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Review Article

Association of Lifestyle and Medication for Primary Cardiovascular Prevention in The Elderly

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Abstract

The increase in the Brazilian elderly population draws attention to the need to adopt measures that mainly aim to offer a better quality of life to individuals belonging to this age group. The manifestations of atherosclerotic disease may have even more deleteleric repercussions in elderly individuals. Most of the time they imply a long period of hospitalization or home restriction to the bed, predisposing the individual to other pathologies that are difficult to recover in this age group. Not to mention the large number of fatal cases and long-term disability. Advanced age alone should not be considered as a limiting factor for therapeutic intervention in cases of dyslipidemias. The analysis of life expectancy and quality are extremely important. Dietary guidance is extremely important and should be very judicious, maintaining the caloric and vitamin intake of the elderly. General recommendations prevail, such as acquisition and maintenance of ideal weight, regular physical activity, suspension of smoking, among others. We must keep in mind the greatest difficulty of adherence to non-pharmacological treatment in this group of patients, since our intervention will be done in habits that persist for a long time; if we are facing primary prevention and this fact is detected, we should prolong the phase of non-pharmacological treatment. When prescribing lipid-lowering drugs for individuals over the age of 65 it is necessary to remember that there are numerous changes in the "aged" organism and therefore treatment should be started with lower doses than those usually prescribed for young adults. Statins are lipid-lowering drugs that have shown better efficacy in the elderly and are therefore the drugs of choice.

Keywords: Primary prevention; Elderly population; Cholesterol; Lifestyle; Statins

Abbreviations: CAD: Coronary Artery Disease; HDL: High Density Lipoprotein; LDL-c: Low Density Lipoprotein Cholesterol

Introduction

The prevention of coronary artery disease (CAD) in the elderly should be multifactorial, involving not only the classical factors related to diet, exercise and drug therapy and here in this study the use of Statin as a fundamental element of evaluation, as well as psychosocial factors. Encouraging lifestyle modification for healthy attitudes, with basic dietary recommendations such as increasing fruits and vegetables in food, as well as fiber, decreases the risk of cardiovascular events including death from coronary heart disease. Diets should be carefully elaborated and individualized, generally accommodating the rigid preferences of these patients, as there is a risk of malnutrition, depression or coexisting diseases, which may result in very marked weight loss, a very common thing in this

population range. Mediterranean diets may be a good option for the elderly population, as can be seen below.

The study of the dietary patterns of Crete, from much of the rest of Greece and southern Italy, in the early 1960s, revised in 2000, includes the following characteristics: abundance of planted foods (fruits, vegetables, grains, other forms of cereals, potatoes, beans, nuts and seeds); minimally processed, seasonal and locally grown foods; fresh fruits as the typical daily dessert, with sweeteners containing concentrated sugars or honey, consumed a few times a week; olive oil as the main source of fat; dairy products (mainly cheeses and yogurts) consumed daily in small and moderate amounts; fish and birds consumed in small and moderate quantities; weekly consumption from zero to four eggs, red meat consumed in small quantities; and wine consumed in small and moderate quantities, usually with meals.

Low adherence also in this population range is the main limiting factor for the efficacy of statin therapy in the elderly. However, some factors should be improved for the adequacy of preventive actions. A first to be questioned is cognitive deficit, which affects 50% of elderly individuals with heart disease, particularly when ventricular dysfunction is present. The pattern of cognitive dysfunction here is represented by lack of attention and this will be relevant for non-adherence to treatment. Another factor is the use of hypotensive agents, often generating excessive drop in blood pressure, determining a marked decrease in cognitive function. It has also been shown that low socioeconomic status is not only a risk factor for mortality from CAD in men and women, but influences participation in secondary prevention and/or rehabilitation programs [1-5].

Considering the pleiotropic effects of statins, both the classics (already proven in several large studies), as well as those related to the improvement of osteoporosis, for example, there is still a lack of large studies, which allows us to say that, improving the socioeconomic conditions of patients, adherence and results can be extraordinarily improved. These factors will always be the basis of treatment of the entire elderly population, especially those selected for drug therapy.

Primary Prevention in the Elderly and Cholesterol

The high risk attributable to the elderly is a guarantee for an effort in primary prevention, especially when a high level of serum cholesterol is combined with other risk factors linked to CAD. There are elements of similarity for primary prevention in the elderly over 65 years of age, compared to middle-aged patients:

1. There is similarity of pathological processes
2. Epidemiology shows that high cholesterol confers high risk attributable in the elderly
3. Angiography-related trials reveal that even in advanced disease, patients respond to cholesterol-lowering therapy with reduced risk

The rule "1% in cholesterol reduction offers 2% reduction in risk", from Gotto (1996) should be attenuated in the case of the elderly. This attenuation may be characteristic for a high-risk population (middle-aged patients with hypercholesterolemia and patients with CAD, for example). The absolute risk increases with age, just as the benefits of drug therapy also increase. Many years of drug therapy in the elderly will not be required to achieve beneficial results. Here two main factors will be analyzed in relation to the selection for drug therapy: a) general prognosis; b) risk.

Patients with relative and prolonged healthy life should pay for treatment. Pharmacokinetic studies in a limited number of patients receiving simvastatin (40 mg - daily) indicate that the mean plasma level of inhibiting activity in relation to HMGCoA reductase is about 45% higher in geriatric patients (70 to 80 years of age) than in young adults (aged 18 to 30 years). However, data obtained from clinical studies suggest that the efficacy and safety of the use of simvastatin in geriatric patients aged 65 years or older are similar to those observed in young adults, when considering the benefit risk ratio. It is also worth mentioning that the frequency of liver or cardiac dysfunction and concomitant diseases and therapies observed in the elderly should always be considered when analyzing the potential benefits of anti-chronic therapy. Remembering that renal dysfunction is common in geriatric patients (generally related to glomerular filtration), this aspect should be analyzed primarily before lipid-lowering therapy. If there is evidence of severe renal dysfunction, the dose adjustment will be made and the patient will be closely monitored.

Diet is always necessary. Risks are represented not only by Low Density Lipoprotein Cholesterol (LDL-c), but also by the presence or absence of major risk factors: hypertension, diabetes, low High-Density Lipoprotein (HDL) and smoking. Subclinical evidence of advanced atherosclerotic disease may suggest the need for drug therapy. In the case of women, some special considerations should be made: CAD is a leading cause of mortality in women over 65 years of age; there are a lower number of cases of early CAD in women; less attention has been given to elucidation of cholesterol in women (treatment is due to high probability); and doubts persist whether LDL-c is atherogenic in women. Epidemiological studies have shown that increased total cholesterol, decreased HDL cholesterol and increased triglycerides are related to increased coronary events in women. (IAS - International Atherosclerosis Society). The protective effect of estrogen still remains not completely resolved.

Pleiotropic effects

Using the current scientific experience and accumulated knowledge about statins [6-9], one can cite classic concepts of

pleiotropism already defined and concepts to be proven. As for the classic pleiotropic effects of vastatine, it can be cited: increased endothelial function; decreased platelet aggregation; decrease in Plasminogen Activator Inhibitor I (PAI-I); decreased plasma viscosity; decrease in tissue factor; decrease in the targeting molecules; decreased cell proliferation; decreased proliferation of cell migration; decreased oxidation proliferation; increased nitric oxide synthesis and reduction of insulin resistance.

A large percentage of elderly people have excess calcium in the aortic valve. Excessive calcium can impair the opening of the aortic valve and only valve replacement surgery can solve the problem. There is still limitation to the recommendation of the use of statin for this purpose [8]. A decline in the immune response and an increase in susceptibility to inflammation with aging have been well established. Statin can offer benefit in this case. The concept that progressive atherosclerosis is accompanied by chronic inflammation has been well established in a number of observational studies in middle-aged men and women. These observations also now extend to elderly patients [10]. The elderly evaluated in the Helsinki study showed that the measurement of C-reactive protein predicted cardiovascular and total mortality, especially in the 75-year age group [11].

Furthermore, further studies are needed to confirm the additional benefits in the use of statin stems from improving cognitive function and reducing the risk of transient ischemic stroke. In a recent analysis of Woscops, there are findings suggesting that statin use determines an additional benefit in the risk of developing glucose intolerance and type 2 diabetes in five years of study. There is still no definitive explanation for this improvement. Osteoporosis is a devastating change in the elderly and the use of statins can delay bone resorption by down-regulation in osteoclasto function. Low-level lipids can promote bone mineralization [12]. The effects of statins are modest, basically the same as those obtained with the use of hydroxychloroquine. Therefore, statin cannot, in this case, be used as monotherapy, but in combination with other agents. Statin seems to reduce the incidence of atrial fibrillation in individuals older than 65 years in patients with atrial enlargement and ventricular hypertrophy. It is noted that there is anti-inflammatory, antioxidative, antihypertrophic and antifibrotic activity.

Adverse effects

In general, the adverse effects of statin are relatively mild and transient (flatulence, dyspepsia, headache, and rash). However, adverse effects such as myopathies and liver toxicity have been reported [13]. Most liver abnormalities occur within the first 90 days of therapy and require monitoring, with pyruvic glutamic transaminase (PGT) being the most sensitive. Enzymatic elevations may not be related to hepatotoxic and often self-limited consequences: they either have spontaneous resolutions or are resolved with dose reduction. The incidence of myopathy is also very low. The incidence of concomitant medications may increase the incidence of myopathies, and here it is worth mentioning in particular the association with fibrates. Myopathy characterized by myalgia and muscle fatigue and may progress to rhabdomyolysis. It has a clinical diagnosis accompanied by an increase in CPK by up to 10 times the normal upper limit. Not being treated, it can evolve to death. Rhabdomyolysis can be the result of a wide range of diseases, which can coexist in patients who use Statin and abuse alcohol, have seizures, use illicit or prescribed drugs, have hereditary, metabolic diseases and infections. The incidence of myopathy may also be higher in the elderly.

From 1977 to 2000, according to a review by Omar and Wilson, by the Food and Drug Administration (FDA-USA), there were 871 cases of rhabdomyolysis, 38 of which followed death [14,15]. In 48 of the 164 Trials of statin and LDL-c studied, the number of participants with one or more symptoms of possible cause of the drug were non-specific from the clinical point of view, that is, they were similar to those treated with placebo, even in the case of those who received a high dose of drugs (e.g., 80 mg). Only less than 2% of the treated patients had symptoms such as muscle pain and diarrhea, with all six Statins used (rosvastatin, atorvastatin, lovastatin, fluvastatin, pravastatin, and simvastatin). Analyzing the research results with 35,000 treated patients and 158,000 people observed, between treated and placebo group, rhabdomyolysis was diagnosed in eight treated patients and five placebo patients, none of them progressing to serious disease or death. There was no failure of liver function in the patients observed and treated.

In study 4S there was no absence of adverse events related to simvastatin therapy. The Woscops, Afcaps and Texcaps studies showed no evidence of adverse effects from statin use for five years. There was no increase in deaths from non-cardiovascular causes, cancer or violence. In the Woscops study there was a significant decrease in cardiovascular death in statin therapy and also a reduction in total mortality (first primary prevention study with reduction of all causes of mortality). We should also mention the drugs and substances that interfere with statin metabolism. These interferences are as follows:

a) Inhibition of cytochrome P-450 3A4 and increased serum concentration of statin: clarithromycin, erythromycin, troleandomycin, cyclosporine, tacrolimus, delavirdine, ritonavir, fluconazole, itraconazole, ketoconazole, fluoxetine, grapefruit, mibefradil, nefazodone, verapamil

b) Induction of cytochrome P-450 3A4 and reduction of serum statin concentration: barbiturates, carbamazepine, griseofulvin, nafcilin, fentoin, rifampicin, troglitazone

c) Inhibition of cytochrome P-450 2C9 and may increase serum fluvastatin concentration: amiodarone, cimetidine,

sulfametoxazoltrimetoprin, fluoxetine, fluvoxamine, isoniazid, itraconazole, ketoconazole, metronidazole, ticlopidine

Induction of citrus as P-450 2C9, which may lower serum fluvastatin concentration: barbiturates, carbamazepine, phentoin, primidon, rifanpicin. The longest period of questioning regarding the use of these drugs occurred in 2001, with the removal of one of the class members - ceryvastatin - due to a higher incidence of rhabdomyolysis, including deaths, especially at the higher dose than recommended or in the association with genfibrozil. The dose and type of lipid reduction therapy is as important as drug therapy for the 40% of patients who require more than 30% LDL reduction. The benefits of acquiring this reduction have been weighed against its risks. Statins show in their use that serious adverse effects are rare and similar to the levels seen with placebo. There are about one billion prescriptions of statins, with 73 cases of fatal rhabdomyolysis, which is the most serious documented event. And yet 40% of these cases studied were associated with the use of ceryvastatin. The great importance of statin remains, and, according to European, American and Brazilian consensus, most patients do not meet the goals recommended by undertreatment, discontinuity of treatment, for not performing lifestyle modification or by isolated or associated factors, which act to the detriment of improving the quality and quantity of life of patients [16].

In conclusion, the benefits of statin in reducing cardiovascular risk are well documented. People with a cardiovascular risk as low as 0.5% per year can benefit. The only study in which the benefit was not demonstrated was ALLHAT-LLT. There is evidence that consensus is not followed properly, and even high-risk patients are not adequately treated. Epidemiological studies show a substantial decrease in coronary mortality since 1970, also among the elderly, indicating that preventive interventions are effective, even in the older population segments [17-20].

Regarding secondary prevention, statin use consistently shows a reduction in all causes of mortality, coronary events, non-hemorrhagic stroke, and intermittent claudication in elderly individuals with CAD, including those aged 81 years or older. Despite the evidence, the drug is underutilized. In the classical studies for this population and substudies, men and women who presented an LDL-c above 125-mg/dl, despite the diet performed, should be treated for the LDL goal below 100 mg/dl. In relation to primary prevention, the position of geriatric societies, including the Brazilian one, is that young elderly aged 65 to 80 years without CAD evidenced, with a total cholesterol greater than or equal to 240 mg-dl or an LDL-c greater than or equal to 160 mg/dl and another risk factor such as systemic arterial hypertension/diabetes mellitus/ smoking/or HDL less than 35 mg/d, despite the diet they would be treated with Statin, with a cholesterol below 200 mg/dl and LDL-c below 130 mg/dl.

Finally, the idea of treating elderly patients earlier and continuously, either by classical and/or subclinical clinical signs and symptoms seems absolutely indicated today. It is necessary to establish favourable and unfavourable criteria for such a decision. As elements in favor are listed: physiologically healthy patients; classically also those with stroke, CAD and peripheral vascular disease: diabetes; discrete comorbidity without limitation of quality of life and expected longevity; optimists, motivated, non-smokers, former smokers, physically active, with good cognitive function, socially active and with adequate economic condition. Unfavorably are the physiologically old. Absence of stroke or diabetes. multiple comorbidities, with impairment of quality of life and limited longevity expectancy. Depressed patients, smokers, sedentary, impaired cognitive function, socially isolated, insufficient economic condition. Finally, taking into account the spectacular growth of the population over 65 years of age, including the increased longevity and knowing that if the current conditions of eating error, physical inactivity and inadequate treatment are modified, statin therapy undoubtedly represents a highly positive influence on the survival of this population group.

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None.

Conflict of Interest

No conflict of interest.

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