CLINICAL STUDIES

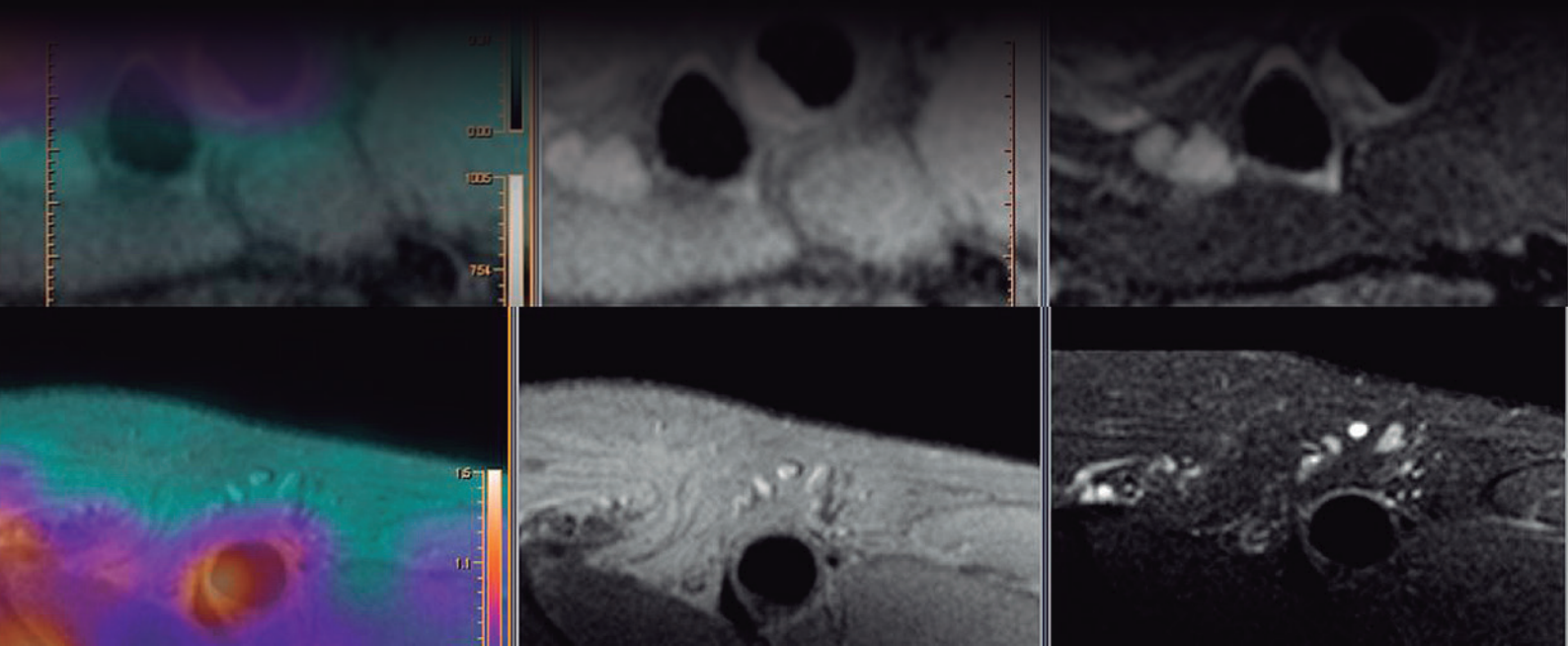
PESA CNIC-SANTANDER

Fuster-CNIC-Ferrer Cardiovascular Polypill and SECURE Trial

STEMI trials: The Metroprolol program

TAN SNIP

AWHS



PESA CNIC-SANTANDER

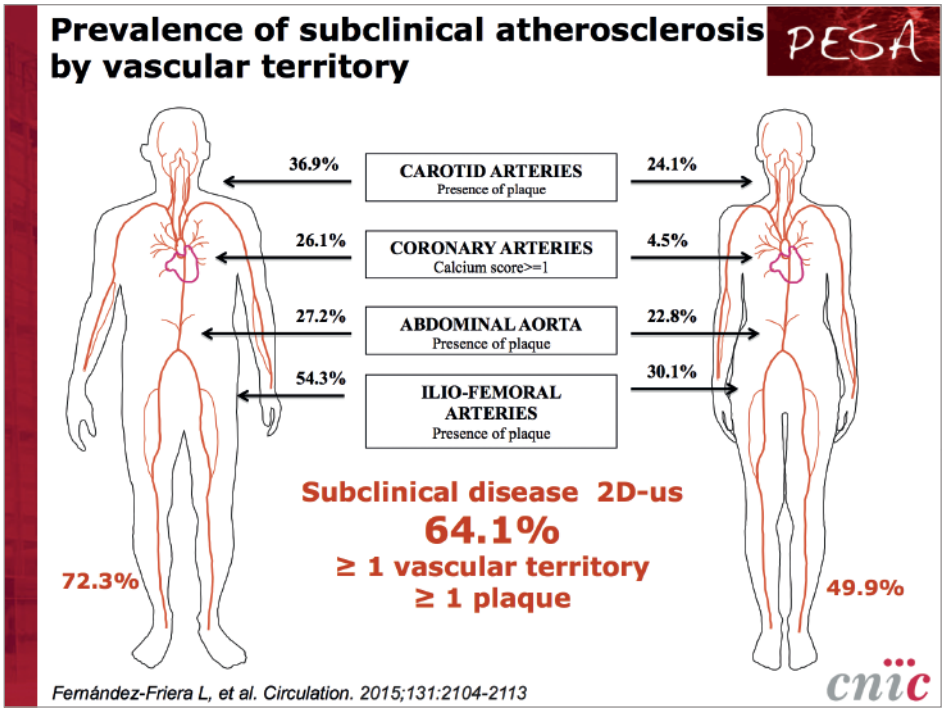
(Progression of Early Subclinical Atherosclerosis)

Noninvasive imaging techniques provide invaluable tools for identifying individuals with subclinical alterations indicating increased risk of cardiovascular events. This field has been boosted by the development of basic techniques (2D/3D vascular ultrasound and coronary calcium score by computed tomography) and advanced imaging techniques (magnetic resonance imaging and positron emission tomography) that can be applied to large populations. Several studies currently underway, such as the High-Risk Population (HRP) study led by Valentín Fuster in the USA, are pioneering the application of these techniques to population studies. Most studies to date have examined populations composed of individuals above the age of 60 years. However, atherosclerotic disease in this group has already several decades of evolution and may be too advanced for prevention of future events.

The PESA CNIC-Santander trial is an ambitious study designed to identify new imaging and biological factors associated with the presence and progression of early phases of atherosclerosis. PESA has recently completed the prospective enrolment of 4184 healthy subjects aged 40 to 54 years (2635 men and 1549 women) who have undergone a multi-territory screening for subclinical atherosclerosis by noninvasive 2D/3D ultrasound in the carotid, abdominal aorta and ilio-femoral arteries together with coronary artery calcium score by computed tomography. Participants have additionally been assessed for a complete set of cardiovascular risk factors (including lifestyle and psychosocial factors) and have provided blood samples for advanced "omics" and future biobanking analyses. In addition, 940 individuals in whom a significant plaque burden was detected by ultrasound and CT underwent advanced imaging by ^{18}FDG PET/MRI at the CNIC Advanced Imaging Unit during 2013 and 2014. The study has also received approval for research into the association between atherosclerosis initiation/progression and telomere dysfunction in circulating leukocytes, and leukocyte samples have been collected from a subgroup of 1456 PESA participants.

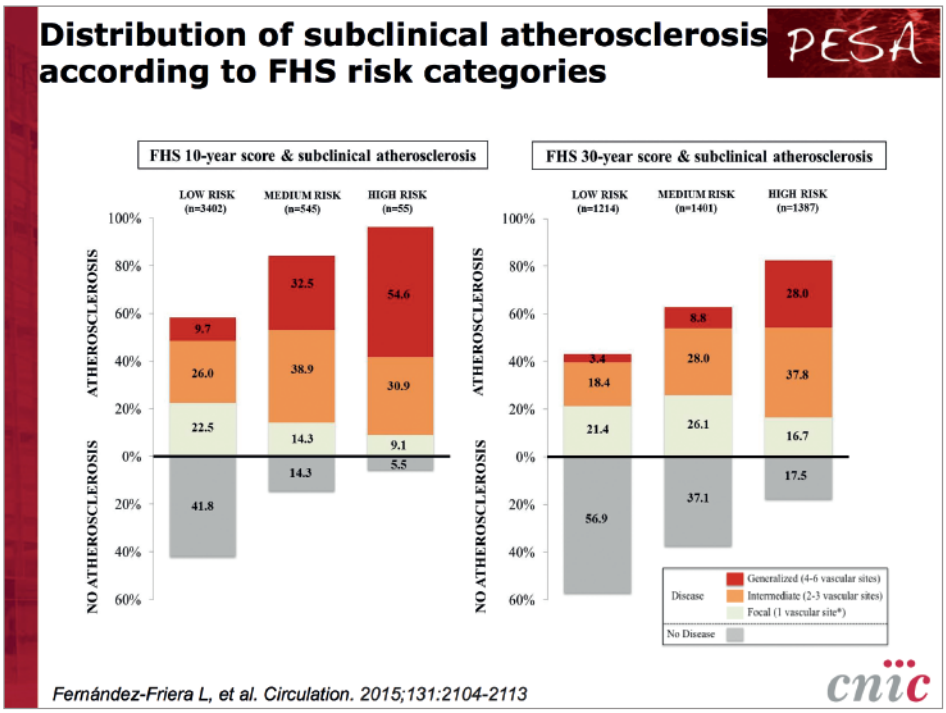
All PESA participants are followed-up at 3 and 6 years to assess the progression of atherosclerotic plaques and to determine how the detection of subclinical disease impacts the risk of future cardiovascular events. By the end of 2015, more than 2600 participants had already had their 3-year follow-up visit (visit 2). Similarly, in July 2015 we began a 3-year follow-up MRI analysis of the 940 individuals assessed with advanced PET/MRI technology at baseline. This intermediate vascular MRI study includes cardiac MR sequences that will allow comprehensive characterization of subclinical myocardial disease.

In Jun 2015, the PESA trial baseline findings were published in *Circulation* (2015). The results of this analysis show that subclinical atherosclerosis is highly prevalent in this middle aged asymptomatic population. Interestingly, the most frequently affected vascular site in the early stages of atherosclerosis is the iliofemoral territory. Subclinical atherosclerosis was found in most individuals classified at high risk on traditional scales (FHS 10- and 30-year scores), but was also present in nearly 60% of participants classified at low risk, with intermediate or generalized disease in one third of participants. Ongoing PESA follow-up over at least 6 years will enable the study of associations between subclinical disease evaluated at baseline and subsequent cardiovascular events.



PESA CNIC-SANTANDER

(Progression of Early Subclinical Atherosclerosis)



Distribution of subclinical atherosclerosis detected by noninvasive imaging according to Framingham Heart Study risk (FHS) categories. Vascular sites examined were the right and left carotids, the abdominal aorta, and the right and left iliofemoral arteries (presence of plaque by 2D ultrasound), as well as the coronary vessels (coronary artery calcification score). FHS risk scores were classified as low (<10%), moderate (≥10%–20%), or high (>20%).

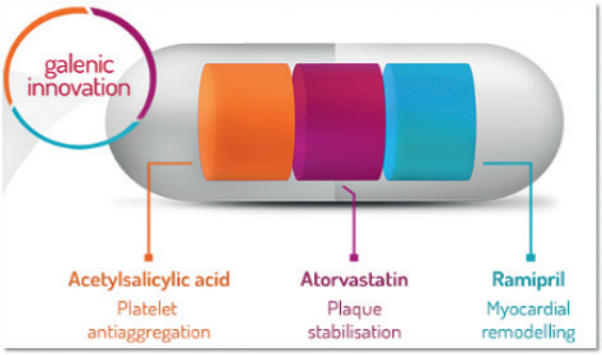
SELECTED PUBLICATIONS

Fernández-Friera L, Peñalvo JL, Fernández-Ortiz A, Ibañez B, López-Melgar B, Laclaustra M, Oliva B, Mocoroa A, Mendiguren J, Martínez de Vega V, García L, Molina J, Sánchez-González J, Guzmán G, Alonso-Farto JC, Guallar E, Civeira F, Sillesen H, Pocock S, Ordovás JM, Sanz G, Jiménez-Borreguero LJ, Fuster V. **Prevalence, Vascular Distribution, and Multiterritorial Extent of Subclinical Atherosclerosis in a Middle-Aged Cohort: The PESA (Progression of Early Subclinical Atherosclerosis) Study.** *Circulation* (2015) 131: 2104-13

Fernandez-Ortiz A, Jimenez-Borreguero LJ, Penalvo JL, Ordovas JM, Mocoroa A, Fernandez-Friera L, Laclaustra M, Garcia L, Molina J, Mendiguren JM, Lopez-Melgar B, de Vega VM, Alonso-Farto JC, Guallar E, Sillesen H, Rudd JH, Fayad ZA, Ibanez B, Sanz G and Fuster V. **The progression and early detection of subclinical atherosclerosis (PESA) study: rationale and design.** *Am Heart J* (2013) 166: 990-8

Fuster-CNIC-Ferrer Cardiovascular Polypill

It's been nearly a decade since the CNIC and Ferrer teamed up to realize Dr. Fuster's vision of a cardiovascular polypill to make cardiovascular treatment accessible worldwide, improve treatment adherence, and provide a cost-effective public health strategy for the prevention of myocardial infarction.



The Fuster-CNIC-Ferrer CV Polypill includes aspirin (100 mg), ramipril (in doses of 2.5, 5, or 10 mg to allow for titration), and atorvastatin (20 mg). This first-in-class medication has so far been approved by the medicines agencies of 15 European countries (Austria, Belgium, Bulgaria, Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Rumania, Spain, and Sweden) for use in secondary prevention of CV events. These regulatory approvals add to the existing marketing in Mexico, Guatemala, Dominican Republic, Nicaragua, Honduras, Argentina and, more recently, Chile.

The Fuster-CNIC-Ferrer CV Polypill is indicated for secondary prevention of CV events as substitution therapy in adult patients adequately controlled with the monocomponents given concomitantly at equivalent therapeutic dosages. Currently the polypill has been marketed in Spain, Portugal, Romania and Germany under two different brand names: Trinomia® and Sincronium ®.

In the coming years, the Fuster-CNIC-Ferrer CV polypill will be launched in more European countries and worldwide.

SECURE Trial

secure

SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE IN THE ELDERLY

HORIZON 2020

SECURE (Secondary Prevention of Cardiovascular Disease in the Elderly Population): the first clinical trial to investigate the efficacy of a Polypill in reducing cardiovascular mortality in secondary prevention.

PI: Dr. Valentin Fuster, MD, PhD
Co-PI: Jose M Castellano, MD, PhD
Scientific Coordinator: Hector Bueno, MD, PhD
Project Director: Ester Cunha Pavon

Cardiovascular disease (CVD) has become the number one cause of death among men and women aged over 65 in Europe, and the magnitude of the burden of CVD is expected to grow in parallel with the projected population aging. Moreover, the number of EU citizens over 65 is projected to almost double by 2060 – rising from 85 million in 2008 to 151 million in 2060. Improving the survival of CHD patients has created a large population of older adults eligible for secondary prevention.

SECURE Trial

Despite ground-breaking advances in therapy, CVD mortality rates remain high, mainly because patients do not follow ideal medical management (either through nonadherence or lack of access to medications). One of the barriers to adherence that has been consistently highlighted in registries, studies and trials is pill number and treatment complexity. The last decade has seen a surge of technical innovation to develop a polypill strategy that would improve adherence and at the same time improve medication access in low and middle income countries.

The FOCUS (Fixed-dose Combination Drug for Secondary Cardiovascular Prevention) study, funded under the EU Seventh Framework Programme and coordinated by the CNIC under the direction of Dr. Valentín Fuster, was the first to demonstrate that a polypill strategy significantly improves adherence in a secondary prevention population.

The CNIC was recently granted H2020 funding to carry out the first ever clinical trial to test the impact of a polypill strategy on hard cardiovascular outcomes. The SECURE (Secondary Prevention of Cardiovascular Disease in the Elderly Population) trial, led by Drs Fuster and Castellano, will enroll 3600 patients over 65 years of age in Spain, Italy, Germany, France, Czech Republic, Hungary and Poland. Patients will be randomized to the Fuster-CNIC-Ferrer Cardiovascular Polypill and followed for 2-4 years. The kick-off meeting of the SECURE project was held in Madrid in May 2015. Patient recruitment will begin in early 2016. The results of the SECURE study will help shape clinical recommendations for better use of medication in patients with ischemic heart disease across the world.

The Fuster-CNIC-Ferrer Cardiovascular Polypill is now a reality worldwide. The polypill has been approved for commercialization in more than 25 countries and has been approved by the major regulatory agencies. After the success of FOCUS, SECURE will provide the final evidence to enable millions of patients worldwide to benefit from simpler, more effective and cost-effective chronic treatments to decrease cardiovascular mortality and morbidity.

SELECTED PUBLICATIONS

Castellano JM, Sanz G, Peñalvo JL, Bansilal S, Fernández-Ortiz A, Alvarez L, Guzmán L, Linares JC, García F, D'Aniello F, Arnáiz JA, Varea S, Martínez F, Lorenzatti A, Imaz I, Sánchez-Gómez LM, Roncaglioni MC, Baviera M, Smith SC Jr, Taubert K, Pocock S, Brotons C, Farkouh ME, Fuster V. **A polypill strategy to improve adherence: results from the FOCUS project**. *J Am Coll Cardiol* (2014) 64: 2071-82

Castellano JM, Fuster V. **Polypill, el policomprimido cardiovascular: del concepto a la realidad en España**. *Rev Esp Cardiol* (2015) 15: 19-24

Bansilal S, Castellano JM, Fuster V. **Global burden of CVD: focus on secondary prevention of cardiovascular disease**. *Int J Cardiol* (2015) 201(Suppl 1): S1-S7

Castellano JM, Bueno H, Fuster V. **The cardiovascular polypill: clinical data and ongoing studies**. *Int J Cardiol* (2015) 201(Suppl 1): S8-S14

Tamargo J, Castellano JM, Fuster V. **The Fuster-CNIC-Ferrer Cardiovascular Polypill: a polypill for secondary cardiovascular prevention**. *Int J Cardiol* (2015) 201(Suppl 1): S15-S22

STEMI trials: The Metoprolol program

Acute myocardial infarction (AMI) is the main cause of death in western countries. The best strategy to limit myocardial damage is to perform an early coronary reperfusion. However, reperfusion itself comes at a price of additional myocardial damage, known as ischemia/reperfusion (I/R) injury.

The duration of ischemia can only be shortened through coordinated healthcare policies aimed at early detection and transfer of patients to hospitals with angioplasty capabilities. I/R injury, on the other hand, could potentially be reduced by pharmacological approaches; but despite great efforts, no therapy has been shown to consistently limit this phenomenon.

ß-blockers are a class of drugs that have been used to treat cardiovascular conditions for several decades. ß-blockers reduce mortality when administered after an AMI, and are a class IA indication in this context. There is a lack of information on the infarct-limiting effect of ß-blockers in patients undergoing reperfusion (current state-of-the-art treatment for infarction). Based on strong preclinical data, the CNIC initiated a program of clinical research with the long-term aim of demonstrating a reduction of events by the prereperfusion metoprolol administration in STEMI patients. The first trial was METOCARD-CNIC, recruiting patients with anterior STEMI presenting early (<6 hours from symptom onset). The EARLY BAMI trial is the validation study, recruiting a less restricted population with STEMI in any location presenting within 12 hours of symptom onset. In both trials, metoprolol or comparator (control/placebo) was administered before mechanical reperfusion.

The METOCARD-CNIC multicenter randomized clinical trial has already been completed. A total of 270 patients were recruited mainly by the emergency medical services. Metoprolol administration was associated with significantly smaller infarctions as evaluated by cardiac magnetic resonance (CMR) one week after infarction (Circulation 2013;128:1495-503), and with better long-term LVEF on 6-month CMR (J Am Coll Cardiol. 2014;63:2356-62). Metoprolol also significantly reduced the incidence of severe cardiac dysfunction and the incidence of heart failure readmissions.

The EARLY BAMI trial is a multinational randomized clinical trial conducted in Holland and Spain. More than 600 STEMI patients have been recruited to date. The primary endpoint is infarct size evaluated by CMR one month after reperfusion. All CMR studies are being analyzed in the central core lab at the CNIC. It is anticipated that more than 300 patients will undergo CMR to meet the power calculation. The CNIC is coordinating the Spanish branch of the trial. EARLY BAMI is the result of a multidiciplinary effort bringing together several partners. Patients are recruited by the Emergency Medical Service SUMMA112 during transit to one of the following participating hospitals within the codigo infarto Madrid: Hospital Fundación Jiménez Díaz, Hospital 12 de Octubre, Hospital Clínico San Carlos, Hospital Puerta de Hierro, Hospital Gregorio Marañón, Hospital de la Princesa, Hospital Ramón y Cajal, Hospital Fundación Alcorcón, and Hospital Principe de Asturias. All CMR studies in Spain are being performed at the CNIC using a unique magnet system. Reporting of the primary outcome is expected during 2016.

After these two trials testing the effect of early intravenous metoprolol on infarct size, the next step will be a larger multinational events-powered clinical trial led by the CNIC. More than 1200 STEMI patients will be recruited in more than 3 European countries.

Members of the METOCARD-CNIC and EARLY BAMI research group.

TAN SNIP: *Trans-Atlantic Network to Study Stepwise Noninvasive Imaging as a Tool for Cardiovascular Prognosis & Prevention*

TANSNIP unites 4 projects with the shared goal of building a model of cardiovascular risk based on detection, quantification and characterization of subclinical atherosclerosis and using this model to improve risk stratification and enable novel targeted therapies and risk reduction strategies. This transatlantic network brings together leading international experts from complementary fields, pools data from existing patient cohorts, and combines resources and knowhow in state-of-the-art imaging modalities, sophisticated biomarker platforms, and population sciences.

Existing tools for characterizing atherosclerosis and determining the risk of its complications are inadequate, and these deficiencies limit effective management across the spectrum of this common disease. Consequently, opportunities for early, cost-effective interventions in subclinical disease are missed, while high-risk populations with manifest disease are administered treatment almost indiscriminately. This leads to a high numbers-needed-to- treat (NNT), unnecessary patient risk, wasted resources, and unsustainable costs for health care providers.

The CNIC's international partners in TANSNIP are the US-based High-Risk Plaque Initiative (HRP), the Icahn School of Medicine at Mount Sinai (ISMMS) in New York, and the VU University Medical Center in Amsterdam. Within Spain, partners are the *Consejería de Sanidad de la Comunidad autónoma de Madrid*, *Banco Santander*, the *Sociedad Española de Cardiología*, and the *Fundación Interhospitalaria para Investigación Cardiovascular*.

The different research partners work on complementary aims under the TANSNIP umbrella, and the CNIC's current focus is on Aim 1, based on the PESA-CNIC cohort. This aim examines whether a personalized worksite based lifestyle intervention, driven by imaging data (3D-ultrasound of carotid and ilio-femoral arteries and coronary calcification) results in changes in behavior, improved control of risk factors and reduced progression of subclinical atherosclerosis plaque burden (SAPB).

AIM 1 (PESA-CNIC cohort)

Design

The study population for this part of the TANSNIP study consists of participants in the PESA study: employees aged 40 to 60 years of the Banco de Santander Headquarters in Madrid (Spain). Two parallel randomized controlled trials (RCT) are being conducted within the PESA cohort population. One RCT focuses on a sample of employees with high imaging-defined CV risk, whereas the second RCT is being conducted on a sample with low imaging-defined CV risk. In both RCTs, the participants are randomized to receive a comprehensive 3-year worksite lifestyle intervention or standard occupational health care. The worksite-based lifestyle intervention program consists of three elements: (A) twelve 1-hour sessions of personalized lifestyle counseling; (B) provision of a pedometer (Fitbit) for self-monitoring of physical activity; and (C) use of a sit-to-stand workstation (optional). Data will be collected at baseline and at follow-up at 1 year (T1), 2 years (T2), and 3 years (T3).

Endpoints

The primary outcome measure is BEWAT (a compilation score of moderate-vigorous physical activity, sedentary behavior, dietary fruit and vegetable intake, smoking, body weight and blood pressure), which will be assessed at baseline and years 1, 2 and 3. **Secondary outcomes** are changes in lifestyle (physical activity, standing behavior, diet, smoking, vitality, and quality of life), risk-factor profile, anthropometric measures, blood biomarkers, work-related outcomes (including work productivity and sickness absenteeism), health care comsumption, and intervention process evaluation measures.

Hypothesis

We predict that individual awareness of CVD risk stratification based on subclinical atherosclerosis imaging, accompanied by a comprehensive 3-year worksite-based lifestyle intervention, will lead to a reduction in the prevalence of CV risk factors related to lifestyle and an increase in physical activity, compared to standard practice. We further predict that the level of compliance with the 3-year worksite-based lifestyle intervention will be higher in the high imaging-defined CV risk group than in the low imaging-defined CV risk group.

TAN SNIP: *Trans-Atlantic Network to Study Stepwise Noninvasive Imaging as a Tool for Cardiovascular Prognosis & Prevention*

AIM 1 (PESA-CNIC cohort)

Inclusion data and intervention program

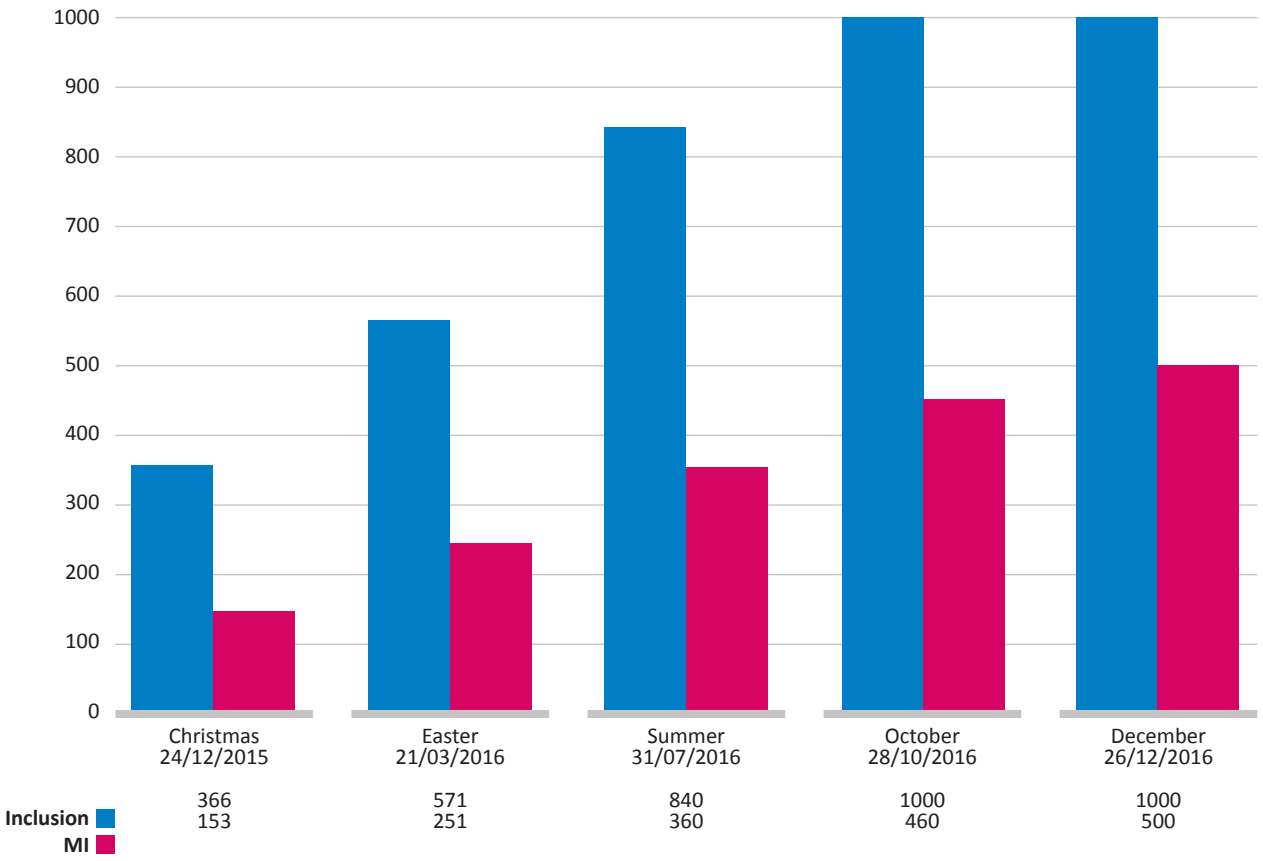
TANSNIP started including participants in May 2015 and the first MI session took place in June 2015. So far, a total of 339 participants have been included in the trial (170 in the control group and 169 in the intervention group). Of these, 95 participants belong to the high-risk imaging-defined RCT and 244 to the low-risk RCT. In the intervention group 154 participants have already received at least one motivational interview, 125 participants are using the Fitbit activity monitor, and 128 participants are willing to use the sit-stand workstation (54 workplace workstations have been installed so far). The expected inclusion and motivational interview schedule is shown in Figure 2. Inclusion is expected to be complete in October 2016, at which stage 500 motivational interviews will have been performed. The study is scheduled for completion in September 2019.

On December 2, 2015 the first scheduled 6-month focus group was held, with 5 participants from the intervention group who had completed the first 7 motivational interviews. Overall, the participants expressed themselves very satisfied with the intervention program.

As a quality-control measure, every 6 months randomly-selected motivational interviews are recorded and the study technicians are asked to complete a survey.

Scientific output

An abstract of the protocol paper has been submitted to the annual meeting of the International Society of Behavioural Nutrition and Physical Activity (ISNBPA), to be held in Cape Town, June 8-11, 2016. The full protocol paper is being finalized, and next year attention will be given to raising the study's media profile

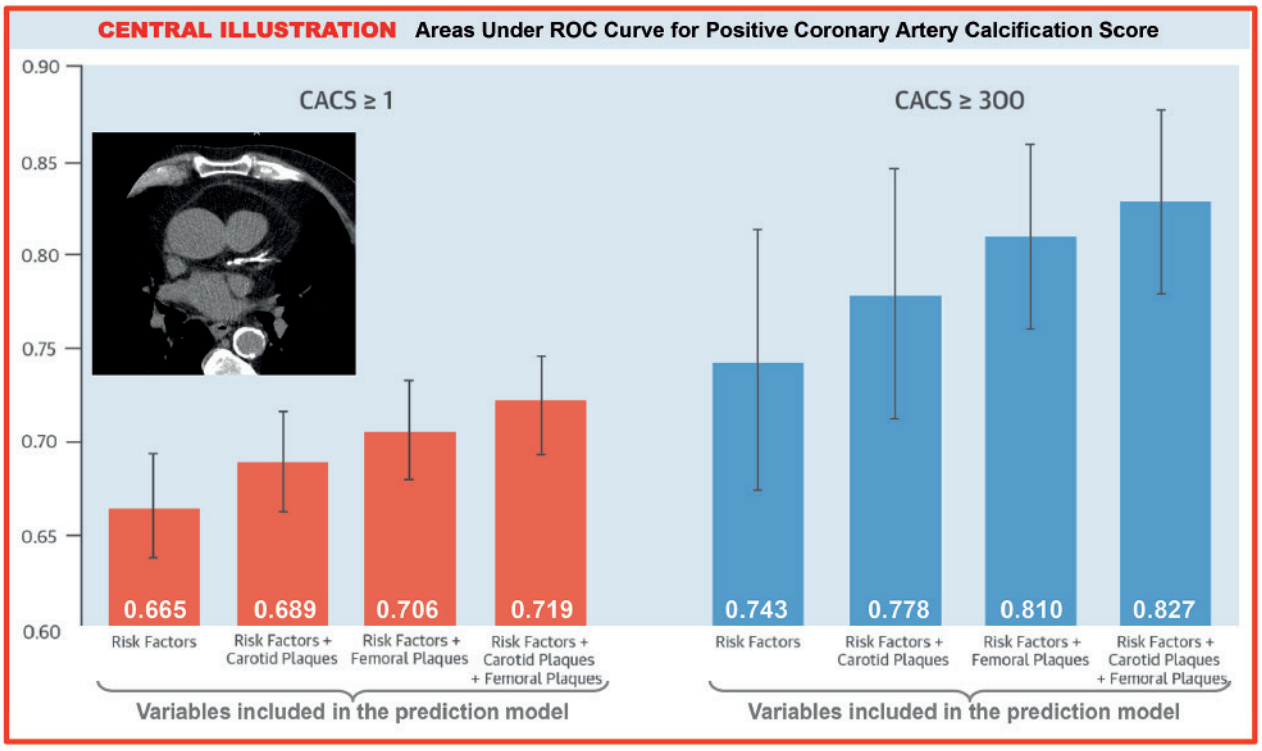


AWHS

The Aragon Workers Health Study (AWHS) is is a project conducted in collaboration with the *Instituto Aragonés de Ciencias de la Salud* (IACS) and the General Motors factory in Zaragoza. The AWHS was designed to evaluate the trajectories of traditional and emergent CVD risk factors and their association with the prevalence and progression of subclinical atherosclerosis in a population of middle-aged men and women in Spain. The study examines the development of cardiovascular disease and its risk factors by monitoring factory workers at their annual medical checkups.

The AWHS is an observational, prospective cohort study including more than 5000 participants. Recruitment began in 2009 and all workers at the factory fulfilling the inclusion criteria and willing to participate have now made their initial visit. In 2011, a screen was begun to detect subclinical atherosclerosis among 40-54-year-old participants, based on vascular 2D and 3D ultrasound in carotid, aorta and ilio-femoral arteries and on measurement of coronary artery calcification by computed tomography (CT). At the end of 2014, more than 2500 participants had been studied and the screen was concluded.

In 2012, the study's general methods were published (1) in an open access journal to support a more focused future publication of the ongoing research subprojects and to provide a clear description of the study to support fund-attracting strategies. The main results of vascular imaging studies at baseline will be published early in 2016 (2). Subclinical atherosclerosis was highly prevalent in this middle aged male cohort and, interestingly, association with risk factors and coronary calcium was found to be stronger for femoral plaques than for plaques in the carotid arteries. These data strongly support the screening of femoral plaques as a strategy for improving cardiovascular risk scales and predicting coronary disease.



Modified from Laclaustra M et al. *J Am Coll Cardiol* 2016 (in press)

SELECTED PUBLICATIONS

Laclaustra M, Casasnovas JA, Fernández-Ortiz A, Fuster V, León-Latre M, Jimenez-Borreguero LJ, Pocovi M, Hurtado-Roca Y, Ordovas JM, Jarauta E, Guallar E, Ibañez B, Civeira F. **Femoral and carotid subclinical aterosclerosis: risk factors and coronary calcium. The Aragon Workers' Health Study.** *J Am Coll Cardiol* (accepted)

Casasnovas JA, Alcaide V, Civeira F, Guallar E, Ibañez B, Borreguero JJ, Laclaustra M, León M, Peñalvo JL, Ordovás JM, Pocovi M, Sanz G, Fuster V. **Aragon workers' health study--design and cohort description.** *BMC Cardiovasc Disord* (2012) 12: 45