Recommendations for the Use of Statins in Patients with Diabetes Mellitus or Prediabetes. Conclusions of a Consensus Group

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Abstract

The contribution of statins in the treatment of cardiovascular risk of lipid origin has been a determining factor in the reduction of morbimortality from cardiovascular diseases due to a decrease in risk. However, statins are not exempt from possible adverse effects. One of them is their capacity to cause disorders in the carbohydrate metabolism, increasing the risk of new-onset diabetes in patients treated with statins significantly, although the cardiovascular benefit of their use is always higher. Yet, especially in diabetic or pre-diabetic patients, the statin of choice may condition the safety in this area, given that the diabetogenic profile of the different molecules differ.

In particular, the objectives of this study were to summarize the expert's opinion on whether all statins have a similar or different diabetogenic effect and to establish recommendations on the statin selection based on the patient characteristics.

In order to ascertain the opinion of the experts (primary care physicians and other specialists with experience in the management of this type of patient) we conducted a Delphi study to evaluate the consensus rate on diverse aspects related to the diabetogenicity of different statins, and the factors that influence their choice.

On the basis of the consensus agreements reached among practitioners of different specialities, and considering the availability of greater and better scientific evidence, this work groups together the recommendations to consider when selecting a statin in individuals with prediabetes or diagnosed diabetes. Such recommendations are grouped in relation with the patient, each individual's own carbohydrate metabolism, and the specific characteristics of every statin. These recommendations could facilitate the rational use of one statin or another in order diminish the diabetogenic potential shown by some of them.

Keywords: Diabetes; Prediabetes; Statins; Selection criteria

Introduction

In spite of the clinical benefit of statins in cardiovascular prevention, it is necessary to point out their possible adverse effects. In this sense, it is important to mention that their diabetic effects may mitigate their benefits, even though the cardiovascular benefit will always outweigh the risk resulting from the appearance of diabetes. Therefore, any statin with sufficient hypocholesterolemic capacity to achieve the objective of lipid control, and with neutral or beneficial effects on the carbohydrate metabolism and on the risk of developing diabetes, should be of choice, above all in patients with real or potential alterations in glucose metabolism.

Thanks to randomised clinical studies, post-hoc studies, large-scale meta-analyses and Mendelian randomisation methods, it has been possible to confirm that statins may increase the risk of diabetes, especially in those patients with a metabolic predisposition to suffer from it. The intensity of the statin, its dose and the duration of the treatment

may be other determining factors in such effects (Table 1), and the mechanisms may be diverse (Table 2). However, some of the statins have shown to be safer in this field: this is the case of pravastatin, although there are discordant results, and pitavastatin, with consistent results across the studies that show favourable data for its use [1].

The impact of this data is that the choice of a specific statin in a patient with frank diabetes or at risk of suffering from it, should attend not only to its LDL-reducing capacity, but also to its safety or the associated side-effects on carbohydrate metabolism. In this sense, it is necessary to formulate some questions that should be addressed. Are all the statins equal? What does the choice of the statin depend upon? What are the variables to be considered when selecting a statin? And finally: How does any pre-existence or possible existence of carbohydrate metabolism disorder, whether prediabetes or diagnosed diabetes mellitus, influence this choice?

In fact, the *European Atherosclerosis Society* (EAS) has established recommendations for the use of statins in patients with a high risk of

Table 1: Comparative diabetogenic effect between statins (excluding pitavastatin)

Quality	Statin	Increase in risk	Comparator
Statin	Rosuvastatin	+ 25 %	Pravastatin
	Atorvastatin	+ 12 %	
	Simvastatin	+ 11 %	
Dose	High dose	+ 30 %	Low dose
	Moderate dose	+ 22 %	
Potency	High potency	+ 22 %	Pravastatin
	Moderate potency	+ 11 %	

Table 2: Most plausible mechanisms of statin diabetogenicity

Blockade of calcium channels in beta cells, with a consequent reduction in insulin secretion
Blockade in the synthesis of intermediate products of intracellular cholesterol metabolism
Reduction in glucose transporter GLUT4, which controls insulin-mediated cellular intake
Reduction of the Coenzyme Q10 levels, with subsequent reduction of GLUT4
Cholesterol overload in beta cells, with possible cytotoxic effect

developing diabetes [2], and suggests the monitorization of baseline glucose and glycosylated haemoglobin levels at the beginning of the treatment and three months later, although there are no referral criteria for selecting drugs.

Development of Diabetes Mellitus in Patients treated with Statins

Logically, the most consistent evidence comes from the meta-analyses. A first meta-analysis with 5 studies had not shown an increased risk of diabetes [3], but it was previous to the inclusion of the JUPITER study [4] with rosuvastatin, in which a 26% increase in the risk of appearance of new cases of diabetes was confirmed. Once the studies with rosuvastatin are included, the increase in globally considered risk rose to 13% [5], although the inclusion of studies with pravastatin concealed this effect, since the WOSCOPS study with this statin had shown a favourable effect on diabetogenic risk [6]. However, it is not unequivocal that pravastatin produces this favourable effect, because in the LIPID study [7] it was neutral and in the PROSPER study the risk was increased by 32 % [8].

A classical evidence is discerned from a global meta-analysis with different statins that included 13 studies with approximately 100,000 participants [2,9] in which a global increase in the risk of diabetes of 9% at four years was confirmed.

Not all statins display the same risk. A comparative analysis shown a significant increase in the risk of diabetes with rosuvastatin (42%), atorvastatin (25%) and simvastatin (14%) and a non-significant increase with fluvastatin (4%) and pravastatin (2%) [10]. These data are consistent with the increase attributed to the different statins when compared with pravastatin [11]: 22% with atorvastatin, 18% with rosuvastatin, and 10% with simvastatin; without increased risk with lovastatin or fluvastatin.

Two further meta-analyses, the first with 5 studies [12] and the second with 17 studies [13] showed that the risk, although variable with different statins, depends on the dose (25% with 20 mg of rosuvastatin, 15% with 80 mg of atorvastatin, and 7% with 40 mg of pravastatin).

Thus, while rosuvastatin, atorvastatin and simvastatin have shown an increase in risk, pravastatin, lovastatin and fluvastatin generally do not. With respect to pitavastatin, the clearest evidences are in two studies: an individualised meta-analysis of the effects of pitavastatin in 15 studies with more than 1,600 patients without diabetes treated with different doses of pitavastatin, in which no significant variations arose in baseline glycaemia, in the levels of glycosylated haemoglobin, and in the incidence of new-onset diabetes [14]; and the most recent results from the J-PREDICT study, in which a decrease of 18% of the incidence of diabetes occurred when pitavastatin was used in patients with prior glucose intolerance, compared with isolated interventions in lifestyle [15]. Comparatively there are numerous studies showing that pitavastatin is safer than other statins with regard to alterations in glucose metabolism, particularly in relation to atorvastatin, when the method used is direct comparison on the effects on baseline glycaemia, glycosylated haemoglobin values and the incidence of new-onset diabetes [16].

From what has been shown to date by the comparative data and the specific studies on the drug [14,15], it is deduced that pitavastatin is a statin with a medium-high potential regarding LDL reduction, and a neutral or positive effect on glucose metabolism, without any increase (or even with a decrease) on the risk of new-onset diabetes. Therefore, it has been considered as a statin of choice in the treatment of dyslipidaemia in diabetic patients or those at risk of developing diabetes [16].

Methodology to Register Experts' Opinion in Our Medium

Trying to formulate practical recommendations that may serve as a guide when treating patients with prediabetes or diabetes mellitus, or even at risk of developing it, with statins, a determining factor is the analysis of the scientific evidence available, and also to find out the opinion of experts in the management of these situations, revealing their level of agreement/disagreement with certain practices.

This would allow us to establish the degree of consensus/discrepancy in the opinion of expert clinical practitioners in the management of patients with dyslipidaemias, regarding the influences in therapeutic decision-making, with a special focus on patients with carbohydrate metabolism disorders, and in the selection of a statin according to its capacity to interfere with it.

In prior studies [17-19], it has been described the method used to obtain this opinion from a broad group of experts, consisting on a modified Delphi method.

The modified Delphi method [20] was used to reach the greatest consensus possible from a broad panel of dyslipidaemia experts. It is a structured technique for remote consensus, which maintains its key advantages (controlled interaction, opportunity to reconsider an opinion and statistical validation of consensus) over other technical alternatives and it addresses some of their major drawbacks (opinion biases). Its execution required two successive waves of a structured survey filled out through an online platform. The doctors were able to confidentially compare their personal opinions with the overall opinion of the panel when answering the second wave and could reconsider, where appropriate, their initial criteria on issues where there was no consensus. The study was conducted in four phases: (a) the selection of a scientific committee, responsible for the formulation of the survey questions; (b) the selection of an expert panel of professionals from four specialties (cardiology, endocrinology, internal medicine, nephrology) and family and community medicine with experience in the field of dyslipidaemia; (c) an online survey in two waves and (d) an analysis of results and discussion of conclusions in a meeting held by the scientific committee.

The project's scientific committee revised the contents of the Delphi questionnaire. A bibliographic search prioritising systematic reviews was conducted as well as another critical synthesis of scientific literature through the consultation of bibliographic databases (MEDLINE, EMBASE and the Spanish Medical Index), and a manual review of the references

obtained to find other references that may be of interest by using keywords such as dyslipidaemia, diabetogenicity or impaired glucose metabolism. Each survey question submitted to the panel for assessment was devised in the form of a positive or negative statement, as a clinical recommendation responding to interesting or controversial aspects in the clinical management of patients with dyslipidaemia and impaired glucose metabolism. The final version of the questionnaire included in this article contained 2 blocks of questions: a) Opinion on the profile of statins in the treatment of dyslipidaemia in patients with impaired glucose metabolism and b) Recommendations for the selection of the lipid-lowering treatment of choice in patients with impaired glucose metabolism.

The experts proposed were selected by the committee based on their medical and scientific expertise and considering their interest in dyslipidaemia. For their recruitment, a "snowball" strategy was used from personal contacts of the committee members, who in turn proposed new candidates from their professional environment [21]. Following this process, 506 professionals were invited of which 497 experts from all autonomous communities in Spain agreed to participate. All of them were practitioner clinical doctors: 58.4% primary care physicians; 13.7% endocrinologists; 13.9% internal medicine; 7.0% cardiologists; and 7.0% nephrologists.

A single type of rating scale was proposed for all questions, and the categories were divided into three regions (Disagree; Neutral; Agree), in order to identify the prevalent opinion. All questions had to be answered in wave 1. In wave 2, the questions for which consensus was not achieved in wave 1 was asked again. Consensus was deemed to be reached when a question obtained at least 80% of responses grouped in consensus in disagreement or scores in consensus in agreement.

Multidisciplinary Consensus

The *mission* of the consensus was none other than gathering the opinion on clinical practice in the management of dyslipidaemias in patients with carbohydrate metabolism alterations, whether present or potential and thus identifying the best possible practices among the experts. It is also necessary to recognise those elements that enable the correct selection of a statin for these patients. Consequently, the consensus *values* are none other than those generated by a group of experts with experience in the management of these patients and the use of these drugs, and- ultimately - should allow the definition of a set of recommendations for the selection and use of statins, helping in the decision-making. This is the main goal of the study.

The issues consensuated refer to three fundamental aspects: A) the management of dyslipidaemia in these patients, both from the viewpoint of detection, as the treatment and its monitoring; B) the selection of statins in these patients, as well as the elements that support it; and C) the different diabetogenicity of statins and - in consequence - the diabetogenic profile of the statins available.

Tables 3-5 summarily include the aspects agreed on by consensus in these three aspects. Regarding A) the management of dyslipidaemia: aspects relating to the selection of patients for screening initial therapeutic approach and the parameters to be followed and controlled; B) the factors that condition the selection of a statin both at the time of prescription and during the follow-up and C) the diabetogenic profile of statins, whether it can be considered a class effect or - to the contrary - it is more specific to the particular drug, which would modify the selection of the statin in cases of prediabetes or diabetes.

Once opinions were collected on the basis of the scientific evidence available, different recommendations have been proposed for clinical practice and offered in a panel.

Table 3: Agreements on the management of dyslipidaemia in patients with glucose metabolism alterations

Screening in selected patients	With diabetes or prediabetes
	With history of cardiovascular diseases
	With family history of cardiovascular diseases
	With arterial hypertension
	With abdominal obesity
Initial therapeutic approach	Statin as treatment of choice
	Statin and dose selection according to basal LDL and target LDL
	Statin replacement in case of side effects
Parameters to monitor and control	Complete lipid profile: CT, LDL, HDL, TG
	HbA1C in diabetics
	Baseline glycaemia
	Arterial pressure
	Hepatic enzymes
	Renal function
	Weight
	Estimated cardiovascular risk

Table 4: Elements for drug selection in patients with glucose metabolism disorders

At the time of prescribing	LDL reduction capacity
	Risk of interactions
	Complete lipid profile (CT, LDL, HDL, TG)
	Hepatic enzymes
	Polypharmacy
	Estimated cardiovascular risk
	HbA1C in diabetics
During monitoring	Complete lipids profile (CT, LDL, HDL, TG)
	Hepatic enzymes
	Estimated cardiovascular risk
	HbA1C in diabetics
	Baseline glycaemia
	Polypharmac

Table 5: Selection of statin in patients with alterations in glucose metabolism

Selection based on	Age of the patient
	Estimated cardiovascular risk
	Estimated diabetes mellitus risk
	Fasting plasma glucose levels
	Patient's HbA1c levels
	Regular monitoring of glucose levels
	Renal function / albuminuria levels
	Polypharmacy, where applicable
	Selection of a statin that does not worsen carbohydrate metabolism
General diabetogenic profile	Differs among the different statins
	Not all have diabetogenic effects: • Atorvastatin is considered the most diabetogenic • Pitavastatin does not have a diabetogenic profile
Selection of drug	In the opinion of the experts, pitavastatin is the best choice in pre-diabetic or diabetic patients

Recommendations for Clinical Practice

In general, the recommendations available refer to very basic aspects, such as the special attention to high-risk patients with diabetes, the control of baseline glycaemic markers and the optimisation of the hypocholesterolemic treatment by selecting statins and doses that guarantee the achieving of the LDLc objectives with the lowest impact on

glucose metabolism [22], even those that have shown a more favourable effect on diabetic patients with incompletely controlled diabetes mellitus type 2 [23].

Moreover, it is necessary to consider some factors that condition the diabetogenic response of statins, pointing out the more susceptible groups. These include, in addition to individual factors, the presence of risk factors for diabetes mellitus such as BMI>30 kg/m^2, triglycerides>150 mg/dl, baseline glucose>100 mg/dl, family history of diabetes mellitus, old age, post-menopausal women or the long-term use of statins [4,9,10,22,24].

Therefore, and with regard to a guide that includes - and details - the main aspects to be considered in the choice of a statin for the treatment of dyslipidaemia in patients with prediabetes or diabetes mellitus, the main recommendations resulting from the opinion of the experts and the more relevant scientific evidence have been grouped in four sections, according to the variables to be considered:

- Patient characteristics:
  o Assess age
  o Assess individual cardiovascular risk
  o Assess renal function (and albuminuria, where applicable)
  o Consider, when present:
    ▪ Multi-pathology
    ▪ Comorbidity
    ▪ Polypharmacy
- Patient's carbohydrate metabolism:
  o Assess, specifically the risk of diabetes
  o Consider fasting glucose levels
  o Consider glycosylated haemoglobin levels
  o Regularly monitor glucose levels
- Dyslipidaemia treatment:
  o Consider that statins have different diabetogenic profiles, with different risks of altering carbohydrate metabolism
  o Select the most convenient statin for patients with:
    ▪ High risk of diabetes (visceral obesity, metabolic syndrome)
    ▪ Prediabetes or specific circumstances
    • Altered baseline glycaemia
    • Oral glucose overload intolerance
    ▪ Frank diabetes mellitus
- Statin of choice:
  o Select a statin with evidences showing that it does not worsen carbohydrate metabolism and does not increase the risk of new-onset diabetes (currently pitavastatin, according to the specifications shown in the summary of product characteristics.
  o Use this statin in diabetic and pre-diabetic patients and those at risk of developing diabetes mellitus.

Finally, it is necessary to point out that other additional factors, not directly related with hypocholesterolemic potential must be considered when assessing the use of a statin in those patients with carbohydrate metabolism disorders. Among them, and with regard to a more suitable selection as indicated in the recommendations, worth mentioning in addition to the absence of diabetogenicity:

- Reduction of the residual risk of lipid origin in patients under statin treatment. This is of particular interest in patients with high cardiovascular risk (as is the case of diabetic patients or those in secondary prevention). It enables a parallel improvement in non-LDLc-dependent dyslipidaemia, based on a decrease in triglycerides and an increase in HDL-c [25,26].

- Minimise the risk of pharmacological interactions through a more CYP450-independent metabolism; which permits a safer use in patients with multi-pathology, comorbidity and polypharmacy [27].

- Safety in the renal patient: This is a transcendental aspect that frequently forces an adjustment in statin dose in the presence of renal insufficiency. In this sense, recent evidences indicate that not all statins display the same renal safety profile (progression of the CKD and/or effects on albumin/proteinuria) [28]. The selection of a statin in renal patients with nephropathy whether associated with diabetes or not [21,29], must guarantee its safe use. This does not seem to be always considered by prescribing practitioners [30].

In consequence, the elements to be considered to minimise a possible deterioration in glucose metabolism in patients subjected to treatment with statins are numerous although not excessively complex. Perhaps the most important thing to be aware is that, although it may be a class effect and dependent on doses, duration and intensity of the treatment, the diabetogenic potential of statins differs among them. In fact, the medicines agencies of the European member states where pitavastatin has marketing authorization, have recently recognised that the scientific evidence points that pitavastatin does not produce an increase in new cases of diabetes mellitus, being included in the respective summary of product characteristics for its consideration when prescribing statins [31]. All this must be carefully assessed especially in patients who simultaneously have a high cardiovascular disease and diabetes mellitus risk, where it is necessary to select a statin without diabetogenic effect.

Recent data [23] could be to identify a correlation between baseline serum HbA1c levels and the beneficial effects of lowering HbA1c in patients with type 2 diabetes receiving pitavastatin treatment. The correlation between baseline HbA1c and improvements in HbA1c remained significant after adjusting for age, estimated glomerular filtration rate, BMI, dose of pitavastatin and baseline HDL-C. Only the patients with poorly controlled diabetes experienced a benefit from lowering glucose with pitavastatin treatment in this study [23], and this might explain why the beneficial effect on glucose with pitavastatin treatment is not always consistent between studies [32-35]. Further large-scale trials are warranted to assess the outcomes of long-term clinical events from pitavastatin treatment; but other than decreasing LDL-C in patients with type 2 diabetes who were naive to statins (pitavastatin treatment) increasing HDL-C in patients with a lower baseline HDL-C level, and decreased HbA1c in those with a higher baseline HbA1c level.

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