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Mini Review

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Hypolipidemic trials in the elderly - a recent historic standpoint

Abstract

In spite of the first trials on the effect of cholesterol reduction and its beneficial impact on morbidity and mortality in the elderly many have already proven the antecipated positive results. 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 coronary artery disease. There are elements of similarity for primary prevention in the elderly over 65 years of age, compared to middle-aged patients. This consideration opened the need for scientific evidence with confirmed levels of evidence. The first studies were WOSCOPS, AFCAPS/TEXCAPS, Heart Protection Study, PROSPER, ALLHAT (Antihipertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial), REVERSAL, Health Study, ASCOT (Anglo Scandinavian Cardiac Outcomes), MIRACL, Post CABG, AVERT, ACCESS, ASSET, ATGOAL, CHALLENGE, CURVES, BELLS, ARBITER, NASDAC, PROVE-IT and DEBATE. Positive evidences were shown from the first to the last trial recalled in this historical beginning.

Keywords: elderly, primary prevention, cholesterol, trials, coronary heart disease

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Abbreviations: CAD, coronary artery disease; HPS, heart protection study; lDL, low-density lipoprotein

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Only recent Trials have included the elderly population in significant numbers in primary prevention studies. It is important to recall the meaning and the purpose of the clinical trials. Although conducting a well-designed clinical trial may appear straightforward, it is founded on rigorous methodology and oversight governed by key ethical principles. In this review, we provided an overview of the ethical foundations of the trials designs, trials oversights, and the process of obtaining approval of a therapeutic, from its pre-clinical phase to post-marketing. One of the limitations in primary prevention studies was the use of agents that produced a moderate reduction in serum cholesterol level. In the WOSCOPS study, published in 1995, pravastatin versus placebo was used for men (high risk). Pravastatin reduced total cholesterol by 20% and LDL cholesterol by 26%. There was a reduction in the main coronary events by 31% compared to those of patients treated with placebo. A similar reduction was observed for coronary procedures and coronary mortality.[1,2] All causes of mortality were reduced by 22%. Elderly patients at WOSCOPS had a similar reduction when compared to younger patients.

The AFCAPS/TEXCAPS study used lovastatin versus placebo and showed a reduction in the frequency of major coronary events (unstable angina, infarction, sudden death). Lovastatin reduced LDL cholesterol by 25%. After five years of treatment, the main coronary events were reduced by 37%, and 22% of the patients were older than 65 years. Older patients responded similarly to younger patients. AFCAPS/TEXCAPS maintains the concept that cholesterol reduction therapy is effective for primary prevention in elderly patients.

The heart protection study (HPS)[3] was published in 2002 in Oxford (UK) and involved 20,536 people, with equivalent numbers of men and women, for treatment with simvastatin at a dose of 40mg against placebo. Women and elderly patients were well represented. According to this study, it was possible to observe benefits in the treatment with simvastatin in patients with low LDL cholesterol, in women and in the elderly. HPS data suggest that patients at high cardiovascular risk benefit from statin therapy, regardless of baseline LDL cholesterol levels.

The 2002 PROSPER study,[4] evaluated a population 75 years of age on average, and the group contained 52% of women. People were recruited in primary and secondary prevention conditions. This population reflects elderly patients in general clinical practice, for whom statin treatment should be taken into account. PROSPER brought information on the safety and efficacy of the use of pravastatin to the group, characterized as being of patients with various pathologies and using polypharmacy. The treatment of elderly individuals for three years with pravastatin produced 15% relative reduction (21% absolute reduction) in the risk of primary outcome. During this period, patients had fewer coronary events than those using placebo and an apparent decrease in transient ischemic attack.

The study of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial), conducted in 2002, evaluated the effects of pravastatin versus the common preventive care for all causes of mortality in the hypercholesterolemic, hypertensive and other risk factor for coronary artery disease (CAD).[5,6]

The REVERSAL study evaluated aggressive statin therapy and progression or regression of coronary arteriosclerosis in patients aged 30 to 75 years. Intensive atorvastatin 80mg/day was effective in stopping CAD in all patients. The interruption of the progression of CAD in this study was associated with a greater reduction in the inflammatory process in the group that used atorvastatin in relation to pravastatin.[7]

The 2002 cardiovascular HEALTH STUDY aimed to establish the association between statin use and all causes of mortality and/or incidence of cardiovascular events. A seven-year population of 1,250 women and 664 men aged between 65 and 80 years with hypercholesterolemia but free of cardiovascular disease was investigated for seven years. Of the patients, 13% were treated with statin. Statin treatment significantly reduced all causes of mortality in 44% of cases and reduced cardiovascular events in 56% of cases, according to this study.[8–10]

The 2003 Study by ASCOT (Anglo Scandinavian Cardiac Outcomes) evaluated the treatment of amlodipine versus atenolol. In the treatment of dyslipidemia with atorvastatin versus placebo it was possible to evaluate the primary efficacy, nonfatal acute myocardial infarction and fatal CAD for 3.5 years. The results showed a 36% reduction in the incidence of acute non-fatal myocardial infarction and fatal CAD. Hypertensive elderly also had a significant reduction in cardiovascular disease when treated with HMGCoa inhibitor.[11]

The MIRACL study evaluated myocardial ischemia and reduction with aggressive lipid reduction therapy and observed results with 80 mg of atorvastatin administered 24 to 96 hours after hospitalization for acute coronary syndrome. Four months of follow-up allowed a significant low value of fatal and non-fatal stroke, in addition to coronal events.[12]

The Post CABG study (post-revascularization with bridge) showed that aggressive cholesterol reduction therapy is an important strategy to maximize postoperative beneficial effects.

The AVERT study[13] aimed at evaluating angioplastic revascularization and usual medical therapy compared with aggressive therapy brought results that demonstrate few events, and also delay in the occurrence of the next event in those patients treated with atorvastatin at a dose of 80mg, without angioplasty. This study suggests that, in a period of more than four months, statin therapy is better than anatomical intervention, altering the course of coronary heart disease.

The ACCESS study used atorvastatin versus other statins in ATP-II in patients aged between 18 and 80years, and showed superiority in achieving the recommended goals.

The ASSET study evaluated the use of atorvastatin versus simvastatin in patients with and without type 2 diabetes, aged 18 to 80 years, and demonstrated greater efficacy in achieving ATP-II goals.

The ATGOAL study evaluated the use of atorvastatin from 10 to 80mg in patients aged 18 to 80years in reaching the ATP III goal at 8 weeks.

The CHALLENGE study evaluated the use of atorvastatin versus simvastatin by comparing efficacy and safety in relation to ATP II targets at the ages of 18 to 80years and shows the superior efficacy of the use of atorvastatin for six weeks.

The CURVES study evaluated the use of atorvastatin versus other statins in the 18-80 age group and the efficacy in achieving goals at 8weeks.

The BELLS study evaluated the use of statin in postmenopausal women.

The ARBITER study evaluated the reduction of intima thickness with the use of atorvastatin to verify its superiority in relation to pravastatin.

The NASDAC study evaluated aggressive treatment for atorvastatin atherosclerotic disease at a dose of more than 10 mg to achieve ATP III goals, and demonstrate proven efficacy at 8weeks.

The PROVE-IT study analyzed the use of atorvastatin 80 versus pravastatin 40mg for acute ischemic syndrome with less than 10 days and cholesterol less than or equal to 240mg/dl, resulting in a 16% reduction in the risk of death or cardiovascular event of maximum severity, already reported from six months of treatment.

The DEBATE study[14,15] with elderly people aged 75 years or older evaluated the treatment of multifactorial aspects of cardiovascular disease. In one group, lifestyle modification was instituted and received cardiovascular pharmacological treatment with statin, aspirin, beta-blocker, and angiotensin--modifying enzyme inhibitors. The control group received usual treatment. The results showed a significant decrease in serum cholesterol and PCR-US-2003.

By interpreting the majority of clinical trials in the elderly populations as to the present, it is important to state that in patients. In patients aged 75 years and older, lipid lowering was as effective in reducing cardiovascular events, as it was in patients younger than 75 years. These results should strengthen guideline recommendations for the use of lipid-lowering therapies, including non-statin treatment, in older patients.

Conclusion

In conclusion, in this review it is very important that clinical trials are interpreted correctly. The impact of clinical trials not only extends to the individual patient by establishing a broader selection of effective therapies, but also to society as a whole by enhancing the value of health care provided. However, clinical trials also have the potential to pose unknown risks to their participants, and biased knowledge extracted from flawed clinical trials may lead to the inadvertent harm of patients. Although conducting a well-designed clinical trial may appear straightforward, it is founded on rigorous methodology and oversight governed by key ethical principles. In this review, we provided an overview of the ethical foundations of trials designs, trials oversights, and the process of obtaining approval of a therapeutic, from its pre-clinical phase to post-marketing surveillance.

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Conflicts of interest

No conflict of interest.

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