The Evolving Science of Health
Imaging, Genetics and Behavior

The Heart and the Brain

Lima, Nov 17, 2018
No Disclosures
From Aging / Disease to Youth / Health

NHLBI $-1

CABG - ASA
Imaging-MRI
PCI- Rapamycin
FREEDOM

Secondary
50-100 yrs

Primary
25-50 yrs

Primordial
00-25 yrs

1) TANSNIP

4) HRP
PESA
AWHS

6) SHE

7) HARLEM
NY - NIH
VILLAGE

50/50

3) AGING

1) IIIP

4) 1) IIIP

5) IIIP

6) SHE

7) HARLEM
Morphology and Function of Platelets

1975-1985, Periop. ASA + Dipyridamole On Early Postop. SVBG Patency

**Distal Anastom.**

- **Cumulative occlusion rates (%)**
- **Days**
- **Placebo**
- **Treated**

**Patients**

- **Placebo**
- **Treated**

**References**

V Fuster, JH Chesebro et al., *Circ* 1986; 73:227
1985 -1995, **High Risk Plaque**

Mild at Angiography, **Significant at IVUS & Pathology**

**STABLE PLAQUE**
Angiogr., IVUS

**UNSTABLE PLAQUE**
Angiogr., IVUS, Pathology

**RUPTURED PLAQUE**
Pathology

---

*Modified from G Niccoli et. al. JACC Cardiovasc Imag. 2013;6:1108*


1995–2005, Restenosis & Sirolimus DES

Gallo R, Fuster V, Badimon JJ et al. Circ 1999; 99; 2164
Worthley SG, Badimon JJ, Fuster V. Circ 2000; 101: 2956
SO Marx & A Marks Circ. 2001; 104: 852
2005 – 2010, Outcomes – Death / Stroke / Mi

5-Year Event Rates: 26.6% vs. 18.7%

Logrank P=0.005

Environment vs Genetics

AV Khera, V Fuster, PM Ridker et al., NEJM 2016; 375:2349
The Evolving Science of Health Imaging, Genetics and Behavior

The Heart and the Brain

Lima, Nov 17, 2018
Subclinical Atherosclerotic Burden—N= 12,000
Coronary Calcification

2D/3D-VUS

B López-Melgar, V Fuster et. al. J Am Coll Cardiol. 2017;70:301
Subclinical Atherosclerotic Burden
Coronary Calcification & 2D/3D-VUS

4a). The Bioimage Study (N=5808) Cumulative 3-Year MACE Endpoints (N=216)

Reclassification: CAC 24% - cPB 18%


Sept 1, 2017 – 8 Year Follow-up
**The PESA Study (N=4184) – 2D/3D VUS Atherosclerosis Assessment (mm³)**

**Male**
- 40-44 years: 7.7% Generalized (4-6 vascular sites), 28.5% Intermediate (2-3 vascular sites), 23.7% Focal (1 vascular site), 40.1% No Disease
- 45-49 years: 17.2% Generalized, 34.1% Intermediate, 21.9% Focal, 26.8% No Disease
- 50-54 years: 34.1% Generalized, 37.6% Intermediate, 16.2% Focal, 12.1% No Disease

**Female**
- 40-44 years: 2.5% Generalized, 17.2% Intermediate, 21.2% Focal, 59.1% No Disease
- 45-49 years: 8.6% Generalized, 26.1% Intermediate, 21.6% Focal, 45.2% No Disease
- 50-54 years: 11.7% Generalized, 27.1% Intermediate, 25% Focal, 33.3% No Disease

4b2). The PESA Study (N=3860) Femoral And Carotid 3D-VUS Plaque Volume

B López-Melgar, V Fuster et. al. J Am Coll Cardiol 2017;70:301
4b3). The PESA Study (N=4184)
Subclinical Atherosclerosis – FRS & ERS

L Fernández-Friera, V Fuster et al., Circulation 2015; 131:2104
4b4). Absence of Risk Factors
Relation Between LDL-C and Atherosclerosis

L Fernández-Friera et. al. J Am Coll Cardiol 2017;70:2979
4b5). Ideal CV Health Fuster-BEWAT Scores (FBS)

ICHIS AND SUBCLINICAL ATHEROSCLEROSIS EXTENT

<table>
<thead>
<tr>
<th></th>
<th>Poor</th>
<th>Intermediate</th>
<th>Ideal</th>
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<tbody>
<tr>
<td>Generalized</td>
<td>32.0</td>
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<td>36.5</td>
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<td>14.4</td>
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<td>22.1</td>
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<tr>
<td>Free</td>
<td>17.1</td>
<td>35.4</td>
<td>52.6</td>
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FBS AND SUBCLINICAL ATHEROSCLEROSIS EXTENT

<table>
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</tr>
<tr>
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<td>20.0</td>
<td>34.7</td>
<td>47.3</td>
</tr>
</tbody>
</table>
**PET (¹⁸F-FDG), MRI (T1/T2)**

**Study population**
≈950 individuals who had baseline vascular PET/MRI and will returned for follow-up vascular MRI to CNIC

**Imaging protocol**
A cardiac MRI study, including cine (LV function and structure), T1- and T2-mapping (Inflammation and diffuse fibrosis) and LGE (scar)

**Advantages / Requirements**
- Instead of having a vascular PET (30 min), they will have a cardiac MRI (novel heart assessment in PESA)
- Fibrosis quantification: creatinin / Hb
- Additional Budget: contrast for 950 cardiac MRI: 46,400 € (personal included)
PET/MRI Protocol For The Assessment of Multiterritorial Atherosclerosis

L Fernández-Friera, V Fuster, J Sanz et. al. J Am Coll Cardiol. 2018 (Subm.)
Carotid, aortic, and ilio-femoral $^{18}$F-FDG PET/MRI was performed in 755 individuals (age 40-54 years, 83.7% men) with known plaques detected by 2D/3D EV-US and/or EBCT in PESA study. Arterial inflammation was present in 48.2% of individuals (24.4% femorals, 19.3% aorta, 15.8% carotids, and 9.3% iliacs) and plaques in 90.1% (73.9% femorals, 55.8% iliacs, and 53.1% carotids). F-FDG arterial uptakes and plaques significantly increased with cardiovascular risk factors ($p<0.01$). Coincident F-FDG uptakes were present in 11% of plaques and most uptakes were detected in plaque-free arterial segments or 61%. These findings suggest an arterial inflammatory state at early stages of atherosclerosis.

L Fernandez-Friera, V Fuster et al., 2018 (Subm)
Atherosclerosis (MRI) & Inflammation (PET) In Men And Women In PESA

$^{18}$F-FDG PET/MRI in PESA

Atherosclerosis prevalence (positive plaque presence)

- T1-weighted: 53.1%
- T2-weighted: 55.8%

Arterial inflammation prevalence (positive $^{18}$F-FDG uptake)

- PET/MR: 15.8%
- PET/MR: 19.3%
- PET/MR: 9.3%
- PET/MR: 24.4%

L Fernández-Friera, V Fuster, J Sanz et. al. J Am Coll Cardiol. 2018 (Subm.)
### Atherosclerosis (MRI) & Inflammation (PET) in Men and Women in PESA

<table>
<thead>
<tr>
<th>Vascular Territories</th>
<th>Atherosclerosis by MRI</th>
<th>Arterial inflammation by PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid</td>
<td>56.0 / 38.2%</td>
<td>CAROTID 17.3 / 8.1%</td>
</tr>
<tr>
<td>Thoracic Aorta</td>
<td></td>
<td>THORACIC AORTA 15.8 / 5.7%</td>
</tr>
<tr>
<td>Abdominal Aorta</td>
<td>55.4 / 57.2%</td>
<td>ABDOMINAL AORTA 8.9 / 7.3%</td>
</tr>
<tr>
<td>Iliac</td>
<td></td>
<td>ILIAC 10.6 / 2.4%</td>
</tr>
<tr>
<td>Femoral</td>
<td>78.3 / 51.2%</td>
<td>FEMORAL 26.1 / 15.4%</td>
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L Fernández-Friera, V Fuster, J Sanz et. al. J Am Coll Cardiol. 2018 (Subm.)
Relationship of Uptake And Plaque Presence With CVRF Burden, Age & Vascular Territory

L Fernández-Friera, V Fuster, J Sanz et. al. J Am Coll Cardiol. 2018 (Subm.)
Relationship of Uptake And Plaque Presence With CVRF Burden,

L Fernández-Friera, V Fuster, J Sanz et. al. J Am Coll Cardiol. 2018 (Subm.)
Modifiable CV RFrs vs Genetics

AV Khera, V Fuster, PM Ridker et al., NEJM 2016; 375:2349
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The Heart and the Brain

Lima, Nov 17, 2018
Genetic Risk vs Unhealthy Lifestyle and Coronary Disease

A healthy lifestyle score (7) and a polygenic score of DNA sequence polymorphisms (50), we quantified genetic risk for CAD in four prospective cohorts – 7814 participants in the Atherosclerosis Risk in Communities (ARIC) study, 21,222 in the Women’s Genome Health Study (WGHS), and 22,389 in the Malmö Diet and Cancer Study (MDCS) – and in 4260 participants in the cross-sectional BioImage Study. Across four studies involving 55,685 participants, lifestyle and genetic factors were independently associated with susceptibility to CAD. Among participants at high genetic risk, a favorable lifestyle was associated with a 50% lower relative risk of CAD.

AV Khera, V Fuster, PM Ridker et al., NEJM 2016; 375:2349
Polygenic Sc. (50), Lifestyle (4) - 55,685 ARIC, MDCS, BioImage, WGHS.

A. Atherosclerosis Risk in Communities

**Genetic Risk**
- High; hazard ratio, 1.75 (1.46–2.10)
- Intermediate; hazard ratio, 1.27 (1.09–1.49)
- Low (reference)

**Lifestyle Risk**
- Unfavorable; hazard ratio, 1.71 (1.47–1.98)
- Intermediate; hazard ratio, 1.18 (1.02–1.36)
- Favorable (reference)

---

AV Khera, V Fuster et al. NEJM 2016;375:2349
S Jaiswal, V Fuster, et al. NEJM 2017;377:111

>Gen<RF - 50% MACE
Genetics - Statins
TET2 - M1
A Genomic Risk Score for CAD (metaGRS)
Greater Association with Future CAD

Macrophages In Cardiovascular Disease

L Honold et. al. Circ Res. 2018;122:113
Temporal Sequence & Functions of Leukocytes in the CAs

A M1

M2

TET2

Thrombosis promoting factors

Thrombosis resisting factors

Vascular Thrombosis/ACS

Asymptomatic Plaque Healing

Loss of TET2 in Hematopoietic Cells and Atherosclerosis in a Murine Model

A Aortic-Root Sections, According to Tet2 Status

<table>
<thead>
<tr>
<th></th>
<th>5 Wk</th>
<th>9 Wk</th>
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<tr>
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B Size of Aortic-Root Lesions, According to Tet2 Status

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C Aortic Atherosclerosis, According to Tet2 Status

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D Involvement of Aorta, According to Tet2 Status

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Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease


CANTOS: A Gigantic Proof-of-Concept Trial

Borja Ibañez, Valentin Fuster
CANTOS Persistent Stem Cell Driven Inflammation In Atherosclerosis

TR Cimato. Eur Heart J. 2017; 38: 433
ML Senders, ZA Fayad, C Perez-Medina et. al. JACC 2018;71:321

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The Heart and the Brain

Lima, Nov 17, 2018
Environmental vs Genetics

AV Khera, V Fuster, PM Ridker et al., NEJM 2016; 375:2349
From Aging / Disease to Youth / Health

Heart & Brain

Secondary
50-100 yrs

Primary
25-50 yrs

Primordial
00-25 yrs

1) TANSNIP
2) SHE
3) AGING
4) HRP PESA AWHS
5) IIIP 50/50
6) HARLEM NY - NIH VILLAGE
7) HARLEM

CABG -ASA
Imaging-MRI
PCI- Rapamycin
FREEDOM
Risk Factors of CV Disease
White Matter & Lacunar Lesions (DBD)

Cortical atrophy
Plaques and tangles
Synucleopathy
White matter abnormalities?
Stroke
Hypoxia
Obstructive sleep apnea
Diabetes mellitus
Traumatic brain injury
Congestive heart failure
Hypertension

White matter abnormalities
Hypertension
Diabetes mellitus
Congestive heart failure
Kidney or liver disease?
Thyroid disease
Vitamin B₁₂ deficiency

Lacunar stroke
Diabetes mellitus
Hypertension
High cholesterol?
Emboli

Hippocampal atrophy
Hippocampal sclerosis
Obstructive sleep apnea
White matter abnormalities?
Hypoxia
Plaques and tangles
Chronic depression or stress
Hypertension

Reduced cerebral blood flow
Diabetes mellitus
Hypertension
 imread?Cholesterol
Smoking
Cerebral amyloid angiopathy

JC Kovacic, V Fuster et. al. Circulation. 2011;123:1900
Microcirculation, Cognitive – 12 Studies


12. TANSNIP (V Fuster et al) 2017- 2018- 2 Prospective Paths
8. Distribution and Prevalence Dementia

Demented subjects (45%, n=284/627)

10. Cardiovascular Risk Factors From Childhood & Midlife Cognitive Performance

YFS (SP Rovio et al), J Am Coll Card 2017; 69: 2279
12. **TANSNIP Pathways 1, 2, 3**

**STEP 1:** Neurocognitive battery

- Cognitive impaired N=50
- Cognitive Normal N=50

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**CV Risk Assessment**

- CACS

**3DVUS-Carotid Plaque Volume and ileo-femoral**

**PET for Amyloid**

**MRI- functional + Micro/ Macrovasculature**

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**FAD**

N=2750

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The Evolving Science of Health Imaging, Genetics and Behavior

The Heart and the Brain

Lima, Nov 17, 2018
Vascular Siffness

Poor vascular health

Atheroscler. Like

Brain dysfunction

Cognitive impairment

Hypoxia ischemia

Inflammation Oxidative stress

Secretase activity

↓ Aβ, tau clearance

+ AD pathology

↓ BBB
The Aging CV System Interacting With Brain Pulsatility And Perfusion

A de Roos et. al. Circulation. 2017;135:2178
S Strickland, J Clin Invest. 2018;128:556
Possible Influence of Aβ on Fibrin Deposition and AD Pathology

S Strickland, J Clin Invest. 2018;128:556
The Evolving Science of Health
Imaging, Genetics and Behavior

The Heart and the Brain

Lima, Nov 17, 2018
From Aging / Disease to Youth / Health

Heart & Brain

Primordial
00-25 yrs

Primary
25-50 yrs

Secondary
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CABG - ASA
Imaging-MRI
PCI- Rapamycin
FREEDOM

1) SHE
2) TANSNIP
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4) HRP
   PESA
   AWHS
5) IIIP
   NY - NIH
   VILLAGE
6) SHE
7) HARLEM
   NY - NIH
   VILLAGE

Heart & Brain

50-100 yrs
5). A Health Center In The Adult Brain (?)

To Stimulate / Motivate

NHLBI
Kenya Model -BP

GHS, Cardona, Spain

JACC 2016; 67:476
From Aging / Disease to Youth / Health

Heart & Brain

**Primordial** 00-25 yrs

**Primary** 25-50 yrs

**Secondary** 50-100 yrs

CABG - ASA Imaging-MRI PCI- Rapamycin FREEDOM

4) HRP PESA AWHS

1) 1)

2) TANSNIP

5) IIIP 50/50

3) AGING

6) SHE

7) HARLEM NY - NIH VILLAGE
6). Child’s Brain Development
Less Networking Brings Attention

Increasing Communications among Brain Regions over Time

JN Giedd. Scientific American 2015;312:32
6a). CHILDREN’S PROGRAM – N=50,000

EDUCATIVE GOAL: HEALTHY HABITS FOR CHILDREN BETWEEN 3 & 5 YRS

- HOW YOUR BODY & HEART WORK
- HEALTHY FOOD HABITS
- PHYSICAL ACTIVITY
- EMOTIONAL HABITS TO AVOID ADDICTIONS

CHILDREN

- 3-5
  - Valentin Fuster
  - Monstruos supersanos
  - Pequeña Ciencia de la Salud

- 6-8
  - Valentin Fuster
  - La Cocina de la Salud
  - Corazon y Mente

- 9-14
  - Ferran Adrià Valentin Fuster Josep Corbera
  - La Ciencia y la Vida
  - El circulo de la motivacion

GENERAL PUBLIC

- Valentin Fuster
  - La Mediana Ciencia de la Salud
CHILDREN’S PROGRAM – N=50,000

Pre-school & Primary Study (CCAA Madrid)
- **C1**: 6 y.o. 5
- **C2**: 6 y.o. 5
- **C3**: 12 y.o. 11

24 schools/2,062 children
21 schools/469 children (who started at 3 y.o.)

Primary Study (CCAA Madrid)
- **C1**: 6 y.o. 12
- **C2**: 6 y.o. 12
- **C3**: 6 y.o. 12
- **C4**: 6 y.o. 12

48 schools/1,769 children

Secondary Study (CCAA Catalonia - Madrid)
- **C1**: 8
- **C2**: 8
- **C3**: 8

24 High schools / 1,200 children

**Intervention** | **Control** | **Pre-school** | **Primary** | **Secondary**
From Aging / Disease to Youth / Health

Heart & Brain

Secondary
50-100 yrs

Primary
25-50 yrs

Primordial
00-25 yrs

4) HRP
PESA
AWHS

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7) HARLEM
NY - NIH
VILLAGE

1) CABG -ASA
Imaging-MRI
PCI- Rapamycin
FREEDOM

2) TANSNIP

3) AGING
50/50

117x292
50-100 yrs
25-50 yrs
00-25 yrs

6) SHE
7) HARLEM
4) HRP
PESA
AWHS

50/50

Village
### 7a). HARLEM - THE FAMILIA STUDY

<table>
<thead>
<tr>
<th>Children 3 Groups</th>
<th>Caregivers 3 Groups</th>
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<tbody>
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<td>(1)</td>
<td>(2)</td>
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#### (1)
- **Start**
- **KAH-BEA Mol. Genomics**
- **S-KAH-BEA**
- **Contr./Interv. Intervention**
- **Control PPPI IIIP**

#### (2)
- **Start**
- **BEWAT Point of Care**
- **3D-US Mol. Genomics**

#### (3)
- **BEWAT Point of Care**
- **3D-US Mol. Genomics**

### Table

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<thead>
<tr>
<th>Year</th>
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<tr>
<td>1st</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>2nd</td>
<td>O</td>
<td>I</td>
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<tr>
<td>3rd</td>
<td>I</td>
<td>O</td>
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<tr>
<td>4th</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

### Diagram

- **KAH-BEA**
- **S-KAH-BEA**
- **BEWAT**
- **3D-US**
- **Mol. Genomics**

---

**Note:** The diagram and table represent a study design with different groups and years, focusing on children and caregivers with interventions and control groups.
From Aging / Disease to Youth / Health

Heart & Brain

Primordial
00-25 yrs

Primary
25-50 yrs

Secondary
50-100 yrs

CABG - ASA
Imaging - MRI
PCI - Rapamycin
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1) 1)
2) TANSNIP
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PESA
AWHS

6) SHE

7) HARLEM
NY - NIH
VILLAGE

5) IIIP
50/50
7b). NIH-NY

**PPG**

**PI: Valentin Fuster**

**N=2,500**
From Genetics to Environment

Primordial
00-25 yrs

Primary
25-50 yrs

Secondary
50-100 yrs

CABG-ASA
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4) HRP
PESA
AWHS

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7) HARLEM
NY-NIH
VILLAGE

NY - NIH VILLAGE
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The Heart and the Brain

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Platelet Studies “In Vivo”

1975, Pigs

1976, Dogs
Scintiphoto of Intact Dog
At 30 Hrs. Post IV $^{111}$In-labeled Platelets

Untreated
Uptake in Graft Region

Treated with ASA + Dipyridamole
No Uptake In Cardiac Region

V Fuster et. al. Circ.1979;60:1508
Randomized Trials With Drug-eluted Stents
Restenosis Rate At 6 Months

Trial: N: Drug: Funding:
ASPECT 177 Paclitaxel Cook Inc.
RAVEL 238 Sirolimus Cordis, J&J
SCORE 106 QP-2 (Taxol) Quanam
TAXUS-1 61 Paclitaxel Boston Sc.

RAVEL (MC Morice, JE Sousa et al.) ESC- Sept 2001
J-F Toussaint, V Fuster et al. ATVB 1995; 15:1533 - Diffuse
V Fuster, JJ Badimon, L Badimon NEJM 1992; 326:242 & 310 - Diffuse
E Falk, PK Shah, V Fuster Circ 1995; 92:657
Variables included in the prediction model

AWHS - M Lacaustra, V Fuster et al. JACC 2016; 67: 1263
Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease


Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prevention Setting


Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease


Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Morphology and Function of Platelets

1975-1985, *Periop. ASA + Dipyridamolone On Early Postop. SVBG Patency*

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- **Treated**

**Patients**

- **Placebo**
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Logrank P=0.005

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- **Ideal:** 13.9 (Generalized), 28.8 (Intermediate), 21.9 (Focal), 52.6 (Free)

**FBS AND SUBCLINICAL ATHEROSCLEROSIS EXTENT**

- **Poor:** 28.5 (Generalized), 34.8 (Intermediate), 16.7 (Focal), 20.0 (Free)
- **Ideal:** 15.1 (Generalized), 28.9 (Intermediate), 21.3 (Focal), 47.3 (Free)

*JM Fernandez-Alvira, V Fuster, S Pocock et al 2017;70:2463*
**Caixa Program Project**

**Project Leader:** Valentín Fuster, MD, PhD

**ANIMAL MODELS**

**Epidemiology Imaging**

**Genomics Bioinformatics**

**UNIVERSITY OF VIRGINIA**

**PARTNER INSTITUTION**

- **José J. Fuster (PhD):** clonal hematopoiesis, experimental atherosclerosis models
- **Gary Owens (PhD):** experimental atherosclerosis models
- **Stephen S. Rich (PhD):** molecular genomic epidemiology

**HOST INSTITUTION**

- **Valentín Fuster (MD, PhD):** cardiologist, imaging, epidemiology, public health
- **Juan Miguel Fernández-Alvira (PhD):** epidemiology, public health
- **Stuart Pocock (PhD):** medical statistics
- **Ana Dopazo (PhD):** genomics
- **Fátima Sánchez-Cabo (PhD):** bioinformatics
- **Vicente Andrés (PhD):** cardiovascular aging, experimental atherosclerosis models
Immunity in Atherogenesis