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Statins, do or don't?:

myths of diabetic dyslipidemia

Diabetes Mellitus (DM) is a chronic condition with a high prevalence (14.4% in Spain in 2023, according to the website of the Spanish Society of Diabetes, with nearly a third—30.3%—going unnoticed) and a worrisome rising incidence. It is usually associated with other conditions such as dyslipidemia, high blood pressure, smoking, etc., all of which combined significantly increase the overall cardiovascular risk of a person with DM. Regarding dyslipidemia, of note that, as it is the case with people without DM, different "myths" arise, which we will attempt to break down and rationalize.

MYTH #1: "CHOLESTEROL CAN BE LOWERED SOLELY WITH DIET AND EXERCISE"

Diet and physical activity affect cholesterol levels, but they are not the only factors. Therefore, following a healthy diet is very important. The dietary pattern with the highest level of evidence is the Mediterranean Diet, as demonstrated by the PREDIMED study, along with engaging in moderate-intensity physical activity to reduce the risk of arteriosclerotic vascular events (ischemic heart disease and/or ischemic stroke).

American and European guidelines on prevention of cardiovascular diseases recommend pharmacological interventions vs dyslipidemia in participants with a high or very high risk of cardiovascular disease, which is often the case in people with DM [1].

This should always be preceded by appropriate lifestyle interventions, including diet and regular physical activity. If the goals cannot be achieved this way, statins should be the first-choice drug.

MYTH #2: "IT'S NOT A BIG DEAL TO HAVE HIGH CHOLESTEROL, AS A MATTER OF FACT, IT CAN BE A GOOD THING"

Cholesterol per se performs important functions in the body and is essential for life [2]. However, its important functions occur at cellular level, not in the vascular bed, where it can lead to complications by producing fat deposits called atherosclerotic plaques—which limit blood flow—which can, in turn, damage certain organs or cause a heart attack or stroke [3].

Almost 3 million deaths worldwide are related each year to high LDL cholesterol levels [4].

Diabetic dyslipidemia, or atherogenic dyslipidemia, is a lipid/lipoprotein disorder defined by triglyceride (TG) levels ≥1 50 mg/dL (1.7 mmol/L), HDL cholesterol levels (cHDL) < 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women, and a higher concentration of small, dense low-density lipoproteins (LDL-c) that are common in patients with T2DM [5] and are characterized by a higher atherogenic potential.

Atherosclerotic cardiovascular disease (ASCVD) becomes accelerated in people with diabetes because dyslipidemia, hyperglycemia, oxidative stress, and inflammation play a role through various mechanisms that operate on the arterial wall, promoting atherosclerosis. Additionally, some unique characteristics predispose people with type 1 diabetes mellitus to accelerated atherosclerosis.

We have sufficient evidence confirming that the lower and earlier we can reduce LDL-c levels, the lower the likelihood of having a major vascular event, both in the general population and in those with DM [6].

MYTH #3: "DON'T TAKE THOSE PILLS; THEY WILL MAKE YOUR MUSCLES HURT"

This is a widely discussed and disseminated message among users, especially critics of statins. To justify this, we summarize the data from the SAMSON study [7], which clearly illustrates what the **nocebo effect** is.

The SAMSON is a multicenter, double-blind, crossover, and placebo-controlled trial conducted in the United Kingdom, which included a total of 60 participants with a past medical history of statin-induced muscle intolerance. Participants were given 12 bottles (1 per month); 4 contained 20 mg atorvastatin tablets, 4 contained placebos identical in appearance to the previous ones, and 4 bottles were empty. Participants were instructed to follow a specific sequence (randomized) in taking the bottles and to report their muscle symptoms daily using a visual analog scale (0 to 100) via an online app.

A total of 49 out of the 60 participants completed the study over 12 months. Symptom scores were 8.0 during the empty bottle period, 16.3 on atorvastatin, and 15.4 on placebo. Although the differences were statistically significant between taking pills—atorvastatin or placebo—and not taking them, there were no differences between taking atorvastatin or placebo. The number of symptoms reported when taking statins was practically the same as those reported when taking placebo. Using individual patient data, neither the initial symptom intensity nor the degree of relief after stopping the pills were useful to distinguish be- »

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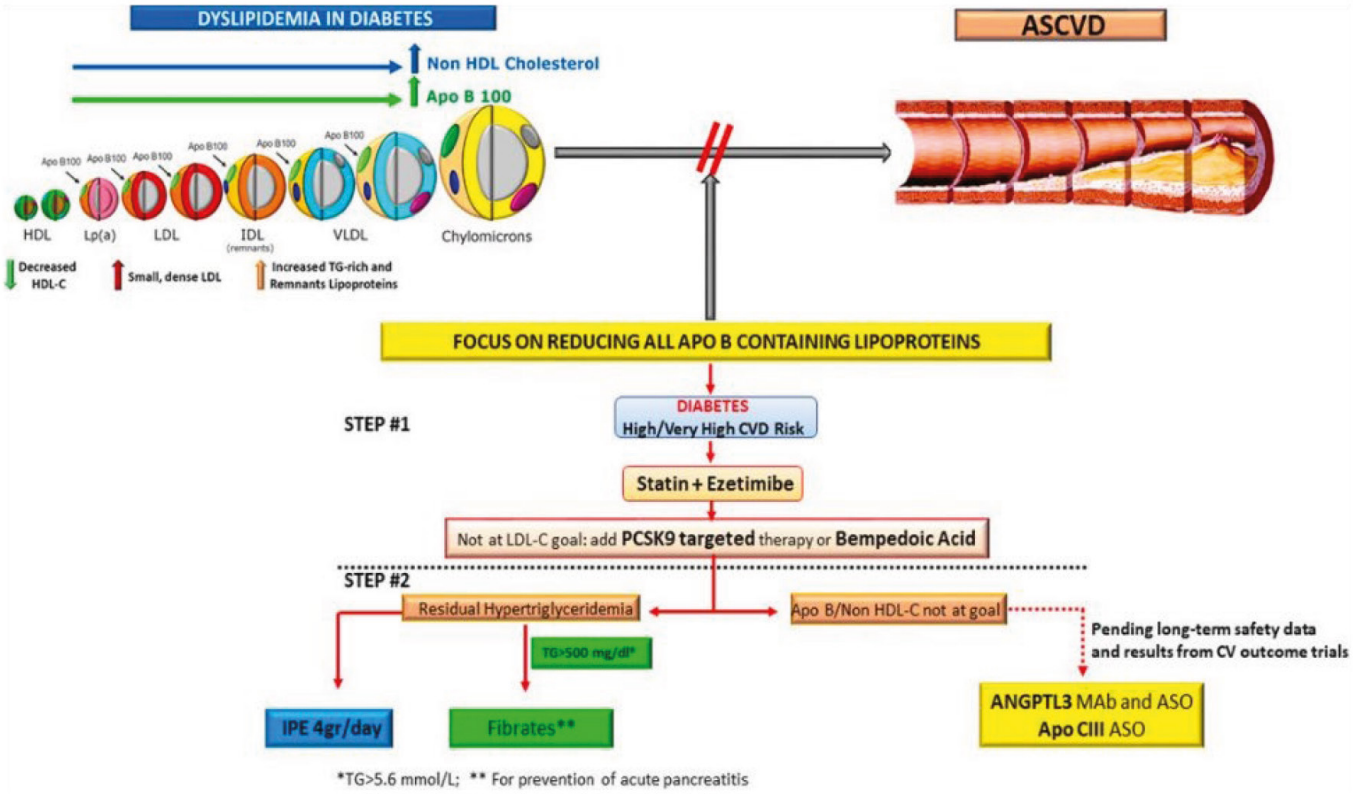


tween statin use and placebo. Patients on atorvastatin were no more likely to discontinue it than those on placebo, and symptom relief was no different when stopping either. A total of 50% of the patients (n = 30) who were evaluated 6 months after the trial said they were already on statins.

The results of this study should be seriously considered when establishing causality between the onset or disappearance of muscle symptoms and statin use or discontinuation, as it is highly likely to be related to the nocebo effect. An editorial provocatively entitled "Your myalgia is not due to statin intolerance" accompanies the publication of the article.

In a different study [8], one-fifth of patients considered intolerant reported muscle symptoms even on placebo, suggesting that these symptoms may not be related to statin use. These patients could potentially benefit from optimized statin therapy for better cardiovascular risk control.

MYTH #4: "STATINS ARE HARMFUL, AND LABS KEEP LOWERING CHOLESTEROL TARGETS SO THAT MORE PEOPLE HAVE TO USE THEM"

Statins act as competitive inhibitors of the enzyme hydroxy-methylglutaryl-CoA reductase (HMG-CoA reductase) by blocking the hepatic synthesis of LDL-c.

They remain the cornerstone of dyslipidemia treatment in patients living with diabetes. Just like in those without T2DM, statins reduce the risk of atherosclerotic cardiovascular disease (ASCVD) by a mean 20% for every 1 mmol/L (39 mg/dL) decrease in LDL-c, regardless of other characteristics [9]. These data from the meta-analysis, as well as landmark studies in diabetes such as the CARDS and HPS, support the use of statins as first-line therapy to reduce both LDL-c and the risk of ASCVD.

The treatment of dyslipidemia, particularly with statins, has shown immense benefits in preventing clinical ASCVD. However, many patients do not achieve the recommended LDL-c levels outlined in various clinical practice guidelines (CPGs). **ASCVD is, to this date, the leading cause of morbidity and mortality in patients with DM [10]**.

Studies indicate that the risk is several times higher vs individuals without diabetes [11]. Additionally, the risk increases in metabolic syndrome (MetS) and predia-

LANDMARK STUDIES ON DIABETES, SUCH AS THE CARDS AND HPS, SUPPORT THE USE OF STATINS AS FIRST-LINE THERAPY TO REDUCE LDL-C AND LOWER THE RISK OF CARDIOVASCULAR EVENTS (CVE)

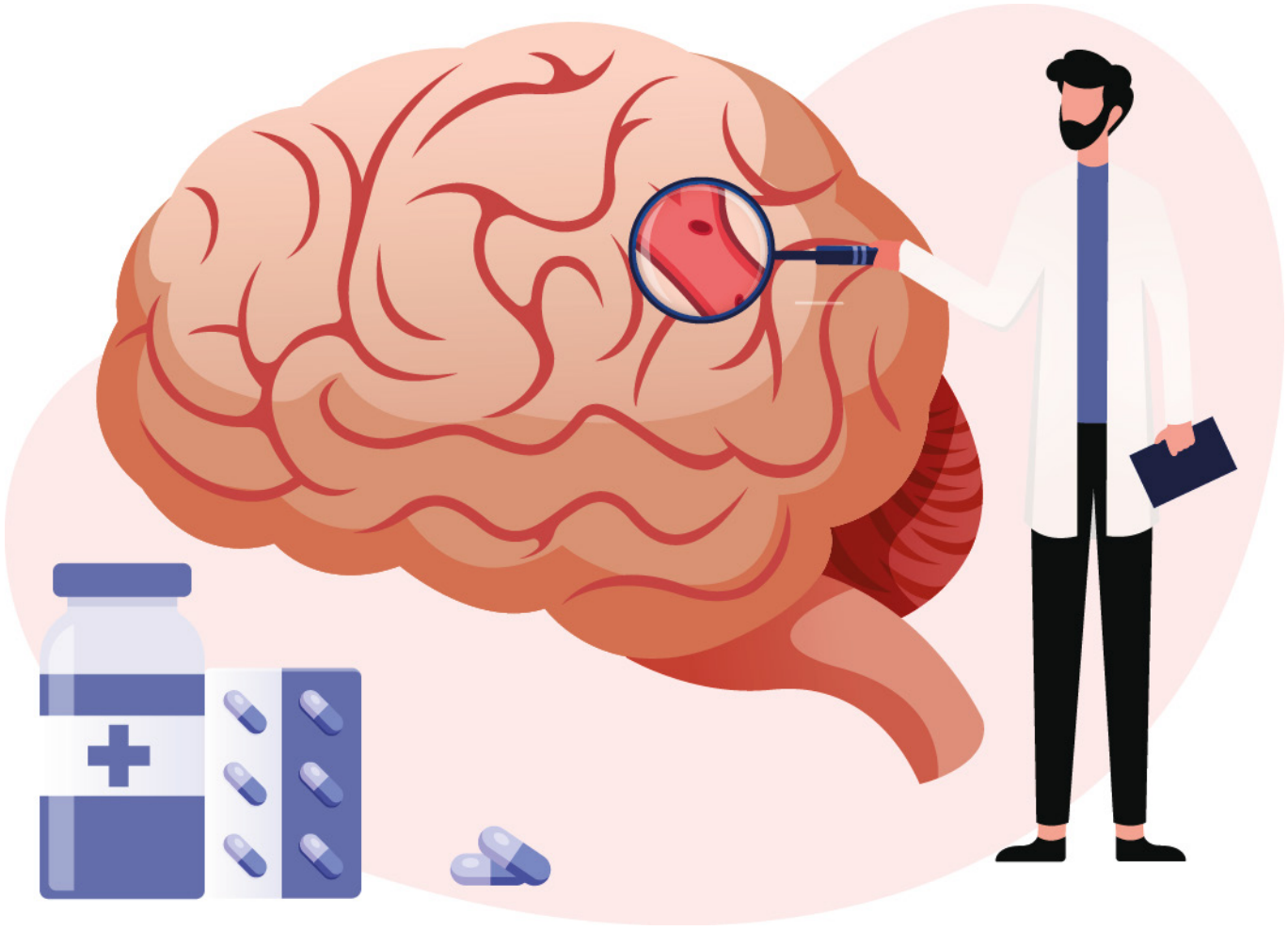
» betes. Much of the increased risk in people with T2DM, prediabetes, and MetS can be attributed to the clustering of several ASCVD risk factors, such as dyslipidemia, hypertension, hyperglycemia, obesity, and systemic inflammation.

Although between 90% and 95% of people with diabetes have T2DM, the risk of ASCVD also increases in T1DM [10]. Although atherosclerosis begins early in life, even in the absence of diabetes, this early onset of atherosclerosis occurs more frequently in the presence of T1DM. Autopsy studies have shown accelerated atherosclerosis in young individuals with T1DM vs age-matched controls without DM [12]. Moreover, a high prevalence of asymptomatic coronary atheromatous lesions has been detected in T1DM due to coronary artery calcification in intracoronary ultrasound.

ASCVD mortality has decreased in people living with and without diabetes in recent decades [11,12,13], probably largely attributable to better glycemic control, advances in the treatment of associated cardiovascular disease (CVD) risk factors, and the use of emerging drugs with favorable cardiovascular effects. However, these benefits are offset by an alarming increase in the prevalence of diabetes.

A recent systematic review of 57 articles involving 4 million people with diabetes revealed a global prevalence of ASCVD of 32.2%, with coronary artery disease being the most frequently reported type of CVD [14].

The treatment of dyslipidemia, particularly with statins, has demonstrated immense benefits in the prevention of clinical CVD. Perhaps the most compelling evidence that dyslipidemia plays a causal role in the patho- »



MODERATE- AND HIGH-INTENSITY STATINS CAN INCREASE THE RISK OF DIABETES, ESPECIALLY IN INDIVIDUALS WITH METABOLIC SYNDROME (METS)

» genesis of ASCVD in diabetes is provided by clinical trials in which lipid-lowering drugs, particularly statins [15], have led to beneficial clinical outcomes in people living with diabetes. Interestingly, these drugs primarily reduce LDL-c, with minimal to modest effects on triglycerides, the hallmark of diabetic dyslipidemia. No therapeutic approach has had a more profound impact on the prevention of CVD in MetS and T2DM than statins.

Despite data showing that lipid-lowering therapy prolongs the lives of most patients in the primary and secondary prevention of ASCVD, guidelines-guided LDL-c control and risk stratification is not achieved in 75% of individuals [16]. The SANTORINI trial, which included a total of 9044 patients at high or very high cardiovascular risk from 14 Western European countries, showed that only 20.1% reached the LDL-c target [17].

MYTH #5: "STATINS CAN CAUSE DM"

Moderate- and high-intensity statins can increase the risk of diabetes, particularly in individuals with metabolic syndrome (MetS). This risk is counterbalanced by a relative risk of benefit approximately 10 times greater for major vascular outcomes [18]. A meta-analysis [19] on the risk of diabetes associated with statins in primary prevention includes data from 8 studies with 70,453 patients. This updated meta-analysis aims to clarify the association between statin use and new-onset diabetes, especially in a primary prevention context. The unique aspect of the study is the stratification of participants based on their initial risk of diabetes, categorizing them into 2 groups: those with low initial rates (< 7.5 events per 1000 patient-years) and those with high rates (≥ 7.5 events per 1000 patient-years). The »

» meta-analysis reveals a higher overall risk of new-onset diabetes in patients on statins (OR, 1.1), which is consistent with previous literature that shows a marginal but notable increase in risk. This risk amplification becomes even more pronounced (OR, 1.2) in studies including patients with a higher initial risk of diabetes, highlighting the critical role of initial diabetes risk in statin-related diabetes development.

The study concludes that the relationship between statin therapy and diabetes risk is nuanced, **suggesting that the risk of new-onset diabetes depends more on the patients' characteristics than on the specific type of statin used**. However, of note that the overall increased risk is relatively modest vs the substantial cardiovascular benefits provided by statins. Strategies to mitigate diabetes risk in susceptible populations (occurring in about 1% of prediabetic patients on the drug) should be explored, while still leveraging the cardioprotective effects of statins.

MYTH #6: "STATINS CAN CAUSE BRAIN HEMORRHAGES"

One study suggests that statin therapy after an initial intracerebral hemorrhage (ICH) was associated with a reduced risk of ICH-related readmissions and all-cause mortality vs no statin therapy, especially with low/moderate intensity statin therapy and early initiation after the index ICH. Adherence to rosuvastatin was associated with a lower risk of ICH recurrence vs atorvastatin. In patients with a past medical history of statin use before ICH, discontinuation of statins after ICH was associated with a substantially higher risk of ICH recurrence and death [20].

Additionally, there has been concern about the potential development of Alzheimer's disease related to statin use. A study published in the Journal of the American College of Cardiology found no association between statin use and decreased memory or cognitive function. In fact, patients taking statins for heart disease with a genetic predisposition to Alzheimer's showed better results in some memory tests [21]. D

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