Primary Care Cardiovascular Society

Empowering primary care to deliver the best in cardiovascular health

PCCS Triglycerides QI programme

Understanding triglycerides as a cardiovascular risk factor

Professor Raj Thakkar

This programme has been funded by Amarin Corp plc. Amarin were not involved in the development of the programme, content, selection of speakers or their arrangements. All content has been independently developed by the PCCS.

Professor Raj Thakkar disclosures

Primary Care Cardiovascular Society

Empowering primary care to deliver the best in cardiovascular health

The speaker has received honoraria from:

Abbott | Amarin | Amgen | AstraZeneca | Bayer | Boehringer Ingelheim | Daiichi Sankyo | Edwards | Medtronic | Novartis | Omron

The speaker is currently employed by AstraZeneca as:

Head of Medical External Engagement and Innovation

The speaker is currently employed by Healthy.io as:

UK Medical Director

Contents

- What are lipids and triglycerides
- Causes of raised triglycerides
- The role of triglycerides in CVD risk
- Testing for triglycerides: fasting vs. non-fasting levels

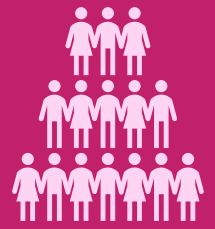
CVD, cardiovascular disease.

CVD is responsible for 26% of all deaths in the UK

Primary Care Cardiovascular Society

Empowering primary care to deliver the best in cardiovascular health

CVD costs the UK economy ~£12 billion annually



>7.6 million people are living with CVD in the UK

480 people die from CVD each day in the UK

CVD causes 1 death every 3 minutes in the UK

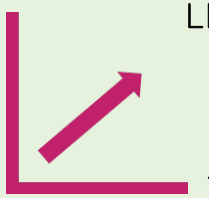
CVD, cardiovascular disease; UK, United Kingdom.

BHF. UK Factsheet January 2025. Available at: https://www.bhf.org.uk/-/media/files/for-professionals/research/heart-statistics/bhf-cvd-statistics-uk-factsheet.pdf. Accessed January 2025.

Atherosclerosis

An accumulation of lipid plaques in artery linings causes atherosclerosis[1]

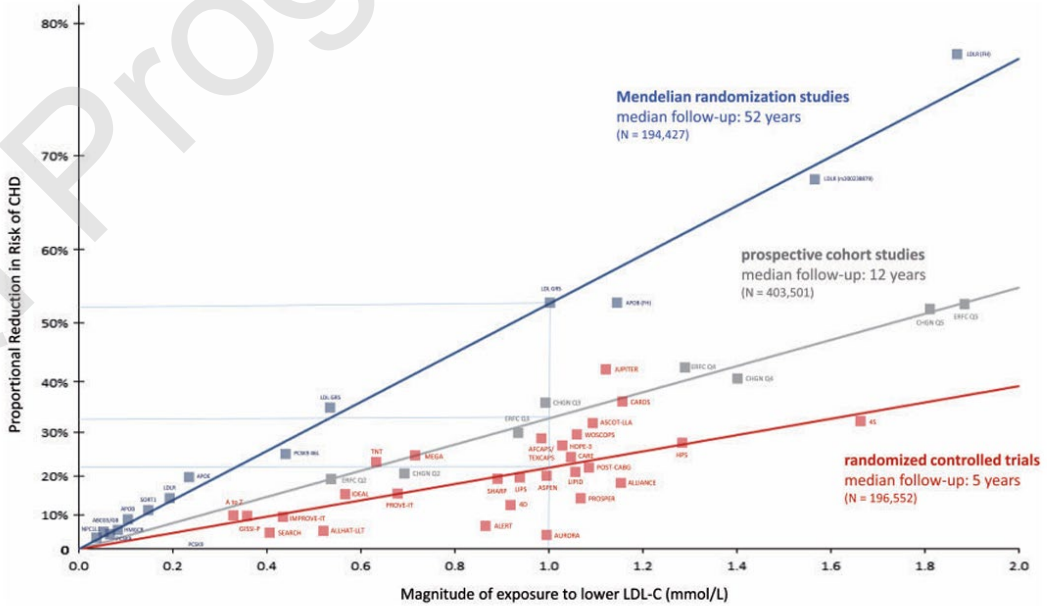
This can be caused by risk factors such as raised systolic BP, diabetes mellitus and smoking, which may all cause ASCVD[1]



LDL-C is an important contributor to atherosclerosis[2] and its concentration is directly proportional to atherosclerosis formation. This is known as the LDL-C hypothesis[3]

"For every 1 mmol/L reduction in LDL-C, there is a reduction in annual CV risk of up to 28%, regardless of the intervention[4]"

Effect of LDL-C on risk of ASCVD by magnitude and duration of exposure[1]



For illustrative purposes only, individual trials should not be directly compared.

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CV, cardiovascular; LDL-C, low density lipoprotein cholesterol.

1. Ference BA, et al. Eur Heart J 2017;38:2459–2472; 2. Qiao YN, et al. Front Physiol 2022;13:931931; 3. Linton MF, et al. The role of lipids and lipoproteins in atherosclerosis. In: Feingold KR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com. Available at: https://www.ncbi.nlm.nih.gov/books/NBK343489/. Accessed November 2024; 4. CTT Collaboration. Lancet 2010;376:1670–1681.

What are lipids?[1,2]

Primary Care Cardiovascular Society

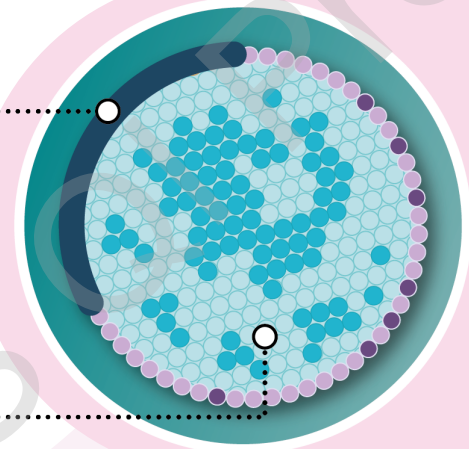
Empowering primary care to deliver the best in cardiovascular health

Lipids are organic compounds which are parcelled into lipoprotein particles, since they cannot freely circulate in the blood.[1,2]

TG rich lipoprotein particles include VLDLs and chylomicrons and are created following absorption, when triglycerides and cholesterol couple with apoproteins, phospholipids, and unesterified cholesterol.[2]

An outer layer of phospholipids, free cholesterol and proteins known as apolipoproteins[2]

An inner core of triglycerides and cholesterol[2]



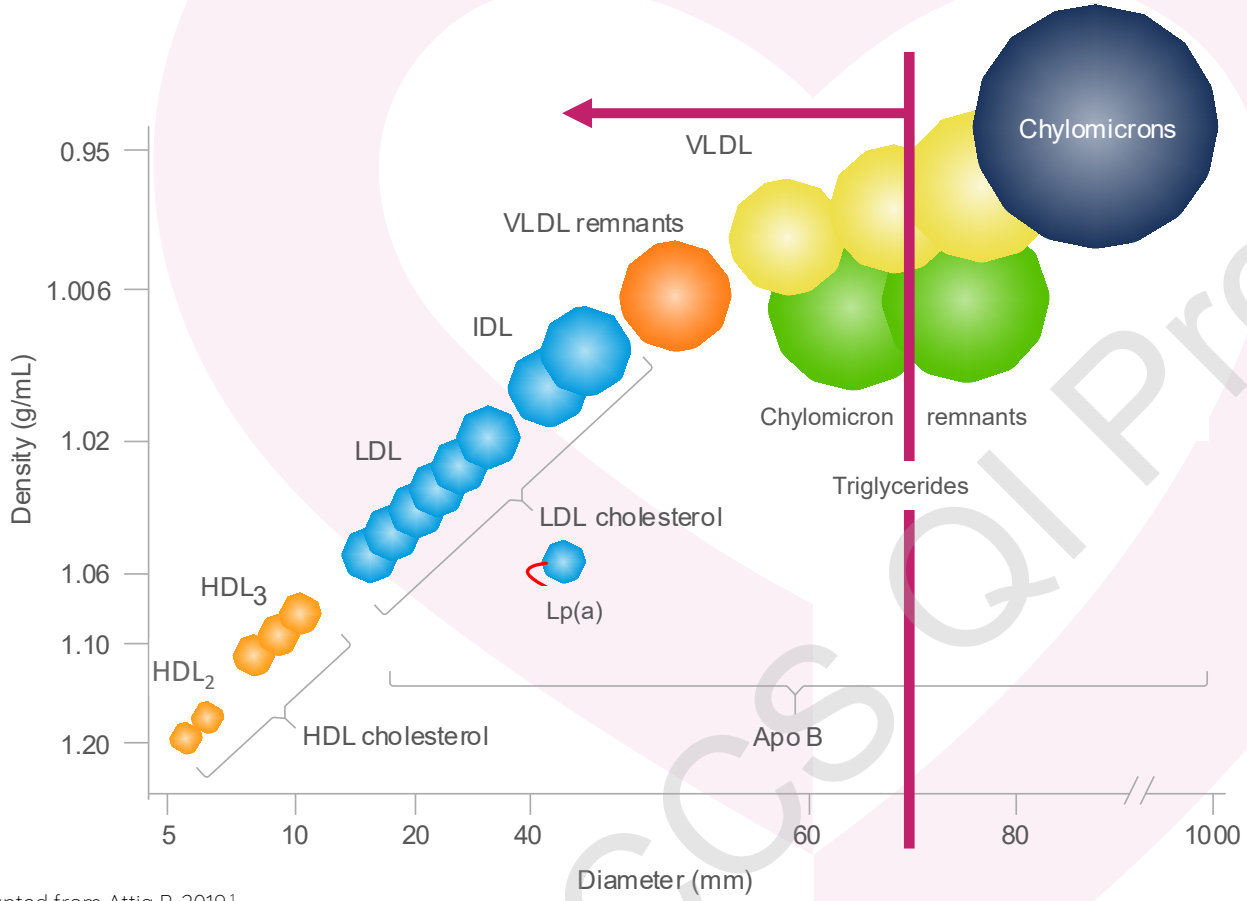
LIPOPROTEINS CONTAIN:

- Triglycerides
- Phospholipid
- Cholesteryl ester
- Free cholesterol
- Apolipoprotein

VLDLs, very low-density lipoproteins.

1. Natesan V and Kim SJ. Biomol Ther (Seoul). 2021;29:596–604; 2. Feingold KR. Introduction to Lipids and Lipoproteins. In: Feingold KR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com. Available at: https://www.ncbi.nlm.nih.gov/books/NBK305896/. Accessed November 2024.

Establishing a full lipid profile is important in ASCVD[1]



Adapted from Attia P, 2019.[1]

Which particles are associated with CVD risk?

1) All particles containing apoB (i.e. not HDL)[1]
2) Any particle with a diameter <70 nm can enter the endothelial wall[2]

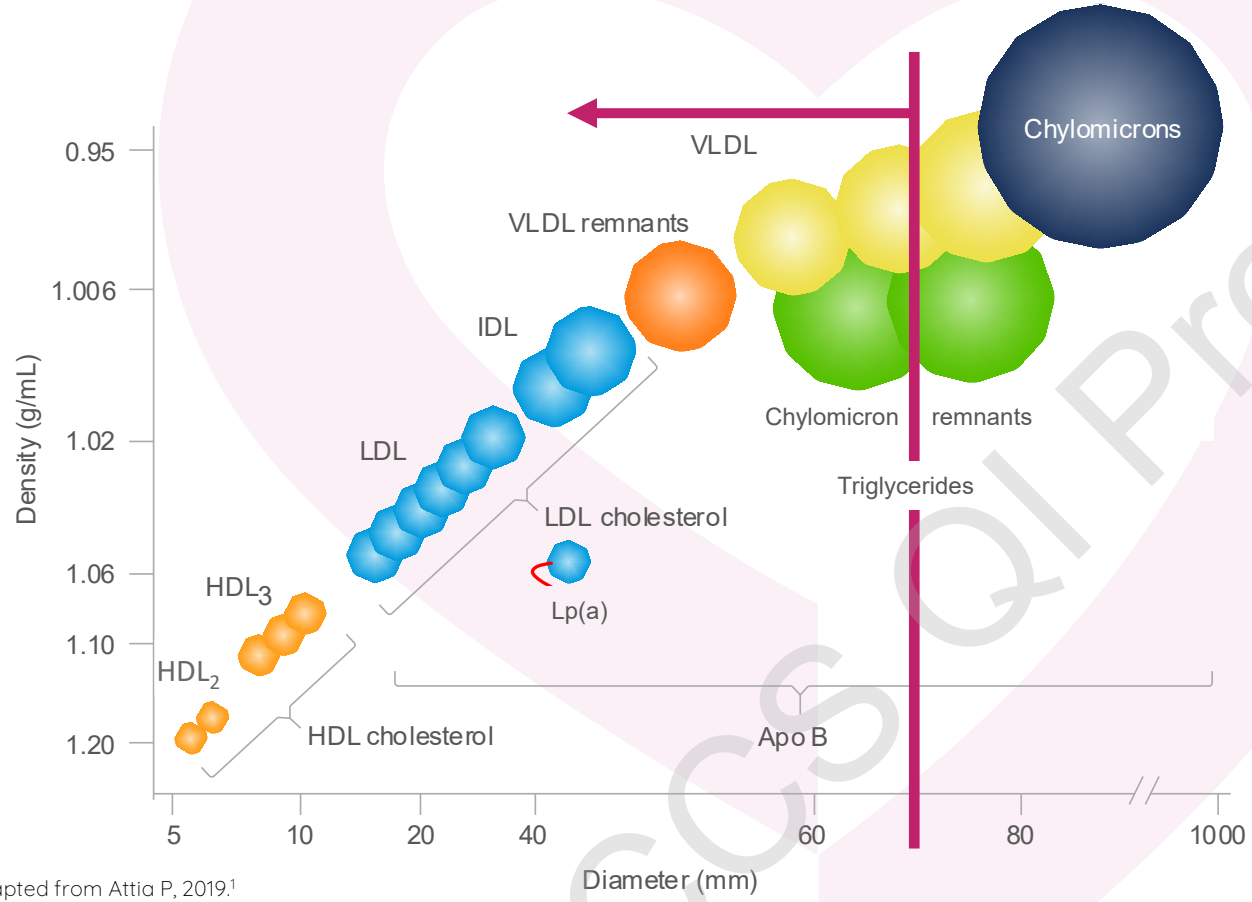
Cholesterol cargo mainly carried in ApoB containing lipoproteins

- ApoB containing lipoproteins – LDL inc. LP(a), TGs
- >90% of ApoB containing particles are LDL [unless high TGs e.g. DM]
- Non-HDL = ApoB – all carry CVD risk
- Statin treated patients: non-HDL (ApoB) related to risk

ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein a; TG, triglycerides; VLDL, very-low-density lipoprotein.

1. Attia P. Measuring cardiovascular disease risk and the importance of apoB. 22 December 2019. Available from: https://peterattiamd.com/measuring-cardiovascular-disease-risk-and-the-importance-of-apob-part-1/. Accessed November 2024; 2. Borén J, et al. Eur heart J 2020;41:2313–2330.

Demystifying non-HDL and LDL



Adapted from Attia P, 2019.[1]

- LDL levels = include LP(a)
- Non-HDL is higher than LDL
- Difference between non-HDL and LDL due non-LDL ApoB particles = remnant cholesterol
- Remnant cholesterol = triglyceride rich
- TGs independent risk factor for CVD[2]

ApoB, apolipoprotein B; CVD, cardiovascular disease; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein a; TC, total cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein.

1. Attia P. Measuring cardiovascular disease risk and the importance of apoB. 22 December 2019. Available from: https://peterattiamd.com/measuring-cardiovascular-disease-risk-and-the-importance-of-apob-part-1/. Accessed November 2024; 2. Johannesen CDL, et al. J Am Coll Cardiol 2021;77:1439–1450.

What are triglycerides

- Fats are ingested during a meal and broken down by pancreatic lipase and bile salts in the small intestine into FFAs[1]
- TG rich particles are synthesised in the liver by a process called lipogenesis[1,2]

Triglycerides are the storage form of long chain fatty acids:[2]

- Important source of energy
- Structural fatty acids needed for formation of phospholipids in cell membranes

The liver and gut package triglycerides, cholesterol and fat-soluble vitamins into lipoproteins for delivery to other tissues.[2]

FFA, free fatty acids; TG, triglycerides.

1. Betts JG, et al. OpenStax: Anatomy & Physiology – Chapter 24: Metabolism and Nutrition. 2013. Available at: https://openstax.org/books/anatomy-and-physiology/pages/24-3-lipid-metabolism. Accessed November 2024; 2. BJC. Lipids module 1: Lipid metabolism and its role in atherosclerosis. June 2024. Available at: https://bjcardio.co.uk/2024/06/lipids-module-1-lipid-metabolism-and-its-role-in-atherosclerosis-2/. Accessed November 2024.

Causes of raised triglycerides

Primary Care Cardiovascular Society
Empowering primary care to deliver the best in cardiovascular health

Hypertriglyceridaemia can be classified either according to:

- Severity of triglyceride elevation or
- Whether it is primary or secondary

Primary HTG is rarely monogenic and typically polygenic in nature

Secondary causes of HTG: lifestyle factors, medical conditions, and medications

Diet

- Alcohol excess
- Positive-energy balanced diet with saturated fat or high glycaemic index
- Ketogenic diet

Systemic

Obesity, Diabetes mellitus
Hypothyroidism
Renal diseases, Nephrotic syndrome
Autoimmune disorders, *e.g.*, systemic lupus erythematosus (SLE)
HIV associated dyslipidaemia
Pregnancy (the third trimester)
Low exercise

Drugs

Beta-blockers (nonselective), thiazides
Corticosteroids
Tamoxifen
Raloxifene
Oestrogens (oral, not transdermal) (e.g. contraceptives, postmenopausal hormone therapy)
Protease inhibitors
Retinoic acid
Isotretinoin
Sirolimus
L-Asparaginase
Bile acid resins
Phenothiazines
Antipsychotics (second generation)
Immunosuppressants

HIV, human immunodeficiency virus; HTG, hypertriglyceridaemia.

Rygiel K. Curr Cardiol Rev 2018;14: 67–76.

Raised triglycerides may cause pancreatitis and CV events

Primary Care Cardiovascular Society

Empowering primary care to deliver the best in cardiovascular health

Reduce risk of pancreatitis by managing TG

Hypertriglyceridaemia-induced acute pancreatitis Carr et al (2016)[1]

The median admission TG concentration was 29.6 mmol/L
(range 13 mmol/L – 110.3 mmol/L)

TGs over 5mmol/L led to
4x risk
of pancreatitis
(12 per 10,000 pt years vs 2.7 per 10,000 for TGs under 1mmol/L)[2]

Reduce risk of cardiovascular events by managing TG

TGs over 5mmol/L led to

78 MIs per 10,000 patient years

vs

22 per 10,000

for TGs under 1mmol/L[2]

CV, cardiovascular; TG, triglycerides; pt, patient.
1. Carr RA, et al. Pancreatology 2016;16:469–476; 2. Pedersen SB, et al. JAMA Intern Med 2016;176:1834–1842.

Triglycerides can help to identify adult statin-treated patients with remaining CV risk[1–3]

Primary Care Cardiovascular Society

Empowering primary care to deliver the best in cardiovascular health

Elevated levels of triglycerides have been shown to be independent markers of CV risk across epidemiological studies[4]

International guidelines recognise that **CV risk is increased with TGs >1.7 mmol/L**[5]

~40% of adults with diabetes have TG levels ≥1.7 mmol/L regardless of statin use (as shown in a US observational study)[6]

CV, cardiovascular; TG, triglyceride.

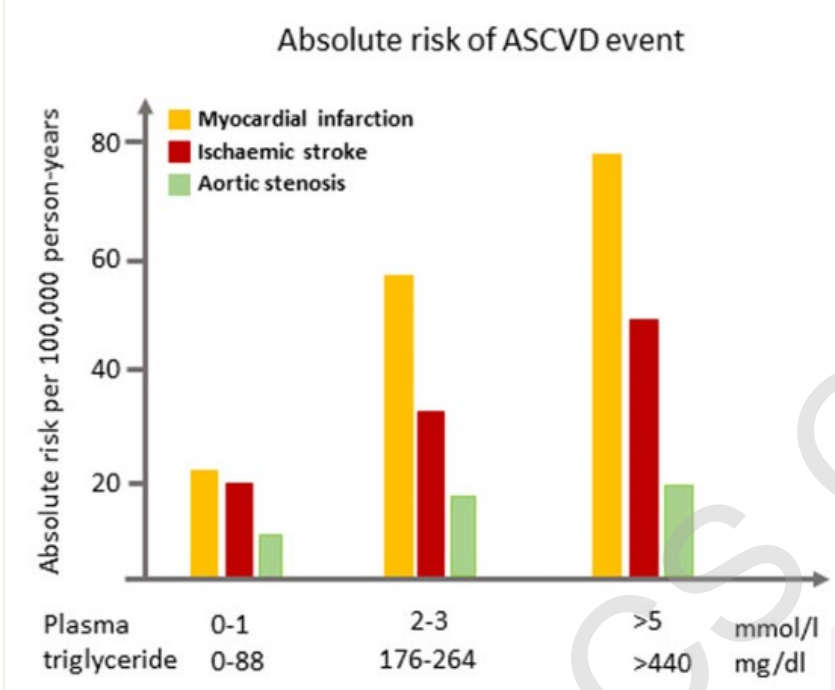
1. Lawler PR, et al. Eur Heart J 2020;41:86–94; 2. Toth PP, et al. J Am Heart Assoc 2018; 7:e008740; 3. Schwartz GG, et al. J Am Coll Cardiol 2015;65:2267–2275; 4. Ganda OP, et al. J Am Coll Cardiol 2018;72:330–343; 5. Visseren FLJ, et al. Eur Heart J 2021;42:3227–3337; 6. Fan W, et al. Diabetes Care 2019;42:2307–2314.

Evidence for the role of TG in ASCVD risk – Population studies

Primary Care Cardiovascular Society

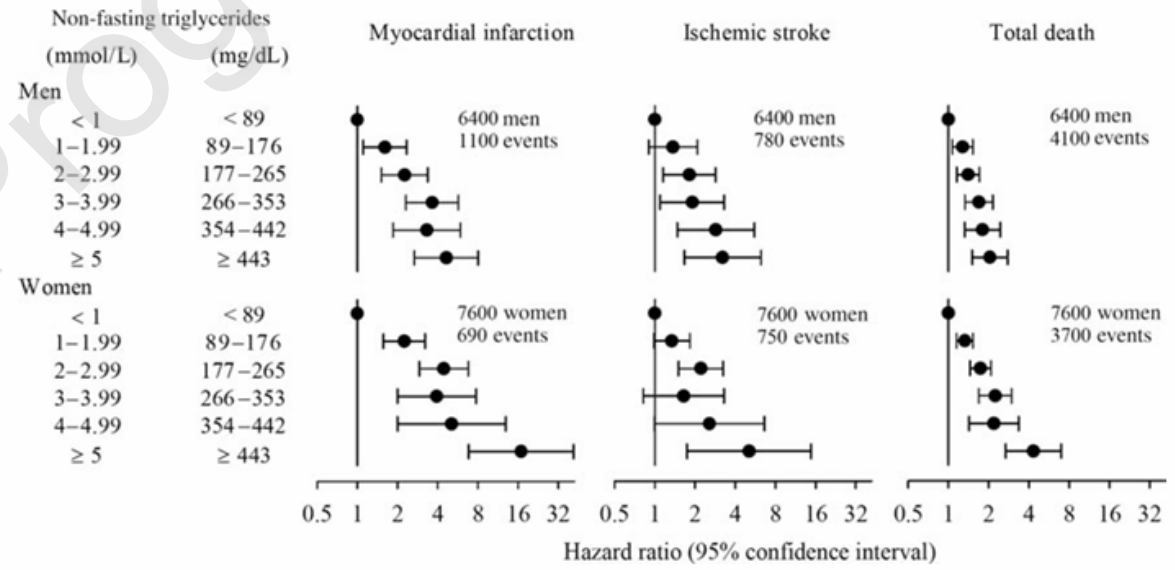
Empowering primary care to deliver the best in cardiovascular health

Absolute risk of CV morbidity as a function of increasing non-fasting plasma TG in the general population.[1]



Based on data from more than 100,000 individuals in the Copenhagen General Population Study.

Relationship of non-fasting TG (up to and >5 mmol/L or 440 mg/dL) and risk of MI, ischaemic stroke and total mortality.[2]



Results are shown as age-adjusted hazard ratios from the Copenhagen City Heart Study with 26–31 years of follow-up. Reproduced with modification from Nordestgaard et al and Freiberg et al.[2-4]

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; MI, myocardial infarction; TG, triglycerides.

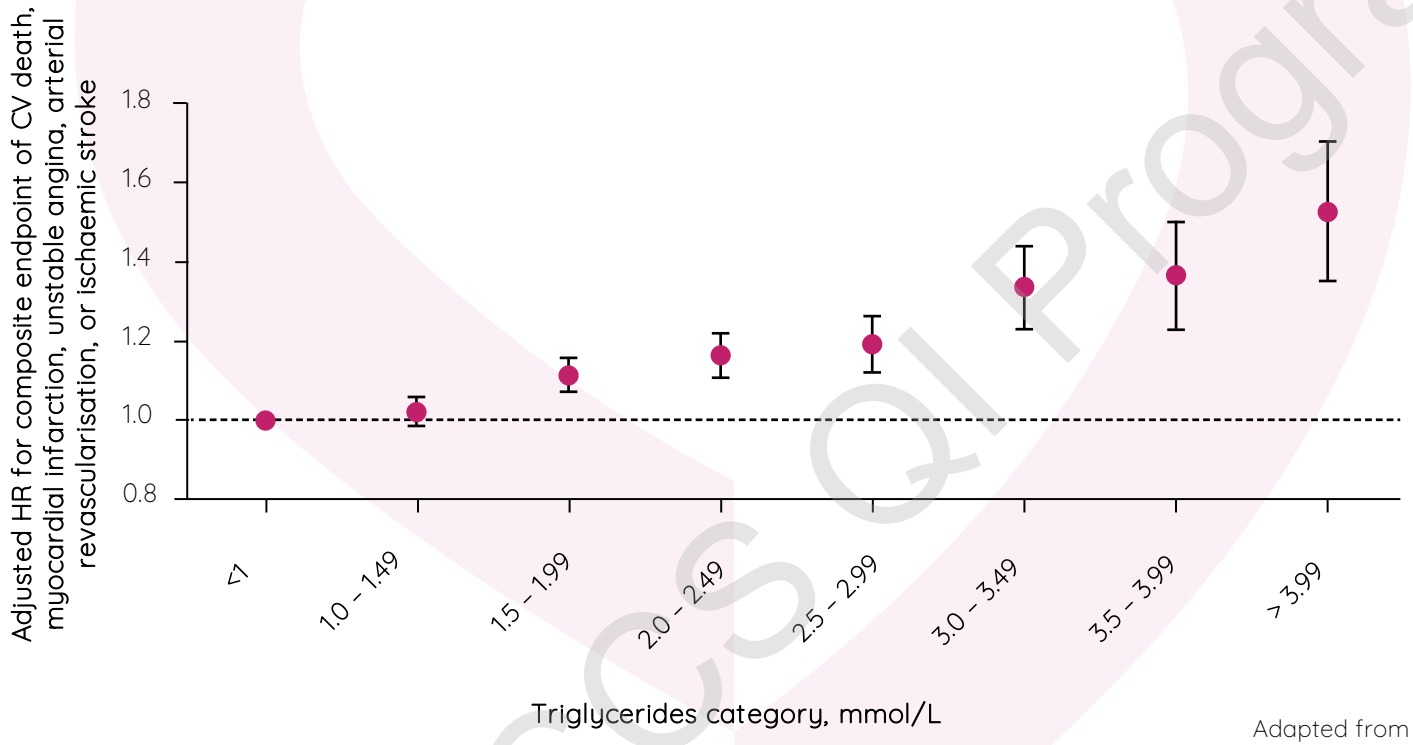
1. Ginsberg HN, et al. Eur Heart J 2021;42:4791–4806; 2. Chapman MJ, et al. Eur Heart J 2011;32:1345–1361; 3. Nordestgaard BG, et al. JAMA 2007;298:299–308; 4. Freiberg JJ, et al. JAMA 2008;300:2142–2152.

CV risk increases in patients with elevated TG levels[1]

Primary Care Cardiovascular Society

Empowering primary care to deliver the best in cardiovascular health

Risk of ASCVD events associated with TG levels among patients with prevalent ASCVD



Elevated TG levels are a risk marker of CV risk independent of LDL-C levels[2]

Adapted from Lawler PR, et al. Eur Heart J 2020.[1]

Observational data from Canadian CANHEART cohort, 196,717 patients aged ≥40 years with prior history of MI, unstable angina, non-haemorrhagic stroke, peripheral arterial disease, or prior coronary revascularisation. 95.5% of patients up to age 66 were on statins. 54.1% of patients in the study had diabetes.

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglycerides.

1. Lawler PR, et al. Eur Heart J 2020;41:86–94; 2. Schwartz GG, et al. J Am Coll Cardiol 2015;65:2267–2275.

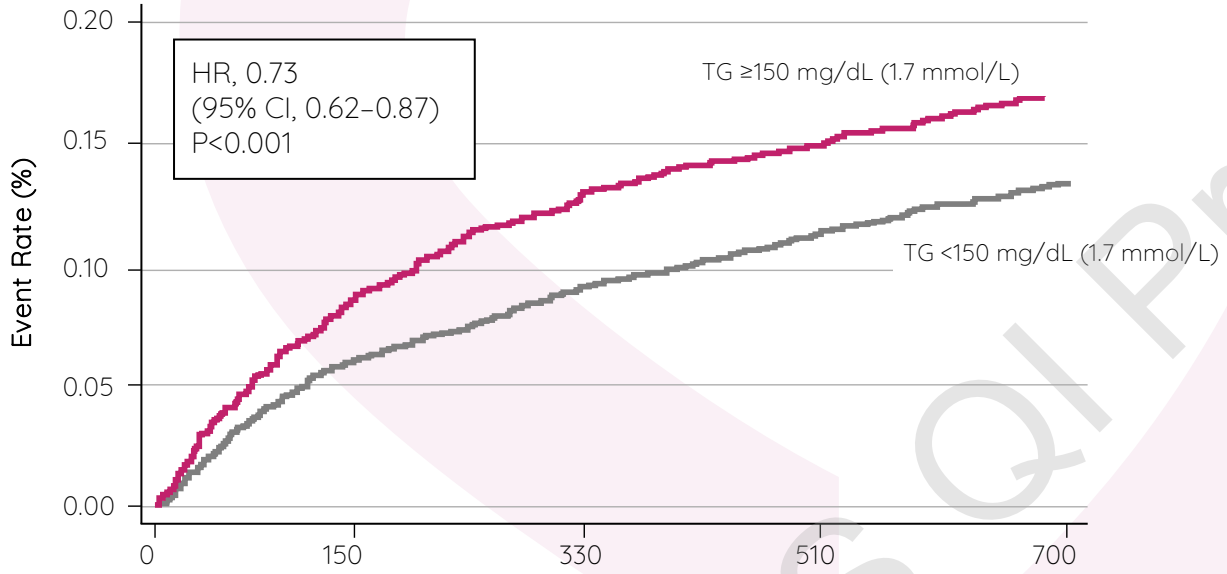
A CV risk is present in patients with elevated TG levels[1]

Primary Care Cardiovascular Society

Empowering primary care to deliver the best in cardiovascular health

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

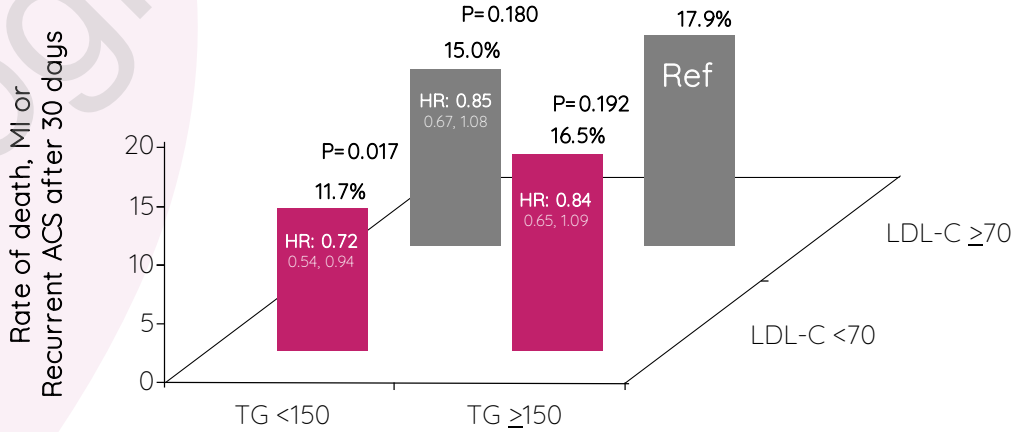
PROVE-IT TIMI 22 trial: 4,162 men and women hospitalised for ACS with TC 240 mg/dL (6.21 mmol/L), or 200 mg/dL (5.17 mmol/L) if receiving LLT, were randomly assigned to receive intensive therapy (atorvastatin 80 mg daily) or standard therapy (pravastatin 40 mg daily) for a mean follow-up period of 2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



No. at Risk

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

Estimates of death, myocardial infarction, and recurrent acute coronary syndrome between 30 days and 2 years of follow-up based on TG <150 mg/dL.



Event rate and adjusted hazard of death, MI and recurrent ACS between 30 days and 2 years of follow-up with achieved LDL-C and TG based on the designated cut-points of 70mg/dL and 150mg/dL, respectively. The referent (Ref) group is LDL-C 70mg/dL and TG 150mg/dL. This model is adjusted for age, gender, low HDL-C, smoking, hypertension, obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment effect. The 95% confidence intervals are located below the HRs.

Adapted from Miller M, et al. J Am Coll Cardiol 2008.

ACS, acute coronary syndromes, CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MI, myocardial infarction; TC, total cholesterol; TG, triglycerides. 1. Miller M, et al. J Am Coll Cardiol 2008;51:724–730.

To fast, or not to fast

Primary Care Cardiovascular Society

Empowering primary care to deliver the best in cardiovascular health

- Non-fasting gives more accurate ASCVD risk[1]
- If non-fasting TG raised, a fasting level can help to define LDL-C more accurately (>4.5 if using Friedewald equation, Sampson considered to be able to cater for higher TGs)[2]
- For day-to-day practice, use non-fasting

Friedewald equation:[3]	$LDL\text{-}C = \text{Total Cholesterol} - HDL\text{-}C - TG/2.2$
Sampson equation:[3]	$LDL\text{-}C = TC/0.948 - HDL\text{-}C/0.971 - (TG/8.56 + TG \times \text{non-}HDL\text{-}C/2140 - TG^2/16100) - 9.44$

ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

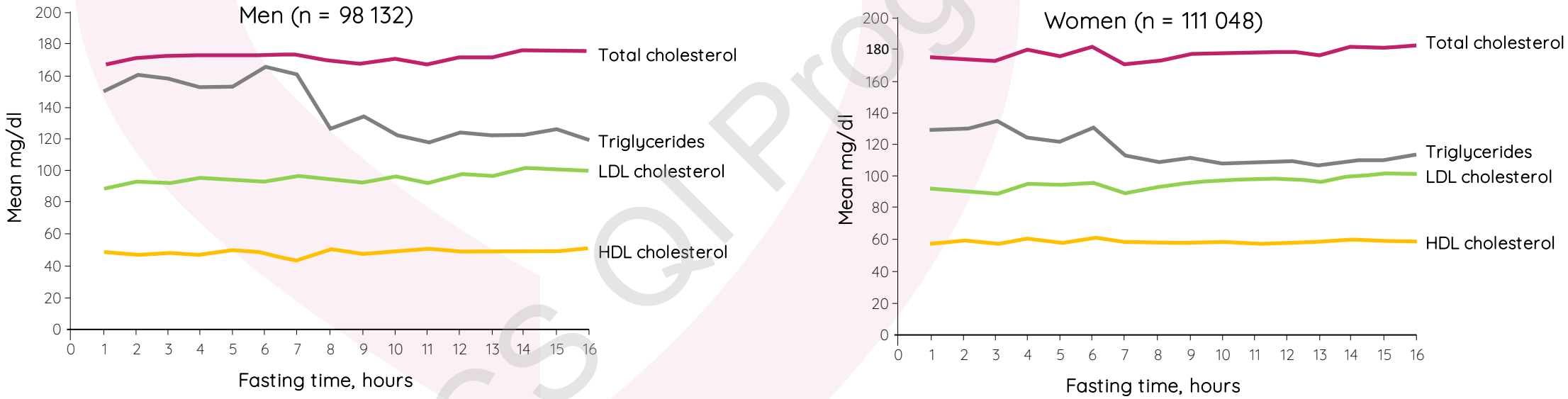
1. Keirns BH, et al. J Nutr Sci 2021;10:e75; 2. van den Berg MJ, et al. Am J Cardiol 2016;118:804–810; 3. Koch CD and El-Khoury JM. Clinical Chemistry 2020;66:1120–1121.

Effects of fasting on serum lipids

Primary Care Cardiovascular Society

Empowering primary care to deliver the best in cardiovascular health

Mean concentrations of lipids and lipoproteins as a function of the period of fasting following the last meal in men and women from the Canadian general population[1]



Adapted from Nordestgaard BG, et al. Eur Heart J 2016.[1]

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Nordestgaard BG, et al. Eur Heart J 2016;37:1944–1958.

Summary

- TG are an important source of energy and are necessary for formation of phospholipids in cell membranes[1]
- TG may be raised by dietary or systemic factors or as a result of medication[2]
- Raised TG may cause pancreatitis and CV events[3,4] and TGs are an independent risk factor for CVD[5]
- Non-fasting TG levels provides a more accurate indicator of ASCVD risk[6]

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; TG, triglycerides.

1. BJC. Lipids module 1: Lipid metabolism and its role in atherosclerosis. June 2024. Available at: https://bjcardio.co.uk/2024/06/lipids-module-1-lipid-metabolism-and-its-role-in-atherosclerosis-2/. Accessed November 2024; 2. Rygiel K. Curr Cardiol Rev 2018;14: 67–76; 3. Carr RA, et al. Pancreatology 2016;16:469–476; 4. Pedersen SB, et al. JAMA Intern Med 2016;176:1834–1842; 5. Johannesen CDL, et al. J Am Coll Cardiol 2021;77:1439–1450; 6. Keirns BH, et al. J Nutr Sci 2021;10:e75.