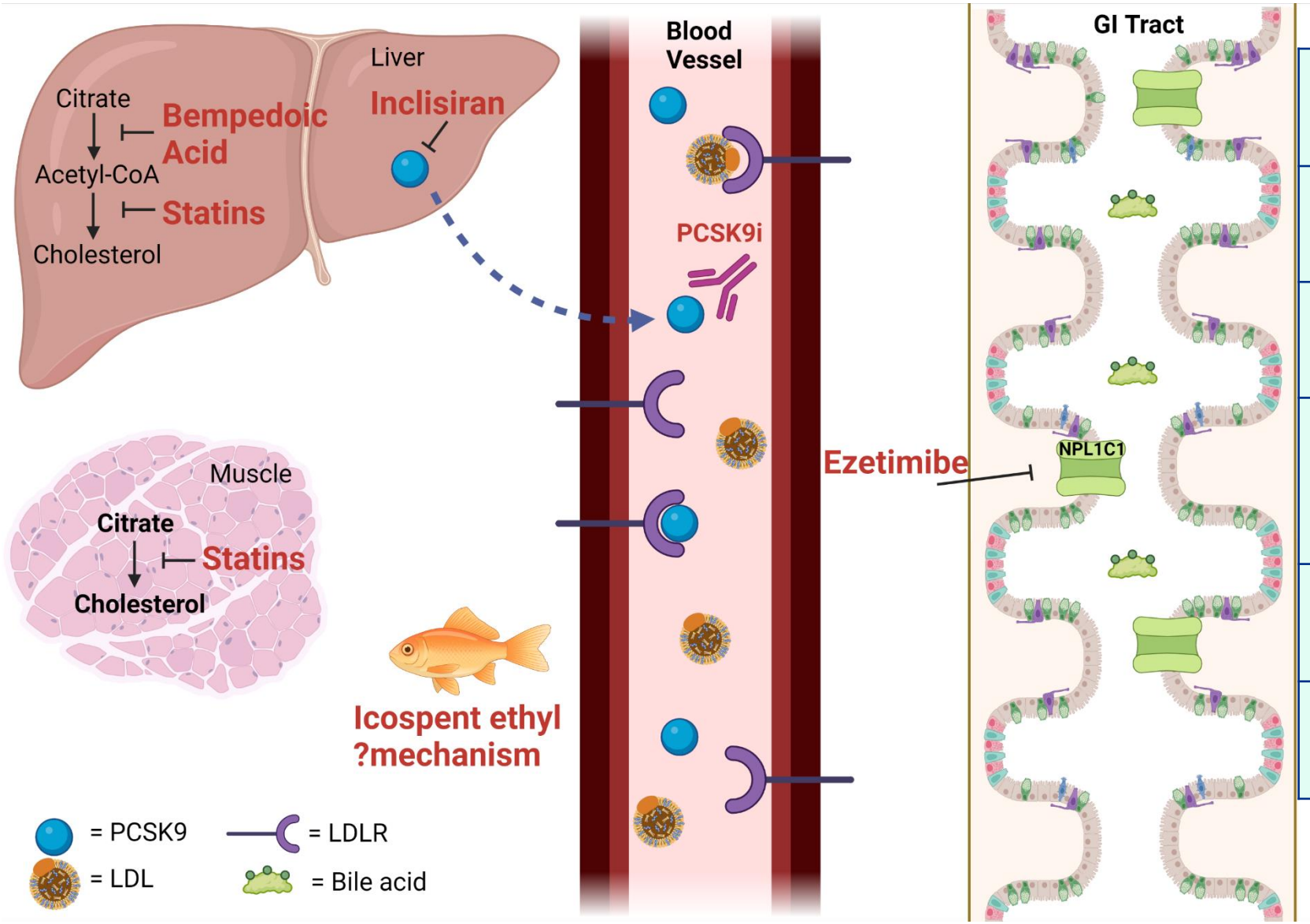
ACCELERATED ACCESS COLLABORATIVE

NHS England

This resource relates to NICE guidance:
CG181, CG71, TA385, TA393/394, QS100



Choices of Lipid Lowering Medications



Dose mg/day	5	10	20	40	80
Fluvast	-	-	21 %	27 %	33 %
Pravas	-	20 %	24 %	29 %	-
Simva	-	27 %	32 %	37 %	**42 % ***
Atorva	-	37 %	**43 %**	**49 %**	**55 %**
Rosuv	38 %	**43 %**	**48 %**	**53 %**	-

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LDL lowering therapy available

NHS
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Standard available LDL lowering drug / drug class	Administration	LDL-C reduction
High intensity statin	Once daily oral tablet	> 40-50%
Ezetimibe	Once daily oral tablet	24%
PCSK9i: Aliro-/ Evolo-cumab	S/C injec. every Two wk	> 60%
Bempedoic acid	Once daily oral tablet	28%
Inclisiran (trial data awaited)	S/C injec. every 6 mnth	52%

- Note ICPE reduces CVD risk (and triglycerides) but is not recommended as a lipid lowering drug but a CVD risk reduction drug in those with high triglycerides

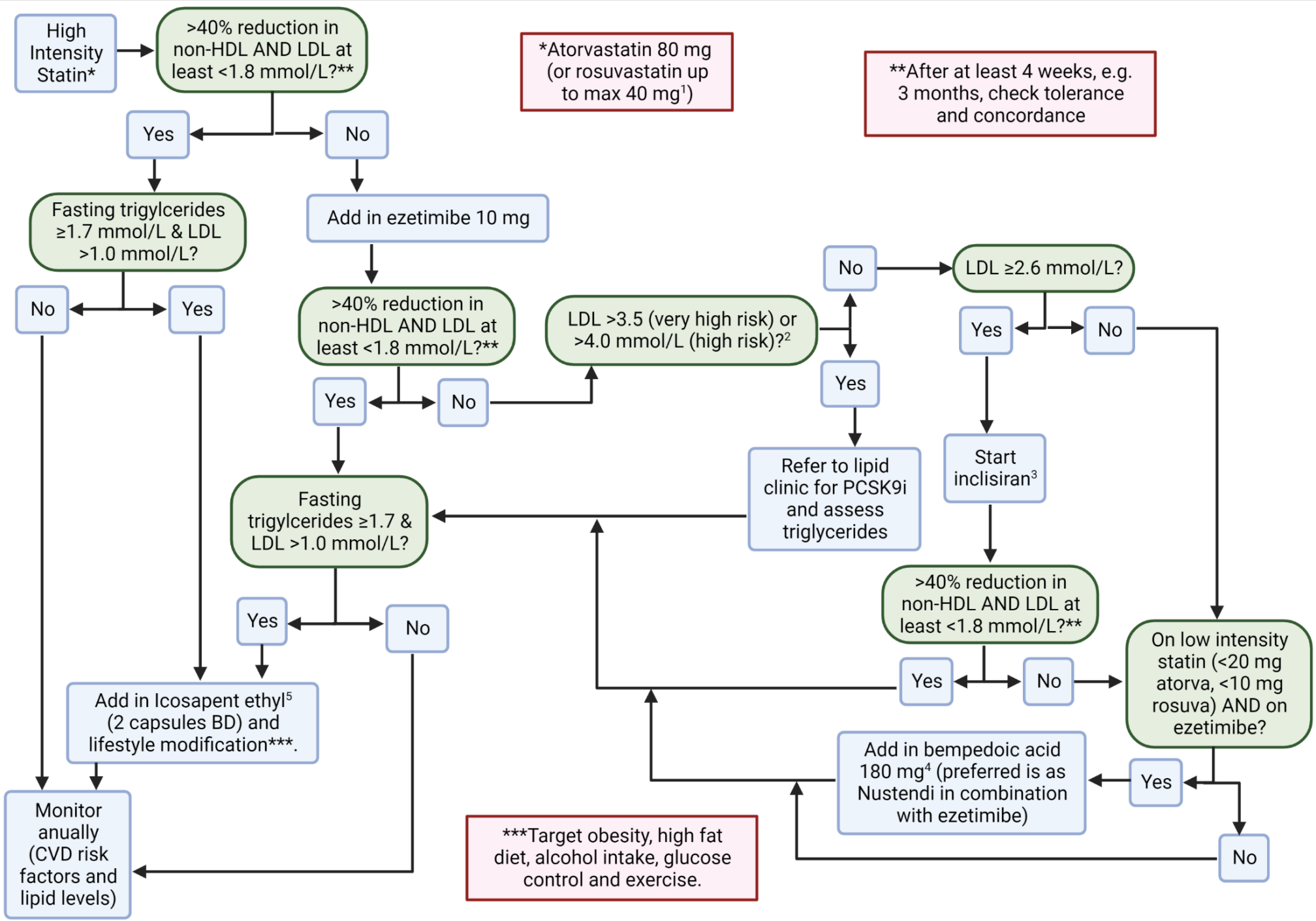
European Heart Journal. 2020;41(1):111–188.

	Alirocumab or Evolucumab			Inclisiran
	Without CVD	With CVD		With CVD[1]
		High risk of CVD[1]	Very high risk CVD[2]	
Primary non-FH or mixed dyslipidaemia	Not recommended	**>4.0 mmol/l**	**>3.5 mmol/l**	**≥2.6 mmol/l**
Primary heterozygous-FH	>5.0 mmol/l	>3.5 mmol/l		

Values only if LDL-C is persistently >value.

1 High risk CVD is a history of: ACS (MI or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; chronic heart disease; ischaemic stroke; peripheral arterial disease.

2 Very high risk CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed.


High Intensity Statin*
>40% reduction in non-HDL AND LDL at least <1.8 mmol/L?**
Yes
No
Fasting trigylcerides ≥1.7 mmol/L & LDL >1.0 mmol/L?
No
Yes
Add in ezetimibe 10 mg
>40% reduction in non-HDL AND LDL at least <1.8 mmol/L?**
Yes
No
LDL >3.5 (very high risk) or >4.0 mmol/L (high risk)?2
No
Yes
LDL ≥2.6 mmol/L?
Yes
No
Refer to lipid clinic for PCSK9i and assess triglycerides
Start inclisiran3
Fasting trigylcerides ≥1.7 & LDL >1.0 mmol/L?
Yes
No
Add in Icosapent ethyl5 (2 capsules BD) and lifestyle modification***.
>40% reduction in non-HDL AND LDL at least <1.8 mmol/L?**
Yes
No
On low intensity statin (<20 mg atorva, <10 mg rosuva) AND on ezetimibe?
Add in bempedoic acid 180 mg4 (preferred is as Nustendi in combination with ezetimibe)
Yes
No
Monitor anually (CVD risk factors and lipid levels)
*Atorvastatin 80 mg (or rosuvastatin up to max 40 mg1)
**After at least 4 weeks, e.g. 3 months, check tolerance and concordance
***Target obesity, high fat diet, alcohol intake, glucose control and exercise.

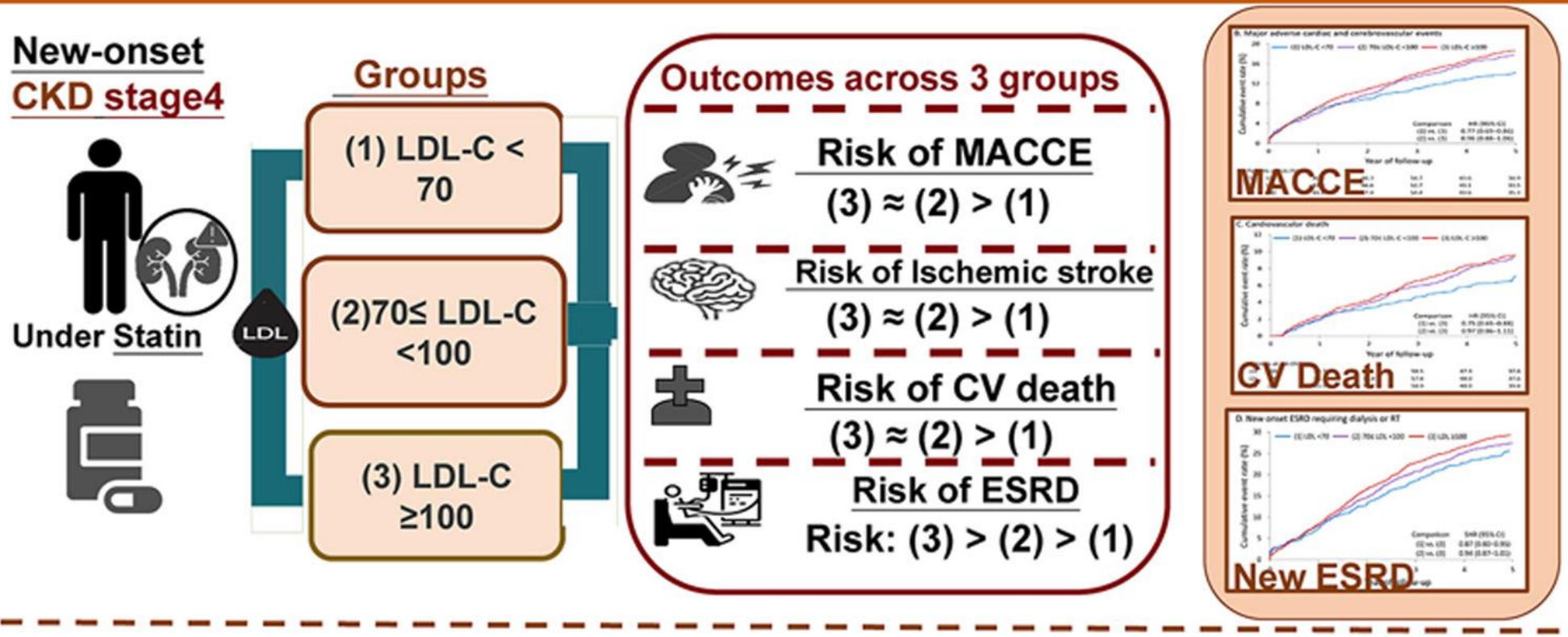
Why: statin hesitancy – no one need ever have atherosclerosis

University Hospitals Sussex NHS Foundation Trust

- To reduce your risk of atherosclerotic complications
- To reduce your risk of other macrovascular and microvascular complications e.g. renal failure, dementia
- Secondary prevention - first and last event and the disease regresses
- **1.4.18 Do not rule out treatment with atorvastatin 20 mg for the primary prevention of CVD just because the person's 10-year QRISK3 score is less than 10% if they have an informed preference for taking a statin or there is concern that risk may be underestimated. [NICE CG181 2023]**

LDL <1.8 in CKD stage 4 is a/w improved renal and CVD outcomes

The Role of Maintaining Lower LDL-C level during Statin Treatment for Advanced CKD patients



Conclusion: In CKD stage 4 patients under statin treatment, LDL-C< 70 is associated with lower risks of MACCE, CV death and new-onset ESRD compared to high LDL-C groups

Questions