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The Cholesterol and Statins Relationship with the Acute Coronary Syndrome: A Review

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Review Article

ABSTRACT

Introduction: Atherosclerosis is one of the major risk factors for the development of coronary artery disease (CAD) and thus acute coronary syndrome (ACS). The contribution of lipid profile to these conditions justified the existence of 200 million people in the world medicated with statins. However, scientific research shows that although statins are effective in lowering cholesterol levels, the relation between this lowering with morbidity and mortality reduction associated with cardiovascular disease (CVD) has been questioned. This review's objective to find what has been published in order to try and answer two questions:

1. Is cholesterol the main risk factor for the development of ACS?

2. Will statins be a treatment with a significant impact in reducing the morbidity and mortality of ACS?

Methods: A bibliographic search was conducted in the PubMed and Google Scholars databases of relevant scientific articles between 2014 and 2018 in the English language.

Results: The efficacy of statins as lipid-lowering drugs is undeniable, but their impact on the morbidity and mortality of ACS is dubious. Criticism emerges from investigations as JUPITER, AFCAPS/TEXCAPS, PROVE-IT-TIMI-22 and TNT studies, some of them sponsored by the pharmaceutical industry. New theories on the pathogenesis of ACS have been delineated as the contribution of inflammatory mechanisms in the process of atherogenesis.

Discussion: Cost-effectiveness, statin effectiveness, and other investigations of ACS contributors should be considered, such as inflammation and insulin resistance theory.

Statins also have an anti-inflammatory effect (pleiotropic effect) and therefore studies are being conducted to determine whether the reduction of inflammation will be as effective in reducing adverse CV events regardless of statins-proven hypolipidaemia. Furthermore, insulin resistance may play a major role in this atherogenic inflammatory process.

Conclusion: A complete and combined treatment is required not only for dyslipidemia but also for insulin resistance, never forgetting the changes in the dietary pattern.

Keywords: Cholesterol, Statins, Hydroxymethylglutaryl-CoA reductase inhibitors, Acute coronary syndrome, Atherogenesis, Cardiovascular disease, Primary prevention, Secondary prevention, Dyslipidemia, Inflammation, Cardiovascular risk factors, Insulin resistance

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INTRODUCTION

Cardiovascular diseases (CVD) (coronary heart disease, stroke and peripheral arterial disease) are the leading cause of death in European Union countries. Despite this fact, there has been a gradual decrease in the proportion of deaths due to CVD. In Portugal 29.7% of the deaths were due to CVD in 2015 [1].

In Europe, CVD is accountable for 45% of deaths, with ischemic heart disease being the cause for 862000 deaths among men and 877000 deaths among women. With regard to disability-adjusted life years (DALYs), this indicator allows measuring the impact of mortality and morbidity on people's quality of life by sum the years of potential life lost due to premature mortality and the years of productive life lost due to disability. According to data from the World Health Organization (WHO), CVD was the cause for a decrease of more than 64 million DALYs in Europe (23% of all DALYs lost) in the last decade [2].

On the subject of coronary artery disease (CAD), atherosclerosis is unequivocally one of the main risk factors for its development and is therefore one of the therapeutic targets [3]. Reference authors state that in developed countries, more than 60% of CAD is due to hypercholesterolemia. This clinical condition may be partly reversed by changes in lifestyle, and is often controlled by the prescription of lipid-lowering drugs such as statins [4]. According to the WHO, between 2000 and 2013, there was an increase in the prescription of these drugs in all European countries, with a more significant increase in Slovakia and the United Kingdom. Currently, it is estimated that more than 200 million people worldwide take statins [5].

The possible relationship between hypercholesterolemia and CAD has long been studied and subject of many scientific studies, a reference being the Framingham Heart Study [6].

Among modifiable risk factors, dyslipidaemia in general and hypercholesterolemia in particular are the main determinants of the atheromatosis process. Dyslipidaemias are evidenced by the elevation of total serum cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides, and by the decrease in high-density lipoprotein (HDL). In addition to these factors, several clinical conditions such as diabetes, arterial hypertension, low levels of physical activity, smoking and obesity are important risk factors in the multifactorial process of atheromatosis. Elevated concentrations of lipoproteins, inflammatory cells and fibrous elements, responsible for the remodelling of the arterial matrix, are deposited in the tunica intima of the arteries and lead to the formation of atherosclerotic plaques. Ultimately, these plaques may lead to vascular lumen obstruction and consequently acute ischemic syndrome, such as CAD, stroke and peripheral arterial disease [7].

In order to reverse the increased incidence of CVD, there was a need to establish target values for low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C) and triglycerides, as well as algorithms for calculating cardiovascular risk for individuals, for example, Systemic Coronary Risk Estimation (SCORE) [8].

Currently, the guidelines recommend the use of drugs to lower LDL-C as a primary and secondary prevention form [9]. Thus in 2013 American College of Cardiology/American Heart Association (ACC-AHA) defined four groups of individuals with benefit in the use of statins for the prevention of CVD:

Patients with clinically evident atherosclerotic CVD.

Patients with primary LDL-C elevations $\geq$ 4.9 mmol/L (190 mg/dl).

Middle-aged individuals between 40-75 years of age with diabetes and LDL-C levels of $\geq$ 1.8 mmol/L (70 mg/dl).

Middle-aged people with an estimated risk of at least 7.5% atherosclerotic cardiovascular (CV) at 10 years and LDL-C levels of $\geq$ 1.8 mmol/L (70 mg/dl) [10].

Recent studies have demonstrated the beneficial effect of statins not only with regard to cholesterol reduction, but also due to its pleiotropic effects. Thus researchers defend the use of this pharmacological group in the improvement of endothelial function, in the reduction of proliferation of the cells responsible for vascular and myocardial remodelling, as well as in the reduction of inflammation, oxidation of atherosclerotic plaques and promoting their stabilization [11,12].

In contrast, in the last decade scientific studies have shown that although statins are effective in lowering cholesterol levels, this doesn't apply to the reduction of CVD-associated morbidity and mortality, in addition to the adverse effects associated with them [13]. The authors of these studies warn that most of the studies that show beneficial results of the use of statins as a primary prevention method in morbidity and mortality are financed by the pharmaceutical industry. In this way, they question the veracity of the results [14].

Due to this dichotomy, this review aims to find what has been published in order to try and answer two main questions:

Is cholesterol the main risk factor for the development of acute coronary syndrome (ACS)?

Will statins be a treatment with a significant impact in reducing the morbidity and mortality of ACS?

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MATERIALS AND METHODS

Published papers searched in the PubMed and Google Scholars database between February 2018 and April of 2018 were included. The online paper search was conducted using the terms, or combination of them: cholesterol, statins, hydroxymethylglutaryl-CoA reductase inhibitors, acute coronary syndrome, atherogenesis, cardiovascular disease, primary prevention, secondary prevention, dyslipidaemia, inflammation, cardiovascular risk factors, insulin resistance.

The papers were examined and filtered on the following inclusion criteria: being “published in English”, being “published between 2014 and 2018”. From this initial sample, the abstract and article were analysed.

Articles in which treatment of hypercholesterolemia applied to groups of individuals and specific pathologies, such as children, the elderly, individuals with renal disease, and articles whose treatment of dyslipidaemia was a pharmacological group other than statins were excluded.

With the application of these inclusion and exclusion criteria, eighty articles were analysed.

RESULTS

Dyslipidemias are metabolic alterations of lipoproteins due to disturbances in one or more phases of their metabolism and which are characterized by variations in their serum levels beyond the reference values. This pathology may alone or in association with other CV (CV) risk factors, lead to the development of atherosclerosis [15]. The high concentrations of LDL-C potentiate the development of atherosclerotic coronary disease that is also determined in part by HDL-C levels, which is seen as an independent risk factor [16].

There is ample scientific evidence that the decrease in LDL-C levels unequivocally inhibits the progression of atherosclerotic disease and decreases the incidence of ACS [17].

Statins (Simvastatin, Rosuvastatin, Atorvastatin, Pravastatin) are, of all drugs with lipid-lowering action, the most prescribed. These are used in the treatment of dyslipidemias without disregarding lifestyle changes [18,19].

They are used as a primary prevention method in the case of high levels of LDL, cholesterol and triglycerides, as well as secondary prevention in individuals with a history of an ischemic cardiovascular event [20].

This pharmacological group inhibits the synthesis of intracellular cholesterol through the reversible and competitive inhibition of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase). Its mechanism of action is the mimicking of the substrate that binds to the catalytic site of the enzyme and consequently inhibits the synthesis of mevalonic acid. This product is the precursor of cholesterol and many other isoprenoid units, which also justifies the pleiotropic effects of statins.

HMG-CoA reductase inhibitors allow an increase in the expression of LDL receptors in hepatocytes, and thus justify a lower concentration of LDL-C. They also have an effect on increasing HDL-C concentration and decreasing circulating lipoproteins containing Apo B and triglycerides. It should be noted that statins have potency, efficacy and pharmacokinetic profile that differ from each other. Thus, a distinct dose-efficacy relationship justifies the analysis of the baseline level of LDL-C in the percentage of LDL reduction that is to be achieved [21,22].

When deciding whether to prescribe statins in the context of atherosclerotic CVD, it is recommended to calculate cardiovascular risk, which is defined as the probability of an individual developing an atherosclerotic cardiovascular event in a certain period of time. Many evaluation systems are available and different calculation tools are used by different entities [23,24].

In the most recent guidelines that use ACC / AHA Pooled Cohort Equations to calculate cardiovascular risk, it is recommended to prescribe these lipid-lowering drugs to low-risk individuals (7.5% risk of a cardiovascular event within a 10-year interval). Prior to this update, statins were recommended in subjects with cardiovascular risk greater than 20% [25].

Recently, a study compared the number of US adults for whom statin therapy is recommended by comparing the National Cholesterol Education Program's Third Adult Treatment Panel (ATP-III) guidelines implemented since 2002 and the ACC- which were published in 2013. In this study, there was an increase from 43.2 million individuals to 56 million eligible for statin therapy, with most of this increase, from 10.4 million to 12.8 million, occurring in individuals without CVD. Under the new guidelines, subjects who are eligible for statin therapy have a significantly lower LDL-cholesterol level (LDL-cholesterol $\geq$ 190 mg/dl or $\geq$ 70 mg/dl and with the diagnosis of diabetes mellitus) [26].

The two guidelines differ in the selection of individuals for treatment with statins. While ATP-III is based on LDL-cholesterol levels, ACC-AHA selects individuals based on the 10 year cardiovascular risk calculation. Given this increase in the population in which statin therapy is recommended and taking into account the adverse effects resulting from

taking this therapy, it is necessary to discuss with the patient the benefits of the therapy taking into account their comorbidities, which is also recommended in the new guidelines, in order to avoid overtreatment [27].

The efficacy of statins as lipid-lowering drugs is the subject of a large number of published papers. An example of this is a meta-analysis involving 18 randomized, case-control trials, with 14,303 patients showing the benefit of using HMG-CoA reductase inhibitors as a form of secondary prevention. In this meta-analysis patients started statin therapy 14 days after the onset of ACS and the results were a reduction in the risk of death, myocardial infarction and stroke, although not statistically significant. This reduction in the risk of death and complications as well the occurrence of unstable angina was evidenced in the 4 months following the SCA episode, since the beginning of therapy [28].

The recognized adverse effects and resistance to these drugs potentiated the study of new therapeutic targets in the treatment of atherosclerosis and subsequent decrease in adverse cardiac events [29]. In recent years new lines of thought were delineated in the pathogenesis of ACS, with further study of atherogenesis. The researchers emphasize the importance of understanding the contribution of immune-mediated mechanisms in inflammation that occur in ischemic heart disease. In addition, they emphasize that the inflammatory mechanisms associated with atherosclerosis and its complications can be modulated by anti-inflammatory interventions [30,31].

Many components of innate, cellular and humoral immunity are involved at the beginning of the atherogenesis process, as well as in its progression and future complications [32]. In the process of atherogenesis, pro-inflammatory monocytes and circulating T cells adhere to the endothelial cells through adhesion molecules, allowing a passage of them into the vascular artery wall mediated by chemotaxis that is regulated by cytokines. At the level of the intima, the differentiation of monocytes into macrophages perpetuates and amplifies the local inflammatory process. After the oxidized LDL particles' phagocytosis, a process of intracellular cholesterol precipitation occurs and leads to the activation of NLRP3 family proteins, which, in turn, will allow the formation of the inflammassoma. This induces cell death and allows the activation of interleukin-1β (IL-1β). Interleukin is preponderant in the expression of leukocyte adhesion molecules, as well as activation of metalloproteinases (MMP), interleukin-6 and prostaglandin-E2 [33].

With the continuous recruitment of proinflammatory cells, cytokines and the accumulation of lipids, the apoptosis and necrosis phenomena induce the formation of a necrotic center in the atherosclerosis plaque. This necrotic center has the peculiarity of being surrounded by a hypoxic environment that constitutes an important trigger for neovascularization [34]. In addition, in the later phase of the process the action of pro-inflammatory cytokines and MMP leads to rupture of the atherosclerotic plaque fibrotic capsule with consequent activation of the coagulation cascade and formation of occlusive or sub-occlusive thrombus [35].

Thus, science shows that although statin therapy substantially reduces the occurrence of CV events, many of the treated individuals will be targeted for recurrence of these events despite being medicated with HMG-CoA reductase inhibitors. Thus, the development of new drugs targeting the previously described inflammatory pathways appears promising and requires further studies [30-32].

Clinical trials support the assay of biomarkers of the inflammatory state as predictors of baseline risk and recurrence of CV events (such as acute myocardial infarction, stroke) [36]. In the clinical trial Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT-TIMI-22), after the diagnosis of ACS, one group of patients was treated with atorvastatin 80 mg and the remainder with pravastatin 40 mg. Both were followed up for 2 years. The results showed that in the group with a statin prescription at a higher dose the reduction of the risk of death, myocardial infarction and unstable angina was 16% higher than the prescribed group with a lower dosage. In this last group, there was also a more modest reduction of LDL-C and C-reactive protein (CRP) levels, denoting one of the pleiotropic effects of statins, reducing inflammation [16,37,38].

Another well-known sub-study, Cholesterol and Recurrent Events (CARE), evidenced the use of pravastatin in reducing CRP levels, independent of LDL-C levels, with a significant reduction in CV events. This drug was used as secondary prevention during the 5 year follow-up of individuals with a history of acute myocardial infarction. In the placebo group, there was an increase in CRP levels in the 5 years following acute myocardial infarction. In the statin prescription group, serum levels of inflammatory biomarkers were reduced, which did not correlate with the magnitude of LDL-C changes. In this way, the researchers reinforce the potential effects of this statin in addition to the lipid-lowering effect [39].

Still on this topic about the prescription of HMG-CoA reductase, all researchers and clinicians do not accept its prescription as a secondary and primarily primary prevention form. As a result, recent scientific studies have criticized the clinical trials that led to the increase in the prescription of this drug and became famous as: JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial), Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS), PROVE-IT-TIMI-22 e Treating to New Targets (TNT) [40].

JUPITER is one of the most recognized studies in the statin approach. In this multicenter, randomized, double blind study with a placebo and a control group, subjects who were followed had normal LDL-C (LDL-C<130 mg/dL), but increased levels of CRP (CRP>2 mg/L). With rosuvastatin's use, there was a reduction of about 50% in LDL-C and 27% in

CRP levels. There was also a 44% reduction in adverse cardiovascular events (acute myocardial infarction, stroke, hospitalization due to unstable angina, arterial revascularization or death of cardiovascular etiology). In addition, there were no statistically significant differences between the treated group and the control group with regard to side effects, with the exception of an increased relative risk to 25% of diabetes mellitus in the rosuvastatin group. Although this study has demonstrated the efficacy of therapeutics in reducing acute phase reactant levels, it is unknown whether the reduction of CRP alone can reduce vascular event rates [41].

Regarding secondary prevention, the efficacy of statins in decreasing the risk of all causes of death in individuals with a prior history of coronary disease is unanimous. But is this reduction of morbidity and mortality visible when using statins as a primary prevention? A meta-analysis involving 11 clinical trials with 65,229 participants considered having a high cardiovascular risk, without previous history of AMI or stroking did not show a reduction in the risk of all causes of death in this study group. The latter was treated with statins at a dose ranging from 10 to 40 mg per day, with an average treatment period of 3.7 years [42].

In another meta-analysis, 13 trials were involved. In six of these trials involving 11435 women without CV disease, it was found that prescribing statins had no significant effect on reducing the risk of death, AMI's occurrence, on revascularization or coronary disease. However, in the remaining 8 clinical trials and which included 8282 women with a history of CV disease, statins prescription had a significant effect on reducing the above-mentioned parameters. In conclusion, the researchers support the use of HMG-CoA reductase inhibitors as a secondary prevention method, and highlight the lack of evidence of its use as a primary prevention method.

Another research work developed in 2003 aimed to study the effect of statins in reducing the progression of atherosclerotic plaque in the coronary arteries. For this purpose, 182 asymptomatic patients were evaluated for 1.2 years with tomography measurements at the beginning and at the end of the study. Patients with LDL-C $\leq$ 80 mg/dl at the end of the study were compared with those who have LDL-C levels >80 mg/dl. The results did not show statistically significant differences in the progression of calcified atherosclerotic plaque development in both groups (9.3%/year versus 9.1%/year, respectively). The researchers concluded that there should be a more complex relationship between statins, LDL-C and coronary heart disease, and further studies are needed [43].

In this topic of atherosclerosis beyond pharmacological treatment, an adoption of a healthier lifestyle is preponderant. One of the most important and recognized determinants of lifestyle is the diet. Thus, the treatment of dyslipidemia and the prevention of the development of CVD should always be accompanied by a diet low in saturated fats that will lead to a decrease in the serum concentration of LDL-C and consequently, a decrease in adverse cardiovascular events [44,45].

The Oslo Diet-Heart Study shows the relationship of dietary changes with different adverse cardiac events. In this study 412 men with a history of AMI were randomly placed in the control group, with maintenance of their diet saturated fat habitual or in the experimental group where a polyunsaturated diet was instituted. Both groups were followed for a period of 5 years. In the experimental group there was a 14% reduction in serum cholesterol levels, as well as a decrease in the main cardiac adverse events: 37% lower risk of AMI and 66% unstable angina [46].

Smoking, overweight and obesity, frequent consumption of foods rich in saturated fat and sedentary lifestyle are recognized as major risk factors for CV events. So, in conclusion, the clinicians should advise patients to incorporate healthier eating habits into their daily lives [47].

DISCUSSION

Statins are the most prescribed drugs in medical history. They are presented as possible protectors of ischemic cardiac events and their complications, reducing the associated morbimortality. In recent years, the medical community's view of the truthfulness of these benefits has been dubious, especially in its use as primary prevention [48].

Numerous published papers support the use of these lipid-lowering drugs as a primary prevention for the development of ischemic heart disease. But the most critical claim is that these different scientific studies (that allegedly prove this theory), are not comparable, in order to draw such conclusions. They claim that the benefits of these drugs cannot be determined based on the percentage reduction in LDL-C levels between the control group and the group being treated. Epidemiological data indicate that the absolute difference in LDL-C levels between the two groups is the most informative measure. Disagreement with the use of HMG-CoA reductase inhibitors is also justified because the reduction of all causes of death over a period of 5 years is not statistically significant. Regarding these facts, the medical and scientific community does not have a unanimous opinion regarding the guidelines of its prescription [49,50].

In clinical practice, the prescription of these drugs should be weighed, especially when the goal is primary prevention. The cost-effectiveness, the effectiveness of statins for a given LDL-C value and the investigation of other contributing factors for the development of ischemic heart disease are factors that the clinician should take into consideration [51].

Concerning the cost-effectiveness of statins, the known adverse effects of HMG CoA reductase inhibitors are not negligible. Statins have **short-term effects** of rash, headaches, abscesses, nausea, dyspepsia, flatulence, constipation, memory disorders, and sexual dysfunction [52].

With regard to the **long-term effects**, although rare can be serious. The most frequently reported effect affects the musculoskeletal system and is dose-dependent on the statin concerned. These can go from tolerable myalgias or condition myositis to marked rhabdomyolysis. In this latter condition there is an increase in serum creatine kinase (CK) levels above 10 times the normal upper limit [53].

In the long term, diabetes, peripheral neuropathy, and increased risk of neoplasia are also other adverse factors to consider [51,54]. Peripheral neuropathy is documented as a side effect of statins, but others admit the presence of predisposing factors in the individual for its development beyond taking the HMG-CoA reductase inhibitors. Neuropathy is thought to be a reflection of the disturbance of the neuronal membrane constitution, with cholesterol being one of its major components, as well as in the inhibition of coenzyme Q10 [54].

Regarding diabetes mellitus, a multicenter, observational and retrospective study was performed, including 136 966 patients, aged 40 years or older, without previously diagnosed or treated diabetes, with a recently prescribed statin after a cardiovascular event. In this study, atorvastatin $\geq$ 20 mg, rosuvastatin $\geq$ 10 mg or simvastatin $\geq$ 40 mg was defined as "high potency statin"; all other treatments with HMG-CoA reductase inhibitors were considered to be of low potency. After the first two years of regular use of this drug, there was a 15% increase in new cases of diabetes with higher potency compared to those with lower potency, with an increase in the higher risk in the first 4 months of its use takes. Thus researchers warn that higher doses should preferably be reserved for patients who do not respond to low potency treatments given the increased risk of developing this endocrinopathy [55].

At the cancer level there is a huge dichotomy, if on the one hand there are studies mentioning the increased risk of developing neoplasia, there are others to reinforce the prescription of HMG-CoA reductase inhibitors for their anti-carcinogenic effect. In fact, statins inhibit the synthesis of selenoproteins and interfere with the immune function in natural killer cells justifying a possible increased risk of neoplasia. However, these drugs are also recognized by their anti-angiogenic, anti-proliferative and anti-inflammatory effect, justifying a possible anti-carcinogenic effect [56].

A meta-analysis aimed to assess the relationship of pravastatin and the increased risk of neoplasia and whether this risk was age-dependent. Of the 22 studies under analysis, the researchers concluded that the relationship between the use of this drug and the increased risk of neoplasia was not statistically significant. However, analyzing the results by the age of the participants, it was verified that pravastatin would have a pro-carcinogenic effect (p=0.006). Thus, the authors emphasize the importance of carrying out more studies that verify this possible association [57].

In contrast, statins act by inhibiting the mevalonate pathway, with consequent inhibition of protein prenylation. The inhibition of this pathway is fundamental since the mutation of the p53 enzyme present in a large number of neoplasia seems to stimulate this metabolic pathway. Thus, HMG-CoA reductase inhibitors may constitute a therapeutic target in concomitance with conventional chemotherapeutic treatment [58]. In the case of breast cancer, statins show an inhibitory effect on Rho proteins responsible for metastatic invasion and the Ras family with a consequent decrease in the probability of mutation and differentiation of cancer cells [59].

Due to the lack of consensus on the efficacy of these drugs as a primary form of prevention for individuals with limited cardiovascular risk, the cost-benefit ratio should be even more carefully weighted [60].

Still in this cost-benefit approach, it is pertinent to consider the Number Needed to Treat (NNT). This indicator represents the average number of patients who need to be treated to prevent one additional bad outcome. Cochrane discloses that for every 1000 subjects receiving statins as primary prevention for a period of 5 years, 18 will prevent the occurrence of a cardiovascular event (NNT = 55) [61].

In this cost-benefit relation of the use of the HMG CoA reductase inhibitors it is also important to emphasize the metabolic consequences of its use. Statins act on the enzyme HMG CoA reductase, inhibiting cholesterol synthesis and coenzyme Q10 biosynthesis. Coenzyme Q10 plays an important role in the prevention of lipid peroxidation associated with the atherogenic process [62]. In addition to its antioxidant action, coenzyme Q10 improves energy production by the cardiac muscle and has membrane stabilizing properties [63]. Given this conditioning, many studies have been developed on the necessity of supplementation of this coenzyme to the individuals medicated with statins [64]. The data demonstrate that despite the decrease in serum levels of coenzyme Q10, intramuscular levels of this enzyme before and after initiation of treatment with statins is inconsistent or do not have statistical significance. These questions are about of need for supplementation, especially if the justification is the improvement of muscular symptoms [65].

About the metabolic changes induced by statins, in addition to the depletion of coenzyme Q10, vitamin K2 synthesis is also affected. Vitamin K2 is a cofactor that ensures the carboxylation of glutamic acid to form γ carboxyglutamate. This protein matrix protects the blood vessels from calcification because it binds to calcium. Thus, the use of statins inhibits

the formation of vitamin K2 and accelerates coronary arteries' calcification, which is an important marker of atherosclerosis [66]. Stimulation of atherosclerosis, the opposite effect for which statins were designed, is also given by the inhibition of selenium-protein synthesis. Forrester et al, highlight the inhibition of the synthesis of glutathione perioxidase, a selenium-protein, which will contribute to an increase in oxidative stress. This is related to atherogenesis, carcinogenesis and aging [67]. Given this paradox of the pro-atherosclerotic effect resulting from the side effects of HMG CoA reductase, further clinical studies are needed to confirm this.

What about the effectiveness of statins: Will there be a minimum LDL-C value from which the effectiveness of statins is negligible?

In the JUPITER study, 73% of subjects treated with rosuvastatin achieved cholesterol levels below 70 mg/dl and a 55% reduction in major CV events. In the individuals that did not reach this level, the reduction of the main CV events was 9%. In this study, 4,154 participants achieved LDL-C levels below 50 mg/dl, with a consequent reduction in risk of CV events of 65% and 46% reduction in associated mortality. But they did not experience a risk of CV events significantly different from those who had LDL-C levels above 50 mg/dL. Thus, if there is a minimum threshold from which statins are not effective, this will be an LDL-C value below 50 mg/dl [68,69].

Considering the cost-benefit ratio of statins and their effectiveness for lower LDL-C values, the truth of the cholesterol theory as the main factor in the genesis of ischemic heart disease is also debatable by researchers. Other hypotheses have been studied.

With the knowledge of the pleiotropic effects of statins, especially in the reduction of inflammatory markers, the scientific community is confronted with a new paradigm: Is the reduction of inflammation, objectified by CRP levels, so effective in decreasing adverse CV events independently of levels of LDL-C? [70].

This paradigm is now the target of two recognized studies, which are still on-going: The Cardiovascular Inflammation Reduction Trial and Canakinumab Anti-inflammatory Thrombosis Outcomes Study. In the first study the researchers allocated 7000 patients with coronary heart disease and persistently elevated CRP in the placebo group very-low-dose-methotrexate (VLDM, 10 mg weekly). The aim is investigating whether taking low-dose methotrexate reduces heart attacks, strokes, or death in people with type 2 diabetes or metabolic syndrome that have had a heart attack or multiple coronary blockages and to date the results have not been reported [71]. In the second study, Canakinumab, an IL-1β monoclonal antibody, was used. In the group of subjects treated with the monoclonal antibody there was a decrease in CRP levels and no reduction in LDL-C levels was obtained. After the 3.7 years follow-up, the antibody-treated group evidenced a decrease in the rate of recurrence of adverse cardiovascular events when compared with placebo regardless of LDL-C levels. But there was no significant difference in all-cause mortality comparing the two groups [72].

Is very-low-dose-methotrexate and IL-1 beta inhibition in CAD going to hit the clinic soon? We don't know, but the role of inflammation in atherothrombosis should be the subject of additional scientific studies to see if there is a prospect of new therapeutic targets [73].

But beyond that of high levels of cholesterol will there be another factor that accelerate the process of atherosclerosis and therefore increases the risk of CVD?

Scientific papers have recently emerged to identify insulin resistance as the main predisposing factor in atherogenesis [74]. Insulin-resistance contributes to several chronic pathologies such as dyslipidemia, hypertension, hyperglycemia, formation of glycation end products and provides an inflammatory, prothrombotic and pro-oxidative environment [75]. IR is associated with elevated serum levels of CRP and histological and functional alterations of the tunica intima of vascular walls [76]. This evidence justifies the compromise of homeostasis of the vascular wall, visible by the endothelial damage caused by the glycotoxicity and lipotoxicity generated by the pro-inflammatory state caused by IR [77].

The hyperglycemia consequent to the IR process stimulates the pancreatic β cells to produce more insulin. Elevated serum levels of insulin promote atherosclerosis by stimulating smooth muscle proliferation in the arterial wall, which predisposes to arterial stiffness as well as to its narrowing. Hyperinsulinemia also contributes to lipolysis, with consequent increase in serum levels of fatty acids. These will be incorporated by the hepatocytes leading to the formation of VLDL, LDL, triglycerides, also being described decreases in the concentration of HDL [78].

Still on IR, it contributes to platelet aggregation and high serum levels of fibrinogen. Both phenomena are part of the pathophysiology of thrombus formation that condition the onset of ischemic heart disease [79].

Lifestyle and dietary pattern seems to be a key point in the prevention of atherosclerotic phenomena. Modest and severe obesity, for many considered the epidemic of the 21st century, are the main factors for IR development.

Both in the approach to dyslipidemia and IR, clinicians call for a diet low in saturated fats. The high consumption of this type of fats and trans fatty acids (particularly hydrogenated vegetable oils) associated with low levels of omega-3 fatty acids contributes to IR. One of the reasons mentioned is the effect of this diet on the composition of the cell membrane,

leading to a decrease in its fluidity with consequent decrease in insulin-receptor uptake and in the decrease of its action [80].

Key Learning Points

In recent years we have been attending debates in the medical and scientific community on the contribution of cholesterol to ischemic heart disease and the benefits of using statins in reducing cholesterol levels and morbidity and mortality associated with ischemic heart events.

If on the one hand there are advocates of the use of HMG CoA reductase inhibitors as primary and secondary prevention, there are those who only advocate its use as secondary prevention.

The most critical investigators claim the most diverse justifications. On the one hand, they believe there are other more solid theories to justify the relationship between atherosclerosis and ACS, namely the inflammatory process. Proponents of this theory show that inflammation will condition oxidation of lipoproteins and may even have an effect on the rupture of the fibrotic capsule of the atherosclerotic plaque. Further studies should be performed to evaluate the relevance of new therapeutic targets in the approach to atherosclerosis and ischemic heart disease.

Another argument pointed out by the more skeptical about the use of statins as a primary preventive method concerns the cost-benefit relationship. There are many adverse effects that often lead to discontinuation of therapy. In addition to the muscular symptoms, statins lead to certain metabolic repercussions, namely in the decrease of levels of coenzyme Q10, selenium-proteins and vitamin K2. Such interferences in metabolism aren't negligible and should be taken into account.

In turn, insulin resistance also appears to have its contribution in the process of atherogenesis. In part, due to their contribution to an inflammatory, prothrombotic and pro-oxidative environment, they compromise homeostasis of the vascular wall. Thus, regarding the ischemic heart disease, the numerous studies published so far aren't unanimous in naming cholesterol as the main risk factor. ACS is pathology with multifactorial etiology and treating the patient pharmacologically for a single etiological factor doesn't appear to have a significant impact in reducing morbidity and mortality.

CONCLUSION

A comprehensive and combined treatment is required not only for dyslipidaemia but also for insulin resistance, regarding their relationship with ACS.

This same treatment should include changes in the dietary pattern and other non-pharmacological measures, besides the use of statins or other pharmacotherapeutic agents.

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