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**

DECLARATION OF INTEREST

Editor-in-Chief of:

- **Curr Med Res Opin**
- **Expert Opin Pharmacother**
- **Angiology**
- **Curr Vasc Pharmacol**
- **Open Cardiovasc Med J**
- **Expert Rev Cardiovasc Ther**
- **Clinical Lipidology**
- **Journal of 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 2001

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?

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?

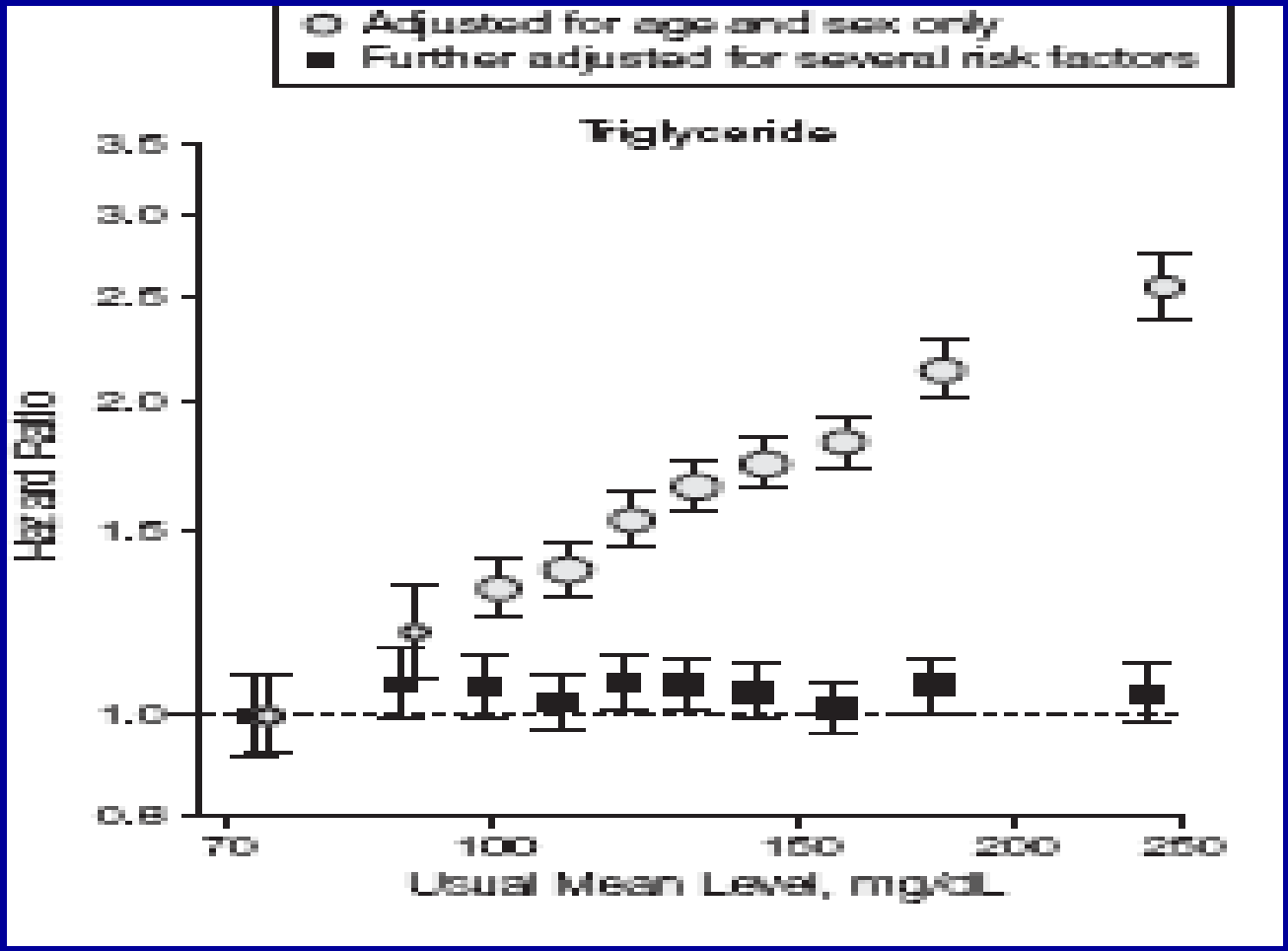
WHY TREAT ELEVATED TG LEVELS?

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

Reykjavik (fasting) and the European Prospective Investigation of Cancer (EPIC)-Norfolk studies (non-fasting)

The data suggest no important differences in the strength of associations between TGs and CHD in studies of fasting participants compared with studies of non-fasting participants

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

TG LEVELS AND VASCULAR DISEASE

Prospective cohort study of 7587 women and 6394 men from the general population of Copenhagen, Denmark, aged 20 to 93 years, followed up from baseline (1976-1978) until 2004

Elevated non-fasting TG levels were associated with increased risk of MI, IHD, and death in men and women

Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A.
***JAMA* 2007; 298: 299 - 308**

TG LEVELS AND VASCULAR DISEASE

Copenhagen study

Non-fasting TG levels were associated with risk of ischemic Stroke

JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA* 2008; 300: 2142 - 52

TG LEVELS AND VASCULAR DISEASE

Non-fasting TG levels appear to be a strong and independent predictor of future risk of MI, particularly when the total cholesterol level is also elevated.

LDL particle diameter is associated with risk of MI, but not after adjustment for TG level.

Increased TG level, small LDL particle diameter, and decreased HDL-C levels appear to reflect underlying metabolic perturbations with adverse consequences for risk of MI.

Elevated TG levels may help identify high-risk individuals.

Stampfer MJ, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA* 1996; 276: 882 - 8

TG LEVELS AND VASCULAR DISEASE

Non-fasting TG levels appear to be a strong and independent predictor of future risk of MI, particularly when the total cholesterol level is also elevated.

LDL particle diameter is associated with risk of MI, but not after adjustment for TG level.

Increased TG level, small LDL particle diameter, and decreased HDL-C levels appear to reflect underlying metabolic perturbations with adverse consequences for risk of MI.

Elevated TG levels may help identify high-risk individuals.

Stampfer MJ, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA* 1996; 276: 882 - 8

TG LEVELS AND VASCULAR DISEASE

Prospective study of 26,509 initially healthy US women (20,118 fasting and 6391 non-fasting) participating in the Women's Health Study (WHS), enrolled between Nov 1992 and July 1995; follow-up: median of 11.4 years.

Non-fasting TG levels were associated with incident CV events, independent of traditional cardiac risk factors, levels of other lipids, and markers of insulin resistance; in contrast, fasting TG levels showed little independent relationship.

Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA* 2007; 298: 309 - 16

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.**

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.**

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

TREATMENT

There are also studies with other drugs:

Orlistat, vildagliptin, alogliptin, sitagliptin, metformin, acarbose, pioglitazone, sulfonylureas and insulin

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

POSTPRANDIAL HYPERLIPIDEMIA REVISITED IN AN ERA OF NONFASTING LIPID PROFILE TESTING: A 2018 EXPERT PANEL STATEMENT ON CLINICAL ASSESSMENT AND THERAPEUTIC INTERVENTIONS - Supplementary Material

Genovefa D Kolovou, Gerald F. Watts, Dimitri P Mikhailidis, Pablo Perez-Martinez, Samia Mora, Helen Bilianou, George Panotopoulos, Niki Katsiki, Teik C Ooi, José Lopez-Miranda, Anne Tybjærg-Hansen, Nicholas Tentolouris, Børge G Nordestgaard.

Summary of PPL studies, LIPOTEST composition, effect of several drugs on PPL, candidate genes, PPL in various conditions/populations (FH, MetS, DM,NAFLD, children) and treatment options.

POSTPRANDIAL HYPERLIPIDEMIA REVISITED IN AN ERA OF NONFASTING LIPID PROFILE TESTING: A 2018 EXPERT PANEL STATEMENT ON CLINICAL ASSESSMENT AND THERAPEUTIC INTERVENTIONS

Genovefa D Kolovou, Gerald F. Watts, Dimitri P Mikhailidis, Pablo Perez-Martinez, Samia Mora, Helen Bilianou, George Panotopoulos, Niki Katsiki, Teik C Ooi, José Lopez-Miranda, Anne Tybjærg-Hansen, Nicholas Tentolouris, Børge G Nordestgaard.

Categories of nonfasting triglycerides	Plasma triglycerides in mmol/L	Plasma triglycerides in mg/dL
Desirable	< 2	<175
Undesirable	≥ 2	≥175

POSTPRANDIAL HYPERLIPIDEMIA REVISITED IN AN ERA OF NONFASTING LIPID PROFILE TESTING: A 2018 EXPERT PANEL STATEMENT ON CLINICAL ASSESSMENT AND THERAPEUTIC INTERVENTIONS

Genovefa D Kolovou, Gerald F. Watts, Dimitri P Mikhailidis, Pablo Perez-Martinez, Samia Mora, Helen Bilianou, George Panotopoulos, Niki Katsiki, Teik C Ooi, José Lopez-Miranda, Anne Tybjærg-Hansen, Nicholas Tentolouris, Børge G Nordestgaard.

The Expert Panel suggests not to perform a fat tolerance test in individuals with nonfasting or fasting triglyceride levels <1 mmol/L* (89 mg/dL) *or >2 mmol/L (175 mg/dL) on two separate occasions.

Pérez-Martínez P, Mikhailidis DP, Athyros VG, Bullo M, Couture P, Covas MI, de Koning L, Delgado-Lista J, Díaz-López A, Drevon CA, Estruch R, Esposito K, Fitó M, Garaulet M, Giugliano D, García-Ríos A, Katsiki N, Kolovou G, Lamarche B, Maiorino MI, Mena-Sánchez G, Muñoz-Garach A, Nikolic D, Ordovás JM, Pérez-Jiménez F, Rizzo M, Salas-Salvadó J, Schröder H, Tinahones FJ, de la Torre R, van Ommen B, Wopereis S, Ros E, López-Miranda J.

Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation. *Nutr Rev* 2017; 75: 307 - 26