University Hospital Southampton NHS
NHS Foundation Trust

SUGAR FALL INPATIENT CARE FOR DIABETES

University of Southampton

Reducing cardiovascular risk – (part 2)

Philip Newland-Jones
Consultant Pharmacist Diabetes & Endocrinology
Clinical Director Diabetes & Endocrinology UHSFT
Honorary Associate Professor in Diabetes & Endocrinology

@PNewlandJones

@pnewland-jones.bsky.social

Overview

University Hospital Southampton NHS
NHS Foundation Trust

- Lipids overview
- Treatment options
- Triglycerides as a CV risk marker
- Icosapent ethyl

What's in the 'Full Lipid Profile'?

University Hospital Southampton NHS
NHS Foundation Trust

- **Total cholest**
- **HDL Cholest** particles – 'goo
- **Triglycerides**

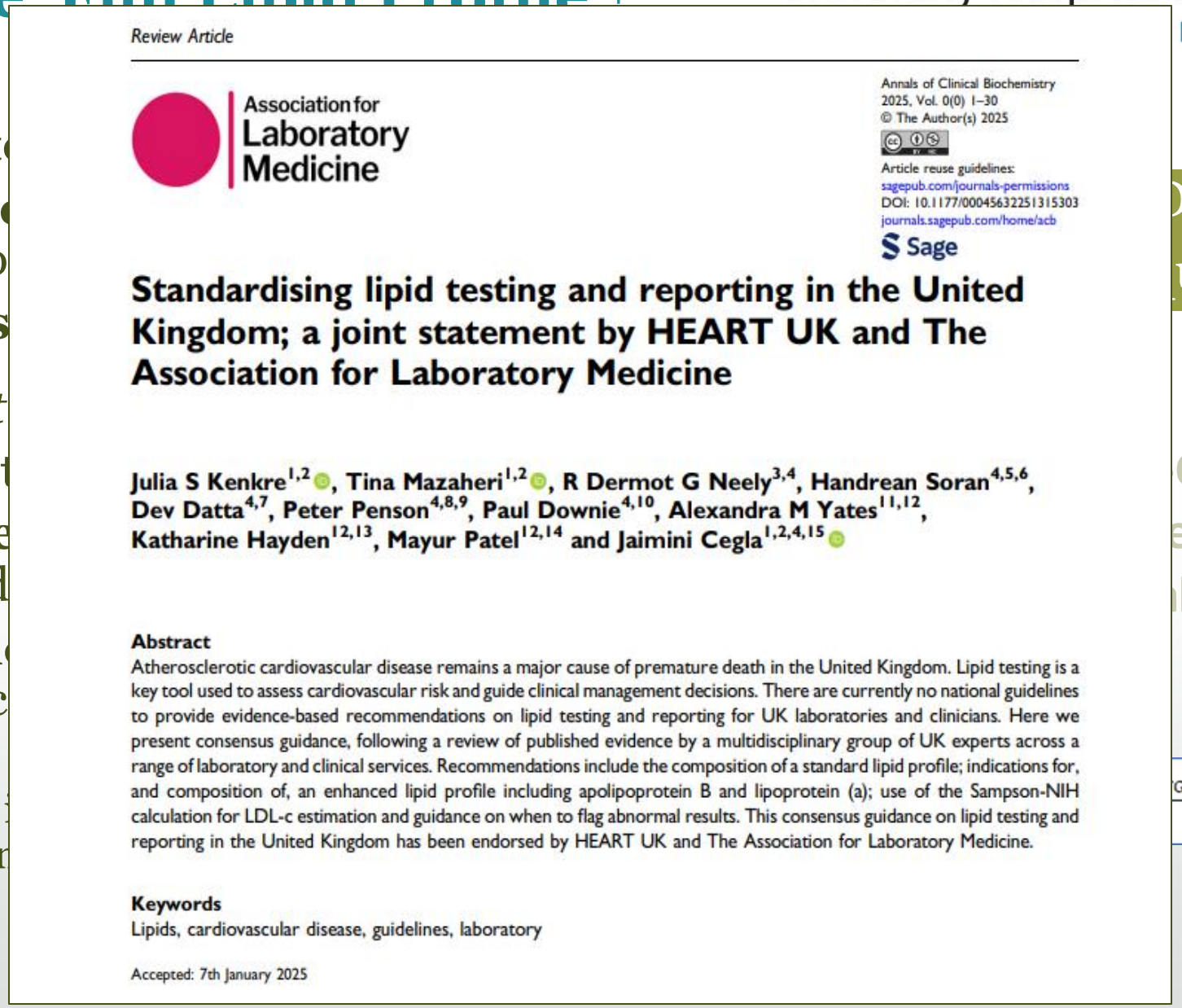
Other paramet

- **Chol:HDL rat**
- **LDL Choleste** particles – 'bad
- **Non-HDL Ch** all 'atherogenic LDL)
  - Used less in guidelin

DL-C using uations

C – (TG /2.2)
esterol – TG/2.2)
ld

$$\left(\frac{TG \times NHDLC}{2140} - \frac{TG^2}{16100}\right) - 9.44$$



Review Article

Association for Laboratory Medicine

Annals of Clinical Biochemistry
2025, Vol. 0(0) 1–30

DOI: 10.1177/00045632251315303
journals.sagepub.com/home/acb
Sage

Standardising lipid testing and reporting in the United Kingdom; a joint statement by HEART UK and The Association for Laboratory Medicine

Julia S Kenkre[1,2], Tina Mazaheri[1,2], R Dermot G Neely[3,4], Handrean Soran[4,5,6], Dev Datta[4,7], Peter Penson[4,8,9], Paul Downie[4,10], Alexandra M Yates[11,12], Katharine Hayden[12,13], Mayur Patel[12,14] and Jaimini Cegla[1,2,4,15]

Abstract

Atherosclerotic cardiovascular disease remains a major cause of premature death in the United Kingdom. Lipid testing is a key tool used to assess cardiovascular risk and guide clinical management decisions. There are currently no national guidelines to provide evidence-based recommendations on lipid testing and reporting for UK laboratories and clinicians. Here we present consensus guidance, following a review of published evidence by a multidisciplinary group of UK experts across a range of laboratory and clinical services. Recommendations include the composition of a standard lipid profile; indications for, and composition of, an enhanced lipid profile including apolipoprotein B and lipoprotein (a); use of the Sampson-NIH calculation for LDL-c estimation and guidance on when to flag abnormal results. This consensus guidance on lipid testing and reporting in the United Kingdom has been endorsed by HEART UK and The Association for Laboratory Medicine.

Keywords

Lipids, cardiovascular disease, guidelines, laboratory

Accepted: 7th January 2025

Importance of Full Lipid Profile

University Hospital Southampton NHS
NHS Foundation Trust

Total Cholesterol 8.5mmol/L

HDL-Cholesterol 1.8mmol/L

Triglycerides 1.1mmol/L

LDL-C 6.2mmol/L

Non-HDL-C 6.7mmol/L

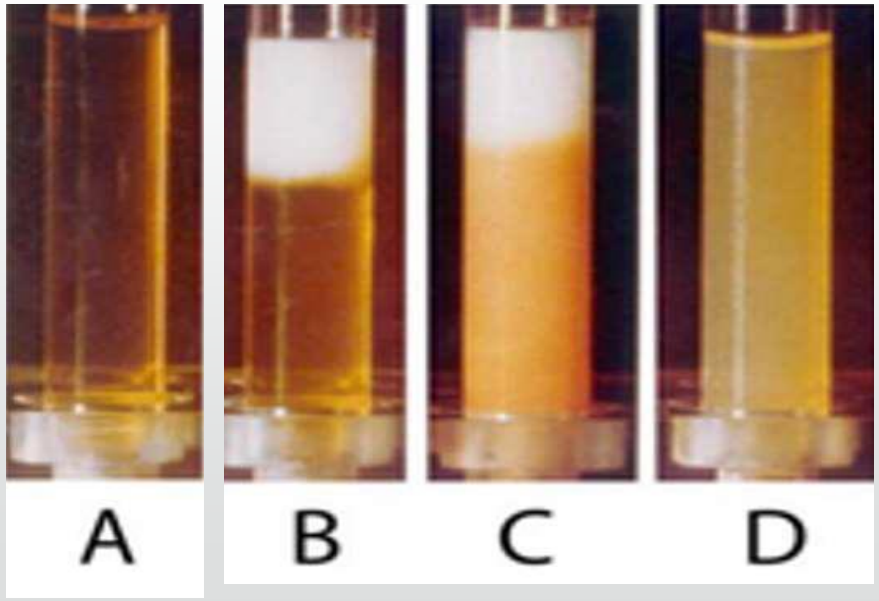
Total Cholesterol 8.5mmol/L

HDL-Cholesterol 1.8mmol/L

Triglycerides 23mmol/L

LDL-C NA

Non-HDL-C 6.7mmol/L

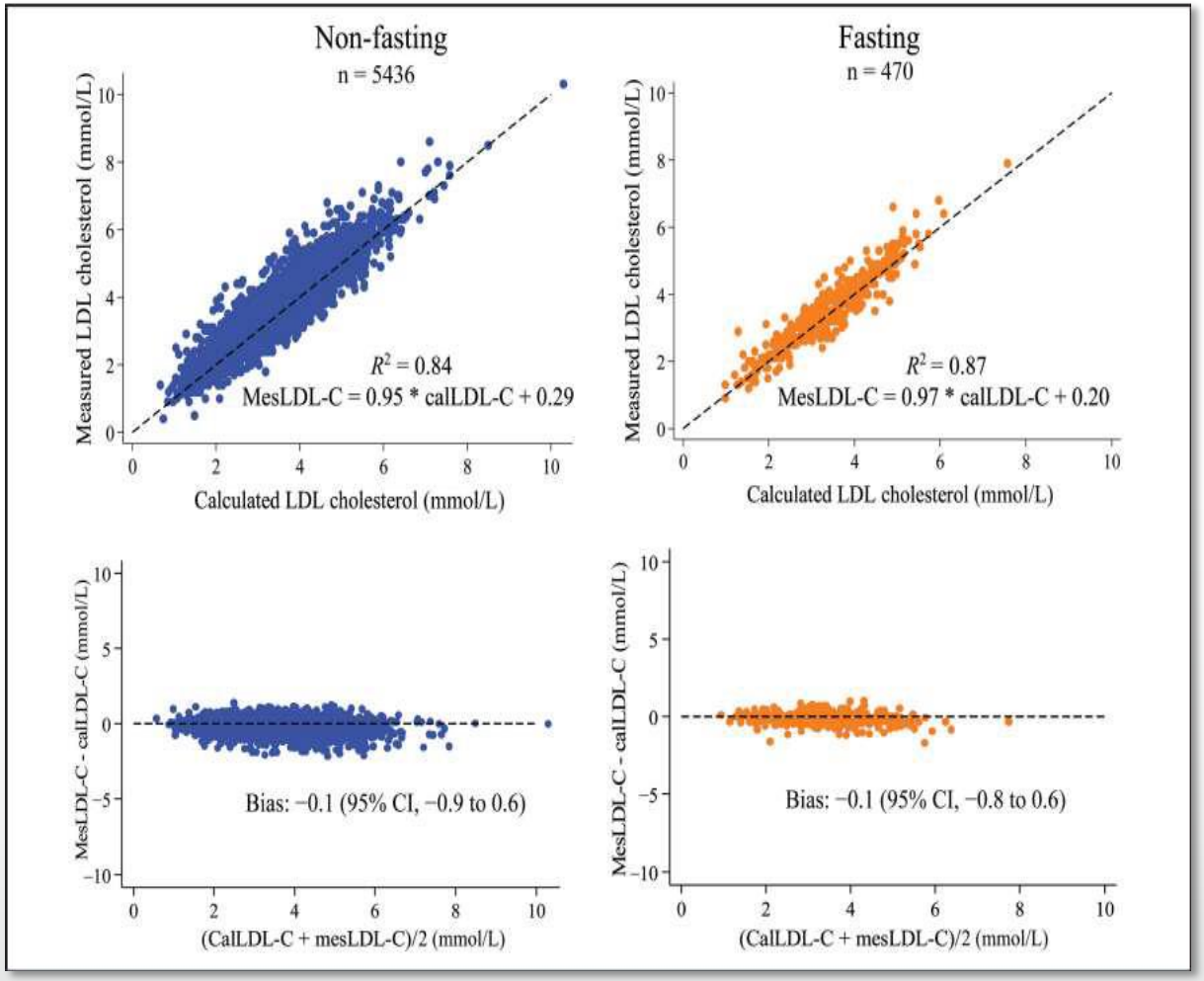


Fasting versus non fasting[1]

University Hospital Southampton NHS
NHS Foundation Trust

Observational data, comparing random vs. non-fasting samples indicate that the maximal mean changes at 1–6 h after habitual meals are not clinically significant:

- +0.3mmol/L for triglycerides
- -0.2 mmol/L for total cholesterol
- -0.2mmol/L for LDL-C



Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine

References: 1. European Heart Journal (2016) 37, 1944–1958 doi:10.1093/eurheartj/ehw152

Lowering LDL-C correlates with reduced CVD risk[1]

1 mmol/L reduction in LDL-C reduces the risk of major vascular events by 22%[1,2]

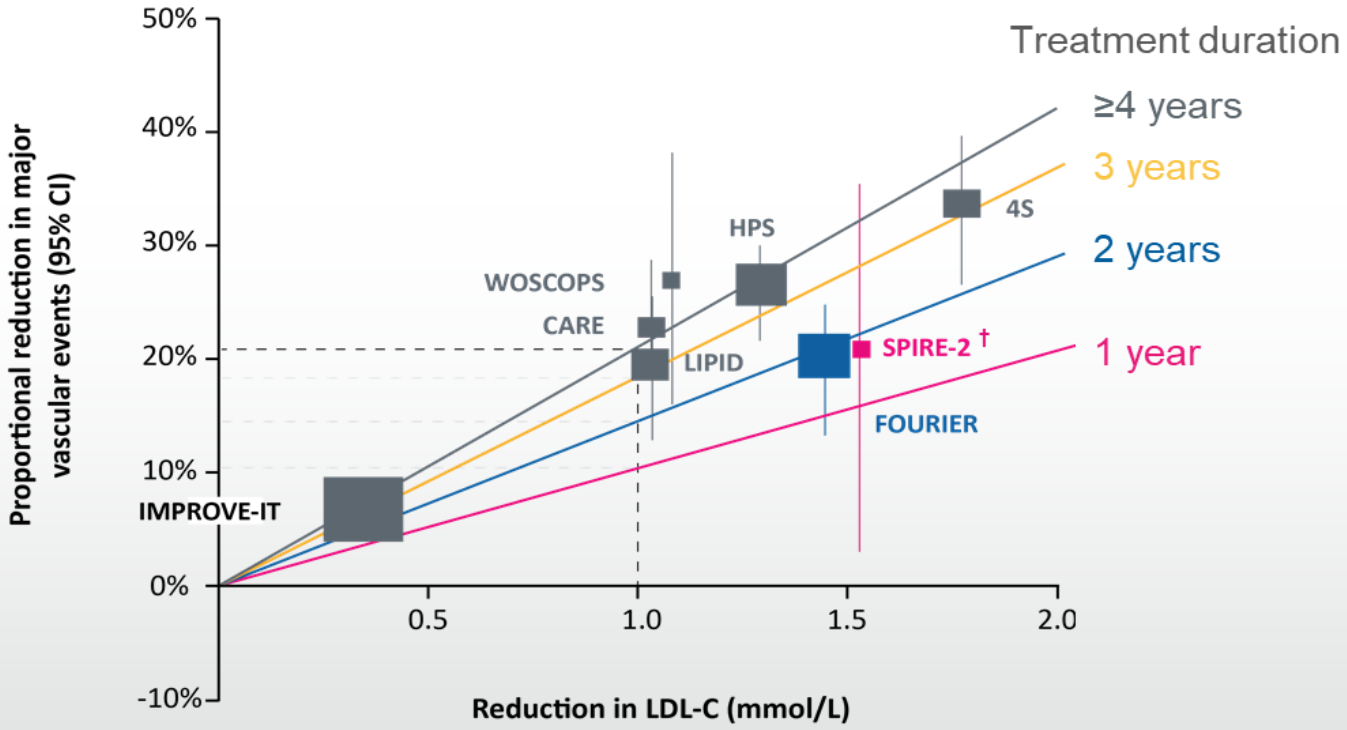


Figure adapted from Ference BA, et al. Eur Heart J 2018.

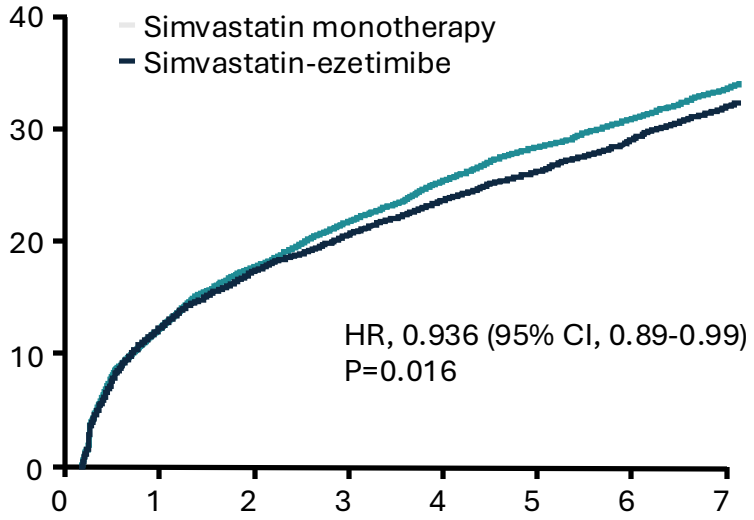
ASCVD: atherosclerotic cardiovascular disease; CI: confidence interval; CVD: cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; LLT: lipid lowering therapy.

References: 1. Ference BA, et al. Eur Heart J 2018;39:2540–2545; 2. Baigent C et al. Lancet 2010;376:1670–1681

Patients on statins continue to experience CV events[1]

A double-blind, randomised study with 18,144 patients who had been hospitalised for ACS within the preceding 10 days and had LDL-C levels of 1.3 to 2.6 mmol/L[1]

IMPROVE-IT: first occurrence of a 3-point MACE composite*



Adapted from Cannon C, *et al. N Engl J Med*. 2015.[1]

LDL-C (mmol/L; all patients)	Baseline	1 Year
Simvastatin		
N	9,009	6,939
Mean	2.4	1.8
Median (25th, 75th)	2.4 (2.0, 2.8)	1.7 (1.4, 2.1)
Ezetimibe/simvastatin		
N	8,990	6,864
Mean	2.4	1.4
Median (25th, 75th)	2.4 (2.0, 2.8)	1.3 (1.0, 1.6)

Outcome	HR (95% CI)	P-value
3 point MACE*	0.936 (0.89–0.99)	0.016
5 point MACE†	0.95 (0.90–1.0)	0.04
CV death	1.00 (0.89–1.13)	NS
All-cause death	0.99 (0.91–1.07)	NS

*Death from CV disease, major coronary event or nonfatal stroke.

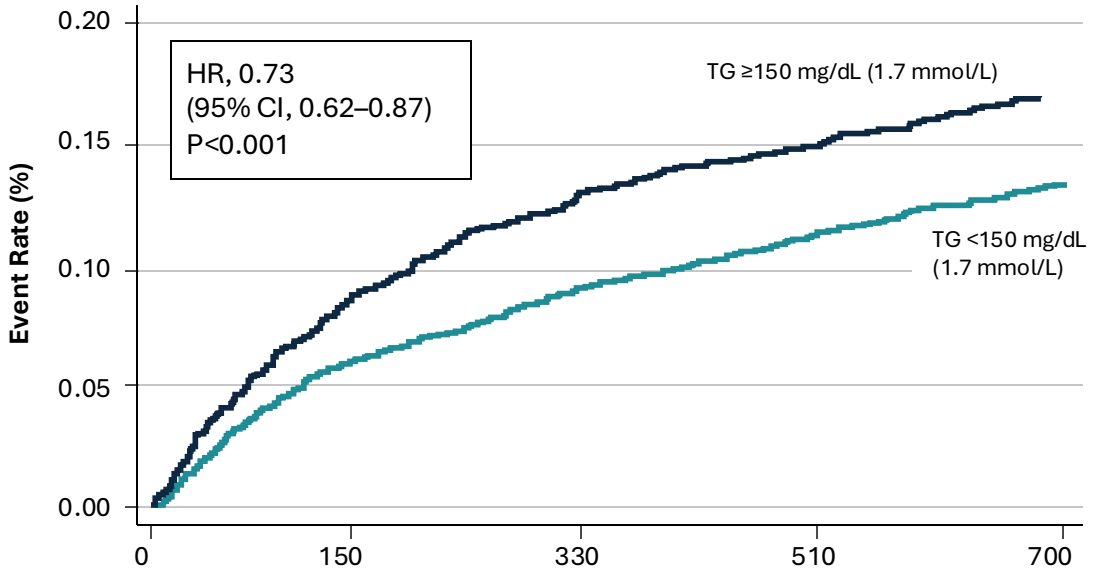
†Death from CV causes, non-fatal MI, hospitalisation for unstable angina, all revascularisation ≥30 days and non-fatal stroke.

ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction.

References: 1. Cannon C, *et al. N Engl J Med*. 2015;372(25):2387–2397.

CV risk is present in patients with elevated TG levels[1]

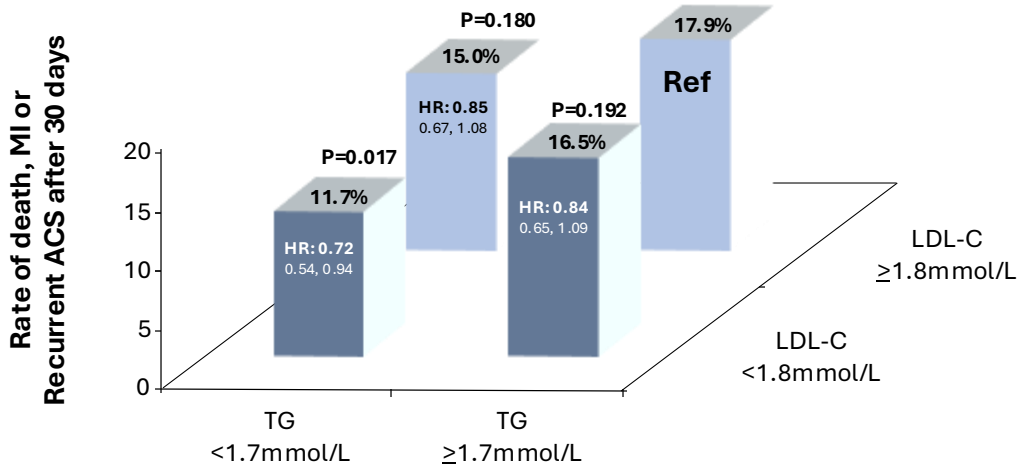
Post-hoc analysis of 3,718 patients from the PROVE-IT TIMI 22 trial who survived event free >30 days



No. at Risk

TG ≥150	1,157	1,066	1,017	659
TG <150	2,242	2,119	2,041	1,278

Adapted from Miller M, *et al. J Am Coll Cardiol.* 2008.[1]



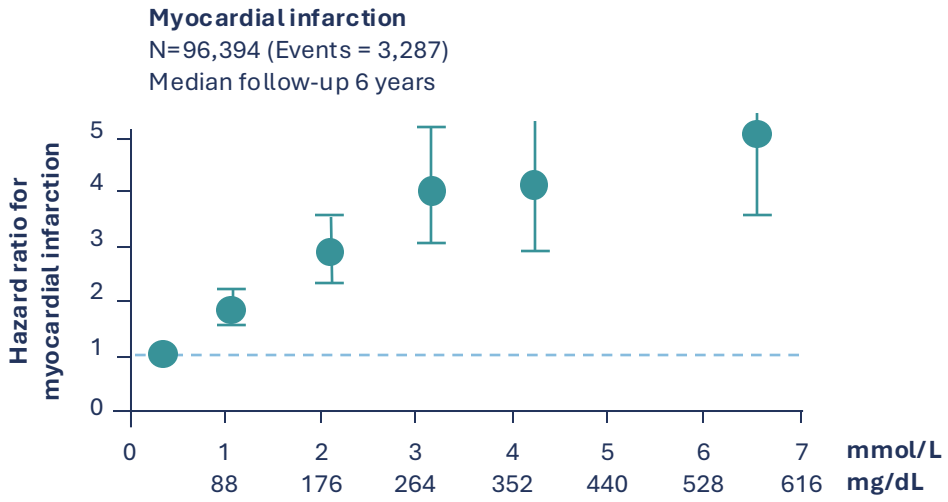
Adapted from Miller M, *et al. J Am Coll Cardiol.* 2008.[1]

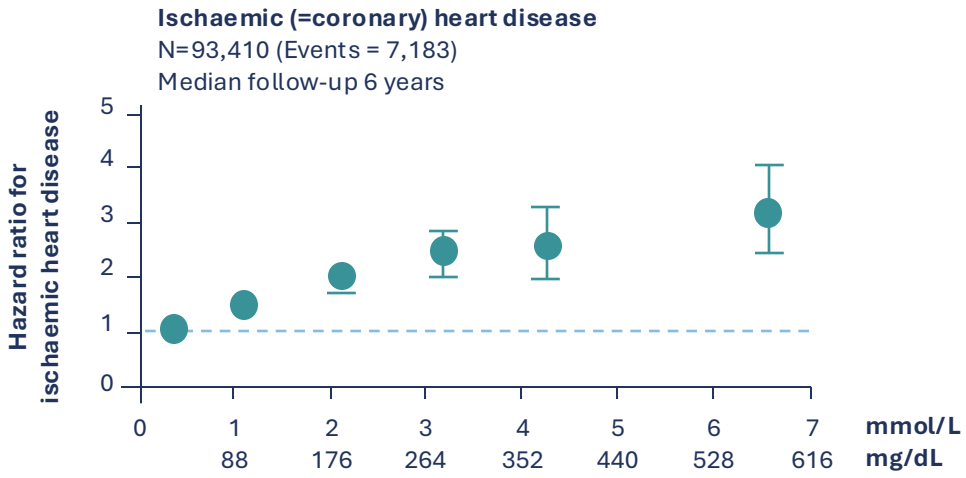
PROVE-IT TIMI 22 trial: 4,162 men and women hospitalised for ACS with total cholesterol 240 mg/dL (6.21 mmol/L), or 200 mg/dL (5.17 mmol/L) if receiving lipid-lowering therapy, were randomly assigned to receive intensive therapy (atorvastatin 80 mg daily) or standard therapy (pravastatin 40 mg daily) for a mean follow-up period of 2 years[1]

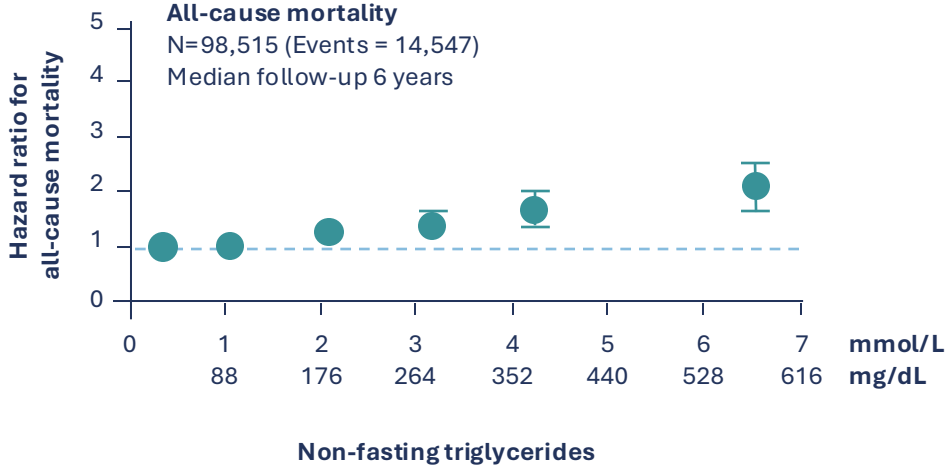
ACS, acute coronary syndrome; CV, cardiovascular; HR, hazard ratio;LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglyceride.

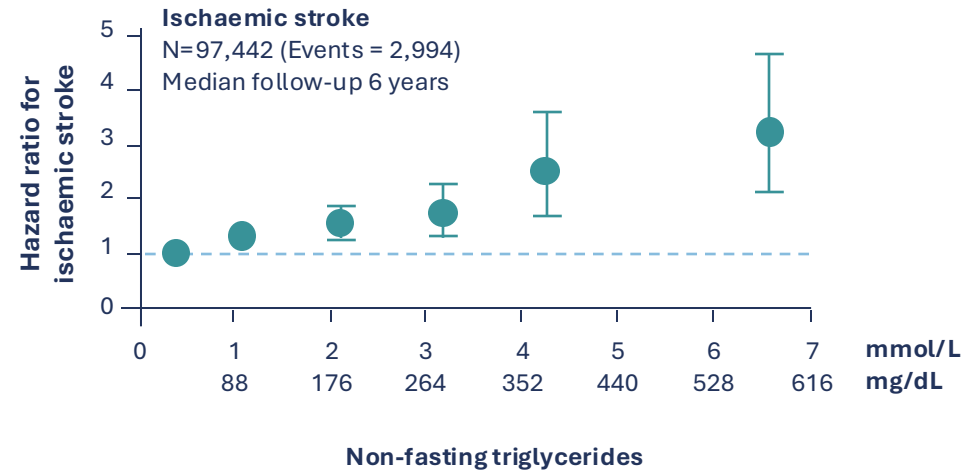
References: 1. Miller M, *et al. J Am Coll Cardiol.* 2008;51:724–730.

Copenhagen City Heart Study: Hypertriglyceridaemia and CVD risk







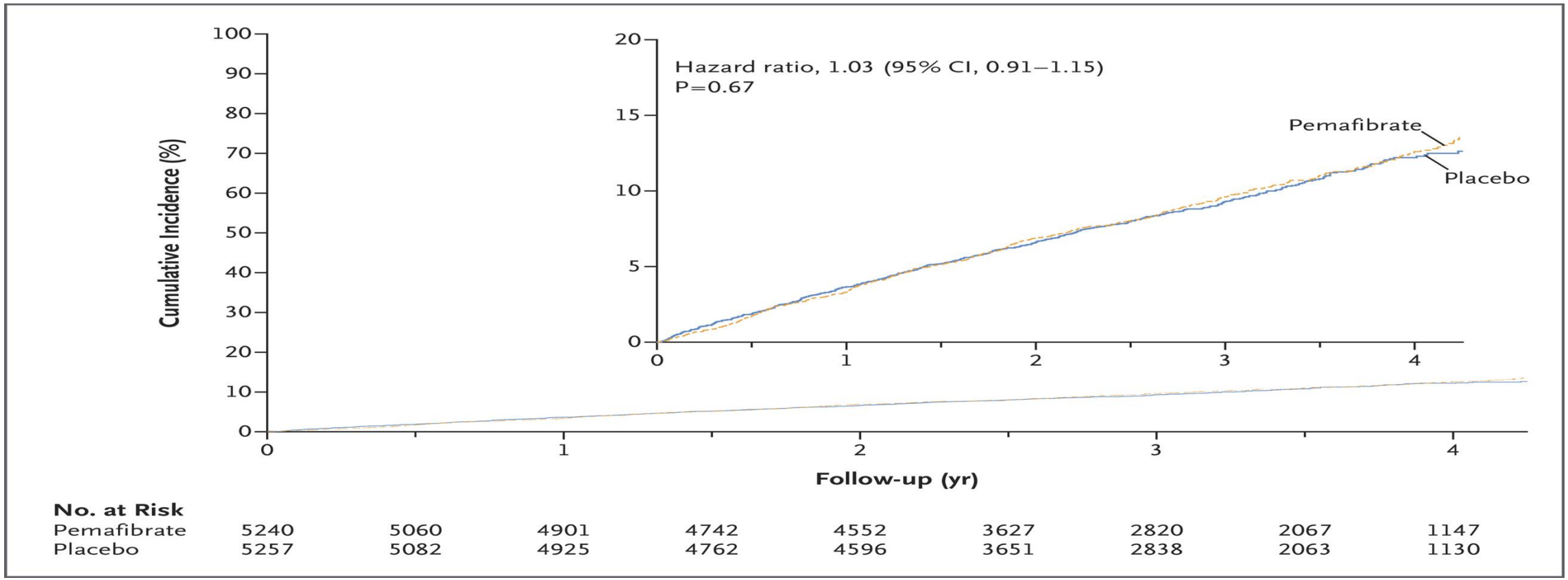


CVD, cardiovascular disease

Adapted from: Nordestgaard BG et a. Lancet 2014; Aug 16;384(9943):626-635;

References: Nordestgaard BG. Circ Res. 2016 Feb 19;118(4):547-63

PROMINENT Study



No. at Risk									
Pemafibrate	5240	5060	4901	4742	4552	3627	2820	2067	1147
Placebo	5257	5082	4925	4762	4596	3651	2838	2063	1130

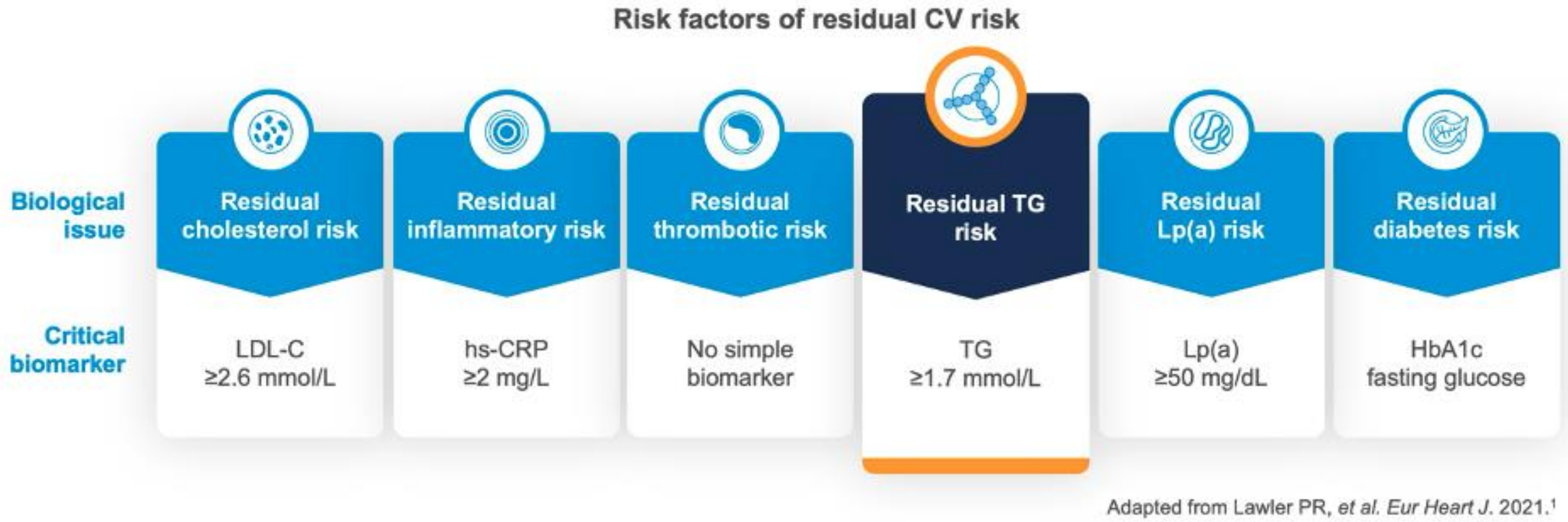
References: N Engl J Med 2022;387:1923-1934

Secondary causes of hypertriglyceridaemia

Causes of Secondary Hypertriglyceridemia		
Lifestyle	**Diseases**	**Medications**
Excess calories	Poorly controlled diabetes	Corticosteroids
Excess dietary fat intake	Hypothyroidism	Oral estrogen
Excess simple sugars	Renal disease	Retinoic acid derivatives
Overweight/Obesity	HIV infection	Beta adrenergic blockers
Alcohol intake	Cushing's syndrome	Thiazide diuretics
Pregnancy	Acromegaly	Protease inhibitors
	Growth hormone deficiency	Bile acid sequestrants
	Lipodystrophy	Anti-psychotic drugs
	Paraproteinemia	Cyclosporine/tacrolimus
	Nephrotic Syndrome	L-asparaginase
	Inflammatory Disorders	Interferon alpha 2b
		Cyclophosphamide

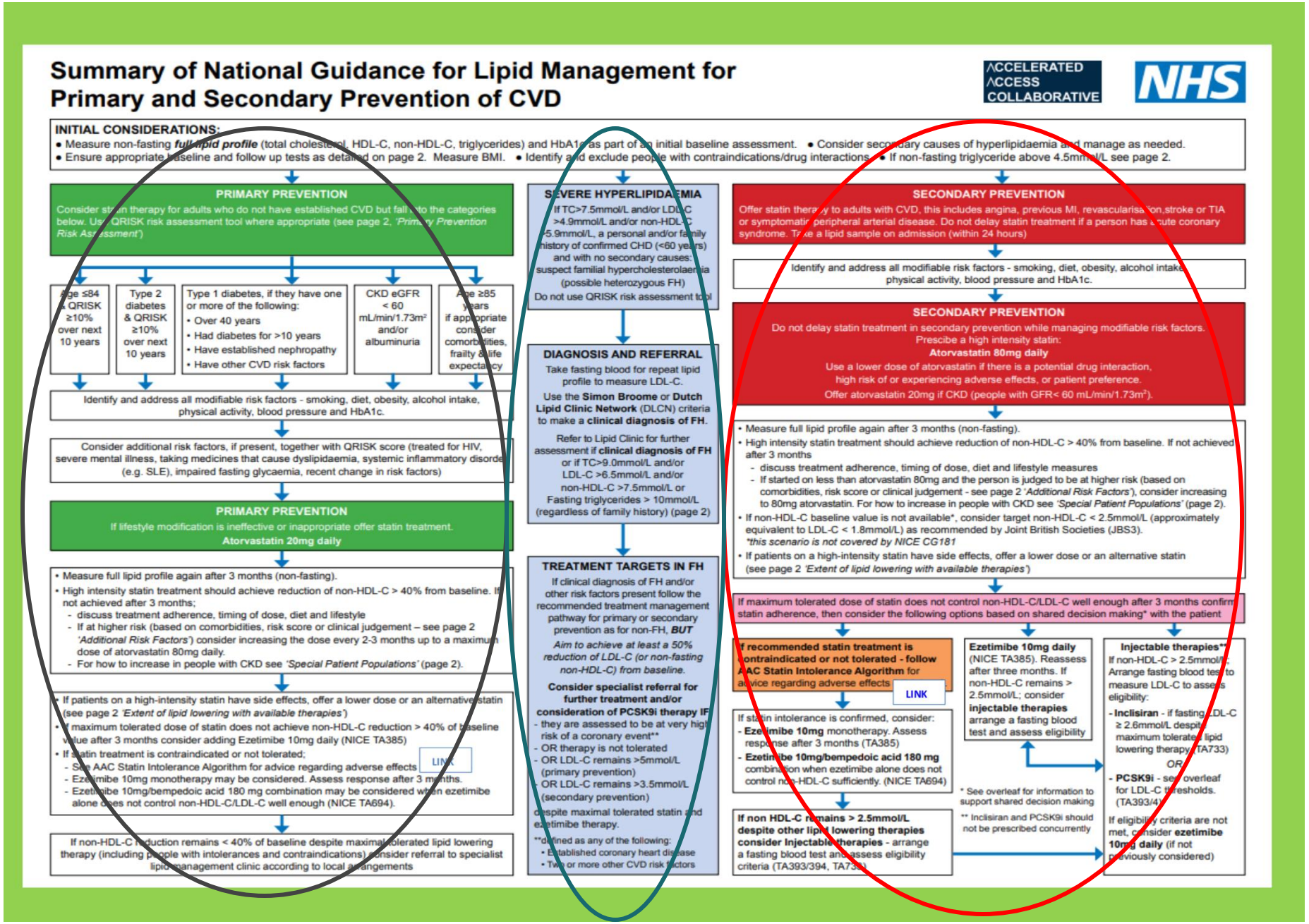
References: Feingold KR. Triglyceride Lowering Drugs. [Updated 2024 Jan 18]. In: Feingold KR, Ahmed SF, Anawalt B, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK425699/

Raised triglyceride levels are a key factor in increasing your patients' CV risk [1-3]



Adapted from Lawler PR, *et al. Eur Heart J.* 2021.[1]

References: 1. Lawler PR, et al. Eur Heart J. 2021;42(1):113–131; 2. Dhindsa DS, et al. Front Cardiovasc Med. 2020;7:88; 3. Miller M, et al. J Am Coll Cardiol. 2008;51:724–730.



Reference: NHS England (2024) Summary of national guidance for lipid management for primary and secondary prevention of cardiovascular disease, NHS Accelerated Access Collaborative. Updated 19 September 2024. Available at: https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/ Accessed: June 2025

2025/2026 QOF INCLUDES TWO CHOLESTEROL INDICATORS[1]

The NHS Long Term Plan calls for **a more proactive, population health management approach to support people to stay healthy and prevent illness.**

1

CHOL003

Percentage of patients on the QOF Coronary Heart Disease (CHD), Peripheral Arterial Disease (PAD), Stroke/Transient Ischaemic Attack (TIA) or Chronic Kidney Disease (CKD) Register **who are currently prescribed a statin, or where a statin is declined or clinically unsuitable, another lipid-lowering therapy[1]**

CHOL003 - 38 points (Increased by 24 points)

2

CHOL004

Percentage of patients on the QOF Coronary Heart Disease (CHD), Peripheral Arterial Disease (PAD), or Stroke/Transient Ischaemic Attack (TIA) Register, **with the most recent cholesterol measurement in the preceding 12 months, showing as ≤2.0 mmol/L if it was an LDL (Low-density Lipoprotein) cholesterol reading or ≤2.6 mmol/L if it was a non-HDL (High-density Lipoprotein) cholesterol reading. For multiple readings on the latest date the LDL reading takes priority.[1]**

CHOL004 - 44 points (increased by 28 points)

The 2025/2026 QOF reflects a continued commitment to the importance of cholesterol management in patients who have had a cardiovascular event, with a target of 2.0 LDL-C mmol/L or lower in those who have a recording of LDL-C in the preceding 12 months[1]

CHD – Coronary Heart Disease; CKD – Chronic Kidney Disease; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; PAD – Peripheral Arterial Disease; QOF – Quality and Outcomes Framework; TIA – transient ischaemic attack

Reference: 1. National Health Service England. https://www.england.nhs.uk/wp-content/uploads/2025/03/quality-outcomes-framework-guidance-for-2025-26.pdf [Accessed April 2025].

NATIONAL GUIDANCE FOR LIPID MANAGEMENT FOR PRIMARY AND SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE[1] (CONTINUED)

Extent of Lipid lowering with available therapies					
Approximate reduction in LDL-C					
Statin dose mg/day	5	10	20	**40**	**80**
Fluvastatin			21%	27%	33%
Pravastatin		20%	24%	29%	
Simvastatin		27%	32%	37%	42%
Atorvastatin		37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	
Atorvastatin + Ezetimibe 10 mg		52%	54%	57%	61%

Adapted from NHS England 2024.[1]

- **Low intensity statins** will produce an LDL-C reduction of 20-30%
- **Medum intensity statins** will produce an LDL-C reduction of 31-40%
- **High intensity statins** will produce an LDL-C reduction above 40%
- Simvastatin 80 mg is not recommended due to risk of muscle toxicity

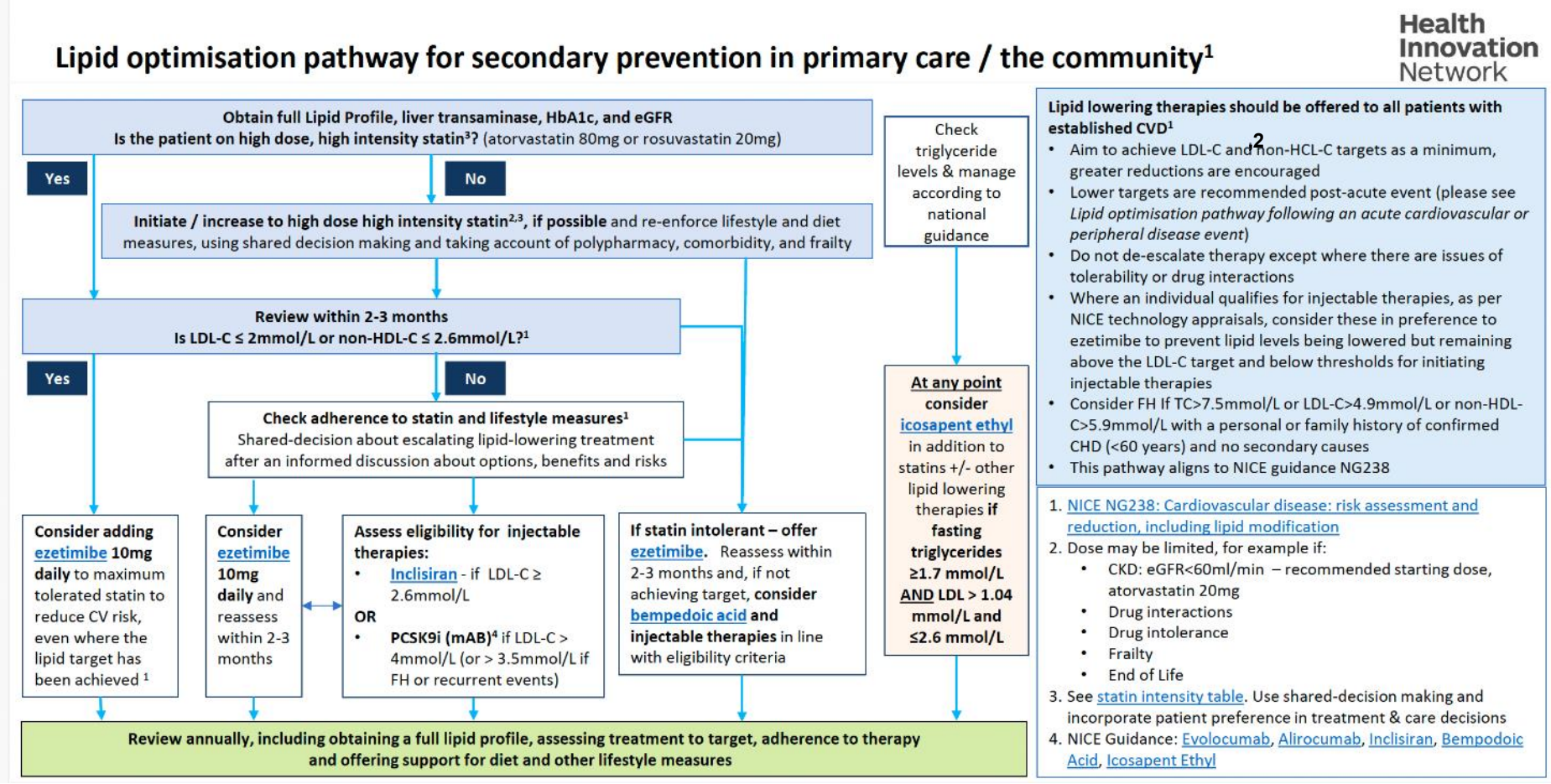
- **Rosuvastatin** may be used as an alternative to atorvastatin if compatible with other drug therapy. Some people may need a lower starting dose (see BNF)
- Low/medium intensity statins should only be used if intolerance or drug interactions
- **Ezetimibe** when combined with any statin is likely to give greater reduction in non-HDL-C or LDL-C than doubling the dose of the statin
- **PCSK9i** (NICE TA393, TA394) alone or in combination with statins or ezetimibe produce an additional LDL-C reduction of approximately 50% (range: 25–70%)
- **Bempedoic acid** when combined with ezetimibe (TA694) produces an additional LDL-C reduction of approximately 28% (range: 22–33%)
- **LEQVIO®** (TA733) alone or in combination with statins or ezetimibe produces an additional LDL-C reduction of approximately 50% (range: 48–52%) but no clinical outcome evidence is currently available

The figure has been reproduced in full, with an excerpt relevant to the topic highlighted. **There are no head-to-head studies between these products, therefore, no direct comparisons can be made.** ***Novartis had no involvement in the development of this figure.*** **Please consult the Summary of Product Characteristics and NICE TA733 before prescribing LEQVIO®.**[2,3]
LEQVIO® is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if: there is a history of any of the following cardiovascular events: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke or peripheral arterial disease, and LDL-C concentrations are persistently 2.6 mmol/l or more, despite maximum tolerated lipid-lowering therapy, that is: maximum tolerated statins with or without other lipid-lowering therapies or, other lipid-lowering therapies when statins are not tolerated or are contraindicated, and the company provides LEQVIO® according to the commercial arrangement.[3]

BNF – British National Formulary; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PCSK9i – proprotein convertase subtilisin/kexin type 9 inhibitor

References: 1. National Health Service England. https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/lipid-management-pathway-version-7-March-2024.pdf [Accessed April 2025]. **2.** LEQVIO® (inclisiran) Summary of Product Characteristics. **3.** National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ta733 [Accessed April 2025].

LIPID OPTIMISATION PATHWAY FOR SECONDARY PREVENTION IN PRIMARY CARE[1,2]



Guidance provided by NHS on the "Lipid optimisation pathway: secondary prevention in primary care and the community":

Where an individual qualifies for injectable therapies, as per NICE technology appraisals, consider these in preference to ezetimibe to prevent lipid levels being lowered but remaining above the LDL-C target and below thresholds for initiating injectable therapies.[2]

Adapted from Health Innovation Network 2024 and NHS England 2024.[1,2]
Reproduced from Health Innovation Network 2024.[1] **Novartis had no involvement in the development of this pathway. LEQVIO® may not be indicated and/or recommended for all patients in this pathway. Please consult the Summary of Product Characteristics and the NICE TAG before prescribing.**
NHS – National Health Service; NICE – National Institute for Health and Care Excellence

Reference: 1. Health Innovation Network. https://thehealthinnovationnetwork.co.uk/wp-content/uploads/2024/06/Lipid-optimisation-pathway-for-secondary-prevention-in-primary-care-and-the-community.pdf [Accessed April 2025]. **2.** National Health Service England. https://www.england.nhs.uk/long-read/lipid-optimisation-pathway-secondary-prevention-in-primary-care-and-the-community [Accessed April 2025].

The Paradox of Choice

University Hospital Southampton NHS
NHS Foundation Trust

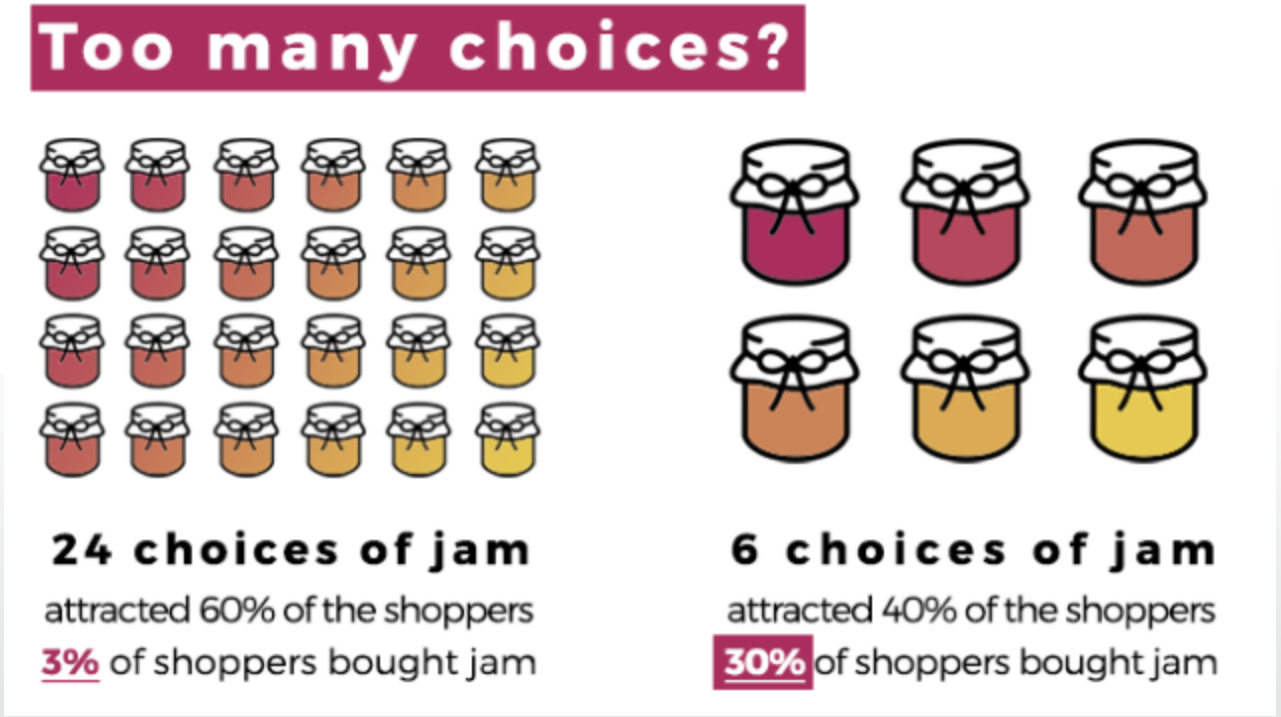
PERSONALITY PROCESSES AND INDIVIDUAL DIFFERENCES

When Choice is Demotivating: Can One Desire Too Much of a Good Thing?

Sheena S. Iyengar
Columbia University

Mark R. Lepper
Stanford University

Current psychological theory and research affirm the positive affective and motivational consequences of having personal choice. These findings have led to the popular notion that the more choice, the better—that the human ability to manage, and the human desire for, choice is unlimited. Findings from 3 experimental studies starkly challenge this implicit assumption that having more choices is necessarily more intrinsically motivating than having fewer. These experiments, which were conducted in both field and laboratory settings, show that people are more likely to purchase gourmet jams or chocolates or to undertake optional class essay assignments when offered a limited array of 6 choices rather than a more extensive array of 24 or 30 choices. Moreover, participants actually reported greater subsequent satisfaction with their selections and wrote better essays when their original set of options had been limited. Implications for future research are discussed.



References: Iyengar SS, Lepper MR. When choice is demotivating: Can one desire too much of a good thing? *J Pers Soc Psychol*. 2000;79(6):995–1006. doi:10.1037/0022-3514.79.6.995

Management of lipids in secondary prevention[1]

SECONDARY PREVENTION

Offer statin therapy to adults with ASCVD, including coronary artery disease, cerebrovascular disease and peripheral vascular disease

Ensure a full lipid profile and lipoprotein (a) is taken on admission (within 24 hours and non-fasting)

Please note: Although AAC national guidelines give a treatment target of LDL-C ≤2.0 mmol/L, local lipid specialists within BNSSG recommend a target of LDL-C ≤1.8 mmol/L (or ≤1.4 mmol/L in high-risk individuals including recurrent disease, elevated Lp(a) ≤90 nmol/L, familial hypercholesterolaemia or diabetes mellitus)

STATIN INTOLERANCE

Defined as inability to take recommended dose of high intensity statin, typically Atorvastatin 40-80 mg once a day

See National Statin Intolerance Management Pathway for further guidance

Prescribe a high intensity statin, typically:
Atorvastatin 80 mg daily

Use a lower dose if there is a potential drug interaction or high risk of experiencing adverse effects

Statin dose optimised/on maximally tolerated dose of statin

LDL-C ≥3.5 mmol/L

Offer Inclisiran/PCSK9 inhibitor

PCSK9 inhibitor is available on referral to the lipid clinic, dependent on patient choice and degree of LDL-C elevation

LDL-C ≥2.6 mmol/L

Offer Inclisiran

Initiated in primary care ideally. Ensure clearly indicated on discharge summary/clinic letter if suggested in secondary care

LDL-C 1.8–2.5 mmol/L

Offer Ezetimibe (plus Bempedoic acid if patient if not on a high intensity dose of statin)

LDL-C <1.8 mmol/L

Consider adding Ezetimibe

LDL-C ≥1.8 mmol/L

Offer Ezetimibe (plus Bempedoic acid if patient if not on a high intensity dose of statin)

Triglycerides ≥1.7 mmol/L and LDL-C 2.6 mmol/L

Offer Icosapent ethyl▼ 1.996 g twice a day

References: 1. Bristol, North Somerset & South Gloucestershire Integrated Care Board (BNSSG ICB), 2025. *Hyperlipidaemia*. Clinical biochemistry guidance. Remedy. Published (content checked 8 August 2024; next review by 2 June 2026). Available at: https://remedy.bnssg.icb.nhs.uk/adults/biochemistry/hyperlipidaemia/ Accessed: June 2025.

MANAGEMENT OF ADDITIONAL CVD RISK FACTORS

Smoking	Refer to https://remedy.bnssg.icb.nhs.uk/adults/self-care/smoking-cessation/ for support to help patients quit smoking
Obesity	Refer patient meeting eligibility criteria to the Bristol Weight Management and Bariatric Service for further support
Blood pressure	Refer to https://remedy.bnssg.icb.nhs.uk/adults/cardiology/hypertension/ for further guidance to meet patients' blood pressure targets
Diabetes mellitus	In patients managed for T2DM, consider SGLT2 inhibitors or GLP-1 analogues if appropriate for their CVD risk reduction properties

NICE TA [805] – (2022)

University Hospital Southampton NHS
NHS Foundation Trust

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides

1 Recommendations

1.1 Icosapent ethyl is recommended as an option for reducing the risk of cardiovascular events in adults. It is recommended if they have a high risk of cardiovascular events and raised fasting triglycerides (1.7 mmol/litre or above) and are taking statins, but only if they have:

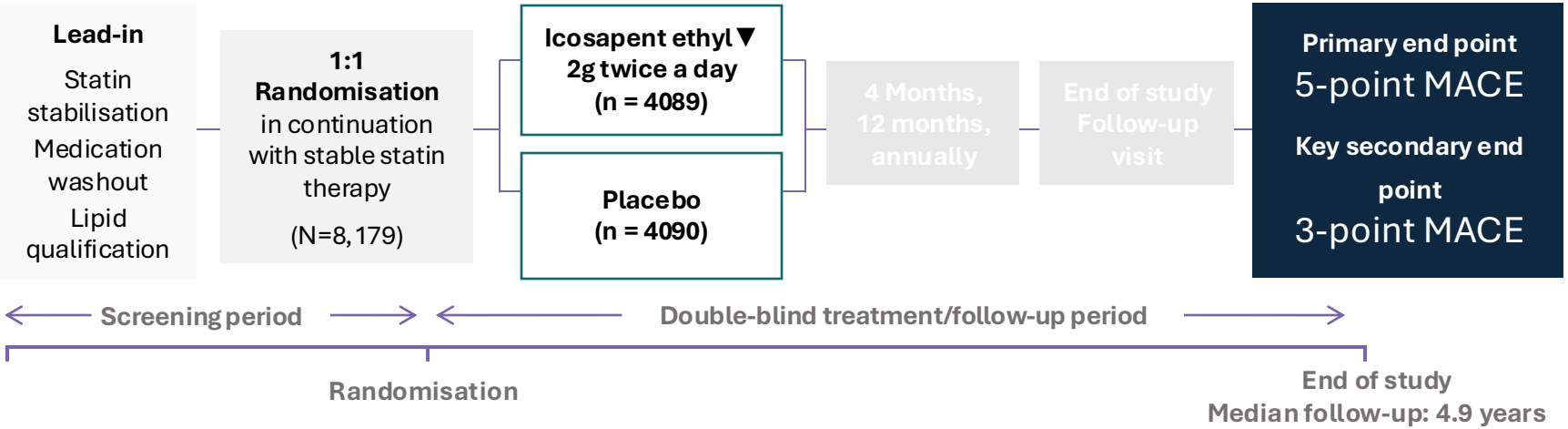
- established cardiovascular disease (secondary prevention), defined as a history of any of the following:
  - acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
  - coronary or other arterial revascularisation procedures
  - coronary heart disease
  - ischaemic stroke
  - peripheral arterial disease, and
- low-density lipoprotein cholesterol (LDL-C) levels above 1.04 mmol/litre and below or equal to 2.60 mmol/litre.

https://www.nice.org.uk/guidance/ta805

REDUCE-IT: Trial design

Key inclusion criteria

- Statin-treated men and women aged ≥45 years
- Established CVD (~70% of patients) or DM + ≥1 risk factor
- TG ≥1.69 and <5.63 mmol/L (135-500 mg/dL)*
- LDL-C >1.06 and ≤2.59 mmol/L (40-100 mg/dL)



Adapted from Bhatt DL, *et al*. *Clin Cardiol*. 2017 and Bhatt DL, *et al*. *N Engl J Med*. 2019.[1,2]

5-point MACE
was defined as a composite of: nonfatal MI, nonfatal stroke, CV death, hospitalisation for unstable angina, or coronary revascularisation.[1,2]

3-point MACE
was defined as a composite of: nonfatal MI, nonfatal stroke, and CV death.[1,2]

REDUCE-IT ClinicalTrials.gov number, NCT01492361.
*Due to the variability of TG, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying TGs ≥1.69 mmol/L. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 1.69 mmol/L to 2.26 mmol/L, with no variability allowance.

CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction; RCT, randomised controlled trial; TG, triglyceride.

References: 1. Bhatt DL, *et al*. *Clin Cardiol*. 2017;40(3):138–148; 2. Bhatt DL, *et al*. *N Engl J Med*. 2019;380(1):11–22.

REDUCE-IT: Baseline characteristics[1]

Characteristics[1]	**Icosapent ethyl▼** (n=4,089)	**Placebo** (n=4,090)
T2DM, n (%)	2,367 (57.9%)	2,363 (57.8%)
TG (mmol/L), Median (Q1–Q3)/(mg/dL), Median (Q1-Q3)	2.5 (2.0–3.1)/216.5 (176.5-272)	2.4 (2.0–3.1)/216.0 (175.5-274)
HDL-C (mmol/L), Median (Q1–Q3)/Median (Q1-Q3)	1.0 (0.9–1.2)/40.0 (34.5-46.0)	1.0 (0.9–1.2)/40.0 (35.0-46.0)
LDL-C (mmol/L), Median (Q1–Q3)/Median (Q1-Q3)	1.9 (1.6–2.3)/74.0 (61.5-88.0)	2.0 (1.6–2.3)/76.0 (63.0-89.0)
TG Category, n (%)		
<1.7 mmol/L (150 mg/dL)	412 (10.1%)	429 (10.5%)
1.7–<2.3 mmol/L (150-200 mg/dL)	1,193 (29.2%)	1,191 (29.1%)
≥2.3 mmol/L (>200 mg/dL)	2,481 (60.7%)	2,469 (60.4%)
hsCRP (mg/L)*	2.2	2.1

Adapted from Bhatt DL, *et al. N Engl J Med.* 2019.[1]

*Median observed value.
HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus.

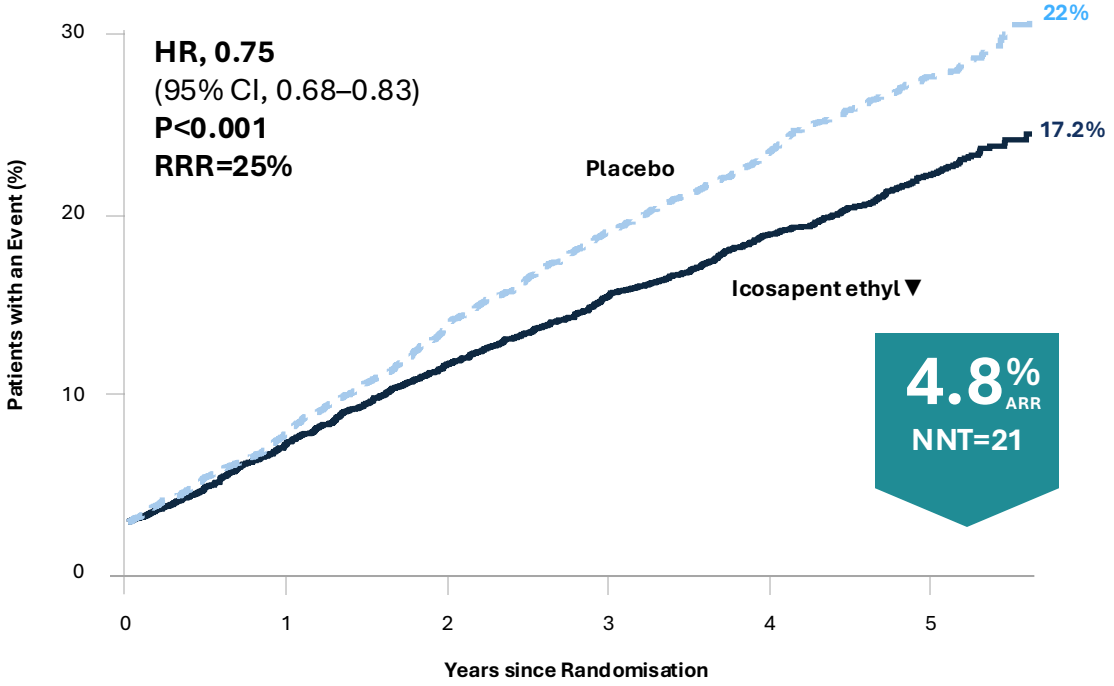
References: 1. Bhatt DL, *et al. N Engl J Med.* 2019;380(1):11–22 and supplementary appendix.

Statistically significant relative reductions in the risk of 5-point and 3-point MACE vs placebo[1]

All patients were on background statin therapy1

Primary composite endpoint

5-point MACE: CV death, MI, stroke, coronary revascularisation, unstable angina

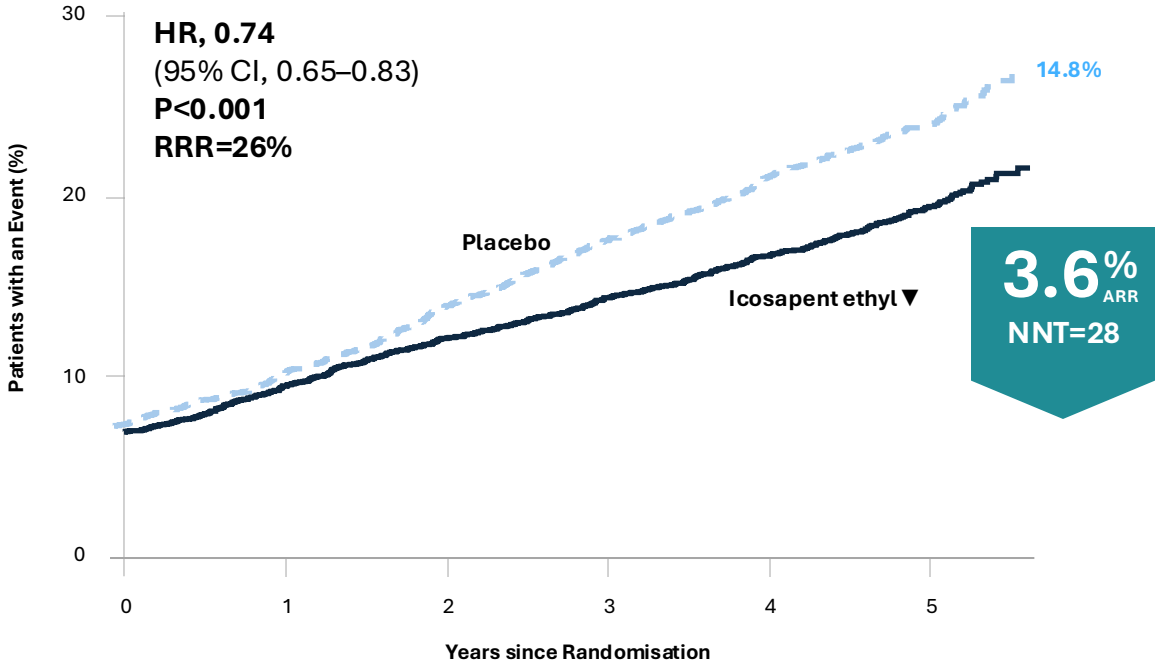


No. at Risk						
Placebo	4,090	3,743	3,327	2,807	2,347	1,358
Icosapent ethyl▼	4,089	3,787	3,431	2,951	2,503	1,430

Adapted from Bhatt DL, *et al. N Engl J Med.* 2019.[1]

Key secondary composite endpoint

3-point MACE: CV death, MI, stroke



No. at Risk						
Placebo	4,090	3,837	3,500	3,002	2,542	1,487
Icosapent ethyl▼	4,089	3,861	3,565	3,115	2,681	1,562

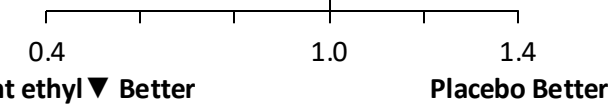
Adapted from Bhatt DL, *et al. N Engl J Med.* 2019.[1]

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction.

References: 1. Bhatt DL, *et al. N Engl J Med.* 2019;380(1):11–22.

Statistically significant reductions in the rates of all hierarchically tested endpoints up to death from any cause vs placebo[1]

Endpoint	HR (95% CI)	Icosapent ethyl▼ n/N (%)	Placebo n/N (%)	HR (95% CI)	RRR	ARR	P-value
Primary Composite (ITT)		705/4,089 (17.2%)	901/4,090 (22.0%)	0.75 (0.68–0.83)	25%▼	4.8%	<0.001
Key Secondary Composite (ITT)		459/4,089 (11.2%)	606/4,090 (14.8%)	0.74 (0.65–0.83)	26%▼	3.6%	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction		392/4,089 (9.6%)	507/4,090 (12.4%)	0.75 (0.66–0.86)	25%▼	2.8%	<0.001
Fatal or Nonfatal Myocardial Infarction		250/4,089 (5.3%)	355/4,090 (8.7%)	0.69 (0.58–0.81)	31%▼	2.6%	<0.001
Urgent or Emergent Revascularisation		216/4,089 (5.3%)	321/4,090 (7.8%)	0.65 (0.55–0.78)	35%▼	2.5%	<0.001
Cardiovascular Death		174/4,089 (4.3%)	213/4,090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.9%	0.03
Hospitalisation for Unstable Angina		108/4,089 (2.6%)	157/4,090 (3.8%)	0.68 (0.53–0.87)	32%▼	1.2%	0.002
Fatal or Nonfatal Stroke		98/4,089 (2.4%)	134/4,090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.9%	<0.001
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke		549/4,089 (13.4%)	690/4,090 (16.9%)	0.77 (0.69–0.86)	23%▼	3.5%	<0.001
Total Mortality		274/4,089 (6.7%)	310/4,090 (7.6%)	0.87 (0.74–1.02)	NS	NS	NS

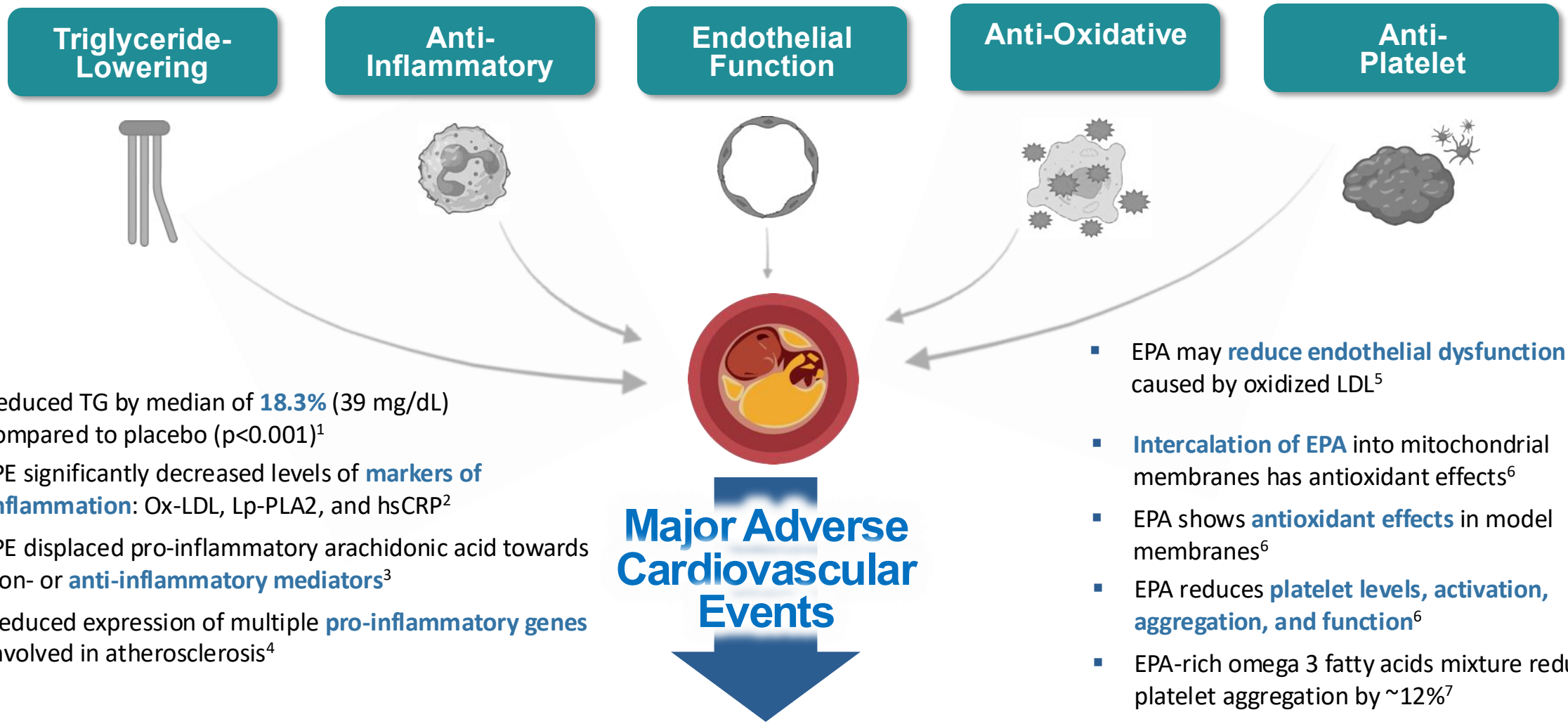


Adapted from Bhatt DL, *et al. N Engl J Med.* 2019.[1]

ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; RRR, relative risk reduction.

References: 1. Bhatt DL, *et al. N Engl J Med.* 2019;380(1):11–22.

IPE▼ reduces risk of MACE most likely by multiple mechanisms



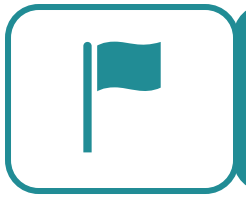
- Reduced TG by median of **18.3%** (39 mg/dL) compared to placebo (p<0.001)[1]
- IPE significantly decreased levels of **markers of inflammation**: Ox-LDL, Lp-PLA2, and hsCRP[2]
- IPE displaced pro-inflammatory arachidonic acid towards non- or **anti-inflammatory mediators**[3]
- Reduced expression of multiple **pro-inflammatory genes** involved in atherosclerosis[4]

- EPA may **reduce endothelial dysfunction** caused by oxidized LDL[5]
- **Intercalation of EPA** into mitochondrial membranes has antioxidant effects[6]
- EPA shows **antioxidant effects** in model membranes[6]
- EPA reduces **platelet levels, activation, aggregation, and function**[6]
- EPA-rich omega 3 fatty acids mixture reduced platelet aggregation by ~12%[7]

MACE=major adverse cardiovascular events
Figure adapted from Bae JH, et al. *Advances in Nutrition.* 2023. https://doi.org/10.1016/j.advnut.2023.03.014

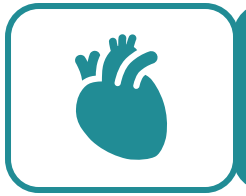
References: 1.Bhatt DL, et al. *New Eng J Med.* 2019;380:11-22; 2. Bays HE, et al. *Am J Cardiovasc Drugs.* 2013:37-46; 3. VAZKEPA SmPC, Annex I, Summary of Product Characteristics; 4. Tsunoda F, et al. *Atherosclerosis.* 2015;241:400-408; 5. Mason RP, et al. *Biomed Pharmacother.* 2018;103:1231-1237; 6. Mason RP, et al. *Arterioscler Thromb Vasc Biol.* 2020;40(5):1135-1147; 7. Phang M, et al. *J Nutr.* 2013;143(4):457-46

Our Role



Recognise “red” flags but also we need to be confident with Lipids and CV risk reduction.

Ensure Lifestyle changes discussed, and secondary causes addressed



Consider further treatment for CV risk reduction with LDL targets and (EPA)

Distilling +++information into a clear message

Considering tablet / treatment burden, explaining why take medicines despite feeling no different

QUESTIONS?