Early Detection of Atherosclerosis: a Randomized Clinical Trial to assess a novel strategy in the Primary Prevention of Cardiovascular Diseases. Rationale and Design.

Authors: Blai Coll¹, Montse Martínez-Alonso², Àngels Betriu¹, Xavier Garcia¹, Maria Garcia¹, Josep MªGutiérrez¹, Antoni Plana³, Placido Santafé³, Miguel Camafort¹, Mercé Borras¹, Elvira Fernández¹.

From ¹ Unitat de Diagnòstic I Tractament de Malalties Aterotrombòtiques (UDETMA), Nephrology Department, ² Institut de Recerca Biomèdica de Lleida at Hospital Universitari Arnau de Vilanova and ³Centre d’Atenció Primària Balàfia-Pardinyes, Lleida. SPAIN.

Montse Martinez: mmartinez@arnau.scs.es; Àngels Betriu: abetriu@sistemes-renals.com; Xavier Garcia: xpujol2@hotmail.com; Maria Garcia: mariagarciam81@hotmail.com; Josep MªGutiérrez: jgutierrez@arnau.scs.es; Antoni Plana: antoniplana@camfic.org; Plácido Santafé: psantafe@comll.cat; Miguel Camafort: Miguel.camafort@gmail.com; Mercé Borras: mborras@arnau.scs.es; Elvira Fernández: efernandez@arnau.scs.es

* Corresponding Author:
Blai Coll, MD, PhD.
Director of UDETMA.
Department of Nephrology. Hospital Arnau de Vilanova.
Avda. Rovira Roure 80. 25198. Lleida. SPAIN
Telephone: +34 973 248100 Fax:+34 973 224902
bcoll@arnau.scs.es

¶ Both authors contributed equally to this manuscript.
Abstract

**Background:** primary prevention in cardiovascular diseases is based on risk scoring. However, the use of validated, non-invasive tests [carotid ultrasound (CUS) and ankle-brachial index (ABI)] aimed at early atherosclerosis detection are not applied in clinical practice.

**Aim:** to demonstrate the efficacy of a novel prevention strategy in the primary prevention of cardiovascular diseases (based on carotid Intima-Media Thickness (cIMT), plaque detection and ABI) compared to the standard clinical care.

**Design:** randomized, open-label, multi center, 2-groups of participants assigned to receive either standard clinical care (N=1474, control) or the group of participants who will be treated according to the results of CUS and ABI (N=1474, intensification). Patients will be recruited (enrollment June 2008-June 2009) from the Primary Care setting.

**Methods:** the end-point is the difference in cIMT along the 2 years of duration of the study. cIMT will be a composite variable of the mean values at the far wall of common carotid, bulb and internal carotid. Standard operational procedures will be used for the measurement of CUS and ABI, resulting in the atherosclerotic disease score (ranging from 0: no atherosclerosis, to 3: severe atherosclerosis). Therapeutic targets (lipids, blood pressure and antiplatelet drugs) will be set accordingly. Univariate and multivariate tests will be applied.

**Discussion:** scientific societies recommend that individuals at intermediate cardiovascular risk should be screened more individually, including non-invasive tests (mainly cIMT, ABI or coronary calcium score). This trial will assess the feasibility of this technical implementation and also it will analyze the effects on cIMT of a prevention strategy based on disease identification rather than risk scoring.

**Trial registration:** clinicaltrials.gov Identifier: NCT00734123.
BACKGROUND

Cardiovascular diseases are the leading cause of death in industrialized countries and primary prevention is a cornerstone in health policies. Risk scoring (Framingham, Score) is the accepted and recommended tool to assess cardiovascular risk, but the appearance of non-invasive techniques (ultrasound, Doppler or computed tomography) aimed at early atherosclerosis detection, has raised a great debate in cardiovascular prevention. The American Heart Association recommends the utilization of these techniques in individuals at intermediate cardiovascular risk and the last European Guidelines for the Management of Arterial Hypertension recommend ultrasound scanning of carotid arteries and ankle-brachial index (ABI) whenever detection of vascular hypertrophy or asymptomatic atherosclerosis is deemed useful. They also conclude that it might be more widely recommended if its availability were greater.

However, these last recommendations have not been universally accepted, and prospective studies testing the implementation of these techniques in the primary prevention strategy are warranted.

Among the non-invasive tests advocated, the measurement of ABI and carotid ultrasound are simple, inexpensive and available methods for a reliable assessment of peripheral arterial disease or carotid atherosclerosis, respectively. Follow-up studies have shown that either an abnormal ABI or an increased carotid Intima-Media Thickness (cIMT)/presence of a carotid plaque provide incremental coronary and all-cardiovascular disease risk assessment information over and above that provided by traditional risk factors. In the Rotterdam study, the authors combined several non-invasive techniques (carotid ultrasound, ABI and abdominal X-ray for aortic aneurysm detection) with the aim to analyze the predictive value of this so-called atherosclerosis score for incident myocardial infarction. The predictive value of each of the individual measures of atherosclerosis was independent of a wide variety of traditional cardiovascular risk factors and of medication use. The aim of the present study is to test the
utility of implementing the measurement of ABI and the performance of carotid ultrasound in the primary prevention of cardiovascular diseases.

**DESIGN**

Randomized, open-label clinical trial of two years follow-up in which the performance of non-invasive tests for atherosclerosis detection will be applied. Participants will be randomized to either standard clinical care (control) or the group of participants who will be treated according to the results of CUS and ABI (intensification). This is a multicenter clinical trial, in which a highly specialized unit in the detection of atherothrombotic diseases is in charge of the design of the study. A primary care center actively participates in the recruitment and follow-up of participants. This center has been selected because it fulfills the eligibility criteria of participants’ recruitment and for the availability of technical issues related with the study. Furthermore, seven primary care providers plus their usual nurse are highly specialized in the identification and treatment of cardiovascular risk factors and nurses are specialized in the design of therapeutic lifestyle changes.

The local Ethics Committee of the Hospital Universitari Arnau de Vilanova approved the study and revised the informed consent and the Clinical Trials.gov released the trial NCT00734123. Participants must agree and sign the informed consent before being included in the study.

**Inclusion criteria**

Male and female subjects, aged 40-74 years old, with at least one of the following criteria will be eligible for the study:

1. SCORE (10 year risk of fatal cardiovascular disease in populations at low cardiovascular disease risk) \(\geq 3\).
2. Early appearance of major cardiovascular events in the family (males<55 or females <65 years old).
3. Type 2 diabetes mellitus.
4. Chronic kidney disease (GFR <60 ml/h).
5. Total cholesterol \(\geq 320\) mg/dL (mmol/l) or LDL cholesterol \(\geq 240\) mg/dL (mmol/l).
We have incorporated all these inclusion criteria (from 2 to 6) since European Guidelines identified these conditions as high cardiovascular risk independently of the results in the Score risk assessment \(^2\).

Additionally, the presence of two or more of the following will also constitute eligibility criteria:

1. Current smoker.
2. Physical inactivity.
3. Abdominal circumference (males > 102cm; females >88cm).
4. High blood pressure (systolic \(\geq 140\) mmHg or diastolic blood pressure \(\geq 90\) mmHg) or under anti-hypertensive therapies.
5. Low HDL cholesterol (males <40 mg/dL; females <50 mg/dL).

The last set of criteria is based on the identification in previous studies \(^12\) and experts’ panel recommendations \(^13\), of these risk factors highly involved in atherosclerosis development and cardiovascular events.

**Exclusion criteria**

The presence of cardiovascular diseases at the moment of the screening, or the presence of a severely ill or bad prognosis disease will be excluding criteria. Pregnant subjects will be excluded of the study due to potential interactions with the results of non-invasive tests.

**Procedures**

The Primary Care physician will identify participants who fulfill the eligibility criteria and will invite them to participate. In case of a negative to participate in the study (exclusion criteria or negative to participate voluntarily), the referring physician will record the potential causes.

Highly specialized and trained Hospital-based personnel will perform the tests, which consist in:

1. Clinical record: complete clinical examination including blood pressure, abdominal perimeter, height and weight. Carotid bruits will be recorded according to predefined criteria \(^14\). The past medical history along with the assessment of known cardiovascular risk factors, such as exercise, smoking, alcohol intake, etc. is also registered. We also check for current medications and educational background.
2. Laboratory variables: we perform full blood analyses including hemoglobin, total leukocytes and platelets. Total cholesterol, HDL and triglycerides are measured according to standard methods. LDL cholesterol is calculated using Friedewald formula. Fasting glucose, liver enzymes and renal function are also measured using standard techniques. Highly sensible C reactive protein is measured using the recommendations of the manufacturer (Roche diagnostics). We also perform mineral metabolism analyses concerning calcium and phosphorus homeostasis. For future objectives, each participant is asked to participate in the collection of biologic samples (serum, plasma and DNA).

3. Measurement of ankle-brachial index: we use a vascular Doppler MD2 Hungleft with an 8MHz transducer and a random-zero sphygmomanometer with the cuff positioned just proximal to the elbow/malleoli. Brachial systolic pressures are obtained in both arms and ankle systolic pressures are measured in the posterior tibial and pedial arteries of both legs. The pulse was located using the Doppler probe, and the cuff then inflated until the pulse was obliterated; the cuff was then deflated and the pressure recorded at the point when the pulse reappeared. We use maximum brachial systolic pressures and record ABI as the lowest value obtained at each territory.

4. Carotid ultrasound: we perform the carotid ultrasound examination with the aim to measure cIMT and to identify the presence of carotid plaques. We use a MicroMaxx, SonoSite with a linear transducer HFL38/13-6 MHz. Each sonographer (3) use the same standard operational procedure, which is as follows:

   a. Trans Loop: a cross-sectional loop of the region of interest (common carotid, bulb and internal) is evaluated. In this projection, the aim is to identify the three main segments that we evaluate and to count the total number of plaques.

   b. Longitudinal images: the aim of this projection is to identify the cIMT of the far wall of common carotid, bulb and internal carotid arteries. Ideally, every single participant should have 6 images for the measurement of the cIMT. As it is defined in the consensus\textsuperscript{15} the order to evaluate the different segments of carotid artery is Common Carotid Artery in the last centimetre, Bulb section
and finally Internal Carotid Artery in the first centimetre. All of these segments are recorded with a static image. The measurement of the cIMT in every segment is performed by an expert technician using the semiautomated, FDA-approved software, SonoCalc IMT®.

c. Pulsed-doppler: we use the colour and pulsed-doppler once an atheromatous plaque is identified, in order to assess hemodynamic consequences (Significant stenosis considered when systolic velocity peak >125 cm/s is reached).

5. Coronary Calcium Score (CCA): In those cases in which, due to anatomical adverse conditions, the carotid ultrasound is not reliable (estimation of 1-3% of participants), we will perform a CCA to assess coronary atherosclerosis.

We then set a diagnosis of atherosclerotic disease, based on the results of non-invasive tests (Figure 1):

1. No atherosclerosis (EA0): ABI >0.9 and cIMT/CCA inferior to the cut-off value representing the 80% reference interval, adjusted by age and sex. Reference interval values have been obtained from previously published observational studies using the same ultrasound procedures.16, 17

2. Mild atherosclerosis (EA1): an ABI 0.7-0.9 and/or cIMT/CCA superior to the cut-off value of the 80% reference interval.

In both cases, the absence of carotid plaques is mandatory.

3. Moderate atherosclerosis (EA2): the presence of a carotid plaque without significant stenosis (<125 cm/second) is diagnostic of moderate atherosclerosis, independently of ABI and cIMT results.

4. Severe atherosclerosis (EA3): an ABI <0.7 or/and the presence of a carotid plaque with significant stenosis (>125 cm/second) is considered as severe atherosclerosis.

Then participants are randomized 1:1 either to:

1. Control group: participants will be cared according to clinical guidelines and therapeutic targets will be consequently set.
2. **Intensification group:** participants randomized to this group will follow special medical recommendations aimed at the accomplishment of different therapeutic targets.

In Table 1 we have depicted the therapeutic targets in both groups of participants, of whom 40% will be followed in the Primary Care Center and 60% will be followed at the Hospital (UDETMA).

The random allocation will be done through the random generation of a real number between 0 and 1 (based in the uniform distribution) after the patient's assessment of eligibility and signature of the informed consent and is performed by the nurses responsible of the enrollment and allocation process. As patients are recruited in a primary care setting, it is expected a worse participation of patients assigned to hospital and therefore, the proportion of patients assigned to hospital is 60% versus 40% in primary care. The random generator algorithm is included in the database and, depending on whether the value is within the intervals [0, 0.3], (0.3, 0.5], (0.5, 0.8] or (0.8, 1], the patient will be allocated to the "control & hospital", "control & primary care", "intensification & hospital" or "intensification & primary care" group, respectively. The randomization process is completely automated and unrestricted to any patient characteristic, and neither technicians nor researchers are allowed to influence on it.

Only the statistician is blinded to group assignment.

Those participants being diagnosed of severe atherosclerosis (EA3), are derived to the specialized physician at the Hospital for further evaluation (Angiographic magnetic resonance, cardiology assessment, etc.), and they are excluded of being randomized.

Researchers at the Primary Care Center and at the Hospital will be responsible of the follow-up, in which therapeutic targets should be accomplished. The way we will reach them have been previously approved and standardized by the Steering Committee of the study and are highlighted in Table 2.

*Lipid lowering intervention*
According to the therapeutic target we will set the percentage of LDL cholesterol reduction to be accomplished, and the type and dose of statins will be prescribed accordingly. Re-evaluation will be performed in 6 weeks from baseline exam.

1. LDL cholesterol reductions of <10%: therapeutic lifestyle changes (TLC).
2. LDL cholesterol reductions of 11-30%: TLC will be implemented along with Simvastatin 10 mg.
3. LDL cholesterol reductions of 31-40%: TLC plus Simvastatin 20 mg.
4. LDL cholesterol reductions of 41-50%: TLC plus either Simvastatin 40 mg or Atorvastatin 20 mg.
5. LDL cholesterol reductions of >51%: TLC plus Atorvastatin 40 mg.

Lipid lowering drugs will be titrated according to the accomplishment of therapeutic targets and to patient tolerance. In selected cases, i.e.: drug intolerance, CK increase, the dose of statins will be reduced and ezetimibe 10 mg. might be added.

**Blood pressure lowering therapies**

Standard European Guidelines will be followed and are summarized in Table 2. In summary, therapeutic lifestyle changes will be advised to every participant and blood pressure lowering drugs will be prescribed when either:

1. Participants do not fulfill with the target after 6 weeks of TLC, or
2. Baseline blood pressure values equal or above 180 or 110 mmHg.

The drug of choice will be an Angiotensin Converting Enzyme (ACE) inhibitor and doses will be titrated according to the accomplishment of the target or participant tolerance to the drug. In those cases with insufficient treatment, a second drug will be added and it will be preferentially a thiazidic diuretic. According to patient tolerance and blood pressure monitorization drugs might be changed or substituted, at physician’s criteria.

**Antiplatelet therapy**

Patients assigned to the intensification group and diagnosed as either moderate or severe atherosclerosis will take aspirin 100 mg per day. In case of contraindication or intolerance, clopidogrel 75 mg. per day will be prescribed.
Other interventions allowed in the study

Therapeutic lifestyle changes are standardized and they mainly consist in:

1. Smoking cessation. No exposure to environmental tobacco smoke recommendation.
2. Weight reduction and weight stabilization. Goal: Body mass index: 18.5 to 25 kg/m²
   Waist circumference: men< 102 cm, women<88 cm.
3. Moderation of alcohol consumption; to limit alcohol consumption to no more than 20–30 g ethanol per day for men and no more than 10–20 g ethanol per day for women.
4. Physical activity; prescription of: 30 minutes, 7 days per week, minimum 5 days per week of moderate-intensity aerobic activity.
5. Reduction of salt intake: recommendation of less than 5 g/day sodium chloride.
6. Increase in fruit and vegetable intake and decrease in saturated and total fat intake;
   patients are advised to eat 4–5 servings or 300 grams of vegetables and fruit per day, to encourage increased consumption of omega-3 fatty acids in the form of fish and to reduce intake of saturated fat and cholesterol.

Rimonabant is also allowed to be prescribed according to EMEA regulations (morbid obesity (BMI>40) or obesity (BMI>35) with several cardiovascular risk factors, at the discretion of the physician.

In patients with Diabetes mellitus, standard targets as far as glycosilated hemoglobin is concerned, will be followed independently of the group of assignment.

Follow-up

The study duration is two years of follow-up, and a complete evaluation will be performed once a year. Standard operational procedures will be exactly the same throughout the study duration.

Physicians participating in the study will be composed of:

1. Seven primary care providers along with their usual nurse (estimated sample size to be followed: 1180 participants).
2. Two physicians specialized in the management of cardiovascular risk factors, along with a specialized nurse in diet counseling and lifestyle modifications (1768 participants).

We will also record major and minor cardiovascular events (angina, need of coronary revascularization, myocardial infarction, sudden death, stroke, transient ischemic attack and symptomatic peripheral arterial disease) of both groups of participants. The duration of it will be beyond the two years duration of the study.

**End point variable**

The end point of the study is the course of carotid IMT during two years of duration of the study. \( \Delta \text{cIMT} = \text{cIMT follow-up} - \text{cIMT baseline} \), where both cIMT at follow up and baseline will be a composite variable of the mean of the cIMT at the far walls of common, bulb and internal carotid arteries of both sides.

**Sample size calculation**

The sample size calculation is aimed to detect differences in the cIMT values associated to the intensification group compared with the control group. According to Bots ML et al\(^1^8\), the mean cIMT increases 0.0147 mm annually on average, based in the pooled values provided by the control groups of 14 clinical trials. Since some of them where performed in patients with coronary disease, who are known to show faster cIMT enlargement, we estimated the mean cIMT increase when only the 4 clinical trials performed in patients free of coronary disease. On average, the use of the inverse of the squared standard error to pool, provided a mean cIMT increment of 0.0123 while it was 0.00973 if the inverse of the sample size was used to pool instead. The sample size calculation was calculated using the 0.00973 mean cIMT (the smallest and most conservative one) and its corresponding standard deviation (obtained by pooling under the assumption of equal variances) of 0.03717. Fixing a type I error of 0.05, a power of 0.90 and a minimum effect to detect in a 25% between those patients assigned to intensification or control group, the minimal sample size required is 1228 patients per group, 2456 in total. Expecting a proportion of 20% or less lost to follow-up patients, it increases to 1474 per group, 2948 in total.
Statistical Analysis Plan

Every participant with at least one follow-up measure of cIMT will be included in the analysis of the intensification effect, which will be performed by intention to treat.

First of all, we will check if there are statistically significant differences in any patient characteristic (in demographical, clinical, laboratory, ABI or carotid ultrasound variables) at baseline between the intensification and control group. Analysis will include the chi-square test with continuity correction or Fisher's exact test when appropriate for the comparison of proportions and the T-test for the comparison of means, unless that a lack of normality is detected, in which case we will use the Mann-Whitney test instead.

In order to measure the effect of the intensification group compared to the control group over the cIMT progression, we will estimate the coefficient of the group in a mixed-effects model of the cIMT at follow-up with the additional covariates: baseline cIMT, time of follow-up and the patient characteristics at baseline that showed statistically significant differences between the two groups according with the previous analysis. The level of atherosclerotic disease at baseline (the classification is defined in the protocol) as well as the level defined by SCORE will be tested for interaction with the intensification group when possible. The setting (hospital or primary care) and patient identifiers will be tested for their contribution as nested random effects to control by them (there is no interest in quantifying differences among patients or settings, only in controlling by their possible effect over the variability of the cIMT values).

As secondary analysis another mixed-effect regression model will be adjusted but with ABI values instead of cIMT as dependent variable in order to look for an effect of the intensification strategy on ABI values. In reference to the presence/absence of plaque model, a non-linear logistic mixed-effects model (since it is a binomial response) will be performed. For both models, covariates will include intensification group, baseline values of the dependent variable, time of follow-up and, as in the main outcome analysis, the patient characteristics at baseline that showed statistically significant differences between the two groups according with the previous analysis. The level of atherosclerotic disease at baseline (the classification is defined in
the protocol) as well as the level defined by SCORE will be also tested for interaction with the intensification group when possible.

Intensification coefficients obtained from the three multivariate models will be accompanied with its 95% confidence interval.

**Discussion**

The standard of clinical care in the primary prevention of cardiovascular diseases is based on risk scoring. In Spain, and also around Europe, the adoption of Score is generally accepted and several versions, according to cardiovascular incidence, have been implemented and validated\(^{19}\). Although the use of these scores is universally available and easy-to-use, they have several flaws. First, the incidence of cardiovascular diseases is far from being diminished, and more than 60% of young patients with myocardial infarction presented with a low-intermediate risk\(^{20}\), in which the therapeutic targets were not strict enough to avoid the clinical event. Second, cardiovascular events are often (30-50%)\(^{21}\) expressed as a fatal event, such as sudden death or massive myocardial infarction, and therefore, a more sensitive method to detect silent and high risk subjects is needed. Furthermore, most of these risk scoring tests are based on 4-6 well-validated cardiovascular risk factors and in the development of atherosclerosis and therefore in the origin of cardiovascular diseases, more than 200 factors have been recognized\(^{22}\). All these factors along with genetic susceptibility are not taken into account by the classical risk scoring approach.

International scientific organizations, such as the National Cholesterol Educational Program and European Guidelines, recommend the application of risk scoring, but also, they suggest implementing new techniques for a better and more individualized cardiovascular risk assessment. This advice is particularly highlighted in those individuals classified at intermediate risk, since they represent a major population at absolute risk of having vascular events in the future. Indeed, the search for organic damage (carotid intima-media thickness>0.9 mm or the presence of a carotid plaque; abnormal ankle-brachial index; echocardiographic and electric abnormalities, etc) are influencing prognosis in patients with high blood pressure, and consequently they might help in the decision making process of prescribing drugs\(^2\).
However, the use of these techniques in an integrated algorithm-based process for the primary prevention of cardiovascular diseases has not been tested. In 2006, the Task Force of the SHAPE organization, a non-for-profit scientific organization aimed at the eradication of heart attack, claimed in a practice guideline, for the use of non-invasive techniques (ankle-brachial index+ coronary calcium score or carotid IMT) as a first step in the assessment of cardiovascular status, in healthy population aged >45 years old. However, this approach is not supported by clinical data.

The aim of our study is to implement a new approach in the primary prevention of cardiovascular disease, and to test its efficacy with the use of a validated surrogate marker such as the cIMT at two years of follow up. For this purpose, we have designed a randomized clinical trial, open-label, with the inclusion of 2948 healthy participants in two separate arms. Among the inclusion criteria we are especially interested in the recruitment and follow-up of participants at intermediate risk (Score ≥3), since it constitutes an intense focus of research. We have also included in the eligibility criteria individuals with a single risk factor such as type 2 diabetes mellitus or chronic renal insufficiency, since they might be of interest to separately analyze the differential effect of the primary prevention strategy. However, having different groups of participants in the eligibility criteria may be interpreted as a limitation of the study.

The inclusion of such different groups is justified as follows. In the recently published European guidelines for the prevention of cardiovascular disease, diabetes mellitus is regarded as a high cardiovascular risk condition, and consequently, therapeutic targets should be placed as secondary prevention (i.e: blood pressure <130/80; total cholesterol <175 mg/dL; LDL cholesterol <100 mg/dL). This recommendation could be interpreted as a contradiction with the objectives of the study, and one could argue that no further assessment (carotid ultrasound, ankle-brachial index) should be done in the diabetic population. However, previous data showed that the use of carotid ultrasound (carotid IMT and carotid plaques) in a cohort of 229 type 2 diabetes mellitus-affected patients (of whom 34 presented cardiovascular events) significantly improves cardiovascular risk prediction [Odds ratio 1.63(1.01-2.63), p=0.04], in comparison with age, suboptimal exercise electrocardiogram, microalbuminuria or non-HDL cholesterol (P
value for all variables \(>0.05\)\(^2\). Similarly, we have also included patients with chronic kidney disease, although this condition has been recently acknowledged as conferring a high cardiovascular risk. Previous data showed that, patients at end-stage chronic kidney disease with the highest tertile of carotid IMT presented a significantly higher risk of all-cause mortality, cardiovascular diseases mortality and morbidity (P values 0.002, 0.01 and 0.001, respectively) than those patients at the lowest tertile\(^2\). Further in both groups of patients the standard control of risk factors are more strict than in non-affected population, but according to the diagnoses of atherosclerotic disease used in the study, participants might be advised to further reduce its values of risk factors (i.e.: a type 2 diabetes mellitus patient, with a moderate or severe atherosclerotic disease diagnoses, we will set LDL cholesterol target to be below 80 or 70 mg/dL, respectively). These are the reasons that lead investigators to include all these different groups of participants. Further, we have also defined in a different set of criteria, the inclusion of healthy subjects with two or more cardiovascular risk factors. Most of these individuals will have a low-risk scoring (Score<3), but we consider relevant to have this group of participants included, since they may represent a huge population to be screened and consequently treated in the future. Nowadays, this group of subjects is poorly defined and data on different primary prevention strategies is lacking. The results of the clinical trial under study might be of great socio-economic interest, especially in the last group of participants. Moreover, those considered as having a low cardiovascular risk, constitute in absolute terms a huge segment of the population susceptible of presenting a cardiovascular event in the future, and consequently, prevention efforts should be directed to these segments of population. This is the main reason to involve these apparently healthy subjects.

We have selected carotid ultrasound and ankle-brachial index techniques because both techniques are fully validated and the body of evidence around them is strong enough to initiate a clinical trial. Moreover, cIMT is recognized by both the Food and Drug Administration and the European Medicines Agency, as a surrogate marker of cardiovascular diseases in clinical trials\(^2\). Second, there is previous data on the combination of both techniques in a population-based study. In fact, the Rotterdam study showed that the combination lead to an atherosclerosis
score, and participants with severe atherosclerosis presented with a hazard ratio for myocardial infarction of 2.77 (1.70 to 4.52) compared with subjects with no atherosclerosis. Third, both techniques are easily applicable in the primary care setting in comparison with the CAC score. We acknowledge, however, that the quality assurance and control, especially of the carotid ultrasound, must be strictly controlled throughout the duration of the trial.

In summary, we consider of great interest to initiate a clinical trial in the primary prevention of cardiovascular disease, focused in testing a new paradigm (the detection of atherosclerosis, rather than risk scoring). The collaboration with the primary care setting modeled in this trial may be also of great value for future global campaigns, since it should enhance cardiovascular prevention strategies.
Authors’ contributions

MM designed the study and is responsible of sample size calculation and the design of the statistical plan analyses. AB, MB, BC, MC, MM and EF participated in the design of the study. AP and PS recruit participants from the Primary Care Setting. AB, BC, MC, AP and PS will follow participants throughout the duration of the study. JMG is in charge of diet intervention and XG and MG perform non-invasive tests to participants. BC participate in the design and in the quality control of non-invasive tests.

Steering Committee Members are: AB, MB, EF, AP, PS, MC and BC.

Acknowledgements

We are especially thankful to all the components of the UDETMA (Teresa Vidal, Vanesa Torres and Elisabet Samso) for their constant support to the project.
Table 1. Therapeutic targets in both groups of participants.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Risk/Severity</th>
<th>LDL target (mg/dL)</th>
<th>Blood Pressure target (mmHg)</th>
<th>Antiplatelet</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROL</td>
<td>Score &gt;5%</td>
<td>&lt;100</td>
<td>&lt;130/85</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Score 3-5%</td>
<td>&lt;115</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTENSIFICATION</td>
<td>No Atherosclerosis</td>
<td>&lt;115</td>
<td>&lt;130/85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild Atherosclerosis</td>
<td>&lt;100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate Atherosclerosis</td>
<td>&lt;80</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Severe Atherosclerosis</td>
<td>&lt;70</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 2. Standardized interventions in both groups of the study.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>LDL reduction, %</th>
<th>CONTROL</th>
<th>INTENSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10%</td>
<td>Therapeutic Life style changes (TLC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11-30%</td>
<td>TLC+ Simvastatin 10 mg.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31-40%</td>
<td>TLC+ Simvastatin 20 mg.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41-50%</td>
<td>TLC+ Simvastatin 40 mg or Atorvastatin 20 mg.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;51%</td>
<td>TLC+ Atorvastatin 40 mg.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood pressure lowering.</td>
<td>TLC+ ACE inhibitor†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antiplatelet drugs.</td>
<td></td>
<td>Aspirin 100 mg or Clopidogrel 75 mg.</td>
</tr>
</tbody>
</table>
REFERENCES


11 SCORE: European Low Risk Chart. www.escardio.org/Prevention


22 Magnus P, Beaglehole R. The real contribution of the major risk factors to the coronary epidemics: time to end the “only-50%” myth. Arch Intern Med 2001;161:2657-60.


