Universitat de Girona

SIMVASTATIN EFFICACY FOR PRIMARY PREVENTION IN PEOPLE OVER 75 YEARS OLD:

A multicenter prospective, randomized, double blind, parallel-group trial.

FINAL DEGREE PROJECT

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I would like to express my gratitude to all the professionals that step by step helped me to improve and carry out this work.

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1. LIST OF ABBREVIATIONS:

ACC /AHA: American College of Cardiology/American Heart Association.

AGICAP: Agència de Gestió I Investigació Clínica en Atenció Primària

CABG: Coronary artery by-pass graft

CBPAAT: Catalan Brief Physical Activity Assessment Tool

CHD: Coronary heart disease.

CVD: Cardiovascular disease.

DDD: Defined daily dose.

DHD: DDD/1000 habitants/day

HDL: High density lipoprotein

HF: Heart failure.

INE: Instituto Nacional de Estadística (Spanish Statistical Office)

LBBB: left bundle branch block

LDL: low density lipoprotein

LVH: left ventricular hypertrophy

MI: Myocardial infarction.

MMSE: Mini Mental State Examination

PCI: Percutaneous coronary intervention

2. ABSTRACT

Background: Cardiovascular diseases are the leading cause of death in Spain, however the incidence of cardiovascular disease rates are among the lowest in the world even the same cardiovascular risk factor exposure. Hypercholesterolemia is the most prevalent cardiovascular risk factor in Spain, and reducing cholesterol levels has become one of the main goals in primary prevention. When hygienic-dietetic measures are not enough statins treatment is recommended. Even when there is a high evidence of their efficacy on reducing cardiovascular events and death on people less than 75 years old at risk, there is a lack of evidence about their efficacy over that age. In a country with the highest life expectancy and a rising number of elderly, the efficacy in overall death and cardiovascular events reduction associated at statin therapy in this population must be assessed.

Objectives: To evaluate the effect of statins in primary prevention compared to placebo in order to reduce mortality and cardiovascular events in people between 75 and 85 years old living in Spain. The secondary objective is to determine the incidence of adverse effects in this population.

Methods: The design is a prospective, randomized, double blind, parallel-group trial that compares Simvastatin (20mg) versus placebo. 1624 patients in the intervention group and 1624 in the control group, between 75 and 85 years old, affected by hypercholesterolemia will be recruited and followed every three months for three years by their own primary care doctors and nurses, members of the AGICAP. The primary care doctors will check the new onset of cardiovascular diseases and any adverse effect.

Key words: Statins, primary prevention, elderly, cardiovascular diseases.

3. INTRODUCTION

3.1 OVERVIEW OF DYSLIPIDEMIA AND CARDIOVASCULAR RISK IN CATALONIA.

In Catalonia and all over Spain the cardiovascular diseases are the leading cause of death (30%) of the country. If we analyze it by sex, in women it's the main cause of death and the second cause in men with a mortality rate of 270,5 and 233,2 per 100.000 habitants respectively, being the ischemic heart disease the principal cause of death in men and the cerebrovascular disease in women. When analyzing the mortality by age, in the population over 79 years old, the mortality rate increases until 3.147,3 deaths per 100.000 habitants (1) . The accumulative incidence of the cardiovascular diseases is high among people over 65 years old which 9'6% suffers of ischemic heart disease , 8'9% of cerebrovascular disease, 4'6% of cardiac insufficiency and 3'1% peripheral arteriopathy(2). At an international level, however, this rates are among the lowest of the world, notwithstanding the fact that frequency of exposure to cardiovascular risk factors is no less among Spaniards than it is in other countries(3). This phenomenon, known as the French Paradox, is also seen in other populations in the Mediterranean area and has been linked to the possible existence of protective factors linked to the Mediterranean diet(4,5).

On the last decades the public health institutions have focused on detecting and lowering the modifiable risk factors levels of the population as hypercholesterolemia, hypertension, smoking, obesity and diabetes mellitus but, even the last trends show a cholesterol levels reduction and an improvement of hypertension control, the obesity rate in men has increased (6) and the smoking rates in Spain continue being among the highest in Europe(7).

The most prevalent risk factor in Spain is hypercholesterolemia, affecting the 41% of the population(8,9). Relationship between total serum cholesterol level and cardiovascular heart disease was proved a couple of decades ago(10) and since then primary prevention has hardly focused on reducing its levels using cholesterol lowering drugs and dietetic measures(11).

3.2 MANAGEMENT OF HYPERCOLESTEROLEMIA

The main goal in primary prevention goes through public strategies trying to modify people lifestyles, recommending low fat diets, giving up smoking and an increase of physical exercise to avoid the apparition of hypercholesterolemia.

When it's already established the aim is to avoid that this people affected, but who already haven't suffered any cardiovascular event, eventually develop. To avoid over treating the population, since few years ago, it is used a baseline risk strategy that recommends lipid lowering treatment, mainly statins, for people with an increased risk >10% of a coronary event or death(11).

To calculate this risk in Catalonia we have a validated algorithm called the Frammingham-Regicor risk predictive function, which avoids the overestimation of the risk comparing with the SCORE or Framminghам algorithms (2'5 times more)(12,13).Risk is assessed by a set of 10-years cardiovascular risk predictive functions that include age, sex, smoking status, blood pressure, cholesterol concentration and diabetes(14).It allows treating only people with a clear benefit, bearing in mind that statins are not exempt of risk. On the other hand, in secondary prevention, statins have demonstrated in several clinical trials a significant reduction of 30% on coronary heart disease (CHD) death and a 22% in all-cause mortality as some meta-analysis summarize(15), therefore they are recommended to everybody.

Although CVD risk estimation is crucial for the treatment decision, Framminghам-Regicor predictive function is only validated for the group of population from 35 to 74 years old(12), as well as all the other risk assessment methods as SCORE (65 years old) and Framminghам (79 years), leaving people over this age without the chances to estimate their cardiovascular risk and leaving the decision of treating or not on the good clinical judgement considering the individual subject's situation; regarding comorbidities, polypharmacy, and possible adverse effects (11)(16)(17).

3.3 EVIDENCE FOR PRIMARY PREVENTION WITH STATINS IN THE ELDERLY

Another additional problem that must be added at the impossibility to estimate the cardiovascular risk is there is no clear evidence so far that such treatment really prolongs life in elderly subjects.

People over 65 years of age comprise a fast growing segment of the population due to the rise of life expectancy (9,2% of the Spanish populations is over 75 years old and it's estimated that it will be the 12'6% by 2029 and 27,5% by 2064(18). As the proportion of elderly people rises, the primary prevention for cardiac and cerebrovascular disease gets more important. Taking this onto account the AHA/ACC 2013 considers that people over 75 years old are on risk itself due to the age of developing a cardiovascular disease in the future and recommends to start taking statins with no need to consider the other risk factors(19). On the other hand, a review of observational studies concluded that the lowest cholesterol levels are associated with higher all-cause mortality among >80 years old and there are no evidence of an effect of lipid-lowering treatment on all-cause mortality above that age. They didn't find sufficient data to make any recommendation regarding >80 years old and lipid-lowering treatment(20).

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) was the first trial designed specifically to investigate the effects of a statin (pravastatin, 40mg/day) in the elderly aged 70-82 years, but it was performed in patients with preexisting vascular disease or at high risk of CVD, including stroke. Although this was not a primary prevention trial, it has to be mentioned that no benefit in terms of reducing mortality was seen in subjects without previously diagnosed CVD(21).

Since Prosper was done at 2002 some other trials have studied statins versus placebo in order to reduce cardiovascular events and mortality in primary prevention but none of them ever included elderly patients over 82 years old.

Table 1. Clinical intervention studies in primary prevention of cardiovascular disease in elderly patients.

Study	N (% elderly)	Age range (yr)	Statin (dose)	Mean follow-up (yr)	Main results	NNT
AFCAPS/TexCAPS[35]	6,605 (21% > 65 yr)	45–73	Lovastatin (20–40 mg)	5.2	37% reduction in non-fatal myocardial infarction, unstable angina and sudden death.	49
ALLHAT-LLT[36]	10,335 (50% > 65 yr)	≥ 55	Pravastatin (40 mg)	4.8	No significant reductions in mortality, coronary heart disease or stroke vs. usual care (4.8 years).	NS
ASCOT-LLA[37]	10,305 (64% > 60 yr)	40–75	Atorvastatin (10 mg)	3.3	36% reduction in non-fatal myocardial infarction and coronary death.	164
CARDS[38]	2,838 (40% > 65 yr)	40–75	Atorvastatin (10 mg)	3.9	37% reduction in fatal and non-fatal myocardial infarction, coronary death, unstable angina, and revascularization.	42
MEGA[39]	7,832 (70% > 55 yr)	40–70	Pravastatin (10–20 mg)	5.0	31% reduction in coronary events. 32% reduction in total mortality.	150
CHS[40]	1,914 (100% > 65 yr)	> 65	Statins	7.3	44% reduction in all-cause mortality. 56% reduction in cardiovascular disease.	46
PROSPER[41]	5,804 (100% > 70 yr)	70–82	Pravastatin (40 mg)	3.2	15% reduction in coronary death, non-fatal myocardial infarction and stroke.	59
JUPITER[42]	17,802 (32% > 70 yr)	60–71	Rosuvastatin (20 mg)	1.9	44% reduction in non-fatal myocardial infarction, cerebrovascular event, revascularization, coronary death and unstable angina.	95

NNT: number needed to treat; NS: non significance.

From Statins for Primary cardiovascular Prevention in the Elderly review(17).

Two meta-analyses of primary prevention trials have been reported. The first included more than 70,000 subjects found some benefits, particularly for all-cause mortality and major coronary and cerebrovascular events, in subjects over 65 years, however, they did not reach statistical significance(22). The most recent meta-analysis pooled data form eight trials enrolling 24,674 subjects and demonstrated that statins significantly reduced the incidence of myocardial infarction by almost 40% and stroke by almost 24%, but did not significantly prolong survival in the median 3.5-year follow-up. From their analysis, 24 or 42 elderly subjects without established CVD would need to be treated with statins for 1 year to prevent 1 MI or 1 stroke, respectively(16). Another authors estimated that NNT were 83 to prevent one cardiovascular event and 142 to prevent one stroke in people over the age of 65. NNT differ depending on the cardiovascular risk; increasing over when low risk people is considered and decreasing for those at higher risk(17). .

3.4 STATIN USE IN ELDERLY

Statins (HMG-CoA reductase inhibitors) are the election treatment to reduce cholesterol levels because it's the only one that have proved reducing coronary events in primary and secondary prevention and, in addition, has proved reducing global and coronary mortality in secondary prevention. Among statins, simvastatin and pravastatin are the drugs from which we have more information about clinical efficacy and safety, accordingly are the most recommended(11).

During the last two decades, the utilization of statins has increased considerably in most western countries. The increase was most pronounced among older persons (aged >75 years old)(23).

Age and sex are physiological factors with a strong influence on lipid profile. Sex differences in lipoprotein levels are further affected by age. In the Framingham Heart Study, low density lipoprotein (LDL) cholesterol concentrations rose progressively with age, until 60 in men and 70 in women(24). In Spain, this trends have also been observed, while in man obesity and hypercholesterolemia tend to stabilize over 65 years old, in women it's seen that cholesterol and triglycerides keeps increasing and reverting the tendencies seen at the other age groups(8,25).

The tendency in the number of acute coronary heart disease between 2005 and 2049 will be stabilized on the population from 25 to 74 years old and will significantly increase among the population over 74 years old due to the aging of the population (26).

The beneficial effect of statins in patients with myocardial infarction and hypercholesterolemia was demonstrated in 1994, showing considerably reduced post-myocardial infarction mortality in middle-aged men. Clinical trials confirmed the efficacy on statins in secondary prevention of CVD and subgroup analyses provided evidence of benefit in older persons. However, the available evidence for statins' efficacy in primary prevention is less robust. As it has been shown, the elderly are underrepresented in most clinical trials and the evidence supporting the use of statins in older individuals derives mainly from sub-group analyses and post-hoc data, so treatment recommendations are sometimes extrapolated from data gathered among younger patients.

Lipid lowering drugs consume in Spain has raised the 442% from 2000 to 2012, from 18,9 DHD to 102,6DHD(27). Atorvastatin and Simvastatin represents de 78% of the total statins consumption(27).

In Spain, satins were the most billed pharmacological group in 2009 (915,38 millions of euros, a 7,20% of the total amount) and, depending on the amount, atorvastatin was the most consumed active principle (633,09 millions of euros, almost 5% of the total amount). Other statins such as fluvastatine and simvastatin are among the thirty most consumed active principles accordingly to the amount (96,28 millions of euros and 92,03 millions of euros, respectively)(28).

In Catalonia ,the data are similar: statins were also the most billed drug in 2009(110.63 million euros,6.1% of the total)and, depending on the amount, atorvastatin was the principle active most consumed (73.2 million euros,4%of the total amount)(29).

The prevalence on statin treatment has increased as well in older persons over 75 years old. A Danish study observed that the share of statin users aged over 75 years old increased from 3,5% to 23,5% between 1996 and 2010 for the whole range of indications(23), yet the evidence of the beneficial effect of statins (in terms of mortality reduction) in older age is being questioned(20).

While statins may appear cost-effective, this must be put into the context of overall or net benefit to the patient. A cost-effectiveness analysis examined treatment consequences of statin use in adults aged 75 to 94 years. They didn't include stroke at their study but found out that eight million additional users would prevent 105,000 (4,3%) incident myocardial infarction and 68,000 (2,3%) cardiovascular heart disease deaths at an incremental cost per disability-adjusted life year of 25,200 dollars(30).The cost of the treatment for these people should also be recorded to calculate the cost benefit. In addition, even small increase in geriatric-specific adverse effects could offset the cardiovascular benefit. The goal is net benefit, not just efficacy.

Within a few years, the young elderly patients treated with statins will belong to the population over 80 years old, and a key question is whether they should continue the lipid-lowering treatment at the highest ages and whether treatment should be initiated among elderly. Statin therapy, especially in older age, is a major challenge; elderly

patients often have multiple comorbid conditions and a high number of concurrent medications that may increase their risk for side-effects and reduce the potential benefits of statin therapy.

New studies to address the use of lipid lowering therapy in the oldest old are needed to assist in appropriate prescribing, improving health outcomes, reducing cost and patient harm.

3.3 ADVERSE DRUG REACTIONS TO STATINS

Safety data from randomized clinical trials report overall good tolerance to statins with little serious adverse effects noted, anyway, the use of statins in clinical practice has been associated with higher rates of side effects and intolerance than in clinical trials, probably due to the patients are not monitored as closely as in clinical trials(31).

Myopathy

The term myopathy designates any non-inherited disorder of skeletal muscle that causes proximal muscle weakness, with difficulty in arising from a chair or raising arms above the head. Duration of statin therapy before the onset of myopathy varies from a few weeks to more than 2 years. Statin-associated myopathy represents a broad clinical spectrum of disorders, from mild muscle aches to severe pain and restriction in mobility, with grossly elevated creatinine kinase (CK) levels(31).

The development of myopathy is induced by a complex interaction between drug, disease, genetics, and concomitant therapy. Several risk factors that predispose patients to myopathy include increase age, female gender, renal or liver disease, diabetes mellitus, hypothyroidism, debilitated status, surgery, trauma, excessive alcohol intake, and heavy exercise. The mechanism by which statins cause myopathy is not completely understood. However, the clinical association appears to be dose dependent, and the risk is known to increase when statins are prescribed in combination with agents that are also myotoxic(31).

The most related complaints at clinical practice are these ones related to muscle. Cross-sectional studies in adults reported that 20% experienced musculoskeletal pain during

statin use. Estimates of the incidence of myopathy vary widely and are unlikely to be determined from since many had a statin tolerance run-in phase or excluded patients with previous reports of statin intolerance. In most statin trials, the rates of adverse events and discontinuations rates appear similar between middle-aged and older patients, (21,32) but a review about statin safety in the elderly found out that in some studies when comparing high dose atorvastatin 80mg daily with moderate dose simvastatin 20-40mg daily, more patients older than 65 years reported adverse events in the high dose atorvastatin group as compared to younger patients and withdrew from the studies(15).

A recent meta-analysis evaluating myopathy in older people found out myalgia as the most commonly reported adverse effect but in lower incidence than the observed on observational studies, ranging from about 5% to 15%. On the other hand, they found consistent results assessing the risk of rhabdomyolysis, which remains a very rare event in older people, and nothing suggested an increased risk of myopathy in the older adult receiving statin therapy(33), result that they justify because of the relatively sparse data and claim for larger reviews in the future to get more precise estimates.

Liver transaminase Elevations

The most common reported side effects from statins beside myopathy are elevation in hepatic transaminases(15). Elevated liver function values greater than 3 times the upper limit of normal have been related to older people taking high dose statins (atorvastatin) but this adverse effect subside when statins are discontinued. This association is not significant at low to moderate doses of statins. The majority of liver abnormalities occur within the first 3 months of therapy and require monitoring(31).

Incident Diabetes

In addition to muscle-related and liver side effects, treatment with statins has been associated with an increased risk for incident diabetes. This modest increase in risk is present for all statins and may relate to drug potency. In higher risk secondary prevention patients with established coronary artery disease, the diabetes risk associated with statin therapy is low in absolute terms when compared with the reduction in cardiovascular evens. However, in lower risk primary prevention patients where statin therapy is increasingly being utilized for vascular prevention there has been

controversy. The risk of developing diabetes on statin therapy appears limited to those with baseline evidence of impaired fasting glucose, metabolic syndrome, severe obesity or elevated HbA1c. (34).

Drug interactions with statins:

Statins are very selective inhibitors of HMG-CoA reductase and usually do not show any relevant affinity toward other enzymes or receptor systems. This suggests that at a pharmacodynamic level satins are not prone to interfere with other drugs; however, at a pharmacokinetic level it's different. Except for Pravastatin and Rosuvastatine, all other statins undergo extensive liver metabolism via the cytochrome P450 (CYP 450 system) which is known as an important cause of drug interactions. Competitive inhibition between drugs at the enzymatic level is common and may serve to alter the disposition of statins, leading to increased plasma levels and greater risk of adverse events, overall myopathy and rarely rhabdomyolysis(31).

In a survey done in America about Understanding Statin Use in America and Gaps in patient Education of over ten thousand current and former statin users, muscle related side effects were reported by 29% of survey participants and 84% of patients were taking at least one additional medication that had potential interaction with their statin(15).

Calcium channels antagonist can interact with statins. Many patients with hypercholesterolemia also have high blood pressure and may be receiving antihypertensive therapy with calcium antagonists, so the prescriptions of any of these drugs in combination have to be considered.

Furthermore, the ageing process is characterized by structural and functional changes affecting all organ systems and results reduced hemostatic capacity. Changes in body composition, hepatic and renal clearance lead to prolongation of plasma elimination half-life. Significant pharmacodynamics changes also occur, which, in general tend to increase sensitivity to drugs(35) . These characteristics in elderly can modify the therapeutic effects and increase the adverse reactions to the drugs.

For all these aspects current treatment guidelines recommend using caution in elderly patients, particularly older than 75 years, with careful assessment of concurrent medications and consideration of initiating statins at lower doses (11).

3.4 JUSTIFICATION:

Spain is among the countries with the highest life expectancy of the world(36), being nowadays situated on 85 years old for women and 80 years old in men, and with beliefs of reaching 88,7 and 84 years old respectively in 2029 according to INE(37). It means an increase of the very elderly people in our population, what has a major impact on healthcare systems. The incidence of cardiovascular disease in all its clinical forms, such as coronary, cerebrovascular and peripheral vascular disease rises sharply with age, as does the prevalence of the main cardiovascular risk factors including obesity, hypertension, dyslipidemia and type 2 diabetes mellitus. Anyway, there are only a few clinical trials that evolve elderly people despite being this group of age the one who have a major risk for cardiovascular diseases.

Available data shows that patients >75 years of age benefit from secondary prevention, but convincing data for routine use of statins in primary prevention in this age groups is lacking. So, the decision about statin treatment risk-benefits in primary prevention must be consensual between the physician and the patient. Even the tendency in those patients with hypercholesterolemia is continuing or starting the treatment with statins in order to reduce their cardiovascular risk, the relationship between total cholesterol and cardiovascular risk is less pronounced above 75 years old. Statins reduce the cardiovascular events, fatal or non-fatal, but even the older have a greater cardiovascular risk, this reduction is less marked. This difference between the younger and the elderly could be associated to the increment of the proportion of deaths of non-cardiovascular due to the increment of associated illnesses that increase with age, like cardiac insufficiency, MPOC or infections that aggravate basal pathologies.

On the other hand, older patients often have more comorbidity and potential for drug-drug interactions compared to younger patients, and these factors must be considered in any treatment decision(38). This can narrow the real benefit from statin therapy, especially as compared to those in the 35-75 years age range. Safety consideration such as musculoskeletal issues may have special relevance in the older patient. Musculoskeletal problems that are minor in a younger patient could limit ambulation and independence in an older patient with significant musculoskeletal problems.

The aim of this study is to give evidence to the clinical decision about whether the statin treatment really brings benefits or it's a superfluous therapy in people between 75 and 85 years.

Considering that we are living in the Mediterranean area, where we have a high prevalence of cardiovascular risk factors but a low incidence of myocardial infarction, a clinical trial must assess the efficacy in overall death and cardiovascular events reduction associated at statin therapy in our country, as well as the adverse events incidence in people over 75 years old.

The evidence we have comes from sub group-analysis and post-hoc data from different clinical trials performed in another countries, which have different epidemiological characteristics and which, moreover, any of them was especially designed to study the statin use in elderly people in primary prevention.

A randomized clinical trial evaluating the discontinuation of statins in people with limit life expectancy found out an improvement of quality of life when stopping statin medication, in possible relation to a reduction of the adverse effects. There were no differences on survival between patients who continued and discontinued statin therapy. The effect of statins on reducing plaque growth may be more important early on the disease course than in advanced stages(39). For patients with advanced illness, underlying organ failure (kidney, liver, and heart) potentially offsets the beneficial effects of statins even when reduction in low-density lipoproteins levels is achieved. This finding of a decreased survival benefit in sicker patients and a greater benefit in healthier patients has been demonstrated in many clinical trials, especially among those with heart failure (40) or those undergoing dialysis. Taking this in consideration, plus the fact that elderly people are usually more affected for different organ insufficiencies as cardiac or renal, due to the aging, the benefit from discontinuing or not starting statins treatment even having high cholesterol levels must be assessed.

In addition, as pointed before, statin drug consumption has sharply risen the last years in Spain. The medical interest of statins it's at the same title as antihypertensive and antidiabetic drugs and along with the increase of life expectancy it can have a big impact on public health and health costs.

4. QUESTION,OBJECTIVES AND HYPOTHESIS

Question: Are statins more effective than placebo in primary prevention to reduce the mortality and cardiovascular events in patients with hypercholesterolemia over 75 years old?

Hypothesis:

Primary hypothesis:

- The group of patients with hypercholesterolemia over 75 years old doesn't get benefit of the treatment with statins to reduce mortality and the cardiovascular events.

Secondary hypothesis:

- The adverse effects of the statins are higher between elderly people over 75 years old, reducing the benefit of this treatment in primary prevention.

Objectives:

Primary objective:

- To evaluate the effect of Simvastatin 20mg in primary prevention compared to placebo in order to reduce mortality and cardiovascular events in people between 75 and 85 years old living in Spain.

Secondary objective:

- To determine the incidence of adverse effects of Simvastatin 20mg therapy in the elderly between 75 and 85 years old.

5. METHODS

5.1 STUDY DESIGN:

A prospective, randomized, double blind, parallel-group trial that compares Simvastatin of 20mg versus placebo in primary prevention of cardiovascular events and mortality in the Catalan population with hypercholesterolemia over 75 and 85 years old.

5.2 STUDY POPULATION:

Inclusion criteria:

People between 75 and 85 years old, with total cholesterol over 250mg/dl demonstrated in two determinations, who don't have personal antecedents of ischemic heart disease, peripheral arterial disease, stroke or transient ischemic attack.

12 derivation electrocardiograms will be done to test the participants at rest to detect asymptomatic ischemic heart disease.

Exclusion criteria:

- Age over 85 years old or below 75 years old.
- Total Cholesterol $\leq$ 249mg/dl.

If they have:

- Previous cardiovascular disease like: IAM, Angina, stroke, Transient Ischemic attack or peripheral vascular disease.
- Poor cognitive function at baseline (Mini Mental Score Examination below 24). See annex 1
- Inability to give informed consent.
- Inability to tolerate oral medication or a history of significant malabsorption.

- Complex Chronic patients: defined as patients who suffer a big morbidity and high risk of decompensation of their chronic illnesses as well as several urgent hospitalizations.

- A life expectancy below one year.

- High dependency for daily activities: Modified Barthel index below 60 (Shah version)(41). See appendix 2.

- Subjects with cancer who are actively receiving chemotherapy and potential subjects considered at high risk of recurrence or the development of metastatic disease within the time frame of the conduct of the clinical trial.

- Subjects who are receiving routine intramuscular injections (IM) or for whom the IM therapy is anticipated during the course of the study. Elevations of creatinine kinase is known to occur with IM injection, hence the elimination of the use of IM injections with concomitant medications will minimize the diagnostic of CK elevations.

- Chronic Renal insufficiency and a creatinine clearance of < 30ml/min/1.732 by MDRD formula.

- Abnormal laboratory findings including:

    - Creatinine Kinase >3.0x upper limit of normal (ULN).

    - Alanine amino transferase (ALT) or aspartate amino transferase (AST)>2xULN.

    - Direct bilirubin >1.5xULN.

5.3 SAMPLE SIZE

Power calculator GRANMO, with the POISSON approximation was used. Accepting an alpha risk of 5% and a beta risk below 20%, with a 21,6% cardiovascular diseases incidence in two side test, 1624 subjects at the statins group and 1624 at the control group are necessary to recognize as statistically a relative risk greater or equal than 1.3 , with a reason between the samples equal 1 and an anticipated drop-out rate of 20%.

Considering a cardiovascular disease mortality rate of 31% according to the Spanish Statistical Office (INE) (1) and a cardiovascular incidence of 21,6% (9,6% of coronary heart disease, 8,9% of stroke plus a 3,1% of peripheral arterial disease) (2) ,the sample size will have adequate power to show significant reductions in the primary outcomes.

5.5VARIABLES

INDEPENDENT

The administration of **Simvastatin 20mg** once a day. We have chosen this statin because it has demonstrated efficacy in reducing cardiac mortality, there are results published about safety in 10 years and it's the cheapest statin on the market. The dose will allow reducing the 35% of the basal cholesterol levels (11). Considering the age of our population a low dose is recommended to reduce adverse events (15).

COVARIABLES

Demographic:

Age: Looking at the birth date from the identity card or passport, in years.

Sex: Sex on birth (male or female).

Race: White, Black, South-American Hispanic or Other.

Cardiovascular risk factors:

Anthropometric measurements: Subjects will be asked to stay in underwear.

- *Weight* : will be measured with a precision scale which will be weekly calibrated (in kilograms)
- *Height:* will be measured vertically in centimeters.
- *Body mass index* will be calculated with the previous measures following the formula: weight (kg) / height^2 (m^2).

- *Waist circumference* will be measured on the midway between the lowest rib and the iliac crest using a homologated soft tape measure (in cm). Patients will be classified by the presence of abdominal obesity or not, defined as a >88cm in women and > 102cm in men(42).

Tobacco consumption: Participants will be asked if they are current smokers or have given up smoking for less than 1 year. If they have a positive answer they will be classified as smokers. If they have smoked in the past and give it up more than one year ago will be considered as ex-smokers and if they have never smoked they will be registered as non-smokers.

Hypertension: Patients who have a systolic blood pressure≥140mmHg and/or diastolic blood pressure≥90mmHg (42).

Patients who are already diagnosed and taking antihypertensive drugs will also be classified as hypertensives.

Blood pressure will be measured by a nurse after 5 minutes of rest in a sitting position and under standardized conditions. The values will be calculated as the mean of 3 readings, separated by 2 minutes in each arm. The appropriate cuff size as well as an automatic and validated device will be used. The subject will be told before coming that should avoid any type of exercise at least one hour before the measurements. To avoid white coat hypertension, if the measures at the office are >140/90 we will proceed to 24-h ABP with a validated device, programmed to register BP at 20-min intervals for the 24-h and performed on working days. Patients will be instructed to maintain their usual activities, and to keep the arm extended and immobile at the time of each cuff inflation(43).

Diet: we will use a validated questionnaire about the adherence in Mediterranean diet(44) and will classify them as a Mediterranean diet followers (≥ 7 points) or not. See Annex 3.

Physical activity: We will use the validated Catalan or Spanish versions of the Brief Physical Activity assessment Tool (CBPAAT-EBPAAT), considering that our population are pensioners and it doesn't include the physical activity intensity at work(45). We will classify them using depending if they follow an adequate physical activity or if on the other hand their physical activity is insufficient and need for advice. See Annex 4.

Alcohol consumption: A questionnaire about alcohol consumption in the last 7 days will be included through a detailed questionnaire about alcohol types and volume to calculate the dairy intake and the total intake par week. We will categorize the participants in at risk or without risk depending if they consume more grams of alcohol par week than the recommended: over 280grams/week if he is a male or 170grams/week if she is a female. If in one day they overpass the 50g of alcohol they will also be considered at risk even they don't overpass the maximum recommended grams per week (46). See Annex 5.

Laboratory data: The blood sample will be taken after 12 hours fasting. The patients will be told that they should avoid exercising the day before the blood test in order to not altering the muscular enzymes:

- *Lipid profile*: Cholesterol and triglycerides concentration by enzymatic methods and HDL cholesterol after Apo B containing lipoprotein precipitation. LDL cholesterol will be determined by the Friedewald formula. All the results will be given in mg/dl.

- *Glucose* concentration (mg/dl) and *glycated hemoglobin* (%).

- *Phospocreatinine-kinasa* (CPK), in units per liter (u/L).

- *Transaminases*: AST (aspartate aminotranferase) and ALT (alanine aminotransferase) in international units/liter (IU/L)

- Creatinine (mg/dl) and urine albumin (mg) to calculate the *albumin/creatinine ratio (mg/mmol)*

Diabetes: all subjects with a base line examination glycaemia ≥126mg/dl will be considered diabetic as well as all the others previously diagnosed and taking hypoglucaemiant drugs .

Number of pills taken: Polymedication increases the risk of toxicity, medical interactions and adverse effects. The number of pills par day will be registered and subdivided in categories: below 3 pills, between 3 and 5 or more than 5 pills (if the patient is taking more than one pill from the same medication par day it will only be counted once).

DEPENDENT VARIABLES:

Primary Outcomes

The definitions for cardiovascular endpoint events for clinical trials from the Clinical Data Interchange Standard Consortium (CDISC)(47) and the American College of Cardiology and the American Heart Association ACC/AHA. are used(48):

1) MORTALITY

Mortality: defined as death occurring after initiating the treatment of the medical trial.

Mortality will be registered to calculate the overall mortality rate but, at the same time, the cause of death will be registered for further analysis. Every cause will be registered following these definitions criteria:

I. Cardiovascular cause of death.

- Acute myocardial infarction: refers to a death by any mechanism (arrhythmia, heart failure, low output) within30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)). The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Death resulting from a procedure to treat a myocardial infarction (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction will also be considered death due to acute MI.

- Sudden cardiac death: refers to a death that occurs unexpectedly, not following an acute myocardial infarction (MI), and includes the following deaths:

a) Death witnessed and occurring without new or worsening symptoms.

b) Death witnessed within 60 minutes of the onset of the new or worsening cardiac symptoms, unless the symptoms suggest acute MI.

c) Death witnessed and attributed to an identified arrhythmia (e.g. captured on an electrocardiographic (ECG) recording. witnessed on a monitor, or unwitnessed but found on implantable cardioverter- defibrillator review.

d) Death after unsuccessful resuscitation from cardiac arrest (e.g. implantable cardioverter defibrillator (ICD) unresponsive sudden cardiac death, pulseless electrical activity arrest).

e) Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology.

f) Unwitnessed death in a subject seen alive and clinically stable ≤ 24houres prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided if available).

- Death due to Heart Failure (HF): refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology (see HF definition below). Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valve disease.

- Death due to Stroke: refers to death after stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should

be verified to the extent possible by the diagnostic criteria outlined for stroke (see stroke definition).

- Death due to Cardiovascular Procedures: refers to death caused by the immediate complications of a cardiac procedure.
- Cardiovascular hemorrhage: refers to a death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.
- Other cardiovascular causes: cardiovascular death not included in the above categories but with a specific known cause, such as a pulmonary embolism or peripheral arterial disease.

II. **Non cardiovascular cause of death:** When a cardiovascular cause of death is excluded and it's on the following list:

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory (e.g., Systemic Inflammatory Response Syndrome (SIRS)/ Immune (Including autoimmune and anaphylaxis from environmental allergies).
- Hemorrhage that is neither cardiovascular bleeding nor a stroke.
- Non-CV procedure or surgery.
- Trauma
- Suicide
- Non-prescription drug reaction or overdose.

- Prescription drug reaction or overdose (may include anaphylaxis).
- Neurological (non-cardiovascular).
- Malignancy.

III. **Undetermined cause of death:** refers to a death not attributable to one of the above categories, of CV death or to a non-CV cause, or when the attribution of causality may be limited or impossible if information available at the time of death is minimal or nonexistent.

2) THE INCIDENCE OF CARDIOVASCULAR EVENTS

- **Myocardial infarction:** Refers to the evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

In general, the diagnosis of MI requires the combination of:

- Evidence of myocardia necrosis (either changes in cardiac biomarkers or post mortem pathological findings)
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging.

Criteria for Myocardial Infarction

a) Clinical Presentation: The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (eg., trauma, surgery, pacing, heart failure, hypertrophic cardiomyopathy…). Supporting information from myocardial imaging and coronary imaging should be considered to differentiate acute MI from the background disease process.

b) Biomarker Elevations: The upper reference limit for myocardial necrosis form the laboratory should be used. Troponins are preferred but CK-MB should be used if troponins are not available, and total CK may be used in the absence of CK-MB and troponin.

c) Electrocardiogram (ECG) Changes:

- ECG manifestations of acute myocardial ischemia [in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)]:

    - ST elevation:

        - New ST elevation at the J point in two continuous leads with the cut points: ≥ 0.1mV in all leads other than leads V2-V3 where the following cut-points apply: ≥0.2mV in men ≥40years (≥0.25 mV in men <40 years) or ≥0.15mV in women.

    - ST depression and T-wave changes:

        New horizontal or down sloping ST depression ≥ 0.05mV in two contiguous leads and/or new T inversion ≥ 0.1 mV two contiguous leads with prominent R wave or R/S ratio >1.

➢ **Hospitalization for unstable Angina:**

1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring at rest or in an accelerating pattern with episodes associated with progressively decreased exercise capacity.

   AND

2. Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms. Hospitalization is defined to an inpatient unit or a visit to an emergency department that results in at least 24 hours stay.

   AND

3. At least one of the following:

a) New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as LBBB or LVH):

- Transient ST elevation (duration < 20 minutes).

  New ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V2-V3 where the following cut-points apply:

  ≥0.2mV in men ≥ 40 years (≥0.25mV in men < 40 years) or

  ≥0.15 mV in women.

- ST depression and T-wave changes

  New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or new T inversion ≥0.3mV in two contiguous leads with prominent R wave or R/S ratio >1.

b) Definite evidence of inducible myocardial ischemia as demonstrated by:

- An early positive exercise stress test, defined as ST elevation or ≥mm ST depression prior to 5 mets.

  OR

- Stress echocardiography (reversible wall motion abnormality) **OR**

- Myocardial scintigraphy (reversible perfusion defect), **OR**

- MRI (myocardial perfusion deficit under pharmacological stress) and believed to be responsible for the myocardial ischemic symptoms/signs.

c) Angiographic evidence of new or worse ≥ 70% lesion (≥50% for left main lesion) and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.

d) Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s).

AND

4. Negative cardiac biomarkers and no evidence of acute MI.

- **Stable Angina:** Defined as clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arm. It is typically aggravated by exertion or emotional stress and relieved by nitroglycerin. We will use the validated Rose questionnaire (49) (see Annex 6). Only patients who obtain a *punctuation of definitive angina* or patients with *possible angina and confirmed diagnosis by a cardiologist* will be registered in this item.

- **Transient ischemic attack:** refers to an episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction.

- **Stroke:** refers to an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction**.**

  The kind of stroke will also be registered:

  - Ischemic stroke**:** Refers to acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke will be classified as ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke**.**

  - Hemorrhagic stroke**:** hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

  - Undetermined stroke: Acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization.

- **Need of a peripheral vascular intervention (PVI):** It refers to a catheter-based or open surgical procedure designed to improve arterial or venous blood flow or otherwise modify or revise vascular conduits. Procedures include: percutaneous transluminal balloon angioplasty, stent placement, thrombectomy, embolectomy, atherectomy, dissection repair, aneurysm exclusion, placement of various devices, intravascular thrombolysis or other pharmacotherapies and open surgical bypass revision.

Secondary Outcomes:

- **Myalgia:** Usually defined as a broad clinical spectrum of disorders, from mild muscle aches to severe pain and restriction in mobility, with grossly elevated creatinine kinase (CK) levels. As a subjective and complex nature of pain that complicates the assessment we will use a normalized ordinal evaluation of pain (see annex 7), which will be categorized in mild (0-3), medium (4-6) or severe (7-10) being zero the absence of pain and 10 a pain impossible to live with, followed by the associated analgesic consumption by number of pills per day (zero, ≤3, >3) in order to more accurately correlate the intensity.

- **Transaminitis (AST/ASLT):** Increased transaminases level coupled with non-specific hepatitis (yes or not).

- **Impaired fasting glucose**: defined as fasting glucose level greater than 100mg/dl but less than 126mg/dl (yes or not).

- **Incident diabetes:** New diagnosis of diabetes during the clinical trial (yes or not).

- **Worsening of the HbA1c** glucose levels on diagnosed diabetic patients, when during the trial HbA1c has increased ≥1 point (yes or not).

5.6 SAMPLE RECRUITMENT

The Catalan population from 75 to 85 years old is 459.677 (50). If we want to study a total of 3248 patients over 75 years old with hypercholesterolemia a multicenter study should be designed. The sample recruitment will be done by the AGICAP (Agencia de Gestio i Investigació Clínica en Atenció Primària), that is a net of more than three hundred certified trained researchers with experience on realizing clinical trials, which also includes an ethics committee for clinical research. The professional teams are distributed in groups through the different provinces of Catalonia.

The sample will be recruited through the computerized clinical history information at the SIDIAP database (Sistemes d'Informació per al desenvolupament de la investigació en Atenció Primària). Patients between 75 and 85 years old with hypercholesterolemia and without cardiovascular events, of the different primary health care centers of Catalonia, will be listed and proportioned to primary care physicians. They will be the responsible to contact and inform them about our clinical trial. If they are interested they will meet for the first appointment to evaluate if they can be included:

In this appointment the nurse will take a blood sample, take the anthropometric measures to calculate the IMC and pass the different questionnaires (MMSE, Barthel, CBPAAT and Mediterranean diet adhesion test). Alcohol consumption will also be questioned and calculated and a 12-lead electrocardiogram will be recorded to discard asymptomatic myocardial ischemia.

On the following visit the doctor will check the blood test parameters, the ECG, the questionnaires, the clinical history and the medication that the patient is taking at the moment.

All the patients that satisfy the eligibility criteria for entering to the study will be invited to participate to the clinical trial. Their physician will provide them the information about the clinical trial and give them the information sheet (see Annex 9) as well as the informed consent (see Annex 10).

At the following visit they must bring the informed consent signed to be scanned.

5.6 STUDY INTERVENTION

Block by gender randomization in the placebo or intervention group will be done by a computer generated random number list, prepared by an investigator with no clinical involvement in the trial.

The study medication will be issued in a double blind fashion. The pharmacy will prepare the medication, placebo or Simvastatin in identical capsules, according to the number list and will send it to every primary care center with the number written on the box.

Throughout the project, all subjects will receive nutritional advice and health counseling, and will be encouraged to follow the diet (see Annex 8) and recommendations, about increment exercising and avoid smoking, from the Catalan Clinical Practice Guide of Hypercholesterolemia and Coronary Risk.

Three months after randomization and the treatment is started, subjects will be called for an appointment to their primary center with their nurse and general practitioner. On that visit the compliance with study medication will be checked by pill counting and they will be counseled on healthy eating and details of any adverse events recorded as well as any primary outcome. Concomitant medication will be noted and the next pack of study medication dispensed. The nurse will take a new fasting venous blood sample drawn for lipid and lipoprotein profiling, biochemistry and hematology safety checks, as well as weight and the vital signs recorded.

This process will be repeated every 3months during the 3 years follow-up of the trial. A new 12-lead electrocardiogram will be done yearly if the patient remains asymptomatic.

Due to the advanced age, every year the inclusion and exclusion criteria will be revaluated.

5.7 DATA COLLECTION

The data will be collected through questionnaires, blood test, physical explorations and information taken from the clinical history (e-cap, shared clinical history and patient medical reports if he has been evaluated or treated on another hospital outside of the computerized net of the primary care center).

The follow-up of the patients will be done by usual visits of the patients to the professionals of its primary attention center. The primary and secondary outcomes will be asked and reported if they have occurred, after checking if they meet all the criteria. In case the patient explains an event while he has been abroad it must be proved by a report before including it to the clinical trial data center.

An online data base with personalized password entrance will be created to include all the records from the visits. By this way it will be computerized and the information easier to send the and work with it. The questionnaires will be added at the program and the physicians will only have to read the questions to the patients and fill in the gaps.

The main researcher will supervise all the data included into the online data center by the different teams working on the clinical trial once a month.

6. STATISTICAL ANALYSIS

In the univariate analysis, we will define variables as categorical or continuous: categorical variables will be described as percentages and proportions. Quantitative variables will be described as mean±Standard deviation or median (quartiles) for continuous variables depending on whether or not they are normally distributed. We will use them to describe the study population and to evaluate group homogenization.

A bivariate analysis will be performed to determine potential confounding factors. Proportions will be compared with the x^2test. The t test or Mann-Whitney and ANOVA/kruska-Wallis test will be used to compare 2 groups or ≥ groups respectively.

In the multivariate analysis for all primary and secondary end points will be the Cox proportional hazards model to investigate the relation between the magnitude of treatment effect and levels of baseline risk factors.

The Cox proportional hazards model for the primary outcomes (mortality and cardiovascular events) will be adjusted for the following major risk factors: age, sex, diabetes, blood pressure, smoker status, Mediterranean diet adhesion, physical activity, alcohol consumption and baseline low and high-density lipoprotein cholesterol levels (HDL, LDL).

For the secondary outcomes (adverse effects) it will be adjusted for age, sex, physical activity and the number of pills taken plus the following ones:

- To assess myalgia we will adjust the pain level (EVA scale) with the CPK levels and the number of analgesics taken.
- To evaluate hyperglycemia, worsening of the glycated hemoglobin and the new onset of diabetes we will adjust for the basal blood glucose and basal glycated hemoglobin.
- In the case of transaminitis we will adjust for basal levels of transaminases.

The outcome measurement for each variable will be the time to first occurrence of the event or study closure, whichever comes first. The primary analysis will be based on the intention-to-treat principle. The proportional hazards assumption will be checked for

each end point. In addition, the hazard ratio for the treatment effect will be estimated along with its 95% confidence interval.

The analysis of the data will be done by the R commander program.

7. LIMITATIONS

One big difficulty we can have is getting a good participation rate. Elderly people can have mobility problems to go to the physician center and it may have an impact on the participation rate or cause a discontinuation of the clinical trial. In addition, the advanced age of the participants, close to the life expectancy, can cause losses during the clinical trial for the natural death of the participants even though, as death is recorded as a main outcome, these losses will be recorded in the statistical analysis.

There are different variables that can increase the incidence of cardiovascular events and death. Although, by randomization this variables will be equally distributed in the two groups and we analyze them in multivariate analysis for adjust de results for the confusion factors.

It’s important to maintain the blindness for avoiding an observer bias during the data collection.

It is a clinical trial, so by definition the study has a higher cost. Especially for the population assessed. Elderly need a closer monitoring because they are more like to suffer drug adverse effects, so more blood tests are needed, which rises the cost. Even so it is the best design to answer our hypothesis.

8. ETHICAL ASPECTS

This clinical trial follows the declaration of Helsinki comprising the ethical principles for Medical Research involving Human Subjects.

The project will be evaluated by the Ethics Committee for Clinical Research from the Investigation and Research Institute in Primary Care Jordi Gol.
Participants will be informed about the project and tests that will be performed. An information sheet (see annex 9) will be given to bring home so they can talk about it with their family if they need. An informed consent must be signed before entering at the clinical trial.

The participants will have free access to all the data obtained from their blood tests, questionnaires and physical explorations.

The data collected from each patient will be treated and used anonymously, preserving the confidentiality of the patients, and the participants will be informed properly before signing the informed according to: "Articulo 5 de la Ley Organica 15/1999, de Regulación del Tratamiento Automatizado de los Datos de Carácter Personal", that they can be automatized and about the rights of the participants about consulting, modifying or deleting their personal data field.
The research project will be performed according to the Spanish laws related to clinical trials: "Ley de garantías y uso racional de los medicamentos y productos sanitarios del Real Decreto Legislativo 1/2015, de 24 de julio" .

All the investigators will have to declare no conflict of interest.

Statins are compared with placebo because there is no evidence of the effectiveness of any other treatment to reduce cholesterol levels in patients over 75 years old.

We have planned interim analysis in order to stop the trial if clinically relevant differences are detected between the two groups.

9. WORK PLAN AND CHRONOGRAM

9.1 TASKS AND RESEARCH TEAM.

Study coordinator/ Principal researcher (SC): He/She is the responsible for the correct operation of the study, the coordination and the supervision of the data registered at the online database by the personnel of the different primary care centers collaborators. He/she will also be the responsible of conveying the data to the statistical specialist and interpreting and analyzing the results.

Primary center physicians: They will be the responsible of the following of the participants every three months. At the first visit they must assess by checking the clinical history if they accomplish the inclusion criteria of the clinical trial and have to evaluate the results of the different questionnaires, ECG and blood test. At every visit they must ask for and check at the clinical history any primary or secondary outcome. They are also the responsible for entering the data into the online database program.

Nurses of the primary care center: They will be the responsible for taking the blood samples, blood pressure and the anthropometric measures of the protocol as well as doing the electrocardiograms and the tests from the first visit.

Statistical Specialist (SS): He will anonymously obtain the sample following the diagnoses entered in database, design the randomization program and interpret and analyze the results by R commander.

Pharmacy: It will provide the Simvastatin 20mg and placebo pills in the same format, specifically codified following the randomization number list, for every patient to the different primary care centers.

9.2 WORK PLAN AND CHRONOGRAM

The research team will be composed by: one study coordinator, primary care physicians and the primary care nurses members of the AGICAP, a pharmacy and one statistical specialist.

The duration of the clinical trial will be 3 years, and it will be organized according the following steps:

1) Protocol design (3 months). It will be done for the study coordinator (**SC**).
2) Initial meeting with all the AGICAP members (**AM**) that will participate in the clinical trial after the AGICAP accepts the protocol and its medical committee gives the approbation .We will explain the protocol and discuss it with all the members to make sure all the researchers and centers agree with the procedures (1 month).
3) Sample recruitment (3months)
4) A videoconference will be done after the sample is collected and before starting the clinical trial to solve all the questions and check that the protocol is understood.
5) Data collection and database elaboration as explained before by the nurses and physicians of the AGICAP **(AM)** (36 months).
6) Videoconferences with all the members will be done every 6 months to answer questions, detect and solve possible problems.
7) Statistical analysis and results interpretation (3 months).
8) A final meeting will be done to explain and discuss the results obtained with all the participant members.
9) Articles redaction and dissemination of the research findings (3 months). The results will be written and edited in order to be published and explained in conferences.

CHRONOGRAM SCHEME

Activities	Personnel	2015	2016				2017				2018				2019			
			1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Protocol design	SC	■																
Initial meeting	SC,AM		◊															
Sample recruitment	AM			■														
Video conference	SC,AM			●		●		●		●		●		●		●		
Data collection	AM			■	■	■	■	■	■	■	■	■	■	■	■	■		
Statistical analysis	SS																■	
Results interpretation	SS,SC																■	
Final meeting	SC,AM																◊	
Articles redaction	SC																	■
Dissemination	SC																	■

SC: Study Coordinator/Princiap researcher.

AM: Nurses and Physicians members of the AGICAP.

SS: Statistical Specialist.

10. FEASIBILITY

The " Institut d'Investigació en Atenció Primària Jordi Gol", IDIAP (www.idiapjgorl.org) is a public organization dedicated to the scientific research in Medicine and Primary care, as well as the formation of qualified researchers. It ensure accredited and motivated researchers from the AGICAP net, confidentiality, good and fast management of the contracts and payments as well as quality and speed in the recruitment.

All the professionals have experience on participating in clinical trials: family doctors, nurses, pediatricians, gynecologists, rheumatologists and pharmacies that work in more than 70 centers in Primary Care of Catalonia, organized in different territories.

They have recruited more than 3500 patients for 324 clinical trials of different of the most prevalent primary care chronic illnesses like cardiovascular diseases, infections or vaccines, mostly in phase III but also in some post authorization clinical trials as the one we are presenting.

The IDIAP will allow that our project be carried out for experienced professionals and have a faster recruitment of the sample than if we previously had to look for health professionals that wanted to collaborate with our clinical trial, train them and recruit the sample by other methods. It would only be possible to be done by close primary care centers of our territory so we would also need more time and it would not be able to be performed in three years and a half as it is planned now.

11. BUDGET

The principal researcher will realize all the tasks related with the coordination, writing and sending e-mails and letters to all the collaborators and patients explaining the project and thanking them. He will also carry out the data supervision, analysis and interpretation of the results obtained as well as writing articles.

The material used for doing the anthropometric measures, blood tests, ECG, measuring the blood pressure and the instruments and spaces needed for the interviews and usual physical exploration will be carried out for the different primary care centers.

Anyway, 3248 patients must be explored. Due to the economically impossibility to pay par hours of work, we will pay a fix price of 12 euros per patient assessed to the nurses and 15 euros per patient to the physicians. In addition we will give them an official paper certificating the collaboration in our clinical trial that can be used for upgrading their professional careers.

Only one meeting will be done physically, all the others will be done by videoconferences to avoid spending in diets and transport.

All the data will be send using secure internet connections to the data center and all the letters will be sent by e-mail to avoid post taxes and saving time.

	Description	**Total Cost**
STAFF		0 euros
SERVICES		
Nurses	12euros x3248 patients	38.976euros
Physicians	15 euros x 3248 patients	48.720euros
Statistic (1 person)	Statistical analysis and data management services.	1000 euros
Computer engineer	Randomization process and online database program performing,	3000euros
Insurance		32.480euros
	SUBTOTAL	**124.176 euros**
MATERIAL: Blood tests	36euros per blood test x 3 extra blood test	350.784 euros

	x 3248subjects=	
Simvastatina 20mg	1,58 euros (28pills) x 36months of treatment = 56,88euros	75.309 euros
Placebo pills	56,88 euros x 1324 patients = 0’03euros/pill 365pillsx3years=1095pills 1095pills x 1324patients x =	43.493.4 euros
Consumables		300euros
	SUBTOTAL	**469.886,4 euros**
TRAVEL AND ALLOWANCES		
Initial Meeting	Snack and drinks for the collaborators:	200 euros.
	SUBTOTAL	**200 euros**
	TOTAL	**594.262,4 euros**

12. CONFLICT OF INTEREST

The authors declare no conflict of interests.

13. IMPACT OF THE PROJECT

If the results are relevant and our hypotheses are validated people over 75 years could stop their statins treatment for hypercholesterolemia. It would have a big economic impact for our public health system, which have to handle the 100% of the treatment costs in the elderly, which means thousands of euros every year.

Primary prevention of the cardiovascular illnesses is a priority in public health politics around the world, whether they are developed countries or not, but there is a lack of evidence about the statins treatment in the elderly, so no matter which be the results of our clinical trial, all the countries can get benefit from the evidence derived and help the physicians around the world to choose the best treatment for their patients.

Elderly are usually unrepresented in clinical trials. Our study is specifically planned to enroll this kind of patients, considering their characteristics and main comorbidities.

The incidence of adverse effects will bring proof about the safety of statins specifically in this group of age and a will allow a better harm and benefit assessment.

14. BIBLIOGRAPHY

1. Datos Estadística de Defunciones por Causa de Muerte. Instituto Nacional Estadistica [Internet]. Madrid; 2015 [cited 2015 Nov 4]; Available from: http://www.ine.es/prensa/np896.pdf

2. Baena-Díez JM, Vidal-Solsona M, Byram AO, González-Casafont I, Ledesma-Ulloa G, Martí-Sans N. The Epidemiology of Cardiovascular Disease in Primary Care. The Zona Franca Cohort Study in Barcelona, Spain. Rev Española Cardiol [Internet]. 2010 Jan [cited 2015 Nov 1];63(11):1261–9. Available from: http://www.sciencedirect.com/science/article/pii/S1885585710702516

3. Marín A, Medrano MJ, González J, Pintado H, Compaired V, Bárcena M, et al. Risk of ischaemic heart disease and acute myocardial infarction in a Spanish population: observational prospective study in a primary-care setting. BMC Public Health [Internet]. 2006 Jan [cited 2015 Nov 2];6:38. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1402280/pdf/1471-2458-6-38.pdf

4. Ferrières J. The French paradox: lessons for other countries. Heart [Internet]. 2004 Jan [cited 2015 Nov 8];90(1):107–11. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1768013/?tool=pmcentrez

5. Estruch R, Ros E, Salas-Salvadó J, Covas M, Corella D, Arós F, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet [Internet]. The New England Journal of Medicine. 2013 [cited 2015 Nov 5]. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1200303

6. Grau M, Subirana I, Elosua R, Solanas P, Ramos R, Masiá R, et al. Trends in cardiovascular risk factor prevalence (1995-2000-2005) in northeastern Spain. Eur J Cardiovasc Prev Rehabil. 2007;14(5):653–9.

7. International comparisons page: Cholesterol. In: WHO Global Infobase [Internet]. 2015 [cited 2015 Nov 11]. Available from: https://apps.who.int/infobase/Comparisons.aspx

8. Gabriel R, Alonso M, Segura A, Tormo MJ, Artigao LM, Banegas JR, et al. Prevalencia, distribución y variabilidad geográfica de los principales factores de riesgo cardiovascular en España. Análisis agrupado de datos individuales de estudios epidemiológicos poblacionales: estudio ERICE. Rev Española Cardiol [Internet]. 2008 Oct 1 [cited 2015 Oct 13];61(10):1030–40. Available from: http://www.revespcardiol.org/es/prevalencia-distribucion-variabilidad-geografica-los/articulo/13126043/

9. Grau M, Elosua R, Cabrera de León A, Guembe MJ, Baena-Díez JM, Vega Alonso T, et al. Cardiovascular risk factors in Spain in the first decade of the 21st Century, a pooled analysis with individual data from 11 population-based studies: the DARIOS study. Rev española Cardiol [Internet]. 2011 Apr [cited 2015 Sep 16];64(4):295–304. Available from: http://www.sciencedirect.com/science/article/pii/S0300893211001515

10. Verschuren WM, Jacobs DR, Bloemberg BP, Kromhout D, Menotti A, Aravanis C, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. Jama [Internet]. 1995 [cited 2015 Nov 20];274(2):131–6. Available from: http://jama.jamanetwork.com.sci-hub.io/article.aspx?articleid=389185

11. Baena Díez, JM; Barcelo Colomer, E; Ciurana Misol, R; Franzi Sisó, A; García Cerdán, MR; Ríos Rodriguez, MA; Ramos Blanes, R; Solanas Saura, P; Vilaseca Canals J. Barcelona: Institut Català de la Salut, 2009. Guies de pràctica clínica i material docent, núm. 1. [Internet]. 2009 [cited 2015 Nov 8]. Available from: http://www.gencat.cat/ics/professionals/guies/docs/colesterol_risc_coronari.pdf

12. Ramos R, Solanas P, Cordón F, Rohlfs I, Elosua R, Sala J, et al. Comparación de la función de Framingham original y la calibrada del REGICOR en la predicción del riesgo coronario poblacional. Med Clin (Barc) [Internet]. 2003 Oct 25 [cited 2015 Nov 1];121(14):521–6. Available from: http://www.elsevier.es/es-revista-medicina-clinica-2-articulo-comparacion-funcion-framingham-original-calibrada-13053388

13. Baena-Díez JM, Grau M, Sánchez-Pérez R, Altes-Vaques E, Salas-Gaetjens LH, Hernández-Ibáñez MR. The REGICOR-Calibrated Function Provides a Better Classification of High-Risk Patients on Statin Treatment in the Spanish Population Than the Framingham or SCORE Classifications. Rev Española Cardiol [Internet]. 2009 Oct [cited 2015 Nov 1];62(10):1134–40. Available from: http://www.sciencedirect.com/science/article/pii/S1885585709733286

14. Comín E, Solanas P, Cabezas C, Subirana I, Ramos R, Gené-Badia J, et al. Estimating Cardiovascular Risk in Spain Using Different Algorithms. Rev Española Cardiol [Internet]. 2007 Jan 1 [cited 2015 Nov 5];60(7):693–702. Available from: http://www.revespcardiol.org/en/estimating-cardiovascular-risk-in-spain/articulo/13109912/

15. Phan BAP, Bittner V. Lipid-lowering therapy in patients 75 years and older: clinical priority or superfluous therapy? Prog Cardiovasc Dis [Internet]. 2014 Jan [cited 2015 Dec 13];57(2):187–96. Available from: http://www.sciencedirect.com/science/article/pii/S0033062014000401

16. Savarese G, Gotto AM, Paolillo S, D'Amore C, Losco T, Musella F, et al.

Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. J Am Coll Cardiol [Internet]. 2013 Dec 3 [cited 2015 Oct 29];62(22):2090–9. Available from: http://www.sciencedirect.com/science/article/pii/S0735109713038801

17. Pedro-Botet J, Climent E, Chillarón JJ, Toro R, Benaiges D, Flores-Le Roux JA. Statins for primary cardiovascular prevention in the elderly. J Geriatr Cardiol [Internet]. 2015 Jul [cited 2015 Nov 20];12(4):431–8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4554788/pdf/jgc-12-04-431.pdf

18. Proyección de la Población de España 2014–2064 [Internet]. Instituto Nacional Estadística. Madrid; 2015 [cited 2015 Nov 8]. Available from: http://www.ine.es/prensa/np870.pdf

19. Lobos Bejarano JM, Galve E, Royo-Bordonada MÁ, Alegría Ezquerra E, Armario P, Brotons Cuixart C, et al. Posicionamiento del Comité Español Interdisciplinario de Prevención Cardiovascular y la Sociedad Española de Cardiología en el tratamiento de las dislipemias. Divergencia entre las guías europea y estadounidense. Rev Española Cardiol [Internet]. 2014 Nov 1 [cited 2015 Nov 8];67(11):913–9. Available from: http://www.revespcardiol.org/es/posicionamiento-del-comite-espanol-interdisciplinario/articulo/90355271/

20. Petersen LK, Christensen K, Kragstrup J. Lipid-lowering treatment to the end? A review of observational studies and RCTs on cholesterol and mortality in 80+-year olds. Age Ageing [Internet]. 2010 Nov [cited 2015 Nov 23];39(6):674–80. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2956535/pdf/afq129.pdf

21. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet [Internet]. 2002 Nov [cited 2015 Sep 8];360(9346):1623–30. Available from: http://www.sciencedirect.com/science/article/pii/S014067360211600X

22. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RGJ, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ [Internet]. 2009 [cited 2015 Jan 3];338:b2376. Available from: http://www.bmj.com.sci-hub.io/content/bmj/338/bmj.b2376.full.pdf

23. Wallach Kildemoes H, Vass M, Hendriksen C, Andersen M. Statin utilization according to indication and age: A Danish cohort study on changing prescribing and purchasing behaviour. Health Policy (New York) [Internet]. New York; 2012 [cited 2015 Nov 12];108(2-3):216–27. Available from:

http://dx.doi.org/10.1016/j.healthpol.2012.08.008

24. Abbott RD, Garrison RJ, Wilson PW, Epstein FH, Castelli WP, Feinleib M, et al. Joint distribution of lipoprotein cholesterol classes. The Framingham study. Arteriosclerosis [Internet]. Jan [cited 2015 Dec 13];3(3):260–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6573877

25. Masiá R, Pena A, Marrugat J, Sala J, Vila J, Pavesi M, et al. High prevalence of cardiovascular risk factors in Gerona, Spain, a province with low myocardial infarction incidence. REGICOR Investigators. J Epidemiol Community Health [Internet]. 1998 Nov [cited 2015 Nov 4];52(11):707–15. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756647/pdf/v052p00707.pdf

26. Dégano IR, Elosua R, Marrugat J. Epidemiología del síndrome coronario agudo en España: estimación del número de casos y la tendencia de 2005 a 2049. Rev Española Cardiol [Internet]. r; 2013 Jun 1 [cited 2015 Jan 6];66(6):472–81. Available from: http://www.revespcardiol.org/es/epidemiologia-del-sindrome-coronario-agudo/articulo/90202772/

27. Agencia Española de Medicamentos y Productos Sanitarios. Informe de utilización de medicamentos U/HLP/V1/17012014: Utilización de medicamentos hipolipemiantes en España durante el periodo 2000-2012 [Internet]. 2014 [cited 2015 Nov 23]. Available from: http://www.aemps.gob.es/gl/medicamentosUsoHumano/observatorio/docs/hipolipemiantes-2000-2012.pdf

28. Subgrupos ATC y Principios activos de mayor consumo en el Sistema Nacional de Salud en 2009. Inf Ter del Sist Nac Salud [Internet]. Madrid; 2010 [cited 2015 Jan 9];34:89–92. Available from: http://www.msssi.gob.es/biblioPublic/publicaciones/recursos_propios/infMedic/docs/vol34n3SubgrATCppiosActivos.pdf

29. Troncoso Mariño A, Martin Cantera C. Novetats sobre estatines :Rosuvastatina i Pitavastatina. Butlletí d'Informació Ter [Internet]. 2011 [cited 2016 Jan 10];22(8):6. Available from: http://medicaments.gencat.cat/web/.content/minisite/medicaments/professionals/6_publicacions/butlletins/butlleti_informacio_terapeutica/documents/arxius/bit_v22x_n08.pdf

30. Odden MC, Pletcher MJ, Coxson PG, Thekkethala D, Guzman D, Heller D, et al. Cost-effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States. Ann Intern Med [Internet]. American College of Physicians; 2015 Apr 21 [cited 2015 Dec 13];162(8):533–41. Available from: http://annals.org.sci-hub.io/article.aspx?articleid=2275384

31. Bellosta S. Safety of Statins: Focus on Clinical Pharmacokinetics and Drug Interactions. Circulation [Internet]. 2004 [cited 2016 Jan 4];109(23_suppl_1):III – 50 – III – 57. Available from: http://circ.ahajournals.org/cgi/doi/10.1161/01.CIR.0000131519.15067.1f

32. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (JUPITER Trial). N Engl J Med [Internet]. 2008;359(21):2195–207. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25651245\nhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4341965\nhttp://www.nejm.org/doi/abs/10.1056/NEJMoa0807646

33. Iwere RB, Hewitt J. Myopathy in older people receiving statin therapy: a systematic review and meta-analysis. Br J Clin Pharmacol [Internet]. 2015 Oct [cited 2015 Aug 31];80(3):363–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26032930

34. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet (London, England) [Internet]. 2012 Aug 11 [cited 2015 Oct 26];380(9841):565–71. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3774022&tool=pmcentrez&rendertype=abstract

35. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol [Internet]. 2004 Jan [cited 2016 Jan 10];57(1):6–14. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1884408&tool=pmcentrez&rendertype=abstract

36. WHO | World Health Statistics 2014. World Health Organization; [cited 2016 Jan 13]; Available from: http://www.who.int/mediacentre/news/releases/2014/world-health-statistics-2014/en/

37. Esperanza de vida [Internet]. Instituto Nacional Estadistica. Madrid; 2015 [cited 2016 Jan 13]. Available from: http://www.ine.es/ss/Satellite?L=es_ES&c=INESeccion_C&cid=1259926380048&p=1254735110672&pagename=ProductosYServicios/PYSLayout

38. Strandberg TE, Kolehmainen L, Vuorio A. Evaluation and treatment of older patients with hypercholesterolemia: a clinical review. JAMA [Internet]. 2014 Sep 17 [cited 2015 Dec 13];312(11):1136–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25226479

39. Kutner JS, Blatchford PJ, Taylor DHJ, Ritchie CS, Bull JH, Fairclough DL, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. JAMA Intern Med [Internet]. 2015 [cited 2015 Dec 31];175(5):691–700. Available from: http://archinte.jamanetwork.com.sci-hub.io/article.aspx?articleid=2204034

40. Goudev A, Ph D, Grande P, Gullestad L. Rosuvastatin in Older Patients with Systolic Heart Failure. N Engl J Med [Internet]. 2007 [cited 2016 Jan 2];357:2248–61. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa0706201

41. Cid-Ruzafa J, Damián-Moreno J. Valoración de la discapacidad física: el indice de Barthel. Rev Esp Salud Publica [Internet]. MSSSI; [cited 2015 Nov 16];71(2):127–37. Available from: http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1135-57271997000200004&lng=es&nrm=iso&tlng=es

42. Coll de Tuero G, Dalfó i Baqué A de la FVWM, Gibert i Llorach E, Isnard Blanchar MM, Martínez Alonso V P, Vilaubi JM, Roca-Cusachs Coll A, Salleras Marcó N de la S. Hipertensió arterial [En línia] Barcelona: Institut Català de la Salut, 2012. Guies de pràctica clínica i material docent, núm. 6 [Internet]. 2012 [cited 2016 Jan 7]. Available from: http://www.gencat.cat/ics/professionals/guies/hipertensio/hipertensio.htm

43. Gorostidi M, Banegas JR, de la Sierra A, Vinyoles E, Segura J, Ruilope LM. Ambulatory blood pressure monitoring in daily clinical practice - The Spanish ABPM Registry experience. Eur J Clin Invest [Internet]. 2015 Nov 6 [cited 2015 Nov 12]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/26541761

44. Martínez-González MA, Fernández-Jarne E, Serrano-Martínez M, Wright M, Gomez-Gracia E. Development of a short dietary intake questionnaire for the quantitative estimation of adherence to a cardioprotective Mediterranean diet. Eur J Clin Nutr [Internet]. 2004 Nov 26 [cited 2015 Sep 25];58(11):1550–2. Available from: http://dx.doi.org/10.1038/sj.ejcn.1602004

45. Puig Ribera A, Peña Chimenis O, Romaguera Bosch M, Duran Bellido E, Heras Tebar A, Solà Gonfaus M, et al. How to identify physical inactivity in primary care: validation of the Catalan and Spanish versions of 2 short questionnaires. Aten Primaria [Internet]. Elsevier; 2012 Aug 1 [cited 2015 Nov 13];44(8):485–93. Available from: http://www.elsevier.es/es-revista-atencion-primaria-27-articulo-como-identificar-inactividad-fisica-atencion-90148950

46. Rebagliato Nadal O, Camallonga Claveria B. Alcohol. In: 3 clics: Atencion primaria basada en la evidencia [Internet]. 2014 [cited 2016 Jan 7]. Available from: http://www.ics.gencat.cat/3clics/main.php?page=GuiaPage&idGuia=62

47. Standardized Definitions for Cardiovascular and Stroke End point Events in Clinical TrialsDefinitions for CDISC [Internet]. 2014 [cited 2015 Nov 24]. Available from: http://www.cdisc.org/system/files/all/standard/Draft Definitions for CDISC August 20, 2014.pdf

48. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards. J Am Coll Cardiol [Internet]. Journal of the American College of Cardiology; 2015 Jul 28 [cited 2015 Nov 24];66(4):403–69. Available from: http://content.onlinejacc.org/article.aspx?articleid=2087908

49. Cosín J, Asín E, Marrugat J, Elosua R, Arós F, de los Reyes M, et al. Prevalence of angina pectoris in Spain. PANES Study group. Eur J Epidemiol [Internet]. 1999;15(4):323–30. Available from: C:\Users\Eugene\Documents\Academic\Library\Cosin, J. et al. (1999) Eur J Epidemiol 15, 323-30.pdf\nhttp://www.ncbi.nlm.nih.gov/pubmed/10414372

50. Idescat. Anuari estadístic de Catalunya. Població. Per sexe i grups d'edat [Internet]. 2015 [cited 2015 Dec 16]. Available from: http://www.idescat.cat/pub/?id=aec&n=253

ANNEX

ANNEX 1: MINI MENTAL STATE EXAMINATION

MINI MENTAL STATE EXAMINATION (MMSE)

Basat en Folstein et al. (1975), Llop et al. (1979)

Nom: Home [ ] Dona [ ]
Data: D. naixement: Edat:
Estudis/Professió: Núm. Història:
Observacions:

A quin any estem? 0-1 A quina estació? 0-1 A quin dia (data)? 0-1 A quin mes? 0-1 A quin dia de la setmana? 0-1	**ORIENTACIÓ TEMPORAL** (màx. 5)	
En quin hospital (o lloc) estem? 0-1 A quin pis (o planta, sala, servei)? 0-1 A quin poble (ciutat)? 0-1 A quina província som? 0-1 A quin país (o nació, autonomia)? 0-1	**ORIENTACIÓ ESPACIAL** (màx. 5)	
Anomeni tres paraules pesseta-cavall-poma (o pilota-bandera-arbre) a raó d'1 per segon. Després es demana al pacient que les repeteixi. Aquesta primera repetició atorga la puntuació. Atorgui 1 punt per cada paraula correcta, però continuï dient-les fins que el subjecte repeteixi les 3, fins un màxim de 6 vegades. Pesseta 0-1 Cavall 0-1 Poma 0-1 (Pilota 0-1 Bandera 0-1 Arbre 0-1)	Núm. de repeticions necessàries **FIXACIÓ RECORD** immediat (màx. 3)	
Si té 30 euros i me'n va donant de tres en tres, Quants li'n van quedant?. Detingui la prova després de 5 sostraccions. Si el subjecte no pot realitzar aquesta prova, demani-li que lletregi la paraula MÓN a l'inrevés. 30 0-1 27 0-1 24 0-1 21 0-1 18 0-1 (O 0-1 D 0-1 N 0-1 U 0-1 M 0-1)	**ATENCIÓ CÀLCUL** (màx. 5)	
Preguntar per les tres paraules esmentades anteriorment. Pesseta 0-1 Cavall 0-1 Poma 0-1 (Pilota 0-1 Bandera 0-1 Arbre 0-1)	**RECORD DIFERIT** (màx. 3)	
DENOMINACIÓ. Mostrar-li un llapis o un bolígraf i preguntar què és això?. Fer el mateix amb un rellotge de polsera, llapis 0-1, rellotge 0-1. **REPETICIÓ.** Demanar-li que repeteixi la frase: "ni sí, ni no, ni però " (o "en un trigal había cinco perros") 0-1. **ORDRES.** Demanar-li que segueixi l'ordre: "agafi un paper amb la mà dreta, doblegui'l per la meitat, i posi'l al terra". Agafa amb la mà dreta 0-1 doblega per la meitat 0-1 posa a terra 0-1. **LECTURA.** Escrigui legiblement en un paper "tanqui els ulls". Demani-li que ho llegeixi i faci el que diu la frase 0-1. **ESCRIPTURA.** Que escrigui una frase (amb subjecte i predicat) 0-1. **CÒPIA.** Dibuixi 2 pentàgons intersectats i demani al subjecte que els copiï tal qual. Per atorgar un punt han de ser presents els 10 angles i la intersecció 0-1.	**LLENGUATGE** (màx. 9)	
Puntuacions de referència: 27 o més: normal 24 o menys: sospita patològica 12-24: deteriorament 9-12: demència	**PUNTUACIÓ TOTAL** (màx. 30 punts)	

a.e.g.(1999)

ANNEX2: MODIFIED BARTHEL, VERSION OF SHAH ET AL.(41)

	INCAPAÇ DE FER-HO	INTENTA PERÒ INSEGUR	NECESSITA CERTA AJUDA	MÍNIMA AJUDA NECESSÀRIA	TOTALMENT INDEPENDENT
HIGIENE PERSONAL	0	1	3	4	5
BANYAR-SE	0	1	3	4	5
MENJAR	0	2	5	8	10
UTILITZAR WC	0	2	5	8	10
PUJAR ESCALES	0	2	5	8	10
VESTIR-SE	0	2	5	8	10
CONTROL DE FEMTA	0	2	5	8	10
CONTROL D'ORINA	0	2	5	8	10
DESPLAÇAR-SE	0	3	8	12	15
CADIRA DE RODES	0	1	3	4	5
TRASLLAT CADIRA/LLIT	0	3	8	12	15

RESULTATS:

0-20 Dependència total

21-60: Dependència severa

61-90: Dependència Moderada

91-99: Dependència escassa.

100: Independència.

ANNEX 3: MEDITERRANIAN DIET ADHESION QUESTIONNAIRE (44)

	SÍ
1. Oli d'oliva (≥1 cullerada al dia)	+1
2. Fruita (≥1 vegada al dia)	+1
3. Verdura o amanida (≥ 1 vegada al dia)	+1
4. Fruita (≥ 1 vegada al dia) i verdura (≥ 1 vegada al dia)[a]	+1
5. Llegumts (≥2 vegades a la semana)	+1
6. Peix (≥ 3 vegades a la semana)	+1
7. Vi (≥ 1 vegada al dia)	+1
8. Carn (<1 vegada al dia)	
9. Pa blan (< 1vegada al dia) i arròs (< 1 vegada al dia) o pa integral (> 5 a la setmana)[b].	

a: S'hi afegeix un punt si es consumeix almenys una ració al dia de fruita i verdura.

b: S'hi afegeix un punt si el consum de pa blanc i/o arròs és baix o si el consum de pa integral és alt.

Si s'obté un **resultat igual a 7 punts o més** indica l'adhesió a una dieta mediterrània i cardiosaludable (11).

ANNEX 4: CATALAN BRIEF PHYSICAL ACTIVITY ASSESSMENT TOOL(45)

Questionari d'activitat física breu per les consultes d'atenció primària:

A) Quantes vegades per setmana realitza vostè 20 MINUTS d'activitat física INTENSA que el faci respirar ràpid i amb dificultat? (per exemple, footing, aixecar pesos, excavar, bicicleta rápida, o caminar a un ritme que li impedeixi parlar amb normalitat).

- 3 o més vegades per semana
- 1-2 vegades per semana
- Mai

Puntuació:

- 4
- 2
- 0

B) Quantes vegades per semana realitza vostè 30MINUTS d'activitat física MODERADA o passeja de forma que augmenti la seva freqüència cardíaca o respiri amb major intensitat de lo normal? (per exemple, tasques domèstiques, carregar pesos lleugers, anar amb bicicleta a una marxa regular, jugar amb nens, a petanca o un partit de dobles de tenis).

- 5 o més vegades per semana.
- 3-4 vegades per semana
- 1-2 vegades per semana
- Mai

Puntuació:

- 4
- 2
- 1
- 0

Puntuació total A + B: _____

Puntuació ≥ 4= Suficientment actiu (animi al pacient a CONTINUAR la seva activitat)

Puntuació 0-3= Insuficientment actiu (animi al pacient a AUGMENTAR la seva activitat).

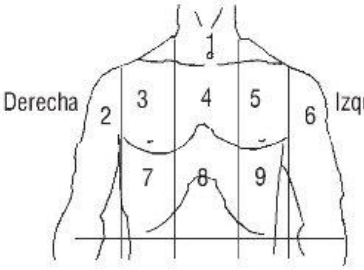
ANNEX 5: ALCOHOL CONSUMPTION TABLE

TIPUS DE BEGUDA	QUANTITAT	UNITATS	GRAMS D'ALCOHOL
Vi, cava (12º)	1 got	1	10 g
	1 ampolla	7,5	75 g
Cervesa, sidra (5º)	1 canya	1	10 g
	1 litre	5	50 g
Licors, whisky, rom, conyac (40º)	1 copa (50 cc)	2	20 g
	1 combinat	2	20 g
	1cigaló (25 cc)	1	10 g
	1 litre	40	400 g
Generosos (20º)	1 copa (50 cc)	1	10 g
(xerès, vermut)	1 vermut (100 cc)	2	20 g
	1 litre	20	200 g

ANNEX 6. ROSE QUESTIONNAIRE FOR STABLE ANGINA

1. ¿A veces tiene algún dolor o molestia en el pecho? Sí/No

2. ¿En qué lugar localiza este dolor o molestia?



– Esternón: – superior (1); – medio (4); – inferior (8)
– Tórax anterior izquierdo (5)
– El brazo izquierdo (6)
– Resto

3. ¿Lo siente también en algún otro sitio? Sí/No

4. Cuando camina a paso normal en llano, ¿esto le produce molestias? Sí/No

5. Cuando camina cuesta arriba o a paso rápido, ¿esto le produce molestias? Sí/No

6. Cuando caminando tiene algún dolor o molestia en su pecho, ¿qué hace?

– Para
– Disminuye la marcha
– Continúa al mismo paso

7. ¿Desaparece el dolor o la molestia en el pecho si se queda quieto? Sí/No

8. ¿En cuánto tiempo desaparece?

– 10 minutos o menos
– Más de 10 minutos

9. ¿Ha visto a un médico a causa de este dolor? Sí/No

10. En caso afirmativo, ¿qué dijo que era?

Clasificaciones del dolor torácico

– Ausencia de dolor torácico: p1) no
– Dolor torácico no de ejercicio: p1) sí; p3) y p4) no
– Angina de pecho definitiva: p1) sí; p3) o p4) sí; p2) sitios 4, 5 u 8; p5) para o disminuye la marcha; p6) sí; p7) 10 minutos o menos
  – Angina de pecho grado I: p1) sí; p3) no; p4) sí
  – Angina de pecho grado II: p1) sí; p3) sí; p4) sí
– Angina de pecho posible: p1) sí; p3) o p4) sí; no respuesta o no se cumple al menos uno de los cuatro criterios adicionales

ANNEX 7: EVA SCALE

ANNEX 8: DIETETIC RECOMMENDATIONS FOR HYPERCHOLESTEROLEMIA (11)

	Aliments recomanables (tots els dies)	**Aliments que cal consumir amb moderació (2-3 dies/setmana)**	**Aliments no recomanables (excepcionalment)**
Cereals[2] (preferentment integrals)	Farines, blat, pa, cereals d'esmorzar, arròs, pasta, galetes (preferentment integrals).	Pastes italianes amb ou, rebosteria[2] i galetes[2] preparades amb oli d'oliva o de llavor.	Croissants, ensaïmades, productes de pastisseria en general.
Productes lactis	Llet i iogurts descremats, formatge blanc descremat.	Llet i iogurts semidescremats, formatges amb baix contingut de greix, formatge fresc tipus mató o de burgos.	Llet entera, llet condensada, crema, nata, iogurt normal, formatges molt grassos, flams d'ou.
Sopes	Sopes casolanes de verdures, consomés		Sopes elaborades amb nata líquida, sopes comercials
Peix	Peix blanc i blau[2] (a la planxa, bullit o fumat), evitant menjar-ne la pell.	Peixos fregits en oli adequat, bacallà salat, tonyina i sardines en llauna[2]	Peixos fregit en oli o greixos desconeguts o no recomanables, ous de peix, caviar i substituts
Marisc	Ostres, escopinyes, petxines de pelegrí, cloïsses.	Musclos, sípia, pop, calamars, gambes, escamarlans, llagosta, llagostins.	
Carns[1]	Pollastre i gall d'indi (sense pell), conill	Vedella, vaca, bou, cavall, porc (només parts magres), pernil del país (sense el greix visible), salsitxes de vedella o pollastre, xai, fetge (2 vegades/mes) carn de caça, cabrit	Ànec, oca, embotit en general, salami, foie gras, pastís de carn, pell de les aus, bacó, hamburgueses, frankfurts, vísceres, salsitxes de porc
Ous	Clares i succedanis d'ou sense colesterol	Tres ous sencers a la setmana (màxim)	
Aliments greixosos[2]	Oli d'oliva verge, olis poliinsaturats (gira-sol, blat de moro, nous, safrà bord), olis monoinsaturats (oli d'oliva refinat)	Margarines toves (no hidrogenades)	Mantega, llard, cansalada, salsa de carn, oli de palma, oli de coco, margarines dures (hidrogenades)

[1]Totes les carns han de consumir-se retirant-ne el greix visible abans de cuinar-les, i menjar-ne no més de 150 grams cada vegada. Pot ser suficient consumir-ne 2-3 vegades a la setmana i poden ser substituïdes per altres aliments com el peix o els llegums.

	Aliments recomanables (tots els dies)	Aliments que cal consumir amb moderació (2-3 dies/setmana)	Aliments no recomanables (excepcionalment)
Fruites, verdures, tubercles i llegums	Totes. Tot tipus de verdures fresques o congelades i llegums, patata bullida, tota fruita fresca i en conserva (sense sucre)	Patates fregides[2] en oli adequat, olives[2], alvocats[2]	Patates, verdures o arròs fregit en olis desconeguts o no recomanables, patates de xurreria
Postres	Sorbets i púdings amb llet descremada, gelatines, merenga, macedònia de fruita natural, melmelada[2], mel[2], sucre[2], gelats d'aigua	Flam sense ou, fruites en almívar[2]	Gelats, púdings i postres amb llet sencera, ou o nata. Pastisseria comercial en general.
Pastisseria[2.] fleca	Productes elaborats amb llet descremada	Pastissos preparats amb oli o margarines insaturades	Galetes, productes de fleca comercial, coques farcides comercials.
Dolç	Edulcorants, sucre[2], dolços d'ametlles i mel[2], ametlles garrapinyades[2]	Massapà[2], caramels[2]	Xocolata, caramels de cafè amb llet, dolços de coco.
Fruita seca[2]	Prunes, panses, figues, dàtils, ametlles, avellanes, castanyes, nous, pinyons, pipes de gira-sol sense sal, cacauets naturals, festucs anacards		Coco, pipes de gira-sol salades.
Begudes	Aigua, cafè, te, infusions, sucs naturals	Orxata de xufla[2], begudes o refrescos ensucrats[2]	Begudes amb xocolata, cafè irlandès
Espècies i salses per condimentar	Herbes aromàtiques, pebre, mostassa en gra, sal amb moderació, sofregits[2], vinagre i all i oli[2]	Condiments d'amanida pobres en greix, beixamel, maonesa	Condiments d'amanida rics en greixos saturats (fets amb mantega, margarina, llet sencera o greixos animals)

[2]Aliments a limitar degut al seu valor calòric en cas d'hipertrigliceridèmia o sobrepès.

*Observacions :

Salses: evitar les salses fetes amb greixos saturats (mantega, llet entera o llard). Utilitzar les salses preparades amb brou vegetal, llet descremada o oli cru.

Formes de cocció: fer servir poc oli (oliva, gira-sol o blat de moro), restringint-lo especialment en el pacient amb excés de pes. En qualsevol cas s'evitarà que l'oli fumegi i l'ús dels olis fregits. Es recomanen les preparacions a la planxa, al forn, al vapor, els bullits, a la graella.

El consum de begudes alcohòliques s'ha de moderar.

Aquesta dieta caldrà modificar-la en cas de diabetis, obesitat, hiperuricèmia o hipertensió arterial.

ANNEX9: PATIENT INFORMATION SHEET

FULLA D'INFORMACIÓ PEL PACIENT

TÍTOL DE L'ASSAIG CLÍNIC**:** Eficàcia de la Simvastatina per prevenció primària en Ancians Majors de 75 anys: Assaig clínic prospectiu, multicèntric, aleatoritzat, amb doble cec i grups paral·lels.

INTRODUCCIÓ:

Ens dirigim a vostè per informar-lo sobre un estudi d'investigació en el que se'l convida a participar. L'estudi ha set aprovat pel Comitè Ètic d'investigació de l'IDIAP Jordi Gol i per l'Agència Espanyola del Medicament i Productes Sanitaris (AEMPS), d'acord amb la legislació vigent, el Reial Decret 223/2004, de 6 de febrer, pel qual es regulen els assajos clínics amb medicaments.

La nostra intenció és tan sols que vostè rebi la informació correcta i suficient per que pugui avaluar i jutjar si vol participar o no en aquest estudi. Per això llegeixi aquesta fulla informativa amb atenció i nosaltres li aclarirem els dubtes que li puguin sorgir després de l'explicació. A més, pot consultar amb les persones que consideri oportú.

PARTICIPACIÓ VOLUNTÀRIA

Ha de saber que la seva participació en aquest estudi és voluntària i que pot decidir no participar o canviar la seva decisió i retirar el consentiment en qualsevol moment, sense que això alteri la relació amb el seu metge ni es produeixi perjudici algun en el seu tractament.

DESCRIPCIÓ DE L'ESTUDI:

L'excés de colesterol en la sang afavoreix la formació de dipòsits de greix en les parets de les artèries. Aquests dipòsits dificulten el pas de la sang i són motiu de malalties del cor i de la circulació. Aquest tipus de malalties són la primera causa de mort a Espanya en persones de més de 79 anys però, al mateix temps, la incidència d'aquestes malalties en el nostre país és de les més baixes del món.

Quan els nivells de colesterol no es poden tractar només amb la realització d'una dieta baixa en greixos i l'augment de l'exercici físic cal fer tractament amb fàrmacs. Aquests fàrmacs són típicament estatines.

Les estatines són medicaments que fa anys que estan comercialitzats i que han demostrat reduir la mortalitat, així com les malalties del cor i circulatòries de la població tant en persones sanes com en aquelles que ja han patit aquest tipus de malalties prèviament. Actualment, però, no es disposa de prou informació sobre el seu benefici en persones per sobre dels 75 anys d'edat .

L'objectiu del nostre estudi és determinar l'eficàcia del tractament amb Simvastatina 20mg (un tipus d'estatina) per reduir la mortalitat i els esdeveniments cardiovascular en persones de més de 75 anys amb hipercolesterolèmia.

Els resultats que s'obtinguin permetran que en un futur es disposi de la informació necessària sobre si els pacients que tenen nivells alts de colesterol a l'arribar a l'edat esmentada cal que

continuïn o iniciïn de nou aquest tractament o si, per altra banda, aquest no aporta cap benefici i amb el control de la dieta i realitzant exercici físic de forma habitual és suficient.

PROCEDIMENTS DE L'ASSAIG CLINIC

Els pacients rebran de forma aleatoritzada tractament amb Simvastatina 20mg o placebo una vegada al dia. Al ser un procés aleatoritzat tots els pacients tindran les mateixes possibilitats de rebre Simvastatina o placebo.

En la primera visita se li farà una entrevista sobre antecedents de malalties així com diverses preguntes de qüestionaris breus, una exploració física, un electrocardiograma i un anàlisi de sang.

La durada de l'estudi és de 3 anys. Durant aquest temps caldrà que faci controls amb el seu metge i infermera d'atenció primària cada 3 mesos, on se li repetiran els anàlisisde sang i algunes de les preguntes per valorar la presencia de malalties del cor, circulatòries i de possibles efectes adversos.

BENEFICIS I RISCS DERIVATS DE LA SEVA PARTICIPACIÓ EN L'ESTUDI.

En general són fàrmacs molt ben tolerats i amb pocs efectes adversos. Alguns d'aquests poden ser l'aparició de constipació, flatulència, lleus dolors musculars, lleu elevació dels enzims hepàtics i possible augment dels nivells de glucosa en sang. Per aquest motiu es fa un seguiment estret a tots els participants.

Les persones que es detecti que puguin tenir algun risc amb el tractament seran excloses de l'estudi.

SEGURO

Segons lo establert en el Reial Decret 223/2004, sobre Assaigs Clínics amb Medicaments el promotor de l'assaig clínic ha contractat una pòlissa de responsabilitat civil amb la companyia MARSH que cobreix els possibles danys i perjudicis que li pugui ocasionar la seva participació en l'assaig clínic.

COMPENSACIÓ ECONÒMICA

La seva participació en l'estudi no suposarà cap gasto. Vostè no haurà de pagar el tractament ni rebrà una compensació econòmica.

CONFIDENCIALITAT

El tractament, la comunicació i la cessió de les dades de caràcter personal de tots els subjectes participants s'ajustarà a lo disposat a la " Ley Orgánica 15/1999, de 13 de diciembre de protección de datos de caràcter personal". D'acord amb el que estableix la llei mencionada, vostè o el seu fill podran exercir els drets d'accés, modificació, oposició i cancel·lació de dades, pel que hauran de dirigir-se a seu metge de l'estudi. Les dades recollides per l'estudi estaran identificades mitjançant un codi i només el seu metge de l'estudi podrà relacionar aquests dades amb la seva història clínica.

Només es transmetran a tercers i a altres països les dades de recollides per l'estudi que en cap cas continguin informació que el pugui identificar directament, com nom, cognoms, direcció, número de la seguretat social etc. En el cas de que es produeixi aquesta cessió, serà pels mateixos fins de l'estudi descrit i garantint la confidencialitat com a mínim amb el nivell de protecció de la legislació vigent en el nostre país. L'accés a la seva informació personal quedarà restringida als metges i col·laboradors de l'estudi, autoritats sanitàries (Agència espanyola del Medicament i Productes Sanitaris), al Comitè Ètic d'Investigació Clínica i personal autoritzat pel promotor, quan es precisi per comprovar les dades i procediments de l'estudi, però sempre mantenint la confidencialitat dels mateixos d'acord a la legislació vigent.

Si vostè decideix retirar el consentiment per participar en aquest estudi, cap nova dada serà afegida a la base de dades i podrà exigir la destrucció de totes les mostres identificables prèviament retingudes per evitar la realització de nous anàlisis.

Per portar a terme el projecte que hem exposat i atenent a les disposicions legals vigents li sol·licitem la seva autorització. Abans i després de firmar aquest document, del qual es quedarà vostè una copia, pot preguntar tot el que cregui convenient als metges o personal sanitari responsable de l'estudi.

ANNEX 10: INFORMED CONSENT.

CONSENTIMENT INFORMAT

Jo (nom i cogonoms) ……..
amb DNI…….

He llegit i entès la fulla d'informació que se m'ha entregat.

He pogut fer preguntes sobre l'estudi.

He rebut información sobre l'estudi.

He parlat amb:

……(nom del metge/investigador)

Comprenc que la participación és voluntària.

Comprenc que puc retirar-me de l'estudi:

- ✓ Quan vulgui
- ✓ Sense haver de donar explicacions.
- ✓ Sense que això repercuteixi en els cuidats mèdics.

Dóno la meva conformitat per participar en aquest estudi i dono el meu consentiment per l'accés i utilització de les dades en les condicions detalladles en la fulla d'informació.

Firma del participant:	Firma de l'investigador:
Nom i Cognoms:	Nom i Cognoms:
Data:	Data: