

FROM GENES TO HEALTH AND HEALTH TO GENES ^{1,2,3}

1 TRANSLATIONAL – CLINICAL INVESTIGATION

GENES ↔ CELL ↔ TISSUE ↔ PHYSIOL. ↔ PHENOTYPE ↔ POPUL. ↔ HEALTH

TRAINING / MENTORS

ENABLING APPROACHES

Imaging: Non Inv. Molec.

Clinical Proteomics

Inform. / Science / Techn.

Behav. Instrum./ Technol.

Clinical Trials Infrastr.

4

SPECIFIC AIMS

Genetics /Proteomics /Embryogenesis

Regenerative Biol./ Replac. Therapy

Immunobiol./ Inflammation / Thromb.

Public Health / Genom. Proteo.

NHLBI SPARK I 1998-2002

Circ 1999; 99:1132 & 2064 - Defined Circ 2002;106:162 – Update

NHLBI SPARK II 2003-2007 - Prospective (Jan 20, 2003)

NHLBI – Site Visit - March 17, 2006

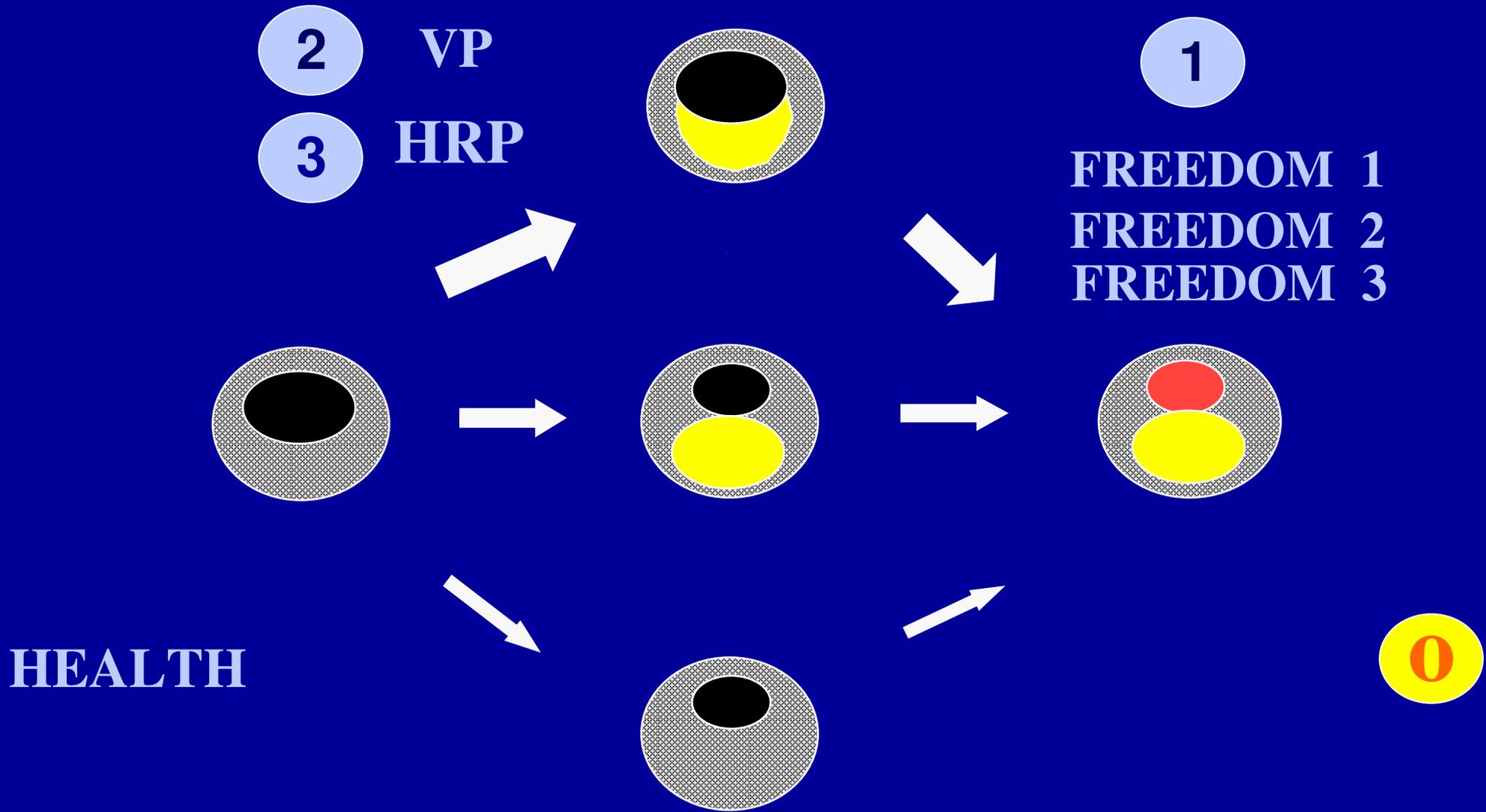
*CVD & Imaging 2007-2017 - From Treatment
to The Understanding and Protection of Health*

The “Academician’s Vision”

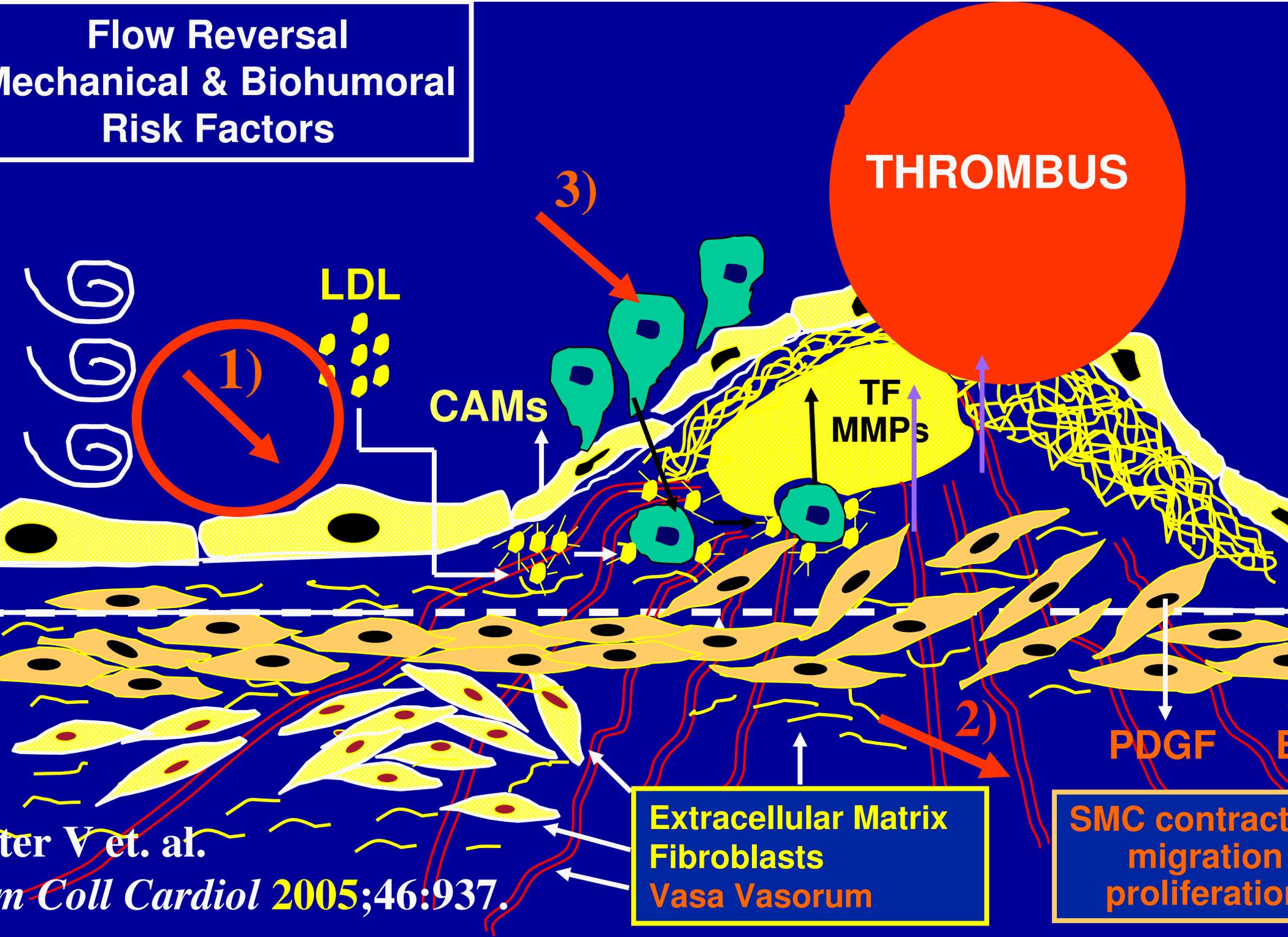
The “Clinician’s Vision”

The “Epidemiologist’s Vision”

CVD & Imaging 2007-2017 - From Treatment To The Understanding & Protection of Health

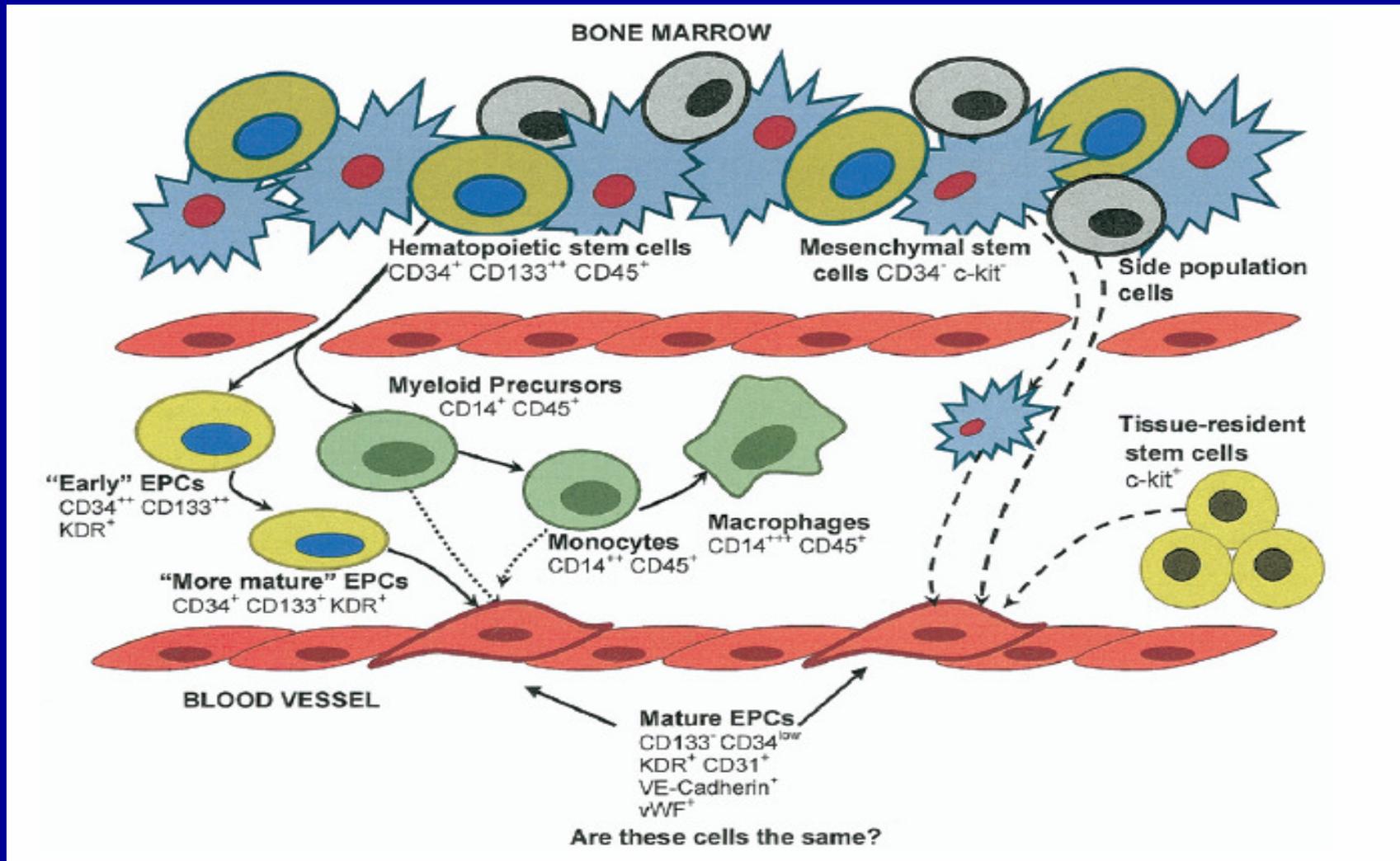


**Flow Reversal
Mechanical & Biohumoral
Risk Factors**



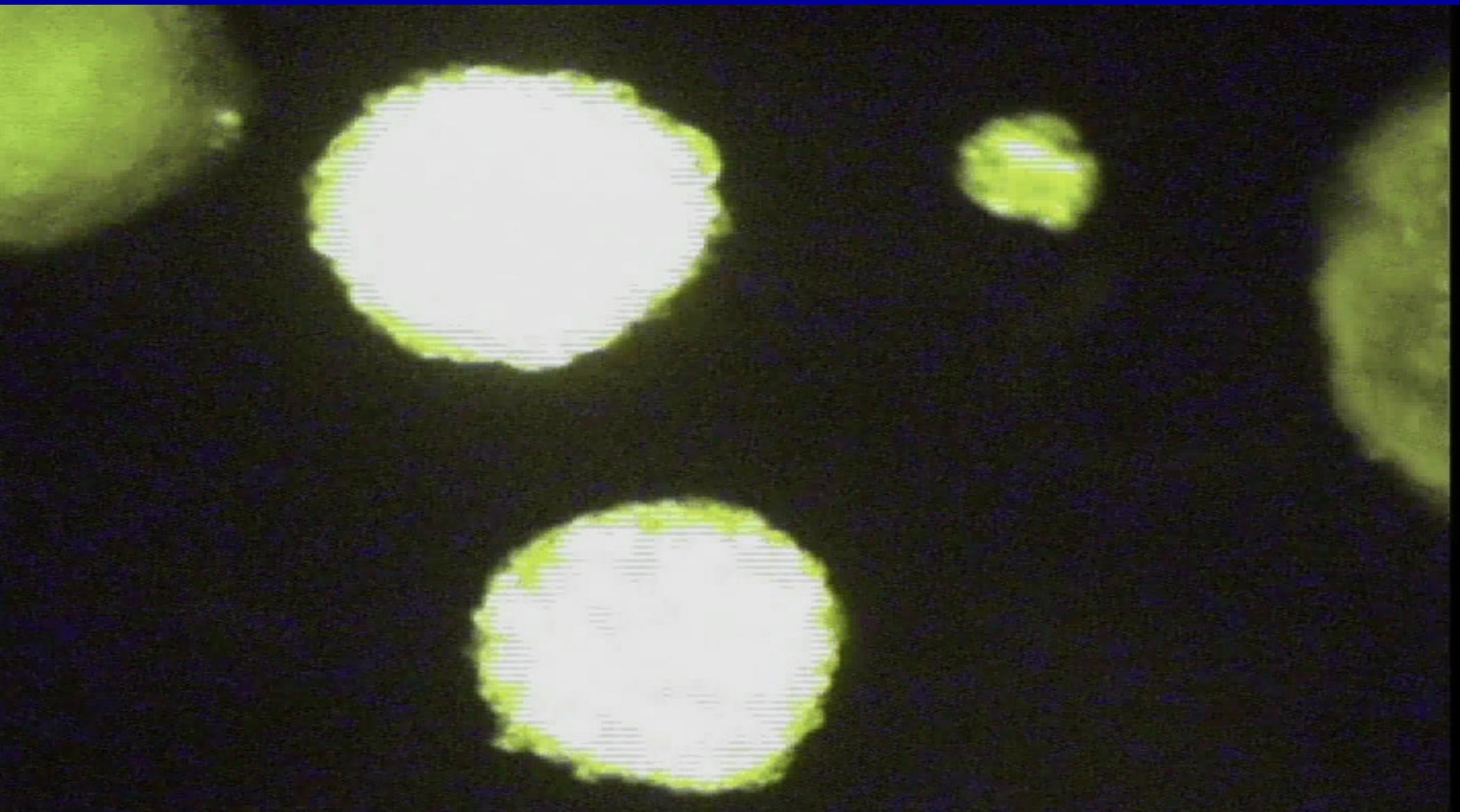
ter V et. al.
m Coll Cardiol 2005;46:937.

Potential Origin and Differentiation of Endothelial Progenitor Cells



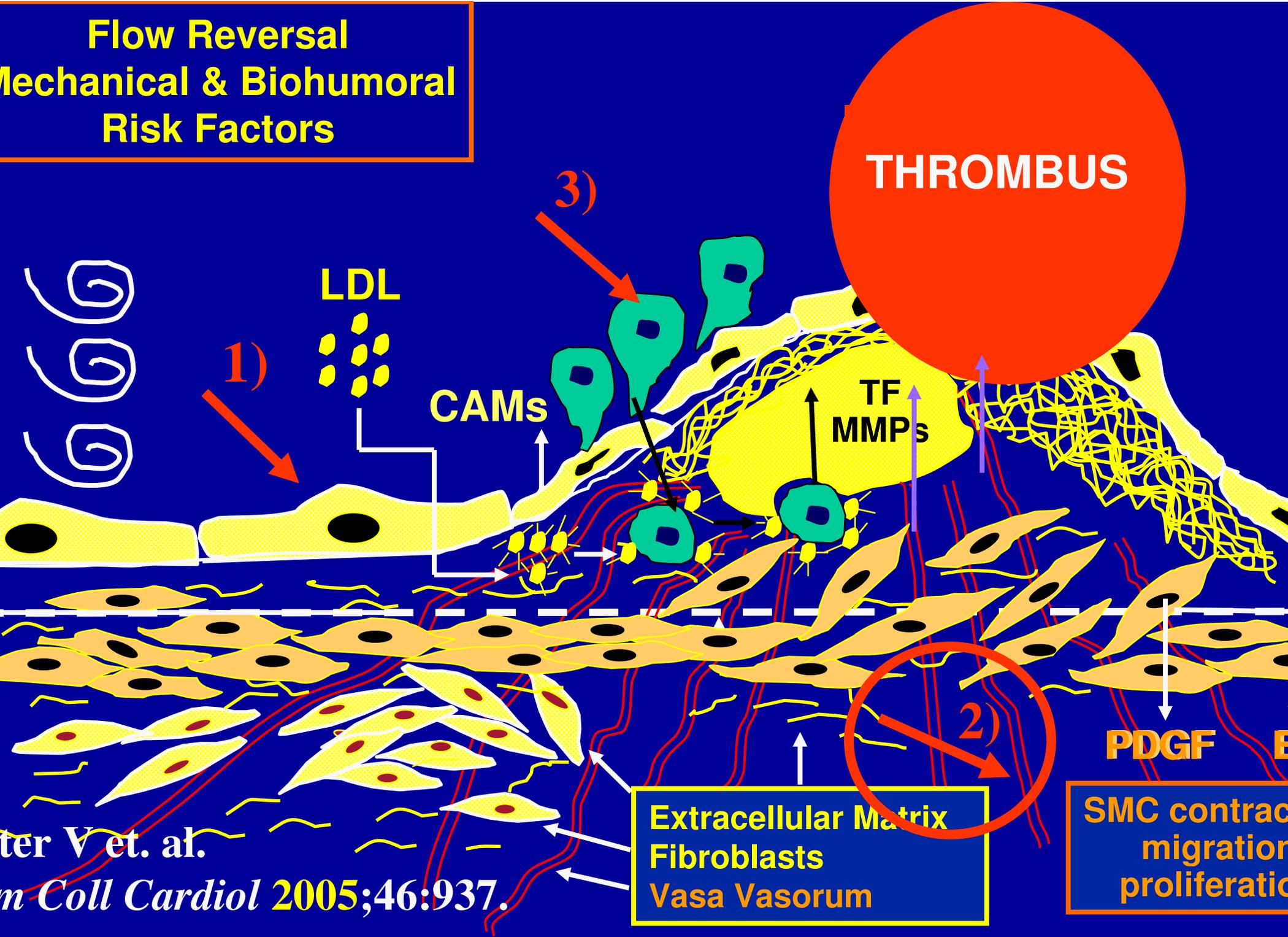
Shantsila E et. al. *J Am Coll Cardiol.* 2007;49:741.

Embryonic Stem Cell Derived, Cardiovascular Progenitor Cells (FLK Positive Cells)



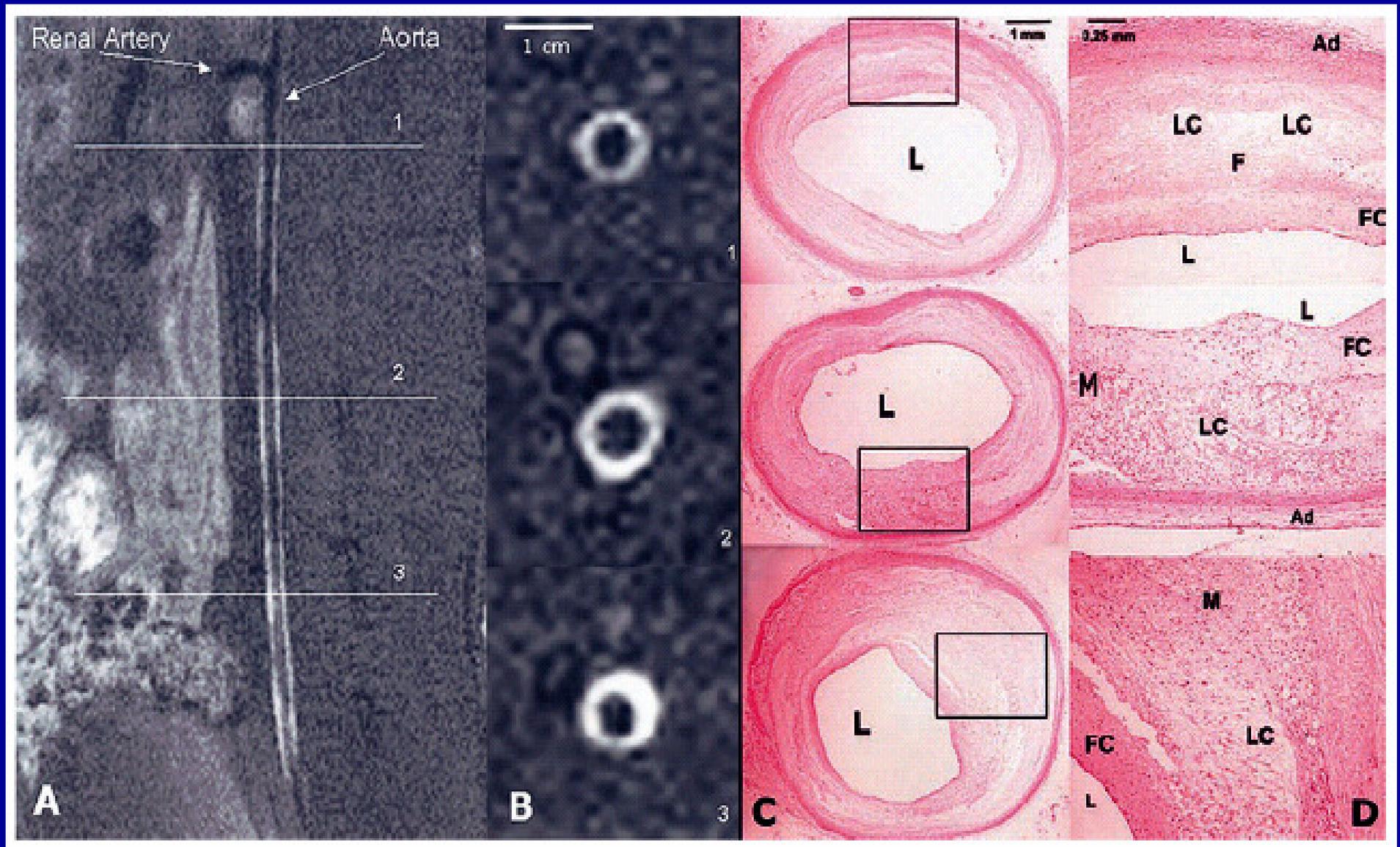
Adler, ZA Fayad, S Kattman, G Keller et al 2007 (Subr)

**Flow Reversal
Mechanical & Biohumoral
Risk Factors**



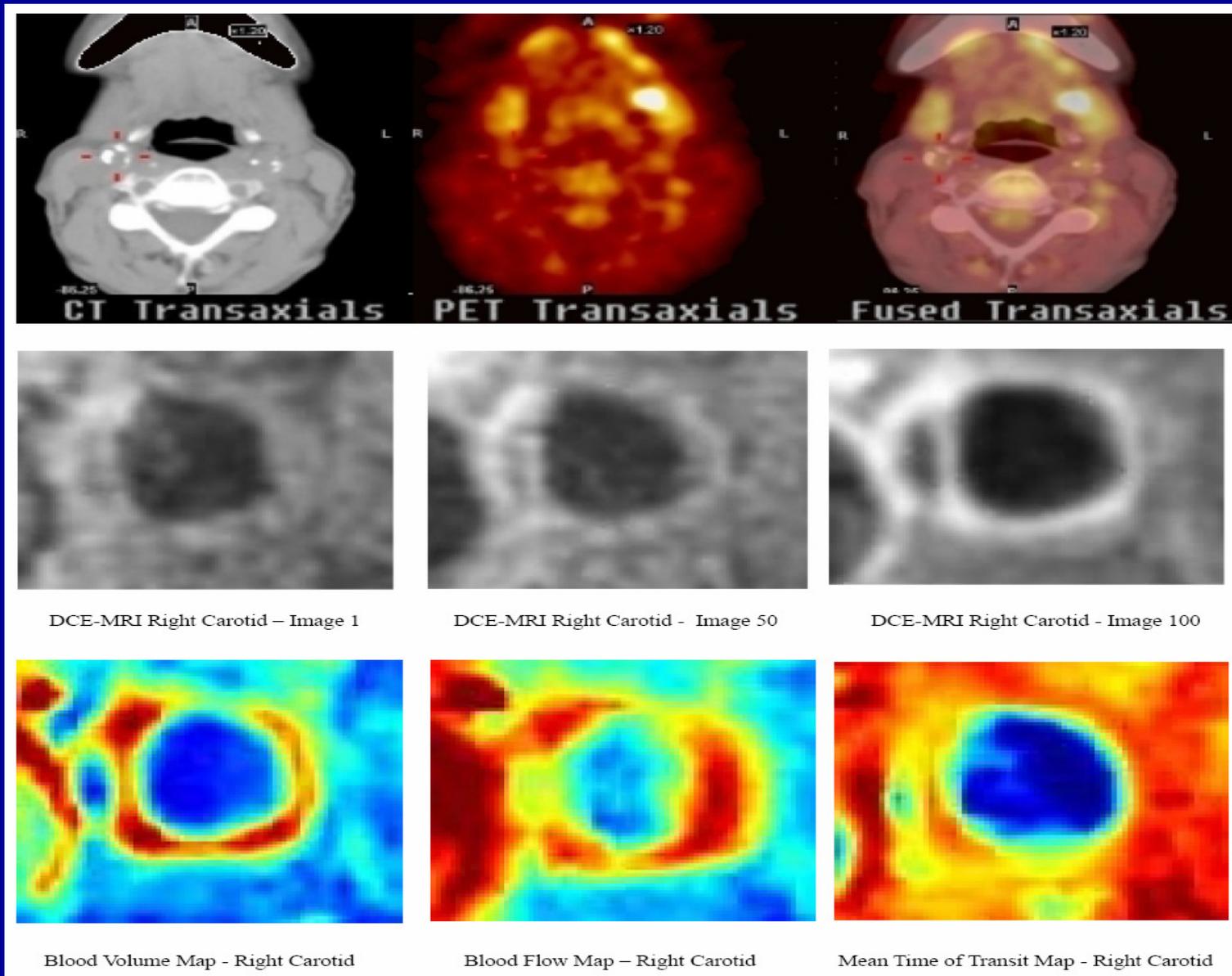
ter V et. al.
m Coll Cardiol 2005;46:937.

Vasa Vasorum and Gadofluorine-Enhanced M



Sirol M et al. *Circulation*. 2004;109:2890-2896

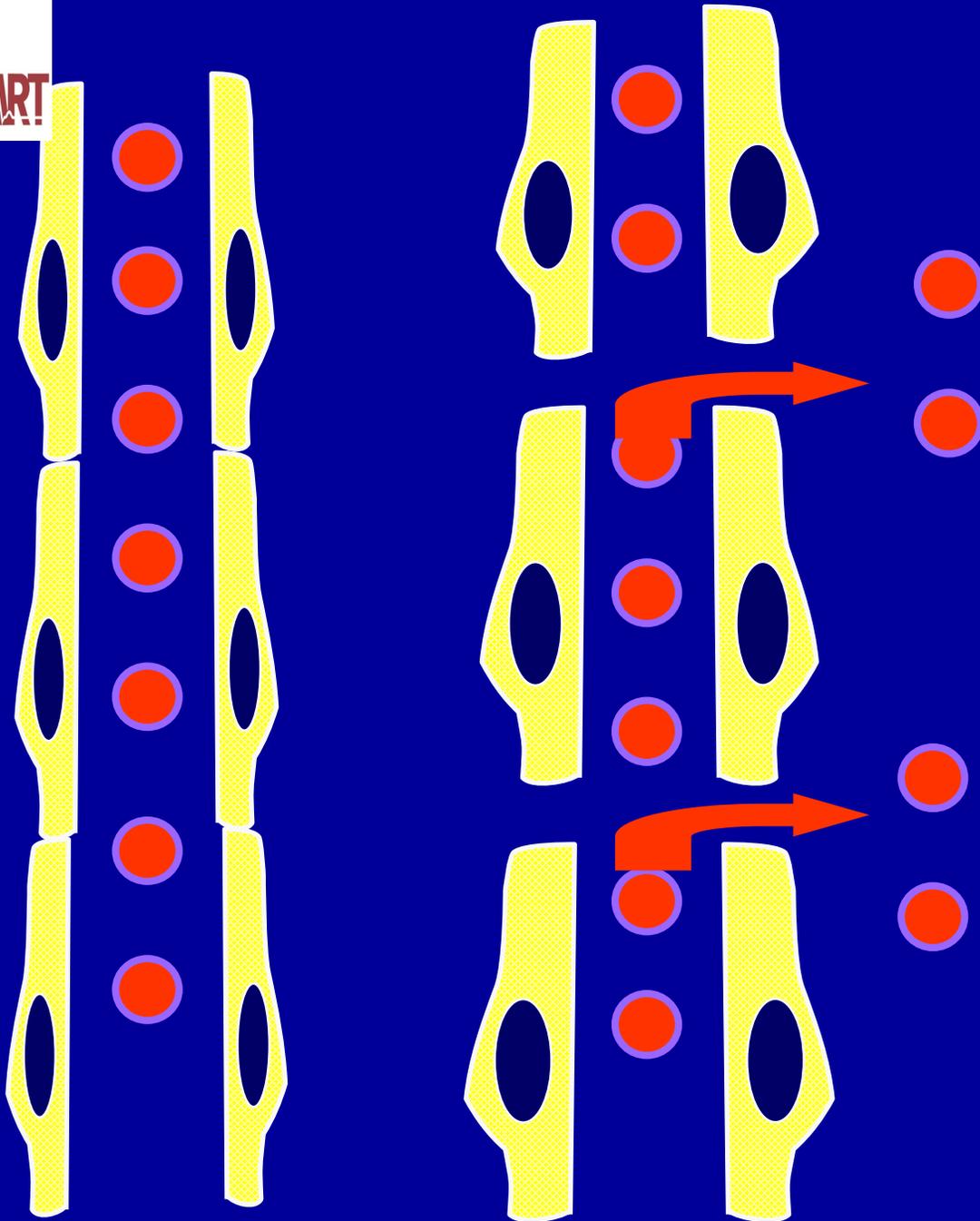
Correlation Between ^{18}F FDG-PET/CT And Dynamic Contrast Enhanced MRI Parameters In Human Patients



Arteries Dysfunction

Intraplaque Hemorrhage

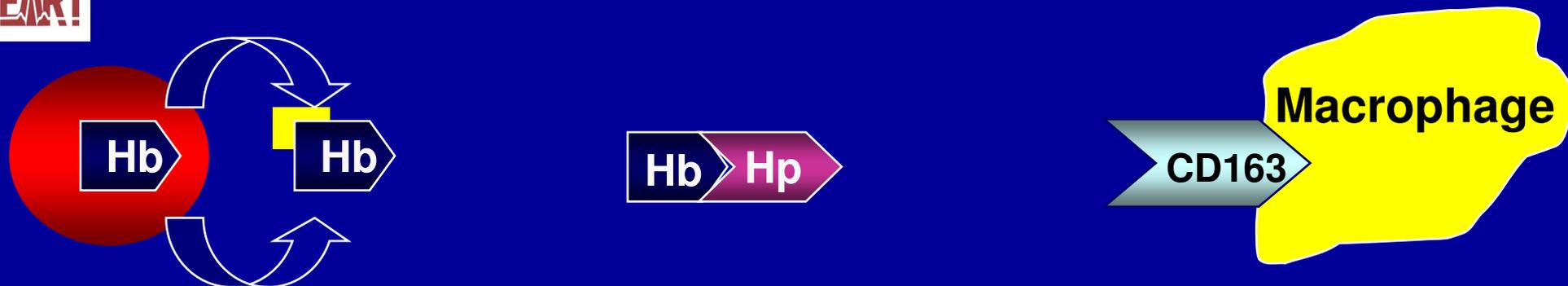
HEART



Morphology

**Molecular Determinants
Of Instability
(Hypoxia?)**

Defense against Intra-Plaque Hemorrhage



Hp-1

Haptoglobin (Hp) Gene*
Two Alleles

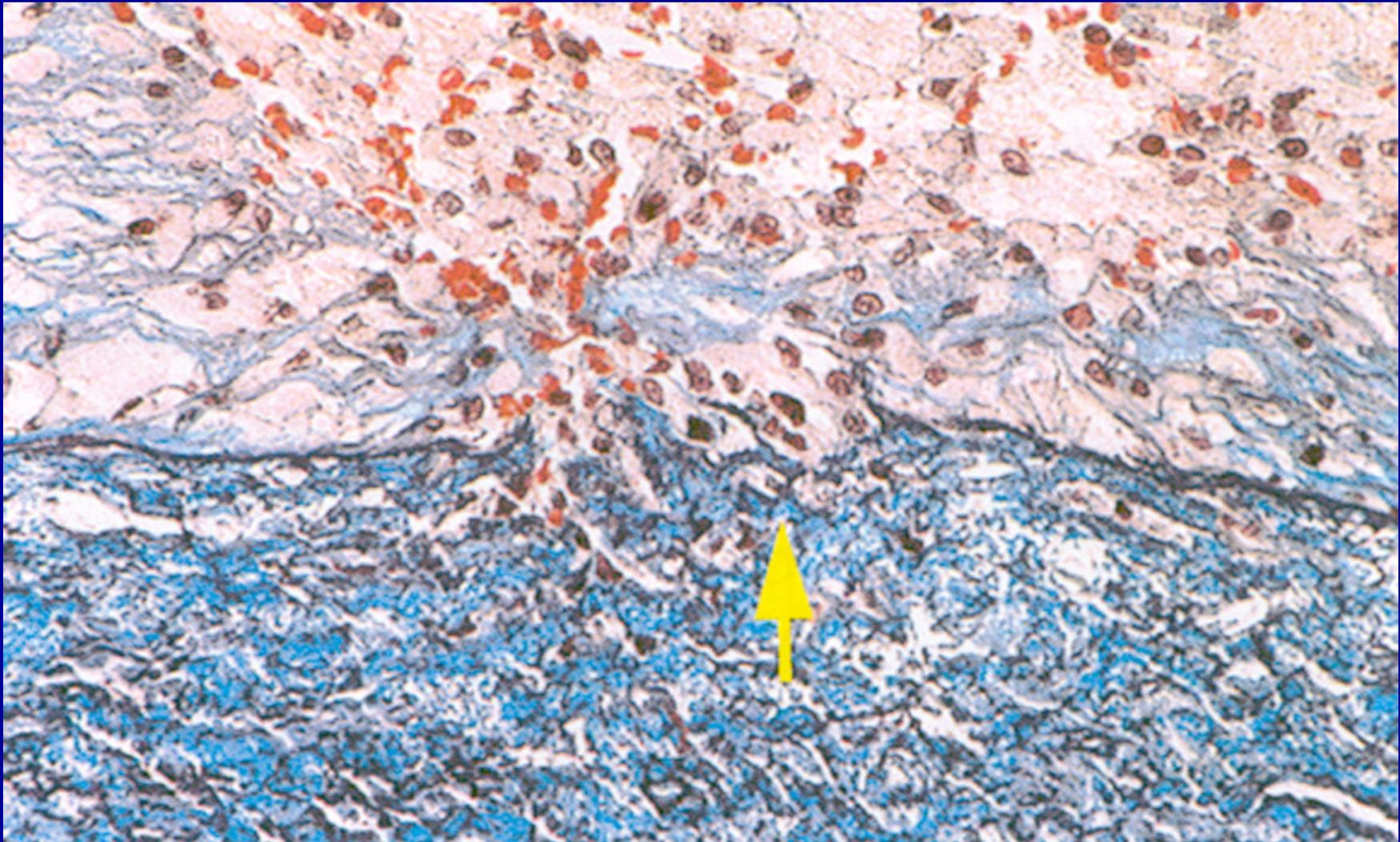
Hp-2

▶ **Hp-2** is an **inferior** protein when compared to **Hp-1**

*** Chromosome 16q22**

Bowman BH, et al. Adv Hum Gen **1982**;12:189 - Clin Chem **1996**; 42:
Moreno PR, Levy AA, Fuster V.ATVB **2007** (In Press)

PLAQUE WITH INFLAMMATION & RUPTURED IEL



Moreno PR, Purushothaman K-R, O'Connor WN, Fuster V, *Circ*. **2002**;105:250

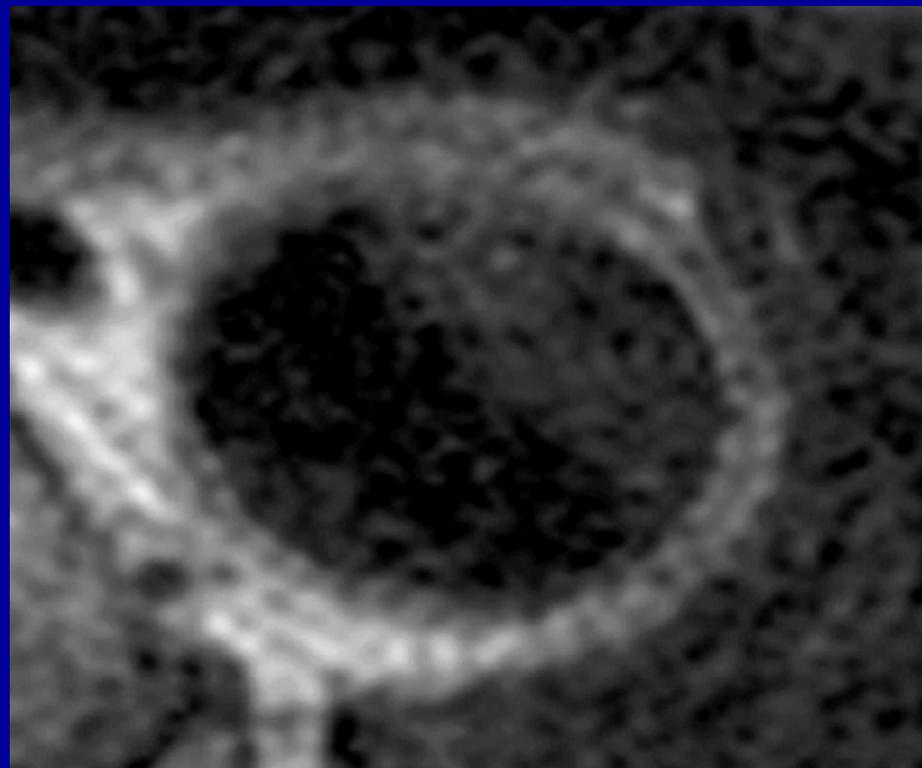
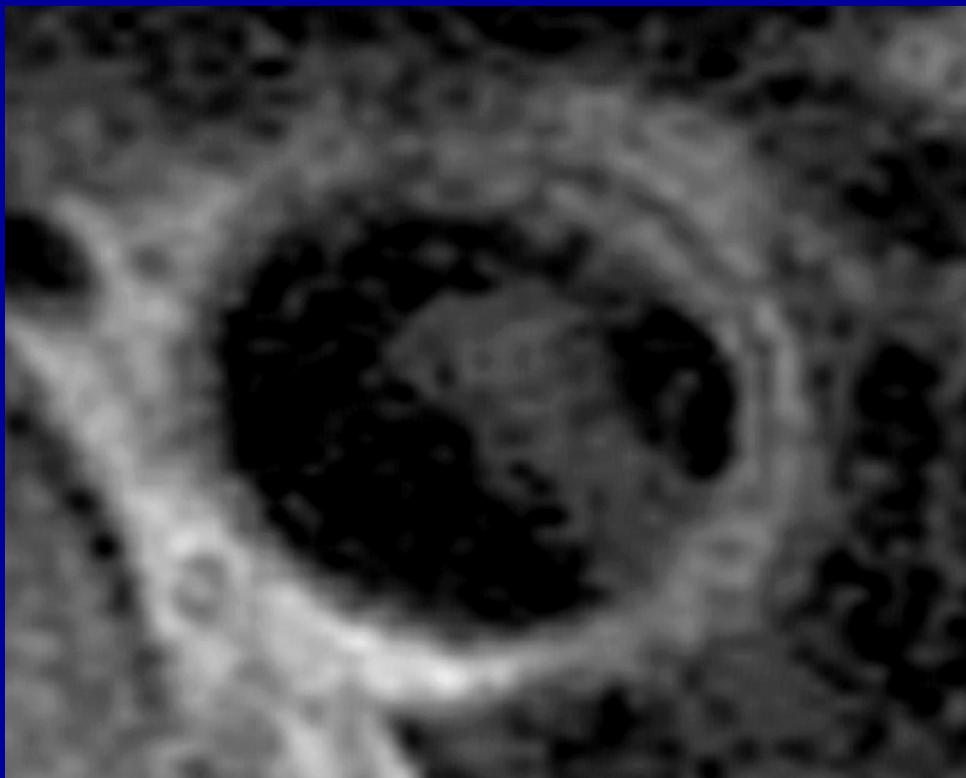
Moreno PR, Purushothaman KR, Fuster V, et al. *Circ* **2004**;110:2032

Moreno PR, Purushothaman KR, Levy AA, Fuster V. *Circ* **2007 (In Press)**

MRI-LIPID LOWERING (SIMVASTATIN 20 or 80 mg/d) AND REGRESSION OF ATHEROSCLEROSIS

Baseline

24 months follow up



Corti, ZA Fayad, V Fuster, et al. *Circ.* **2001**;104:249-252

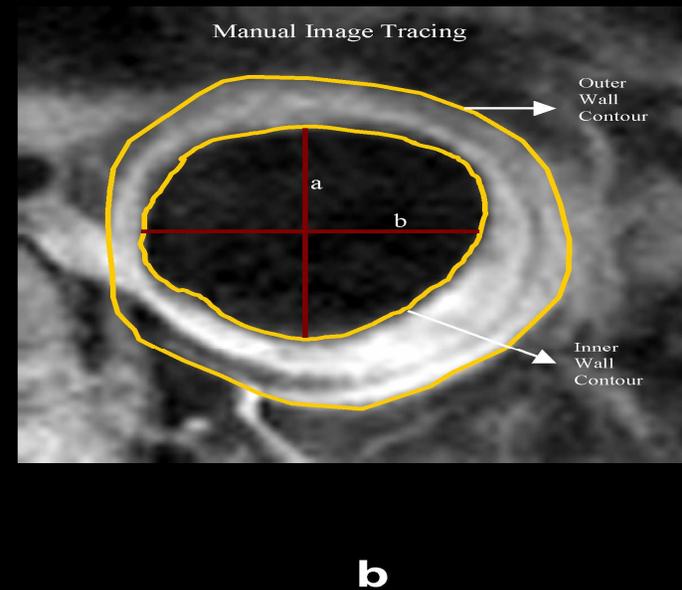
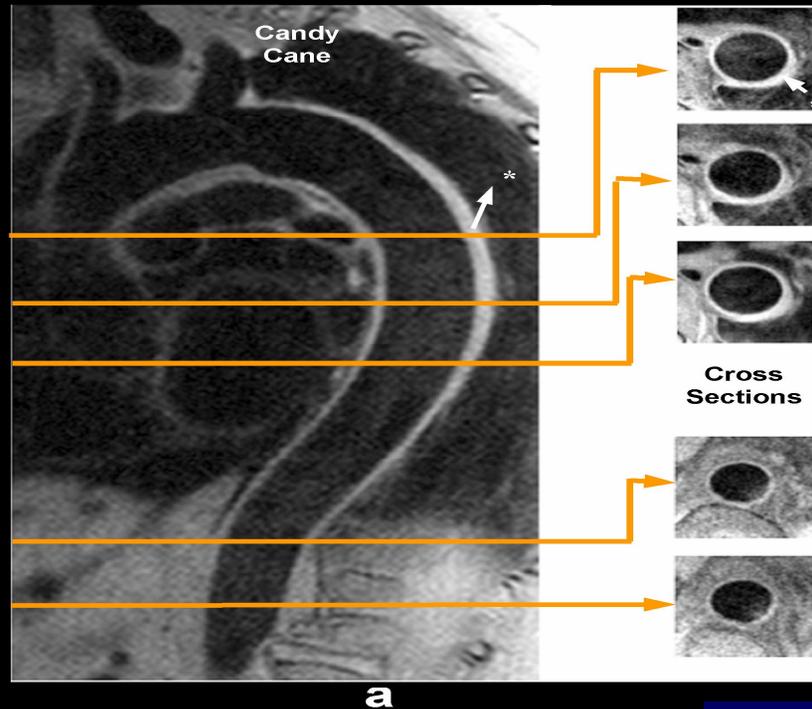
Corti, V Fuster, ZA Fayad, et al. *Circ* **2002**;106:288

Corti, J J Wentzel, Z A Fayad, et al. *JACC* **2005**;46:106

C Lima et al., *Circ* **2004**; 110:2336 (Hopkins, Baltimore)

BAD - Multi Slice Black Blood Imaging

Rapid Extended Coverage (REX) Turbo Spin Echo Technique

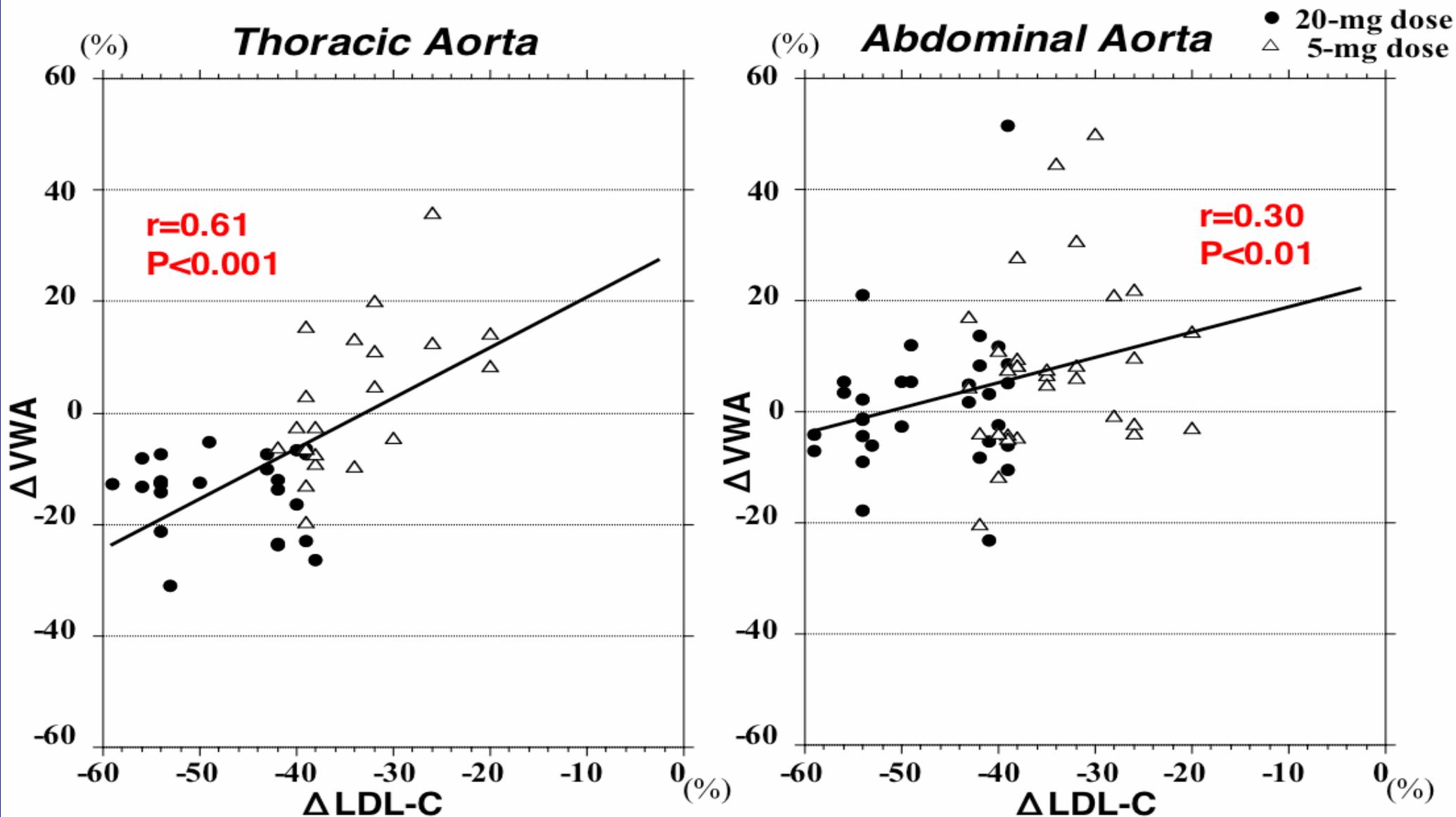


Longitudinal View

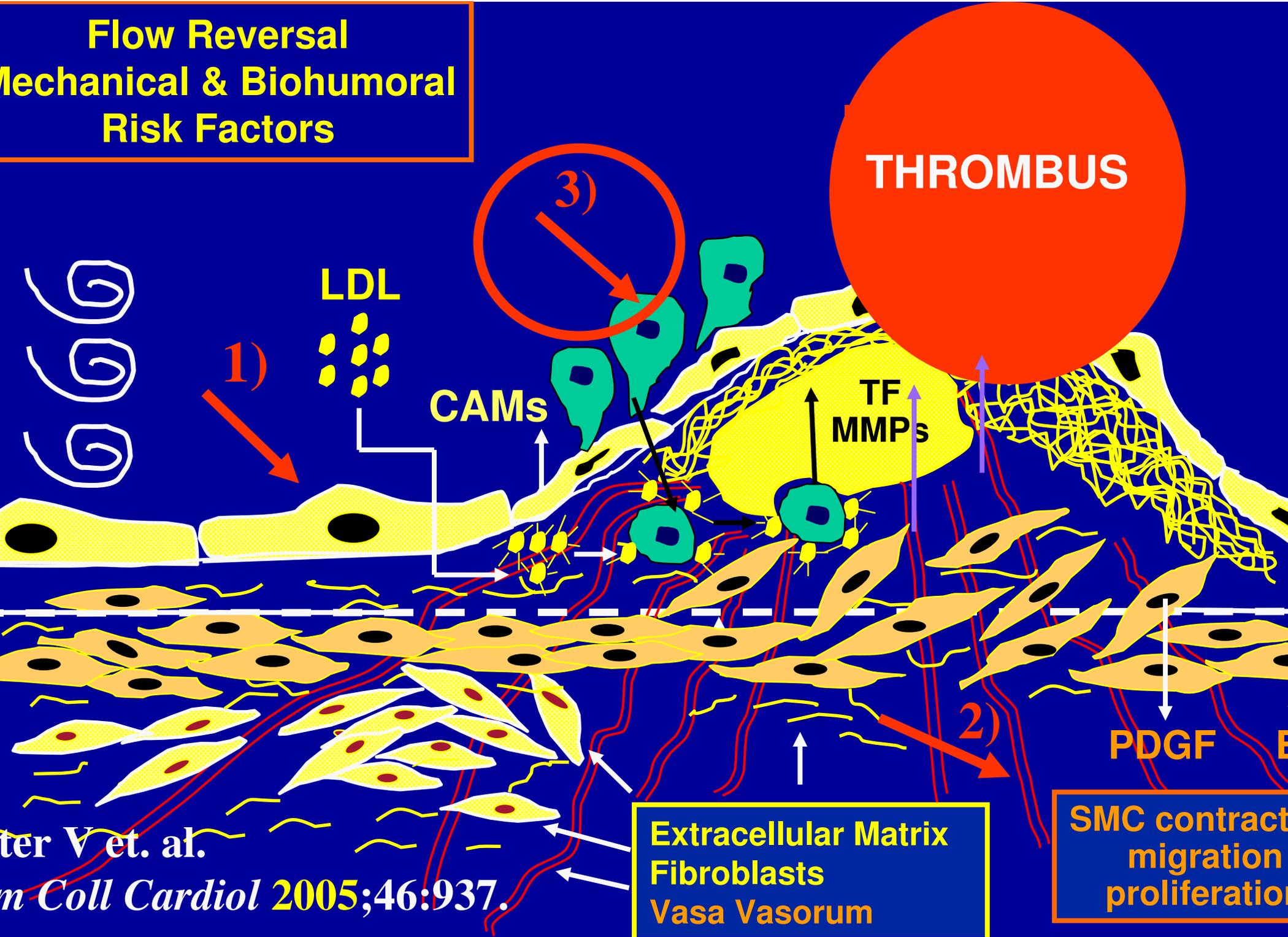
Mid heart Aorta- 12 slices

Yonemura A, Momiyama Y, Fayad ZA et al. JACC 2005; 45: 733-740
 Momiyama Y, Yonemura A, Fayad ZA et al 2007 – Up to 2 years
 follow-up (Fayad ZA, Mani V, Fuster V et al.) 2007 – Predicts CAD

Correlating Change in Vessel Wall Area From Baseline to 1-yr and % Reduction in LDL-C Levels (Δ LDL-C)



**Flow Reversal
Mechanical & Biohumoral
Risk Factors**

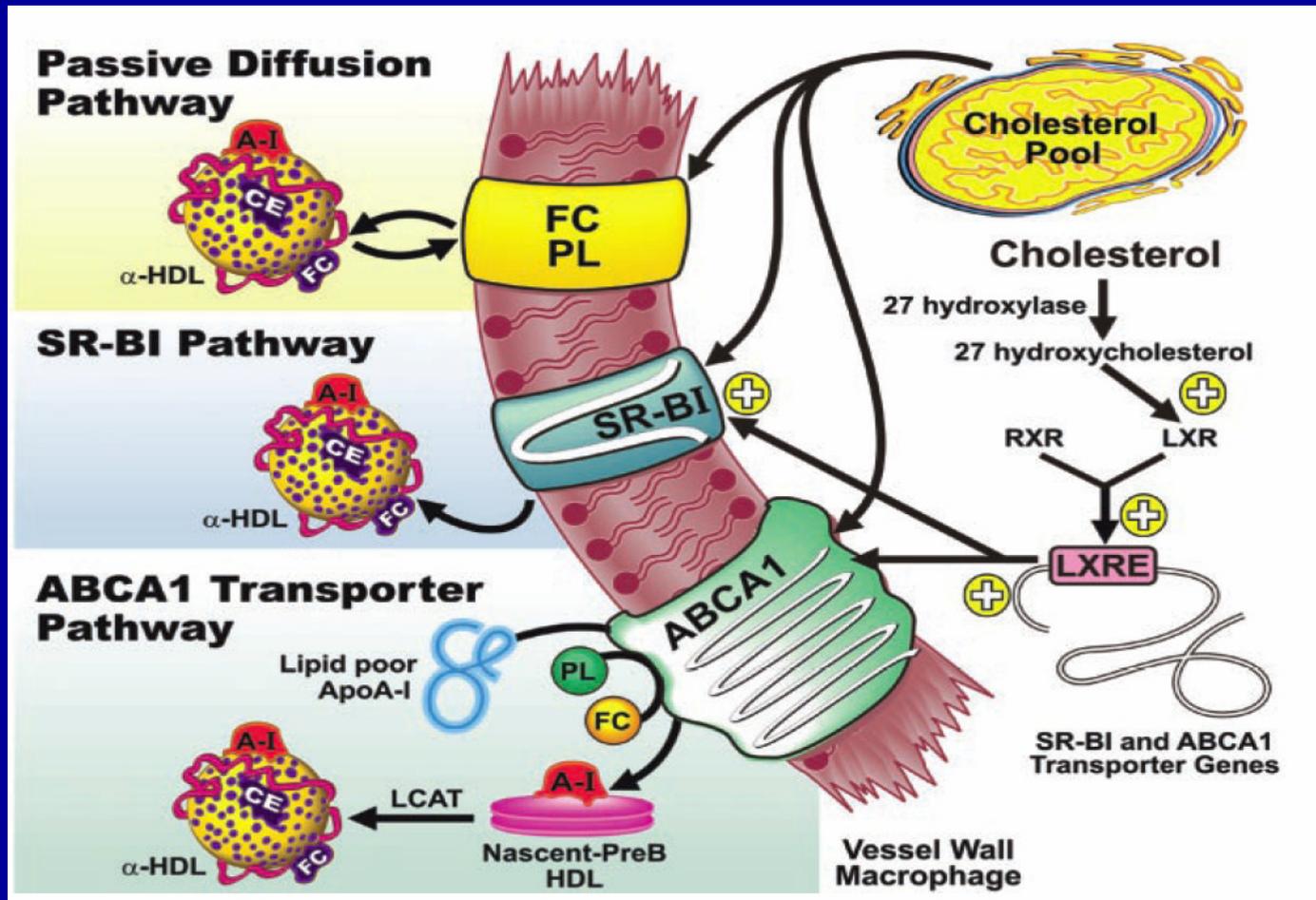


ter V et. al.
m Coll Cardiol 2005;46:937.

**Extracellular Matrix
Fibroblasts
Vasa Vasorum**

**SMC contracture
migration
proliferation**

PPAR, HDL-C: A New Potential Therapeutic Target for the Prevention of Cardiovascular Disease

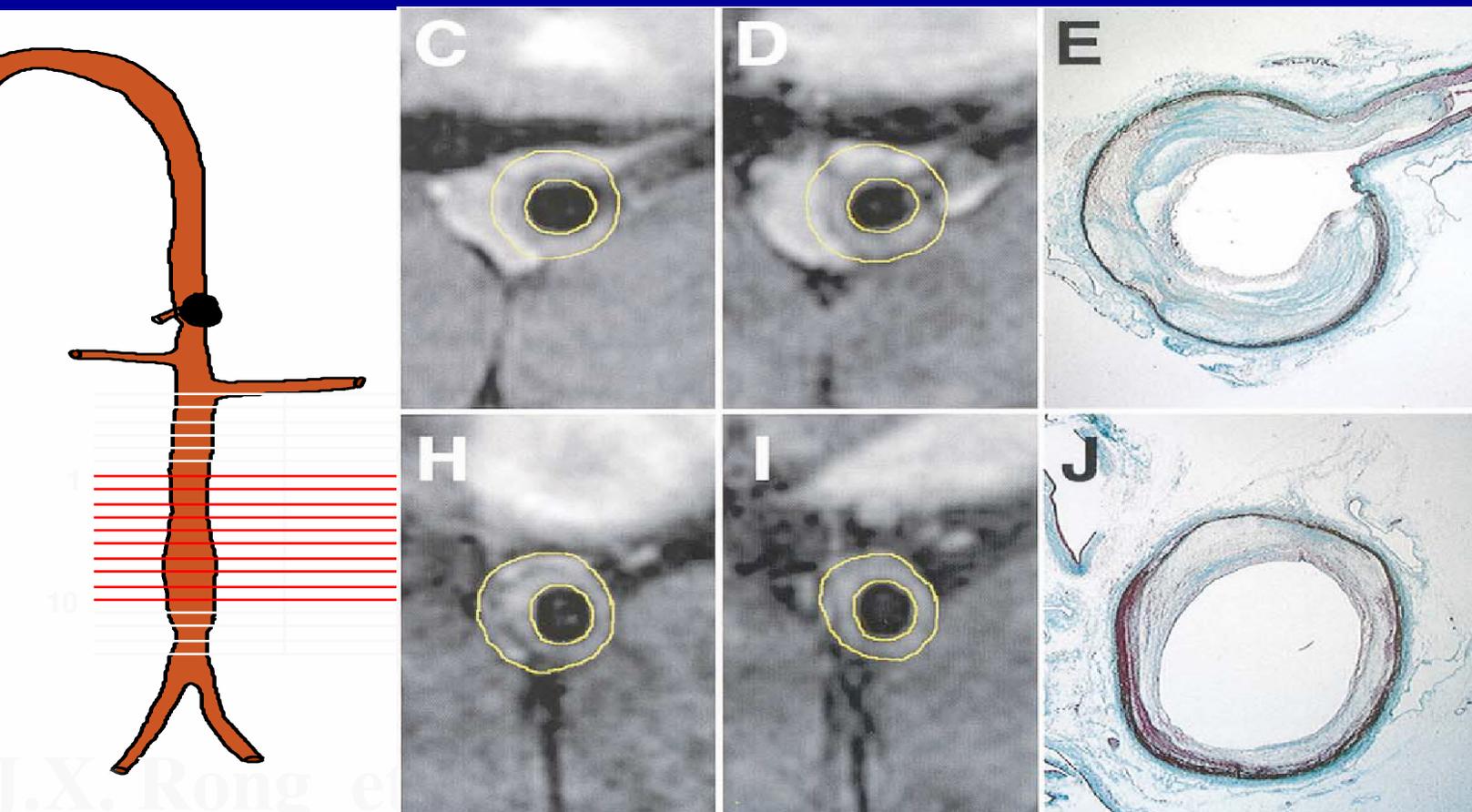


3 major pathways by which HDL may mediate cholesterol efflux from the cholesterol-loaded macrophages and 3 major family molecules being involved - PPAR, HDL, CETP

Bryan Brewer, *H Arterioscler Thromb Vasc Biol* **2004**;24:387.

MRI - HDL-Cholesterol

Rabbit / IV HDL, Apo E / HDL, Rabbit / PPAR-γ / Fenofibr



High-chol. Di

Simv. + PPA

Badimon JJ, Badimon L, Fuster V, JCI 1990; 85:1234 - Apo A1 in Rabbit
 Rong JX et al Circ 2001;104:244;
 Corti R. et al JACC. 2004;43:464 - Corti R et al ,Atheroscl.2007:190:106
 Jensen SE JAMA 2003;290:2292 - Apo A1 in Humans - IVUS

8) **FREEDOM**, Asian, 64 yrs, DM2, ex-smoker
BAD, CT - FDG Uptake Aortic Arch

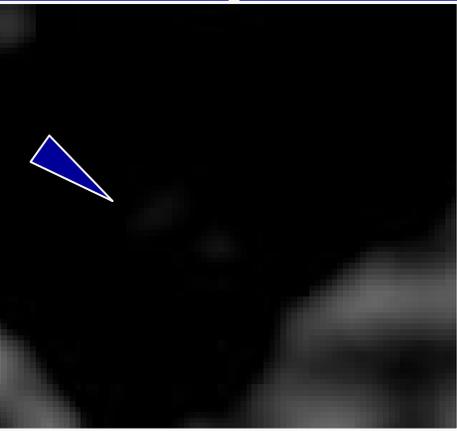


Detection of Macrophages in Aortic Atherosclerosis of Hypercholesterolemic Rabbits with 64-Slice CT.

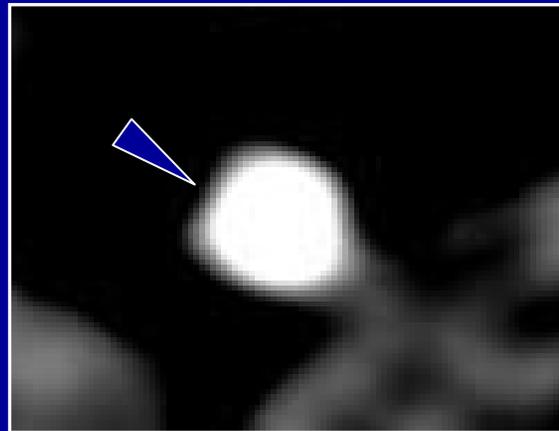
Novel Contrast Agent N1177

Fused MPR of angiography and hour acquisition

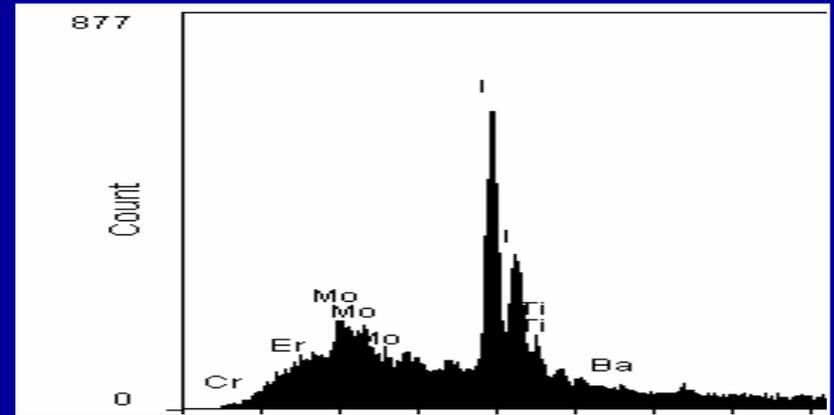
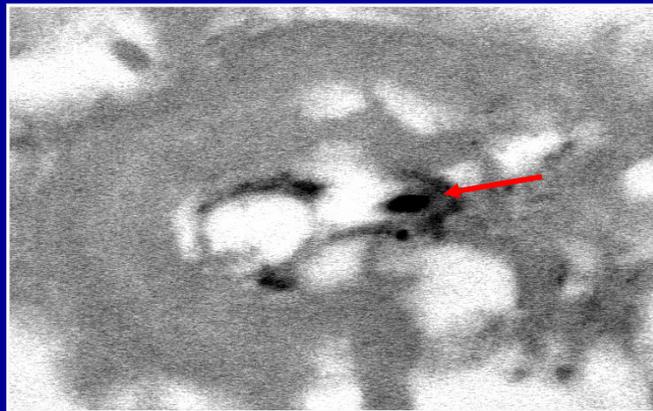
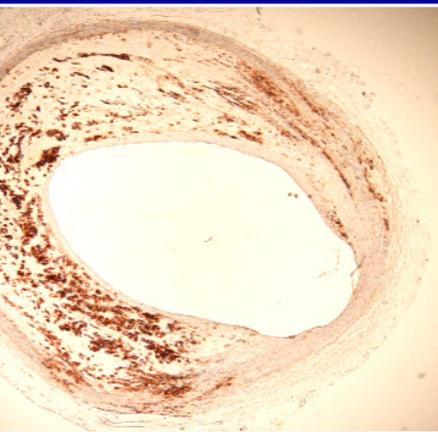
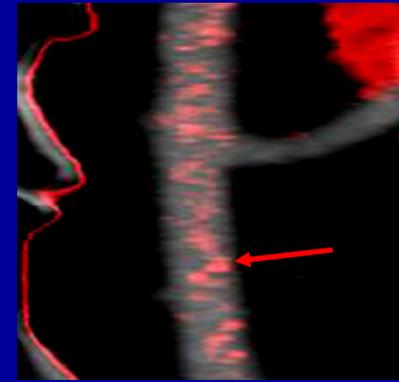
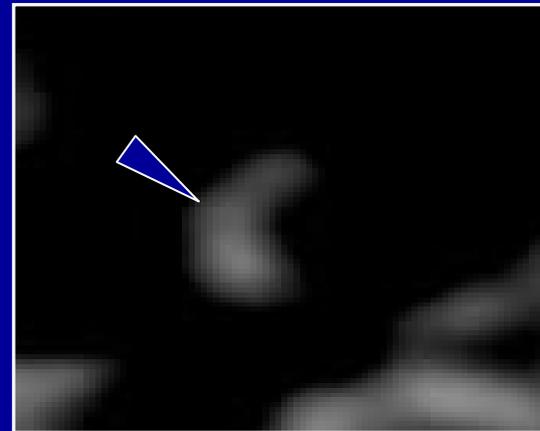
Before injection



During injection



2 hours after N1177

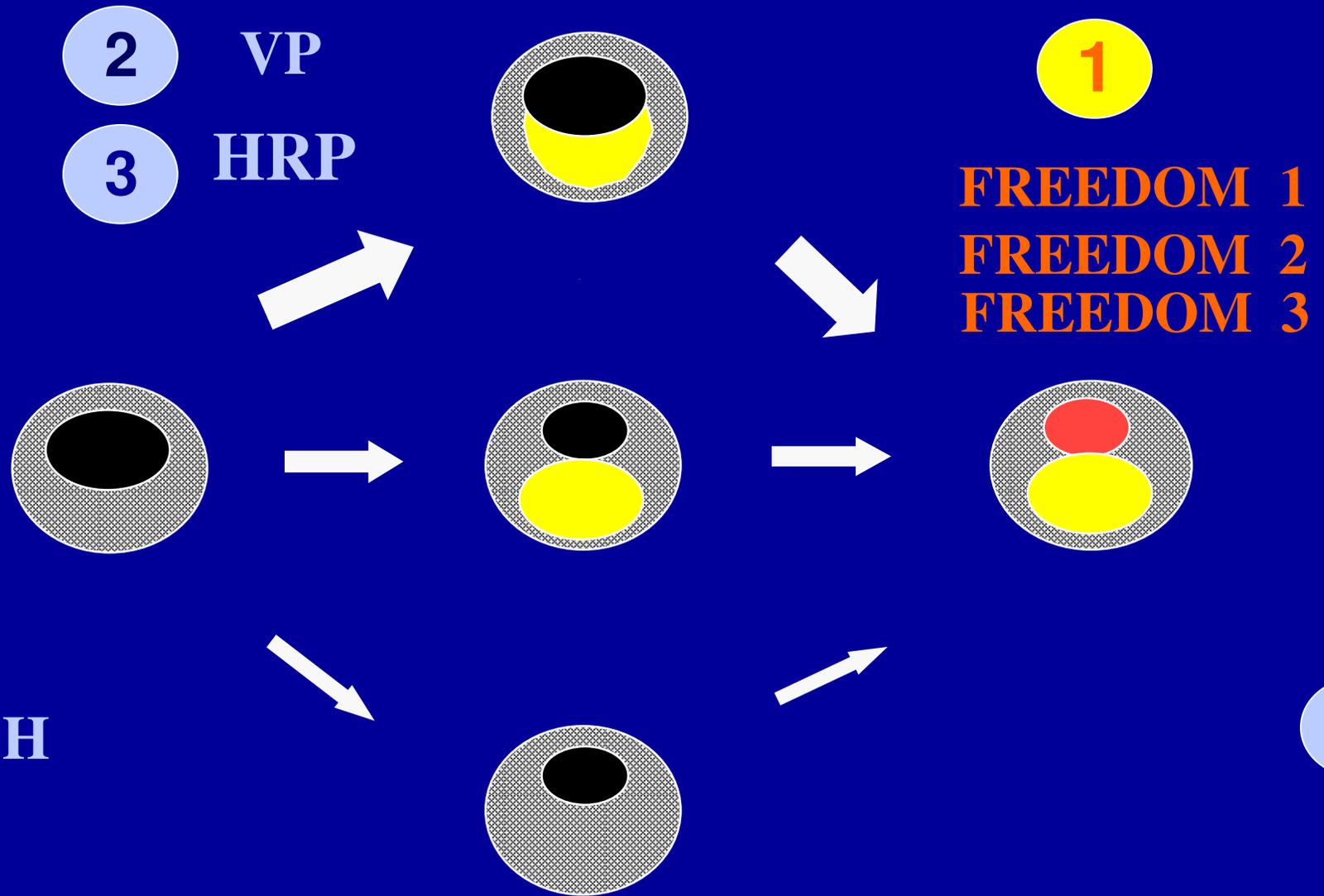


Transmission EM

Absorption spectrum on Scanning EM

afil F, Fuster V, Fayad ZA et. al. *Nature Med.* 2007;13:636

CVD & Imaging 2007-2017 - From Treatment To The Understanding & Protection of Health





FREEDOM 1 - 2 - 3 (NHLBI 2005-2010)

FUTURE REVASCLARIZATION EVALUATION IN PATIENTS WITH DIABETES MELLITUS: OPTIMAL MANAGEMENT OF MULTIVESSEL DISEASE

-) EPC Markers**
-) Statins: Crestor 20**
-) Niacin 2000 IR,**

Risk Factor Profile,

**BAD / MRI – AoCo / MRI - CT / PET
Clinical Events**



FREEDOM -3

TYPE 2 DIABETES MELLITUS PATIENTS WITH MULTI VESSEL CA



PLAQUE IMAGING : BURDEN , CHARACTERISTICS , VULNERABILITY

**MRI : CAROTID , AORTA , CORONARY
PET- CT: CAROTID , AORTA ,CORONARY**



AGGRESSIVE: RISK FACTOR MODIFICATION



**REPEAT PLAQUE IMAGING: 18 MONTHS AND 3 YEARS
DEATH / NON FATAL MI / NON FATAL STROKE / REVASCULARIZATION: 3 YEA**

**CORRELATION: PLAQUE BURDEN / CHARACTERISTICS / VULNERABILITY
WITH: CLINICAL EVENTS AND RISK FACTOR BURDEN**

INTEGRATED PLAQUE SCORE: TO PREDICT CLINICAL EVENTS

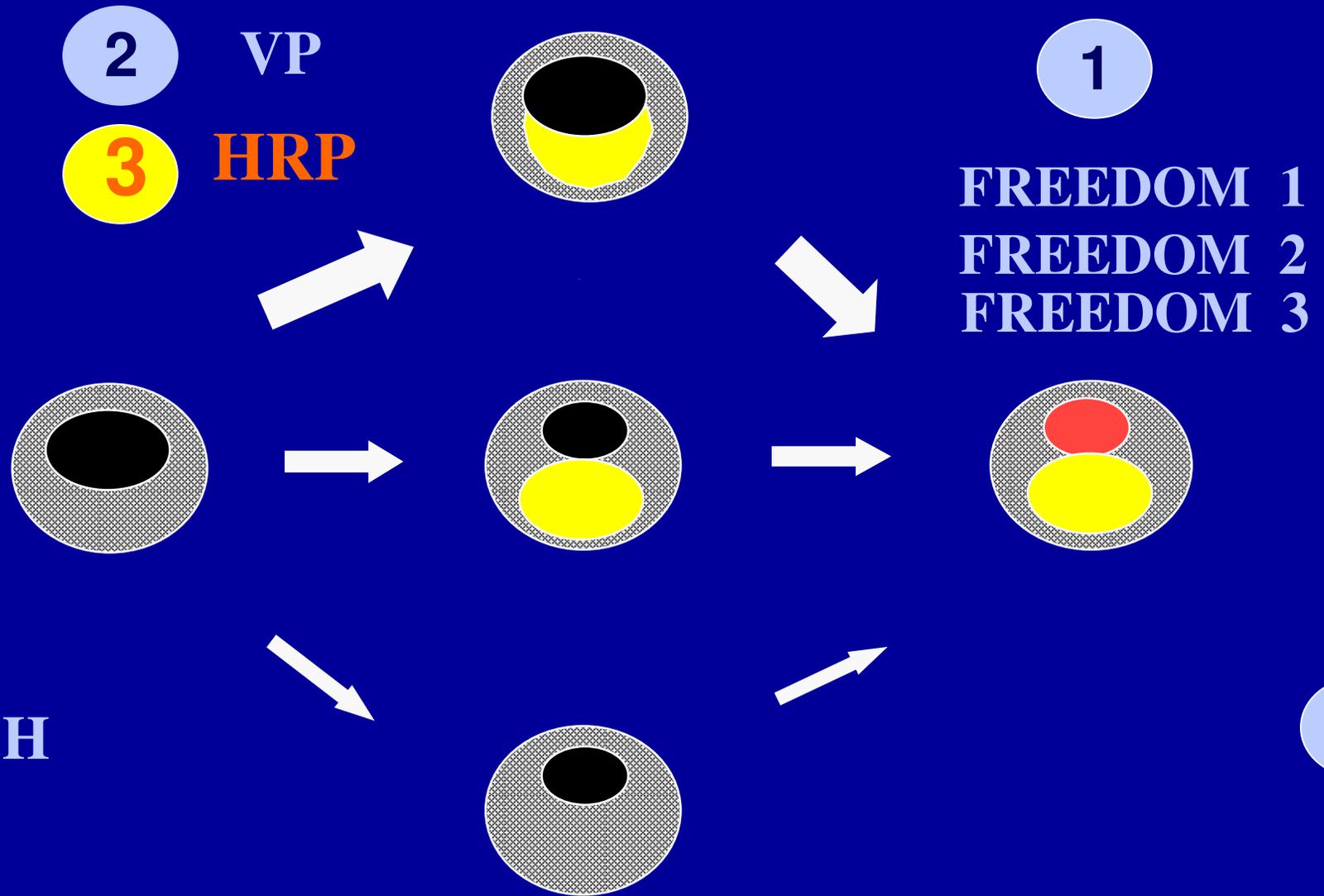
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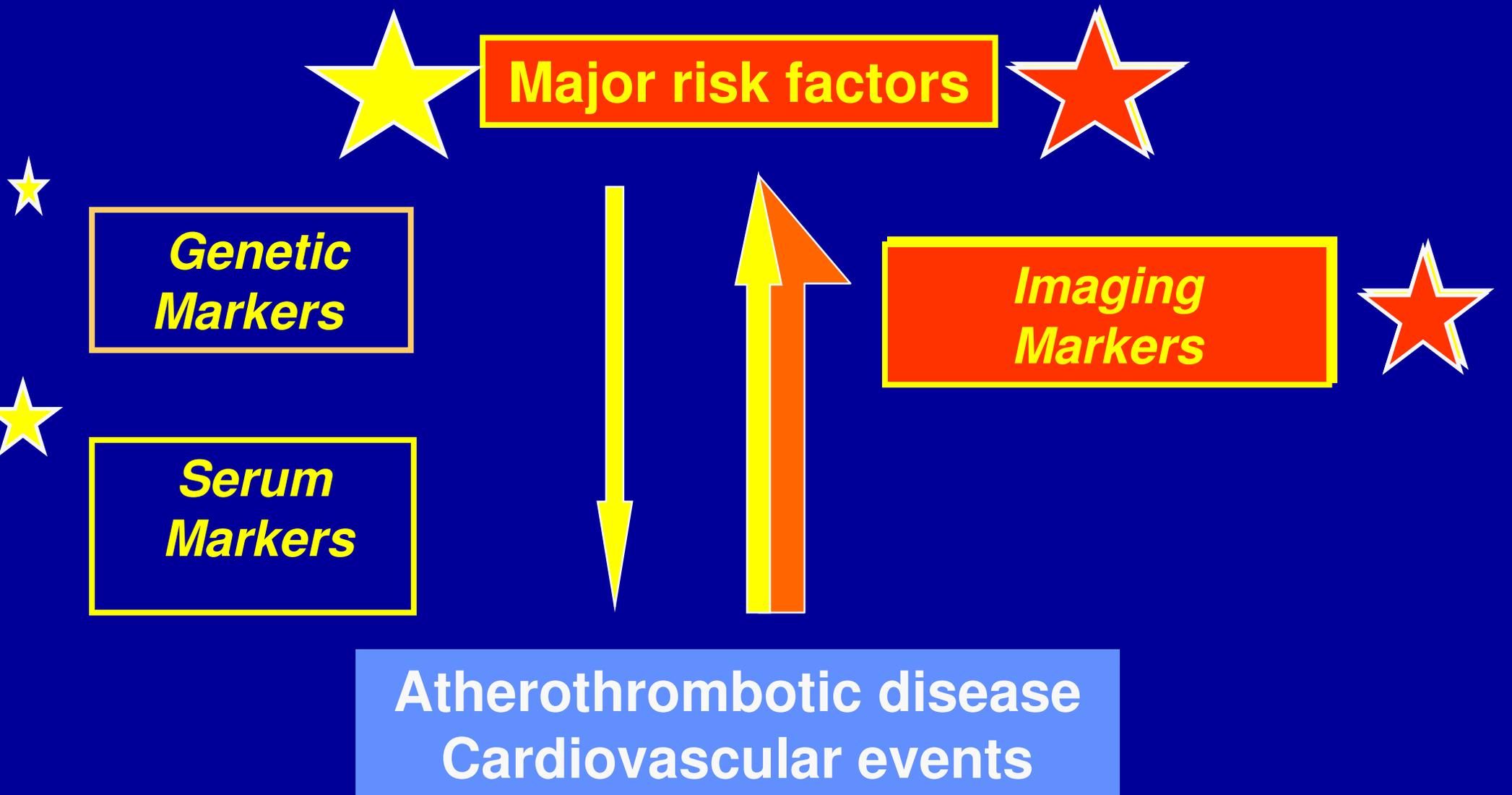
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RISK FACTORS, GENETIC MARKERS, SERUM MARKERS, BIOIMAGING





HRP - Scientific Program Board

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Wolfgang Falk, MD, PhD (Co-Chair)

Man José Badimon, PhD

Mat Daemen, MD, PhD

Mehdi A. Fayad, PhD

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Anton van der Steen, PhD

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Chun Yuan, PhD

Humana and Joint Steering Committee

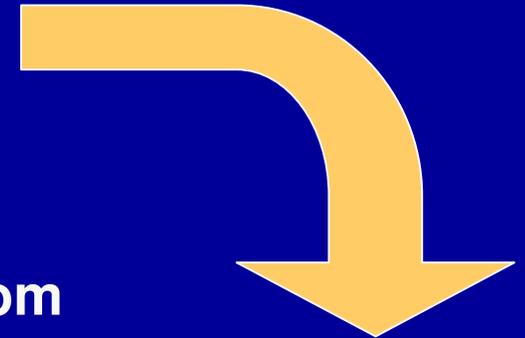
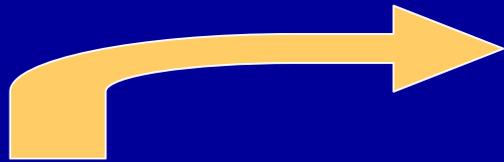
AstraZeneca

BG Medicine

Merck & Co., Inc.

Philips Medical Systems

Imaging Data Handling: Overview



US Upload to secure eRoom



3T MR



CT



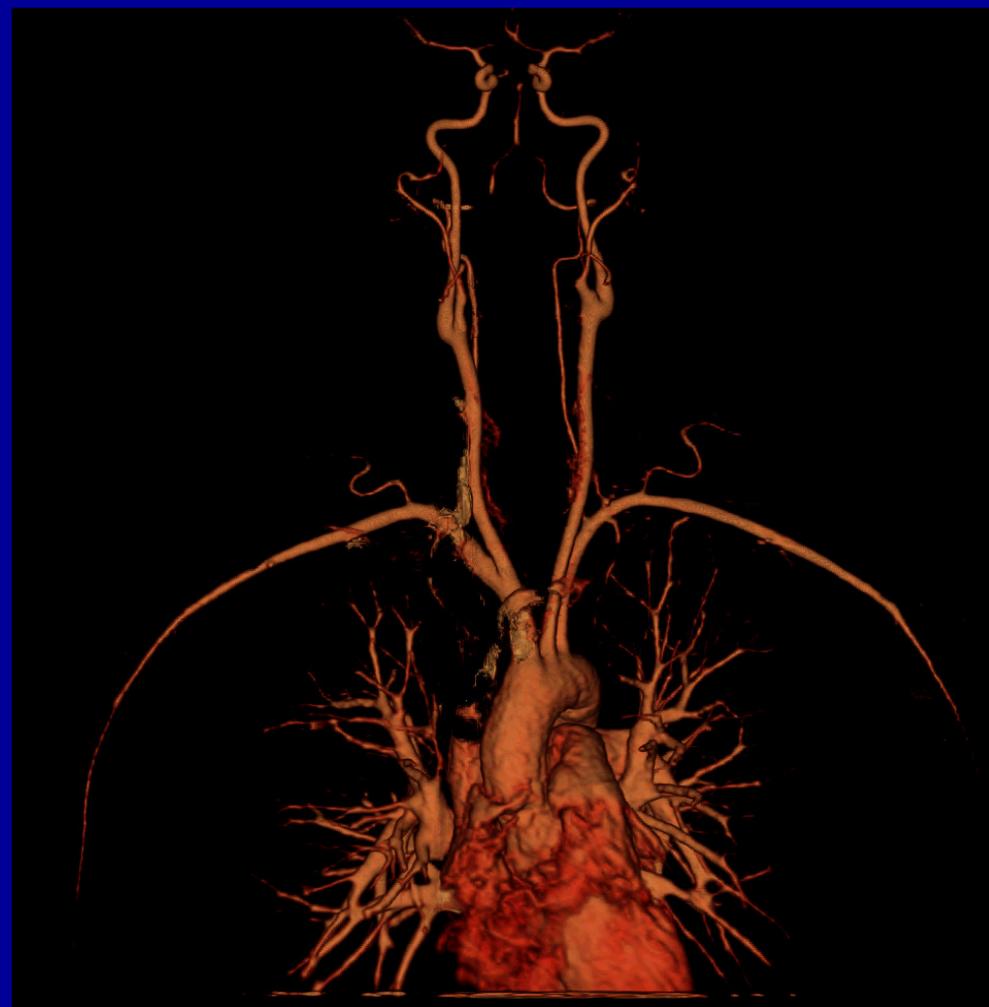
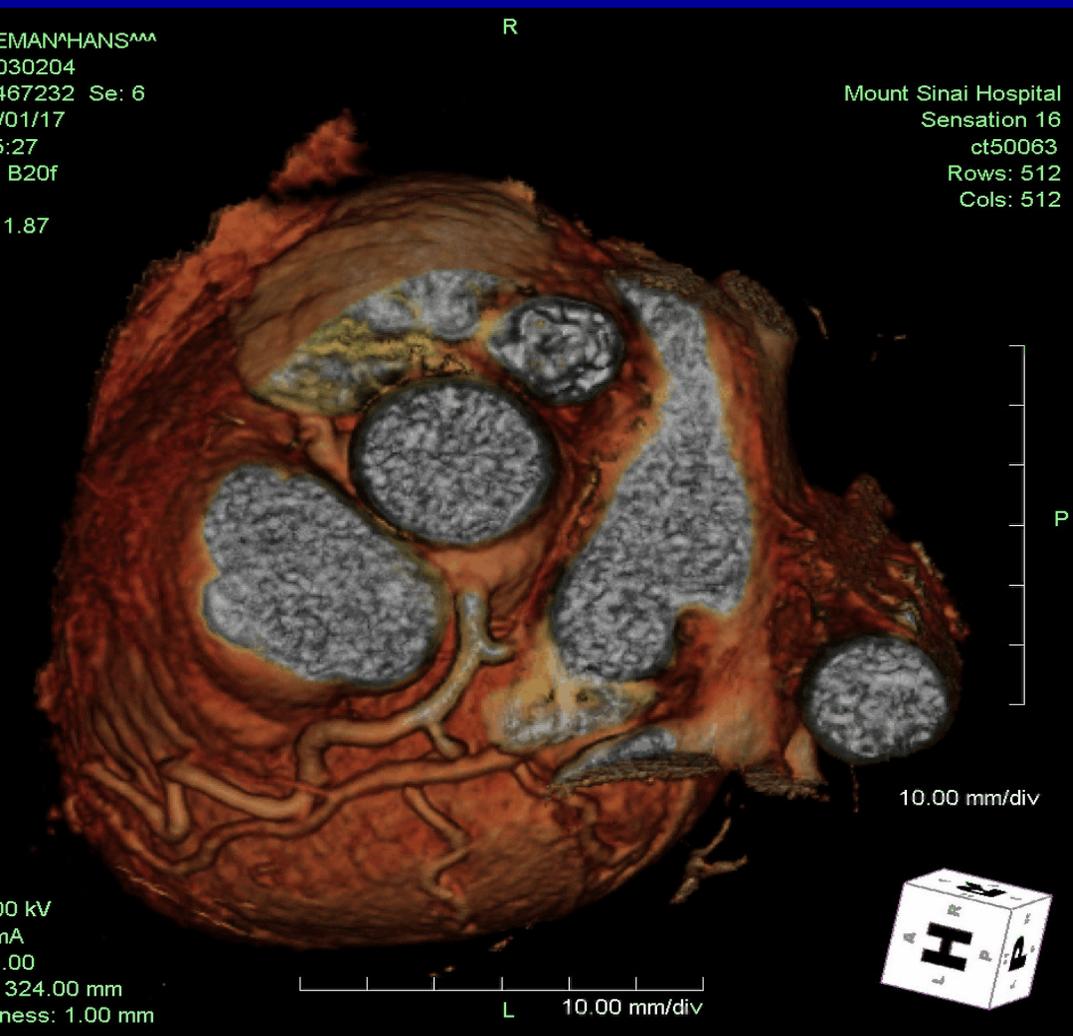
PET/CT



**Images retrieved by
Sinai core imaging**

5) CT- Angio

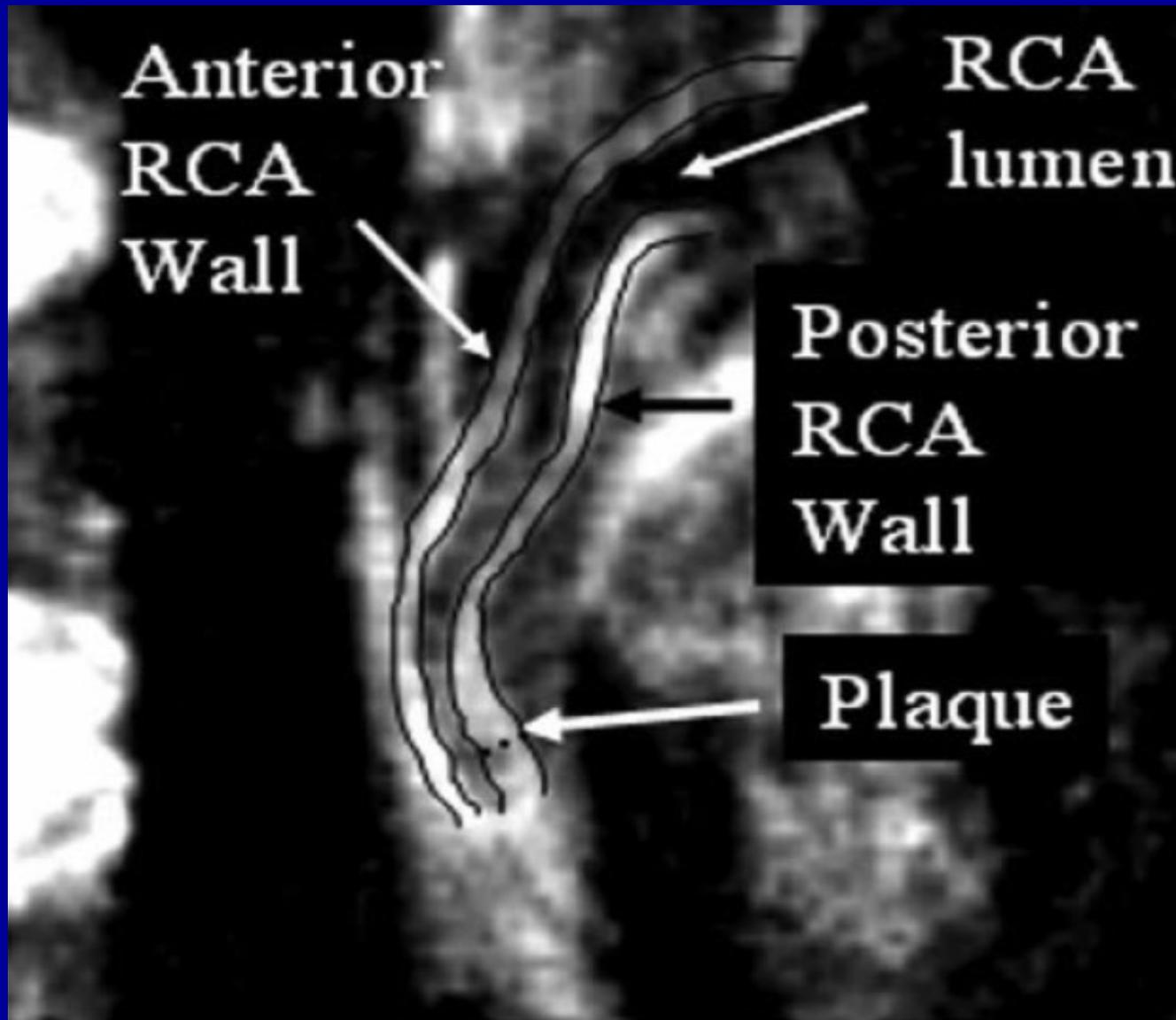
6) MRA



Fuster V, Kim RJ, Circ **2005**;112:135

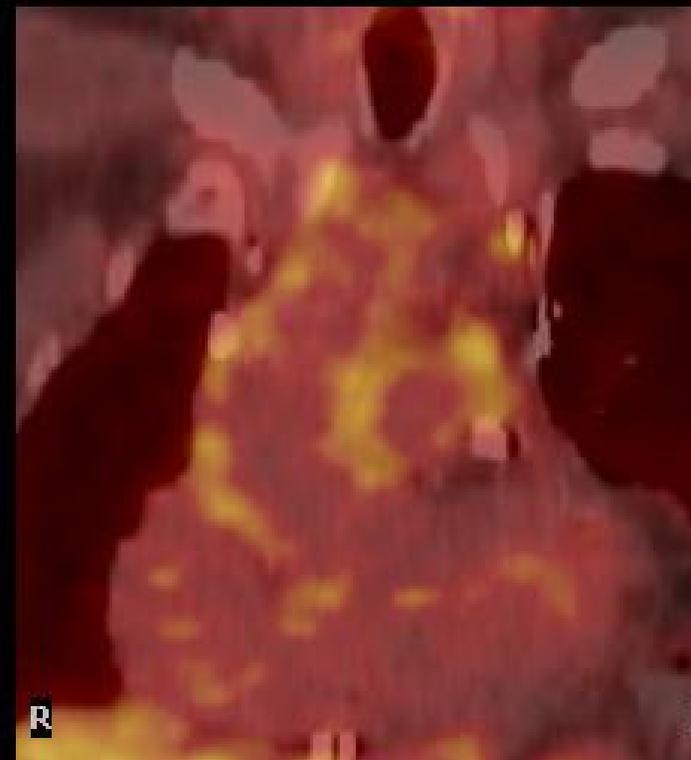
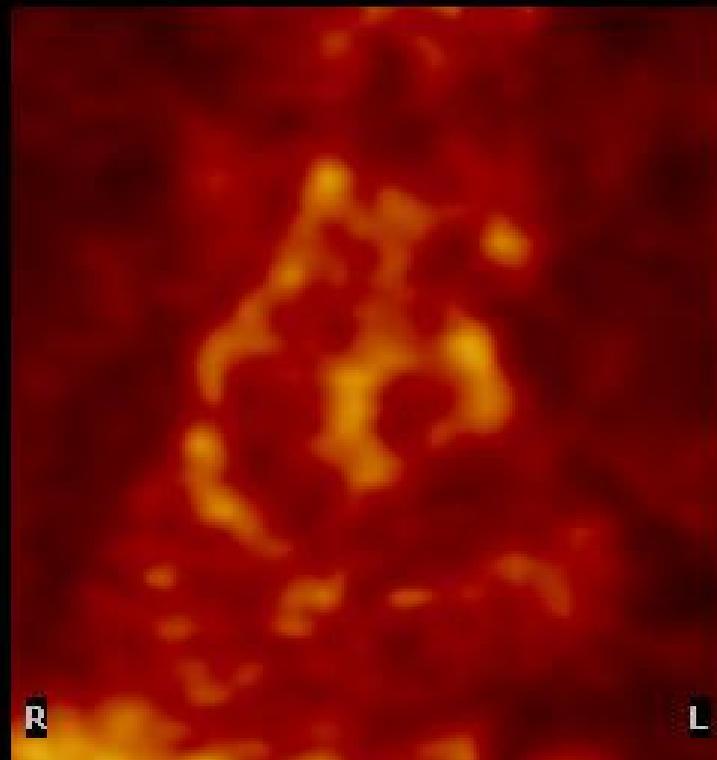
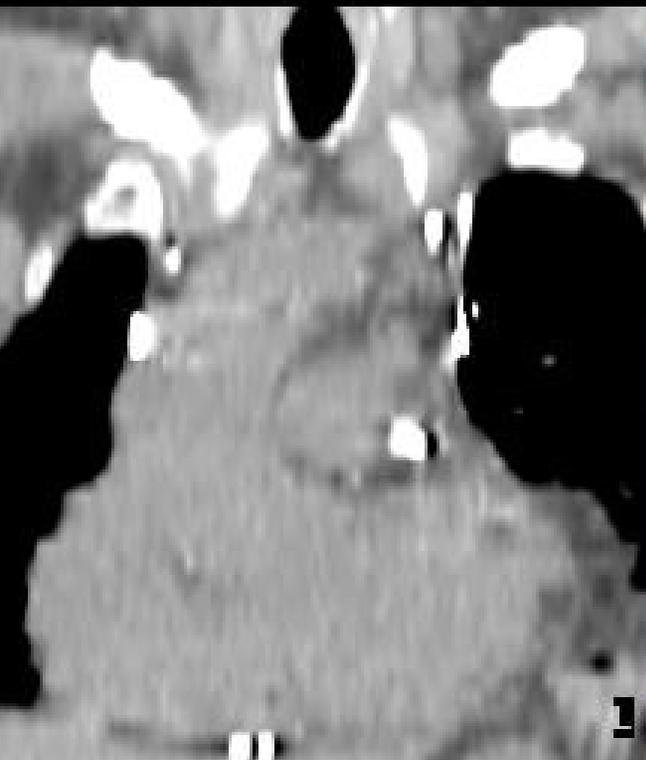
Robin Roberts – Good Morning America – Jan 31, **2006**

7) To Quantify Coronary Plaque Burden (CPB)



ong Kim, W et. al. *Circulation* 2007;115:228 (Aarhus).

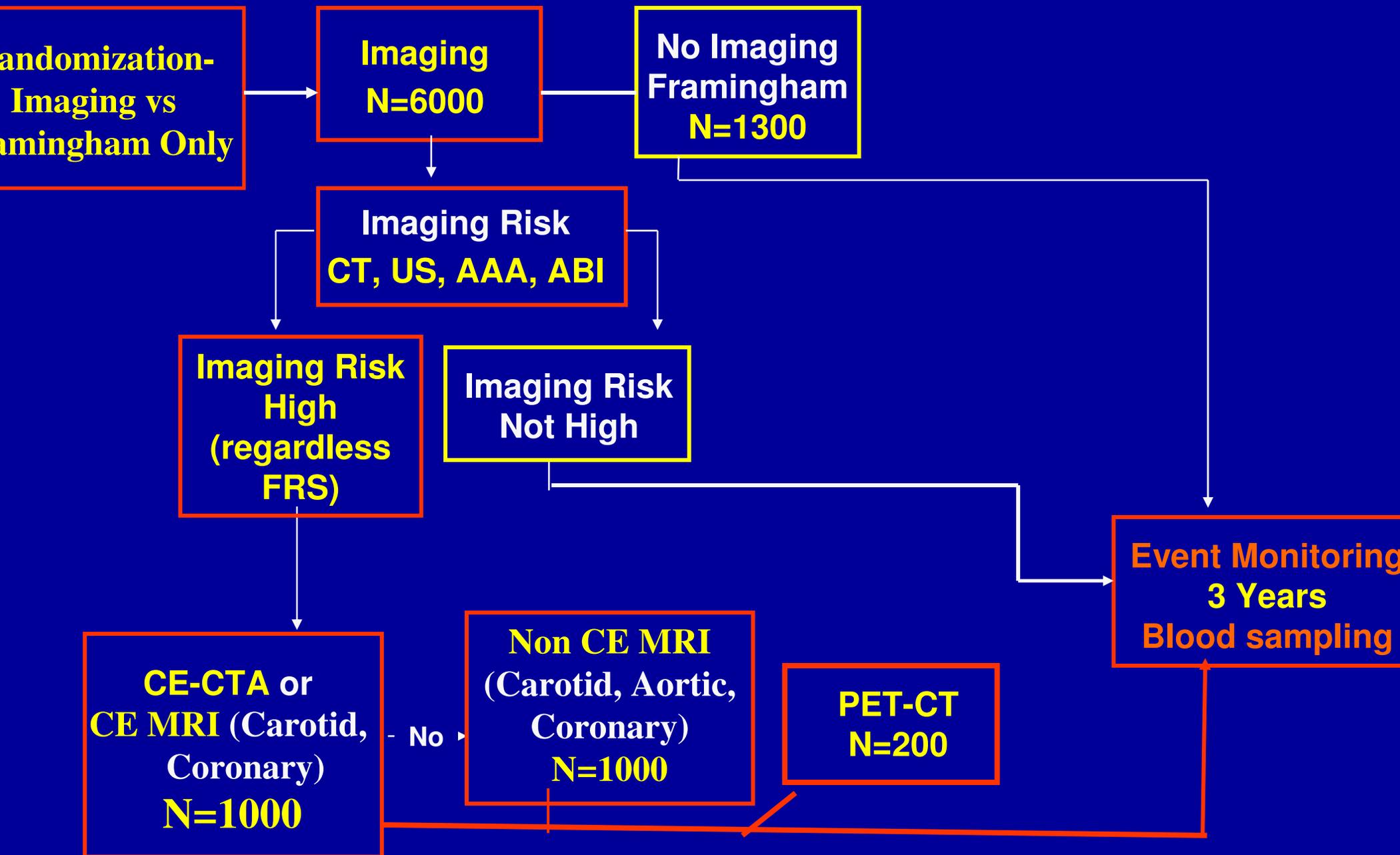
Asian, 64 yrs, DM2, ex-smoker
BAD, CT- FDG uptake ascending aorta

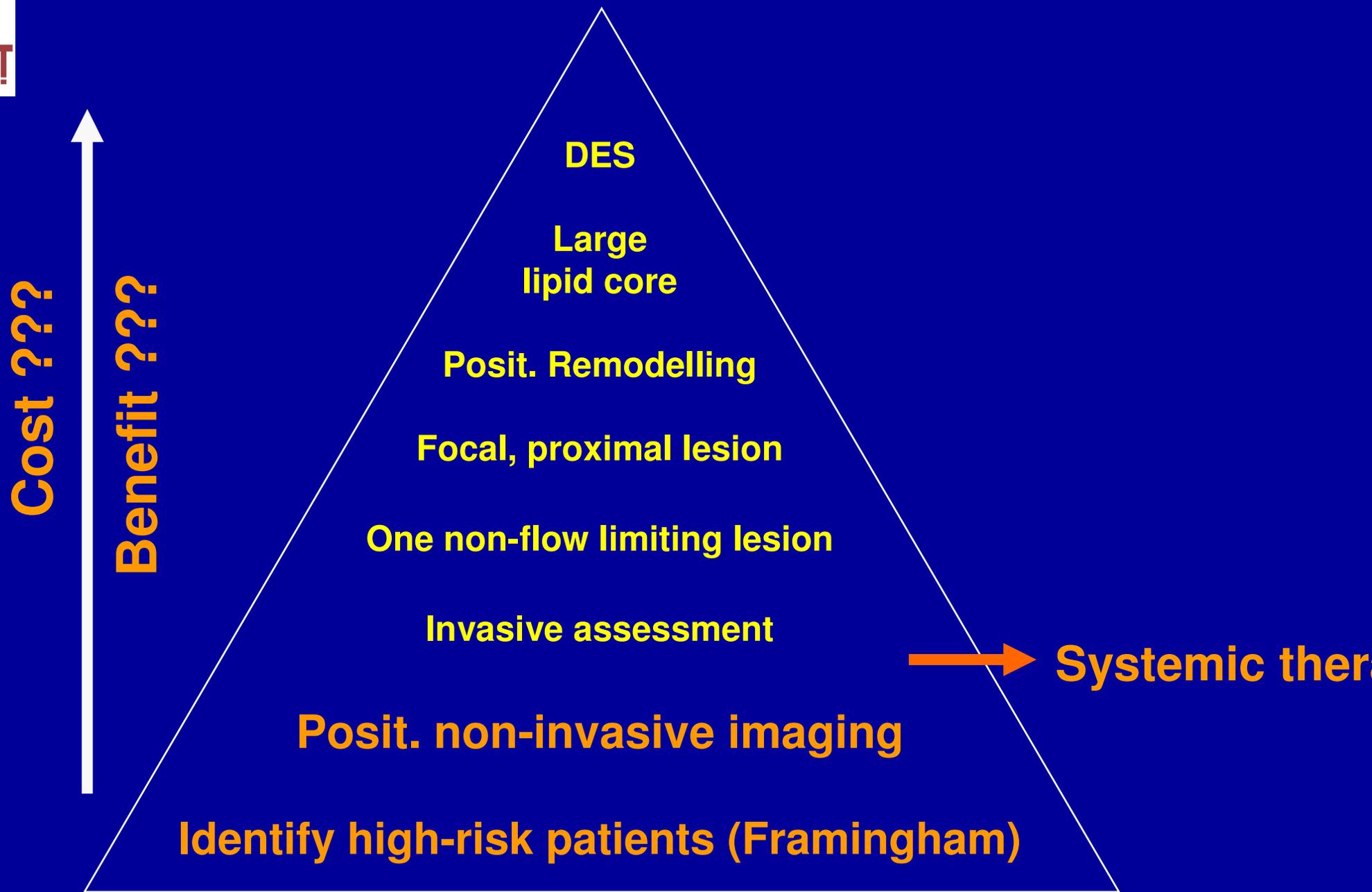


n 26 Pts. Inflammation: Inverse Colocalization with CCS
Colocalized with Lipid Rich Areas
More Predominant in Diabetics

F Rudd, ME Farkouh, V Fuster, ZA Fayad, JACC 2007;50:892
Tahara et al JACC 2006; 48:1825 (Kurome) - Simvastatin

HRP – BIOIMAGING - BASELINE EVALUATION AND FOLLOW-UP





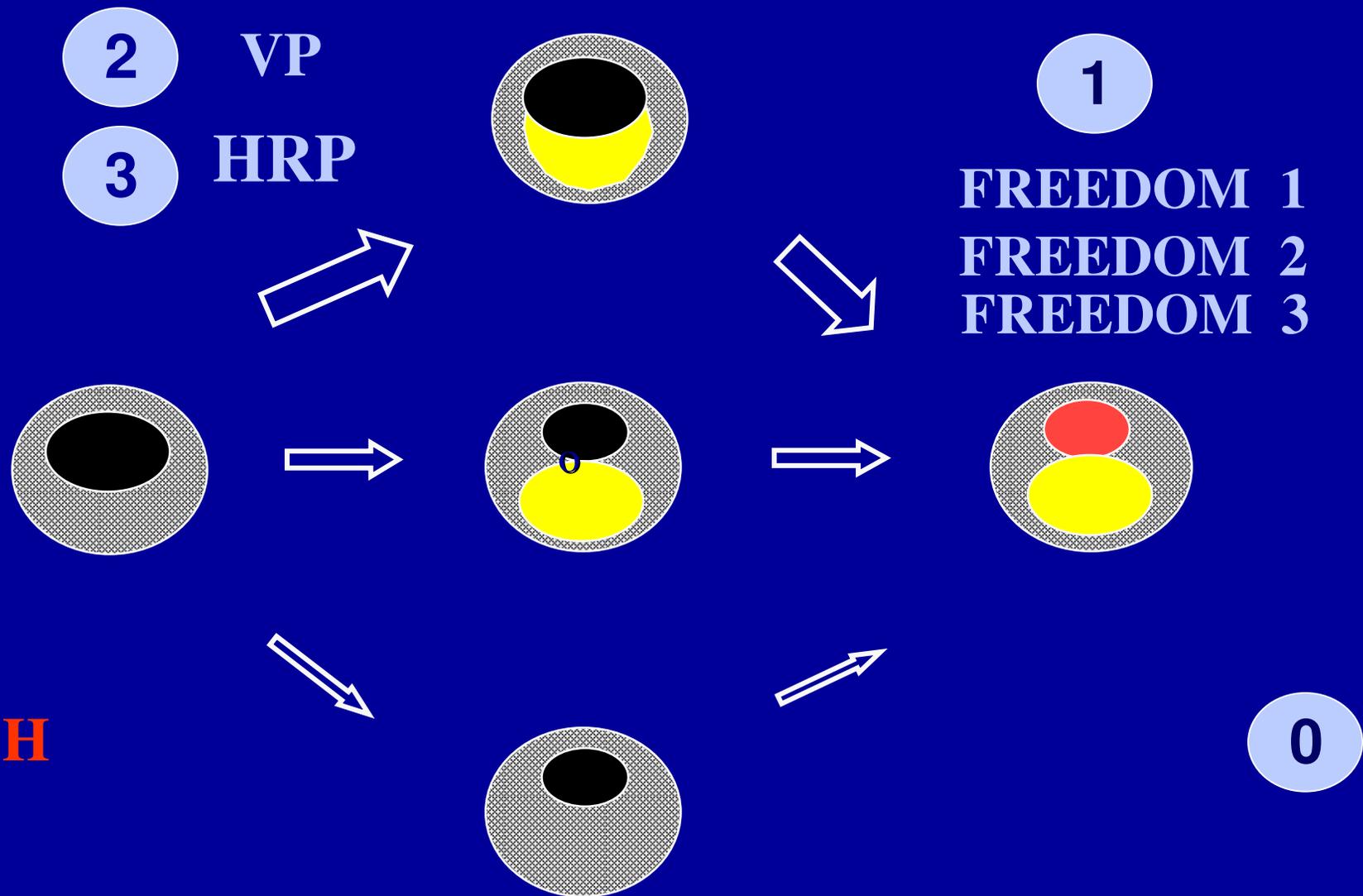
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1) CHILDREN: MODULATE BEHAVIOR

Young children (3-10 years):
Plaza Sésamo Colombia,

The child
as Scientific object



Youth leadership through the Colombia enterprise:
Global Youth Meeting for Health, Delhi, November 2006
Khan, ED. *Science* 2007;316:835.

WORLD HEART
FEDERATION®



And still we rise

The GRENADA Heart Project



EUROACTION
8 countries 24 centres
8657 subjects

Europe



2) WHF – The Grenada Heart Project



1975



2000

PETITE MARTINIQUE PILOT SURVEY PRELIMINARY RESULTS OF CONCERN

- **High prevalence of hypertension**
 - 23% by self report
 - 28% > 140/90 mm Hg

- **High prevalence of diabetes**
 - 9.8% by self report
 - 8.5% > 126 mg/dl glucose

3) Health System, Regulations & Law



Garmot, M. *Lancet* 2006;368:341. **ADULTS DON'T CHANGE**

4a) New Perspective on Nonprescription Statins: An Opportunity for Patient Education and Involvement

Valentin Fuster, Am. J. Card **2007; 100: 907**



4b) POLYPILL

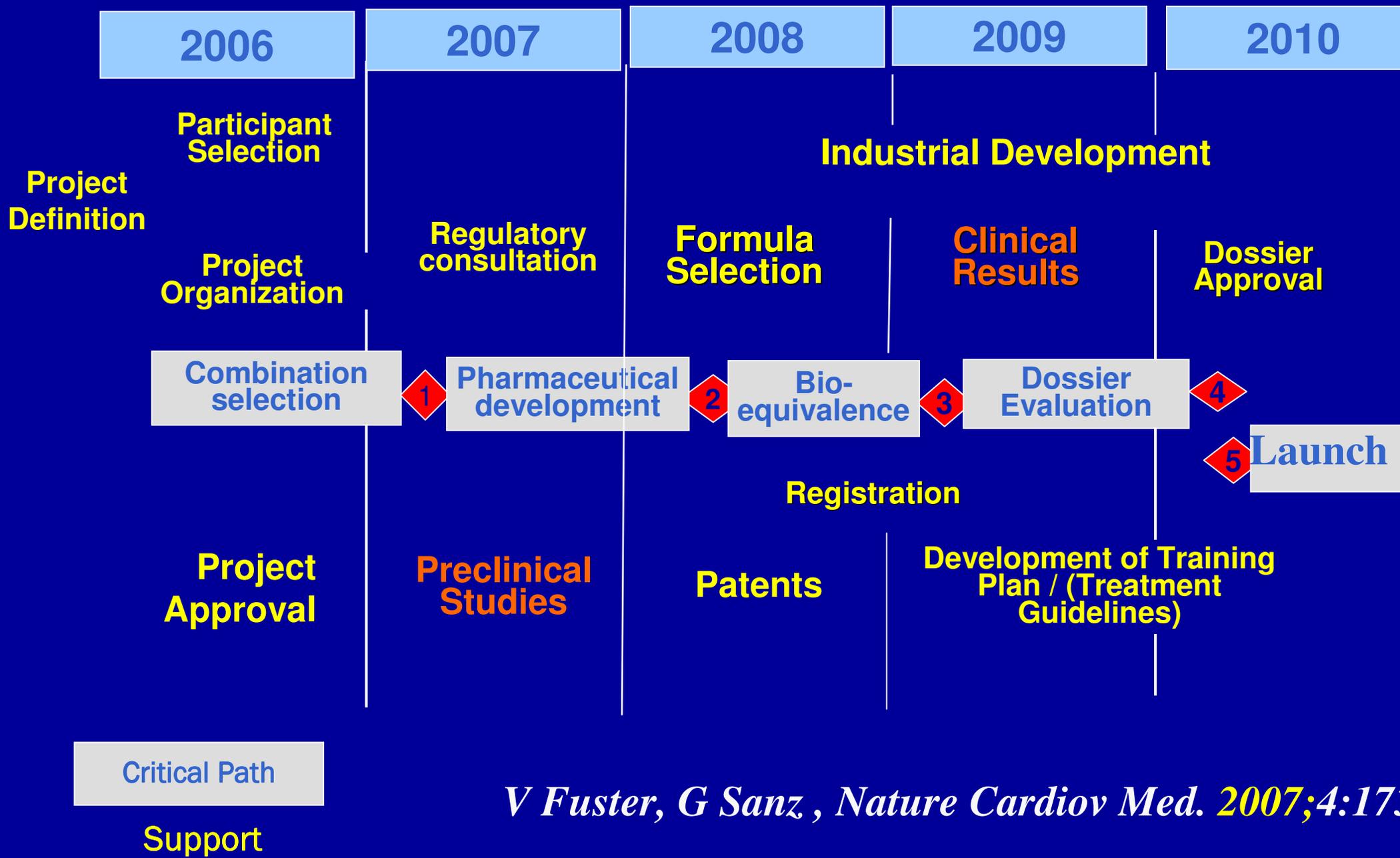
CORONARY DISEASE & CORONARY EQUIVALENTS

- **ASA**
- **STATIN**
- **ACE INHIBITOR**
- **BEHAVIOR MODIFICATION**

ECONOMIC, SIMPLE (ADHERENCE)

Fuster V, Sanz G, Nature Cardio Med. 2007;4:173

4b) Preliminary schedule

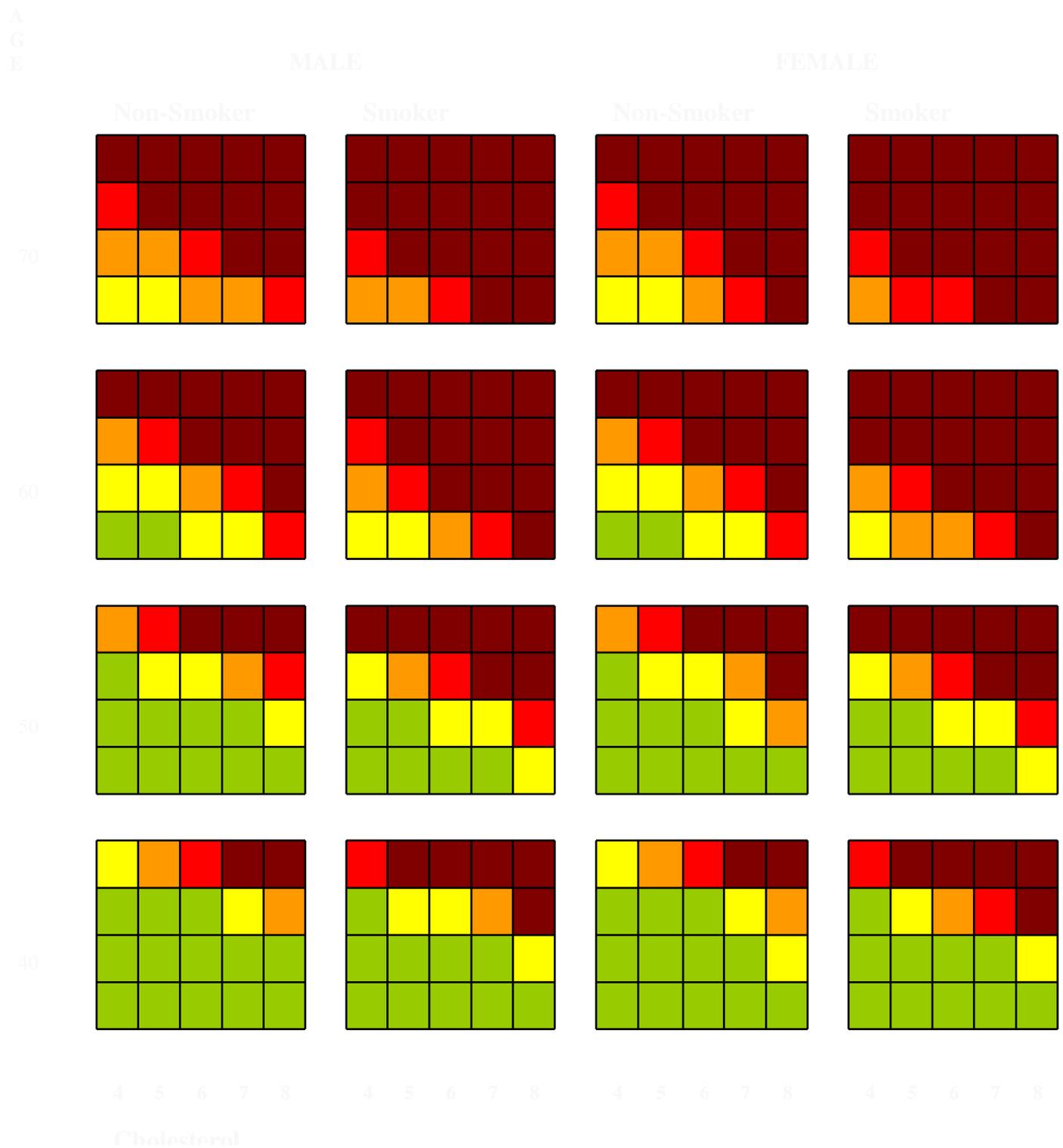


**5) Why have a package?
TO ADDRESS NCD BY PHC**



IO/ISH-Modified simple variables 2007 (3 vs >3)

lood pressure
elt” Perimeter
olesterol
ood sugar (2)
oking
ysical Activity
ge
X



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ENABLING APPROACHES

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Clinical Proteomics

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Behav. Instrum./ Technol.

Clinical Trials Infrastr.

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Genetics /Proteomics /Embryogenesis

Regenerative Biol./ Replac. Therapy

Immunobiol./ Inflammation / Thromb.

Public Health / Genom. Proteo.

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Circ 1999; 99:1132 & 2064 - Defined Circ 2002;106:162 – Update

NHLBI SPARK II 2003-2007 - Prospective (Jan 20, 2003)

NHLBI – Site Visit - March 17, 2006

Training / Mentors

CVMR-ISL

SH Aguiar MD
S Amaerbiaken MD
C Calcagno MD
JC Cornily MD
Zahi Fayad, PhD
Fabien Hyafil PhD
Vitalii Itskovich, PhD+
Michael J Lipinski
V Mani M
James HF Rudd MD
Javier Sanz, MD
Mark Sirol, MD
E Vucic MD

CV Research Fellows

Sameer Bansilal
Roberto Corti, MD
Juan F Viles MD
Randolph Hutter MD
Borja Ibanez MD
Claudia Calcagno PhD

Cardiology

Valentin Fuster, MD, PhD
Juan J Badimon, PhD
Michael Poon, MD
Stella Palentia, RN
Don Smith, MD
Pedro R Moreno MD
Michael E Farkouh

Molecular Biology

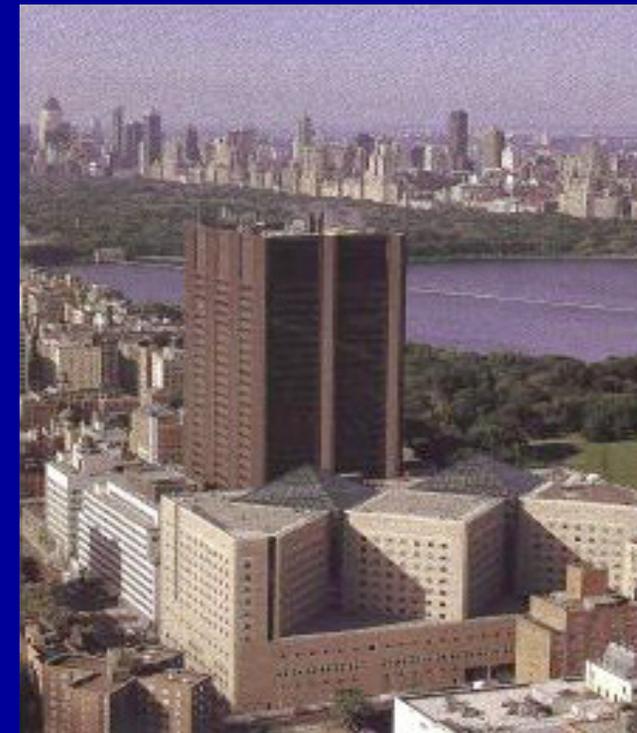
Edward Fisher, MD, PhD
AP Levy MD
Ernane Reis, MD

Neurology

Jessey Weinberger, MD

Pathology

John Fallon, MD, PhD
KR Purushothaman, MD



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NIH-HL 94013
NIH-HL 61801
NIH-HL 07208