

atherosclerosis

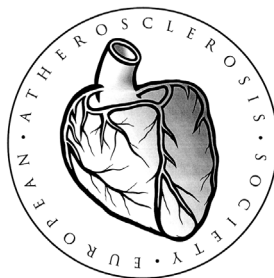
supplements

Editor: Alberico L. Catapano

A review of the evidence on reducing macrovascular risk in patients with atherogenic dyslipidaemia: A report from an expert consensus meeting on the role of fenofibrate–statin combination therapy



Official Journal of the European Atherosclerosis Society
Affiliated with the International Atherosclerosis Society and
the Society of Atherosclerosis Imaging and Prevention



ATHEROSCLEROSIS

SUPPLEMENTS

Editor: Alberico L. Catapano

Official Journal of the European Atherosclerosis Society
Affiliated with the International Atherosclerosis Society and
the Society of Atherosclerosis Imaging and Prevention

Volume 19 (2015)

A review of the evidence on reducing macrovascular risk in patients with
atherogenic dyslipidaemia: A report from an expert consensus meeting on
the role of fenofibrate–statin combination therapy

Carlos Aguiar, Eduardo Alegria, Riccardo C. Bonadonna, Alberico L. Catapano,
Francesco Cosentino, Moses Elisaf, Michel Farnier, Jean Ferrières,
Pasquale Perrone Filardi, Nicolae Hancu, Meral Kayikcioglu, Alberto Mello e Silva,
Jesus Millan, Željko Reiner, Lale Tokgozoglu, Paul Valensi, Margus Viigimaa,
Michal Vrablik, Alberto Zambon, José Luis Zamorano, Roberto Ferrari

Available online at www.sciencedirect.com

ScienceDirect



ELSEVIER

Amsterdam • Boston • London • New York • Oxford • Paris • Philadelphia • San Diego • St. Louis

© 2015 Elsevier Ireland Ltd. All rights reserved.

This journal and the individual contributions contained in it are protected under copyright by Elsevier Ireland Ltd., and the following terms and conditions apply to their use:

Photocopying

Single photocopies of single articles may be made for personal use as allowed by national copyright laws. Permission of the Publisher and payment of a fee is required for all other photocopying, including multiple or systematic copying, copying for advertising or promotional purposes, resale, and all forms of document delivery. Special rates are available for educational institutions that wish to make photocopies for non-profit educational classroom use.

For information on how to seek permission visit www.elsevier.com/permissions or call: (+44) 1865 843830 (UK) (+1) 215 239 3804 (USA).

Derivative Works

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution.

Permission of the Publisher is required for all other derivative works, including compilations and translations (please consult www.elsevier.com/permissions).

Electronic Storage or Usage

Permission of the Publisher is required to store or use electronically any material contained in this journal, including any article or part of an article (please consult www.elsevier.com/permissions).

Except as outlined above, no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior written permission of the Publisher.

Notice

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made.

Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made of it by its manufacturer.

Ⓢ The paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).

ATHEROSCLEROSIS

Official Journal of the European Atherosclerosis Society
Affiliated with the International Atherosclerosis Society and
the Society of Atherosclerosis Imaging and Prevention

EDITOR-IN-CHIEF

S.E. Humphries (London)

ASSOCIATE EDITORS

S. Agewall (Oslo)

M. Arca (Rome)

J. Armitage (Oxford)

R. Asmis (San Antonio)

A. Barakat (Paris)

H. Barrett (Perth)

M. Blaha (Baltimore, MD)

A. Catapano (Milan)

D. Chan (Perth)

Y.S. Chatzizisis (Boston, MA)

G. Dallinga-Thie (Amsterdam)

S. Devaraj (Sacramento, CA)

E. Emanuele (Robbio)

G.P. Fadini (Padova)

C. Falcone (Pavia)

M. Federici (Rome)

K. Ikewaki (Saitama)

I. Jialal (Sacramento, CA)

F. Kronenberg (Innsbruck)

Z. Mallat (Cambridge)

Y. Momiyama (Saitama)

E.D. de Muinck (Linköping)

D.B. Panagiotakos (Athens)

P. Raggi (Atlanta, GA)

R.D. Santos (Sao Paulo)

A. Schmidt-Trucksäss (Basle)

A. Sposito (Campinas)

M. van Greevenbroek
(Maastricht)

P. Welsh (Glasgow)

A. Zampelas (Athens)

REVIEWS EDITOR

A. von Eckardstein (Zürich)

SUPPLEMENTS EDITOR

A. Catapano (Milan)

EDITORIAL BOARD

J. Auer (Braunau)

M. Austin (Seattle)

L. Badimon (Barcelona)

P.J. Barter (Sydney)

M. Boehm (Bethesda, MD)

M.J. Bown (Leicester)

H. Bujo (Chiba)

S.-M. Brand-Herrmann (Münster)

S. Calandra (Modena)

G. Camejo (Mölnal)

M. Castro Cabezas (Rotterdam)

M.J. Chapman (Paris)

A. Cignarella (Padova)

M. van Eck (Leiden)

E. Ercan (Çanakkale)

Z.A. Fayad (New York, NY)

S.J. George (Bristol)

J. Golledge (Townsville)

A. Hirayama (Tokyo)

M. Hofker (Groningen)

E. Hurt-Camejo (Göteborg)

K. Kajinami (Kanazawa)

S. Kasayama (Osaka)

W. Koenig (Ulm)

L. Kritharides (Sydney)

C. Lamina (Innsbruck)

M. Law (London)

A.P. Levy (Haifa)

M.I. Mackness (Manchester, UK)

L. Masana (Reus)

E. Moriguchi (Porto Allegre)

Y. Nakamura (Kyoto)

K. Nasir (Boston, MA)

D. Neely (Newcastle upon Tyne)

P.J. Nestel (Melbourne)

A. Newby (Bristol)

G. Pasterkamp (Utrecht)

Z. Reiner (Zagreb)

R.S. Rosenson (New York, NY)

P. Rubba (Naples)

L.L. Rudel (Winston-Salem, NC)

D. Sviridov (Melbourne)

L. Tannock (Lexington, KY)

L. Tokgözoğlu (Ankara)

G.F. Watts (Perth)

P. Weinberg (London)

O. Wiklund (Göteborg)

S. Yamashita (Osaka)

P. Yaqoob (Reading)

EDITORIAL ASSISTANTS

S. Leigh & K. Henderson (London, UK)



European Atherosclerosis Society

Atherosclerosis is the disease of arteries that is the usual cause of heart attacks and stroke. The European Atherosclerosis Society, founded in 1964, is devoted to advancing knowledge of the causes, natural history, treatment and prevention of the disease, as stipulated by the Society's constitution. Currently composed of over 450 researchers in basic as well as clinical science, membership is open to scientists working in Europe and corresponding membership can be obtained by non-Europeans.

The European Atherosclerosis society organizes a large annual congress and several additional yearly educational activities including our Summer School for young scientists and several collaborative workshops with the IAS and other European Scientific Societies. The society develops guidelines for the treatment and prevention of Atherosclerosis and is a member of the European Joint Prevention Committee. EAS supports outstanding young scientists and EAS members through a series of Grants, Awards and Fellowships. This financial support helps with travel to meetings, research stipends and other educational possibilities.

Major decisions are made by all Society Members by ballot or when assembled at the Annual Members Assembly. An Executive Committee, to which members are elected for a term of three years, takes care of the Society's daily activities. The Society collaborates with other societies in the field of cardiovascular research. Society activities are supported by membership fees as well as by public and private sponsors.

Our Homepage on the Internet:
www.eas-society.org

MEMBERSHIP APPLICATION FORMS:
www.eas-society.org/membership.asp

Executive Committee

President:

Prof. Alberico L. Catapano
Institute of Pharmacological
Sciences, University of Milan
Via Balzaretti 9, 20133 Milan, Italy
E-mail: alberico.catapano@unimi.it

Secretary:

Prof. Petri Kovanen
Director Wihuri Research Institute
Kallioliinantie 4
00140 Helsinki, Finland
Tel: +358 9 681 4131
Fax: +358 9 637 476
E-mail: petri.kovanen@wri.fi

Vice President:

Prof. Olov Wiklund
Department of Cardiology,
Wallenberg Laboratory Sahlgrenska
University Hospital SE-413 45
Gothenburg, Sweden
E-mail: Olov.Wiklund@wlab.gu.se

Treasurer:

Prof. Jan Boren
Institute of Medicine
Wallenberg Laboratory
Sahlgrenska University Hospital
SE-41345 Göteborg
Sweden
Tel: +46 31 342 2949
Fax: +46 31 823 762
E-mail: Jan.Boren@wlab.gu.se

Past President:

Prof. M. John Chapman
Director Dyslipidemia and
Atherosclerosis Research Unit
INSERM (U.551), Hôpital de la Pitié
83, Blvd de l'Hôpital
75651 Paris Cedex 13 France
Tel: +33 1 42 17 78 78
Fax: +33 1 45 82 81 98
E-mail: john.chapman@upmc.fr

EAS Office

Carmel Hayes, Administrative Executive European Atherosclerosis Society, Kronhusgatan 11, SE-41105 Göteborg, Sweden Tel: +46 31 7242795;
Fax: +46 31 7242701; office@eas-society.org
Administrative Assistant: Meredith Lithonen; Tel: +358 4087 7602; E-mail: meredithjbennion@hotmail.com

Committee Members:

Professor Geesje M. Dallinga-Thie
Laboratory of Experimental Vascular Medicine, G1-113, Academic Medical Center, Amsterdam, PO Box 22660, 1100DD Amsterdam, Netherlands;
E-mail: g.m.dallinga@amc.uva.nl

Professor Børge G. Nordestgaard
Department of Diagnostic Sciences, Herlev Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark; E-mail: brno@heh.regionh.dk

Professor Arnold von Eckardstein
University of Zurich, University Hospital of Zurich, Institute of Clinical Chemistry, Rämistrasse 100, 8091 Zürich, Switzerland; E-mail: arnold.voneckardstein@usz.ch

Professor Michal Vrablik
3rd Dept of Internal Medicine, 1st Medical Faculty, Charles University in Prague, U Nemocnice 1, 128 08 Prague 2, Czech Republic; E-mail: vrablikm@seznam.cz

A review of the evidence on reducing macrovascular risk in patients with atherogenic dyslipidaemia: A report from an expert consensus meeting on the role of fenofibrate–statin combination therapy

Carlos Aguiar^a, Eduardo Alegria^b, Riccardo C. Bonadonna^c, Alberico L. Catapano^{*,d},
Francesco Cosentino^e, Moses Elisaf^f, Michel Farnier^g, Jean Ferrières^h,
Pasquale Perrone Filardiⁱ, Nicolae Hancu^j, Meral Kayikcioglu^k, Alberto Mello e Silva^l,
Jesus Millan^m, Željko Reinerⁿ, Lale Tokgozoglu^o, Paul Valensi^p, Margus Viigimaa^q,
Michal Vrablik^r, Alberto Zamboni^s, José Luis Zamorano^t, Roberto Ferrari^u

^aHospital Santa Cruz, Centro Hospitalar de Lisboa Ocidental, EPE, Carnaxide, Portugal

^bCardiology Department, Policlínica Gipuzkoa, San Sebastián, Spain

^cDivision of Endocrinology, Department of Clinical and Experimental Medicine, University of Parma and Azienda Ospedaliera Universitaria of Parma, Italy

^dDepartment of Pharmacological and Biomolecular Sciences, University of Milan, IRCCS Multimedica, Milan, Italy

^eCardiology Unit, Department of Medicine, Karolinska University Hospital, Stockholm, Sweden

^fDepartment of Internal Medicine, University of Ioannina Medical School, Greece

^gPoint Médical, Dijon, France

^hDepartment of Cardiology, Toulouse University School of Medicine, Rangueil Hospital, Toulouse, France

ⁱDepartment of Advanced Biomedical Sciences, Federico II University, Naples, Italy

^jIuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

^kDepartment of Cardiology, Ege University Medical School, Izmir, Turkey

^lHospital Egas Moniz, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal

^mHospital General Universitario Gregorio Marañón, Facultad de Medicina de la Universidad Complutense, Madrid, Spain

ⁿUniversity Hospital Center, School of Medicine, University of Zagreb, Croatia

^oHacettepe University, Ankara, Turkey

^pDepartment of Endocrinology Diabetology Nutrition, Jean Verdier Hospital, APHP, Paris Nord University, CRNH-IdF, CINFO, Bondy, France

^qNorth Estonia Medical Centre, Tallinn University of Technology, Estonia

^r3rd Department of Internal Medicine, 1st Medical Faculty, Charles University, Prague, Czech Republic

^sClinica Medica, Department of Medicine, University of Padova, Italy

^tUniversity Alcalá de Henares, Hospital Ramón y Cajal, Madrid, Spain

^uDepartment of Cardiology and LTTA Centre, University Hospital of Ferrara and Maria Cecilia Hospital, GVM Care & Research, E.S. Health Science Foundation, Cotignola, Italy

Abstract

A meeting of European experts in cardiovascular (CV) disease and lipids was convened in Paris, France, on 10 November 2014 to discuss lipid profile, and in particular atherogenic dyslipidaemia (AD), and associated CV risk. Key points that were raised and discussed during the meeting are summarised in this paper, which also accounts for further discussion and agreement on these points by the group of experts. Elevated levels of low-density lipoprotein cholesterol (LDL-c) are commonly associated with a greater CV risk than low LDL-c levels, and are routinely managed with statins. However, even for patients controlled on statins and achieving low LDL-c levels, abnormal lipid profiles observed in some patients (i.e. elevated triglyceride levels, with/without low levels of high-density lipoprotein cholesterol [HDL-c]) have been linked to the presence of a residual CV risk. Therefore, it is recommended that both triglyceride and HDL-c levels be measured, to allow for the overall CV residual risk to be adequately managed. Favourable safety and clinical data support the combination of statins with other lipid-lowering agents, such as fenofibrate. Patients who have elevated triglyceride levels plus low levels of HDL-c are most likely to achieve clinical benefit from fenofibrate–statin combination therapy. In these patients with AD, achieving target non-HDL-c levels should be a key focus of CV risk management, and the use of non-HDL-c was advocated to provide a better measure of CV risk than LDL-c levels. © 2015 Elsevier Ireland Ltd. All rights reserved.

Keywords: Atherogenic dyslipidaemia; cardiovascular risk; cholesterol; combination therapy; fenofibrate; statins; triglycerides

* Corresponding author. Professor Alberico L. Catapano, Department of Pharmacological and Biomolecular Sciences, University of Milan, Via Balzaretti, 9, 20133 Milan, Italy. Tel.: +39 02 5031 8302; fax: +39 02 5031 8386.
E-mail address: alberico.catapano@unimi.it (A.L. Catapano).

Conversion factors

cholesterol mg/dL = mmol/L × 38.6
triglycerides mg/dL = mmol/L × 88.5
glucose mg/dL = mmol/L × 18

Introduction

A meeting of European experts in cardiovascular (CV) disease and lipids was convened in Paris, France, on 10 November 2014 to discuss current understanding of atherogenic dyslipidaemia (AD) and its associated macrovascular risk. The meeting was co-chaired by Alberico Catapano and Roberto Ferrari who moderated group discussions on the evidence base supporting the role of fenofibrate–statin combination therapy in reducing macrovascular risk in patients with AD, following introductory presentations by Carlos Aguiar, Michel Farnier and Alberto Zambon. This paper summarises the experts' current understanding within the context of the literature, and reviews the key points discussed both during and after the meeting.

Current understanding of atherogenic dyslipidaemia, cardiovascular risk and first-line statin therapy

Atherogenic dyslipidaemia

Atherogenic dyslipidaemia is characterised by increased levels of total triglycerides and very-low-density lipoprotein (VLDL) triglycerides, decreased levels of high-density lipoprotein cholesterol (HDL-c), as well as levels of low-density lipoprotein cholesterol (LDL-c) that are normal or moderately increased (Table 1) [1–4]. The LDL particles in AD are smaller and more dense, and have an increased atherogenic potential [5]; small, dense HDL particles also occur [6].

Prevalence of AD was reported in the Dyslipidemia International Study, which was conducted on 22 063 statin-treated outpatients (with or without diabetes) in Europe and Canada [7], and showed that elevated triglycerides and/or low HDL-c levels were persistent in these patients. AD is, however, generally under-treated and under-controlled [8]; understanding of the pathophysiology underlying AD is limited and further research is warranted.

Lipid abnormalities and associated macrovascular risk

Epidemiological data support the significant association between high levels of LDL-c and increased CV risk compared with low levels of LDL-c. Moreover, there is a high level of concordance between epidemiological, genetic and clinical-trial data sets in support of this relationship [10,11]. For example, observational epidemiology estimates derived from >25 000 individuals in prospective cohort studies showed that a one standard deviation increase in LDL-c was associated with an increased risk of myocardial infarction (MI) (odds ratio [OR]: 1.54; 95% confidence interval [CI]: 1.45, 1.63). Likewise, a Mendelian randomisation study showed that a one standard deviation increase in LDL-c conferred by genetic score increased MI risk significantly (OR: 2.13; 95% CI: 1.69, 2.69; $p = 2 \times 10^{-10}$) [12].

Understanding the direct effects of LDL-c levels on CV risk is simpler than comprehending those based on HDL-c levels and triglycerides. Unlike LDL, HDL is highly heterogeneous in terms of its physicochemical properties, size, shape,

Table 1.
Lipid profile in atherogenic dyslipidaemia [1–4].

Lipid parameter	Atherogenic dyslipidaemia	Thresholds ^a
LDL-c	• Normal/moderate increase in LDL-c levels • Increase in small, dense LDL particles	n/a
HDL-c	• Decrease in HDL-c levels • Increase in small, dense HDL particles	Men: <1.0 mmol/L Women: <1.3 mmol/L
Triglycerides	• Increase in total triglycerides • Increase in VLDL triglycerides	≥1.7 mmol/L

^a According to the International Atherosclerosis Society's definition of the metabolic syndrome [9].

-c = cholesterol, HDL = high-density lipoprotein, LDL = low-density lipoprotein, VLDL = very-low-density lipoprotein.

density, apolipoprotein composition and surface charge, which reflects the diverse functions of HDL [13]. Beyond reverse cholesterol transport, HDL subpopulations also exert antioxidant, anti-inflammatory, cytoprotective, vasodilatory, anti-infectious and immunomodulatory effects [14]; HDL particles may improve glucose metabolism [15] and play a role in the development of type 2 diabetes mellitus (T2DM) [16,17]. HDL-c levels (together with triglycerides) can help in the assessment of the residual CV risk in statin-treated patients who have low LDL-c levels, but may still be at risk for CV events due to high triglyceride and/or low HDL-c levels. Findings from two meta-analyses demonstrated that individuals on statin treatment with low levels of HDL-c (≤ 0.9 mmol/L) experienced a higher incidence of major CV events than those with HDL-c > 1.1 mmol/L, not only in the general population but also in patients with T2DM [18,19]. Importantly, these findings emphasise the higher CV-event burden associated with low levels of HDL-c in patients with T2DM compared with the general population. Although low HDL-c is predictive of increased CV risk, the complexity of its metabolic interrelationship with additional risk factors (e.g. LDL-c and triglyceride levels) must be considered.

The prevalence of low HDL-c and high triglyceride levels in patients with proven CV disease has been evaluated in a number of studies and shows the importance of AD as a potential CV risk factor [20,21]. Furthermore, data from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction), ACCORD-Lipid (Action to Control Cardiovascular Risk in Diabetes), IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering) and TNT (Treating to New Targets) studies demonstrate that higher triglyceride levels are associated with higher rates of death and major CV events [22,23]. In addition, data from these key clinical studies highlight that combinations of high levels of LDL-c plus high triglyceride levels (PROVE IT-TIMI 22) and low levels of HDL-c plus high triglyceride levels (ACCORD-Lipid) are associated with the highest risk of major CV events [23,24]. In the ACCORD-Lipid study in particular, patients with AD (defined as high levels of triglycerides ≥ 2.31 mmol/L) and low levels of HDL-c

Odds ratio for CHD in patients after LDL target ^a		Triglyceride quintile (mmol/L)				
		≤0.8	0.8–1.2	1.2–1.5	1.5–2.1	>2.1
HDL quintile (mmol/L)	>1.4	1.0	0.9	0.8	0.6	0.6
	1.1–1.4	1.3	1.3	1.2	1.2	1.2
	0.9–1.1	1.8	1.9	2.0	2.2	2.4
	0.8–0.9	2.3	2.8	3.4	4.1	5.0
	≤0.8	3.1	4.2	5.6	7.6	10.3

Figure 1. Synergistic detrimental impact of high levels of triglycerides and low levels of HDL-c on residual CV risk in patients on target LDL-c.

^a 345 patients with mean LDL-c <2.1 mmol/L.

CHD = coronary heart disease, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Carey VJ, et al. *Am J Cardiol* 2010 Sep 15;106(6):757–63, with permission from Elsevier.

[≤0.88 mmol/L]) had a 71% greater rate of major CV events compared with patients without AD [24]. These findings have been corroborated by other researchers who identified a synergistic detrimental impact of high levels of triglycerides and low levels of HDL-c on residual CV risk in subjects with target LDL-c levels (Figure 1) [25]. This is reinforced by a meta-analysis of seven clinical trials analysing intravascular ultrasound performed on 3437 patients with coronary artery disease, which showed that despite achieving LDL-c ≤1.81 mmol/L, over 20% of patients continued to show evidence of plaque progression [26]. These patients had notably high levels of triglycerides and apolipoprotein B, demonstrating the need to control atherosclerotic factors beyond LDL-c in the prevention of coronary heart disease (CHD) [26]. Moreover, analysis of data from 3501 individuals in the Framingham Offspring Study found that all combinations of high LDL-c (>3.4 mmol/L), low HDL-c (<1.0 mmol/L) and high triglyceride levels (>1.7 mmol/L), with the exception of isolated hypertriglyceridaemia, led to an increased risk of CV disease [27].

Data from the PROVE IT-TIMI 22 study in subjects who reached target LDL-c levels (<1.8 mmol/L) showed that subjects with low triglyceride levels (<1.7 mmol/L) achieved a greater relative CV-risk reduction than those with triglyceride levels ≥1.7 mmol/L (–28% vs –16%, respectively) [23]. Further data from the study demonstrated that higher triglyceride levels are associated with a significantly increased risk of death, MI or recurrent acute coronary syndrome ($p < 0.001$). A clear association between elevated triglycerides levels and increased risk of CV disease was also identified in the Copenhagen City Heart Study, Copenhagen General Population Study and the Emerging Risk Factors Collaboration [28]. Moreover, findings from the Copenhagen City Heart Study highlighted the association between elevated levels of non-fasting triglycerides and increased risk of MI irrespective of gender [29], as well as increased risk of ischaemic stroke [30]. A meta-analysis conducted on data from the dal-OUTCOMES and the MIRACL (Myocardial Ischemia Reduction with Acute Cholesterol Lowering) trials involving 15 817 and 1501 statin-treated patients with acute coronary syndrome (ACS), respectively, showed that elevated fasting triglycerides (reflecting triglyceride-rich

lipoproteins) were associated with short- and long-term risk of ACS [31]. Based upon all the evidence, it seems that it is currently beyond any doubt that elevated triglycerides are indeed a risk factor for CV events [32].

There is evidence to support an increased risk of CHD and ischaemic stroke associated with lower levels of HDL-c [33]. The importance of AD in cerebrovascular disease was also demonstrated in an exploratory analysis of data from patients with stroke or transient ischaemic attack receiving best medical therapy, including statins, in two prospective randomised trials (PERFORM [Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin with Terutroban in Patients with a History of Ischemic Stroke or Transient Ischemic Attack] and SPARCL [Stroke Prevention by Aggressive Reduction in Cholesterol Levels]) [34]. Patients with AD (low HDL-c ≤1.0 mmol/L; high triglycerides ≥1.7 mmol/L) had an increased residual risk of major CV events *versus* those without AD [34]. Furthermore, analysis of data from the TNT study showed that HDL-c levels remain predictors of residual risk for 5-year major CV events, despite patients having reached target LDL-c levels (<1.8 mmol/L) [35].

Specific triglyceride-rich lipoprotein remnants (i.e. remnant VLDL and intermediate-density lipoproteins [IDL]) have also been linked to CV risk. Preclinical data support the atherogenic-promoting nature of remnant triglyceride-rich lipoproteins [36–38]. An analysis of data from 73 513 subjects in the Copenhagen General Population Study, Copenhagen City Heart Study, and Copenhagen Ischemic Heart Disease Study found robust clinical evidence to support the role of remnant lipoproteins as a CV risk factor [39,40]. Findings from this study showed that causal and observational risk estimates for ischaemic heart disease increased significantly by 182% ($p = 1 \times 10^{-17}$) and 37% ($p = 5 \times 10^{-17}$), respectively, per 1 mmol/L increase in remnant lipoprotein cholesterol levels.

Further clinical evidence suggesting the utility of remnant lipoproteins as a CV risk factor is based on a subgroup analysis from the ACCORD-Lipid study that identified a significantly greater reduction in post-prandial triglyceride levels in patients treated with statin plus fenofibrate compared with those on statin monotherapy ($p = 0.008$) [41]. However, statin plus add-on therapy led to significant

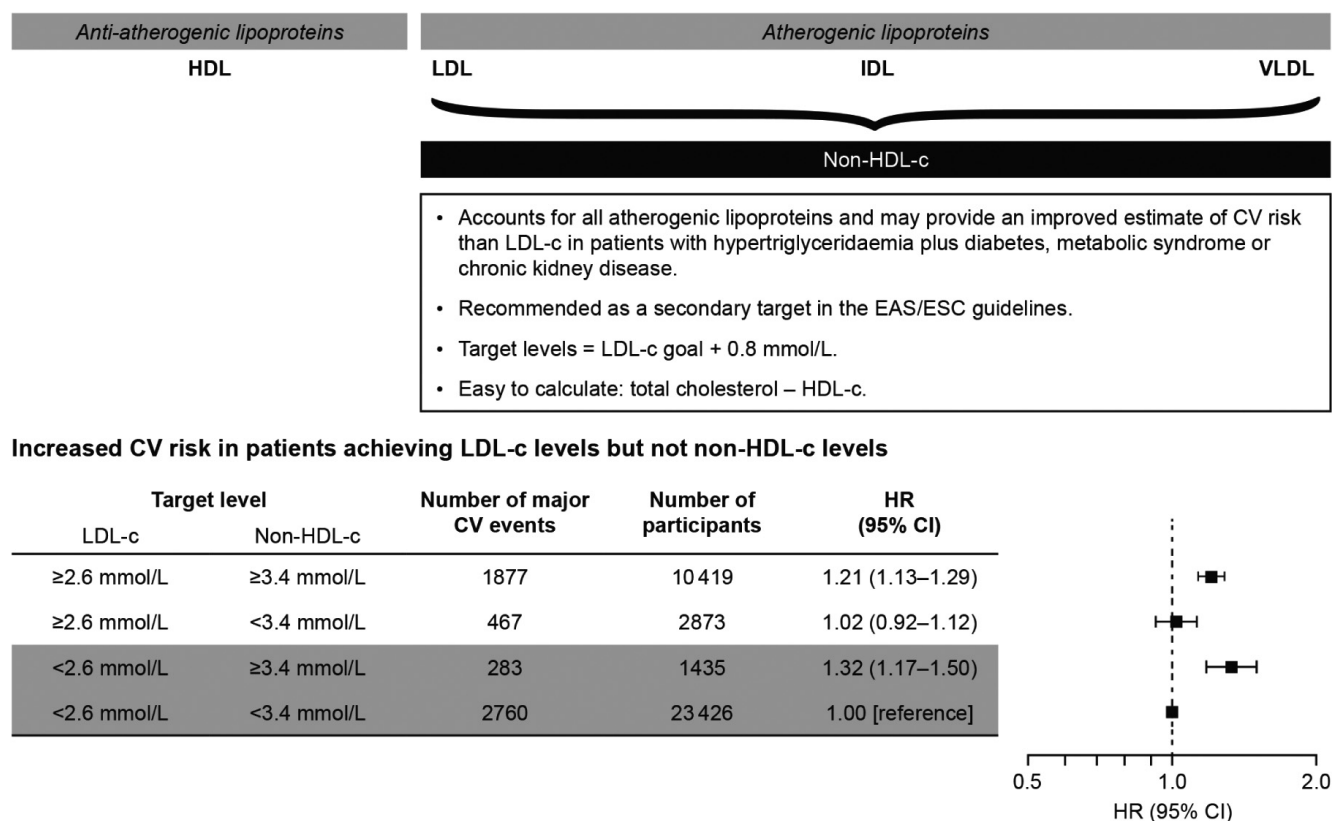


Figure 2. Non-HDL-c: Emerging target for the treatment of (residual) CV risk.

-c = cholesterol, CI = confidence interval, CV = cardiovascular, EAS = European Atherosclerosis Society, ESC = European Society of Cardiology, HDL = high-density lipoprotein, HR = hazard ratio, IDL = intermediate-density lipoprotein, LDL = low-density lipoprotein, VLDL = very-low-density lipoprotein. Boekholdt SM, et al. *JAMA* 2012 Mar 28;307(12):1302-9. Copyright © 2012 American Medical Association. All rights reserved.

reductions in apolipoprotein B48 levels compared with statin monotherapy only in a subset of patients with increased fasting triglyceride levels ($p = 0.003$). These findings should be interpreted with caution given the limited number of genetic variants tested, the use of high-fat meals containing a sizeable fraction of proteins and carbohydrates, and the variable, unspecified use of antidiabetic medications. The last two factors could potentially increase interpatient variability in insulin response. In addition, analysis of data from niacin studies suggests that changes in small LDL particles and triglyceride-rich lipoprotein subfractions are significantly associated with changes in risk of major CV events [42].

Non-HDL-c is well defined as a secondary target in the treatment of dyslipidaemias in the European Atherosclerosis Society (EAS)/European Society of Cardiology (ESC) guidelines, which set a specific target of 0.8 mmol/L higher than the corresponding LDL-c target [11], and its importance is also stressed in the European guidelines on CV disease prevention in clinical practice [43]. Moreover, non-HDL-c measures account for all atherogenic lipoproteins and is believed to provide an improved estimate of CV risk than LDL-c in those who have hypertriglyceridaemia plus diabetes, metabolic syndrome or chronic kidney disease. Optimising secondary targets can be considered in patients at very high CV risk after achieving a target LDL-c; if non-HDL-c is used, the targets should be <2.6 mmol/L (in patients with T2DM and CV disease or chronic kidney disease, and those >40 years of age without CV disease but who have at

least one other CV-disease risk factor or markers of target organ damage) and <3.3 mmol/L in all patients with T2DM. Findings from a meta-analysis of 62 154 statin-treated patients enrolled in eight trials, with data published between 1994 and 2008, demonstrated that patients who achieved target LDL-c levels without reaching target non-HDL-c levels had a 32% increased risk of CV events compared with those who achieved dual target levels for LDL-c and non-HDL-c (Figure 2) [44]. This finding may be due to the presence of unstable atherosclerotic plaques given that non-HDL-c is a far better predictor of plaque inflammation than LDL-c [45], as further evidenced by the previously described meta-analysis of Bayturan and colleagues [26].

Lipid abnormalities and associated microvascular risk

Clinical management of patients with T2DM has been mostly concentrated on prevention of macrovascular complications, more precisely CV disease due to atherosclerosis. However, recent data highlight the importance of microvascular complications, particularly diabetic retinopathy, nephropathy and neuropathy, which are responsible for >50% of the disability burden associated with diabetes and impose an immense health cost [46–52].

Several comprehensive reviews have highlighted AD as an important contributor not only to lipid-related residual macrovascular risk, but also to microvascular complications in patients with T2DM receiving best standards of care

for prevention of CV disease, including intensive statin treatment [53–56]. For example, the Verona Diabetes Study, a longitudinal, observational study in 979 patients with T2DM, highlighted the relevance of a high fasting triglycerides/HDL-c ratio to the increased risk of developing diabetic retinopathy or nephropathy [57]. This association was independent of confounding factors, including glycated haemoglobin, blood pressure, LDL-c, albuminuria, T2DM duration and body mass index. A post-hoc analysis from the ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation) study also highlighted low levels of HDL-c as a prognostic factor for the development of diabetic-related renal events, in particular new-onset albuminuria; however, an association between low levels of HDL-c and the risk of diabetic retinopathy was not established [58].

Most recently, the role of AD in determining microvascular risk has been strengthened by results from the REALIST (REsiduAl risk, LIpids and Standard Therapies) study performed in 13 countries on 2535 patients with T2DM who had diabetic kidney disease, diabetic retinopathy or both complications, and 3683 matched controls [59]. Elevated levels of triglycerides and low levels of HDL-c were both significantly and independently associated with diabetic microvascular complications, specifically diabetic kidney disease, while the association was not robust for diabetic retinopathy. Available data on the relevance of elevated triglycerides for progression of diabetic neuropathy, a causative factor in lower-extremity amputations, are much more modest [60,61].

Simultaneous treatment of multiple risk factors may help reduce the risk of micro- as well as macrovascular complications. The STENO-2 study showed that in patients with T2DM and microalbuminuria, an intensive long-term (mean 7.8 years) multifactorial approach targeting blood glucose, blood pressure and lipids leads to a reduction in the risk of not only cardiovascular disease (hazard ratio [HR]: 0.47; 95% CI: 0.24, 0.73), but also diabetic nephropathy (HR: 0.39; 95% CI: 0.17, 0.87), retinopathy (HR: 0.42; 95% CI: 0.21, 0.86), and cardiac autonomic neuropathy (HR: 0.37; 95% CI: 0.18, 0.79) [62], but the residual risk for these complications remains high.

Collectively, these data suggest a rationale for targeting AD, in addition to best standards of care, to reduce the residual risk of diabetic microvascular complications in patients with T2DM.

First-line therapy of dyslipidaemia and CV risk

There is a substantial evidence base of published data from primary and secondary prevention studies describing the established relationship between reduced incidence of CHD events and low levels of LDL-c due to intensive, primarily statin-based, lipid-lowering therapy [63–66].

Findings from a Cholesterol Treatment Trialists' (CTT) Collaborators meta-analysis demonstrated that statin therapy reduces not only the 5-year incidence of major vascular events by 21% per mmol/L unit reduction in LDL-c, but also the risk of all-cause, all-vascular and CHD-related mortality

[18]. Moreover, findings from another CTT Collaborators group meta-analysis of 14 randomised statin studies in 18 686 patients with T2DM demonstrated that each mmol/L unit reduction in LDL-c levels translates into significantly lower rates of total mortality (–9%; $p = 0.02$), vascular mortality (–13%; $p = 0.008$), MI or coronary mortality (–22%; $p < 0.0001$) and stroke (–21%; $p = 0.0002$) [19].

Beneficial effects of lowering LDL-c levels further were investigated in the long-term IMPROVE-IT (IMPROved Reduction of Outcomes: Vytorin Efficacy International Trial) study conducted in 18 144 patients with post-acute coronary syndrome [67]. In this study, a combination of ezetimibe with simvastatin was associated with a 24% decrease of LDL-c levels at Year 1, compared with simvastatin alone (end of Year 1 mean LDL-c: 1.4 vs 1.8 mmol/L; $p < 0.001$). Simvastatin plus ezetimibe therapy also led to a significant improvement in the primary endpoint of overall CV event rate (7-year composite measure of CV death, MI, unstable angina, coronary revascularisation or stroke) compared with simvastatin alone (32.7% vs 34.7%; $p = 0.016$) (7-year numbers needed to treat [NNT₇] = 50).

However, patients receiving statin treatment may still be at risk of CV events, i.e. residual CV risk, depending on their lipid profile. Further findings from the CTT meta-analysis demonstrated that residual CV risk is high in patients with T2DM and statin-treated vascular disease in comparison to those without T2DM and with placebo-treated vascular disease, as evaluated by rate of vascular disease events (26.3% vs 23.5%, respectively) [19]. Data from several outcome trials highlight the magnitude of the challenge posed by residual CV risk despite statin therapy, with AD being recognised as an important modifiable lipid factor of residual CV risk, especially in patients with insulin resistance, by the Residual Risk Reduction Initiative (R3i) [54,68].

Based on the currently available data, a different approach to lipid-lowering treatment has been advocated for patients with AD beyond statin monotherapy [69]. This may mirror antihypertensive treatment, which evolved from monotherapy several decades ago to include combinations of two, three or even four drugs to lower blood pressure by different mechanisms to achieve optimal effects.

The role of fenofibrate add-on therapy to statins in reducing residual CV risk

Fenofibrate and reduced risk of macrovascular events

Fenofibrate is a peroxisomal proliferator-activated receptor alpha (PPAR α) agonist that exerts a range of lipid-modifying and non-lipid-modifying effects [70]. Lipid effects associated with fenofibrate use include reduced triglyceride levels, increased HDL-c levels and a reduction in the number of small, dense LDL particles, which arise due to changes in the expression of genes that modify lipid metabolism.

Several studies have contributed evidence in support of the clinical benefits of fenofibrate–statin combination therapy. For example, findings from a US multicentre, randomised, double-blind, active-controlled, 18-week study (SAFARI [Simvastatin plus Fenofibrate for Combined

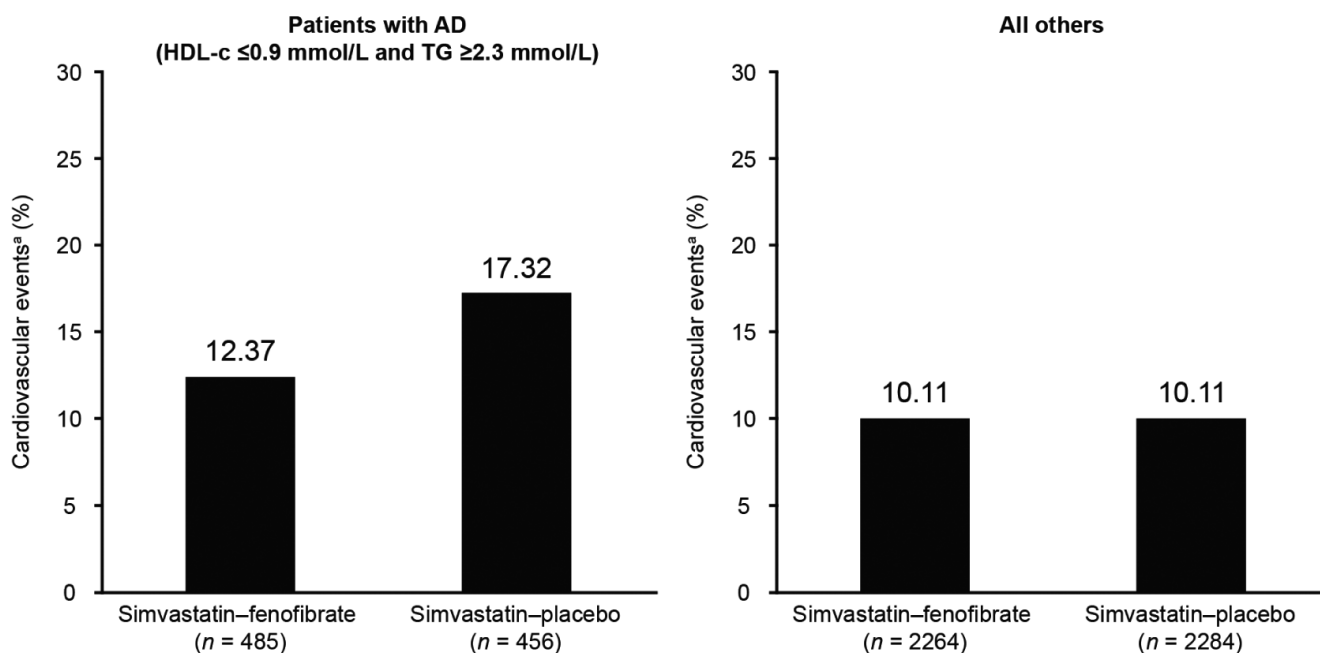


Figure 3. Effect of simvastatin-fenofibrate *versus* simvastatin treatment in patients with AD and in all other patients in the ACCORD-Lipid study.

* Cardiovascular events (primary outcome): first occurrence of non-fatal myocardial infarction, non-fatal stroke or death from cardiovascular causes.

ACCORD = Action to Control Cardiovascular Risk in Diabetes, AD = atherogenic dyslipidaemia, HDL-c = high-density lipoprotein cholesterol, TG = triglycerides.

Adapted from Ginsberg HN, et al. *N Engl J Med* 2010 Apr 29;362(17):1563-74.

Hyperlipidemia]) in 618 patients with combined hyperlipidaemia (fasting triglyceride levels ≥ 1.7 and ≤ 5.6 mmol/L, and LDL-c > 3.4 mmol/L) demonstrated that fenofibrate-simvastatin combination therapy leads to significantly greater improvements in lipoprotein profile (triglycerides, LDL-c, HDL-c, total cholesterol, non-HDL-c, apolipoprotein B and apolipoprotein A-I; $p < 0.001$) compared with simvastatin monotherapy [71]. Improvements were observed within 4 weeks of starting fenofibrate-simvastatin combination therapy and there was evidence to suggest that fenofibrate may mitigate the glucose-elevating effects of simvastatin monotherapy. Moreover, fenofibrate-simvastatin combination therapy led to a significantly greater reduction from baseline in the proportion of small, dense LDL particles at Week 12 (72.2% vs 32.1%; $p < 0.001$), compared to the monotherapy group (81.0% vs 81.6%; $p < 0.001$ vs combination therapy).

Further evidence comes from the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD-Lipid studies, which recruited patients with T2DM but did not require patients to have atherosclerotic CV disease at baseline [24,72-74]. In the FIELD study, 9795 patients with no current statin indication at baseline were randomised to fenofibrate monotherapy or placebo; however, a statin or other lipid-lowering agent could be initiated in either treatment group throughout the course of the 5-year study [72]. Significantly more patients in the placebo group were taking non-study lipid-lowering agents (essentially statins) by the end of the study, compared to patients in the fenofibrate group ($p < 0.0001$). In this study, the baseline triglyceride levels were 1.73 and 1.74 mmol/L in the

placebo and fenofibrate groups, respectively. Fenofibrate was associated with a non-significant 11% relative reduction in the primary endpoint (first occurrence of either non-fatal MI or death due to CV causes) ($p = 0.16$), which corresponded to a significant 24% relative reduction in non-fatal MI ($p = 0.01$). Although the primary endpoint was not met in the FIELD study, significant improvements across a range of secondary, macrovascular-related outcomes were observed in fenofibrate-treated patients compared with those in the placebo group. Of note, a subgroup analysis in patients with low HDL-c levels ($< 1.0/1.3$ mmol/L) and/or high triglyceride levels (≥ 2.3 mmol/L) suggested that these patients might derive particular benefit from fenofibrate-based therapy, with a relative reduction in CV death, MI, coronary/carotid event or revascularisation *versus* placebo of 14%, 13% and 27% in patients with low levels of HDL-c or marked hypertriglyceridaemia (≥ 1.7 mmol/L), or both low levels of HDL-c and high levels of triglycerides (≥ 2.3 mmol/L), respectively [74].

In the ACCORD study, 10 251 patients with T2DM who were at high risk of CV disease were randomised to receive either intensive glycaemic control or standard therapy; a subgroup of patients were also enrolled in the ACCORD-Lipid trial and randomised to receive simvastatin plus either fenofibrate or placebo (Figure 3) [24,75]. The study's primary endpoint (first occurrence of a major CV event, including non-fatal MI, non-fatal stroke, or death from CV causes) was not met, with a non-significant 8% relative-risk reduction reported in the fenofibrate-simvastatin group compared with simvastatin monotherapy. Of note, the median triglyceride levels at baseline in all patients

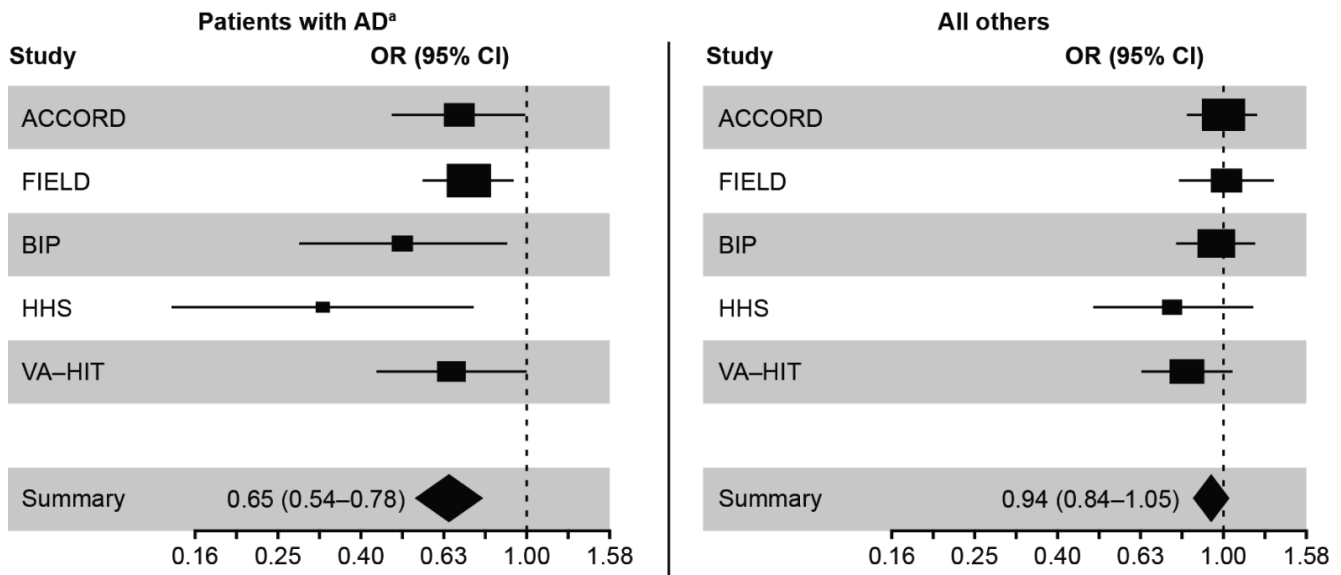


Figure 4. Impact of fibrates on macrovascular events risk according to lipoprotein phenotype [77].

^a 4726 patients with atherogenic dyslipidaemia (defined by ACCORD-LIPID criteria).

ACCORD = Action to Control Cardiovascular Risk in Diabetes, AD = atherogenic dyslipidaemia, BIP = Bezafibrate Infarction Prevention, CI = confidence interval, FIELD = Fenofibrate Intervention and Event Lowering in Diabetes, HHS = Helsinki Heart Study, OR = odds ratio, VA-HIT = Veterans Affairs HDL Intervention Trial.

Sacks FM, et al. *N Engl J Med* 2010 Aug 12;363(7):692–4. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

were 1.8 mmol/L. Importantly, a pre-specified subgroup analysis in patients with AD (high triglyceride plus low HDL-c levels [≥ 2.3 and ≤ 0.9 mmol/L, corresponding to the highest and lowest tertile, respectively; 17% of overall study population]) achieved clinical benefit from combination therapy, as demonstrated by a 31% risk rate reduction in CV death, MI or stroke *versus* placebo (NNT₅ = 20; $p = 0.032$) [24,76]. Therefore, in both the FIELD and ACCORD studies, fenofibrate treatment did not significantly reduce CV events in the total population, in whom overall baseline triglycerides levels were not elevated; however, fenofibrate significantly reduced CV events in patients with AD in both studies. In a subgroup analysis of patients from the ACCORD-Lipid study who had reached target LDL-c levels but failed to reach target non-HDL-c levels on statin at baseline, fenofibrate simvastatin combination therapy led to a significant reduction in CV events compared with simvastatin monotherapy ($p = 0.023$) [76].

Further evidence supporting the clinical benefits of fibrate-based therapy in patients with AD was provided by a meta-analysis of five placebo-controlled studies (ACCORD, FIELD, BIP [Bezafibrate Infarction Prevention], HHS [Helsinki Heart Study] and VA-HIT [Veterans Affairs HDL Intervention Trial]) on a subgroup of 4726 subjects with AD (defined according to ACCORD-Lipid criteria), which found that fibrate use was associated with a 35% reduction in the risk of coronary events (OR: 0.65; 95% CI: 0.54, 0.78) [77] (Figure 4).

Published observational and long-term studies contribute to the evidence base supporting the clinical benefits of combining statins with other lipid-lowering agents in patients with AD. These include subgroup analyses and meta-analyses demonstrating the clinical benefits of

fenofibrate–simvastatin combination therapy. Of note, the 2013 American College of Cardiology/American Heart Association guidelines are essentially based around statin treatment only; and it was suggested that the 2011 EAS/ESC guidelines were more appropriate for use in Europe [78].

The European Medicines Agency approved fenofibrate as an adjunct to improving diet and other non-pharmacological treatments (e.g. exercise, weight reduction) for the treatment of: (1) severe hypertriglyceridaemia, with or without low levels of HDL-c; (2) mixed hyperlipidaemia when a statin is contraindicated or not tolerated; and (3) mixed hyperlipidaemia in patients at high CV risk, in addition to a statin when triglycerides and HDL-c levels are inadequately controlled [79]. Of note, fenofibrate is the only fibrate approved as add-on therapy to a statin in the aforementioned patient group with mixed hyperlipidaemia.

Safety of fenofibrate–statin combination therapy versus statin monotherapy

Fenofibrate can be considered separately from other fibrates based on known differences in the number of nuclear co-factors that are activated or repressed. In particular, fenofibrate does not influence the metabolism or pharmacokinetics of statins, whereas gemfibrozil inhibits statin glucuronidation-mediated lactonisation, resulting in an increased statin plasma concentration and risk of myotoxicity [80]. In the ACCORD-Lipid study, fenofibrate treatment did not increase the risk of myositis or rhabdomyolysis when used in combination with a statin [24].

Of note, fenofibrate–statin combination therapy has been used for a sufficiently long period of time, therefore ongoing

pharmacovigilance activities, as well as randomised clinical trials, would be expected to detect any safety signals and flag any potential issues over its continued use.

A key advantage of fenofibrate–statin combination therapy is its glucose-mitigating effects compared with statin monotherapy in patients with AD (as demonstrated in the ACCORD-Lipid study). Although the impact of fenofibrate treatment on glucose homeostasis and insulin sensitivity is still unclear, it has been proposed that fenofibrate effects on glucose levels may depend on the patient profile, and may be more evident in patients with metabolic syndrome and AD [81,82].

Furthermore, fenofibrate–statin combination therapy does not lead to an increased incidence of adverse events or serious adverse events compared with either monotherapy. The combined therapy has led to significant increases in alanine aminotransferase in a small percentage of patients in the ACCORD-Lipid study that, although not considered serious, do warrant consideration. Increased creatinine production has also been reported in some patients receiving this combined therapy, which is of the same magnitude as that observed with fenofibrate monotherapy and does not seem to have clinically important consequences for patients with T2DM. The reversibility of fenofibrate effects on renal function observed in the ACCORD-Lipid study was analysed in a post-withdrawal study, which showed that the increase in serum creatinine levels was reversible 51 days after the end of treatment [83]. Likewise in the FIELD study, the initial increase in plasma creatinine levels was followed by a smaller long-term creatinine rise in the fenofibrate group *versus* placebo group (7.9 $\mu\text{mol/L}$ vs 9.2 $\mu\text{mol/L}$; $p = 0.01$) [84].

Analysis of data from 9795 patients with T2DM included in the FIELD study demonstrated that 5 years of treatment with fenofibrate led to a significantly greater reduction in urine albumin concentrations compared with placebo (23.7% vs 11.5%; $p < 0.001$) and, in a subset of patients, to a significantly lower annual loss of estimated glomerular filtration rate (eGFR) than placebo (1.19 vs 2.03 mL/min/1.73m²; $p < 0.001$) [84]. Moreover, greater preservation of eGFR in fenofibrate-treated patients was associated with hypertriglyceridaemia at baseline, with or without low levels of HDL-c, and with triglyceride reduction (≥ 0.48 mmol/L) during the 6-week fenofibrate run-in period. In the ACCORD-Lipid study, a significant reduction in the progression of micro- and macroalbuminuria was observed in fenofibrate-treated patients vs those receiving placebo ($p < 0.05$) [24]; no significant changes in end-stage renal disease or mean change in urine albumin/creatinine ratio were observed [85].

Long-term fenofibrate treatment led to a non-significant increased incidence of pancreatitis events *versus* placebo in the FIELD study (0.8% vs 0.5%) [72]. Additionally, a recent meta-analysis on lipid-modifying therapies and risk of pancreatitis reported no association between fibrate therapy and pancreatitis [86].

Beyond efficacy and safety: Advantages of fixed-dose combination therapy

Lipid-lowering drugs are frequently prescribed as part of a combination therapy. However, prescription of complex

drug regimens has been reported as a cause for medication non-adherence [87], with simplification of the drug regimen reported to be associated with increased adherence to lipid-lowering therapy [88].

Insufficient adherence to lipid-lowering drugs has been shown to increase CV morbidity and mortality [89]. In this study, patients with intermediate–high adherence to statin therapy, defined as 61–81% of the proportion of days covered (PDC) by filled prescriptions, and high adherence (PDC >80%) had a reduction in the risk for all-cause mortality compared to patients with low adherence (PDC 21–40%) (47% and 54% vs low adherence, respectively).

Based on experience from hypertension and diabetes studies, several theoretical advantages of fixed-dose over free-dose combination therapies can be proposed, including improved adherence to prescribed medication due to a smaller number of pills, higher persistence with a simple dosing regimen and improved treatment effectiveness, that collectively serve to reduce the overall burden of disease [87,90].

Summary of key discussion points and group consensus

The group noted that understanding of AD pathophysiology is lacking and that research efforts need to be improved to address this important shortcoming. There was also consensus that it might be helpful if the definition of AD could be simplified and made more practical; however, the group recognised that oversimplifying a complex process would be counterproductive.

Based on the available evidence base, the group reached a consensus that individuals with higher levels of LDL-c are exposed to a greater CV risk than their counterparts with lower levels of LDL-c. Moreover, elevated triglyceride levels are associated with an increased risk of death and major CV events, which is further exacerbated by concurrently high levels of LDL-c or low levels of HDL-c. It was noted that although elevated triglyceride levels are required to facilitate subsequent increases in small, dense LDL particles and in small, dense HDL particles, it cannot be inferred that these upstream triglycerides abnormalities are the main driver in this process.

The group recognised that consideration of the complexity and interrelationship between individual risk factors is pivotal to assessing and managing overall CV residual risk. Specifically, it was deemed important to measure levels of both HDL-c and triglycerides. Moreover, it is important to consider different patient subgroups, because although elevated triglyceride levels are usually associated with low levels of HDL-c, some patients may have low HDL-c only or high triglycerides only. Furthermore, there was consensus that there are no data to support prioritising fasting over non-fasting triglyceride levels (or vice versa) when evaluating CV risk in patients with AD; of note, fasting triglycerides are routinely used to assess AD.

The group agreed that there are epidemiological data demonstrating that non-HDL-c is similar to, or even better than, LDL-c as a marker of CV risk. It was acknowledged that calculated values of non-HDL-c are influenced primarily

by levels of triglyceride-rich lipoproteins. Furthermore, it was noted that lower triglyceride levels are often mirrored by lower remnant lipoprotein levels. As such, the group endorsed a paradigm shift away from the current emphasis on triglyceride levels towards an increased clinical focus on remnant lipoprotein levels and their implications for CV risk.

There was consensus that achieving target non-HDL-c levels should be a key focus of CV risk management in patients with AD. The group identified apolipoprotein B levels as the most accurate and stable measure of CV risk; however, limited availability was considered a key barrier to wider routine use. Therefore, non-HDL-c levels and non-fasting triglyceride levels (as a marker of remnant triglyceride-rich lipoproteins) were considered more practical measures of CV risk. It was noted that non-HDL-c is well defined as a secondary target in the treatment of dyslipidaemias in the EAS/ESC guidelines [11], as it is easily calculated, inexpensive, provides a highly stable measure of CV risk over time and provides a very good approximation of apolipoprotein B levels. The group agreed that AD treatment should adhere to current EAS/ESC guidelines and be focused on patients at high or very high risk of CV diseases (based on elevated levels of non-HDL-c and triglycerides, and low levels of HDL-c) and those with exaggerated markers of metabolic syndrome.

There was consensus among the group that statins can reduce CV risk in all patients, but that patient-specific differences may necessitate an individualised approach to CV risk management. The challenge of achieving the high doses of statins reported in some clinical trials may increase the likelihood that add-on therapy with another lipid-lowering agent is initiated. The group agreed that an increased focus on secondary CV prevention is needed. A multifactorial approach involving lifestyle changes and blood-glucose control in diabetic patients should also be reinforced.

The group agreed that safety and clinical outcome data from published observational and long-term studies provide sufficient evidence to support combining statins with other lipid-lowering agents. A review of the evidence base describing fibrates and reduced risk of macrovascular events highlighted that patients who have elevated triglyceride levels plus low levels of HDL-c are most likely to achieve clinical benefit from fenofibrate–statin combination therapy. Fenofibrate has been approved by the European Medicines Agency for the treatment of mixed hyperlipidaemia in patients at high CV risk in addition to a statin when triglycerides and HDL-c levels are inadequately controlled [79]. Of note, careful selection of patients suitable for fenofibrate–statin combination therapy and ongoing vigilance for potential risk of pancreatitis is advocated. The group believed that the clinical-trial evidence base supporting the benefits of this combined therapy is sufficiently robust to convince physicians that there is no requirement to deviate from the standard dosing strategies (e.g. moving from same-day dosing [statin plus fenofibrate each day] to alternate-day dosing [statin only and fenofibrate only on alternate days]), and that such an approach should only be considered when it is necessitated as the result of patient-specific issues, such as tolerability concerns.

Summary of key points and consensus

Topic	Consensus
CV risk	- High LDL-c and triglyceride levels are both associated with an increased risk of CV events; this can be exacerbated by low HDL-c levels. - Non-HDL-c may be a better CV risk marker than LDL-c. - More attention should be given to remnant lipoproteins.
Residual CV risk	Both HDL-c and triglycerides should be measured to evaluate residual CV risk.
Management of patients with AD	- In clinical practice, non-HDL-c and non-fasting triglycerides can help to assess the CV risk, and target non-HDL-c levels should be the focus of CV risk management. - Treatment should adhere to the EAS/ESC guidelines, and focus on patients at high or very high risk (i.e. elevated non-HDL-c and triglyceride levels, low levels of HDL-c) and patients with metabolic syndrome. - An individualised and multifactorial approach to CV risk should be adopted. - An increased focus on secondary prevention is needed. - High risk patients on statin therapy with elevated triglycerides and low levels of HDL-c can benefit from fenofibrate–statin combination therapy.

AD = atherogenic dyslipidaemia, -c = cholesterol, CV = cardiovascular, EAS = European Atherosclerosis Society, ESC = European Society of Cardiology, LDL = low-density lipoprotein, HDL = high-density lipoprotein.

Acknowledgements

The meeting was co-chaired by Alberico L. Catapano and Roberto Ferrari. Medical writing support was provided by Stephen Paterson PhD on behalf of Alpharmaxim Healthcare Communications, and the overall project was funded by Mylan.

Author disclosure information

Carlos Aguiar has received honoraria (for lectures and consultancy) from Abbott and Tecnimede Group; **Riccardo C. Bonadonna** has received honoraria (for lectures and consultancy) from Sanofi, Eli Lilly, AstraZeneca, MSD, Janssen, Boehringer Ingelheim and Abbott; **Alberico L. Catapano** has received honoraria (for lectures) from Abbott, AstraZeneca, Aegerion, Amgen, Eli Lilly, Genzyme, Mediolanum, Merck, Pfizer, Recordati, Rottapharm, Sanofi-Regeneron and Sigma-Tau; **Francesco Cosentino** has received honoraria (for lectures and consultancy) from AstraZeneca, Roche, Bristol-Myers Squibb, MSD, Abbott, Bayer, and research grants from Swedish Heart & Lung Foundation and European Society for Study of Diabetes; **Moses Elisaf** has received honoraria (for lectures and consultancy) and research funding from AstraZeneca, Schering-Plough, Merck, Pfizer, Solvay, Abbott, Boehringer Ingelheim and Fournier, and has participated in clinical trials with AstraZeneca, Merck, Sanofi-Synthelabo, Solvay, GlaxoSmithKline, Novartis, Pfizer and Fournier; **Michel Farnier** has received grant/research support and/or honoraria (for lectures) from Abbott, AstraZeneca, Amgen, Boehringer Ingelheim, Eli Lilly, Genzyme, Kowa, Merck and Co., Novartis, Pfizer, Recordati, Roche, Sanofi-Regeneron and SMB; **Roberto Ferrari** has received honoraria (for lectures, consultancy and travel support) from Servier and has received personal fees from Boehringer Ingelheim, Novartis, Merck Serono and Irbtech; **Jean Ferrières** has received grant and educational support from Abbott, AstraZeneca, Merck, Sanofi and Amgen; **Pasquale Perrone Filardi** has received honoraria (for lectures) from AstraZeneca, MSD and Sanofi; **Nicolae Hancu** has received honoraria (for lectures and

consultancy) from Abbott, AstraZeneca, Berlin-Chemie, Eli Lilly, MSD, Novartis, Sanofi, Servier; **Meral Kayikcioglu** has received honoraria (for lectures and consultancy) and research funding from Abbott, Abdi İbrahim, Actelion, Aegerion, Amgen, Bayer Schering, Merck, Sanofi, Pfizer and has participated in clinical trials with Amgen, Bayer Schering, Merck, Sanofi-Genzyme and Pfizer; **Alberto Mello e Silva** has received honoraria (for lectures and consultancy) from Amgen, Abbott, AstraZeneca, Jaba-Recordati, Janssen-Cilag, Merck, Novartis, Tecnimede; **Jesus Millan** has received honoraria (for lectures and consultancy) from Abbott, MSD, Sanofi and AstraZeneca; **Željko Reiner** has received honoraria (for lectures) from Sanofi-Regeneron and Synageva; **Lale Tokgozoglu** has received honoraria/consultancy fees from Merck, Amgen, Astra, Novartis, Abbott, Daiichi Sankyo, Pfizer, Actelion, Servier, Sanofi, Boehringer Ingelheim, Bayer, GlaxoSmithKline, Menarini, Kowa, Aegerion and Synageva; **Paul Valensi** has received honoraria (for lectures or consultancy) from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novo Nordisk, Novartis, Pierre Fabre, Sanofi and grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Merck Santé and Novo Nordisk; **Margus Viigimaa** has received honoraria (for lectures and consultancy) from AstraZeneca, Abbott, Boehringer Ingelheim and Menarini; **Michal Vrablik** has received honoraria/consultancy fees from Abbott, Actavis, AstraZeneca, Amgen, BMS, Genzyme, KRKA, MSD Idea, Novartis, Pfizer and Sanofi-Regeneron; **Alberto Zambon** has received honoraria (for lectures) from Abbott, AstraZeneca, Amgen, Eli Lilly, Chiesi, Sanofi-Regeneron; **José Luis Zamorano** has received honoraria (for lectures) from Toshiba, Philips and Merck. **Eduardo Alegria** has no conflicts of interest to declare.

References

- Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. *Circulation* 1990 Aug;82(2):495-506.
- Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM. Low-density lipoprotein subclass patterns and risk of myocardial infarction. *JAMA* 1988 Oct 7;260(13):1917-21.
- Musunuru K, Orho-Melander M, Caulfield MP, Li S, Salameh WA, Reitz RE, et al. Ion mobility analysis of lipoprotein subfractions identifies three independent axes of cardiovascular risk. *Arterioscler Thromb Vasc Biol* 2009 Nov;29(11):1975-80.
- Capell WH, Zambon A, Austin MA, Brunzell JD, Hokanson JE. Compositional differences of LDL particles in normal subjects with LDL subclass phenotype A and LDL subclass phenotype B. *Arterioscler Thromb Vasc Biol* 1996 Aug;16(8):1040-6.
- Mikhailidis DP, Elisaf M, Rizzo M, Berneis K, Griffin B, Zambon A, et al. "European panel on low density lipoprotein (LDL) subclasses": a statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses. *Curr Vasc Pharmacol* 2011 Sep;9(5):533-71.
- Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Borén J, Catapano AL, et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J* 2011 Jun;32(11):1345-61.
- Leiter LA, Lundman P, da Silva PM, Drexel H, Jünger C, Gitt AK. Persistent lipid abnormalities in statin-treated patients with diabetes mellitus in Europe and Canada: results of the Dyslipidaemia International Study. *Diabet Med* 2011 Nov;28(11):1343-51.
- Pedro-Botet J, Flores-Le Roux JA, Mostaza JM, Pintó X, de la Cruz JJ, Banegas JR. Atherogenic dyslipidemia: prevalence and management in lipid clinics. *Rev Clin Esp* 2014 Dec;214(9):491-8.
- Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel members. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia - full report. *J Clin Lipidol* 2014 Jan;8(1):29-60.
- Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010 Nov 13;376(9753):1670-81.
- Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011 Jul;32(14):1769-818.
- Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012 Aug 11;380(9841):572-80.
- Toth PP, Barter PJ, Rosenson RS, Boden WE, Chapman MJ, Cuchel M, et al. High-density lipoproteins: a consensus statement from the National Lipid Association. *J Clin Lipidol* 2013 Sep;7(5):484-525.
- Camont L, Chapman MJ, Kontush A. Biological activities of HDL subpopulations and their relevance to cardiovascular disease. *Trends Mol Med* 2011 Oct;17(10):594-603.
- Kontush A. HDL-mediated mechanisms of protection in cardiovascular disease. *Cardiovasc Res* 2014 Aug 1;103(3):341-9.
- Waldman B, Jenkins AJ, Davis TM, Taskinen MR, Scott R, O'Connell RL, et al. HDL-C and HDL-C/ApoA-I predict long-term progression of glycemia in established type 2 diabetes. *Diabetes Care* 2014 Aug;37(8):2351-8.
- Kostapanos MS, Elisaf MS. High density lipoproteins and type 2 diabetes: emerging concepts in their relationship. *World J Exp Med* 2014 Feb 20;4(1):1-6.
- Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005 Oct 8;366(9493):1267-78.
- Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008 Jan 12;371(9607):117-25.
- Reiner Z, De Bacquer D, Kotseva K, Prugger C, De Backer G, Wood D. Treatment potential for dyslipidaemia management in patients with coronary heart disease across Europe: findings from the EUROASPIRE III survey. *Atherosclerosis* 2013 Dec;231(2):300-7.
- Genest JJ, McNamara JR, Salem DN, Schaefer EJ. Prevalence of risk factors in men with premature coronary artery disease. *Am J Cardiol* 1991 Jun 1;67(15):1185-9.
- Faergeman O, Holme I, Fayyad R, Bhatia S, Grundy SM, Kastelein JJ, et al. Plasma triglycerides and cardiovascular events in the Treating to New Targets and Incremental Decrease in End-Points through Aggressive Lipid Lowering trials of statins in patients with coronary artery disease. *Am J Cardiol* 2009 Aug 15;104(4):459-63.
- Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol* 2008 Feb 19;51(7):724-30.
- Ginsberg HN, Elam MB, Lovato LC, Crouse JR, III, Leiter LA, Linz P, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010 Apr 29;362(17):1563-74.
- Carey VJ, Bishop L, Laranjo N, Harshfield BJ, Kwiat C, Sacks FM. Contribution of high plasma triglycerides and low high-density lipoprotein cholesterol to residual risk of coronary heart disease after establishment of low-density lipoprotein cholesterol control. *Am J Cardiol* 2010 Sep 15;106(6):757-63.
- Bayturan O, Kapadia S, Nicholls SJ, Tuzcu EM, Shao M, Uno K, et al. Clinical predictors of plaque progression despite very low levels of low-density lipoprotein cholesterol. *J Am Coll Cardiol* 2010 Jun 15;55(24):2736-42.
- Andersson C, Lyass A, Vasan RS, Massaro JM, D'Agostino RB, Sr., Robins SJ. Long-term risk of cardiovascular events across a spectrum

- of adverse major plasma lipid combinations in the Framingham Heart Study. *Am Heart J* 2014 Dec;168(6):878–83.
28. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet* 2014 Aug 16;384(9943):626–35.
 29. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA* 2007 Jul 18;298(3):299–308.
 30. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA* 2008 Nov 12;300(18):2142–52.
 31. Schwartz GG, Abt M, Bao W, DeMicco D, Kallend D, Miller M, et al. Fasting triglycerides predict recurrent ischemic events in patients with acute coronary syndrome treated with statins. *J Am Coll Cardiol* 2015 Jun 2;65(21):2267–75.
 32. Reiner Z. Are elevated serum triglycerides really a risk factor for coronary artery disease? *Cardiology* 2015 May 12;131(4):225–7.
 33. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009 Nov 11;302(18):1993–2000.
 34. Sirimarco G, Labreuche J, Bruckert E, Goldstein LB, Fox KM, Rothwell PM, et al. Atherogenic dyslipidemia and residual cardiovascular risk in statin-treated patients. *Stroke* 2014 May;45(5):1429–36.
 35. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med* 2007 Sep 27;357(13):1301–10.
 36. Shaikh M, Wootton R, Nordestgaard BG, Baskerville P, Lumley JS, La Ville AE, et al. Quantitative studies of transfer in vivo of low density, Sf 12–60, and Sf 60–400 lipoproteins between plasma and arterial intima in humans. *Arterioscler Thromb* 1991 May;11(3):569–77.
 37. Nordestgaard BG, Tybjaerg-Hansen A, Lewis B. Influx in vivo of low density, intermediate density, and very low density lipoproteins into aortic intimas of genetically hyperlipidemic rabbits. Roles of plasma concentrations, extent of aortic lesion, and lipoprotein particle size as determinants. *Arterioscler Thromb* 1992 Jan;12(1):6–18.
 38. Nordestgaard BG, Wootton R, Lewis B. Selective retention of VLDL, IDL, and LDL in the arterial intima of genetically hyperlipidemic rabbits in vivo. Molecular size as a determinant of fractional loss from the intima-inner media. *Arterioscler Thromb Vasc Biol* 1995 Apr;15(4):534–42.
 39. Varbo A, Benn M, Tybjaerg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol* 2013 Jan 29;61(4):427–36.
 40. Jørgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjaerg-Hansen A. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. *Eur Heart J* 2013 Jun;34(24):1826–33.
 41. Reyes-Soffer G, Ngai CI, Lovato L, Karmally W, Ramakrishnan R, Holleran S, et al. Effect of combination therapy with fenofibrate and simvastatin on postprandial lipemia in the ACCORD lipid trial. *Diabetes Care* 2013 Feb;36(2):422–8.
 42. Zambon A, Zhao XQ, Brown BG, Brunzell JD. Effects of niacin combination therapy with statin or bile acid resin on lipoproteins and cardiovascular disease. *Am J Cardiol* 2014 May 1;113(9):1494–8.
 43. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012 Jul;33(13):1635–701.
 44. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA* 2012 Mar 28;307(12):1302–9.
 45. Zambon A, Puato M, Faggin E, Grego F, Rattazzi M, Pauletto P. Lipoprotein remnants and dense LDL are associated with features of unstable carotid plaque: a flag for non-HDL-C. *Atherosclerosis* 2013 Sep;230(1):106–9.
 46. Koster I, Huppertz E, Hauner H, Schubert I. Costs of Diabetes Mellitus (CoDiM) in Germany, direct per-capita costs of managing hyperglycaemia and diabetes complications in 2010 compared to 2001. *Exp Clin Endocrinol Diabetes* 2014 Oct;122(9):510–6.
 47. Pelletier EM, Shim B, Ben-Joseph R, Caro JJ. Economic outcomes associated with microvascular complications of type 2 diabetes mellitus: results from a US claims data analysis. *Pharmacoeconomics* 2009;27(6):479–90.
 48. Gordoia A, Scuffham P, Shearer A, Oglesby A, Tobian JA. The health care costs of diabetic peripheral neuropathy in the US. *Diabetes Care* 2003 Jun;26(6):1790–5.
 49. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010 Oct;33(10):2285–93.
 50. Fioretto P, Dodson PM, Ziegler D, Rosenson RS. Residual microvascular risk in diabetes: unmet needs and future directions. *Nat Rev Endocrinol* 2010 Jan;6(1):19–25.
 51. The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines. 2015 Dec.
 52. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012 Dec 15;380(9859):2197–223.
 53. Reiner Z. Managing the residual cardiovascular disease risk associated with HDL-cholesterol and triglycerides in statin-treated patients: a clinical update. *Nutr Metab Cardiovasc Dis* 2013 Sep;23(9):799–807.
 54. Fruchart JC, Sacks F, Hermans MP, Assmann G, Brown WV, Ceska R, et al. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. *Am J Cardiol* 2008 Nov 17;102(10 Suppl):1K–34K.
 55. Fruchart JC, Sacks FM, Hermans MP, Assmann G, Brown WV, Ceska R, et al. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in dyslipidaemic patient. *Diab Vasc Dis Res* 2008 Nov;5(4):319–35.
 56. Valensi P, Picard S. Lipids, lipid-lowering therapy and diabetes complications. *Diabetes Metab* 2011 Feb;37(1):15–24.
 57. Zoppini G, Negri C, Stoico V, Casati S, Pichiri I, Bonora E. Triglyceride-high-density lipoprotein cholesterol is associated with microvascular complications in type 2 diabetes mellitus. *Metabolism* 2012 Jan;61(1):22–9.
 58. Morton J, Zoungas S, Li Q, Patel AA, Chalmers J, Woodward M, et al. Low HDL cholesterol and the risk of diabetic nephropathy and retinopathy: results of the ADVANCE study. *Diabetes Care* 2012 Nov;35(11):2201–6.
 59. Sacks FM, Hermans MP, Fioretto P, Valensi P, Davis T, Horton E, et al. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case-control study in 13 countries. *Circulation* 2014 Mar 4;129(9):999–1008.
 60. Callaghan BC, Feldman E, Liu J, Kerber K, Pop-Busui R, Moffet H, et al. Triglycerides and amputation risk in patients with diabetes: ten-year follow-up in the DISTANCE study. *Diabetes Care* 2011 Mar;34(3):635–40.
 61. Wiggins TD, Sullivan KA, Pop-Busui R, Amato A, Sima AA, Feldman EL. Elevated triglycerides correlate with progression of diabetic neuropathy. *Diabetes* 2009 Jul;58(7):1634–40.
 62. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003 Jan 30;348(5):383–93.
 63. Ballantyne CM. Low-density lipoproteins and risk for coronary artery disease. *Am J Cardiol* 1998 Nov 5;82(9A):3Q–12Q.
 64. Catapano AL, Farnier M, Foody JM, Toth PP, Tomassini JE, Brudi P, et al. Combination therapy in dyslipidemia: where are we now? *Atherosclerosis* 2014 Nov;237(1):319–35.
 65. O’Keefe JH, Jr., Cordain L, Harris WH, Moe RM, Vogel R. Optimal low-density lipoprotein is 50 to 70 mg/dl: lower is better and physiologically normal. *J Am Coll Cardiol* 2004 Jun 2;43(11):2142–6.
 66. Fulcher J, O’Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015 Apr 11;385(9976):1397–405.
 67. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015 Jun 18;372(25):2387–97.
 68. Fruchart JC, Davignon J, Hermans MP, Al-Rubeaan K, Amarencu P,

- Assmann G, et al. Residual macrovascular risk in 2013: what have we learned? *Cardiovasc Diabetol* 2014 Jan 24;13:26.
69. Reiner Z. Combined therapy in the treatment of dyslipidemia. *Fundam Clin Pharmacol* 2010 Feb;24(1):19–28.
 70. McKeage K, Keating GM. Fenofibrate: a review of its use in dyslipidaemia. *Drugs* 2011 Oct 1;71(14):1917–46.
 71. Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). *Am J Cardiol* 2005 Feb 15;95(4):462–8.
 72. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005 Nov 26;366(9500):1849–61.
 73. Ting R, Keech A. Fenofibrate and renal disease: clinical effects in diabetes. *Clin Lipidol* 2013;8(6):669–80.
 74. Scott R, O'Brien R, Fulcher G, Pardy C, d'Emden M, Tse D, et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetes Care* 2009 Mar;32(3):493–8.
 75. Chew EY, Ambrosius WT, Davis MD, Danis RP, Gangaputra S, Greven CM, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010 Jul 15;363(3):233–44.
 76. Food and Drug Administration (FDA) Endocrinologic and Metabolic Drugs Advisory Committee. Trilipix (ACCORD) Advisory Committee Meeting. 2011 May 19.
 77. Sacks FM, Carey VJ, Fruchart JC. Combination lipid therapy in type 2 diabetes. *N Engl J Med* 2010 Aug 12;363(7):692–4.
 78. Ray KK, Kastelein JJ, Boekholdt SM, Nicholls SJ, Khaw KT, Ballantyne CM, et al. The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. *Eur Heart J* 2014 Apr;35(15):960–8.
 79. European Medicines Agency (EMA). Assessment report for fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil containing medical products. 2011 Feb 28.
 80. Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos* 2002 Nov;30(11):1280–7.
 81. Krysiak R, Stachura-Kulach A, Okopien B. Metabolic and monocyte-suppressing actions of fenofibrate in patients with mixed dyslipidemia and early glucose metabolism disturbances. *Pharmacol Rep* 2010 Jan;62(1):120–30.
 82. Wysocki J, Belowski D, Kalina M, Kochanski L, Okopien B, Kalina Z. Effects of micronized fenofibrate on insulin resistance in patients with metabolic syndrome. *Int J Clin Pharmacol Ther* 2004 Apr;42(4):212–7.
 83. Mychaleckyj JC, Craven T, Nayak U, Buse J, Crouse JR, Elam M, et al. Reversibility of fenofibrate therapy-induced renal function impairment in ACCORD type 2 diabetic participants. *Diabetes Care* 2012 May;35(5):1008–14.
 84. Davis TM, Ting R, Best JD, Donoghoe MW, Drury PL, Sullivan DR, et al. Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Diabetologia* 2011 Feb;54(2):280–90.
 85. Bonds DE, Craven TE, Buse J, Crouse JR, Cuddihy R, Elam M, et al. Fenofibrate-associated changes in renal function and relationship to clinical outcomes among individuals with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) experience. *Diabetologia* 2012 Jun;55(6):1641–50.
 86. Preiss D, Tikkanen MJ, Welsh P, Ford I, Lovato LC, Elam MB, et al. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. *JAMA* 2012 Aug 22;308(8):804–11.
 87. Maningat P, Gordon BR, Breslow JL. How do we improve patient compliance and adherence to long-term statin therapy? *Curr Atheroscler Rep* 2013 Jan;15(1):291.
 88. Schedlbauer A, Davies P, Fahey T. Interventions to improve adherence to lipid lowering medication. *Cochrane Database Syst Rev* 2010 Mar 17;(3):CD004371.
 89. Degli Esposti L, Saragoni S, Batacchi P, Benemei S, Geppetti P, Sturani A, et al. Adherence to statin treatment and health outcomes in an Italian cohort of newly treated patients: results from an administrative database analysis. *Clin Ther* 2012 Jan;34(1):190–9.
 90. Blonde L, Wogen J, Kreilick C, Seymour AA. Greater reductions in A1C in type 2 diabetic patients new to therapy with glyburide/metformin tablets as compared to glyburide co-administered with metformin. *Diabetes Obes Metab* 2003 Nov;5(6):424–31.