CLINICAL STUDIES

VF-3D-ESSOS

Fuster-CNIC-Ferrer Cardiovascular Polypill and SECURE Trial

ATHEROBRAIN H2H Study

PESA CNIC-SANTANDER

STEMI Trials: The Metoprolol program

TAN SNIP

VF-3D-ESSOS STUDY

MRI is the gold standard for studying cardiac anatomy and function.

Almost all hospitals are today equipped with MRI scanners and have cardiologists with the expertise to perform high quality studies.

A cardiac MRI takes about 45 minutes, and this long duration severely limits the number of scans that can be performed and therefore also limits the diagnostic power of the technique.

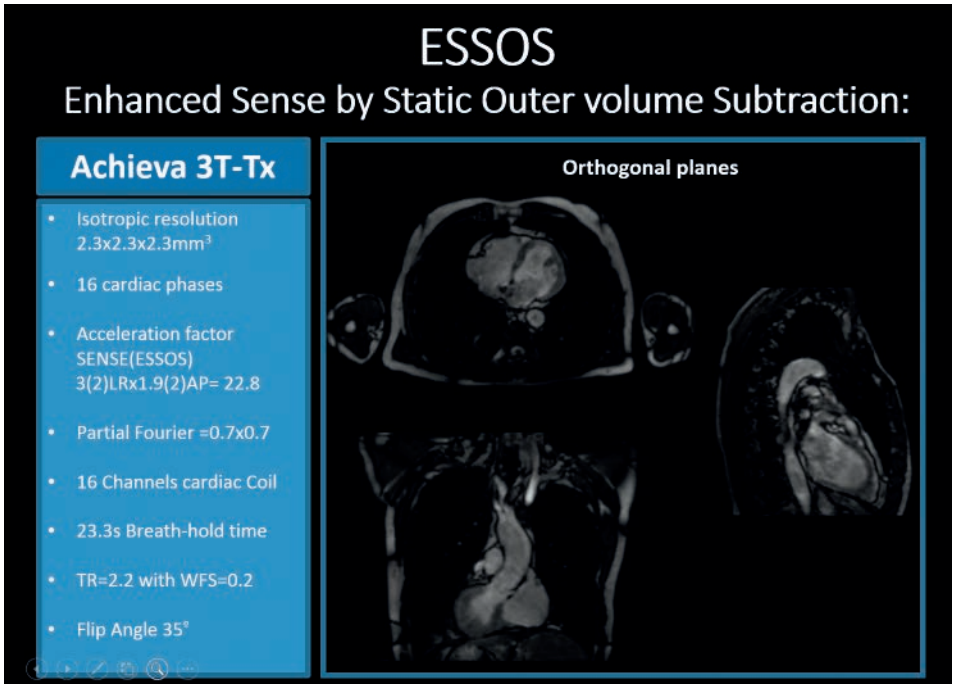
CNIC researchers are working on new MRI sequences to reduce the time of a conventional cardiac study. For this, they are using a novel 3D technology that is able to perform a scan in under 2 minutes.

The VF-3D-ESSOS (Enhanced SENSE by Static Outer volume Subtraction) study is conducted in Madrid. A total of 115 patients with different cardiac and aortic pathologies will be recruited by the participating hospitals:

- **Hospital Universitario Fundación Jiménez Díaz, Madrid**
- **Hospital Universitario Rey Juan Carlos, Móstoles, Madrid**
- **Hospital Universitario Infanta Elena, Valdemoro**
- **Hospital General de Villalba, Villalba, Madrid.**
- **Hospital Universitario Quirón, Madrid**

All participants will undergo an MRI at the CNIC core imaging facility. This MRI examination will include an additional 20-second breath-hold 3D sequence, in addition to the standard sequence. Both sequences will then be analyzed with the same hardware.

If the innovation is successful, all hospitals will be able to implement this technique and perform many more MRI scans, greatly increasing the amount and accuracy of the information obtained.

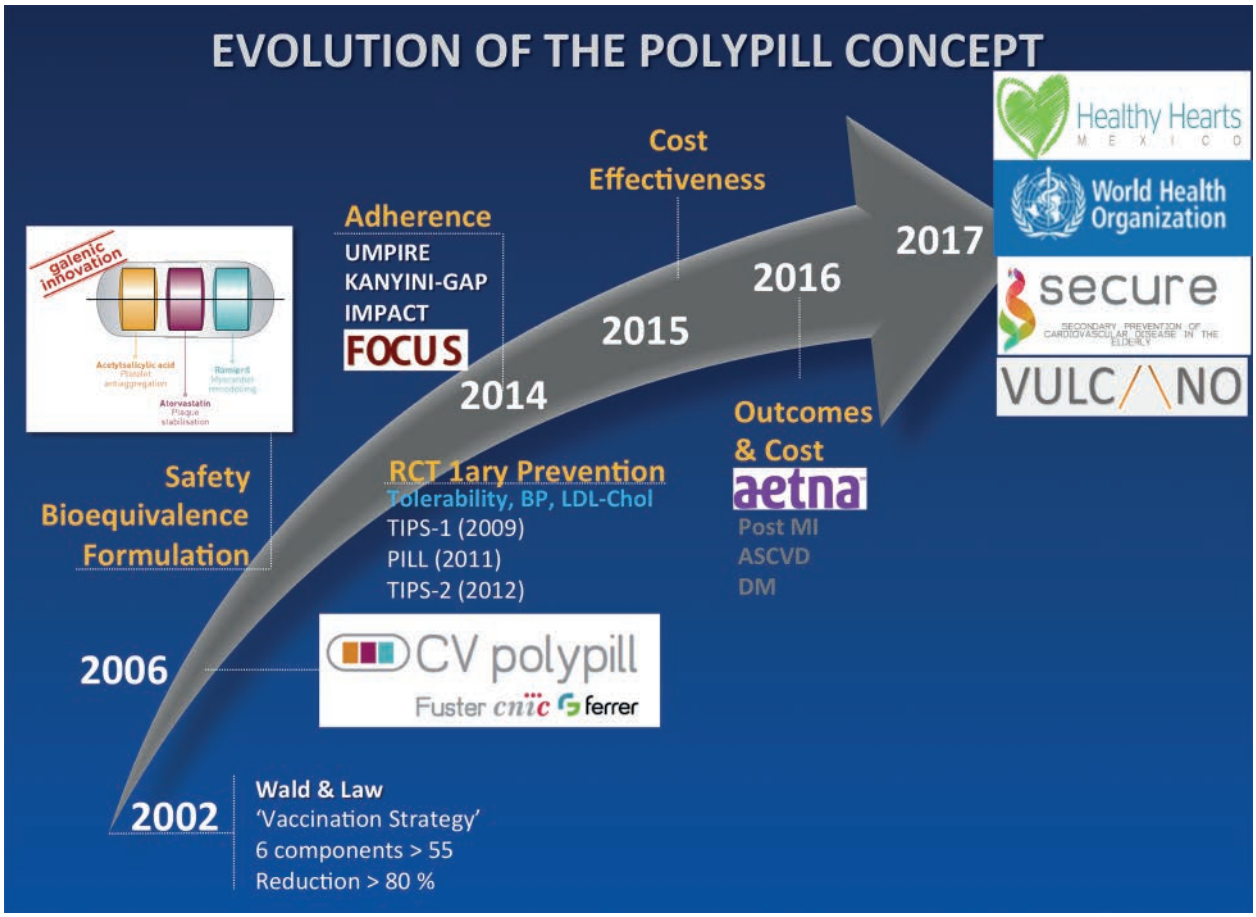


Axial, coronal and sagittal MRI of the same 3D cardiac cine sequence acquired in a breath-hold time of 23s.

Fuster-CNIC-Ferrer Cardiovascular Polypill and SECURE Trial

secure
SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE IN THE ELDERLY

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



10-years evolution of the Fuster-CNIC-Ferrer Cardiovascular Polypill Project

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

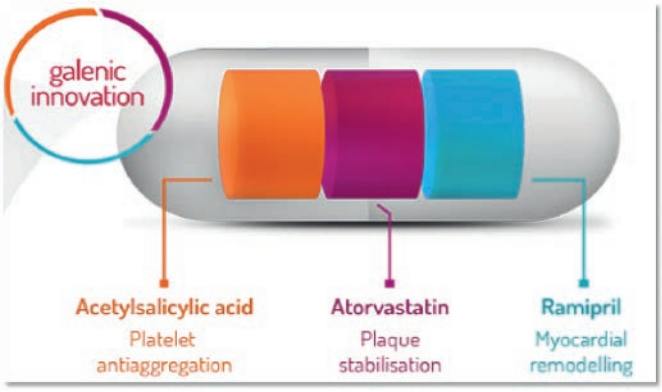
Despite ground-breaking advances in therapeutic interventions, rates of CVD mortality remain high mainly because patients are not receiving optimal medical treatment, either because of nonadherence or lack of access to medicines. A major barrier to adherence is treatment complexity, linked to the number of pills the patient has to take. The past decade has seen a surge of technical innovation in the development of a polypill strategy to improve adherence and accessibility in low and middle income countries.

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

The CNIC was recently awarded a H2020 grant to fund the first ever clinical trial testing the ability of a polypill strategy to reduce 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, the Czech Republic, Hungary, and Poland. Patients will be randomized to the Fuster-CNIC-Ferrer Cardiovascular Polypill vs. usual care and followed for 2-4 years. The kick-off meeting was held in Madrid in May 2015. Patient recruitment in all participating countries began in mid-2016. The results of SECURE will help shape clinical recommendations for the better use of medication in patients with ischemic heart disease across the world.

The Fuster-CNIC-Ferrer Cardiovascular Polypill has been approved for commercialization in more 25 countries and has been approved by the major regulatory agencies. After the success of FOCUS, SECURE will provide the final proof, so that millions of patients worldwide can enjoy simpler, more effective, and cost effective chronic treatment to decrease cardiovascular mortality and morbidity.

Fuster-CNIC-Ferrer Cardiovascular Polypill

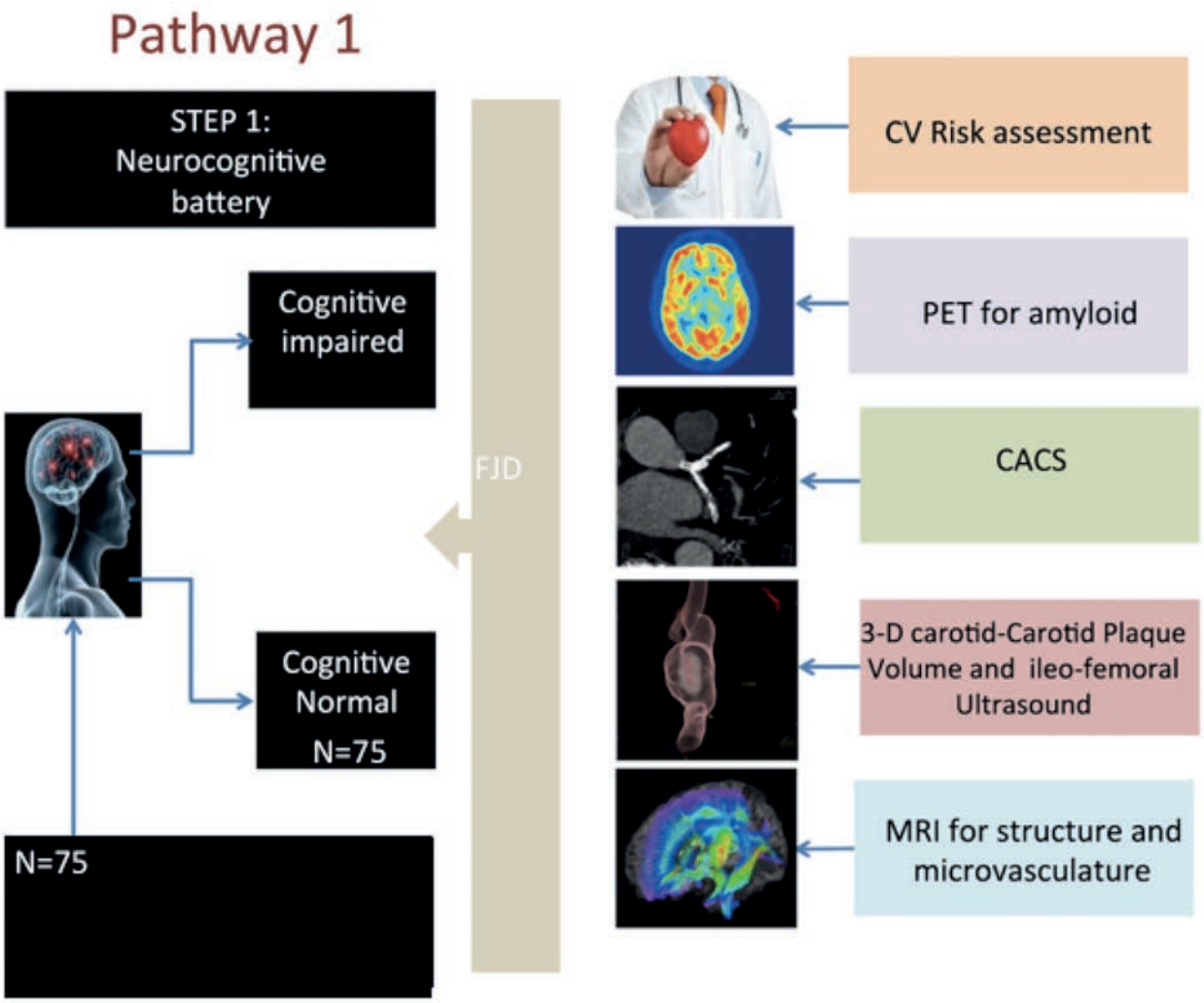


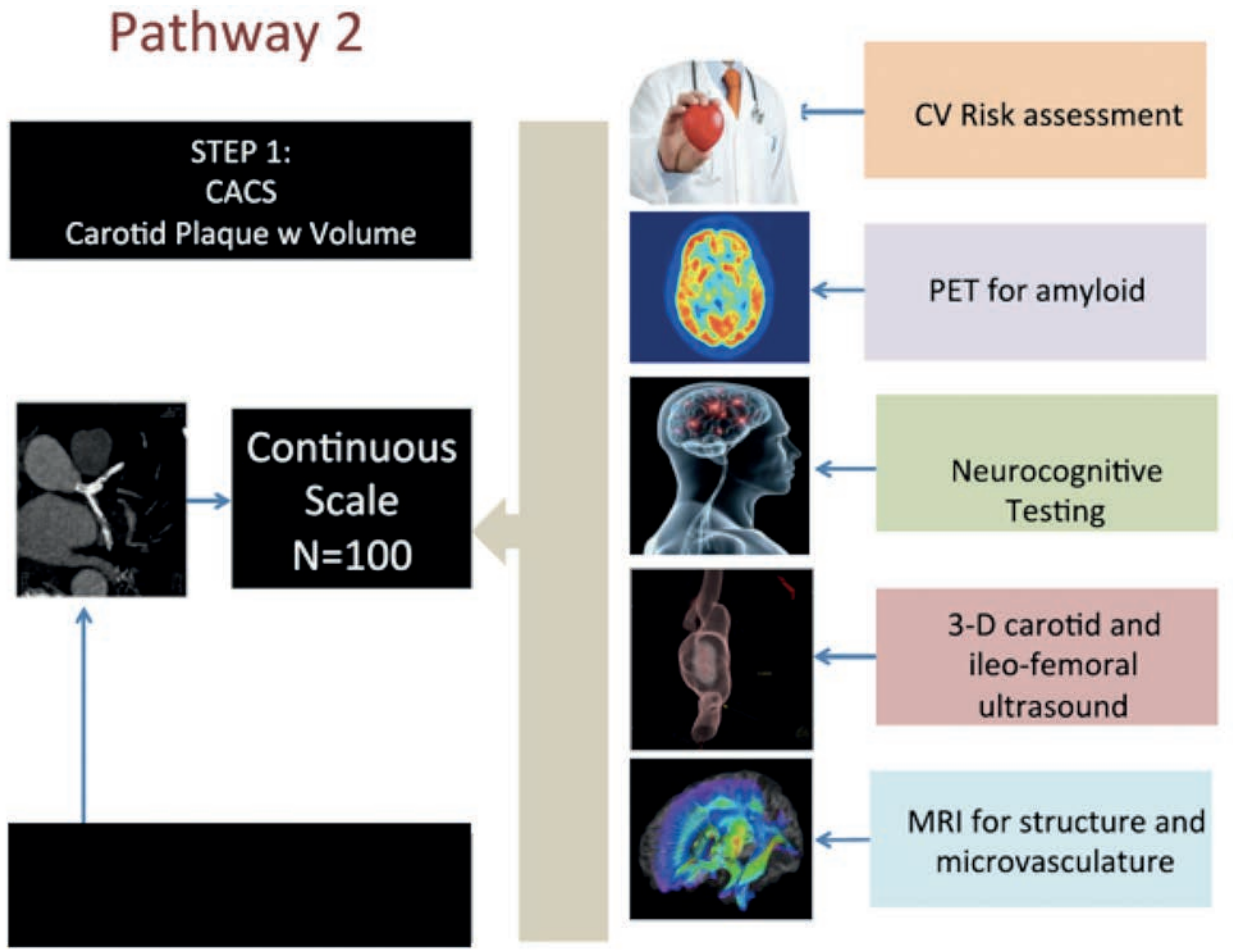
ATHEROBRAIN

Heart to Head (H2H) Spain Study

The Atherobrain - Heart to Head (**H2H**) study is a multicenter research project funded by the *Instituto de Salud Carlos III* (ISCIII) and run through partnership between the *Instituto de Investigación* at *Hospital 12 de Octubre* (i+12), the CNIC Human Imaging Unit, and several hospitals (*12 de Octubre, Gregorio Marañón, Clínico San Carlos, Fundación Jiménez Díaz, and Hospitales de Madrid*).

The H2H study is a prospective cohort study designed to unravel the relationship between subclinical atherosclerosis, cognitive decline, and Alzheimer's disease. The study will recruit 250 people aged 60 to 85 years with no cardiovascular or cerebrovascular disease, who will undergo exhaustive clinical and neurocognitive assessment as well as imaging evaluation, including anatomical and functional cerebral and carotid MRI, β-amyloid PET, 3D vascular ultrasound, and coronary calcium CT. Neurocognitive and MRI imaging will be repeated after 18 months. Two enrolment pathways have been designed: pathway 1 includes 75 participants with mild cognitive impairment and 75 control participants with normal cognition, whereas pathway 2 includes 100 patients with varying levels of coronary artery calcium score by cardiac CT.




Pathway 2
STEP 1:
CACS
Carotid Plaque w Volume
Continuous
Scale
N=100
CV Risk assessment
PET for amyloid
Neurocognitive
Testing
3-D carotid and
ileo-femoral
ultrasound
MRI for structure and
microvasculature

PESA CNIC- SANTANDER

(Progression of Early Subclinical Atherosclerosis)

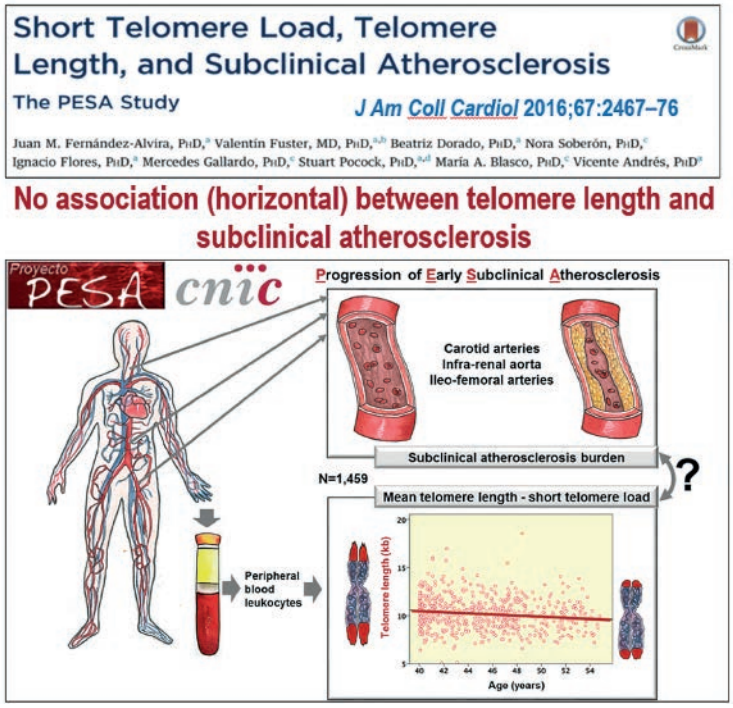
Strategies to identify individuals with subclinical alterations indicating increased risk of cardiovascular events have been boosted by the development of basic noninvasive imaging techniques (2D/3D vascular ultrasound and coronary calcium score by computed tomography) and advanced imaging techniques (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. Atherosclerotic disease in this group has already several decades of evolution and may be too advanced for prevention of future events.

The PESA CNIC-Grupo Santander is an ambitious study designed to identify new imaging and biological factors associated with the presence and progression of early phases of atherosclerosis. In 2014, PESA CNIC- Grupo Santander completed the prospective enrolment of 4184 healthy subjects aged 40 to 54 years (2.635 men and 1.549 women) who underwent 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 were additionally assessed for a complete set of cardiovascular risk factors (including lifestyle and psychosocial factors) and provided blood samples for advanced “omics” and future analyses. In addition, advanced imaging assessment by18FDG PET/MRI technology was performed at the CNIC Advanced Imaging Unit during 2013 and 2014 in 940 individuals in whom a significant plaque burden was detected by ultrasound and CT.

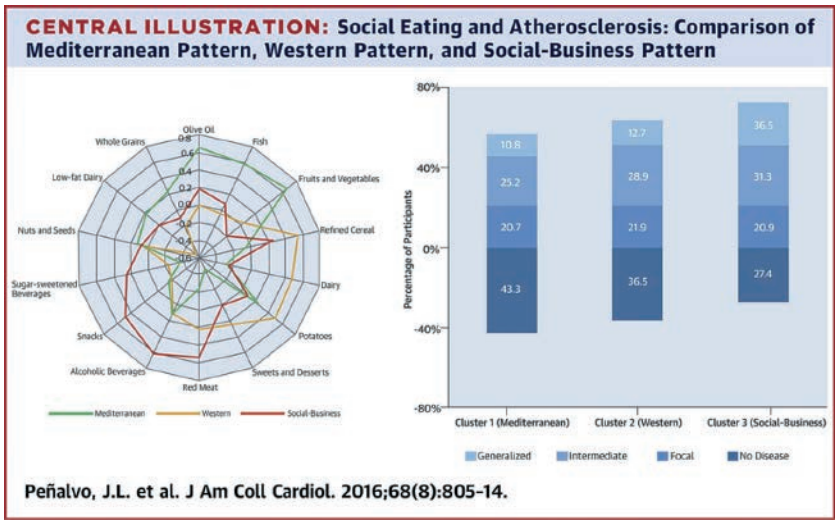
All PESA participants are followed-up at 3 and 6 years to assess the evolution of atherosclerotic plaques and to determine how the detection of subclinical disease may impact the risk of future cardiovascular events. By the end of 2016, more than 3700 participants have already undergone the 3-year follow up visit (visit 2). Similarly, more than 500 individuals have performed, the intermediate vascular MRI study at 3-year including cardiac MR sequences. These cardiac MR studies will allow a comprehensive characterization of subclinical myocardial disease.

The study also received approval for research into the association between atherosclerosis initiation/progression and telomere dysfunction in circulating leukocytes, and leukocyte samples were collected from a subgroup of 1.456 PESA participants. In May 2016 the article entitled “Short Telomere Load, Telomere Length, and Subclinical Atherosclerosis in the PESA Study” with the results, was published in the **Journal of American College of Cardiology, Volume 67, Issue 21; Pages 2467-2476**. The conclusion is that in a cross-sectional study of a middle-aged population, average leucocyte telomere length and short telomere load are not significant independent determinants of subclinical atherosclerosis. However, the longitudinal follow-up of PESA participants will assess long-term associations between telomere length and progression of subclinical atherosclerosis.

Furthermore, in August 2016, the article entitled “Association between a Social-Business Eating Pattern and Early Asymptomatic Atherosclerosis” was published in the **Journal of American College of Cardiology. 2016, Volume 68, Issue 8; Pages 805-814**. This article describe a new social-business eating pattern, followed approximately by 1 in 5 participants enrolled in the PESA cohort, characterized by high consumption of red and processed meat, alcohol, and sugar-sweetened beverages, and by frequent snacking and eating out as part of an overall unhealthy life-style. This eating pattern is associated with an increased prevalence, burden, and multisite presence of subclinical atherosclerosis. These results suggest that diet and overall life-style habits are important in early atherosclerosis and could inform strategies to reduce the burden of CVD in similar populations. Ongoing PESA follow-ups will enable to study the associations between overall life style habits with subclinical disease and subsequent cardiovascular event.



No association (horizontal) between telomere length and subclinical atherosclerosis.



Social Eating and Atherosclerosis: Comparison of Mediterranean Pattern, Wester Pattern, and Social-Business Pattern.

SELECTED PUBLICATIONS

López-Melgar B, Fernández-Friera L, Sánchez-González J, Vilchez JP, Cecconi A, Mateo J, Peñalvo JL, Oliva B, García-Ruiz JM, Kauffman S, Jiménez-Borreguero LJ, Ruiz-Cabello J, Fernández-Ortiz A, Ibáñez B, Fuster V. **Accurate quantification of atherosclerotic plaque volume by 3D vascular ultrasound using the volumetric linear array method.** Atherosclerosis. 2016 May; 248; 230-7.

Fernández-Alvira JM, Fuster V, Dorado B, Soberón N, Flores I, Gallardo M, Pocock S, Blasco MA, Andrés V. **Short Telomere Load, Telomere Length, and Subclinical Atherosclerosis in the PESA Study.** J Am Coll Cardiol. 2016 May 31;67(21):2467-76.

Peñalvo JL, Fernández-Friera L, López-Melgar B, Uzhova I, Oliva B, Fernández-Alvira JM, Laclaustra M, Pocock S, Mocoroa A, Mendiguren JM, Sanz G, Guallar E, Bansilal S, Vedanthan R, Jiménez-Borreguero LJ, Ibañez B, Ordovás JM, Fernández-Ortiz A, Bueno H, Fuster V. **Association between a social-business eating pattern and early asymptomatic atherosclerosis.** J Am Coll Cardiol. 2016 Aug 23;68(8):805-14.

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. β-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 β-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 were recruited. 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. Over 300 patients underwent 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 were 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 were performed at the CNIC using a unique magnet system.

Currently both trials are in the follow-up phase.

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.

The TANSNIP-PESA randomized control trial: a 30-month worksite-based lifestyle program to promote cardiovascular health in middle-aged bank employees

Existing tools for characterizing atherosclerosis and determining the risk of its complications are inadequate. These deficiencies limit effective management across the spectrum of this disease, and therefore opportunities are lost for early, cost-effective interventions in sub-clinical disease, while high-risk populations with manifest disease are administered treatments almost indiscriminately. This leads to high 'numbers-needed-to-treat' (NNT), unnecessary patient risk, wasted resources, and unsustainable costs for health care purchasers.

In a relatively low-risk population (the PESA-CNIC cohort), we will study whether a personalized worksite based lifestyle intervention, driven by imaging data (2D and 3D-ultrasound of carotid and ilio-femoral arteries, and coronary artery calcification) results in changes in behavior, improved control of risk factors, and reduced progression of subclinical atherosclerosis plaque burden (SAPB).

TANSNIP is a randomized control trial (RCT) including middle–aged bank employees from the PESA cohort, stratified by SAPB (high SABP n=260; low SABP n= 590). Within each stratum, participants are randomized 1:1 to join a lifestyle program or receive standard care. The program consists of three elements: (1) 12 personalized lifestyle counseling sessions using motivational interviewing (MI) over a 30-month period; (2) a wrist-worn physical activity tracker, and (3) a sit-stand workstation. The primary outcome measure is a composite score of blood pressure (BP), physical activity, sedentary time, body weight, diet, and smoking (the adapted FUSTER-BEWAT score), measured at baseline and at 1-, 2-, and 3-year follow-up. Secondary outcomes are individual changes in lifestyle behaviors and specific changes in anthropometric measures, blood biomarkers, self-rated health, work-related outcomes (including work productivity and absenteeism), health care consumption, program process measures, and cost measures at different measurement points.

The expectation is that individual awareness of CVD risk stratification in the intervention group will lead to a reduction in the prevalence of CV risk factors related to lifestyle and an increase in physical activity compared with the control group. A second rationale is that the level of compliance with the comprehensive 3-year worksite-based lifestyle intervention will be higher among participants with a high imaging-defined CV risk.

TANSNIP-PESA started including participants in May 2015 and the first MI session took place in June 2015. So far, a total of 1027 participants have been included in the trial (484 from the control group and 477 from the intervention group). Of these, 286 participants belong to the high SAPB group and 675 to the low SAPB group. In the intervention group, 449 participants have already their first MI session; all participants are using the Fitbit activity monitor and 323 (68%) participants are willing to use the sit-stand workstation (60% already have the station installed at their workplaces). Inclusion is scheduled to finalize early in 2017, surpassing the sample size initially expected. The study is scheduled to end in September 2019.

Five focus group have been held with at least 5 intervention group participants who have completed their first 7 MI sessions. Overall, participants indicated that they were very satisfied with the intervention program.

To measure MI session quality and improve the content of the TANSNIP-PESA program, every 6 months random MIs are recorded and participants are surveyed by the study technicians. The overall results of these assessments have been very positive.

In 2016 the trial design paper was published in the American Heart Journal (doi: 10.1016/j.ahj.2016.11.002).

Participating research teams

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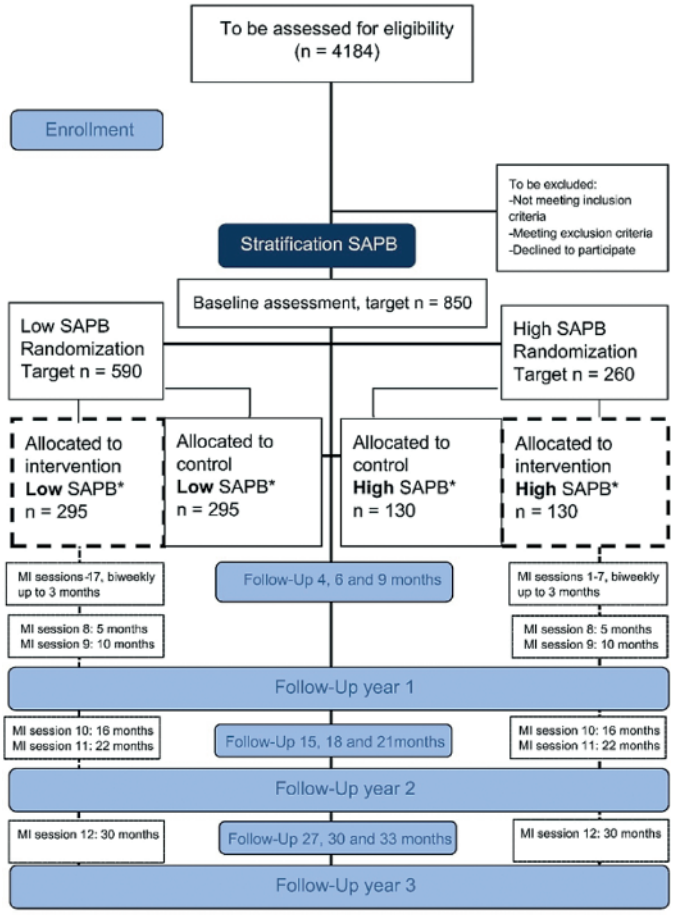
Miriam Fernández Gallardo

Study figure TANSNIP-PESA



SAPB= Subclinical Atherosclerotic Plaque Burden.

Scoring of different elements of the adapted FUSTER-BEWAT primary outcome measure.

SCORE	0	1	2	3	4
Score Systolic/diastolic blood pressure* (mm Hg)	≥140/90	134-139/87-89	128-133/84-86	121-127/81-83	≤120/80
Physical activity (steps/d)	<5500	5500-6999	7000-8499	8500-9999	≥10000
Sitting (h/d)	≥12.5	11-<12.5	9.5-<11	8-<9.5	<8
BMI (kg/m2) †	≥32	30-31.9	27-29.9	25-26.9	<25
Fruit & vegetable consumption (serves/d)	≤1	2	3	4	≥5
Smoking (units/d)	>20	10-20	1-9	<1	0

Total score range 0-24, with a higher score indicating a lower risk score.
* If systolic and diastolic blood pressure do not fall in the same group, then the participant is assigned to the group with the relatively highest blood pressure (i.e. systolic or diastolic)
† At follow-up visits, a >5% decrease in BMI will add 1 extra point in the BMI score except for those participants who have changed BMI categories since baseline or are already in the normal weight category (BMI<25). Similarly, a >5% increase in BMI at follow-up will mean 1 point less in the BMI score except for participants who have changed BMI categories since baseline or with BMI≥32.