Scientific Bases of Health Subclinical Systemic Disease

Imaging  Omics  Behavior
From Aging / Disease to Youth / Health

NHLBI $-1

Secondary
50-100 yrs

Primary
25-50 yrs

Primordial
00-25 yrs

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

Surgery
Intervention
Pharmacology.
Imaging
Genetics/Tr
From Aging / Disease to Youth / Health

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7) HARLEM VILLAGE MEXICO

Surgery Intervention Pharmacology, Imaging Genetics/Tr
Subclinical Atherosclerotic Burden – N = 12,000
Carotid 2D/3D-VUS  Coronary Calcification

The High Risk Plaque (HRP) or BioImage Studym- Events


4a). Subclinical Atherosclerotic Burden
Bioimage HRP - N = 5,808
4a1). The Bioimage Study (N=5808)
Cumulative 3-Year MACE Endpoints (N=216)

Reclassification: CAC 24% - cPB 18%
4a2). Modifiable CV RFrs (7) & Life Style

AV Khera, V Fuster, PM Ridker et al., NEJM 2016; 375:2349
Genetic (50) vs Lifestyle Risk (7) - 55,685
ARIC, MDCS, BioImage, WGHS,

A Atherosclerosis Risk in Communities

<table>
<thead>
<tr>
<th>Genetic Risk</th>
<th>Lifestyle Risk</th>
</tr>
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<tbody>
<tr>
<td>High; hazard ratio</td>
<td>Unfavorable; hazard ratio</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>1.75 (1.46–2.10)</td>
<td>1.71 (1.47–1.98)</td>
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<td>1.27 (1.09–1.49)</td>
<td>1.18 (1.02–1.36)</td>
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<td>Low (reference)</td>
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AV Khera, V Fuster et al. NEJM 2016;375:2349
S Siddhartha, V Fuster, et al. NEJM 2017;377:111

Gen<RF=50% MACE
Lipids
TET2 / M1
CAC Score in the BioImage Study, According to Lifestyle and Genetic Risk

Genetic (50) vs Lifestyle Risk (7) - 55,685
ARIC, MDCS, BioImage, WGHS,

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
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>Gen<RF=50% MACE
Lipids
TET2 / M1
Loss of Tet2 in Hematopoietic Cells and Atherosclerosis in a Murine Model

A. Aortic-Root Sections, According to Tet2 Status

- WT
- KO

B. Size of Aortic-Root Lesions, According to Tet2 Status

- 5 Wk
- 9 Wk

C. Aortic Atherosclerosis, According to Tet2 Status

- WT
- HET
- KO

D. Involvement of Aorta, According to Tet2 Status

- Percentage of Aorta Affected by Lesion

Temporal Sequence & Functions of Leukocytes in the CAs

Local and Systemic Inflammation
Interleukin-1 in Ischemic CVD

P Libby et. al. J Am Coll Cardiol 2016;67:1091 (VF Modified)
Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease


CANTOS: A Gigantic Proof-of-Concept Trial

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

TR Cimato. Eur Heart J. 2017;38:433
Inflammasome Activates IL-1β by Proteolysis to the Mature Form by Caspase-1

Pro IL-1β
33 kDa

Active, Mature IL-1β
17 kDa

The interleukin-1β converting enzyme, surrounded by the danger sensing domain of the NLRP3 Inflammasome

CANAKINUMAB (CVD, HIV)
ANAKINRA (HFpEF, HFrEF)
COLCHICINE (CVD, E)
METHOTREXATE (CVD, E)

P Libby. J Am Coll Cardiol 2017;70:2278 (Modified by VF)
Coronary PET Inflammation Imaging: ACS Culprit vs Bystander Lesions

Increased Bone Marrow, Spleen, and Arterial FDG Uptake After ACS

H Emami, ZA Fayad et. al. J Am Coll Cardiol Img 2015;8:121
CV Events According To Whether At 3 Month on-treatment hsCRP was > or < 2 mg/L

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>(95% CI)</th>
<th>p</th>
</tr>
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<tr>
<td>Placebo</td>
<td>1</td>
<td>(ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>On-treatment hsCRP ≥2.0 mg/L</td>
<td>0.95</td>
<td>(0.84–1.09)</td>
<td>0.48</td>
</tr>
<tr>
<td>On-treatment hsCRP &lt;2.0 mg/L</td>
<td>0.75</td>
<td>(0.66–0.85)</td>
<td>&lt;0.0001</td>
</tr>
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CANTOS (P Ridker et. al.) Lancet 2017 (In Press)
High Risk Plaque Study Participants Who Underwent Carotid Ultrasound (Chicago, Florida)

Addition Data:
- Coronary Calcium Biomarkers
- Genomic markers
- MRI
- PET-CT

3-D Carotid Plaque Volume Ultrasound

CV Risk Assessment

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

PESA (L Fernandez-Friera, A Fernandez-Ortiz, V Fuster et al)
Circulation 2015;131:2104
4b2). The PESA Study (N=3860) Femoral And Carotid 3D-VUS Plaque Volume

4b2). The PESA Study (N=4184)
Subclinical Atherosclerosis & Framingham Risk Score

L Fernández-Friera, V Fuster et al., Circulation 2015; 131:2104
The PESA Study (N=4184)
Subclinical Atherosclerosis & 10 yr European Risk Score

L Fernández-Friera, V Fuster et al., Circulation 2015; 131:2104
4b3). Absence of Risk Factors
Relation Between LDL-C and Atherosclerosis

L Fernández-Friera et. al. J Am Coll Cardiol 2017;70:2979
4b4). Ideal CV Health Fuster-BEWAT Scores (FBS)

ICHs and Subclinical Atherosclerosis Extent

- Poor: 32.0% (36.5% Generalized, 14.4% Intermediate, 17.1% Free)
- Intermediate: 13.9% (28.8% Generalized, 21.9% Intermediate, 35.4% Free)
- Ideal: 5.5% (19.8% Generalized, 22.1% Intermediate, 52.6% Free)

FBS and Subclinical Atherosclerosis Extent

- Poor: 28.5% (28.9% Generalized, 21.3% Intermediate, 16.7% Free)
- Intermediate: 15.1% (23.1% Generalized, 22.5% Intermediate, 34.7% Free)
- Ideal: 7.0% (22.5% Generalized, 47.3% Intermediate, 23.1% Free

4c). Framingham, When Positive Coronary Artery Calcification Score and Ultrasound are Added

Variables included in the prediction model

AWHS - M Lacaustra, V Fuster et al. JACC 2016; 67: 1263
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50/50

Surgery

Intervention

Pharmacology.

Imaging

Genetics/Tr
5a). AMPATH Centers In Kenya
BP Control / Non MD / High Technology

R Vedanthan, V Fuster, NHLBI / Kenya Model (2012-2016)
5b). The Seven Community Study

Spain - E. Gomez, V Fuster et al JACC 2016; 67:476
Cardona Integral – “Fifty-fifty” - 2014
Global Demonstration Project – GHP – 2013
2). 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
hdl cholesterol
Smoking
Cerebral amyloid angiopathy

Microcirculation, Cognitive – 12 Studies

2. HW Querfurth et al. NEJM 2010;362:329 – Isch. 60-90% A’sD
4. CARDIA (K Yaffe et al) Circ 2014;129:1560 - CV RFrs, Cognitive
5. JI Friedman et al. JACC CV Imag. 2014;7:1039 - Imaging
7. FINGER (T Ngandu et al)., Lancet 2015; 385:2255 - Intervention
10. A de Roos et. al. Circ. 2017; 135: 2178- Aging<Pulse/Perf
12. TANSNIP Paths 1 & 2 (V Fuster et al)- 2017-A Prospective
11. Cardiovascular Risk Factors From Childhood & Midlife Cognitive Performance

YFS (SP Rovio et al), J Am Coll Card 2017 (In Press)
**12a. TANSNIP Pathway 1**

**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

**FAD**

N=2750
12b. TANSNIP Pathway 2

STEP 1: CACS
Carotid Plaque w Volume

Continuous Scale N=100

Source- MSH
Coronary CT Suites

CV Risk Assessment

3-D carotid and ileo-femoral ultrasound

PET for Amyloid

Neurocognitive Testing

MRI- functional + Micro/Macrovasculature
From Aging / Disease to Youth / Health

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50-100 yrs

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1) Surgery
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ACC New York, Dec 8, 2017  No Disclosures