POSTPRANDIAL HYPERTRIGLYCERIDAEMIA AND VASCULAR RISK

D P Mikhailidis

BSc MSc MD FCPP FCP FRSPH FFPM FRCP FRCPath

Dept. of Clinical Biochemistry

Royal Free campus

University College London (UCL)

DECLARATION OF INTEREST

- **Attended conferences and gave talks sponsored by *MSD*, *AstraZeneca* and *Libytec***

DECLARATION OF INTEREST

- **Lead: Guidelines for Medical Management of Carotid Artery Stenosis (*Eur Soc Vasc Surg*)**
- **Chairperson: European Expert Panel on Small Dense Low Density Lipoprotein**
- **Co-chairperson: Expert Panel on Post-Prandial Hypertriglyceridaemia**
- **Executive Board member: *International Atherosclerosis Society* (*IAS*), 2016-18**

MY CREDENTIALS

Editor-in-Chief

- *Curr Vasc Pharmacol* **(IF = 2.391)**
- *Curr Med Res Opin* **(IF = 2.757)**
- *Expert Opin Pharmacotherapy* **(IF = 3.894)**
- *Angiology* **(IF = 3.085)**
- *Clinical Lipidology*
- *The Open Cardiovasc Med J*
- *J Drug Assessment*

TRIGLYCERIDES ARE NOT TREATED WELL IN DAILY CLINICAL PRACTICE: why?

TG recommendation

- **Normal: <1.7 mmol/l (150 mg/dl)**
- **Borderline High: 1.7 – 2.25 mmol/l (150 – 199 mg/dl)**
- **High: 2.25 – 5.6 mmol/l (200 – 499 mg/dl)**
- **Very High: >5.6 mmol/l (>500 mg/dl)**

NCEP ATP III 2004

NCEP ATP III - TRIGLYCERIDES

At 5.6 mmol/l (500 mg/dl), the priority is TG levels, not LDL levels

TRIGLYCERIDES

Commercial Promotion?

TRIGLYCERIDES

FASTING or NON-FASTING?

TRIGLYCERIDES

FASTING or NON-FASTING?

Are we are in a constant postprandial state?

TRIGLYCERIDES

FASTING or NON-FASTING?

Kolovou GD, Mikhailidis DP, Kovar J, Lairon D, Nordestgaard BG, Ooi TC, Perez-Martinez P, Bilianou H, Anagnostopoulou K, Panotopoulos G. Assessment and Clinical Relevance of Non-fasting and Postprandial Triglycerides: An Expert Panel Statement. *Curr Vasc Pharmacol* 2011; 9: 258 - 70.

TRIGLYCERIDES

FASTING or NON-FASTING?

Kolovou GD, Mikhailidis DP, Nordestgaard BG, Bilianou H, Panotopoulos G. Definition of Postprandial Lipaemia. *Curr Vasc Pharmacol* 2011; 9: 292 - 301.

FASTING or NON-FASTING?

Nordestgaard BG, et al. European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine joint consensus initiative. 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. ***Eur Heart J* 2016; 37: 1944 - 58**

WHY TREAT ELEVATED TG LEVELS?

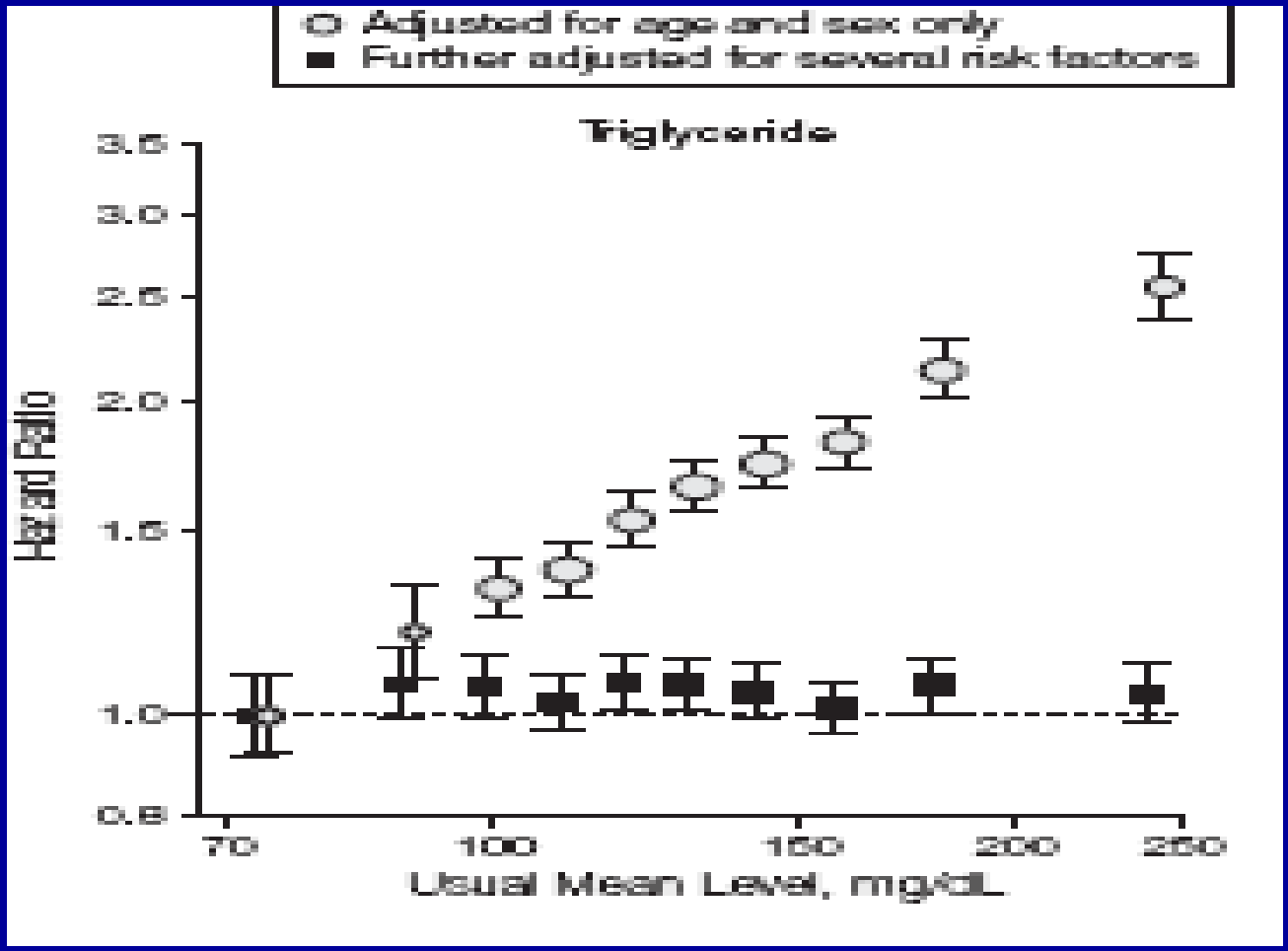
WHY TREAT ELEVATED TG LEVELS?

1. Vascular disease

2. Acute pancreatitis

Emerging Risk Factors Collaboration.

JAMA 2009;302:1993-2000



TG LEVELS AND VASCULAR DISEASE

Risk of vascular events was increased in a meta-analysis of 262,525 participants (10,158 events).

Increase in risk was in the range of 19 – 27% for every 1.0 mmol/l (88 mg/dl) increase in TG levels from the baseline value after a follow up of 4 – 12 years.

N Sarwar et al. *Circulation* 2007; 115: 450 - 8

TG LEVELS AND VASCULAR DISEASE

Links with:

HDL (inverse relationship; quality of HDL?)

LDL (dense LDL – more atherogenic)

Coagulation (e.g. factor VII)

Insulin resistance (e.g. metabolic syndrome, IFG, IGT, DM)

Obesity (NAFLD and vascular risk)

TG LEVELS AND VASCULAR DISEASE

Ideal fasting level: <2.0 mmol/l (175 mg/dl)

Ideal non-fasting level: <2.5 mmol/l (220 mg/dl) anytime after meals or oral fat tolerance test (oFTT)

TG LEVELS AND VASCULAR DISEASE

Non-HDL-C:

1] Total cholesterol – HDL cholesterol

2] Use for as treatment target when TG levels are raised > 2.26 mmol/l (200 mg/dl)

3] Target value: 0.8 mmol/l (30 mg/dl) higher than LDL-C targets (1.8 -2.6 mmol/l; 70 -100 mg/dl)

How to Assess Postprandial Hypertriglyceridaemia - 1?

- **Aim: improve on a random non-fasting sample**
- **Oral Fat Tolerance Test (oFTT)**
- **Those with fasting triglycerides (TG) <1 mmol/L (89 mg/dL) usually do not have an abnormal response to an oFTT**
- **Those with fasting TG ~2 mmol/L (175 mg/dL) or above will mostly have an abnormal response to an oFTT.**

How to Assess Postprandial Hypertriglyceridaemia - 2?

- **Recommend considering PPL testing for those with lipid disorders and fasting TG between 1 - 2 mmol/l (89 - 175 mg/dl).**

- **The Panel proposes that an abnormal TG response to an oFTT is > 2.5 mmol/l (220 mg/dl) in response to a test meal of 75 g fat, 25 g carbohydrate and 10 g proteins.**

Perez-Martinez P, et al. *J Clin Lipidol* 2016; 10: 1163 - 71

- **Two recent studies (CORDIOPREV and GOLDN) including >2,000 patients validated the predictive values reported in the previous expert consensus.**
- **Patients with fasting TG <1 mmol/L (89 mg/dL) commonly do not have an exaggerated response and those with >2 mmol/L (180 mg/dL) usually do.**

How to Assess Postprandial Hypertriglyceridaemia - 3?

Limitations:

- **Cost**: financial (ready to use pack)
- **Cost**: time (2 samples: 0 + 4 h, or even only at 4h). Preparation of the meal.
- **Recognition**: need for more research

REMNANT CHOLESTEROL

- **Non-fasting remnant cholesterol = total cholesterol minus HDL cholesterol minus LDL cholesterol.**

REMNANT CHOLESTEROL

- **Remnant cholesterol is the cholesterol content of TG-rich lipoproteins and is composed of very-low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL) in the fasting state, and of VLDL, IDL, and chylomicron remnants in the non-fasting state.**

- **Increased remnant cholesterol is causally associated with increased risk of CHD and low-grade inflammation.**

Jepsen AM et al. *Clin Chem* 2016; 62: 593 - 604

- **5414 Danish patients diagnosed with ischemic heart disease (IHD). Patients on statins were not excluded. During 35 836 person-years of follow-up, 1319 patients died.**

- **Cumulative survival was reduced in patients with calculated remnant cholesterol ≥1 mmol/L (39 mg/dL) *vs* <1 mmol/L [log-rank, p = 9 × 10(-6); hazard ratio 1.3 (1.2-1.5)], but not in patients with measured LDL-C ≥3 mmol/L (116 mg/dL) vs <3 mmol/L [P = 0.76; hazard ratio 1.0 (0.9-1.1)].**

- **This suggests that increased concentrations of remnant cholesterol explain part of the residual risk of all-cause mortality in patients with IHD.**

Harmful effects of remnant particles

- **Well-executed Mendelian randomization experiments provide firm evidence for the association of APOA5 with TG and risk of atherosclerosis.**

Triglyceride Coronary Disease Genetics C, Emerging Risk Factors C, Sarwar N, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet* 2010; 375: 1634 - 9

Harmful effects of remnant particles

- **Remnant particles cross the endothelium and are retained within the arterial wall, thereby initiating atherogenesis. They are very rich in cholesterol.**

Varbo A, Benn M, Nordestgaard BG. *Pharmacol Therap* 2014; 141: 358 - 67

CONDITIONS ASSOCIATED WITH POSTPRANDIAL HYPERTRIGLYCERIDAEMIA

- **Diabetes, Metabolic Syndrome and Insulin resistance**
- **Obesity**
- **Non-alcoholic Fatty Liver Disease (NAFLD)**
- **Post menopause**
- **Chronic kidney disease**

All are conditions associated with increased vascular risk and some have an increasing prevalence

CONDITIONS ASSOCITED WITH POSTPRANDIAL HYPERTRIGLYCERIDAEMIA

- **Familial hypercholesterolemia (FH) (delayed chylomicron clearance in some reports)**
- **Familial combined hyperlipidaemia (FCH)**

All are conditions associated with increased vascular risk

TREATMENT OF POSTPRANDIAL HYPERTRIGLYCERIDAEMIA

- **Lifestyle (diet, weight, smoking, exercise, alcohol)**
- **Anti-obesity drugs (e.g. liraglutide, orlistat, naltrexone/bupropion)**
- **Lipid lowering drugs (e.g. statins, ezetimibe, fibrates, fish oils; new drugs? PCSK9 inhibitors)**
- **Apheresis**
- **Bariatric Surgery**

TREATMENT

- **LIFESTYLE**

Role of *Mediterranean diet* on MetS components:

Waist circumference (-0.42 cm, 95% CI: -0.82 to – 0.02),
HDL-C (1.17 mg/dl, 95% CI: 0.38 to 1.96),
TGs (-6.14 mg/dl, 95% CI: -10.35 to -1.93),
Systolic BP (-2.35 mmHg, 95% CI: -3.51 to -1.18)
Diastolic BP (-1.58 mmHg, 95% CI: -2.02 to -1.13)
Glucose (-3.89 mg/dl, 95% CI: -5.84 to -1.95)

Kastorini CM, et al. *J Am Coll Cardiol* 2011; 57: 1299 - 313

TREATMENT

- **FIBRATES**

In patients with high TG levels or atherogenic dyslipidaemia phenotype, fibrates were estimated to reduce cardiovascular risk by 28% (95%CI, 15 to 39%; p < 0.001) or 30% (95%CI, 19 to 40%; p < 0.0001)

Bruckert E, et al. Fibrates Effect on Cardiovascular Risk is Greater in Patients with High Triglyceride Levels or Atherogenic Dyslipidemia Profile A Systematic Review and Metanalysis. *J Cardiovasc Pharmacol* 2011; 57: 267 - 72

TREATMENT

STATINS

<u>Effect related to</u>:

A] Baseline TG levels

B] Dose (or LDL-C lowering efficacy) of statin

TREATMENT

NICOTINIC ACID (+ laropiprant)

Tolerability, glycaemia and urate?

Very effective at raising HDL-C

Now essentially a withdrawn drug

Canadian Cardiovascular Society position statement

Fish oils

- **For high triglyceride levels**
- **Epidemiology**

2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. *Can J Cardiol* 2009; 25: 567 - 79

Meta-Analysis: Ezetimibe Added to a Statin

- **n = 5, 039**

- **LDL fall = 23.6%, p< 0.0001**
- **HDL increase = 1.7%, p< 0.0001**
- **TG fall = 10.7%, p< 0.0001**

Note: TG fall may well depend on baseline values (like with satins)

Mikhailidis DP et al. *Curr Med Res Opin* 2007; 23: 2009 - 26

Which of the following drugs can significantly lower triglyceride levels?

- 1) Statins
- 2) Fibrates
- 3) Fish oils
- 4) Ezetimibe
- 5) All of the above

Which of the following drugs can significantly lower triglyceride levels?

- 1) Statins
- 2) Fibrates
- 3) Fish oils
- 4) Ezetimibe
- 5) All of the above

Which of the following conditions is associated with postprandial hypertriglyceridaemia?

- 1) Diabetes
- 2) Metabolic syndrome
- 3) Non-alcoholic fatty liver disease (NAFLD)
- 4) Chronic kidney disease
- 5) All of the above

Which of the following conditions is associated with postprandial hypertriglyceridaemia?

- 1) Diabetes
- 2) Metabolic syndrome
- 3) Non-alcoholic fatty liver disease (NAFLD)
- 4) Chronic kidney disease
- 5) All of the above