Diabetische Dyslipidemie

mechanismen en behandeling

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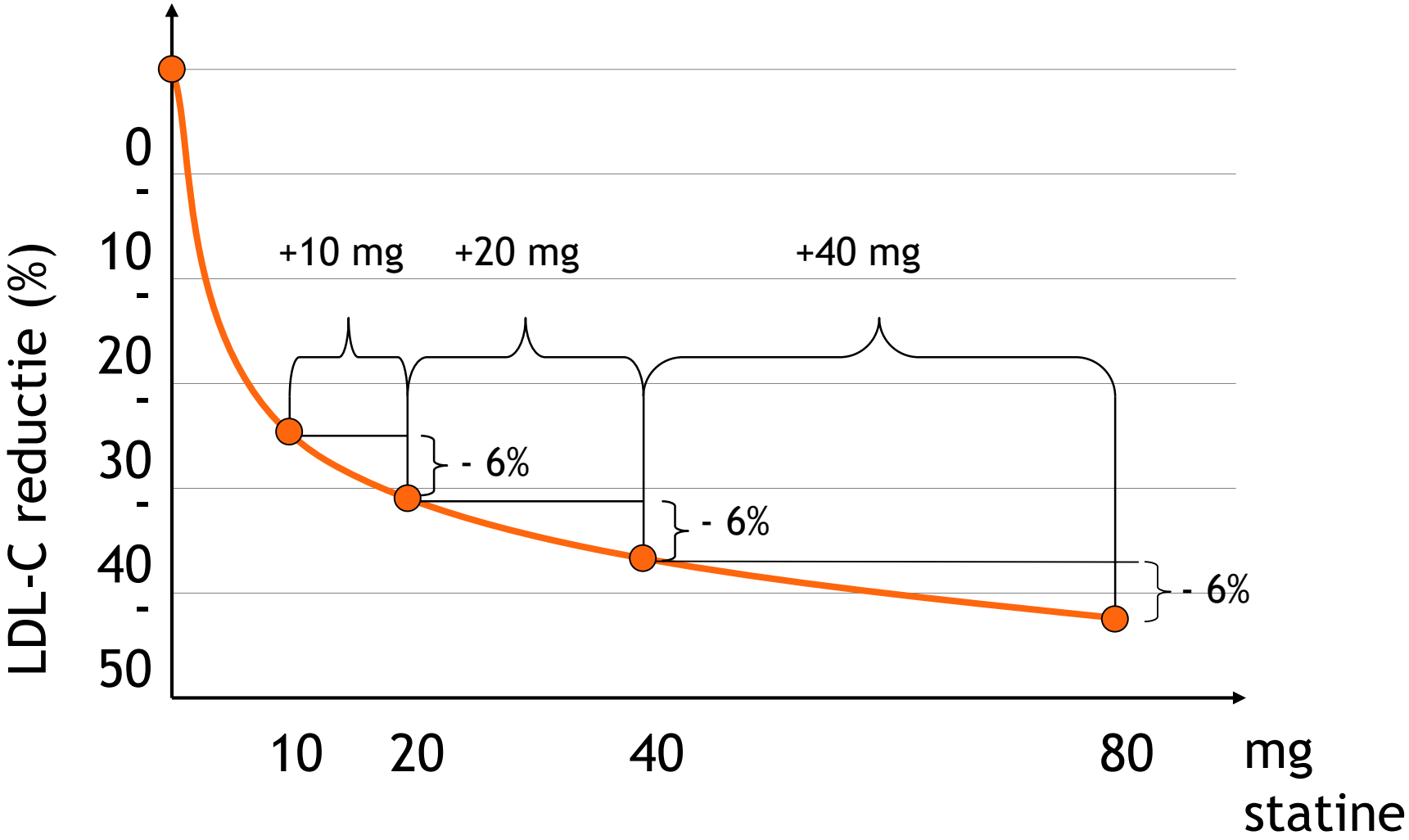
Casus diabetische dyslipidemie

- Dhr Janssen, 4 jaar diabetes
- 55 jaar oud;
- BMI: 34,5 Kg/m2; BD: 135/85

- Med: metformine 2 gram, glimepiride 6 gram, irbesartan 300 mg, simvastatine 30 mg

- Nuchter lab:
- glucose 10,1 mmol/L
- Vetspectrum: TC: 8,9, TG: 7,3; HDLC: 0,7; LDLC:?
- HbA1c: 73 mmol/mol

Statines: ‘regel van zes‘



Casus diabetische dyslipidemie

- Dhr Janssen, 4 jaar diabetes

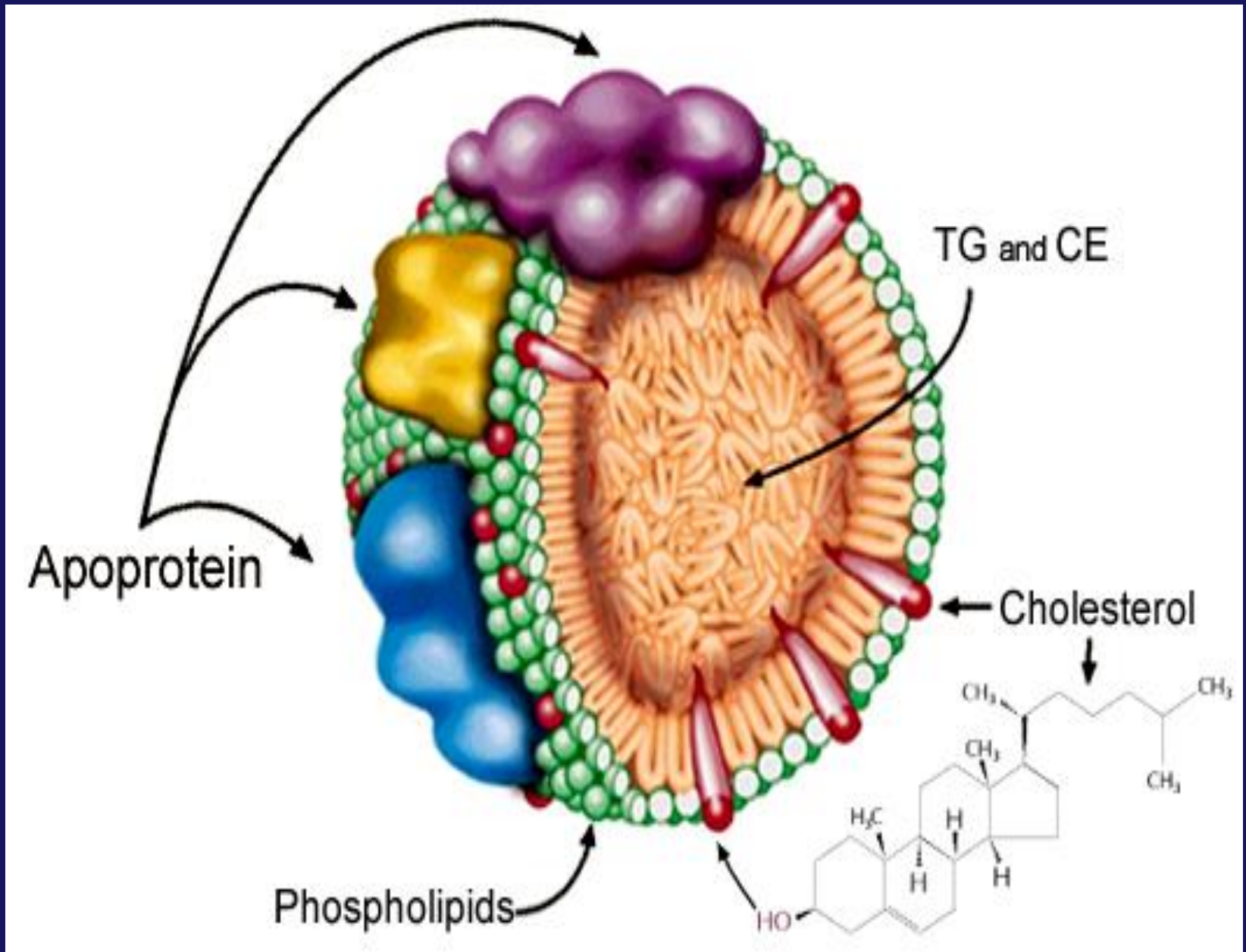
- Med: metformine 2 gram, glimepiride 6 gram, irbesartan 300 mg, simvastatine 40 mg
- Na toevoeging van langwerkende insuline en verdere leefstijlaanpassingen:
- HbA1c: 58 mmol/mol

- Nuchter lab:
- glucose 6,8 mmol/L
- Vetspectrum: TC: 5,9, TG: 3,2; HDLC: 0,9; LDLC: 3,6; apoB: 1,25 g/L

Atherogenic Dyslipidemia in T2DM

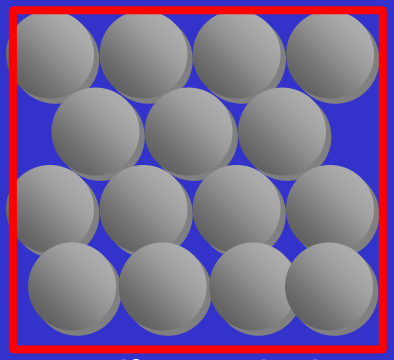
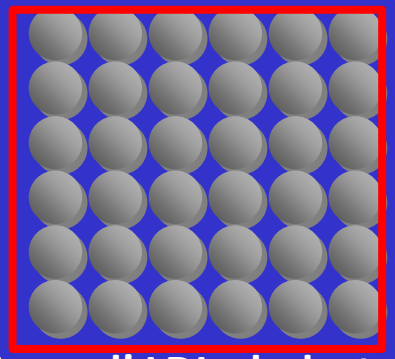
- Elevated TG
- Low HDL-C
- Small dense LDL (high apoB)
- Postprandial hyperlipidemia (atherogenic remnants)

Één apoB per atherogeen lipoporoteïne: apoB is marker voor aantal atherogene partikels en voor small dense LDL



T2DM, Metabolic Syndrome, Dyslipidemia and LDL-size

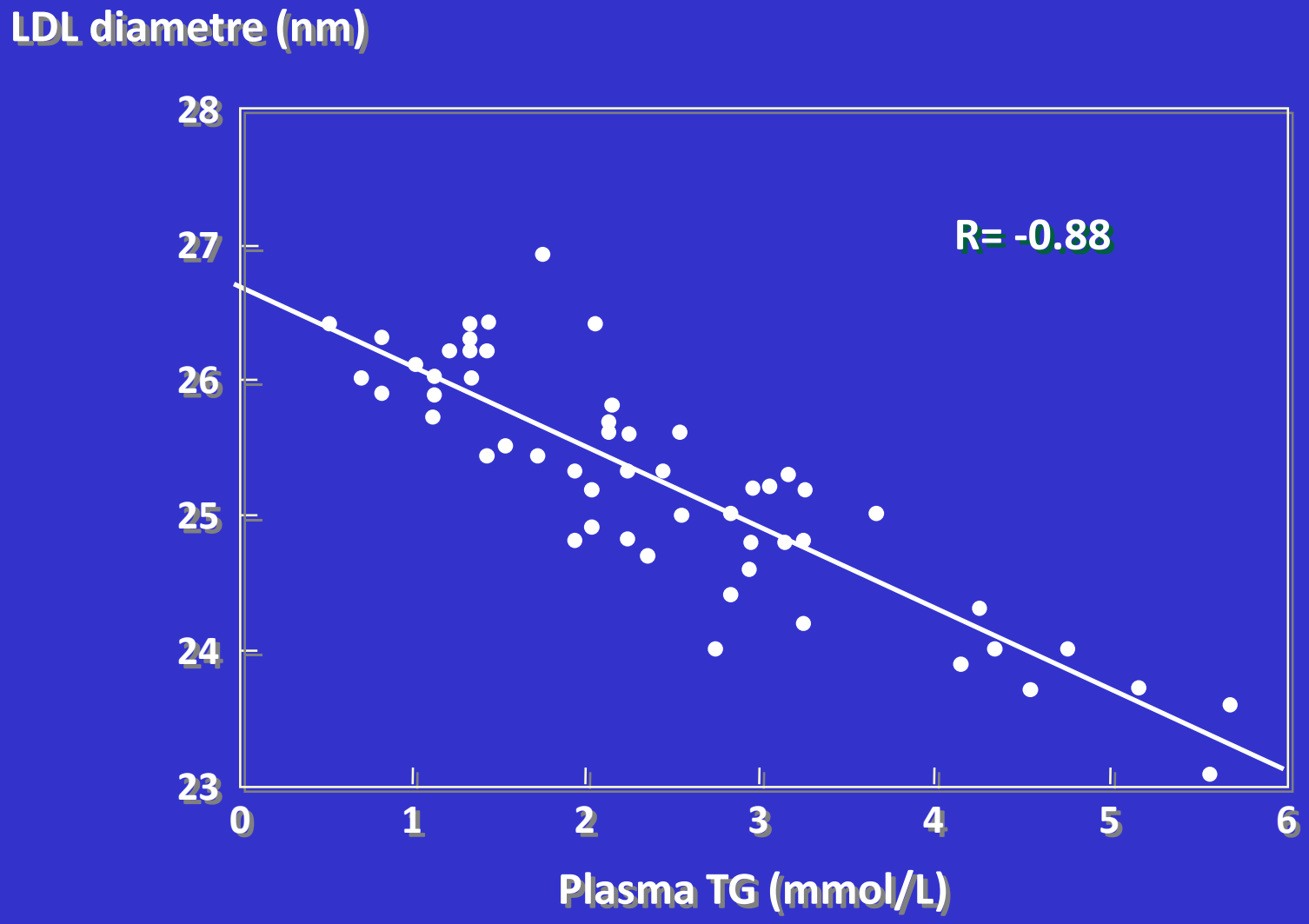
LDL patttern A ⟶ LDL pattern B

No Metabolic Syndr	Metabolic Syndrome
LDL  ‘Normal’ LDL-cholesterol	LDL  ‘Normal’ LDL-cholesterol but: ↑ LDL-apo B ↑ LDL-apo B/CE ↓ LDL-CE/TG

Low ⟶ CHD risk ⟶ High

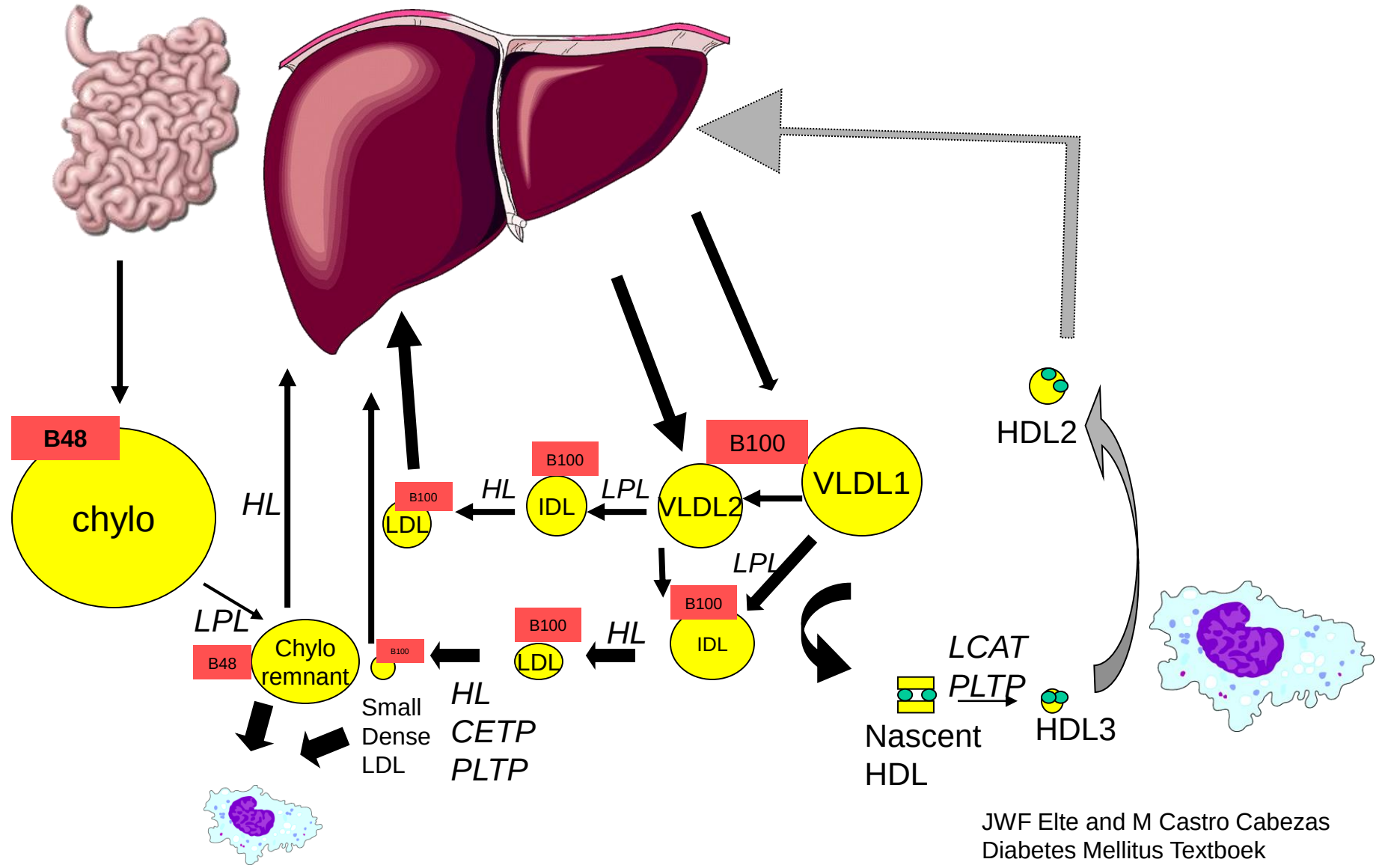
M. Austin JAMA 1988; 269: 1916

Plasma TG: main determinant of LDL size



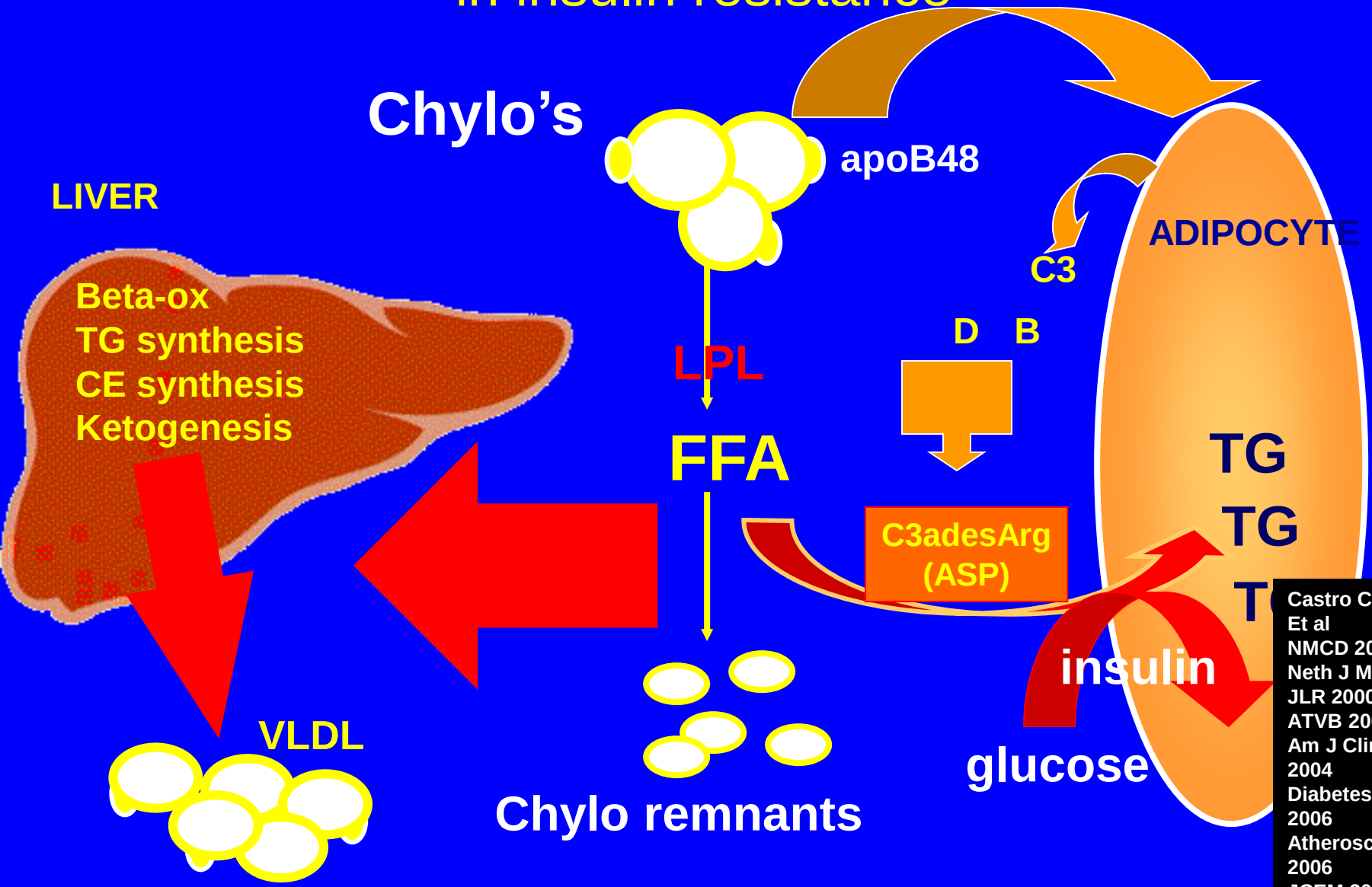
Scheffer et al; Clin Chem 1997;43:1904-12

Lipoprotein metabolism in healthy, lean subjects



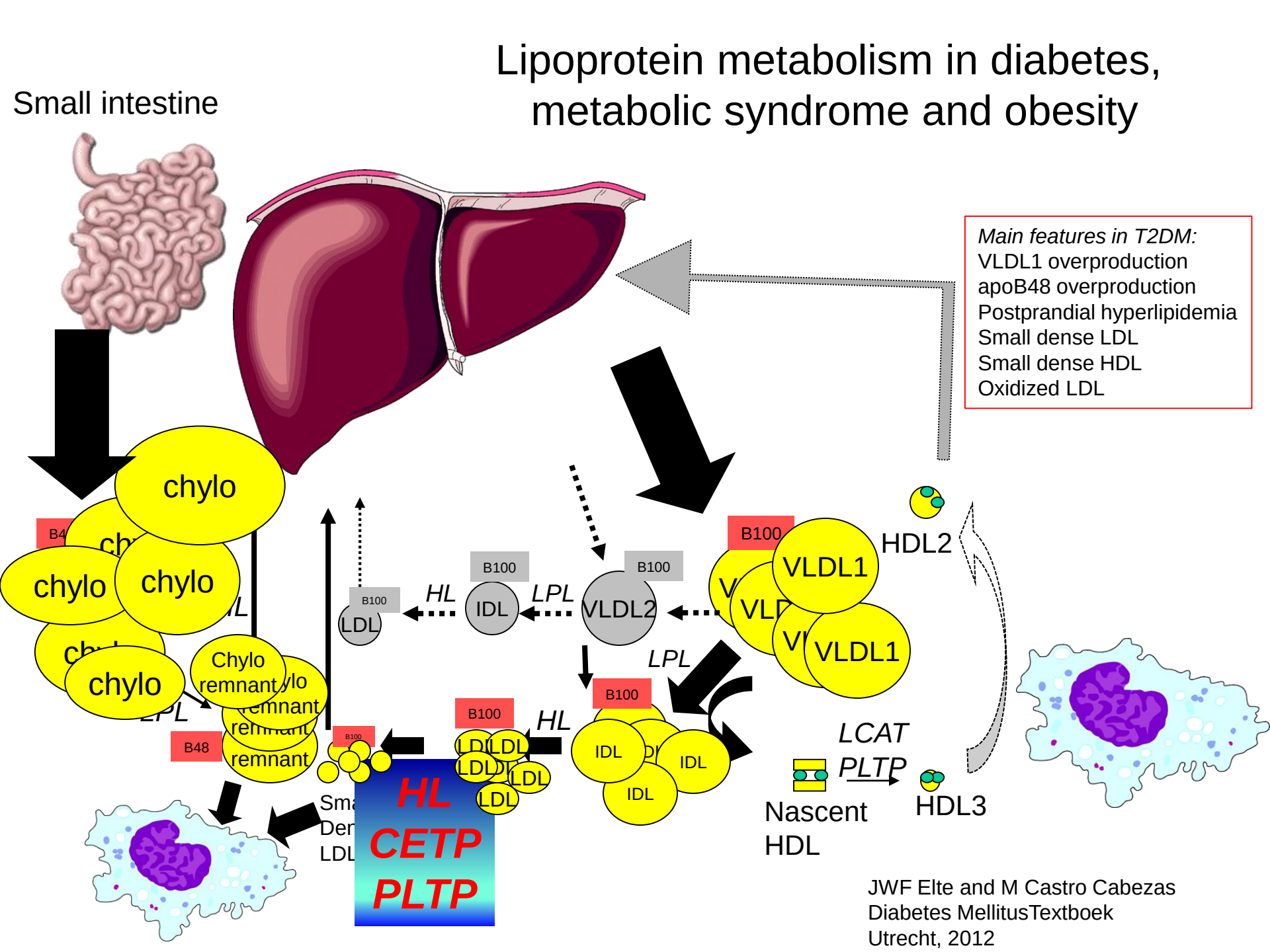
JWF Elte and M Castro Cabezas
Diabetes Mellitus Textboek
Utrecht, 2012

Impaired peripheral fatty acid trapping leads to increased flux of FFA and VLDL overproduction in insulin resistance



Castro Cabezas Et al
NMCD 2001
Neth J Med 2000
JLR 2000/2003
ATVB 2002/2003
Am J Clin Nutr 2004
Diabetes Care 2006
Atheroscl 2005, 2006
JCEM 2004, 2005

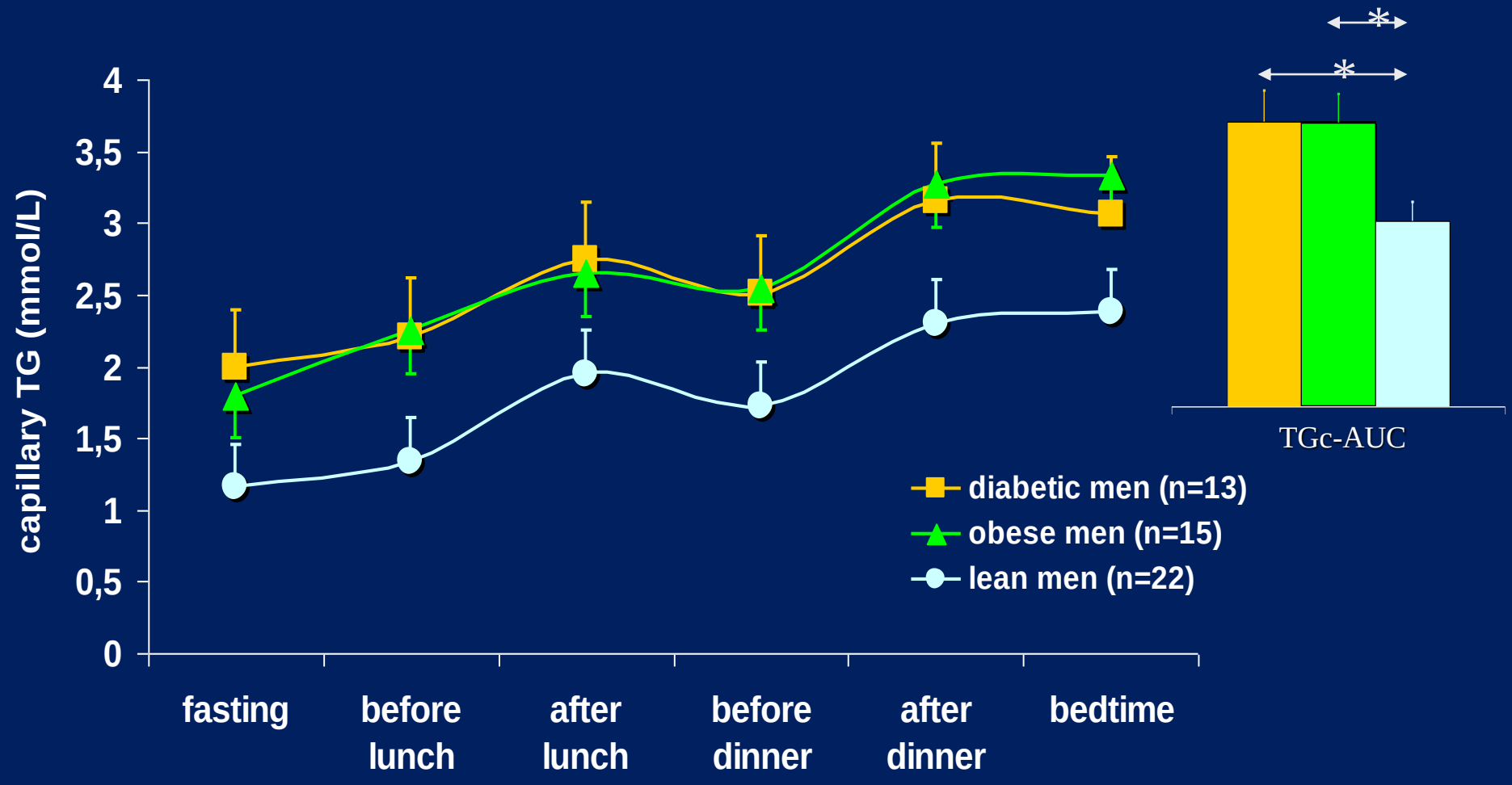
Lipoprotein metabolism in diabetes, metabolic syndrome and obesity



JWF Elte and M Castro Cabezas
Diabetes MellitusTextboek
Utrecht, 2012

Obesity determines diurnal triglyceridemia in type 2 diabetes

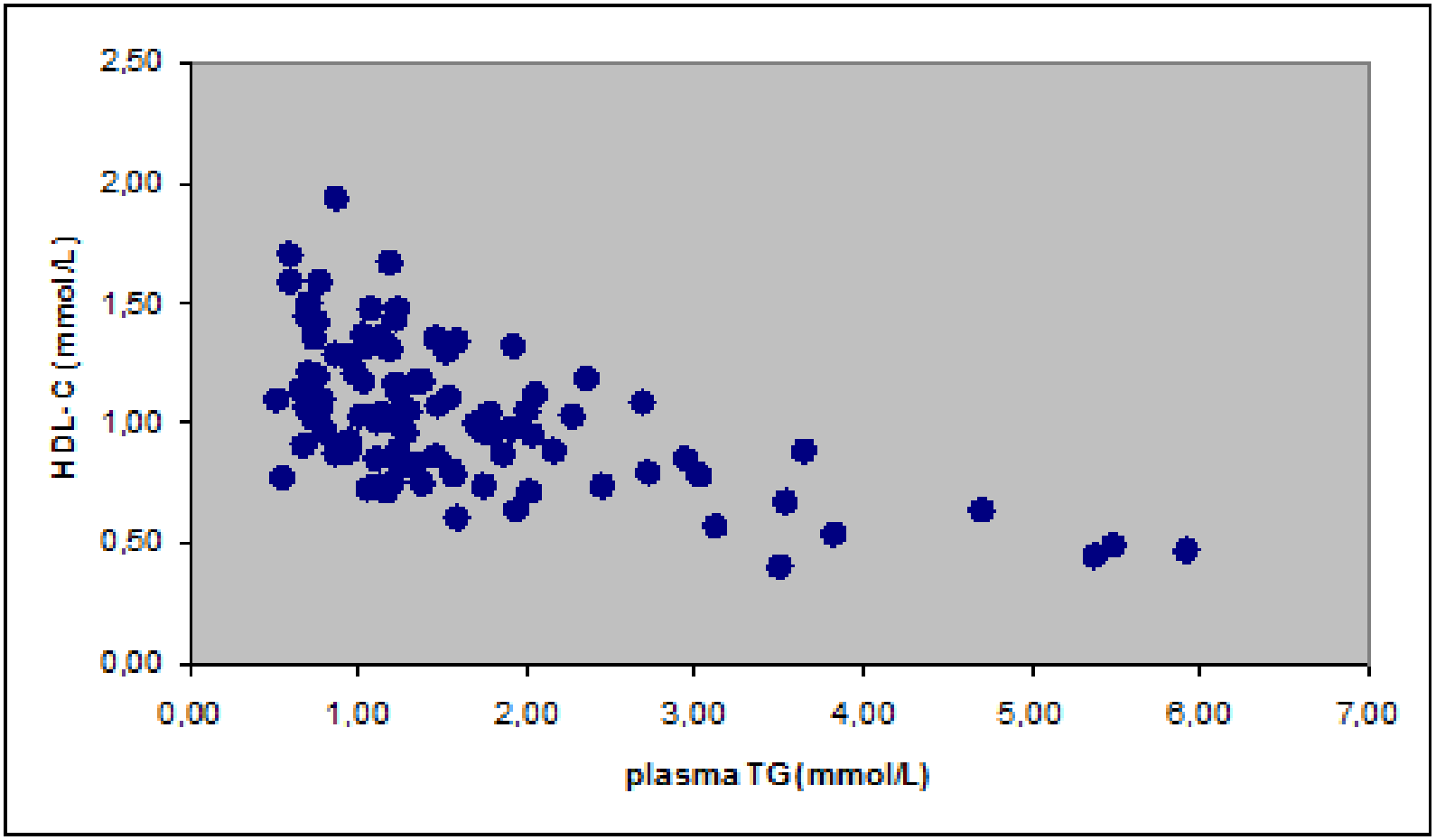
continuous generation of small dense LDL



Van Wijk et al . Metabolism 2003

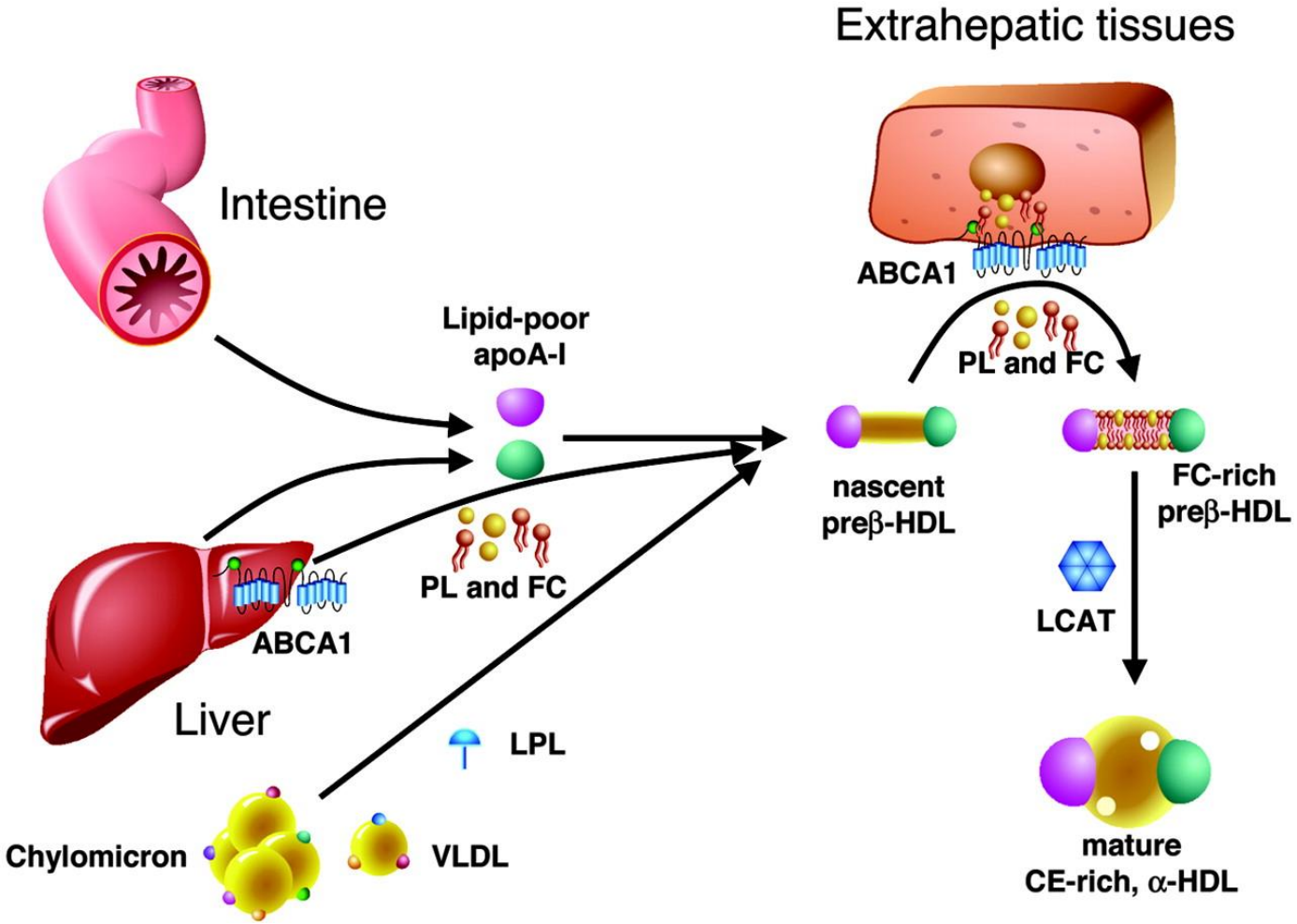
Maar… wat hebben TG met HDL te maken?

Relationship between fasting plasma TG and HDL-C (n=86)



M. Castro Cabezas (data on file)

Secretion, lipid acquisition, and maturation of HDL particles



Lewis, G. F. et al. Circ Res 2005;96:1221-1232

Circulation Research

European Heart Journal Advance Access published August 27, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw272

ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Alberico L. Catapano* (Chairperson) (Italy), Ian Graham* (Chairperson) (Ireland), Guy De Backer (Belgium), Olov Wiklund (Sweden), M. John Chapman (France), Heinz Drexel (Austria), Arno W. Hoes (The Netherlands), Catriona S. Jennings (UK), Ulf Landmesser (Germany), Terje R. Pedersen (Norway), Željko Reiner (Croatia), Gabriele Riccardi (Italy), Marja-Riita Taskinen (Finland), Lale Tokgozoglu (Turkey), W. M. Monique Verschuren (The Netherlands), Charalambos Vlachopoulos (Greece), David A. Wood (UK), Jose Luis Zamorano (Spain)

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CVD risk in observational studies. Evidence for a beneficial clinical effect of raising HDL-C is lacking, with lifestyle modification providing the first option due to its multifaceted effects.

9.5.3 Treatment strategies for subjects with type 2 diabetes and metabolic syndrome

Lifestyle therapy to improve the atherogenic lipid profile should be recommended to all subjects with T2DM and MetS (see section 5). Dietary advice should be tailored according to the individual's needs. If LDL-C goals are not achieved on maximally tolerated doses of statins, drug combinations may offer additional lowering of LDL-C, but the

or slightly elevated. This is explained by subcutaneous administr
tion of insulin that increases LPL activity in adipose tissue and sk
etal muscle and consequently the turnover rate of VLDL particl
However, there are potentially atherogenic changes in the compo
ition of both HDL and LDL particles. In all patients with type 1 d
betes and in the presence of microalbuminuria and renal diseas
LDL-C lowering (at least 30%) with statins as the first choi
(drug combination may be considered if needed) is recommend
irrespective of the basal LDL-C concentration.

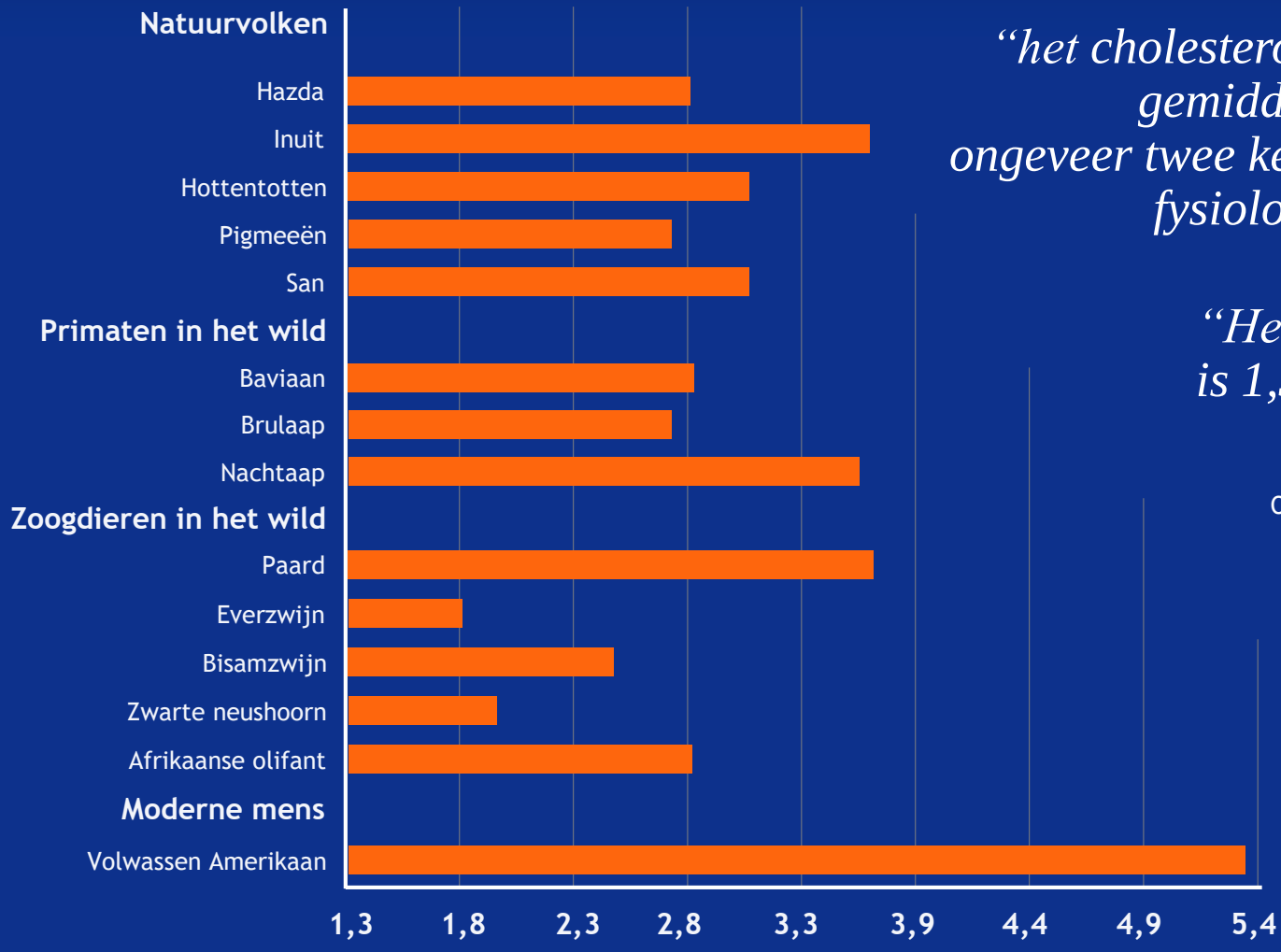
Recommendations for the treatment of dyslipidaemia in diabet
are shown in *Table 26*.

Table 26 Recommendations for the treatment of dyslipidaemia in diabetes

Recommendations	Class [a]	Level [b]	Ref [c]
In all patients with type I diabetes and in the presence of microalbuminuria and/or renal disease, LDL-C lowering (at least 50%) with statins as the first choice is recommended irrespective of the baseline LDL-C concentration.	I	C	64, 357
In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are >40 years of age with one or more other CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is <1.8 mmol/L (<70 mg/dL) and the secondary goal for non-HDL-C is <2.6 mmol/L (<100 mg/dL) and for apoB is <80 mg/dL.	I	B	62, 64
In all patients with type 2 diabetes and no additional risk factors and/or evidence of target organ damage, LDL-C <2.6 mmol/L (<100 mg/dL) is the primary goal. Non-HDL-C <3.4 mmol/L (<130 mg/dL) and apoB <100 mg/dL are the secondary goals.	I	B	62, 64

apoB = apolipoprotein B; CKD = chronic kidney disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoproteincholesterol; MetS = metabolic syndrome; TG = triglycerides.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Wat is een optimaal plasma cholesterolgehalte?

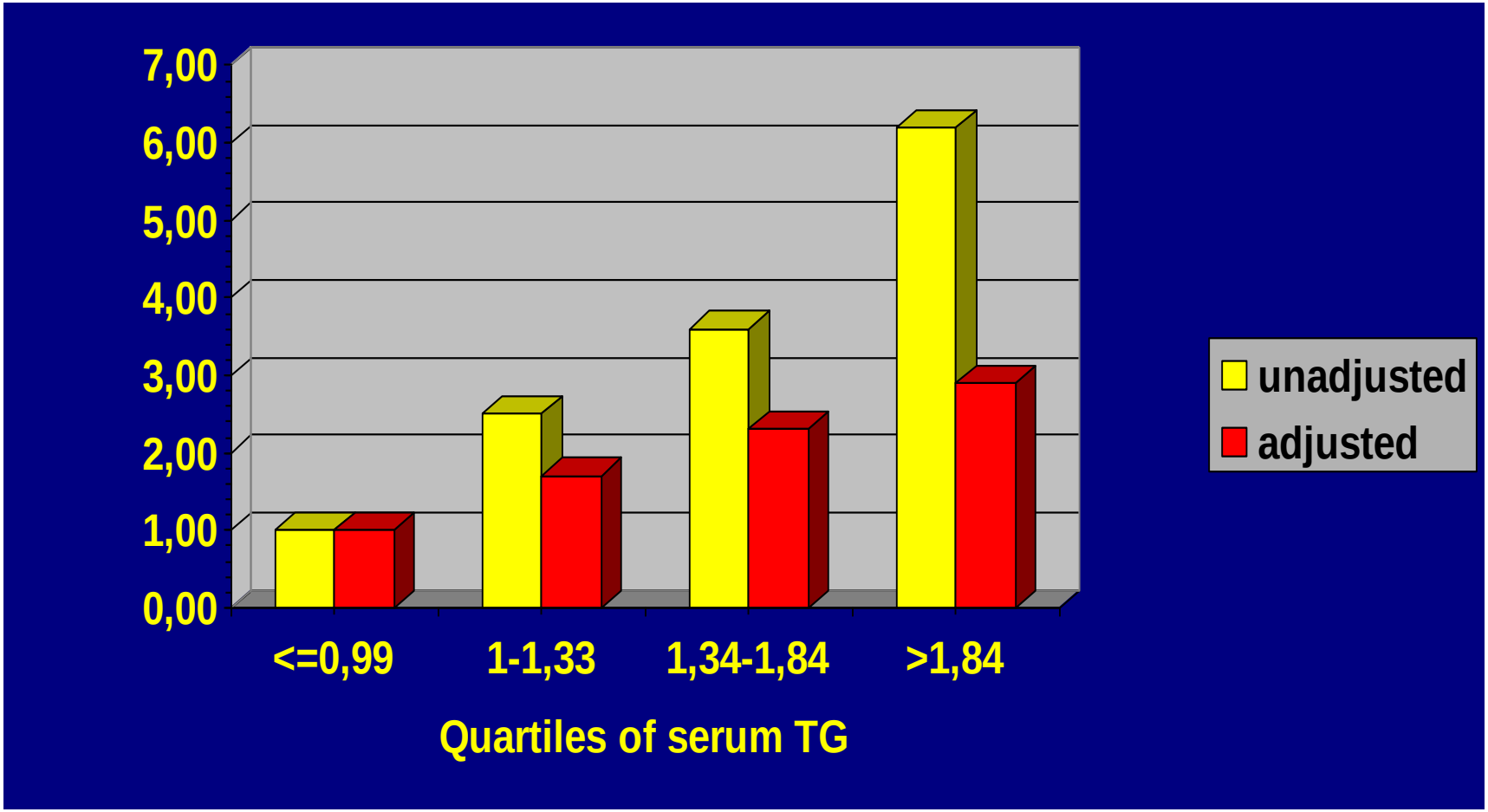


"het cholesterolniveau van de gemiddelde persoon is ongeveer twee keer het normale fysiologische niveau"

"Het optimale LDL is 1,3 - 1,8 mmol/l"

O'Keefe, *JACC* 2004; 2142-6

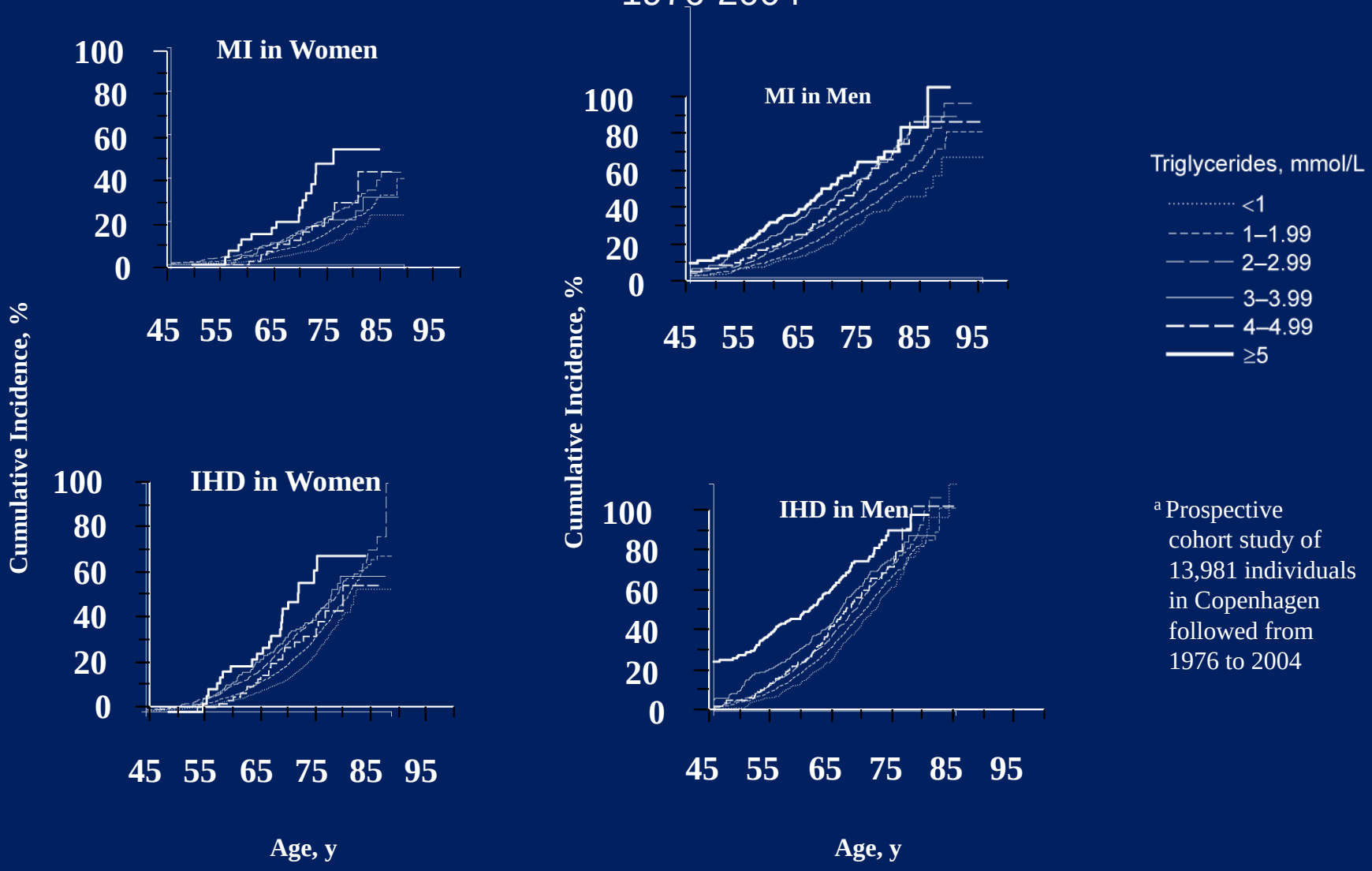
Relative risk of myocardial infarction in serum TG quartiles during 6-13 y follow up in 12.510 men



Adjustment for BMI, age, DM, BP, yr of screening, smoking, chol

L.Stavenow, T Kjellström Atherosclerosis 1999

Cumulative Incidence of MI and IHD by Levels of Nonfasting Triglycerides[a] In a prospective cohort study of 13981 individuals in Copenhagen followed from 1976-2004



[a] Prospective cohort study of 13,981 individuals in Copenhagen followed from 1976 to 2004

MI=myocardial infarction; IHD=ischemic heart disease. Adapted from Nordestgaard BG et al. *JAMA*. 2007;298:299–308.

Atherosclerosis 234 (2014) 473–475

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

The use of the non-fasting lipid profile for lipid-lowering therapy in clinical practice – Point of view

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ARTICLE INFO

Article history:
Received 17 December 2013
Received in revised form
6 March 2014
Accepted 21 March 2014
Available online 31 March 2014

Keywords:
Non-fasting triglycerides
Apolipoprotein B
Non-HDL-C

ABSTRACT

Current guidelines for the management of dyslipidaemias recommend measuring lipid profiles in the fasting state. The primary lipid targets are traditionally plasma total cholesterol and low-density lipoprotein-cholesterol (LDL-C) levels. However, triglycerides, apolipoprotein (apo) B and non-high-density lipoprotein-cholesterol (non-HDL-C) are also suitable parameters to assess cardiovascular risk and to guide lipid-lowering therapy. The advantage of the use of these variables is that they can be used in both the fasting and non-fasting state. In most cases, postprandial lipid profiles in combination with apo B are as useful as fasting lipid profiles for the differentiation between familial lipid disorders, such as heterozygous familial hypercholesterolemia, familial combined hyperlipidemia and familial hypertriglyceridemia. This article will address the interpretation, applications and limitations of a non-fasting lipid profile for daily clinical practice.

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

CURRENT OPINION

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

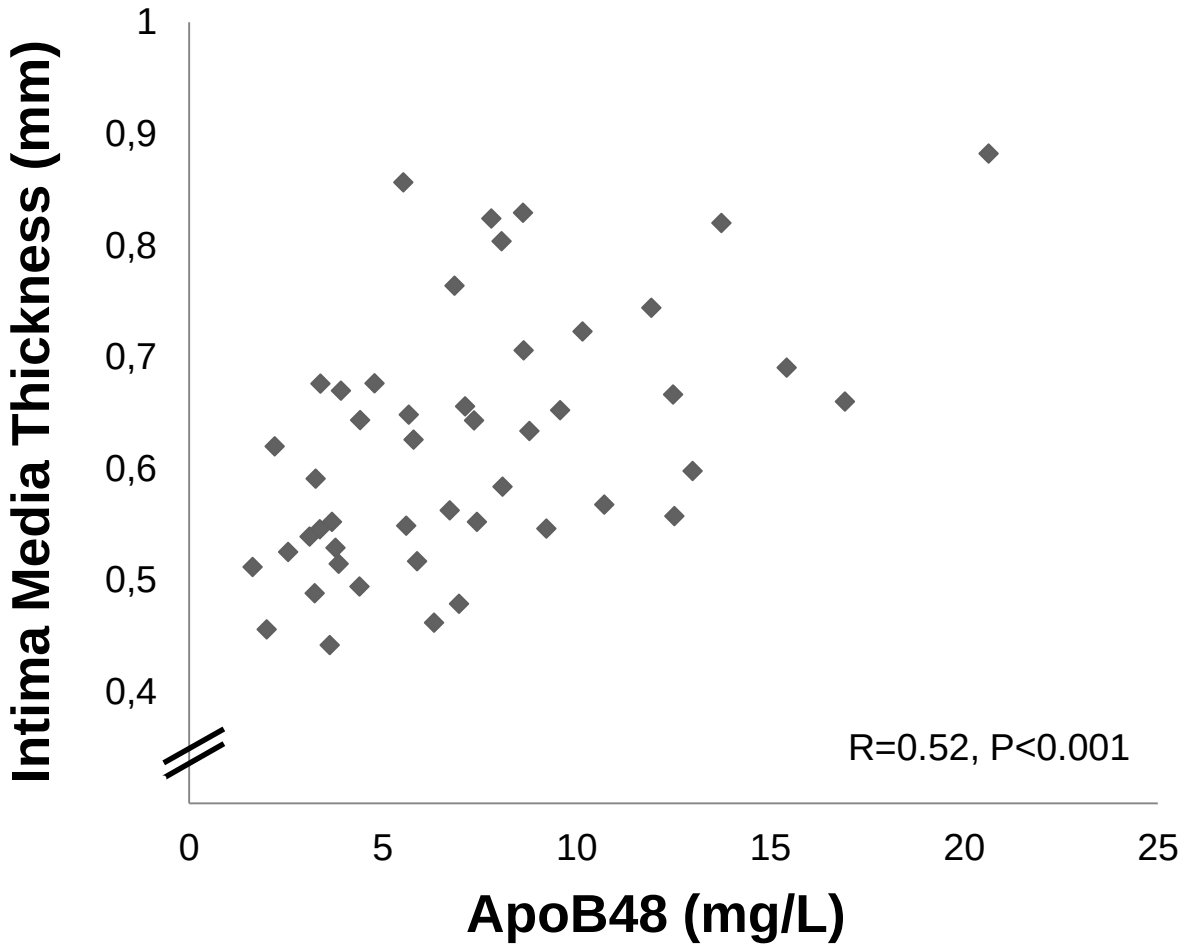
Børge G. Nordestgaard[1]*, Anne Langsted[1], Samia Mora[2], Genovefa Kolovou[3], Hannsjörg Baum[4], Eric Bruckert[5], Gerald F. Watts[6], Grazyna Sypniewska[7], Olov Wiklund[8], Jan Borén[8], M. John Chapman[9], Christa Cobbaert[10], Olivier S. Descamps[11], Arnold von Eckardstein[12], Pia R. Kamstrup[1], Kari Pulkki[13], Florian Kronenberg[14], Alan T. Remaley[15], Nader Rifai[16], Emilio Ros[17,18], and Michel Langlois[19,20], for the European Atherosclerosis Society (EAS) and the

Mean, 75th and 95th cut-off values for fasting and non-fasting **plasma TG** in healthy Dutch subjects

		Males (n=109)			Females (n=104)	
	Mean (SD)	75th percentile	95th percentile	Mean (SD)	75 percentile	95 percentile
Fasting pTG	1,21 (0,67)	1,4	2,2	1,02 (0,60)	1,3	2,1
pTG before lunch	1,31 (0,44)	1,6	2,6	1,22 (0,49)	1,4	2,6
pTG 3 h after lunch	1,77 (0,73)	**2,3**	3,5	1,31 (0,66)	**1,5**	3,4
pTG before dinner	1,83 (0,85)	1,9	3,3	1,29 (0,59)	1,6	3,0

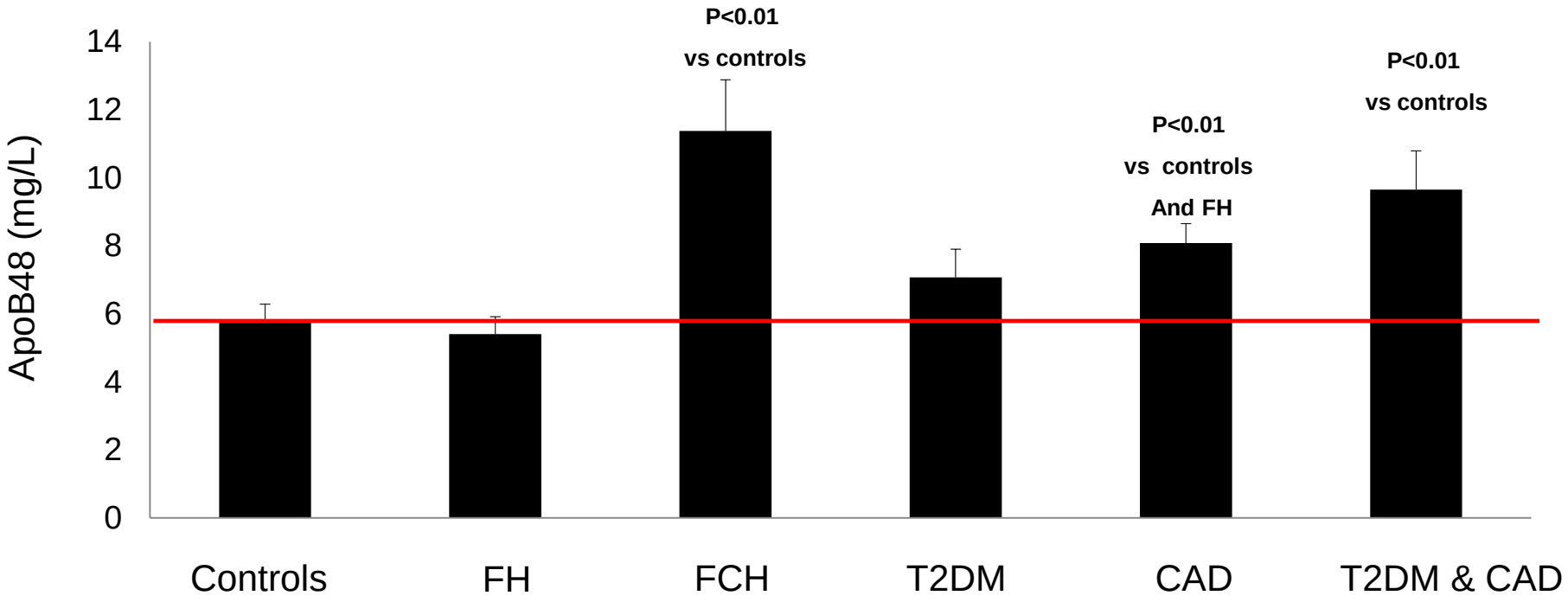
Van Wijk et al Clin Chim Acta 2003

Serum apo B48 is associated with carotid intima media thickness (N=72)



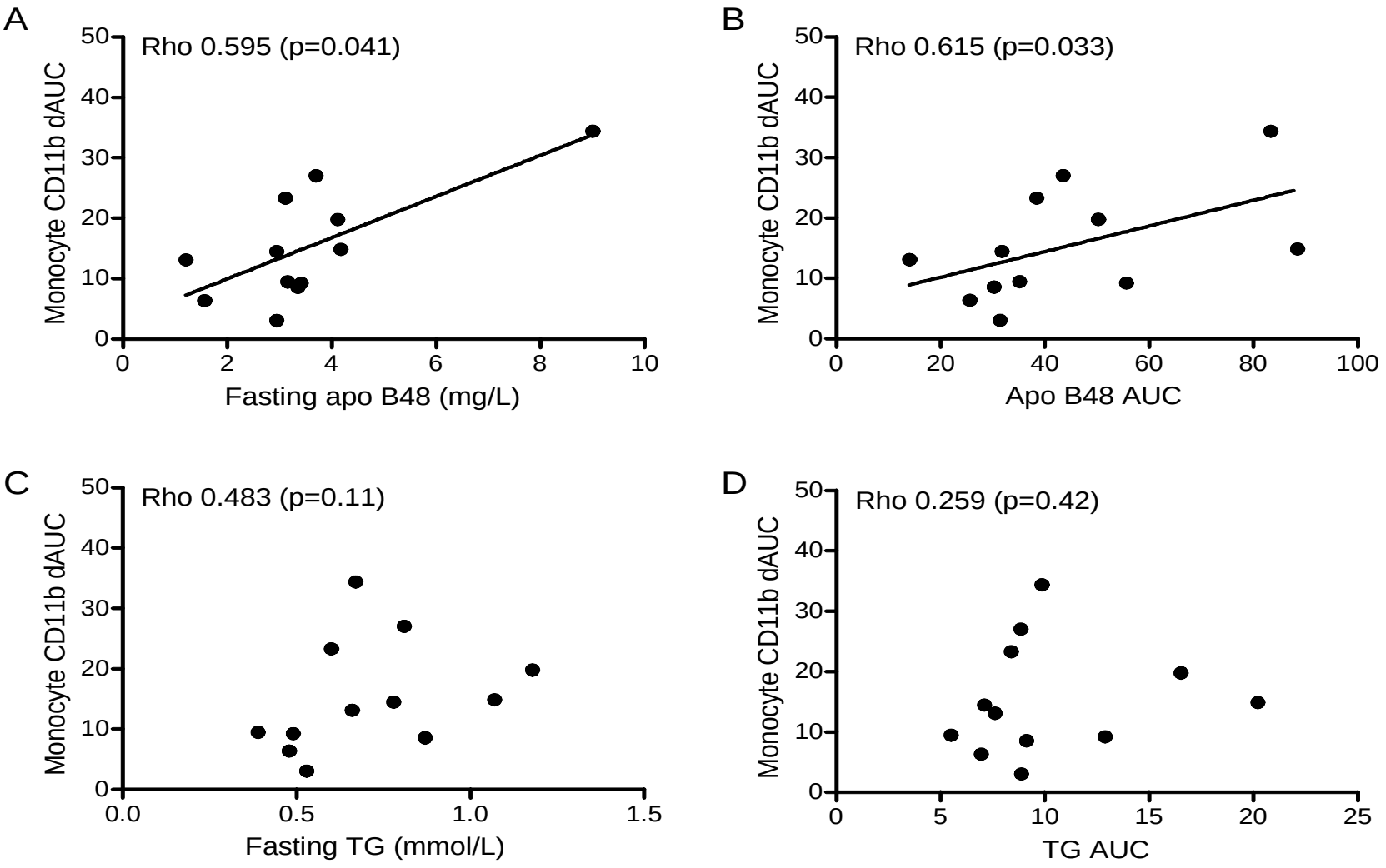
Alipour et al Eur J Clin Invest 2012;42:702-708

Fasting serum apo B48 in different disorders



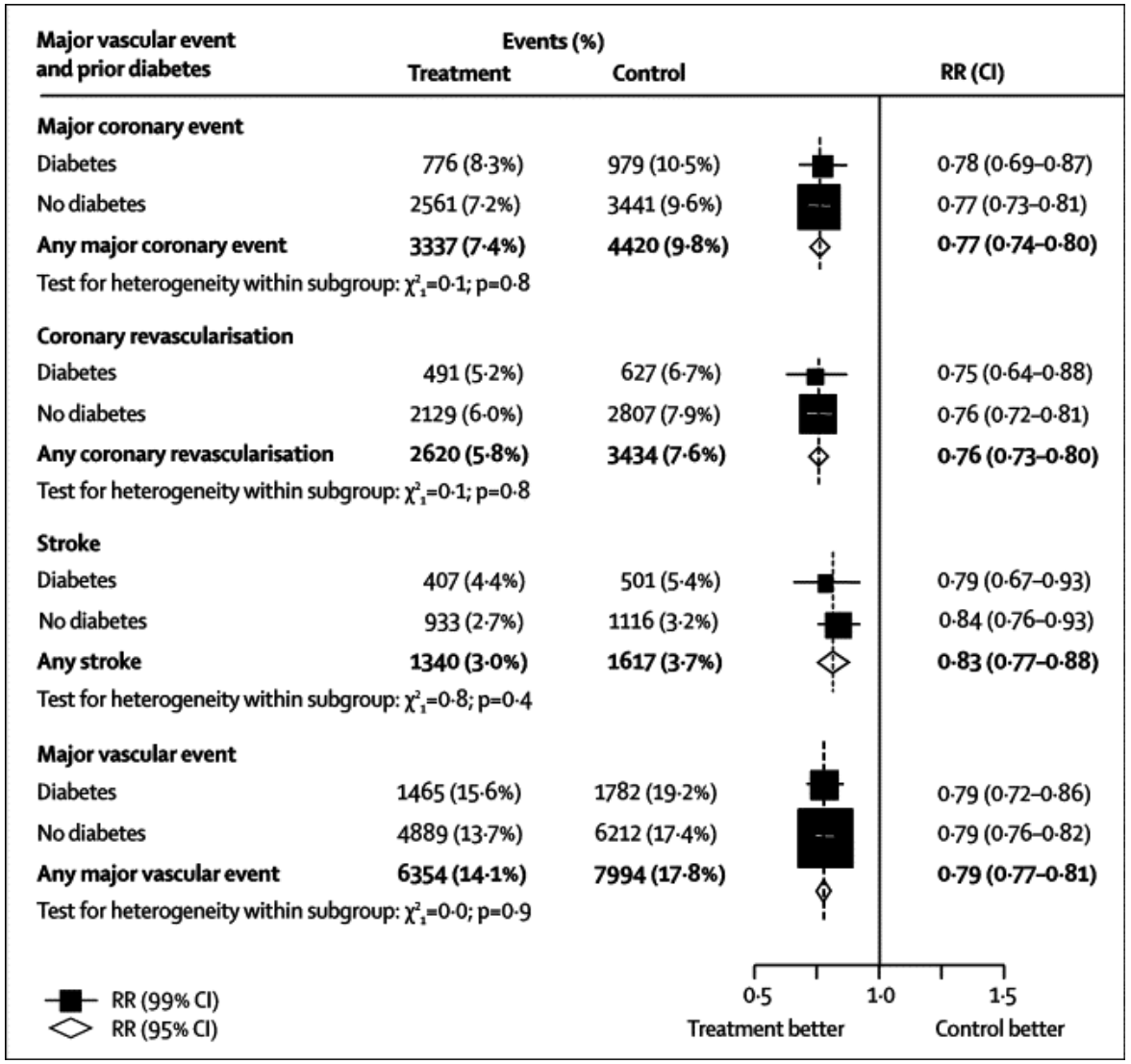
Alipour et al Eur J Clin Invest 2012;42:702-708

Fasting and postprandial apoB48 correlates better with postprandial inflammation than fasting or postprandial TG



MA de Vries et al; Atherosclerosis 2016

Proportional effects on major vascular events per mmol/L reduction in LDLC in participants with or without diabetes



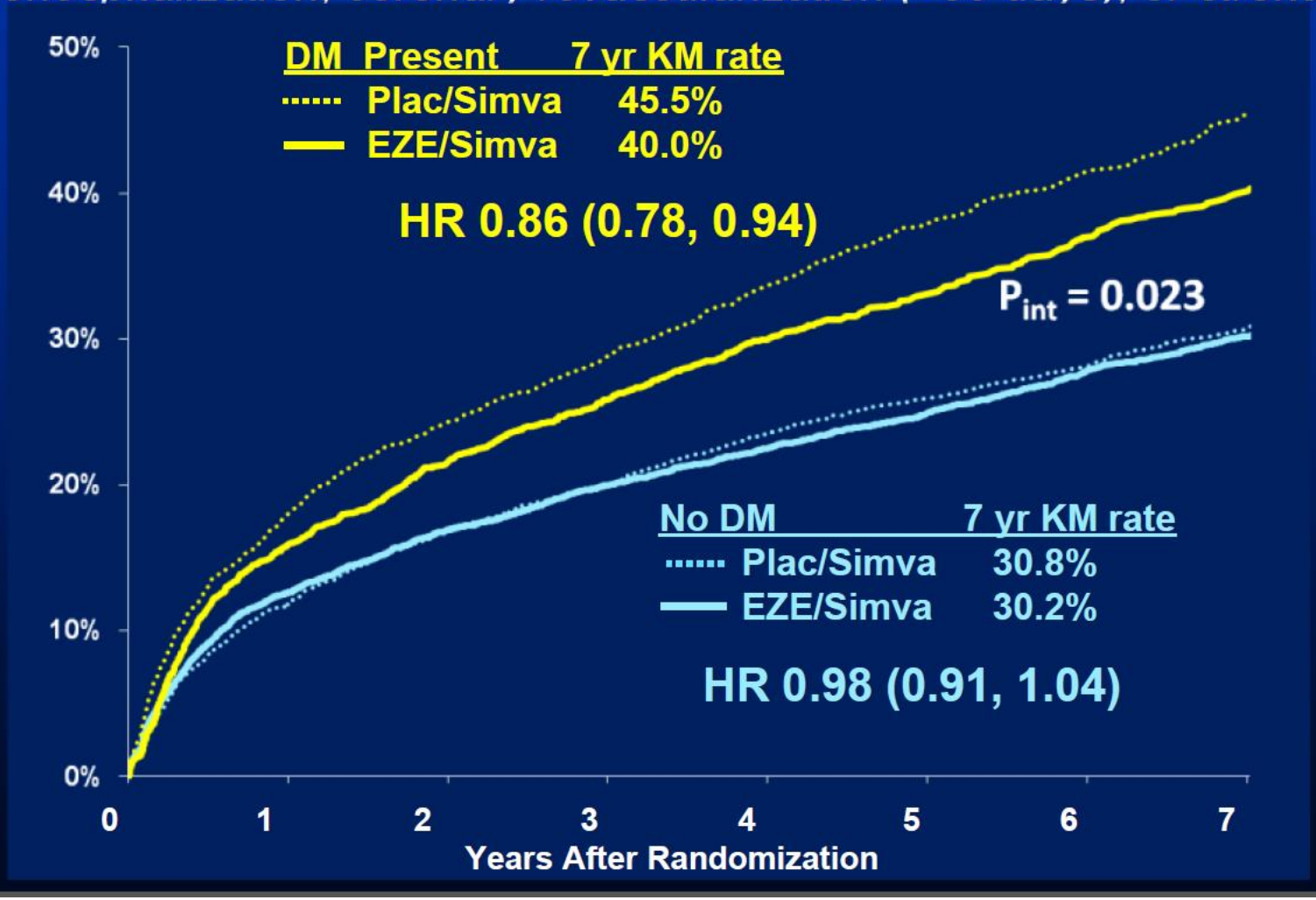
Cholesterol Treatment Trialists' (CTT) Collaborators Lancet, Volume 371, Issue 9607, 2008, 117–125

Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis; Lancet, Volume 371, Issue 9607, 2008, 117–125

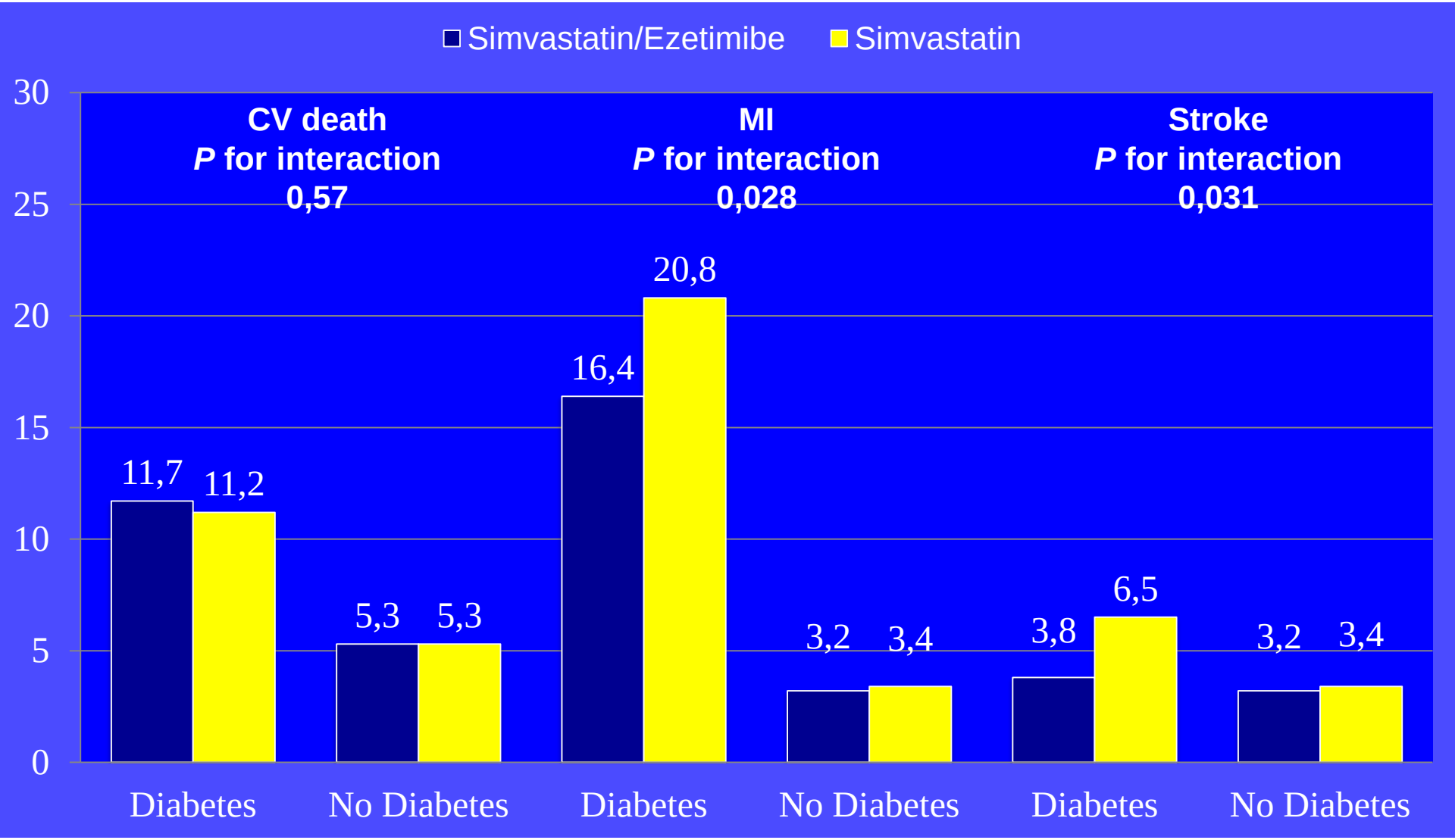
Primary Endpoint — ITT

IMPROVE-IT

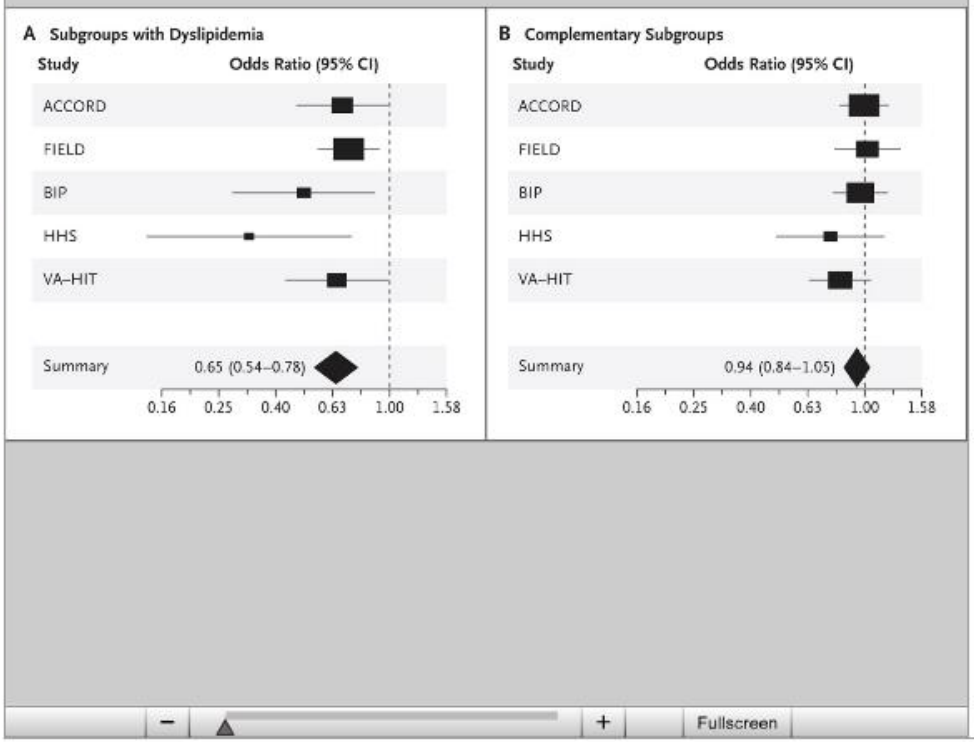
Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



IMPROVE-IT substudy: Greater MI and stroke reduction with Ezetimibe/simvastatin in Diabetic Patients



Effects of fibrate therapy with or without statin in dyslipidemic subjects with low HDLC and high TG compared to those with normal lipids



shown; an odds ratio of less than unity indicates a beneficial therapeutic effect. Panel A shows data from subgroups of patients with dyslipidemia (i.e., high levels of triglycerides and low levels of high-density lipoprotein [HDL] cholesterol), and Panel B shows data from the complementary subgroups without this type of dyslipidemia. The subgroup with dyslipidemia defined according to criteria prespecified in the ACCORD Lipid trial (a triglyceride level of ≥204 mg per deciliter and an HDL cholesterol level of ≤34 mg per deciliter) and the subgroup with levels closest to these lipid criteria in each of the other trials were used. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (Current Controlled Trials number, ISRCTN64783481), the cutoff triglyceride level was greater than or equal to 204 mg per deciliter and the HDL cholesterol level was less than 40 mg per deciliter in men or less than 50 mg per deciliter in women. In the Bezafibrate Infarction Prevention (BIP) study, the triglyceride level was greater than or equal to 200 mg per deciliter and the HDL cholesterol level was less 35 mg per deciliter. In the Helsinki Heart Study (HHS), the triglyceride level was greater than 204 mg per deciliter and the HDL cholesterol level was less than 42 mg per deciliter. In the Veterans Affairs HDL Intervention Trial (VA-HIT;

Adviezen voor de praktijk

- Volg de richtlijnen
- Primair: Verbeter glucose regulatie
- Vraag je af waarom je géén statine aan een diabeet zou geven
- Streef LDL-C< 1,8 mmol/L bij T2DM (vooral bij extra risicofactoren)
- Hoog TG/laag HDLC: overweeg fibraat zeker bij normaal apoB
- Liever combinatie ezetimibe met lagere dosis statine dan maximale statine
- Bij hyperTG (>2,0 mM) met hoog apoB (>0,9 g/L): intensievere statine therapie (small dense LDL!)
- Bij hypertriglyceridemie: denk aan oestrogenen, alcohol, vit A preparaten, voeding
- Bij gecombineerde hyperlipidemie: statine met fibraat (geen gemfibrozil); CAVE: nierfunctie (fibraat) en rabdomyolyse (combi).
- Bij statine intolerante patiënten: monotherapie ezetimibe (20% LDLC reductie), plantenstanolen (10-15% LDL-C daling); PCSK9i
- Harsen gecontraïndiceerd bij verhoogde triglyceriden
- Geen indicatie om standaard CK te controleren zonder klachten bij statine