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CONFERENCE INSIGHT

Advances in the treatment of dyslipidemia

Best choice - best practice

Malaga,
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Contents

Introduction

Cardiovascular disease (CVD) accounts for about 30% of total causes of mortality worldwide. Effective management of CV risk factors, such as dyslipidemia, hypertension and insulin resistance, is crucial for the reduction of CV-related morbidity and mortality.

In more detail, among the CV factors contributing to the risk of myocardial infarction, dyslipidemia is the most relevant, since it accounts for 50% of the total population-attributable risk.

Clinical studies are consistent in demonstrating that statin therapy can improve lipid profiles by reducing low-density lipoprotein cholesterol (LDL-C) levels. Noteworthy, each mmol/L reduction in LDL-C is associated with a 12% reduction in all-cause mortality, a 19% reduction in coronary mortality, and a 22% reduction in the total risk of major vascular events.

However, despite the widespread availability of effective statins, the proportion of patients who fail to achieve their LDL-C targets can be as high as 50%. Therefore, educational activities to support a more correct use of statins in clinical practice appear necessary.

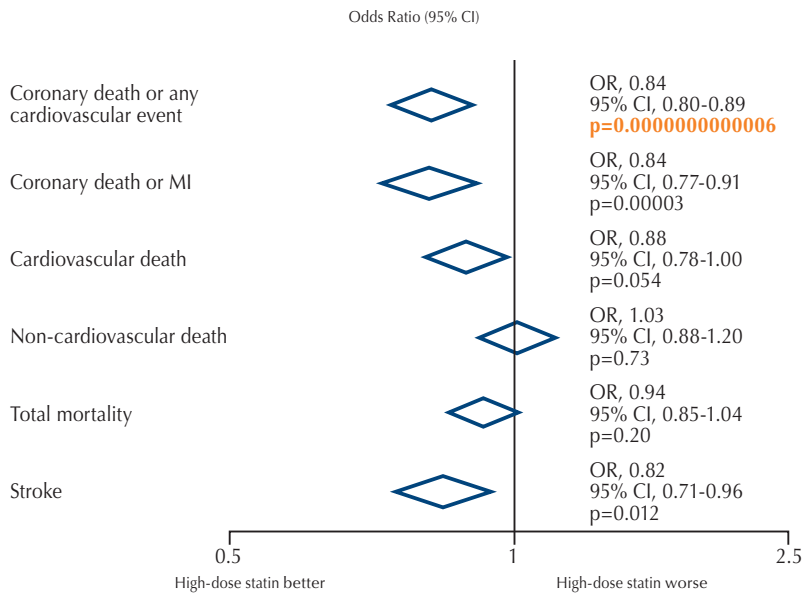
On these bases, Recordati has supported, through an unrestricted educational grant, the symposium "Advances in the treatment of dyslipidemia. Best choice - best practice". This event was held in Malaga, on September 29th-30th 2017 and was aimed at reviewing the efficacy and safety of statin therapy in clinical practice. A special focus was given to pitavastatin, its role in the treatment of dyslipidemia and its additional benefits beyond LDL-C reduction.

The present publication reports the key topics and evidence discussed during the symposium.

Statin as the foundation of the dyslipidemia therapy

From the speech by J. Zamorano, Head of Cardiology, University Hospital Ramon y Cajal, Madrid, Spain

Statin therapy is the cornerstone of dyslipidemia management. This treatment reduces LDL-C levels and therefore the risk of CV events, with intensive therapy being associated with more marked effect compared with standard-dose therapy (Figure 1)[1]. In particular, a 1.0 mmol/L reduction in LDL-C results in a 22% decrease in the risk of major CV events, irrespective of the statin



	Odds Reduction	Event Rates No./Total (%) High Dose	Std Dose
Coronary death or any cardiovascular event	-16%	3972/13,798 (28.8)	4445/13,750 (32.3)
Coronary death or MI	-16%	1097/13,798 (8.0)	1288/13,750 (9.4)
Cardiovascular death	-12%	462/13,798 (3.3)	520/13,750 (3.8)
Non-cardiovascular death	+3%	340/13,798 (2.5)	331/13,750 (2.4)
Total mortality	-6%	808/13,798 (5.9)	857/13,750 (6.2)
Stroke	-18%	316/13,798 (2.3)	381/13,750 (2.8)

Coronary death or any cardiovascular event	OR, 0.84 95% CI, 0.80-0.89 p=0.0000000000006
Coronary death or MI	OR, 0.84 95% CI, 0.77-0.91 p=0.00003
Cardiovascular death	OR, 0.88 95% CI, 0.78-1.00 p=0.054
Non-cardiovascular death	OR, 1.03 95% CI, 0.88-1.20 p=0.73
Total mortality	OR, 0.94 95% CI, 0.85-1.04 p=0.20
Stroke	OR, 0.82 95% CI, 0.71-0.96 p=0.012

Figure 1. Efficacy of intensive vs. standard dose statin therapy: results of a meta-analysis on >27,000 patients[1].

used, or a 1% reduction in LDL-C levels reduces the risk of coronary artery disease by 1%[1,2]. Overall, these effects were shown in almost all populations of patients, either in primary or in secondary prevention (Figure 2)[3], with the exception of those with New York Heart Academy (NYHA) class II-IV heart failure or those on maintenance hemodialysis.

Therefore, intensified efforts are being made to identify individuals at risk of CV events and to prescribe statin therapy in order to achieve LDL-C target goals. These targets are established according to the specific risk of the individual patient, as defined by different guidelines.

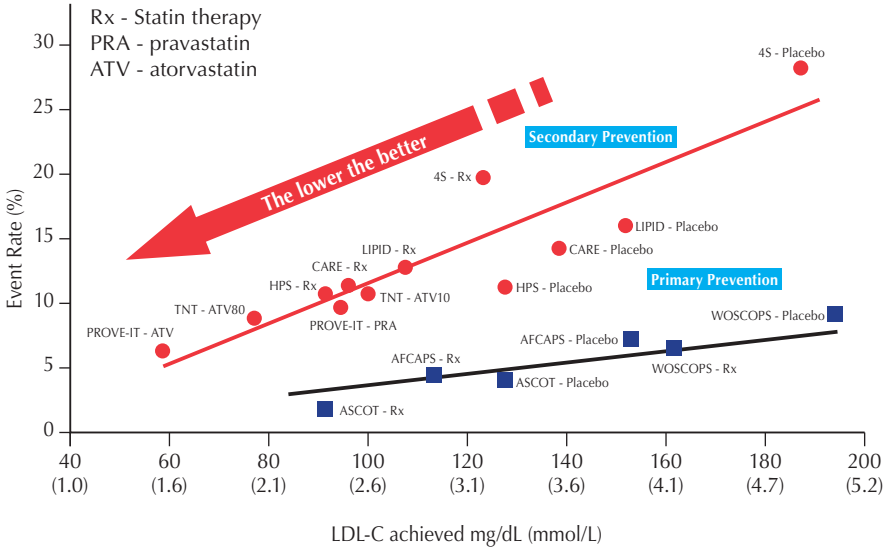


Figure 2. Lowering of CV risk with LDL-C reduction by statin therapy[3].

Latest EAS/ESC guidelines

From the speech by J. Zamorano, Head of Cardiology, University Hospital Ramon y Cajal, Madrid, Spain

The Task Force of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) has recently issued the 2016 ESC/EAS Guidelines for the management of dyslipidemias[4]. According to the guidelines, patients can be stratified by CV risk, as derived from multiple risk factors: very high risk, high risk, moderate risk and low risk (Table 1), with different LDL-C target levels[4].

In order to achieve the desired target LDL-C levels, different strategies can be pursued (Table 2)[4]. Statin therapy should be prescribed up to the highest recommended dose or highest tolerable dose to reach the goal. In the case of statin intolerance or lack of efficacy, combination therapies can be considered[4]. Remarkably, treatment with statins is recommended for older adults with established CVD, with proper titration, in elderly subjects carrying CV risk factors (hypertension, smoking, diabetes) and for the primary prevention of coronary artery disease (CAD) in high-risk women.

In all patients with type 1 diabetes and in the presence of micro-albuminuria and/or renal disease, LDL-C lowering (>50%) with statins as the first choice is recommended irrespective of the baseline LDL-C concentration. In subjects with type 2 diabetes and CVD or chronic kidney disease (CKD), and in those without CVD who are >40 years of age with one or more other CVD risk factors or mark-

Table 1. CV risk categories and LDL-C target levels (see[4] for more details).

Risk class	Patient characteristics	LDL-C levels
Very high risk	Any of the following: • Documented CVD. • DM with target organ damage or with a major risk factor. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE >10%.	<1.8 mmol/L (70 mg/dL) or a reduction ≥50% if the baseline LDL-C is 1.8-3.5 mmol/L (70-135 mg/dL)
High risk	Any of the following: • Markedly elevated single risk factors (e.g. familial dyslipidemias or severe hypertension). • Most other people with diabetes. • Moderate CKD (GFR 30-59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.	<2.6 mmol/L (100 mg/dL), or a reduction ≥50% if the baseline LDL-C is 2.6-5.2 mmol/L (100-200 mg/dL)
Moderate risk	SCORE is ≥1% and <5% at 10 years.	<3.0 mmol/L (<115 mg/dL)
Low risk	SCORE <1%	<3.0 mmol/L (<115 mg/dL)

Table 2. Intervention strategies for LDL-C lowering[4].

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6 mmol/L	100 to <155 mg/dL 2.6 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	≥190 mg/dL ≥4.9 mmol/L
<1	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled
Class/Level	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled
Class/Level	I/C	I/C	IIa/A	IIa/A	I/A
≥5 to <10 or high-risk	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice and drug treatment for most	Lifestyle advice and drug treatment	Lifestyle advice and drug treatment
Class/Level	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high-risk	Lifestyle advice, consider drug[a]	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment
Class/Level	IIa/A	IIa/A	I/A	I/A	I/A

[a]In patients with myocardial infarction, statin therapy should be considered irrespective of total cholesterol levels.

ers of target organ damage, the recommended goal for LDL-C is <1.8 mmol/L (<70 mg/dL). In all patients with type 2 diabetes and no additional risk factors and/or evidence of target organ damage, LDL-C <2.6 mmol/L (<100 mg/dL) is the primary goal. Non-HDL-C <3.4 mmol/L (<130 mg/dL) and apoB <100 mg/dL are the secondary goals.

Statins and Diabetes: What we know, where we are

From the speech by P. Marques da Silva, Arterial Investigation Unit Medicina 4 – Hospital de Santa Marta, Centro Hospitalar de Lisboa Central, EPE

Some evidence seems to support a subtle diabetogenic effect of statin treatment[5]. This effect appears dose- and time-dependent, increasing with more intensive and more prolonged therapy. However, according to a recent systematic review on the topic, treatment of 10,000 patients for 5 years with a statin can cause only 50-100 new cases of diabetes[6]. Therefore, it can be concluded that the absolute risk for development of diabetes can be outweighed by cardiovascular benefit[6].

Noteworthy, a number of population-based studies on the onset of diabetes with statin therapy in FH (familial hypercholesterolemia) patients showed that intensive statin treatment is not associated with an increased risk of new-onset diabetes (Table 3). On the other hand, there is an increased risk of diabetes in patients with familial combined hyperlipidemia (15% vs. 1%, with a mean follow-up of about 10 years).

A number of complex different molecular mechanisms, in particular involving HMG-CoA reductase, can contribute to the potential increase in glycemia associated with statin therapy[7,8]. In particular, statins may decrease insulin synthesis or disturb insulin secretion and may also impair insulin sensitivity of the target cells, causing insulin resistance[9]. In more detail, statins can cause: (i) reduction in tyrosine-specific phosphorylation of IRS-1 in response to insulin; (ii) reduction of small GTP-binding proteins Rab4 and RhoA with interference in translocation of GLUT4 to the cell membrane; (iii) disruption also by the reduction of serine-threonine phosphorylation of AKT and protein kinase 3 (PKC) cascades; (iv) NLRP3 inflammasome activation[8]. Moreover, statin therapy might impair β-cells function[8]. However how these findings relate to patients is unknown.

On these bases, statins should be prescribed on the basis of CV risk and individual patient characteristics[8,9]. Proper monitoring of glycemia remains important. In addition, diet and lifestyle

Table 3. Impact of intensive statin therapy on risk of new-onset diabetes in patients with lipid disorders.

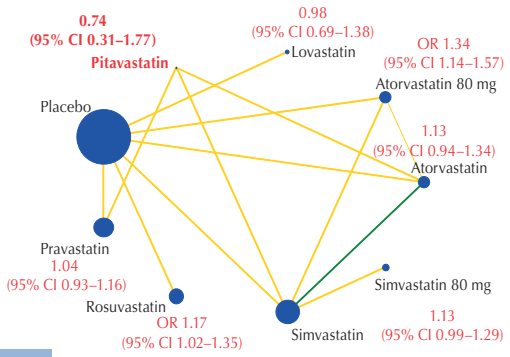
Author and Published year	Country	Study design	Population and the cause of FH	DM-related findings
Vohl et al., 1997	Canada	Case control study	102 patients without FH, 102 hFH patients; a defective allele at LDLR or LDLR mutation	The prevalence of DM was significantly higher in the non-FH group than in the two FH groups ($p<0.05$)
Skoumas et al., 2007	Greece	Cross-sectional study	A total of 1306 subjects: 600 individuals with hFH, and 706 individuals with FCH; LDLR mutation or plasma levels of LDL cholesterol above the 95th percentile	FCH had a significantly increased prevalence of DM (13 vs. 2%, $p<0.001$) vs. FH group, whereas total cholesterol, LDL-cholesterol, and ApoB levels were higher (all $p<0.001$) in FH subjects
Skoumas et al., 2014	Greece	Ambispective cohort study	A total of 523 adult patients (314 hFH and 209 FCH patients); LDL-receptor mutation or plasma levels of LDL cholesterol above the 95th percentile	14% of FCH and only 1% of hFH patients developed DM during follow-up
Kusters et al., 2014	Netherlands	Retrospective cohort study	2144 children with hFH; LDR mutation	Statin treatment was not associated with an increased risk of new onset DM in these patients
Besseling et al., 2015	Netherlands	Cross-sectional study	All individuals (n=63,320) who underwent DNA testing for FH; 3475 were ApoB mutation carriers, 21,606 had the LDLR mutation, and 56 had PCSK9 mutation	The prevalence of T2DM was 1.75% in FH patients (n=440/25,137) vs. 2.93% in unaffected relatives ($p<0.001$). The adjusted prevalence of T2DM by ApoB vs. LDL receptor gene was 1.91% vs. 1.33%
Fuentes et al., 2015	Spain	Cross-sectional and prospective cohort study	2558 FH and 1265 unaffected relatives with a mean follow-up of 5.9 years; LDLR mutation	Finally, in the Kaplan-Meier curve, there are no differences between FH group vs. control group in the incidence of T2DM according the duration of treatment with statins

interventions should be emphasized to help mitigate the risk of new-onset diabetes; if a patient develops diabetes while receiving statins, this condition should be managed in accordance with the appropriate guidelines.

Noteworthy, the diabetogenicity of each single statin is different. Therefore clinicians should individualize statin therapy, and, in some cases, switch to a statin associated with a lower diabetogenic risk[9]. In a recent network meta-analysis of 27 trials, pitavastatin ranked last out of 8 different drug regimens in terms of risk of increasing the incidence of new-onset diabetes during statin therapy (Figure 3)[10].

Network meta-analysis of 27 studies

- Different statins and comorbidities may be associated with different risk profiles for T2DM
- Pitavastatin ranked last out of 8 drug regimens assessed in increasing the risk of new-onset diabetes



Objectives

RCTs have shown mixed findings on the association of statins and diabetes mellitus. Network meta-analysis performed to update evidence and to explore heterogeneity of the results in order to assist clinicians in making more informed treatment choices.

Figure 3. Odds ratio for the development of new-onset diabetes with different statin regimens, according to the results of a network meta-analysis of 27 trials[10].

Diabetes & Pitavastatin: Current evidence

From the speech by J. de Castro, Department of Endocrinology and Diabetes, Armed Forces University Hospital, Lisbon, Portugal

At present, pitavastatin is one of the most potent statins in LDL-C reduction (Figure 4)[11]. The use of this molecule in diabetic patients has been extensively investigated in the J-PREDICT study; this was the first trial to evaluate the effect of a statin on the onset of diabetes as the primary endpoint[12]. In this study, 1240 adult patients with impaired glucose tolerance according

to the WHO criteria were randomly assigned, in a 1:1 ratio, to either lifestyle modification (control) or pitavastatin 1-2 mg/day in addition to lifestyle modification. After a 72-month follow-up, pitavastatin reduced the risk of incident diabetes by 18% compared with strict diet and exercise alone (Figure 5)[12].

The beneficial effects of pitavastatin on glycemic control were confirmed in the LIVES study, a large-scale surveillance of cardiovascular/cerebrovascular events in patients on intensive statin treatment[13]. In the 308 diabetic patients on pitavastatin, HbA_{1c} levels significantly decreased over the first two years of treatment (Figure 6a)[13]. This effect was consistent up to 5 years of pitavastatin therapy (Figure 6b)[13].

Noteworthy, a large meta-analysis of 15 studies versus placebo or other statins (for a total of 1600 patient-years) suggested that pitavastatin has a neutral effect on fasting blood glucose and HbA_{1c} levels in non-diabetic subjects, as a further confirmation of the absence of risk of developing diabetes with pitavastatin in non-diabetic subjects (Figure 7)[14]. In more detail, no

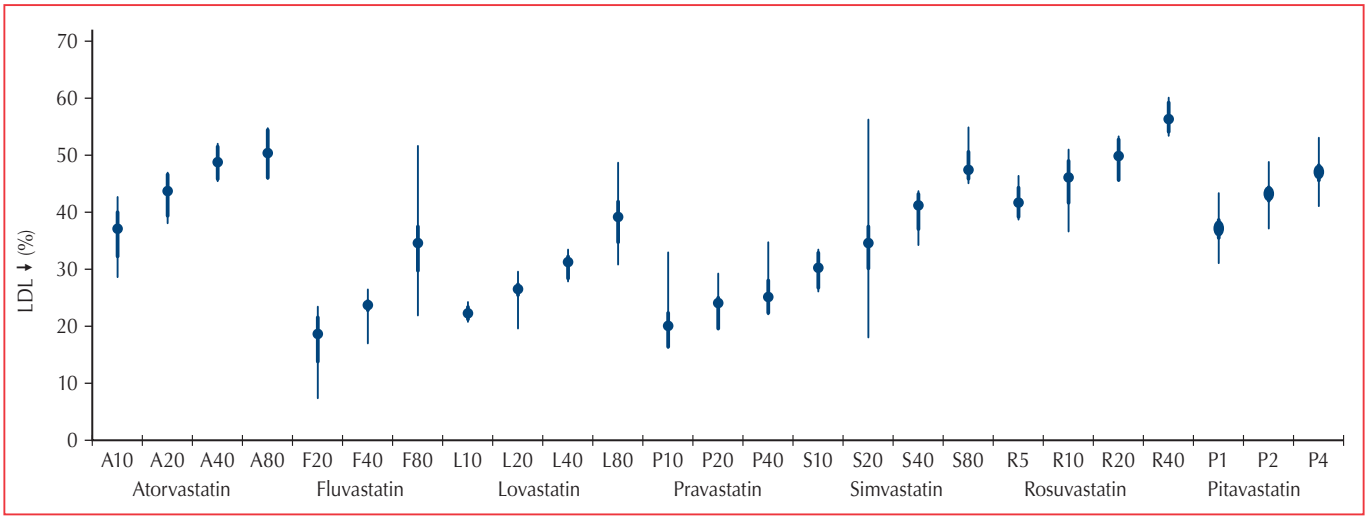


Figure 4. LDL-C reduction with different dosages of different statins.

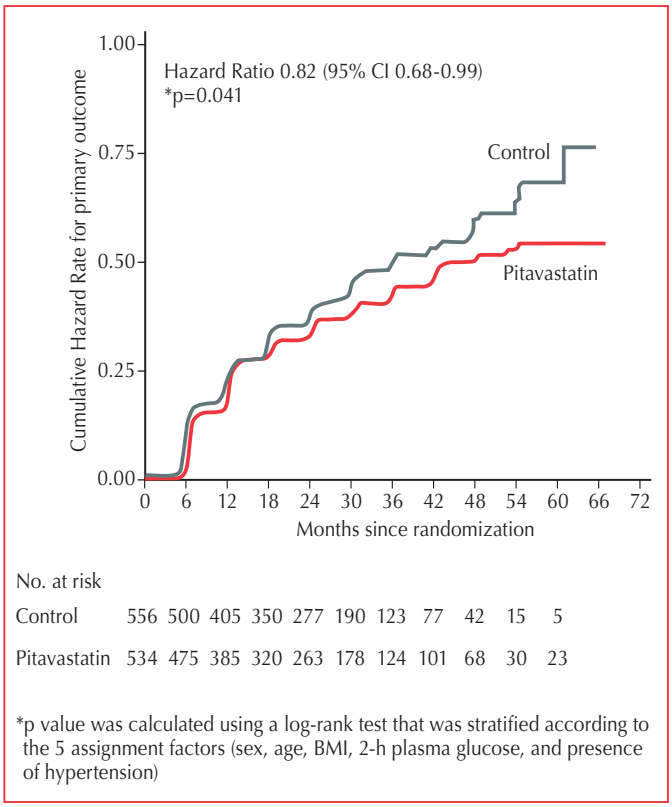


Figure 5. Effect of pitavastatin on the incidence of diabetes in the J-PREDICT study[12].

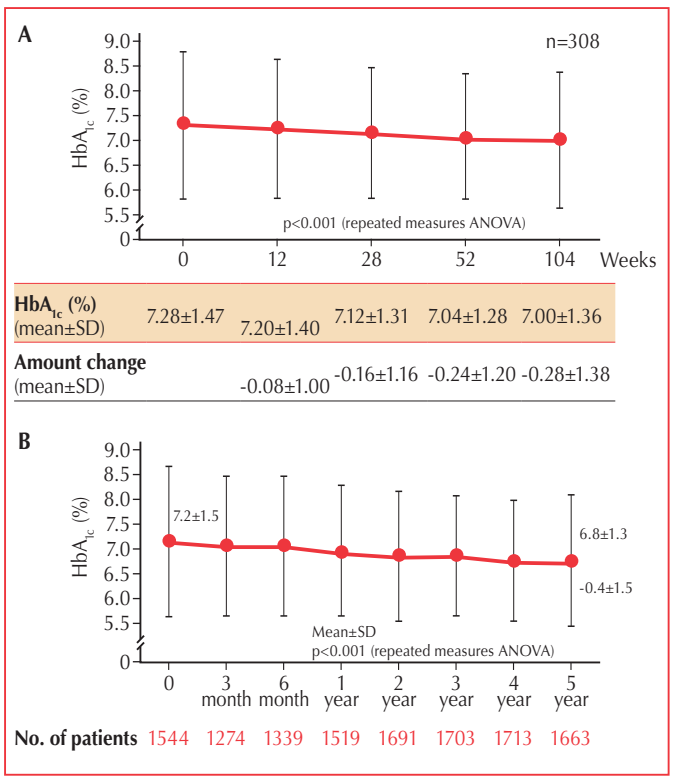


Figure 6. HbA_{1c} levels in diabetic patients treated with pitavastatin in the LIVES study. Panel A): 2-year treatment; Panel B): 5-year treatment[13].

significant differences associated with pitavastatin versus control were observed for fasting blood glucose, glycated hemoglobin or new-onset diabetes. Sensitivity and subgroup analyses (type of control, pitavastatin dose or length of follow-up) did not yield significant results.

According to the above-described, well-grounded evidence, it can be concluded that pitavastatin is a suitable option for the treatment of dyslipidemia in diabetic patients and people at risk for diabetes, with neutral effect on glucose metabolism or onset of diabetes[14].

	Pitavastatin		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Eriksson M et al. 2011	0	218	0	111		Not estimable
NK-104-203	0	202	0	49		Not estimable
PREVAIL-US	0	143	0	131		Not estimable
NK-104-202	0	206	0	54		Not estimable
PAPAGO-T	0	50	0	50		Not estimable
PEACE	0	70	0	81		Not estimable
VISION	0	21	0	21		Not estimable
Stender S et al. 2013	0	597	0	288		Not estimable
INTREPID	0	123	4	124	8.2%	0.11 [0.01, 2.06]
Budinski D et al. 2009	1	576	2	179	12.1%	0.16 [0.01, 1.70]
COMPACT-CAD	1	36	3	35	14.2%	0.32 [0.04, 2.97]
TRUTH	2	38	2	31	19.3%	0.82 [0.12, 5.46]
Saito Y et al. 2002	1	84	1	81	9.2%	0.96 [0.06, 15.16]
Ose L et al. 2009	1	592	0	202	6.8%	1.03 [0.04, 25.11]
NK-104-4.01CH	9	280	2	142	30.2%	2.28 [0.50, 10.42]
Total (95% CI)		**3236**		**1579**	**100%**	**0.70 [0.30, 1.61]**
Total events	15		14			

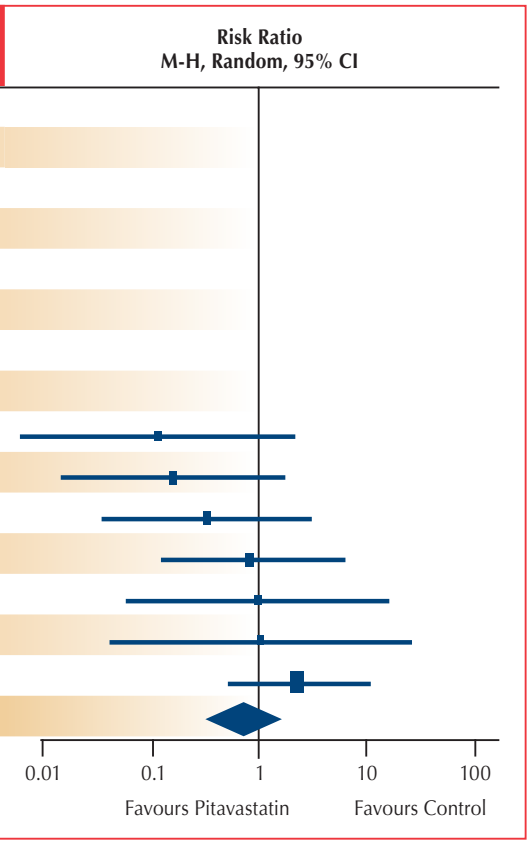


Figure 7. Risk of developing diabetes with pitavastatin: results of a meta-analysis of 15 randomized clinical trials[14].

HDL & Pitavastatin: Current evidence

From the speech by G. Barón Esquivias, Servicio de Cardiología, Hospital Universitario Virgen del Rocío, Sevilla, Spain

HDL-C levels are an independent risk factor for CVD; further to the reduced HDL-C levels frequency observed in patients at CV risk, the presence of dysfunctional HDL particles has been reported[15,16].

The effects of pitavastatin on HDL-C have been investigated in a number of studies, both in the experimental and clinical setting. Overall, pitavastatin increases HDL quality and function by a number of different mechanisms (Table 4)[15]. These include: (i) induction of the production and secretion of hepatic apoA-I – which is more marked than reported with other statins; (ii) an increase in the lipidation of apoA-I to generate HDL particles; (iii) enhancement of the expression of macrophage scavenger receptor class B type I (SR-BI), a HDL receptor involved in the reverse cholesterol transport process; and (iv) inhibition of endothelial lipase, a negative regulator of HDL-C levels[15]. Also given this strong mechanistic rationale, HDL-C increase with pitavastatin is sustained over time (Figure 8)[17].

Noteworthy, the increase in HDL-C levels with pitavastatin is also more evident than with other statins, since a significant increase in HDL-C has been reported when switching from other statins to pitavastatin[13]. Indeed, a sub-analysis of the LIVES study showed that HDL-C was elevated with pitavastatin by 5.9% in all patients and by 24.6% in those with low (<1 mmol/L; 40 mg/dL) HDL-C levels at baseline ($p<0.0001$).

A time-course analysis showed that the elevation in HDL-C in the low-HDL-C group was enhanced by 14.0% and 24.9% at 12 weeks and 104 weeks, respectively[13]. Moreover, pitavastatin produced a significant increase in HDL-C levels in patients switching from other statins, thus suggesting that patients with low levels of HDL-C might benefit from switching to pitavastatin. Collectively, these benefits on HLD-C might translate into enhanced benefit on CV events[18].

Table 4. Possible mechanisms by which pitavastatin increases HDL quality and function[15].

Reference	System	Effects
Maejima et al., 2004	HepG2	↑ apoA-I production and secretion
Maejima et al., 2011	HepG2	↑ ABCA1 mRNA expression
Han et al., 2004	J774, mouse peritoneal macrophages, human monocyte-derived macrophages	↑ SR-BI expression→↑macrophage HDL binding ↑ cholesterol efflux ↑ cholesteryl ester influx
Kojima et al., 2010	HUVEC Mouse aorta and liver Patients with cardiovascular disease	↓ EL expression ↓ EL expression ↑ HDL particle size ↓ plasma EL levels ↑ HDL particle size
Miyamoto-Sasaki et al., 2013	Dyslipidemic subjects treated with pitavastatin 2 mg/day for 4 weeks	↑ HDL-C levels ↑ PL content in HDL ↑ large HDL particle number ↑ HDL-mediated efflux ↑ PON-1 activity
Kawano et al., 2008	Hypercholesterolemic patients treated with pitavastatin 2 mg/day for 4 weeks	↑ HDL2-C ↓ preβ-HDL levels; ↑preβ-HDL disappearance rate ↓ LCAT activity ↓ CETP mass
Orsoni et al., 2016	Insulin-resistant, HTG, hypertensive obese male patients treated with pitavastatin 4 mg/day for 6 months	↓ TG content in HDL2 and HDL3 ↑ CE content in HDL2 and HDL3 ↑ PE plasmalogens and PUPC in HDL3
Igarashi et al., 2007	BAEC	↑ S1P1 receptors ↑ HDL-mediated eNOS stimulation

HUVEC: human umbilical vein endothelial cells; ABCA1: ATP-binding cassette transporter A1; SR-BI: scavenger receptor class B type I; EL: endothelial lipase; PL: phospholipids; PON1: paraoxonase 1; LCAT: lecithin-cholesterol acyltransferase; CETP: cholesteryl ester transfer protein; TG: triglyceride; CE: cholesteryl ester: PE: phosphatidylethanolamine; PUPC: polyunsaturated phosphatidylcholines; BAEC: bovine aortic endothelial cells; S1P1: sphingosine-1-phosphate subtype 1 receptor; eNOS: endothelial nitric oxide synthase.

Treatment with pitavastatin not only increases HDL-C levels. In a prospective, multicenter study 63 patients with coronary artery disease received pitavastatin for 12 months[19]. Mean carotid intima-media thickness decreased with pitavastatin (from 0.99 mm to 0.94 mm; p=0.01) regardless of pretreatment with other statins. In a study on 20 patients under statin therapy but with low HDL-C levels, switching to pitavastatin led to an increase in HDL-C after three months' therapy (from 37 mg/dL to 40 mg/dL; p<0.05)[20]. Moreover, the eleven patients with high-sensitive troponin T – a marker of myocardial damage – at baseline showed a significant reduction in this parameter; its percent reduction correlated with the percent increase in HDL-C (r = -0.68, p<0.05). The Authors concluded that minute myocardial damage is observed in more than half of patients with low HDL-C despite the administration of any statin, and the replacement of their previous statin with pitavastatin further improved their lipid profiles and led to better myocardial protection, possibly mediated via the elevation of the HDL-C levels[20].

In a randomized study on 29 patients with stable coronary artery disease, hypercholesterolemia, and low-HDL, the effects of 30-month treatment with pitavastatin on HDL-C were significant-

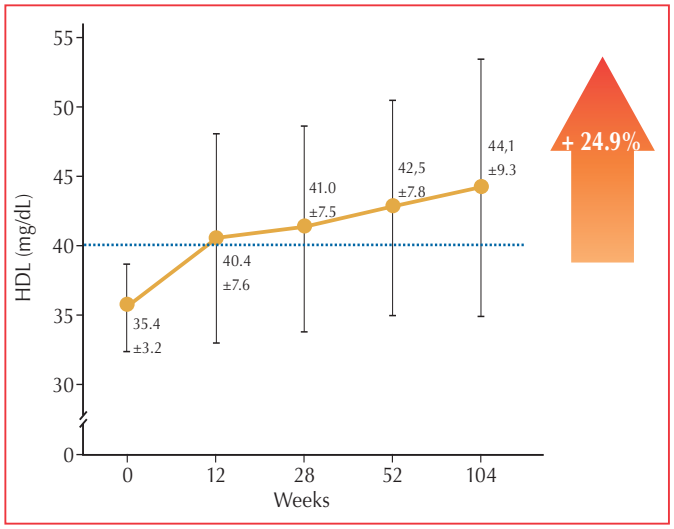


Figure 8. Effect of pitavastatin on HDL-C over 3 years in the LIVES study (n=20,279)[17].

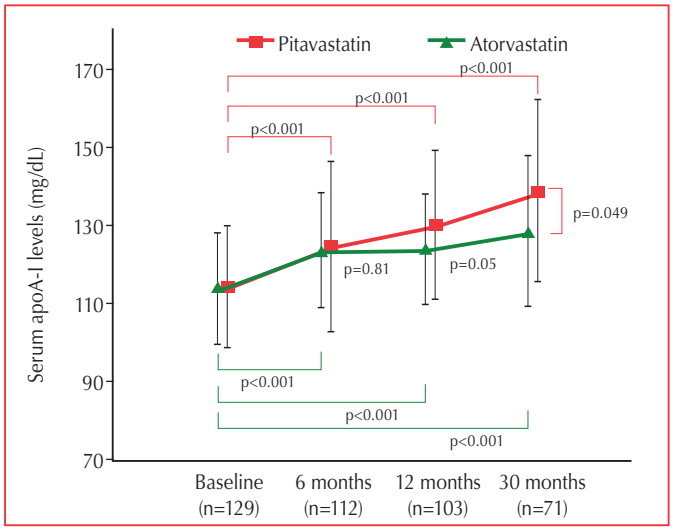


Figure 9. Absolute and % change in apoA-I lipoprotein with pitavastatin or atorvastatin[21].

ly greater than those of atorvastatin (% change: pitavastatin: 20.1%; atorvastatin: 6.3%; p=0.01)[21]. A similar trend was reported for apoA-I) (Figure 9)[21] and adiponectin.

Last, in a study on 30 patients with dyslipidemia, pitavastatin increased the serum HDL-C level by 9% (p<0.05)[22]. In addition, pitavastatin increased the phospholipid content of HDL by 7.8% (p<0.05). The pitavastatin-induced increase in HDL-C was paralleled by an increase in the cholesterol efflux capacity of the isolated HDL fraction (+8.6%; p<0.05 vs. baseline). The post-pitavastatin treatment activity of HDL-associated PON-1 (paraoxonase and arylesterase) was increased by 9% (p<0.05) and 11% (p<0.05), respectively. On these bases, it can be concluded that pitavastatin increases the amount of functional HDL without attenuating HDL quality.

HDL & Pitavastatin: New perspectives

From the speech by J. Chapman, University of Pierre and Marie Curie, Pitié-Salpetriere University Hospital, Paris, France

Subnormal levels of HDL-C or impaired function of these particles constitute a major CV risk factor. Plasma HDL particles are indeed highly heterogeneous in their physicochemical properties, metabolism, and biological activity. Within the circulating HDL particle population, small, dense HDL particles display elevated cellular cholesterol efflux capacity, afford potent protection of atherogenic low-density lipoprotein against oxidative stress and attenuate inflammation. Normalization of both defective HDL function and diminished HDL levels should therefore be the focus of current and future research[23,24]. Proteomic studies have emphasized that HDL is composed of distinct particles containing unique (apolipo)protein complements. Such subspeciation forms a potential basis for understanding the numerous observed functions of HDL[25]. In addition, complex associations exist between HDL-C levels and sociodemographic, lifestyle, comorbidity factors, and mortality. In a recent large (n=631,762) study on data from the CANHEART (Cardiovascular Health in Ambulatory Care Research Team) dataset, individuals with lower HDL-C levels were more likely to have low incomes, unhealthy lifestyle, higher triglyceride levels, other cardiac risk factors, and medical comorbidities[26]. In this study, individuals at the lowest 2 strata of HDL-C levels (≤30 mg/dL and 31-40 mg/dL) had significantly higher overall mortality rates (14.7 per 1000 person-years, and 9.3 per 1000 person-years, respectively) compared with other subjects, although a U-shaped trend for mortality was observed (Figure 10)[26].

LDL particles undergo oxidation upon entry into the arterial intima, driving macrophage foam cell formation and the inflammatory dimension of atherosclerosis. HDL particles may protect LDL against oxidative stress via several mechanisms, central among which appears to be the capacity to accept phospholipid hydroperoxides (PCOOHs) derived from polyunsaturated phosphatidylcholine (PUPC) species in LDL and to reduce them to inactive hydroxides. In the recent CAPITAIN study, insulin-resistant, hypertriglyceridemic, hypertensive, obese males were treated with pitavastatin (4 mg/day) for 180 days, resulting in marked reduction in plasma triglycerides (-41%) and LDL-C (-38%), with a 6% increase in HDL-C apoA-I[27]. In more detail, pitavastatin therapy reduced the content of oxidizable PUPC species in LDL and increased the content of PUPC species in HDL, overall attenuating LDL oxidability.

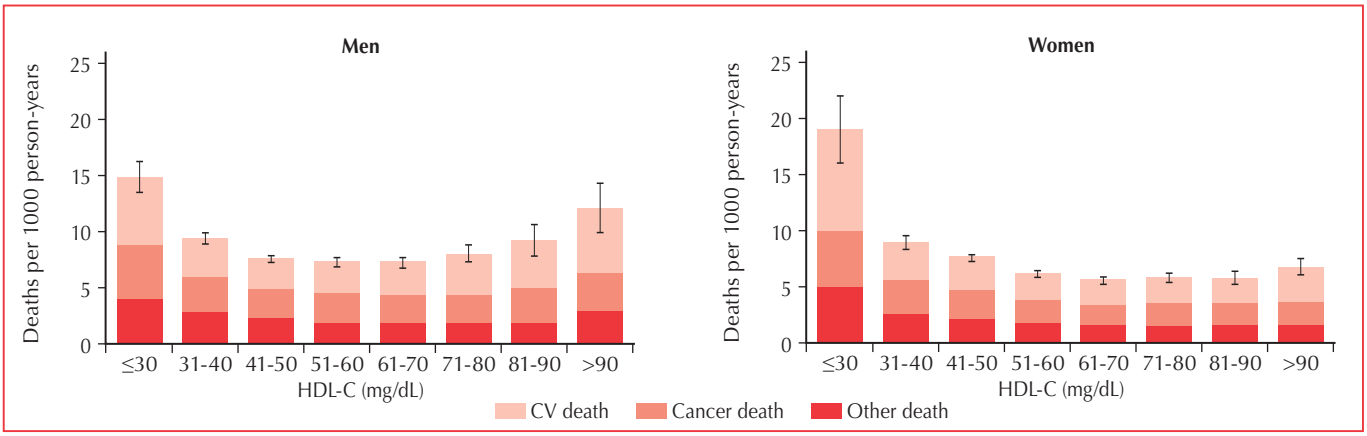


Figure 10. Age-standardized cause-specific mortality in the CANHEART study[26].

Treatment of dyslipidemia in children

From the speech by M. Braamskamp, Department of Vascular Medicine, AMC Amsterdam, The Netherlands

The deposit of cholesterol in the arteries and the development of the atherosclerotic plaques take decades. However, early signs of atherosclerosis are already present in children with hypercholesterolemia. Therefore, for the optimal prevention of CVD, treatment should start from childhood onwards in children with hypercholesterolemia. Current guidelines state that cholesterol lowering treatment with statins should be initiated from the age of 8 years onwards if lifestyle adjustments alone fail to sufficiently lower cholesterol levels[28]. Treatment from early age can lead to a great reduction in the risk of developing CV events during the adult age.

The efficacy and safety of pitavastatin in this setting have been assessed in the PASCAL study[29]. Children were randomly assigned, in double-blind fashion, to 12-week pitavastatin (1, 2 or 4 mg/day) or placebo. At the end of the 12-week period, patients were allowed to enter a 52-week open-label study, during which subjects were up-titrated from 1 mg pitavastatin to a maximum dose of 4 mg in an effort to achieve an optimum LDL-C treatment target of <110 mg/dL (2.8 mmol/L). In total, 106 patients were enrolled (mean age about 10 years). During the 12-week randomized study, pitavastatin significantly reduced LDL-C from baseline, compared with placebo (Figure 11)[29]. Significant improvements were also reported with pitavastatin, compared with placebo, in other lipid parameters. In the open-label extension, reduction of LDL-C was continued over time (Figure 12)[29]. No safety issues were reported.

Noteworthy, the brain is able to synthetize necessary cholesterol to ensure normal function and development. Pitavastatin does not cross the brain-blood barrier and therefore cannot be associated with any adverse effect on cognitive function and physiology.

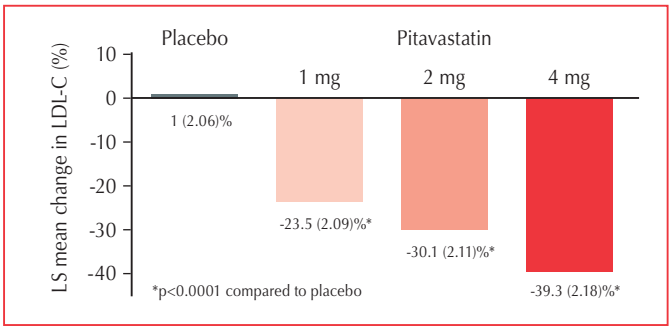


Figure 11. Percentage change in LDL-C from baseline in the 12-week phase of the PASCAL study[29].

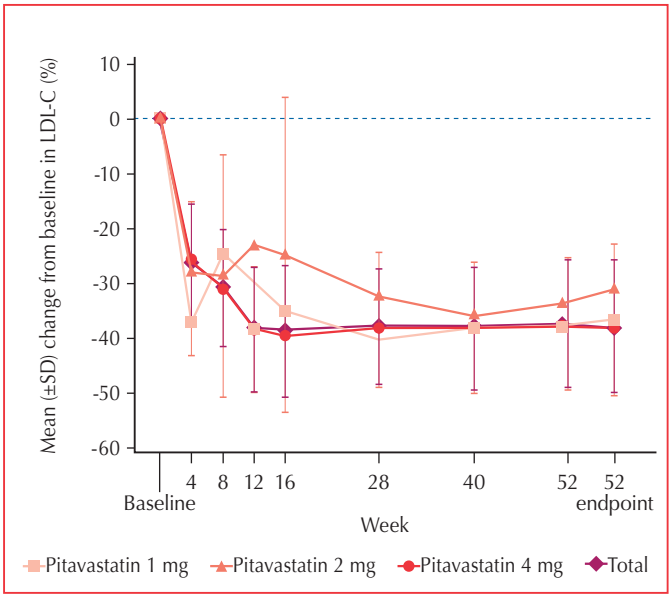


Figure 12. LDL-C reduction over time during the 52-week open-label phase of the PASCAL study[29].

Treatment options in patients with metabolic syndrome: Clinical case

From the speech by R. Baptista, Coronary Care Unit, Cardiology Department, Centro Hospitalar e Universitário de Coimbra, Portugal

Metabolic syndrome is associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality[30]. As such, the presence of metabolic syndrome has a major relevance in clinical practice[5].

We present the case of an overweight patient with metabolic syndrome successfully treated with pitavastatin. Table 5 shows her clinical workup; the patient also presented high blood pressure (157/87 mmHg). As such, the patient met the criteria

for the diagnosis of metabolic syndrome (Table 6).

The patient was given lifestyle counseling, including >30 minutes of daily exercise and Mediterranean diet. She was also prescribed pharmacological therapy with ramipril 5 mg/day, pitavastatin 2 mg/day and metformin 850 mg/day (Table 5). Overall, the patient experienced, over a 6-month period, a marked improvement of her laboratory profile. Noteworthy, the patient independently decided to discontinue pitavastatin for a period, during which she showed a worsening of lipid parameters; they improved following returning to pitavastatin therapy.

Table 5. Clinical workup of the patient.

Ramipril 5 mg		On treatment at this time point	On treatment at this time point	On treatment at this time point
Pitavastatin 2 mg		On treatment at this time point		On treatment at this time point
Metformin 850 mg		On treatment at this time point	On treatment at this time point	On treatment at this time point
	2015/12/21	2016/06/20	2016/12/19	2017/07/17
Fasting glucose, mg/dL	**125**	95	102	102
Serum creatinine, mg/dL	**0.8**	0.81	0.74	0.65
Total cholesterol, mg/dL	**228**	126	227	147
LDL-C, mg/dL	**155**	75	135	73
HDL-C, mg/dL	**46**	46	52	54
TG, mg/dL	**133**	75	200	98
HbA_{1c}, %	**6.1**	6.2	5.9	6.2
Weight, kg	**83**	83	79	82
Waist circumference, cm	**103**			100

Table 6. Fulfilment of the criteria for the diagnosis of metabolic syndrome.

Parameters	NCEP ATP3 2005	IDF 2006	EGIR 1999	WHO 1999	AACE 2003
Required		Waist ≥94 cm (men) or ≥80 cm (women)	Insulin resistance or fasting hyperinsulinemia in top 25 percent	Insulin resistance in top 25 percent; glucose ≥6.1 mmol/L (110 mg/dL); 2-hour glucose ≥7.8 mmol/L (140 mg/dL)	High risk of insulin resistance or BMI ≥25 kg/m² or waist ≥102 cm (men) or ≥88 cm (women)
Number of abnormalities	≥3 of:	And ≥2 of:	And ≥2 of:	And ≥2 of:	And ≥2 of:
Glucose	≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	≥5.6 mmol/L (100 mg/dL) or diagnosed diabetes	6.1-6.9 mmol/L (110-125 mg/dL)		≥6.1 mmol/L (110 mg/dL); ≥2-hour glucose 7.8 mmol/L (140 mg/dL)
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL-C	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL-C	<1.0 mmol/L (40 mg/dL)	<0.9 mmol/L (35 mg/dL) (men); <1.0 mmol/L (40 mg/dL) (women)	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women)
Triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for high triglycerides	or ≥2.0 mmol/L (180 mg/dL) or drug treatment for dyslipidemia	or ≥1.7 mmol/L (150 mg/dL)	≥1.7 mmol/L (150 mg/dL)
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)		Waist ≥94 cm (men) or ≥80 cm (women)	Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m²	
Hypertension	≥130/85 mmHg or drug treatment for hypertension	≥130/85 mmHg or drug treatment for hypertension	≥140/90 mmHg or drug treatment for hypertension	≥140/90 mmHg	≥130/85 mmHg

Treatment options in patients with diabetes: Clinical case

From the speech by L. Perez De Isla, Cardiology Department, Hospital Clínico San Carlos, Madrid, Spain

This is the case of a young patient (16 years) with unspecific palpitations despite normal ECG examination. Investigation of family members revealed that her mother presented abnormal lipid profile and an important family history of CVD: as such, diagnosis of familial hypercholesterolemia was made and both the patient and her mother were subjected to genetic tests which revealed LDLR c.-135 C>G mutation. Also the father of the patient was at high CV risk, due to hypertension, abnormal lipid profile, and tobacco use. After proper investigation of his family history, this man was diagnosed with familial combined hypecholesterolemia.

Figure 13 shows the diagnosis for the patient and her family, the prescribed treatments, and the final outcome. In particular, the patient's father was prescribed pitavastatin, due to the potential risk of new-onset diabetes.

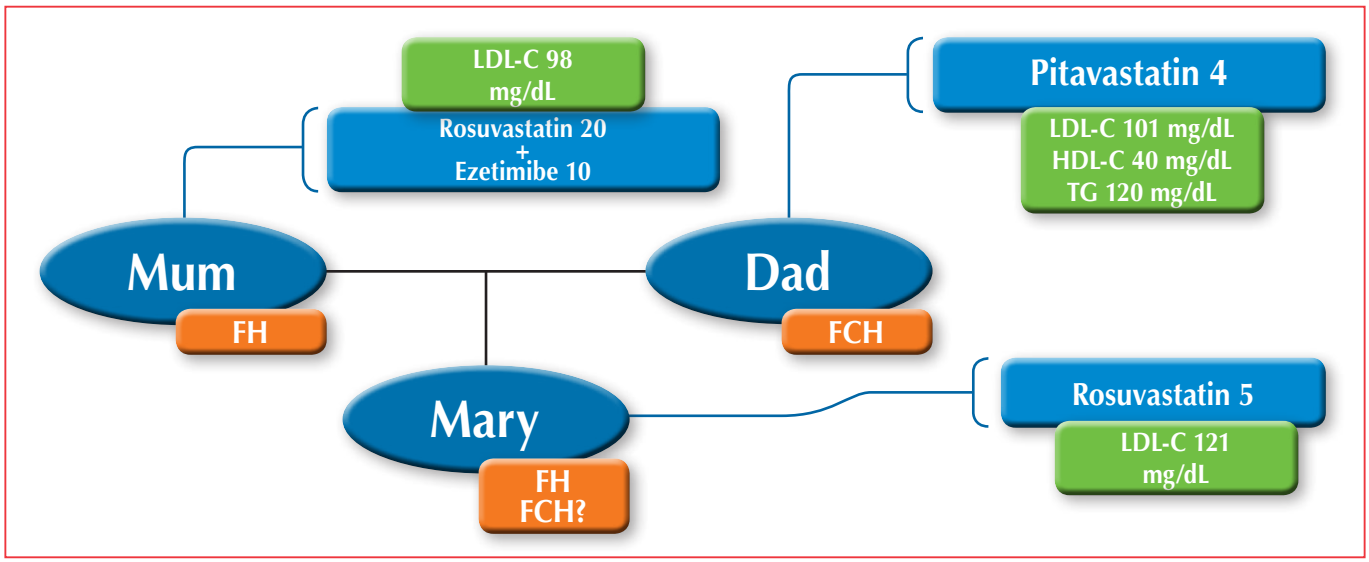


Figure 13. Final diagnosis for the patient and her family, after proper investigation, prescribed treatments, and final outcomes.

Key points

- Pitavastatin is a suitable option for the treatment of dyslipidemia in diabetic patients and people at risk for diabetes, as it is associated with a low or even negligible risk of developing new-onset diabetes.
- Treatment with pitavastatin increases HDL-C levels and improves HDL quality over time.
- Pitavastatin therapy reduces the content of oxidizable species in LDL and increase the same in HDL, overall attenuating LDL oxidability.
- Treatment with pitavastatin attenuated atherosclerotic coronary plaque and results in a high myocardial protection.
- These benefits may translate into a reduced risk of major cardiac events with pitavastatin.
- Pitavastatin is well tolerated and effective in children and adolescents aged 6-17 years.

References

1. Cannon CP, Steinberg BA, Murphy SA et al. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006;48(3):438-45.
2. National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-421.
3. Rosenson RS. Statins: can the new generation make an impression? Expert Opin Emerg Drugs. 2004;9(2):269-79.
4. Catapano AL, Graham I, De Backer G et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2016;37(39):2999-3058.
5. Frayling TM. Statins and type 2 diabetes: genetic studies on target. Lancet. 2015;385(9965):310-2.
6. Collins R, Reith C, Emberson J et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388(10059):2532-61.
7. Rochlani Y, Kattoor AJ, Pothineni NV et al. Balancing primary prevention and statin-induced diabetes mellitus prevention. Am J Cardiol. 2017;120(7):1122-8.
8. Betteridge DJ, Carmena R. The diabetogenic action of statins - mechanisms and clinical implications. Nat Rev Endocrinol. 2016;12(2):99-110.
9. Laakso M, Kuusisto J. Diabetes secondary to treatment with statins. Curr Diab Rep. 2017;17(2):10.
10. Thakker D, Nair S, Pagada A et al. Statin use and the risk of developing diabetes: a network meta-analysis. Pharmacoepidemiol Drug Saf. 2016;25(10):1131-49.
11. Hoy SM. Pitavastatin: a review in hypercholesterolemia. Am J Cardiovasc Drugs. 2017;17(2):157-68.
12. Yamazaki T, Kishimoto J, Ito C et al. Japan prevention trial of diabetes by pitavastatin in patients with impaired glucose tolerance (the J-PREDICT study): rationale, study design, and clinical characteristics of 1269 patients. Diabetol Int. 2011;2:134-40.
13. Teramoto T, Urashima M, Shimano H et al. A large-scale study on cardio-cerebrovascular events during pitavastatin (LIVALO tablet) therapy in Japanese patients with hypercholesterolemia – LIVES study extension. Jpn Pharmacol Ther. 2011;39:789-803.
14. Vallejo-Vaz AJ, Kondapally Seshasai SR, Kurogi K et al. Effect of pitavastatin on glucose, HbA_{1c} and incident diabetes: a meta-analysis of randomized controlled clinical trials in individuals without diabetes. Atherosclerosis. 2015;241(2):409-18.
15. Pirillo A, Catapano AL. Pitavastatin and HDL: effects on plasma levels and function(s). Atheroscler Suppl. 2017;27:e1-e9.
16. Kontush A, Chapman MJ. Functionally defective high-density lipoprotein: a new therapeutic target at the crossroads of dyslipidemia, inflammation, and atherosclerosis. Pharmacol Rev. 2006;58(3):342-74.
17. Teramoto T, Shimano H, Yokote K, Urashima M. Effects of pitavastatin (LIVALO Tablet) on high density lipoprotein cholesterol (HDL-C) in hypercholesterolemia. J Atheroscler Thromb. 2009;16(5):654-61.
18. Teramoto T. The clinical impact of pitavastatin: comparative studies with other statins on LDL-C and HDL-C. Expert Opin Pharmacother. 2012;13(6):859-65.
19. Okumura K, Tsukamoto H, Tsuboi H et al. High HDL cholesterol level after treatment with pitavastatin is an important factor for regression in carotid intima-media thickness. Heart Vessels. 2015;30(2):154-61.
20. Ibuki C, Seino Y, Otsuka T et al. Switching to pitavastatin in statin-treated low HDL-C patients further improves the lipid profile and attenuates minute myocardial damage. J Clin Med Res. 2012;4(6):385-92.
21. Kurogi K, Sugiyama S, Sakamoto K et al. Comparison of pitavastatin with atorvastatin in increasing HDL-cholesterol and adiponectin in patients with dyslipidemia and coronary artery disease: the COMPACT-CAD study. J Cardiol. 2013;62(2):87-94.
22. Miyamoto-Sasaki M, Yasuda T, Monguchi T et al. Pitavastatin increases HDL particles functionally preserved with cholesterol efflux capacity and antioxidative actions in dyslipidemic patients. J Atheroscler Thromb. 2013;20(9):708-16.
23. Kontush A, Chapman MJ. Antiatherogenic small, dense HDL--guardian angel of the arterial wall? Nat Clin Pract Cardiovasc Med. 2006;3(3):144-53.
24. Kontush A, Chapman MJ. Functionally defective high-density lipoprotein: a new therapeutic target at the crossroads of dyslipidemia, inflammation, and atherosclerosis. Pharmacol Rev. 2006;58(3):342-74.
25. Davidson WS, Silva RA, Chantepie S et al. Proteomic analysis of defined HDL subpopulations reveals particle-specific protein clusters: relevance to antioxidative function. Arterioscler Thromb Vasc Biol. 2009;29(6):870-6.
26. Ko DT, Alter DA, Guo H et al. High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: the CANHEART Study. J Am Coll Cardiol. 2016;68:2073-83.
27. Orsoni A, Thérond P, Tan R et al. Statin action enriches HDL3 in polyunsaturated phospholipids and plasmalogens and reduces LDL-derived phospholipid hydroperoxides in atherogenic mixed dyslipidemia. J Lipid Res. 2016;57(11):2073-87.
28. Wiegman A, Gidding SS, Watts GF et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015;36(36):2425-37.
29. Braamskamp MJ, Stefanutti C, Langslet G et al. Efficacy and safety of pitavastatin in children and adolescents at high future cardiovascular risk. J Pediatr. 2015;167(2):338-43.e5.
30. Mottillo S, Filion KB, Genest J et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56(14):1113-32.