



**IMPLEMENTATION OF PROPOSALS FOR MANAGEMENT OF ATHEROGENIC
DYSLIPIDEMIA IN PRIMARY CARE. RESULTS OF THE DAT-AP STUDY.**

**Angel Díaz Rodríguez¹, Adalberto Serrano Cumplido², Jesús Millán Nuñez-Cortés³, M^a Luisa Orera Peña⁴,
Marta Rodríguez de Miguel^{*5}**

¹Primary Care Center. Bembibre. León. Spain

²Primary Care Center. Bizkaia. Spain

³Head of Internal Medicine and Director of Cardiovascular Risk Unit, University Hospital Gregorio Marañón, Madrid,
Spain

⁴Mylan Medical Department

⁵*Mylan Medical Department

***Corresponding Author: Marta Rodríguez de Miguel**

Mylan Medical Department

Article Received on 17/02/2017

Article Revised on 07/03/2017

Article Accepted on 28/03/2017

ABSTRACT

Background and aims: The “DAT-AP” (from the Spanish, “*Dislipemia ATerogénica en Atención Primaria*”, for Atherogenic Dyslipidaemia in Primary Care) study aims to understand the level of inculcation of knowledge on the diagnosis and treatment of Atherogenic Dyslipidaemia in the scope of Primary Care, according to the consensus recommendations published previously. **Methods:** This is a national, multicentre, cross-sectional study, in which 991 Primary Care doctors recorded, in an online computer application, certain characteristics of their clinical practice related to atherogenic dyslipidaemia, particularly in the aspects of: atherogenic dyslipidaemia epidemiology and medical impact, association with cardiovascular risk, detection of atherogenic dyslipidaemia, treatment objectives and therapeutic approach. **Results:** The results can be considered to be reasonably satisfactory as regards the implementation of criteria reached as a consensus for the diagnostic and therapeutic management of atherogenic dyslipidaemia. This includes over 90% of the participants considering the process highly relevant and worthy of attention. However, the consideration of hypertriglyceridemia or low HDL-C as isolated cardiovascular risk factors or the therapeutic approach when these alterations are present merit strategies to reinforce the available scientific evidence; particularly on the benefit of treatment with fibrates, in combination with statins or not.

KEYWORDS: Atherogenic dyslipidaemia; residual risk; primary care.

INTRODUCTION

Cardiovascular disease remains one of the main causes of mortality and morbidity in Spain. ^[1] The introduction of statins to clinical practice represented a great advance in control of hypercholesterolemia and in the subsequent reduction in cardiovascular accidents of an atherothrombotic nature, which has made it possible to reduce cardiovascular risk and the incidence of cardiovascular episodes in Spain. ^[2] However, in spite of the benefit provided by the standard therapy with statins, at doses with great efficacy for reducing LDL-cholesterol (LDL-C) levels, a significant percentage of patients retain what has been called a “residual risk” of cardiovascular accidents ^[3] and part of that risk is of lipid origin. This is particularly important in patients at high risk, especially those with coronary heart disease, metabolic syndrome and type 2 diabetes mellitus, who frequently have a lipid profile characterised by low levels of HDL cholesterol (HDL-C) and elevated levels of triglycerides, as well as a phenotype of smaller, denser LDL particles than normal. This lipid disorder, which is

known as Atherogenic Dyslipidaemia (AD), is accompanied by a significant cardiovascular risk, which is highly characteristic when all its components combine. ^[4-6]

The prevalence of AD is estimated to be 27.1% in patients with moderate to high cardiovascular risk. ^[7] However, AD is underdiagnosed and undertreated in clinical practice. ^[8, 9] This fact is vital, in as much as patients with AD can benefit from the use of drugs that act to normalise HDL-C and triglyceride levels, as numerous clinical trials have demonstrated. ^[10-14] Consequently, proper diagnosis and therapeutic management of AD could reduce the associated residual risk, which has been translated into recommendations included in the clinical practice guidelines. ^[15, 16]

However, the fact that AD is currently an underdiagnosed and undertreated disorder suggests that there is still room to improve awareness of this problem, particularly among doctors who can manage it daily, as

is the case of Primary Care Physicians. The main objective of this study was to determine the level of understanding of the clinical characteristics of AD, as well as the implementation, in Primary Care, of certain clinical habits included in a previously published consensus for the diagnostic and therapeutic management of AD.^[16] A secondary objective was to describe clinical habits in the approach to screening, diagnosis and treatment of AD by the doctors participating in the study.

MATERIALS AND METHODS

Study design and participants

The "DAT-AP" (Atherogenic Dyslipidaemia in Primary Care) study is a descriptive, national, multicentre, cross-sectional study carried out between January and May 2015. The study was approved by the Hospital Clínico San Carlos of Madrid's Clinical Research Ethics Committee. The participants in the study were Primary Care doctors involved in treating AD, who were selected attempting to maintain a geographical stratification in agreement with the distribution throughout Spain.

Study tools

A computer application was developed to collect the data required in the data collection form (DCF) prepared specifically for the study by its scientific coordinators. The DCF was divided into two parts; the first theoretical

on AD and the second practical in nature. The theoretical part consisted of 16 questions grouped in five sections, each with a common thread of knowledge and extracted from the consensus document:^[16] nature of AD; medical impact and epidemiology of AD; cardiovascular risk associated with AD; screening, diagnosis and objectives of control; and treatment.

Each participating investigator was provided with a password and user name in order to access the online platform and complete the form. Neither information from the patient's medical record nor any information on specific patients was collected at any time.

Statistical Analysis

A descriptive analysis was performed using the mean and standard deviation for the quantitative variables and the frequencies and percentages for the qualitative variables. Statistical analyses were carried out using SAS version 9.1.3, Service Pack 3.

RESULTS

The study participants were 991 Primary Care doctors involved in managing patients with AD. Table 1 shows the distribution by Autonomous Region of the participating doctors, with the most frequent representation for Andalusia (16.7%), Valencia (13.3%) and Galicia (11.0%).

Table 1. Participation of Family Doctors by

Region ^a	Participants	%
Andalusia	161	16.7
Aragon	32	3.3
Asturias	30	3.1
Balearic Islands	20	2.1
Canary Islands	47	4.9
Cantabria	19	2.0
Castile and Leon	75	7.8
Castile-La Mancha	44	4.6
Catalonia	85	8.8
Extremadura	24	2.5
Galicia	106	11.0
La Rioja	2	0.2
Madrid	94	9.7
Melilla	3	0.3
Murcia	30	3.1
Navarre	11	1.1
Basque Country	51	5.3
Valencia	128	13.3

Autonomous Region (n = 991)

^a: Autonomous Region

Knowledge and application of the results of the AD consensus

Questions on the nature and impact of AD were answered as shown in Table 2. Of the study participants, 93% indicated that AD is characterised by the association of low HDL-C, elevated triglyceride levels and a high proportion of small, dense LDL-C particles.

The participants indicated HDL-C as the most important for its dependent cardiovascular benefit related to the reverse cholesterol transport from the periphery (45.1%), followed by its anti-thrombotic effect (30.4%). In the opinion of almost 92% of the doctors, AD is the lipid alteration characteristic of patients with type 2 diabetes, visceral obesity and/or metabolic syndrome.

Table 2. Participants' response on general aspects of AD

In your opinion, AD is characterised by:							
						n	%
Association of low HDL-C, high triglycerides, and a high proportion of small, dense LDL particles						920	93.2
High triglycerides, and a high proportion of small, dense LDL particles						54	5.5
None of the above						13	1.3
In your opinion, indicate the cardiovascular benefits derived from HDL-C (1 being the least important and 5 being the most important).							
	1	2	3	4	5	Mean (deviation)	
Reverse cholesterol transport from the periphery, n (%)	148 (15.2)	119 (12.2)	137 (14.1)	131 (13.4)	440 (45.1)	3,6 (1.52)	
Vasodilation effects, n (%)	261 (26.7)	282 (28.9)	213 (21.8)	173 (17.7)	48 (4.9)	2,5 (1.20)	
Anti-oxidant effects, n (%)	116 (11.9)	199 (20.4)	307 (31.4)	264 (27.0)	91 (9.3)	3,0 (1.15)	
Anti-thrombotic effect, n (%)	125 (12.8)	186 (19.0)	139 (14.2)	232 (23.7)	298 (30.4)	3,4 (1.41)	
Anti-inflammatory effect, n (%)	313 (32.2)	189 (19.4)	182 (18.7)	181 (18.6)	107 (11.0)	2,6 (1.39)	
In your opinion, AD is the lipid alteration that is characteristic of patients with							
						n	%
Diabetes, type-2						14	1.4
Visceral obesity						5	0.5
Metabolic syndrome						63	6.4
All						905	91.7
In your opinion, which of the following would suffice to diagnose AD?							
						n	%
HDL-C only						5	0.5
Triglycerides only						4	0.4
HDL-C and triglycerides						951	99.1
In your opinion, in the presence of AD, the primary control objective is							
						n	%
LDL-C						46	4.7
Non-HDL cholesterol						11	1.1
Overall control of the lipid profile (LDL-C, HDL-C, Triglycerides, Non-HDL cholesterol)						930	94.2

Figure 1 shows the level of agreement with the various statements on cardiovascular risk associated with AD and its components. Nearly 97% of the participants agreed with the statement "Clinical evidence shows that AD is a significant cardiovascular risk factor" and 94% were of the opinion that "The association of low HDL-C and elevated triglyceride levels have a synergistic action in relation to cardiovascular risk". Of the surveyed doctors, 91% expressed agreement with the statement "HDL-C needs to be considered in the handling of dyslipidaemias" and 88% with "HDL-C plays a relevant role in AD". Of the participants, 72% supported the statement "It has been demonstrated that the benefit is greater (a 2-3% reduction of coronary risk) if HDL-C is

increased by 1% than if the LDL-C is reduced by 1% (1% risk reduction)". Even though this level of inculcation of knowledge is considered satisfactory, some others are clearly insufficient. As such, only 62% consider that when LDL-C is controlled, the presence of AD increases the risk; and, consequently, only 76% consider that the risk associated with AD is additional to the one linked with elevated LDL-C. On the other hand, only 77% of participants considered that triglycerides have responsibility in the risk associated with AD, a percentage that is insufficient according to all the evidence available in this regard. A still smaller percentage (56%) give HDL-C a value in predicting cardiovascular accidents.

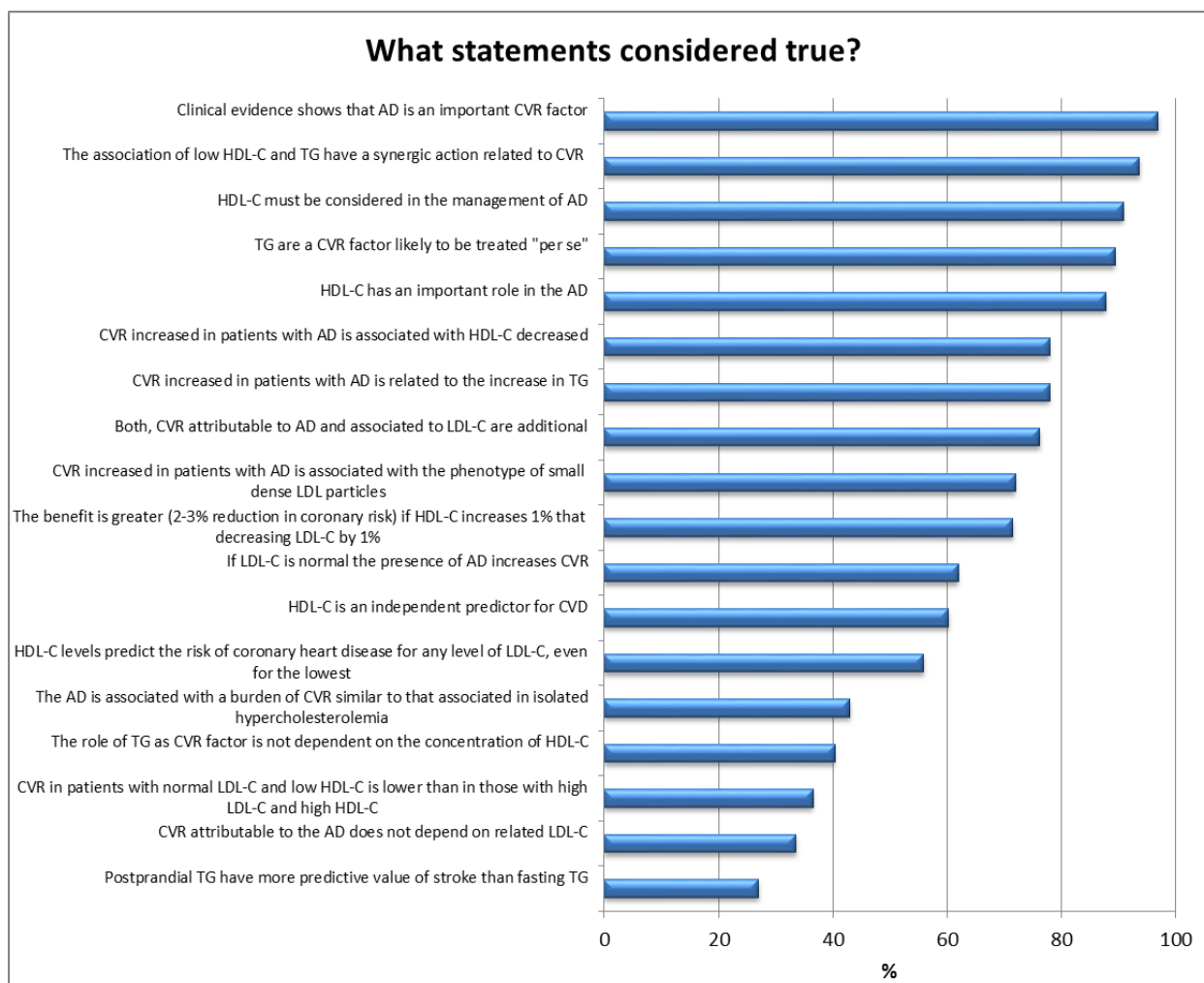


Figure 1. Level of inculcation of knowledge on the association of Atherogenic Dyslipidaemia and cardiovascular risk in Primary Care

[TG]: Triglycerides; [AD] atherogenic dyslipidaemia; [CVD]: cardiovascular disease; [CVR]: cardiovascular risk; [HDL-C]: HDL cholesterol; [LDL-C]: LDL cholesterol.

On the screening, diagnosis and objectives of control of AD (Table 2), 99% of the participants indicated that it would be sufficient to measure HDL-C and triglycerides to diagnose AD. Ninety-four percent stated that, in the presence of AD, the primary objective is overall control of the lipid profile. Figure 2 shows the level of agreement of the participating doctors with statements related to the objectives of control of AD and the treatment interventions to achieve them. Of the participants, 79% were of the opinion that, in patients with high cardiovascular risk, who present AD and LDL-C within target figures, it is more effective to correct the

AD than to try to lower the LDL-C further. Ninety-six percent of the participants indicated agreement with the statement "In patients treated with statins, even at high doses, there is a residual risk, part of which may be lipid related and amenable to additional therapeutic intervention". Over 90% of the participants agreed with the statements "Fenofibrate is the fibrate of choice for association with statins", "Overall control of the lipid profile of patients with AD frequently requires combined lipid-lowering treatment" and "The results of the ACCORD study showed that treating AD in diabetics gave a benefit in cardiovascular risk prevention".

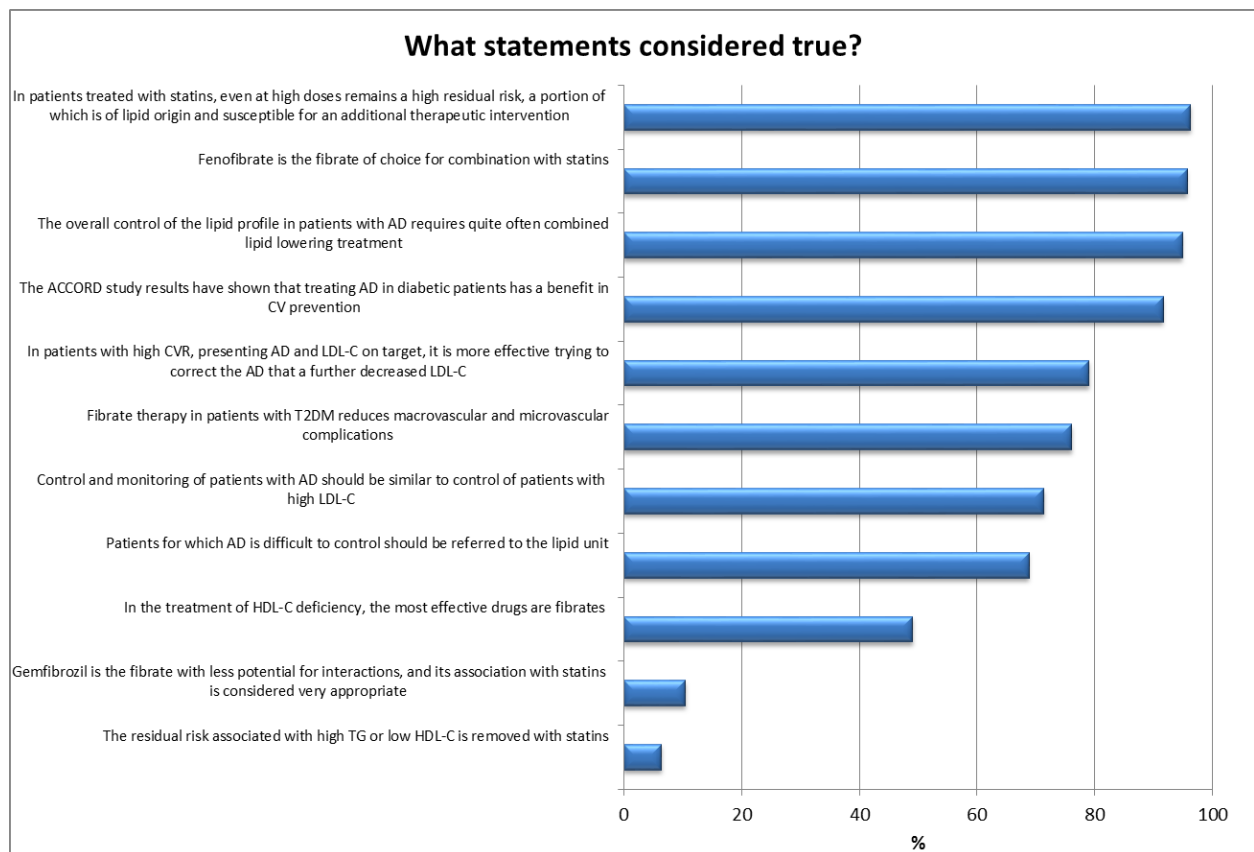


Figure 2. Level of inculcation of knowledge on therapeutic management of Atherogenic Dyslipidaemia in Primary Care.

[AD]: atherogenic dyslipidaemia; [CVR]: cardiovascular risk; [HDL-C]: HDL cholesterol; [LDL-C]: LDL cholesterol; [T2DM]: type 2 diabetes mellitus

The drugs with the greatest efficacy in reducing triglycerides, according to the participants' response, are fibrates (56.6%), statins (17.6%), omega-3 fatty acids (15.9%) and nicotinic acid (9.8%). In treating an HDL-C deficit, in the opinion of those surveyed, the most effective drugs are fibrates (53.9%), statins (26.6%), omega-3 fatty acids (10.3%) and nicotinic acid (9.2%).

DISCUSSION

The present study describes, by means of responses from Primary Care doctors involved in managing AD, the level of inculcation of knowledge on the diagnostic and therapeutic approach to this pathology in the scope of Primary Care, with medical personnel selected from all the Autonomous Regions of Spain. As a comparative reference for the participants, the clinical aspects included in the recommendations previously agreed as a consensus^[16], on improving diagnostic and therapeutic management of this disorder, were taken into consideration.

The importance of controlling hypercholesterolemia in patients at high cardiovascular risk has been known for decades, due to its close causal relationship with coronary syndromes and ischaemic ictus^[17, 18]. The cardiovascular risk associated with hypercholesterolemia has been successfully reduced thanks to the statins, with

these becoming the pillar of treatment present in the most important clinical practice guidelines^[19-21]. However, many patients with controlled LDL-C levels still have a persistent cardiovascular risk, known as residual risk, which is associated with the presence of AD, particularly patients with type 2 diabetes, visceral obesity and/or metabolic syndrome. The majority of the participating doctors were aware of this phenomenon and of its association with insulin resistance states. However, in spite of the demonstrated importance of low HDL-C levels as a source of cardiovascular risk^[22, 23], a substantial portion of doctors do not consider that HDL-C has a relevant role in AD nor that raising its levels by 1% is better than an equivalent reduction in LDL-C. Although the protective actions of HDL-C against developing atherosclerosis are still under study, reverse cholesterol transport (the ability of HDL to transport cholesterol from peripheral tissues to the liver for excretion) would be one of the mechanisms in which the anti-atherogenic properties of HDLs lie^[24], and this fact was clearly indicated by the participants in our study. However, those effects of HDL-C known as pleiotropic (anti-oxidant, anti-inflammatory, vasodilatory, etc.) are not sufficiently well known.

The questions related to the association of AD and cardiovascular risk appear to be those with the lowest

level of inculcation among the participants in the study. It is necessary to improve some key points of knowledge, such as: the cardiovascular risk associated with AD is independent of the risk associated with LDL-C and it is particularly important (for this reason) in those with controlled LDL-C. On the other hand, the inculcation of knowledge on triglycerides as isolated risk factors is clearly insufficient, as is the possibility of using postprandial triglycerides – precisely – to evaluate the risk associated with them.

Practically all those surveyed assert that to diagnose AD it is necessary to quantify HDL-C and triglyceride levels; i.e. to have the complete lipid profile of the patients when evaluating cardiovascular risk and initiating the most appropriate treatment. This coincides with the widely held idea among the participants that part of the residual risk is of lipid origin and is amenable to additional therapeutic intervention, e.g. with a combined lipid-lowering treatment. Fenofibrate was the most frequently selected option (90%) for association with statins and the fibrates were considered to be the most effective for decreasing triglycerides (57%) and elevating HDL-C (54%), in line with the available evidence ^[11, 25, 26]. It is worth emphasising that several years ago the European Medicines Agency (EMA) authorised the use of fenofibrate in patients with mixed dyslipidaemia and high cardiovascular risk in combination with statins when triglycerides and HDL-C are inadequately controlled ^[27] and this has been taken into account in the various recommendation for proper primary prevention of cardiovascular disease ^[15].

Although the level of inculcation of knowledge on the therapeutic management of AD is highly acceptable in some cases, there are parts that should be modified. It is very important to indicate that, surprisingly, a small (10%), but present, proportion indicate the option of associating gemfibrozil with a statin, when this is a combination that needs to be proscribed due to its possible adverse effects. On the other hand, it is somewhat surprising that a substantial percentage (although not the majority) overestimate the effect of statins in reducing triglycerides or increasing HDL when the drugs of choice should be fibrates which are underestimated in this way, according to the practical application of knowledge in the population of doctors included in this study. Also underestimated are the real benefits and the available evidence on the micro- and macrovascular complications of fibrates used in patients with AD.

This study has some limitations, as it had a cross-sectional design and the information was collected in the form of a survey, without the participating doctors having received any specific formal training on AD and without knowing either the exact proportion of patients of this type they deal with in their daily clinical practice, which could indicate their level of familiarity with the process. Nevertheless, the sample size is ample and the

geographical distribution is highly appropriate for evaluating the situation in Spain.

CONCLUSION

Although there is a considerable degree of consensus on the management of AD in the scope of Primary Care, its high prevalence requires additional effort to improve its detection and treatment, both in relation to lifestyle and to the administration of drugs. In this regard, it is necessary to insist on the need to perform a complete lipid profile to evaluate the patient's cardiovascular risk overall and detect the clinical alteration, as well as to treat with combined therapy where this applies in order to tackle the residual risk associated with the existence of hypertriglyceridemia and low levels of HDL-C.

ACKNOWLEDGEMENTS

The authors thank all the physicians who participated in this study, Ana López Fernández (Mylan Spain) and the SANED Group for its role in the study Technical Secretariat and in the statistical analysis of the data.

FUNDING

This study has been sponsored by Mylan Spain.

REFERENCES

1. Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe — epidemiological update 2015. *European Heart Journal* 2015. Oct 21; 36(40): 2673-4.
2. Nichols M, Townsend N, Scarborough P, Rayner M. Trends in age-specific coronary heart disease mortality in the European Union over three decades: 1980–2009. *European Heart Journal* 2013. Oct; 34(39): 3017-27.
3. Fruchart JC, Davignon J, Hermans MP et al. Residual macrovascular risk in 2013: what have we learned? *Cardiovasc Diabetol* 2014; 13: 26.
4. Hopkins PN, Wu LL, Hunt SC, Brinton EA. Plasma triglycerides and type III hyperlipidemia are independently associated with premature familial coronary artery disease. *J Am Coll Cardiol* 2005; 45: 1003-1012.
5. Sarwar N, Sandhu MS, Ricketts SL et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet* 2010; 375: 1634-1639.
6. Li C, Ford ES, Tsai J et al. Serum non-high-density lipoprotein cholesterol concentration and risk of death from cardiovascular diseases among U.S. adults with diagnosed diabetes: the Third National Health and Nutrition Examination Survey linked mortality study. *Cardiovasc Diabetol* 2011; 10: 46.
7. Plana N, Ibarretxe D, Cabré A et al. Prevalencia de dislipidemia aterogénica en pacientes de atención primaria en España con riesgo de enfermedad cardiovascular de moderado a muy alto. Percepción del riesgo cardiovascular. *Clínica e Investigación en Arteriosclerosis* 2014; 26: 274-284.

8. Missault L, Witters N, Imschoot J. High cardiovascular risk and poor adherence to guidelines in 11,069 patients of middle age and older in primary care centres. *Eur J Cardiovasc Prev Rehabil* 2010; 17: 593-598.
9. Millan J, Alegria E, Guizarro C et al. [Dyslipemia in diabetics treated with statins. Results of the DYSIS study in Spain]. *Med Clin (Barc)* 2013; 141: 430-436.
10. The BIP study group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. *Circulation* 2000; 102: 21-27.
11. Scott R, O'Brien R, Fulcher G 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; 32: 493-498.
12. Ginsberg HN, Elam MB, Lovato LC et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010; 362: 1563-1574.
13. Guyton JR, Slee AE, Anderson T et al. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). *J Am Coll Cardiol* 2013; 62: 1580-1584.
14. Arbel Y, Klempfner R, Erez A et al. Bezafibrate for the treatment of dyslipidemia in patients with coronary artery disease: 20-year mortality follow-up of the BIP randomized control trial. *Cardiovasc Diabetol* 2016; 15: 11.
15. Chapman MJ, Ginsberg HN, Amarenco P 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; 32: 1345-1361.
16. Millán Núñez-Cortés J, Pedro-Botet J, Brea-Hernando Á et al. Consenso de expertos sobre propuestas para la mejora del manejo de la dislipemia aterogénica. *Revista Española de Cardiología* 2014; 67: 36-44.
17. Ebrahim S, Sung J, Song Y-M et al. Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study. *BMJ : British Medical Journal* 2006; 333: 22-22.
18. Wu J, Chen S, Zhou Y et al. Non-high-density lipoprotein cholesterol on the risks of stroke: a result from the Kailuan study. *PLoS One* 2013; 8: e74634.
19. Reiner Ž, Catapano AL, De Backer G et al. Guía de la ESC/EAS sobre el manejo de las dislipemias. *Revista Española de Cardiología* 2011; 64: 1168-1168.
20. Perk J, De Backer G, Gohlke H 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; 33: 1635-1701.
21. Ryden L, Grant PJ, Anker SD et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013; 34: 3035-3087.
22. Carey VJ, Bishop L, Laranjo N et al. 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; 106: 757-763.
23. 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; 23: 799-807.
24. Borggreve SE, De Vries R, Dullaart RP. Alterations in high-density lipoprotein metabolism and reverse cholesterol transport in insulin resistance and type 2 diabetes mellitus: role of lipolytic enzymes, lecithin:cholesterol acyltransferase and lipid transfer proteins. *Eur J Clin Invest* 2003; 33: 1051-1069.
25. Tenenbaum A, Fisman EZ. Fibrates are an essential part of modern anti-dyslipidemic arsenal: spotlight on atherogenic dyslipidemia and residual risk reduction. *Cardiovasc Diabetol* 2012; 11: 125.
26. Panel Europeo de Expertos. Versión española del Grupo de trabajo sobre Dislipemia A. Consenso sobre tratamiento farmacológico de la dislipidemia aterogénica con terapia combinada estatina-fenofibrato. *Clínica e Investigación en Arteriosclerosis*.
27. (EMA) EMA. Assessment Report for Fenofibrate, Bezafibrate, Ciprofibrate, and Gemfibrozil Containing Medical Products. In. 2011.