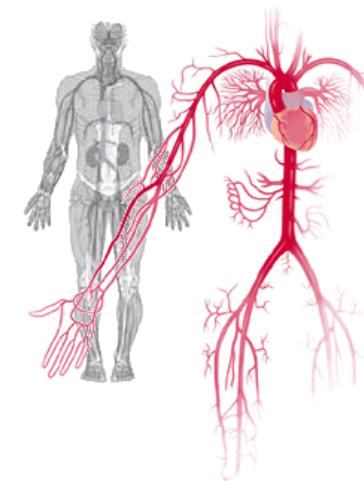




LA VISIÓN GLOBAL DE LA PERSONA ENFERMA



## Reunión de Diabetes y Obesidad



Dr. José Sabán Ruiz

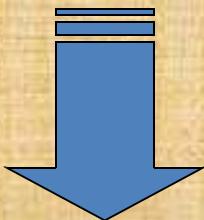
Unidad de Endotelio, y Medicina CM  
Servicio de Medicina Interna  
Hospital Universitario RyCajal

31 de Enero y 1 de Febrero de 2014 | Hotel Meliá Castilla. Madrid

*La Unidad de Endotelio tiene raíces históricas.....*



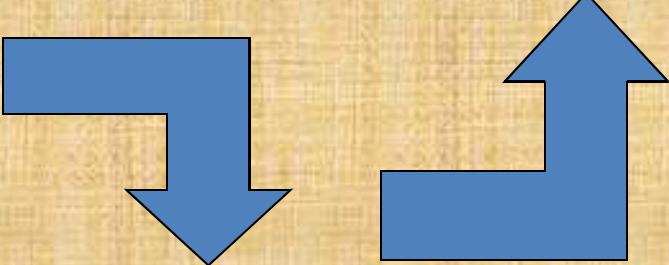
**Unidad de Diabetes  
(1980)**



**Unidad de RCV  
(1990)**

## **Unidad de Endotelio y Medicina Cardiometabólica**

**(2013)**



**Unidad de Patología Endotelial  
(2000)**

© 1986 Elsevier Science Publishers B.V. (Biomedical Division)  
*World Book of Diabetes in Practice*, Vol. 2, L.P. Krall, editor

## **Cardiac complications in diabetes**

**M. SERRANO-RIOS, A. ORDOÑEZ PEREZ AND J. SABAN-RUIZ**

*Professor of Medicine, Department of Internal Medicine, Centro Especial Ramon  
y Cajal, Madrid, Spain*

### **CARDIAC AUTONOMIC AND SOMATIC NEUROPATHY IN DIABETIC PATIENTS WITH AND WITHOUT MICROANGIOPATHY**

**J. Sabán, A. Tobaruela, C. Campos,  
A. Ordóñez, M. Castillo, M. Serrano-Ríos**

Service of Internal Medicine,  
Hospital Ramon Y Cajal, Madrid 28034, Spain



# Medicina Cardiometabólica



Preventiva

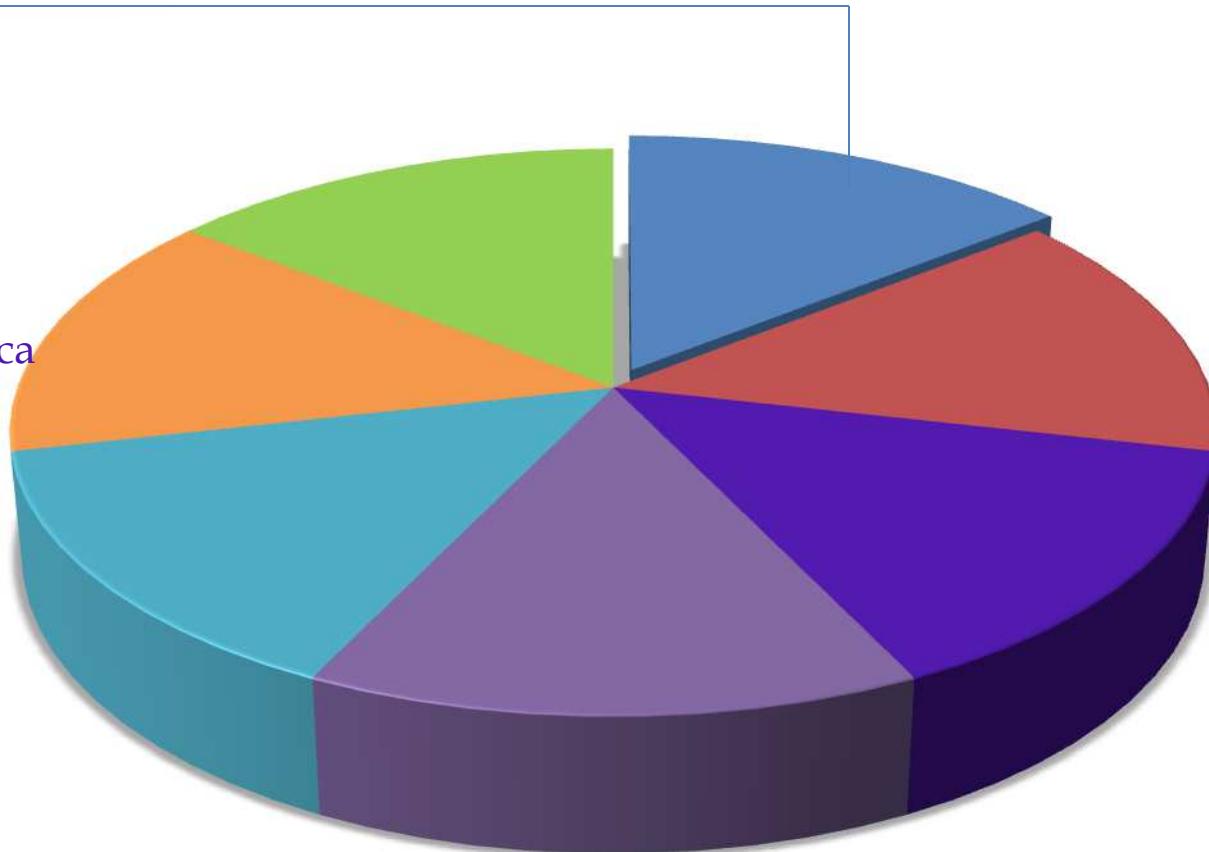
Anticipativa

Predictiva

Personalizada

Translacional

# *Introducción*



Introducción

Corazón y vasos coronarios

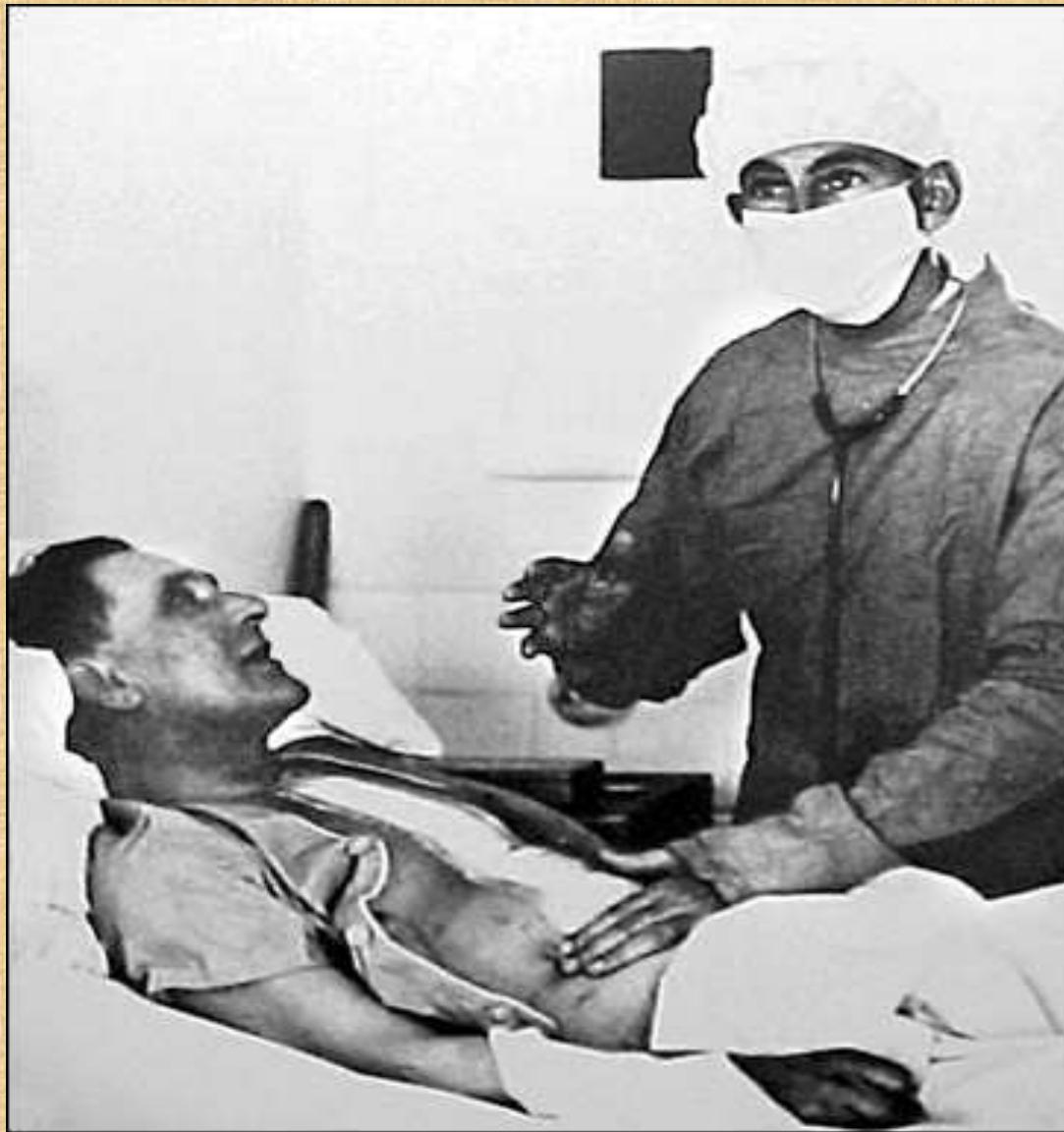
Cerebro-vascular y arteriopatía periférica

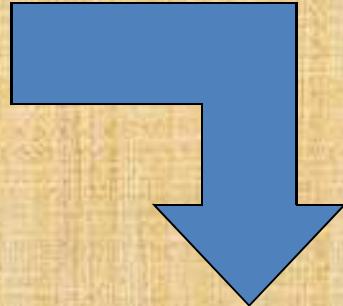
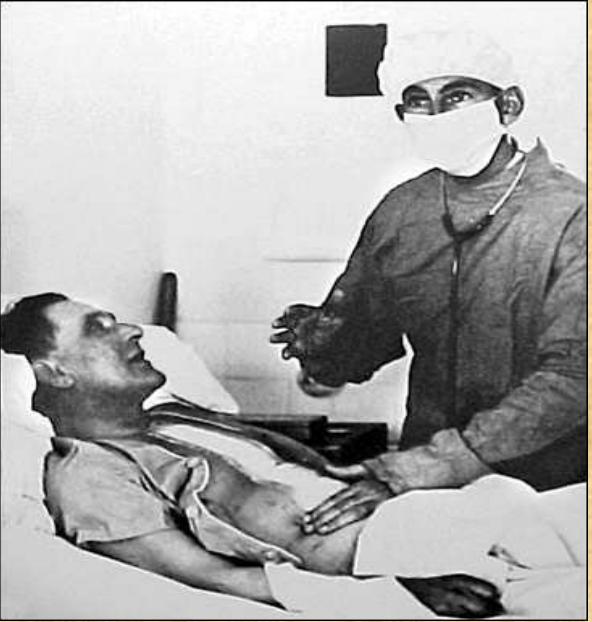
Valor predictivo coronario

Fitness CR

Perspectivas futuras

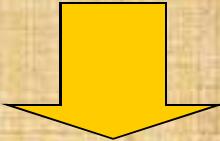
Conclusiones



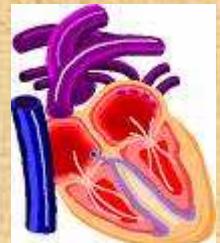


11 años

Pooling Project, 1978



“Make de link”, 2002  
Diabetes, Heart Disease and Stroke”.

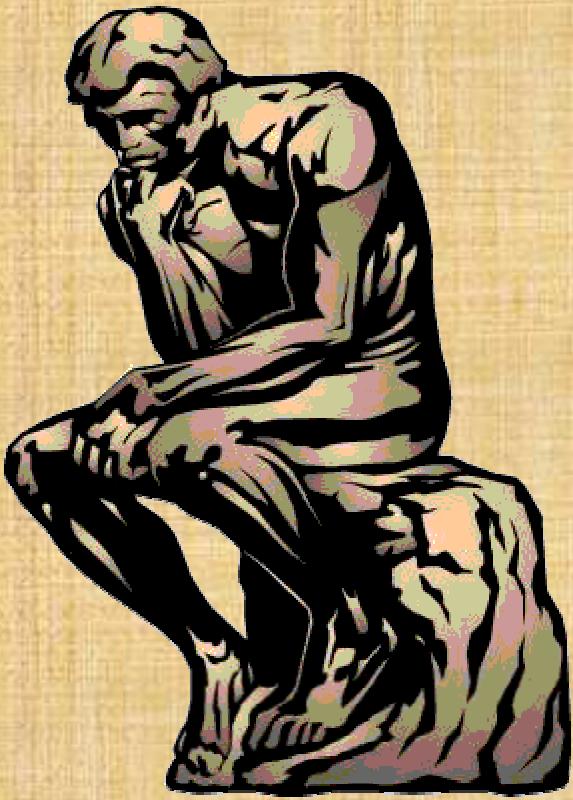


# DM2

# ECV



**Stern MP. Diabetes and cardiovascular disease.  
The "common soil" hypothesis. Diabetes. 1995 Apr;44(4):369-74.**



¿Conocemos la prevalencia de  
macroangiopatía diabética en la DM2?

# Enfermo de alto riesgo para DM2

GAA  
ITG

SM

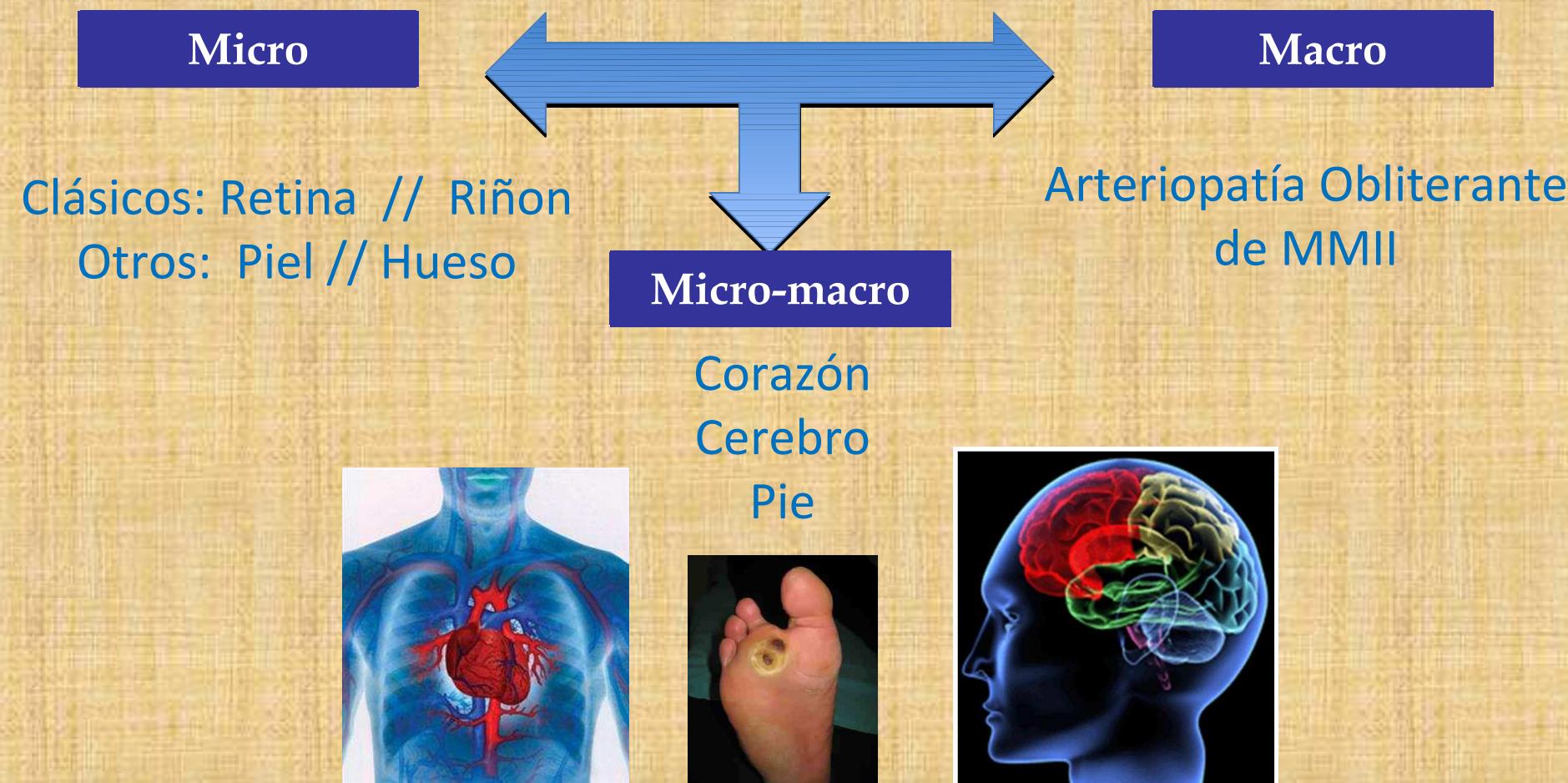
Diabetes  
gestacional

ECV

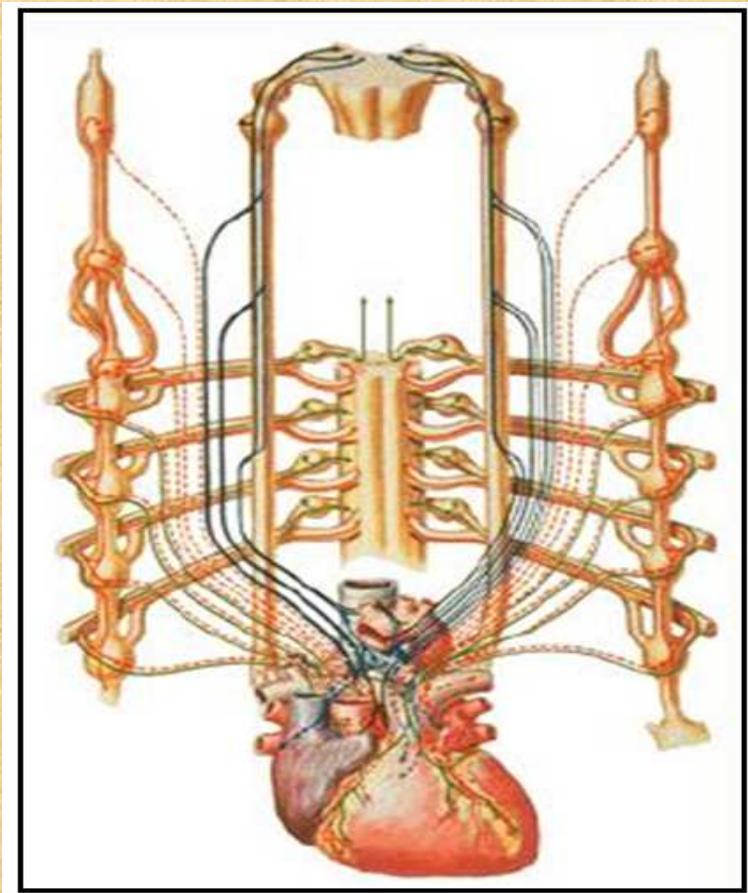
Sobrecarga oral de glucosa

“An OGTT shoul be carried out in patients with CVD”  
Task Force ESC-EASD, 2007

# Impacto vascular del Status hiperglucémico crónico



# Interacción con la Neuropatía



# Epidemiología de la enfermedad aterotrombótica en la DM

Enfermedad  
Coronaria



Ictus



Amputación no traumática de  
MMII



**TAS** ← **UKPDS 23 EC** → **C-HDL**

**C-LDL**

**A1c / Tabaco**

**UKPDS 56 EC**

log c-Total / c-HDL

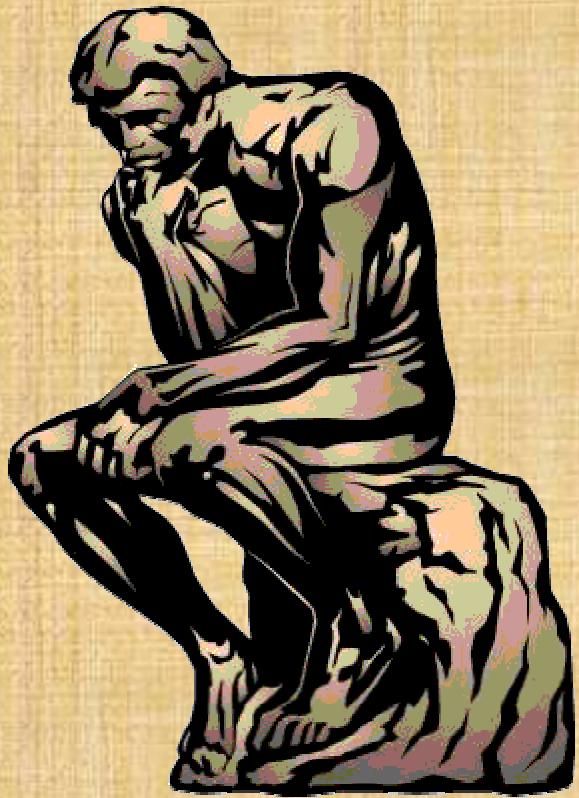
**UKPDS 60 Ictus**

c-Total / c-HDL

no A1c

**UKPDS 66 EC e Ictus fatales**

A1c

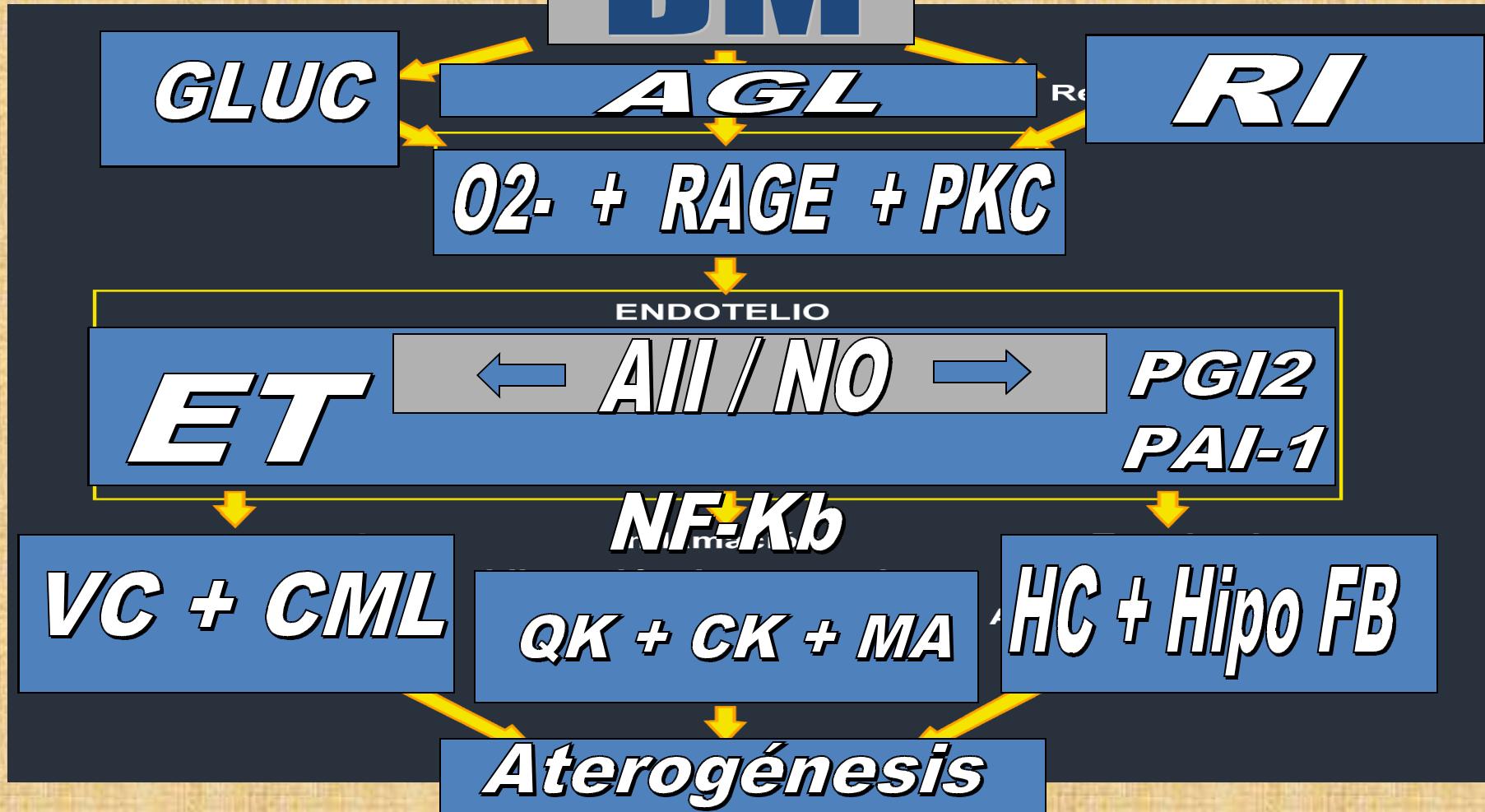


**¿Como interactúan los diferentes factores causales de la enfermedad?**

# Patogenia de la enfermedad aterotrombótica en la DM

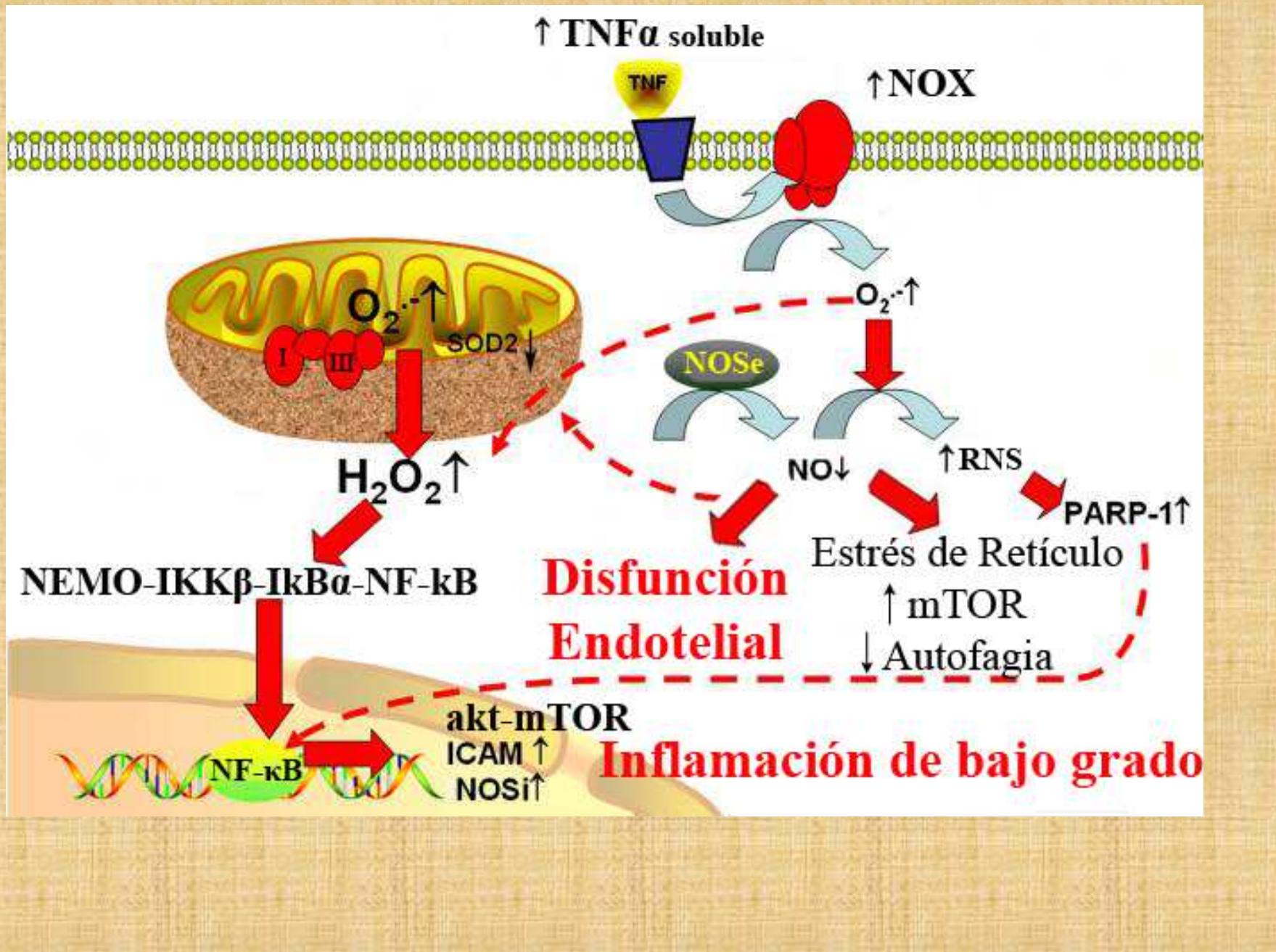
**Hipótesis de Beckman**

# Hipótesis de Beckman



Beckman JA et al. JAMA 2002.





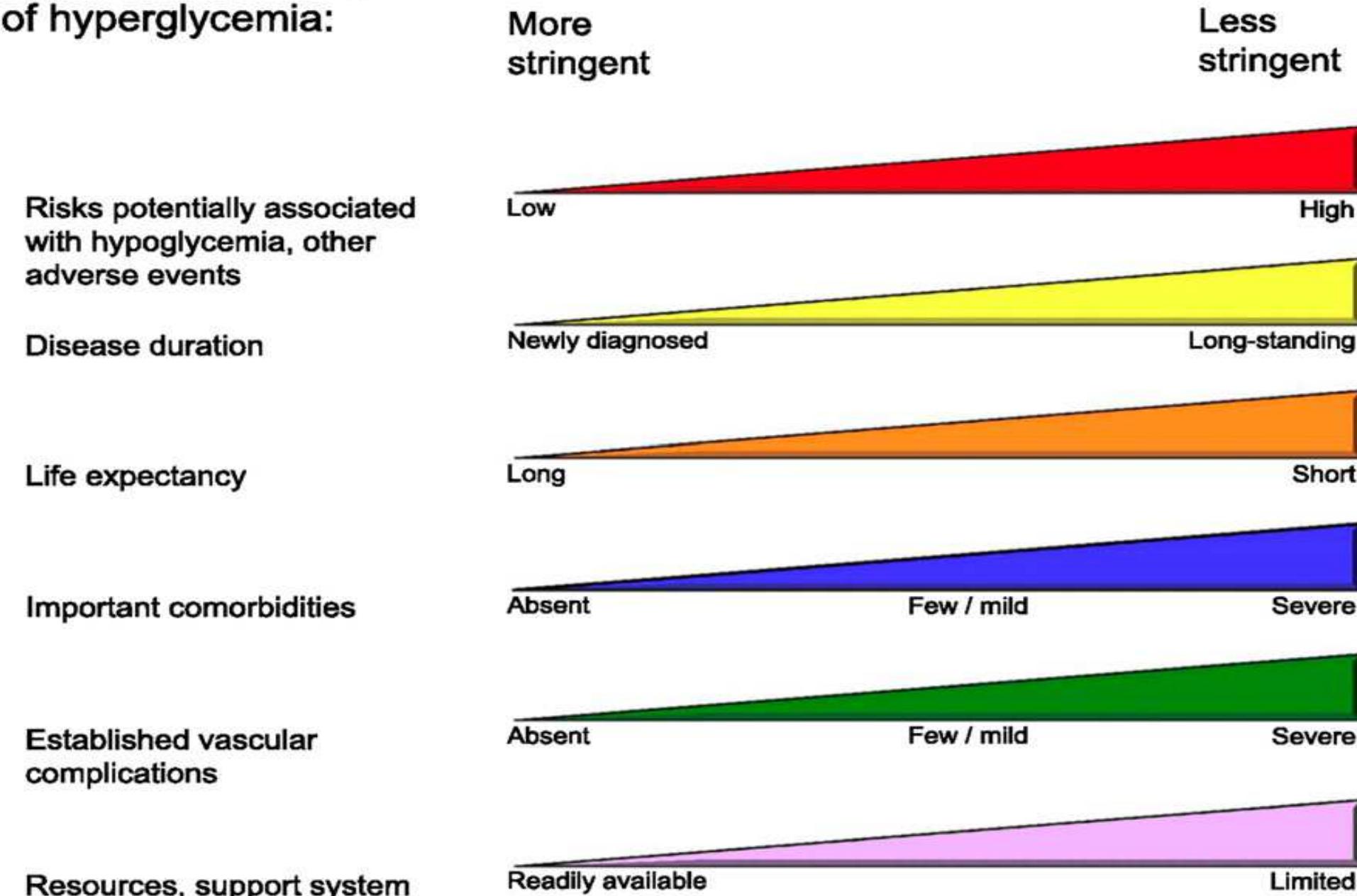
GDMT

(guideline-directed medical therapy)



2012

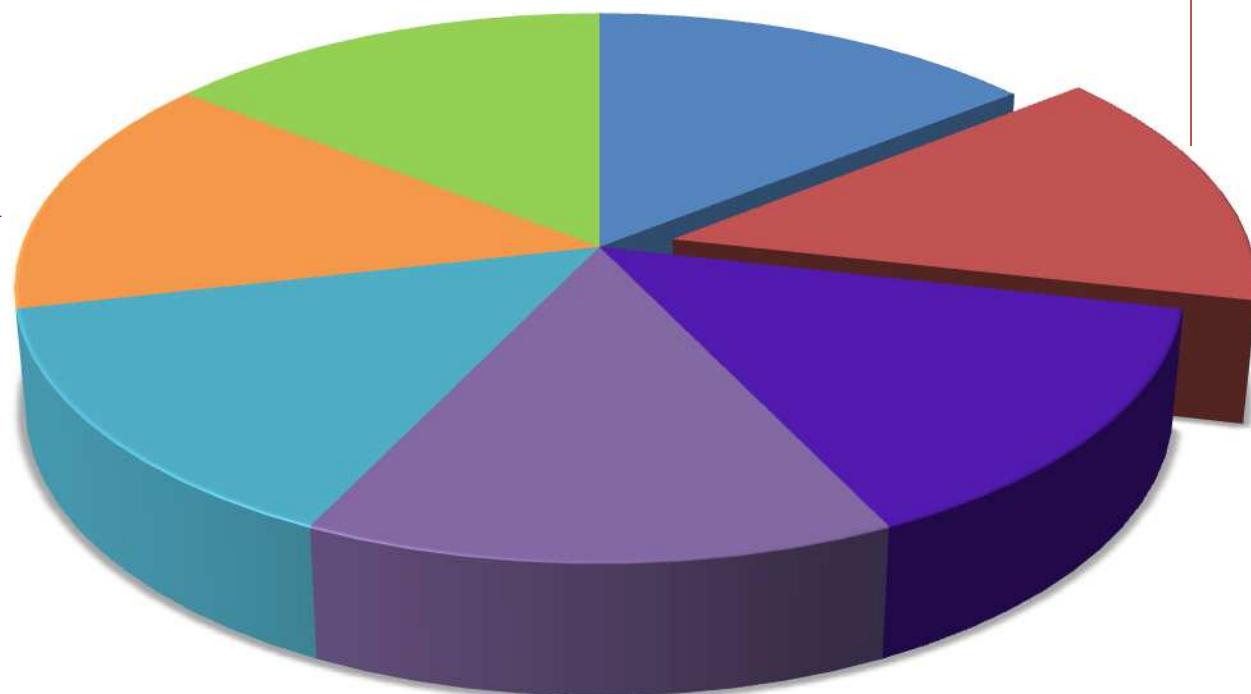
## Approach to management of hyperglycemia:



Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. Ann Intern Med 2011;154: 554-559

# *Corazón y vasos coronarios*

## Introducción



Corazón y vasos  
coronarios

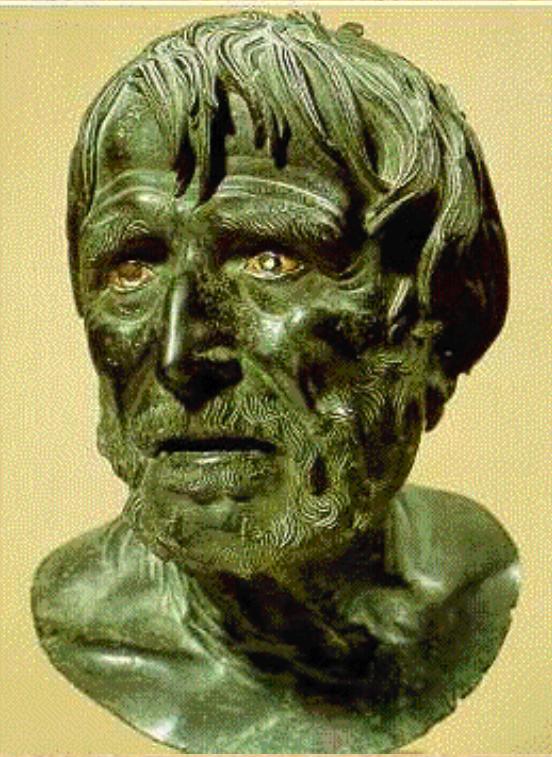
Cerebro-vascular y  
arteriopatía periférica

Valor predictivo  
coronario

Fitness CR

Perspectivas  
futuras

Conclusiones



## Lucio Anneo Séneca

*Mientras ignores qué has de buscar lo que hagas  
no será “viajar” sino andar errante.*



Sin rumbo fijo,

con paso firme.

<http://www.desmotivaciones.com.co>

# *Importancia del Dx precoz*

PREVENCIÓN SECUNDARIA

**INTERVENCION  
AGRESIVA**

**Dx PRECOZ**

PREVENCIÓN PRIMARIA

**PREVENCION  
EFFECTIVA**

**SCA**

**AT-coronaria**

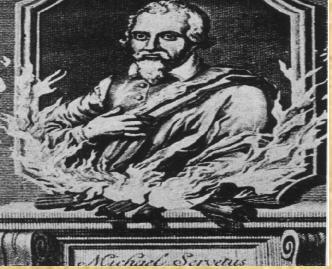


**SUBCLINICA**

**MFRCV**

**FRCV**

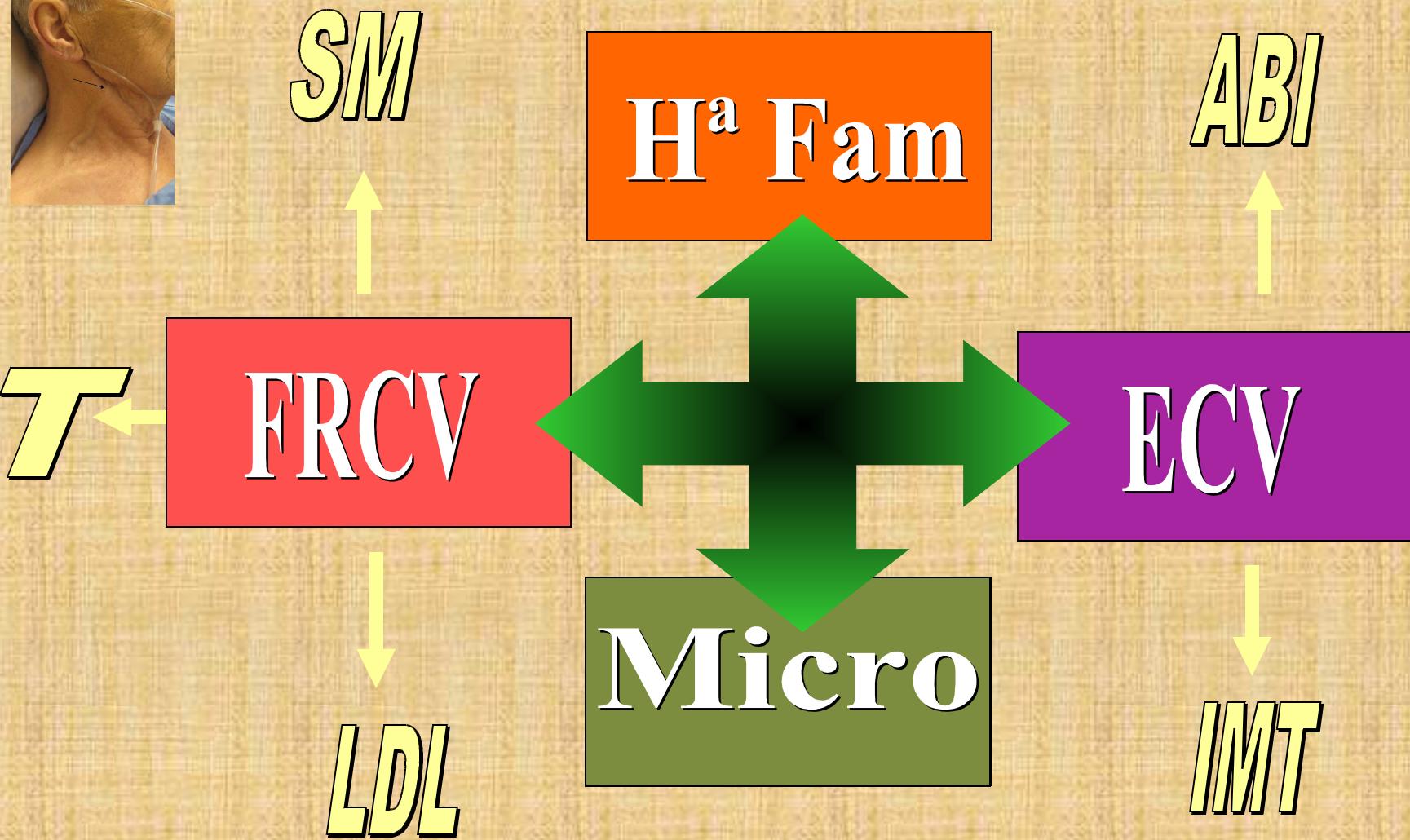
Furberg C.D. et al. JACC. 1996 / Fuster,V. Circulation 1999



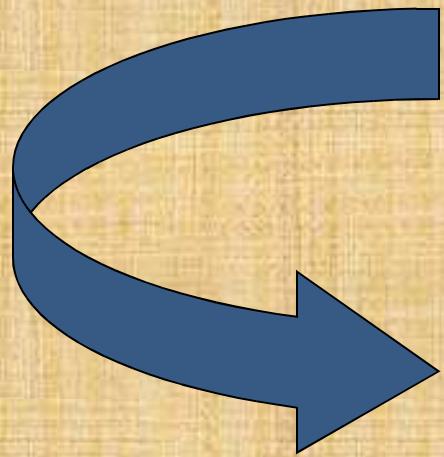
# Unidad de Endotelio y Medicina CM



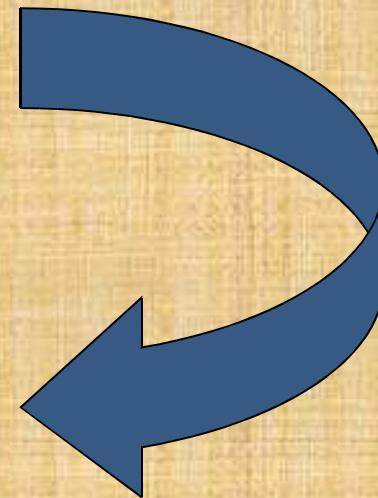
Evaluación clínica, BQ, AT precoz



# Diabetes + HTA



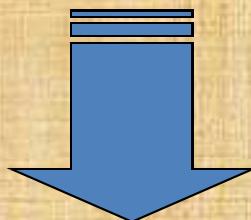
Diferente criterio dx



Diferentes objetivos

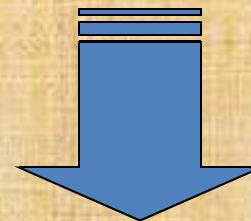
# Highlights del diagnóstico HTA

AMPA  
Finn-HOME Study



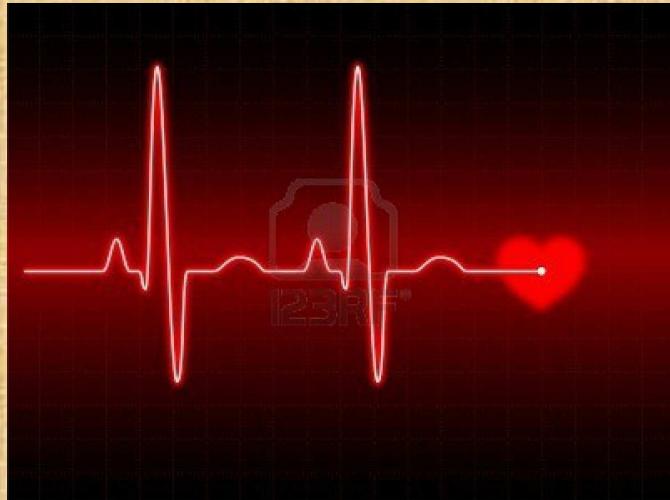
***4 x 7 medidas***

MAPA



*Imprescindible para el Dx  
según la agencia NICE*

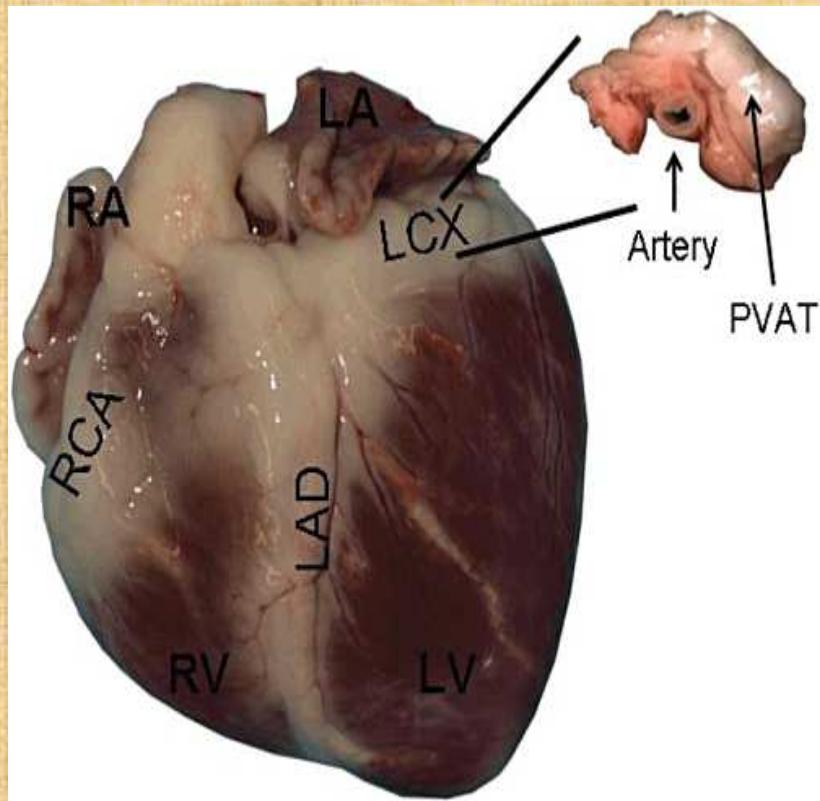
# Screening cardiológico básico



¿A todos?



# Perivascular adipose tissue



Payne GA et al: Epicardial perivascular adipose tissue as a therapeutic target in obesity-related coronary artery disease. Br Pharmacol 2012;165:659-69

# **Exploraciones personalizadas**

**a) Acercamiento convencional:**

**Ergometría con/sin SPECT**

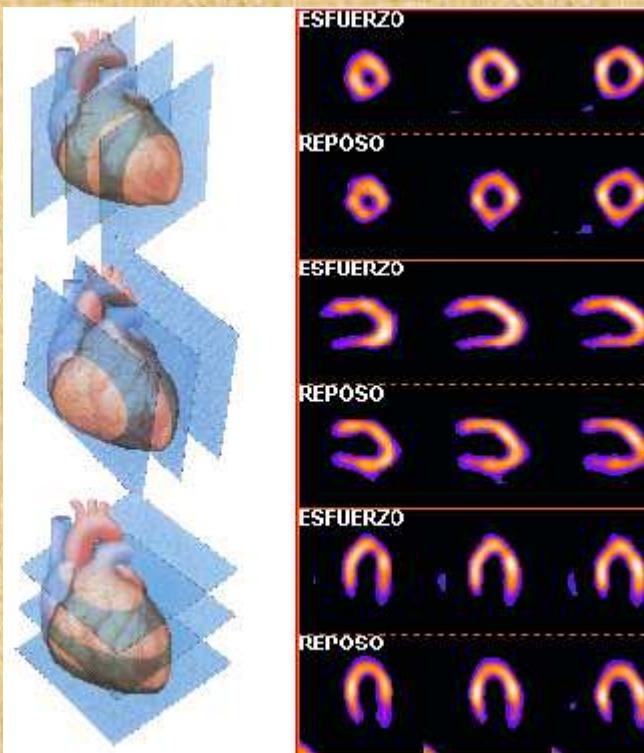
**b) Acercamiento no-convencional:**

**-Ecocardiografía de Estrés**

**-TC coronario**

**-RM cardíaca**

# Ergometría con /sin SPECT

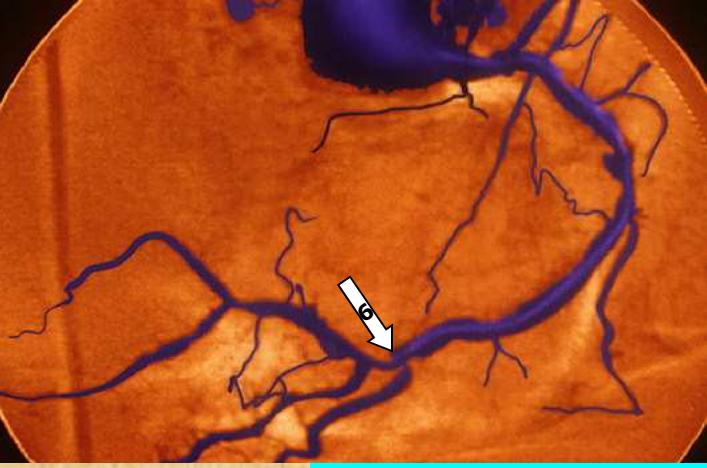


# ADA 2014 Standards of Medical Care in Diabetes

## Diabetes Care Vol 37, Suppl 1 Jan 2014 S14-80



*“the area of screening asymptomatic diabetic patients for coronary artery disease (CAD) remains unclear”*



# "Perfil de riesgo ADA"

EV PERIFERICA O CAROTIDEA

O

1/3

≥ 55 años

y

## DOS DE LOS FACTORES SIGUIENTES

HTA

H<sup>a</sup> familiar  
EC precoz

RNP  
avanzada

LDL

HDL

Tabaquismo

microalb

ADA: Consensus development conference on the Diagnosis of CHD.

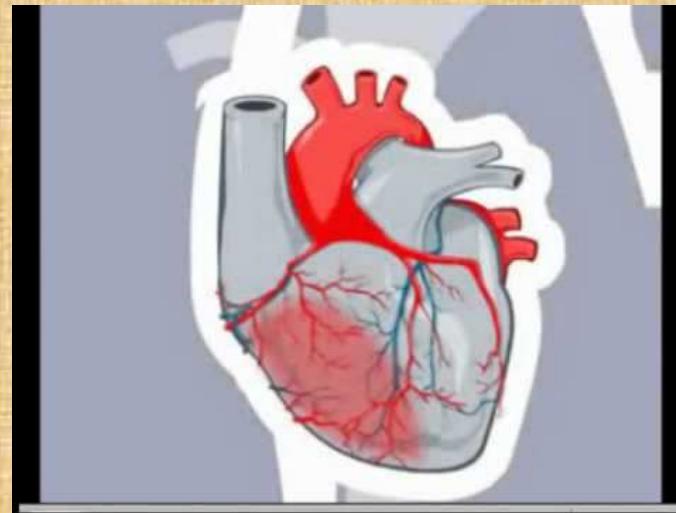
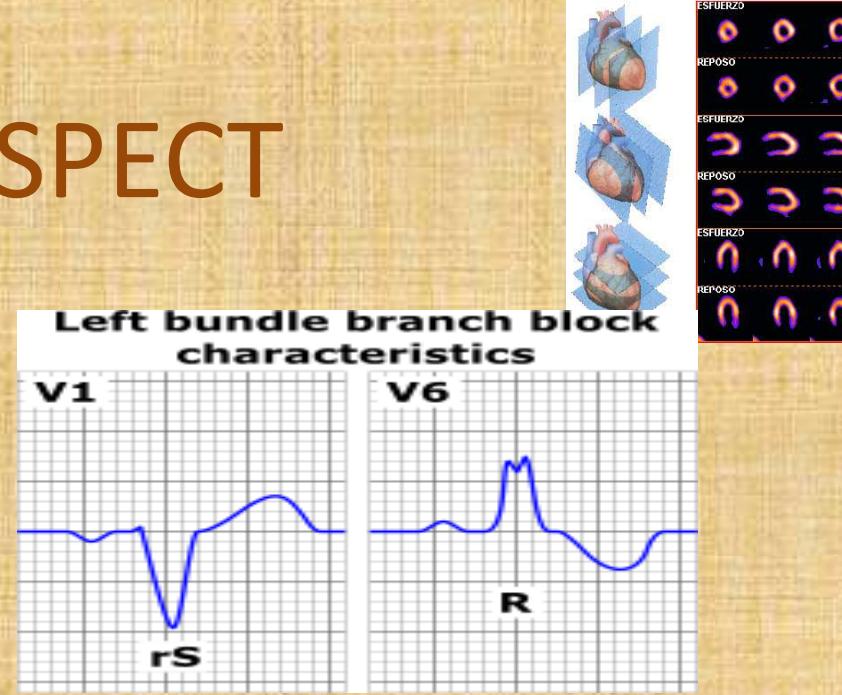
Diabetes Care 21: 1551-9, 1998/ Kharlip J et al. Diabetes Care, 2006.

Poirier P et al: Can J Cardiol 2006; 22 : 9A-15A / Berry C et al. J Am Coll

Cardiol 2007; 49(6):631-642 / ADA: Bax JJ, et al: American Diabetes

Association. Screening for coronary artery disease in patients with diabetes. Diabetes Care 2007;30:2729– 2736

# Indicaciones del SPECT

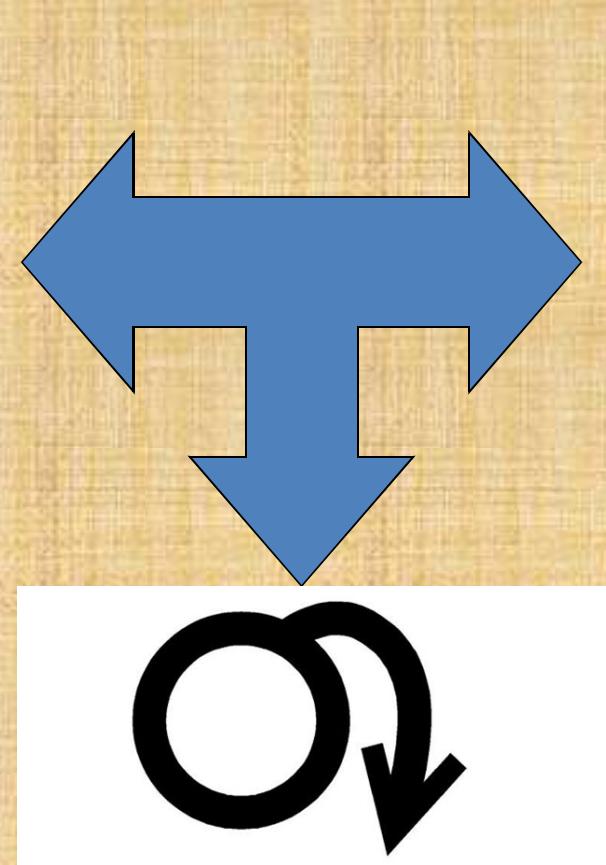


# Ergometría con /sin SPECT

## Situaciones especiales



Miller et al, Am Heart J.  
2004;147:890–6

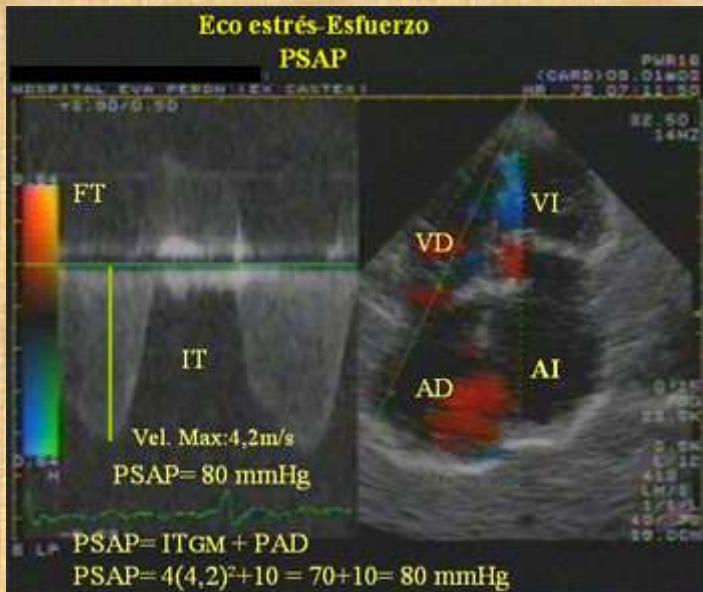


Mangano DT. Anesthesiology  
1990; 72: 153–184

Nehra et al, The Princeton III Consensus, Mayo Clin Proc, 2012, 87: 766-8

# Ecocardiografía de Estrés

dismotilidad del VI asociada a una isquemia parietal inducida por esfuerzo.



Dobutamina  
Dipiridamol  
Adenosina

8% 20%

Marwick TH, et al, Eur Heart J. 2003;24:1223–30  
Faglia E, et al, Am Heart J. 2005;149:e1– e6.

# Cascada Isquémica

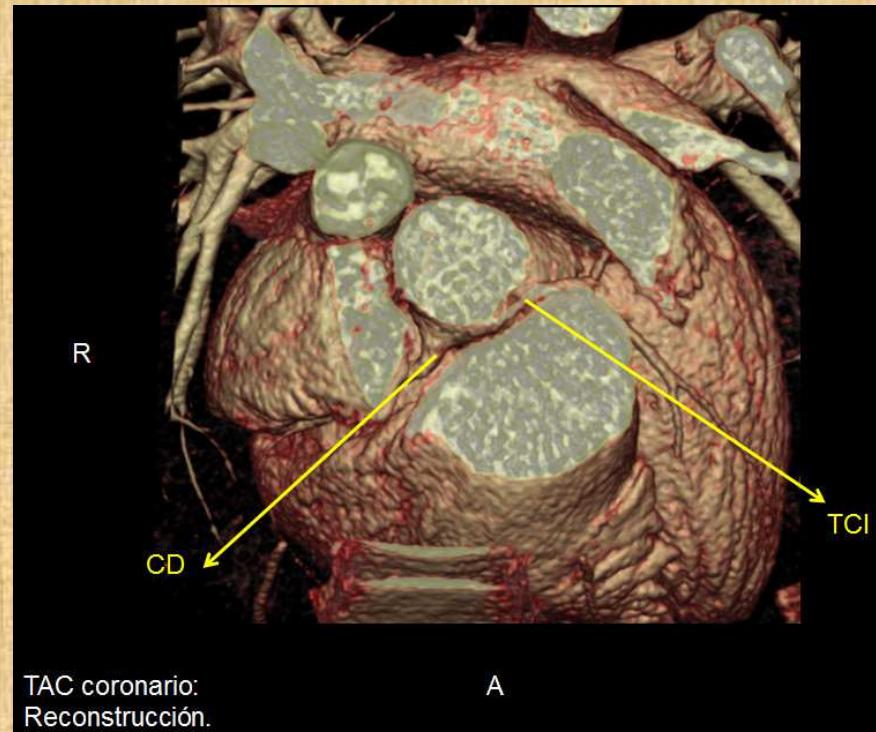
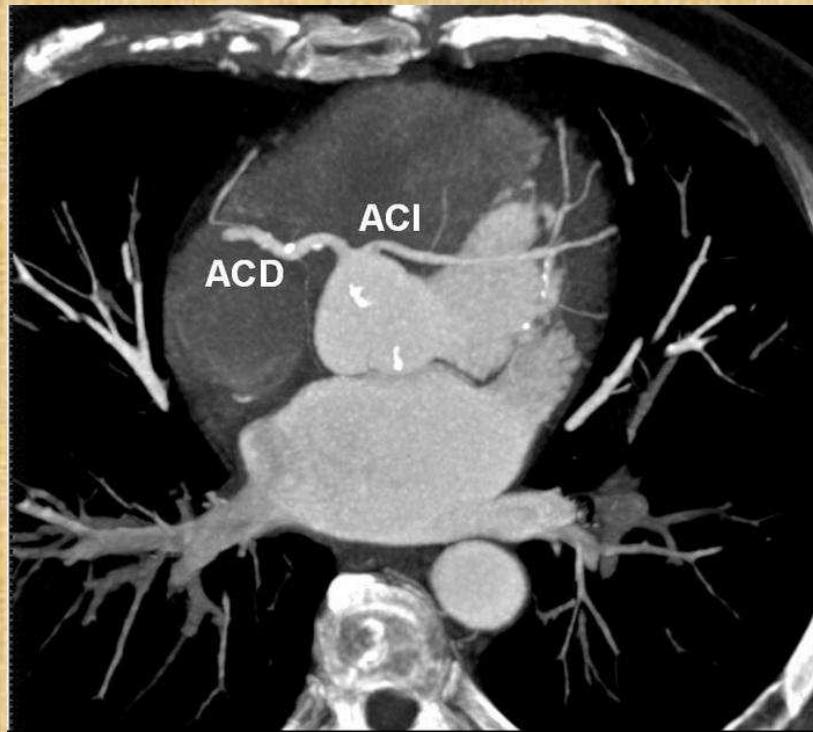


Tiempo de exposición del miocardio a un déficit relativo de oxígeno

Corto plazo → Largo plazo

Adaptada de Shaw LJ et al: J Am Coll Cardiol. 2009;54:1561–75)

# TC coronario



Pundziute G et al, Heart, 2008; 94:48-52

# RM cardíaca



Pennell et al: Eur Heart J. 2004;25:1940–65

Hamdan A et al, J Am Coll Cardiol Cardiovasc Imaging. 2011;4:50–61

# Cerebro-vascular y arteriopatía periférica

Introducción

Corazón y vasos  
coronarios

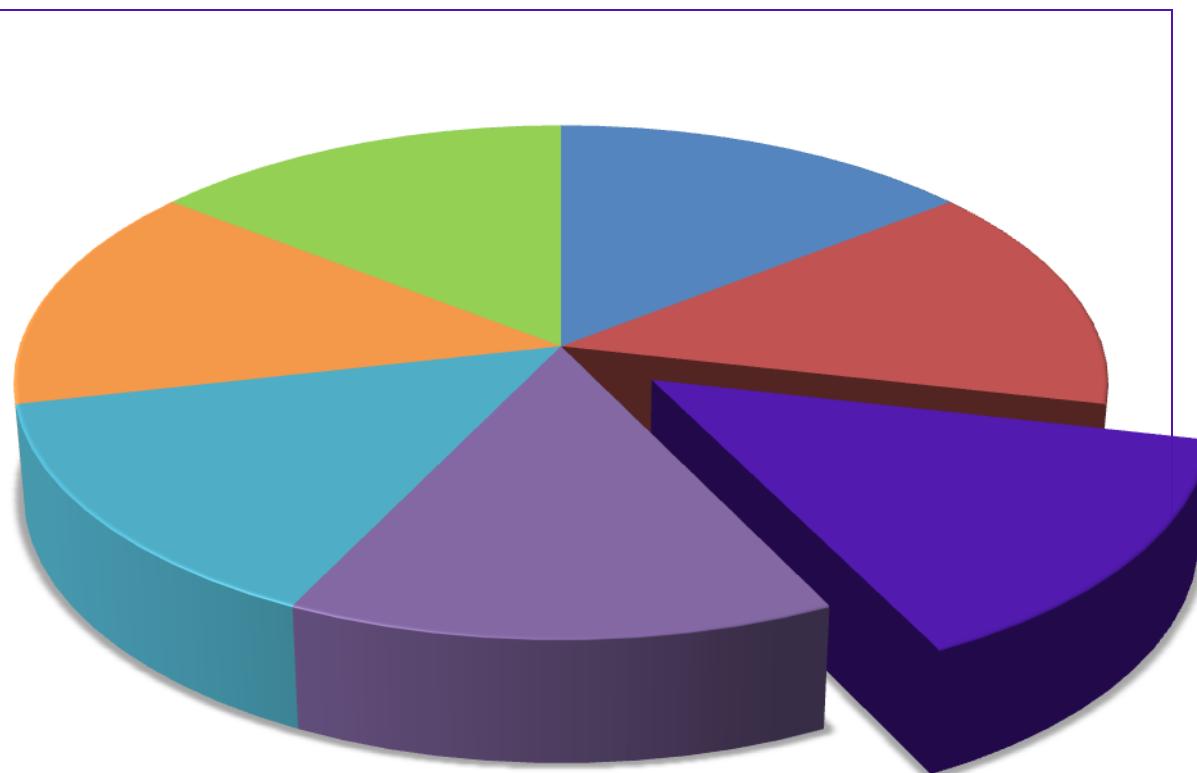
Cerebro-vascular y  
arteriopatía periférica

Valor predictivo  
coronario

Fitness CR

Perspectivas  
futuras

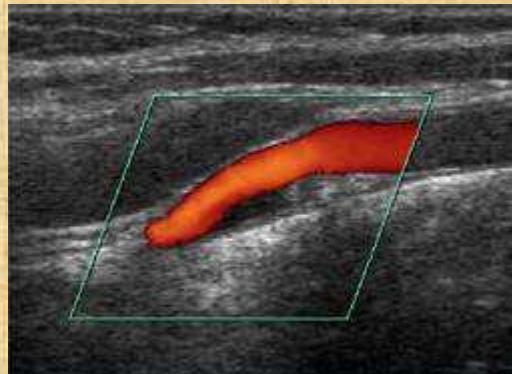
Conclusiones



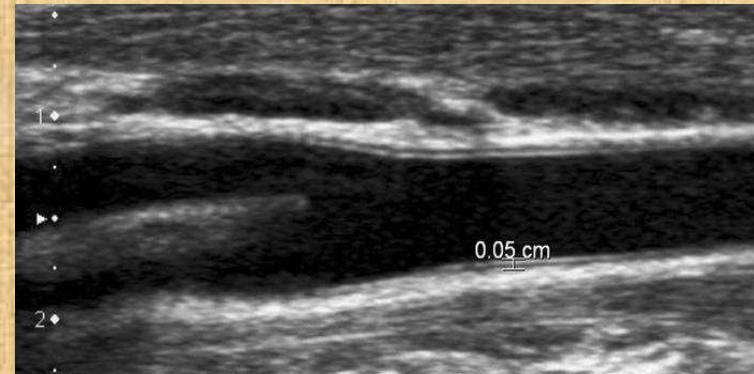
# Eco-doppler de Troncos Supra-Aórticos

## Diagnóstico    Pronóstico

Placas, estenosis  
trombos



C-IMT \*

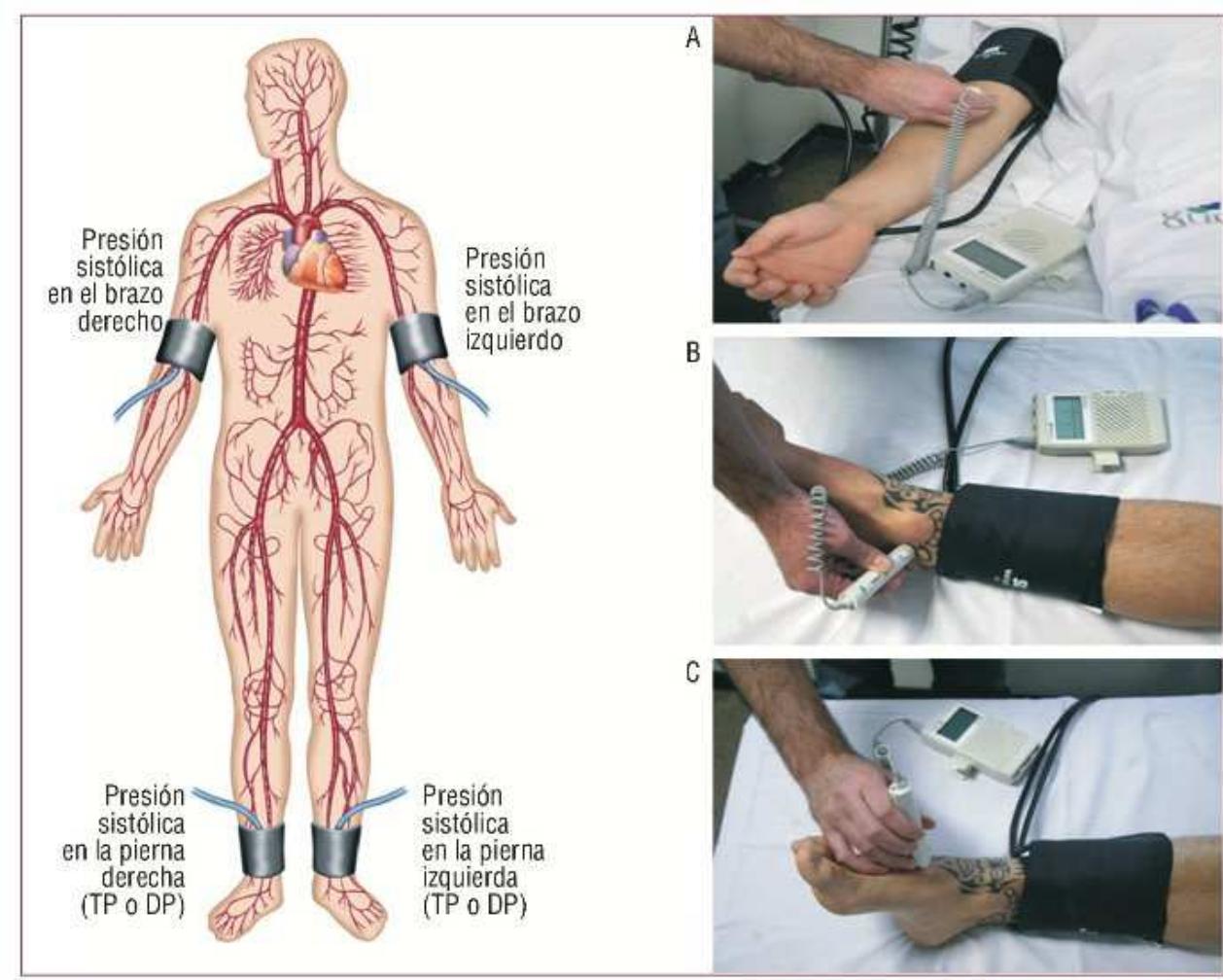


C-EMT \*\*

\* C-IMT: carotid intima-media thickness

\*\*C-EMT: extra-media thickness ([Skilton et al, JACC Cardiovasc Imaging, 2009](#))

# Ecodoppler de MMII Índice Tobillo Brazo –ITB/ABI-



**Carter SA.** Indirect systolic pressures and pulse waves in arterial occlusive diseases of the lower extremities. **Circulation** 1968, 37:624-37

# Indicaciones del ABI

- clínica de claudicación
- pulsos disminuidos
- soplo femoral
- >50 años diabéticos o fumadores
- >70 años.

# Toe-brachial index (TBI)



Disfunción eréctil

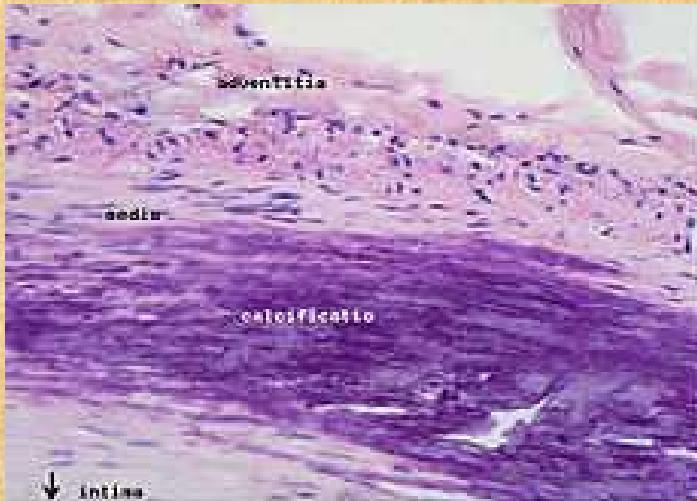
ABI > 1.3

## Puntos de corte del Toe Brachial Index \*

Rango	Valoración
>0.7	Normal
0.5-0.7	Leve
0.35-0.5	Moderada
<0.35 y presión en el primer dedo $\geq 40$ mmHg	Moderada-Severa
<0.35 y presión en el primer dedo $< 30$ mmHg	Severa

\*Massachusetts General Hospital non-invasive lab

# Dx de calcificación medial -Enfermedad de Monckeberg-





Introducción

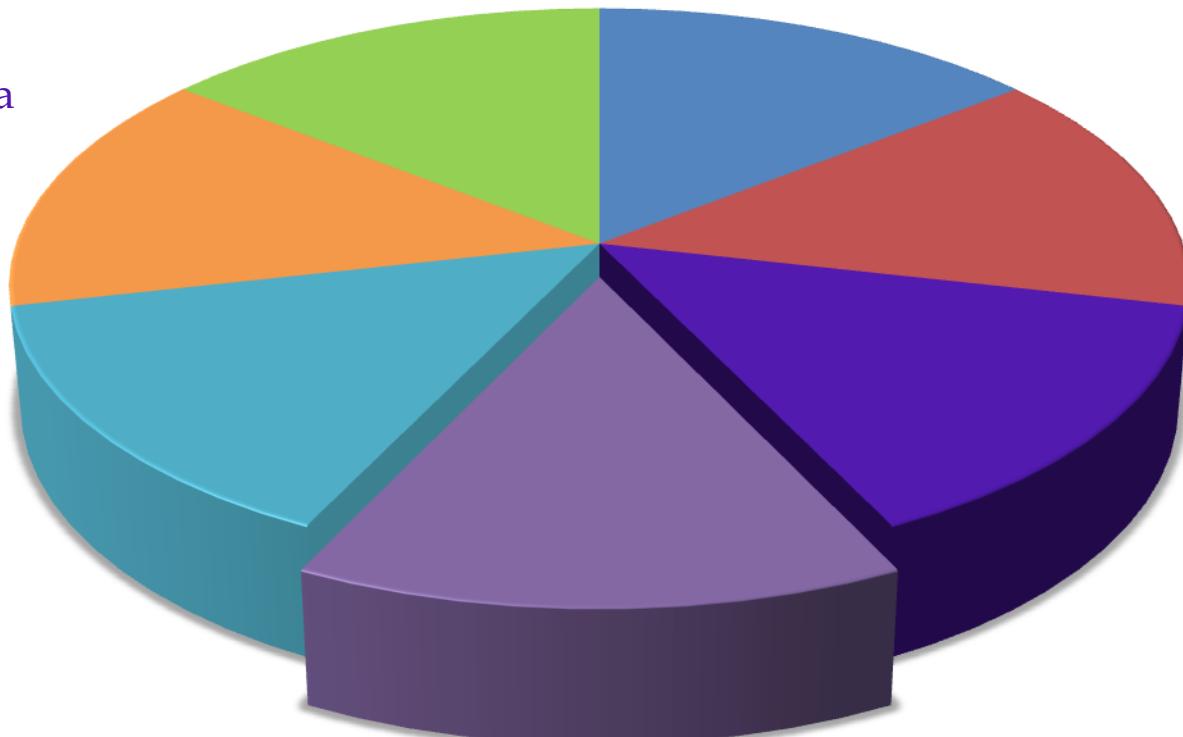
Corazón y vasos  
coronariosCerebro-vascular y  
arteriopatía periférica

Fitness CR



Conclusiones

## *Valor predictivo coronario*



# Superioridad frente a las Escalas de riesgo

En el Cardiovascular Health Study, los marcadores subclínicos **IMT, ABI, CAC, y dismotilidad VI**, predijeron los eventos mejor que las escalas de riesgo

2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Journal of the American College of Cardiology Vol. 56, 2010: -----

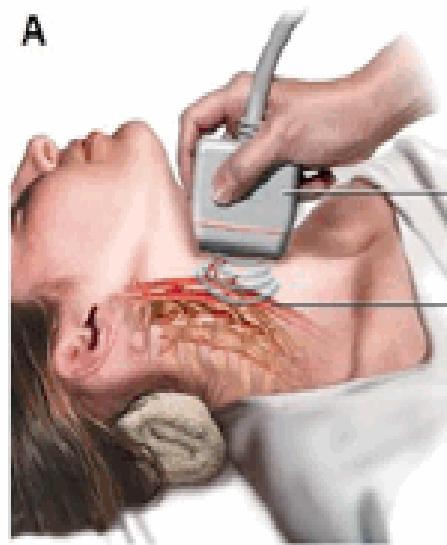
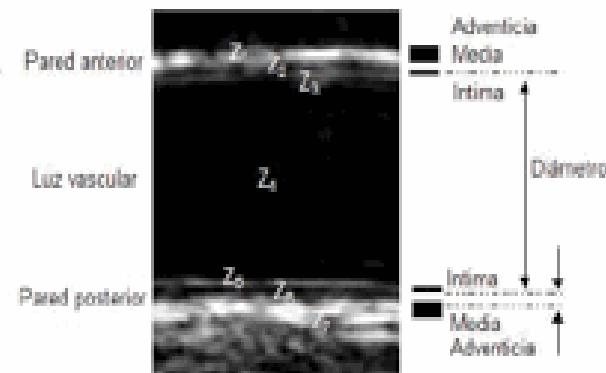
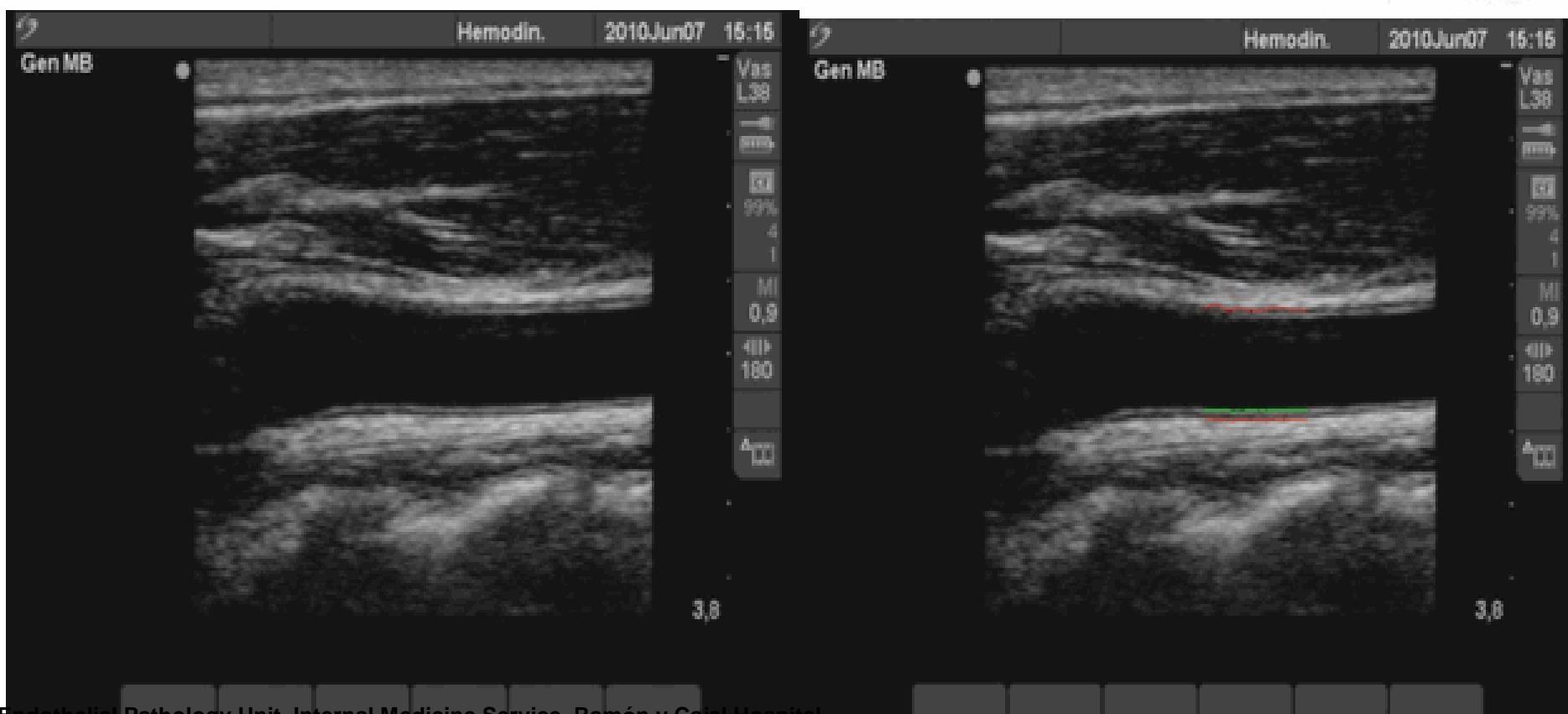
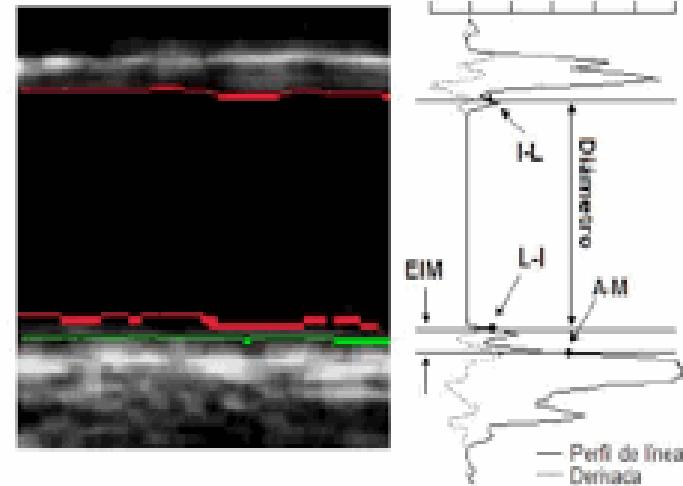
# C-IMT

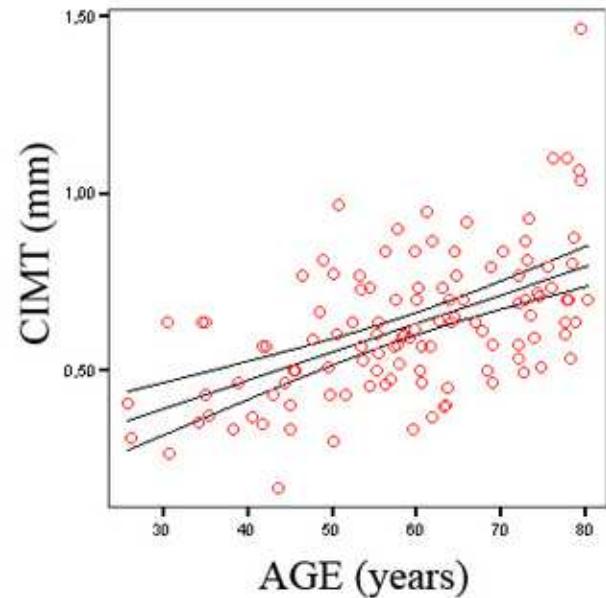
-Es un predictor coronario (O'Leary et al, Eur Heart J, 2010; 31: 1682-9) especialmente útil en sujetos considerados de riesgo intermedio por las escalas de riesgo.

-No es predictor de enfermedad Cerebrovascular y las guías de ICTUS (Brott et al, J Am Coll of Cardiology 2011; 57: 1002-44) ni lo nombran.

**-SORPRENDENTEMENTE no está estandarizada**

En la Unidad de Endotelio seguimos el propuesto por Holaj en 2003 > 0.75

**A****B****C**



Predictor	$\beta$ Coefficient [95%CI]	Standardized $\beta$ Coefficient	p-value
Age	0.008 [0.006; 0.010]	0.536	<0.001
CVD	0.125 [0.022; 0.228]	0.185	0.018
ABI	-0.033 [-0.068; 0.002]	-0.144	0.064

Dependent variable: IMT. Model  $R^2 = 0.349$ .

## Determinant factors of the carotid intima-media thickness in a treated population with moderate-high cardiovascular risk.

Marin E.<sup>II</sup>, Fabregate M.<sup>I</sup>, Tello S.<sup>I</sup>, Fernández A.<sup>I</sup>, Fabregate R.<sup>I</sup>, Redondo S.<sup>II</sup>, Alonso A.<sup>I</sup>, Rodriguez A.<sup>I</sup>, Sabán-Ruiz J.<sup>I</sup>

*I. Endothelial Pathology Unit. Ramon y Cajal Hospital. Madrid. Spain.*

*II. Vascular Surgery Service. Ramon y Cajal Hospital. Madrid. Spain.*

Proceedings of the 8th ICCAD 2009, Medimond ed, pags: 79-82

## THE PHOENIX: HDL-CHOLESTEROL REBORNS FROM ITS OWN ASHES AS THE MOST DETERMINANT METABOLIC FACTOR OF CIMT

### CONCLUSIONS

1. Right and left CIMT are in close agreement with each other.
2. After adjustment for sex and age: HDL-C and ApoA-I were the most determinant factors of CIMT in subjects treated for Hb A1c and LDL-C targets.

### TAKE HOME MESSAGE

- ❖ Casting doubt upon the important role of HDL-C in atherotrombotic disease seems to be a fruitless job.

# ABI

-Es un marcador dual.

-Un FR independiente para amputación en DM.

-Un FR independiente para eventos coronarios en DM y no-DM (si  $<0.9$  incrementa el riesgo un 67%!!!!)

**-Falsos negativos en presencia de CALCIO**

-“U-shape association”:  $>1.3$  tiene

- Mayor riesgo de amputación
- Mayor riesgo coronario.

Tsuchiya M, et al, Diabetes Res Clin Pract 2005;70: 253-62

Allison MA, et al Am J Cardiol 2006;97:181-6),,

# Índices cardíacos

## Ergometría:

- Duke Treadmill Score
- Respuesta hipotensiva

## SPECT:

estudio DIAD, JAMA. 2009;301:1547–55

## Dismotilidad del VI:

Oliveira et al, Cardiovasc Ultrasound, 2009;7:24-26

## CAC Score

# CAC Score

## Unidad de medida: Hounsfield = Agatston

Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15:827–32



bajo riesgo

400-1000

48%

moderado-alto

>1000

SPECT

71.4%



Anand DV, et al. Eur Heart J. 2006;27:713–21.

## PREDICT: Predictors of Cardiovascular Outcomes by Coronary Artery Calcification (CAC) Score

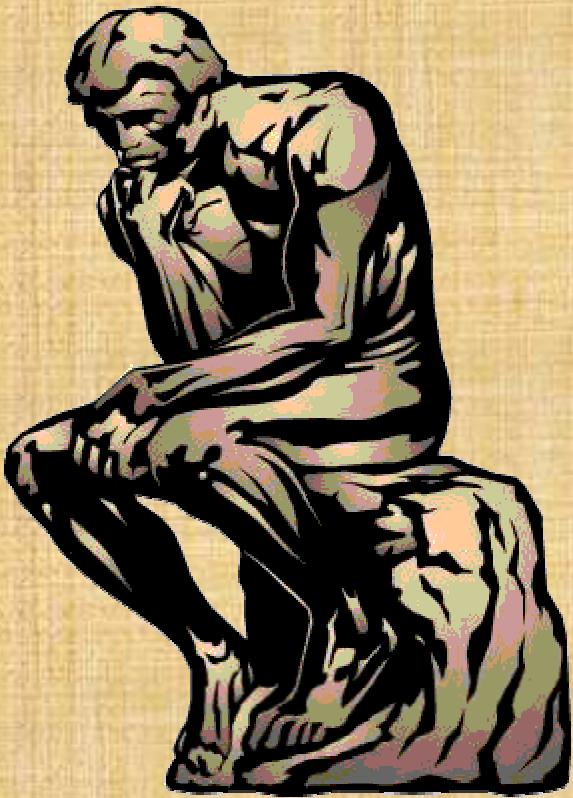
N = 589

eventos (EC o ACV = 66)

seguim: 4 años

CAC Score	Hazard Ratio (95% CI)	p
0–10	1.0 (reference)	--
11–100	5.5 (1.2–24.2)	0.02
101–400	10.5 (2.5–44.5)	0.001
401–1000	11.9 (2.8–52.4)	0.001
1001–10 000	19.8 (4.5–65.6)	<0.001

**LIMITACIONES: COSTE // RADIACIÓN**



¿ Cómo encaja todo esto con las  
nuevas guías de manejo del  
colesterol?

# **ACC/AHA\* (With NHLBI) Guidelines: 4 New Guidelines**

- Cholesterol management
- Risk assessment
- Obesity
- Lifestyle recommendations

\*ACC/AHA have collaborated on guidelines since 1980  
(first guideline was on pacemakers published in 1984)

The cut points for those **intermediate-risk tiebreakers (patient-centric)** are:

- 1-Family history, males less than 55 years of age for first-degree relatives or females less than 65 years
- 2-CRP cut point is 2 mg/L.
- 3-The calcium score cut point is 300 Agatston units
- 4-ABI is 0.9.

**The greatest endorsement is for calcium score.**

**They recommend against carotid IMT**, so that's out for the time being in regard to these new guidelines.

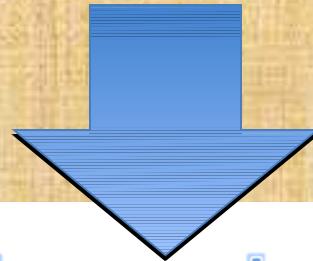
# 2013 ACC/AHA\* Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (>21 yrs)

The Expert Panel Members = ATP-IV.

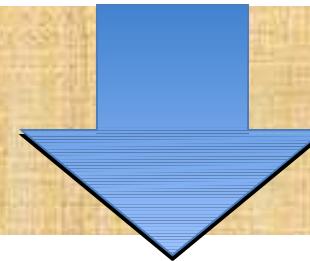
Critical questions (CQs), interpret the evidence and craft recommendations

past 15 years

Treat to target



CHD risk



current

Evidence-based  
Treatment

Evidence-based statin therapy  
net benefit

CHD and stroke risk  
ACVD risk

Pooled Cohort Equations to estimate  
10-year ASCVD risk

\*: ACC American College of Cardiology /AHA : American Heart Association :

# 2013 ACC/AHA\* Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (>21 yrs)

## Patient groups

4 major statin benefit groups

### Secondary prevention

≤75 years >75 years

*clinical ASCVD\* (I)*

### Primary prevention

“Patient centered”

**LDL-C >190 mg/dL (II)**

**DM 40-75 yrs (III) ((IIIa // IIIb))**

**ASCVD risk > 7. 5 % (IV)**

**\*ASCVD:** atherosclerotic cardiovascular disease

# Other groups

- 1- Genetic hyperlipidemias with LDL >160**
- 2- Family history of premature ASCVD**
- 3- High sensitivity C-reactive protein >2 mg/L**
- 4- CAC score  $\geq 300$  Agatston(\*) units or  $\geq 75$  percentile for age, sex, and ethnicity**
- 5- Ankle-brachial index <0.9**
- 6- Elevated lifetime risk of ASCVD**

\*Agatston = Hounsfield

# 2013 ACC/AHA\* Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (>21 yrs)

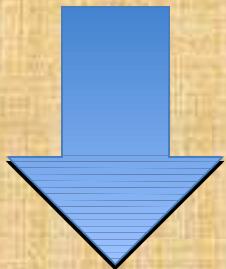


**“Decreasing the statin dose may be considered when 2 consecutive values of LDL-C levels are <40 mg/dL.”**

# New guidelines & DM

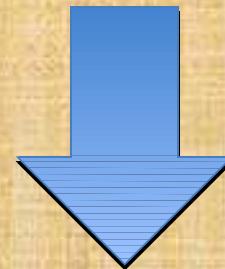
40 -75 years  
ASCVD risk

$\geq 7.5\%$



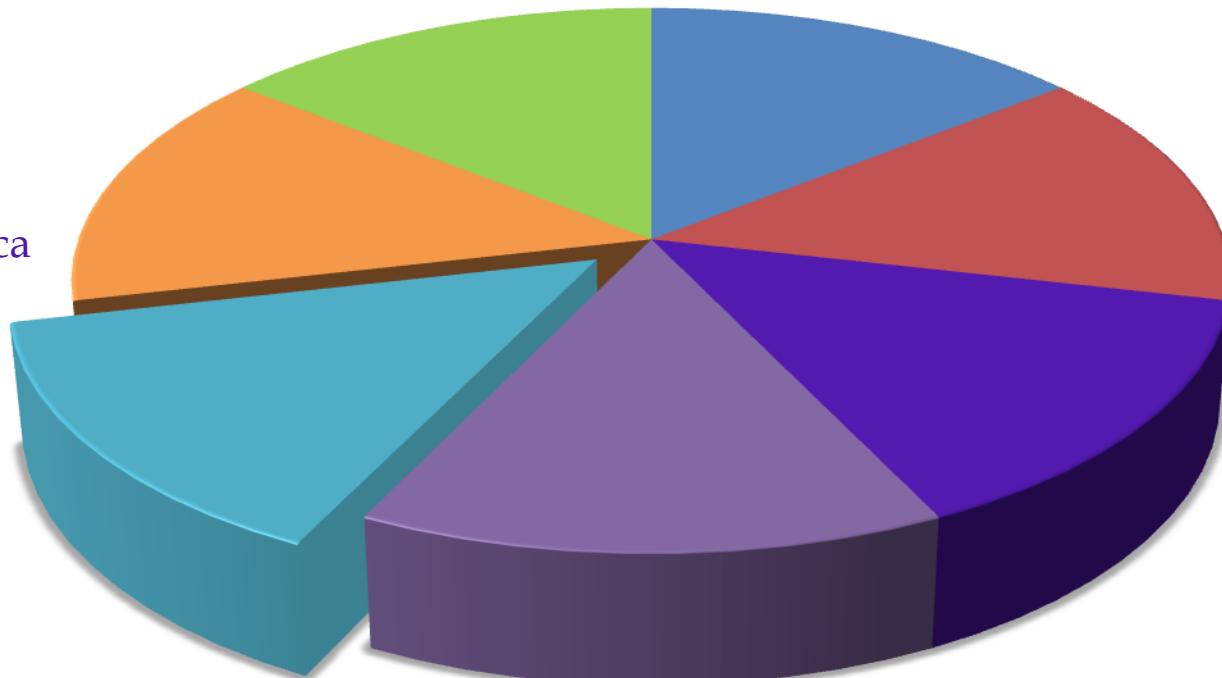
**High-intensity**  
statin therapy

$<7.5\%$



**Moderate-intensity**  
statin therapy

# *Fitness Cardiorrespiratorio*



Introducción

Corazón y vasos coronarios

Cerebro-vascular y arteriopatía periférica

Valor predictivo coronario

Fitness CR

Perspectivas futuras

Conclusiones

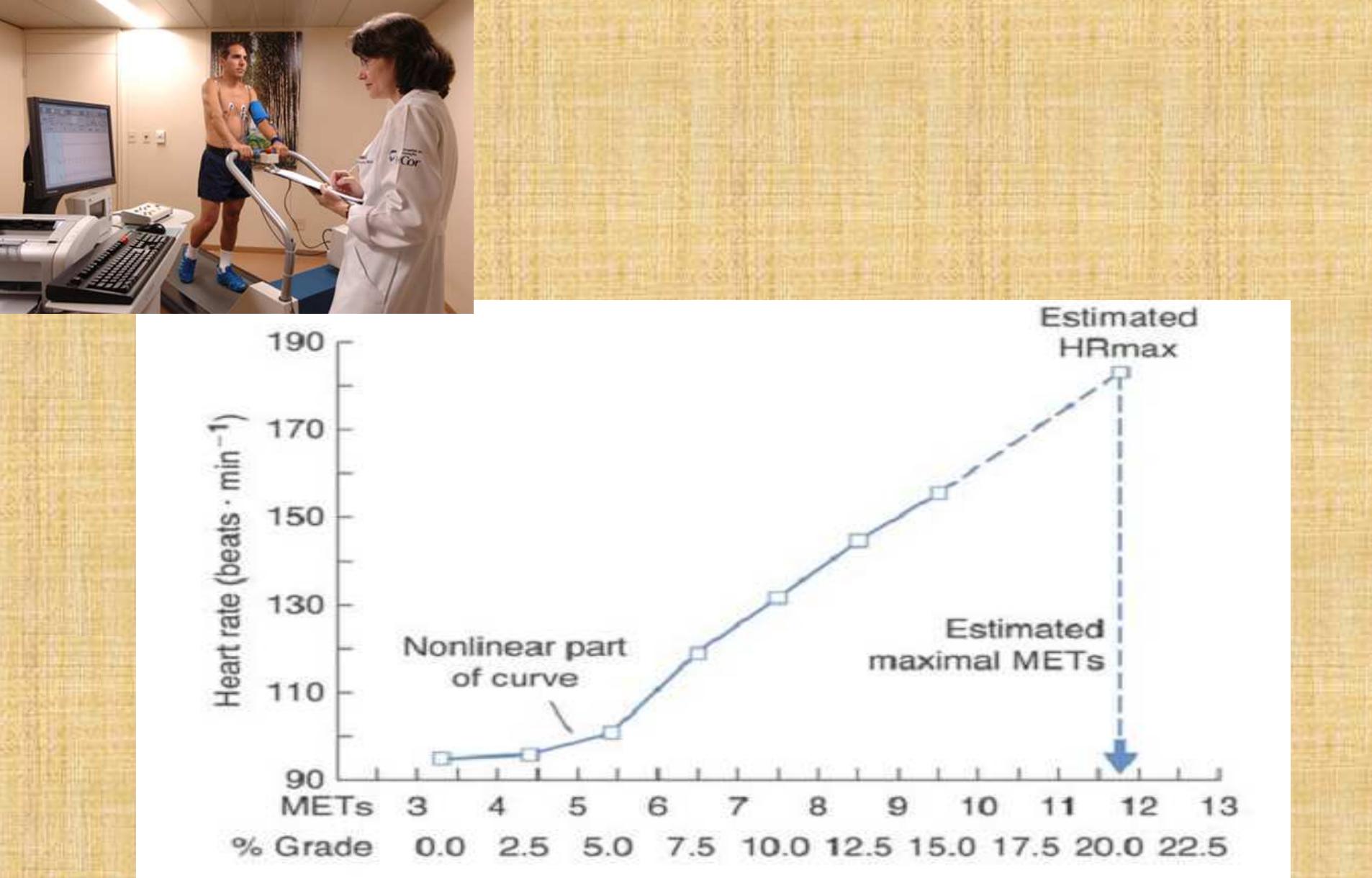
# Utilidad del fitness CR en la predicción de riesgo

**ASH-2012**



La tasa de mortalidad disminuye un **19% por cada MET** en el fitness.

El grupo con mejor fitness tiene una reducción del **35-40% de la mortalidad.** (Veterans Affairs Medical Center)



Test de Balke. U Endotelio. Hosp Ramón y Cajal



Introducción



Corazón y vasos  
coronarios



Cerebrovascular y  
Arteriopatía periférica



Valor predictivo  
coronario



Fitness CR

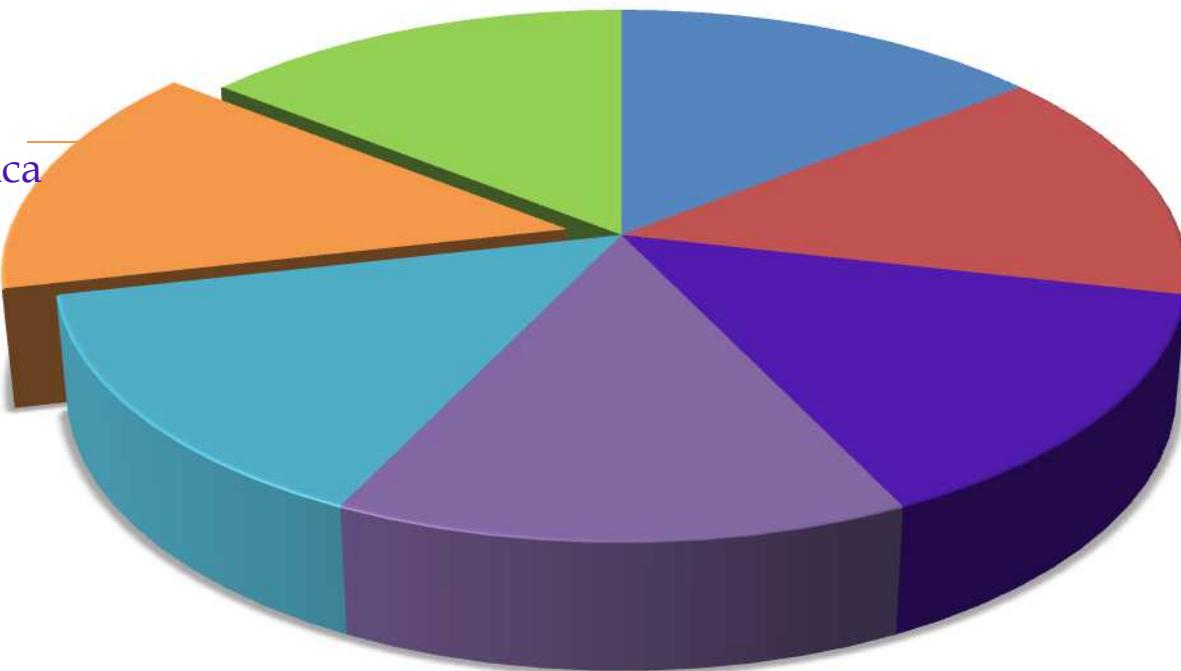


Perspectivas  
futuras

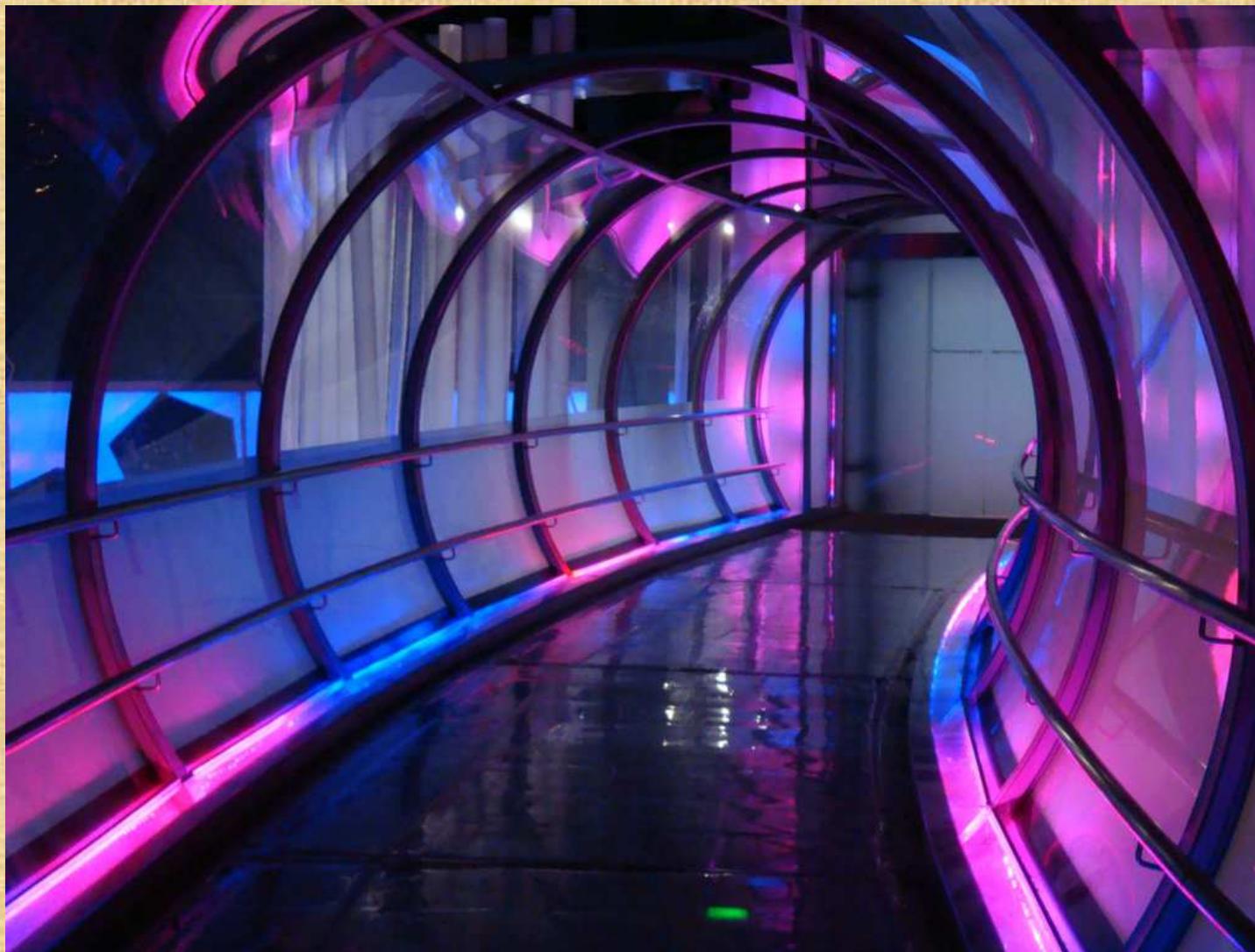


Conclusiones

## *Perspectivas futuras*



# GATEWAY TO THE FUTURE



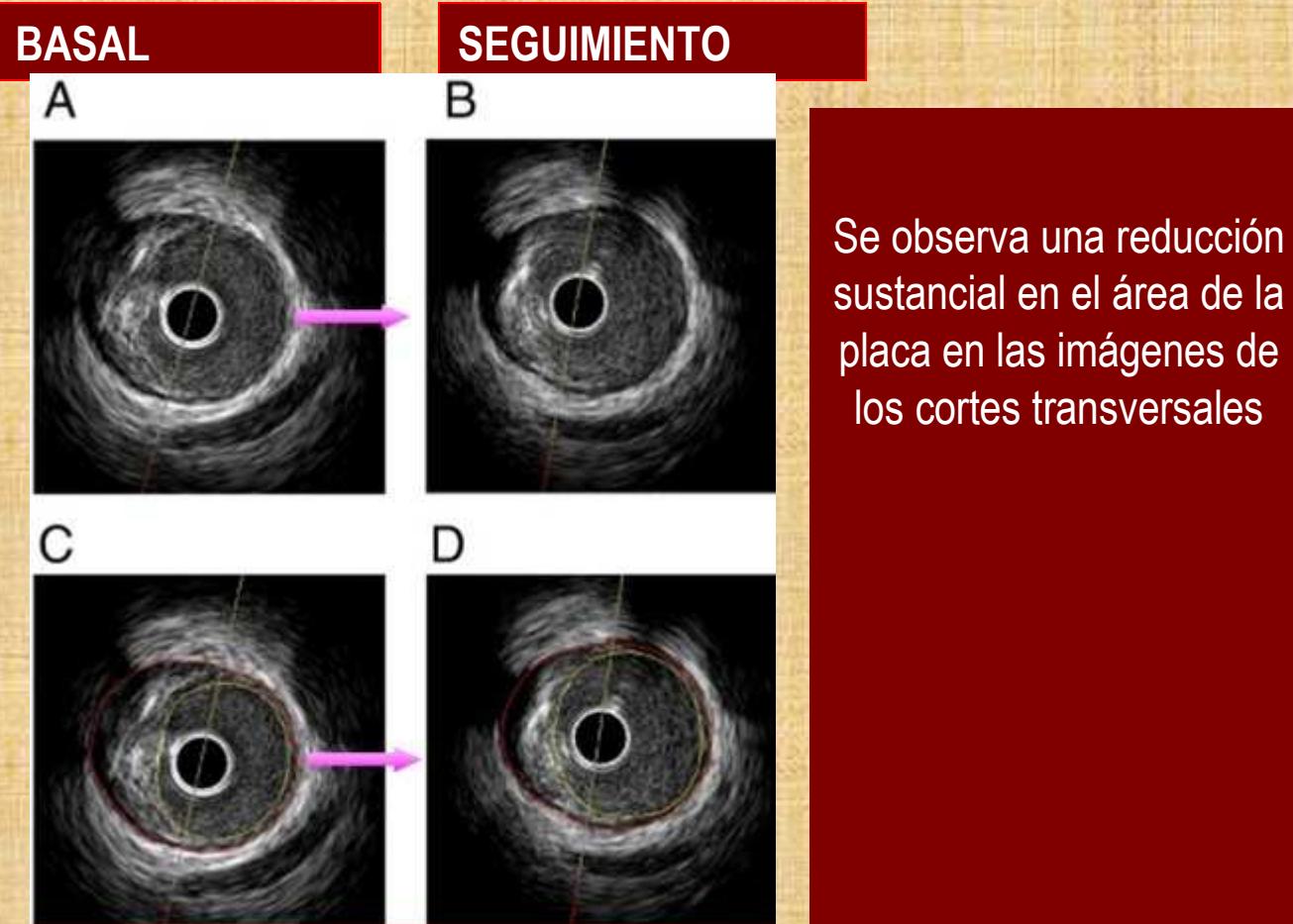
# IVUS

Paciente 64 a. tratado  
con **Pita**

Estudio IVUS

Vol. Placa (mm<sup>3</sup>):  
Basal: 84.6

Seguimiento: 71.8  
% Cambio:-15.1



Hiro T, et al. *J Am Coll Cardiol* 2009;54 ( 4):293-302

Técnicas de imagen no-invasivas del futuro

Targeted contrast-enhanced ultrasound

Rest-stress rubidium-82 PET imaging

PET-SPECT PET-TC PET-MR fused-

Black-blood MRI

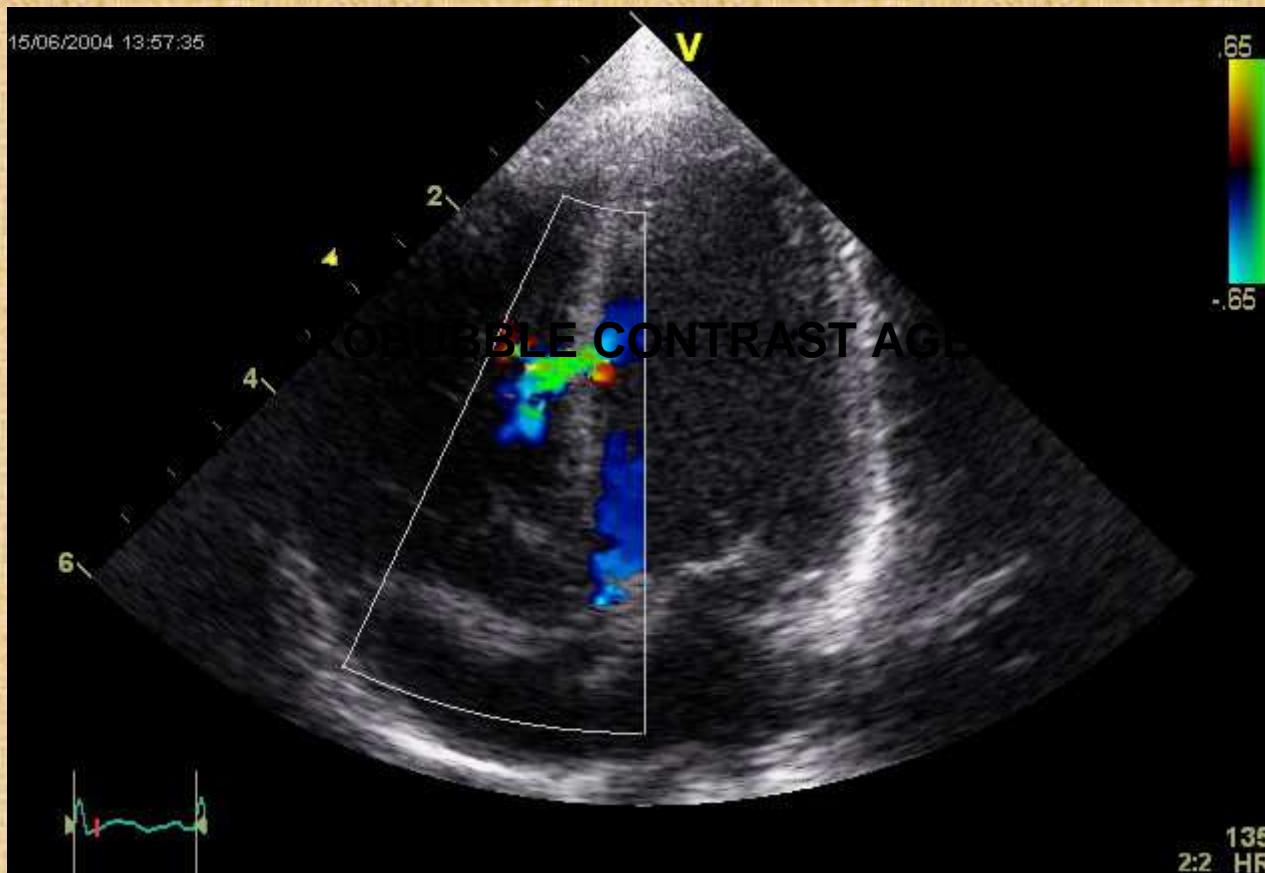
3T MRI

Superparamagnetic iron oxide (SPIO)

Raman spectroscopy

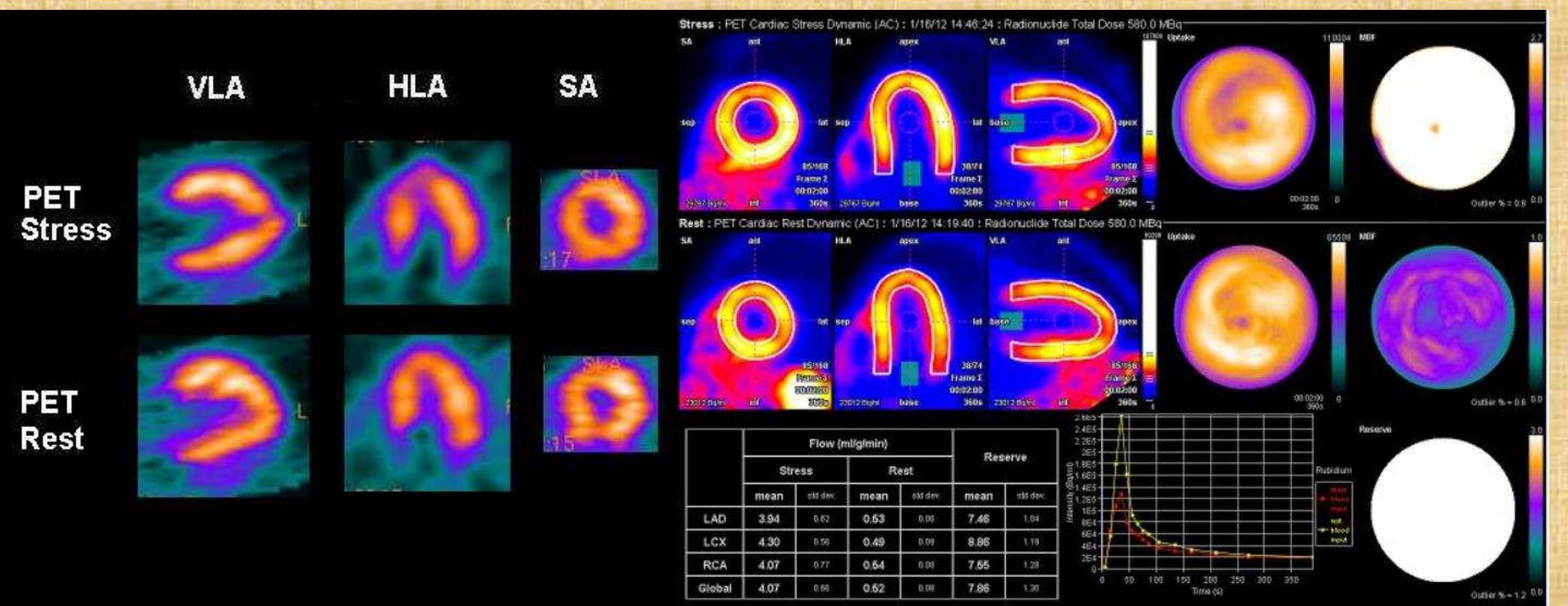
# Targeted contrast-enhanced ultrasound

Contrast-enhanced ultrasound (CEUS)

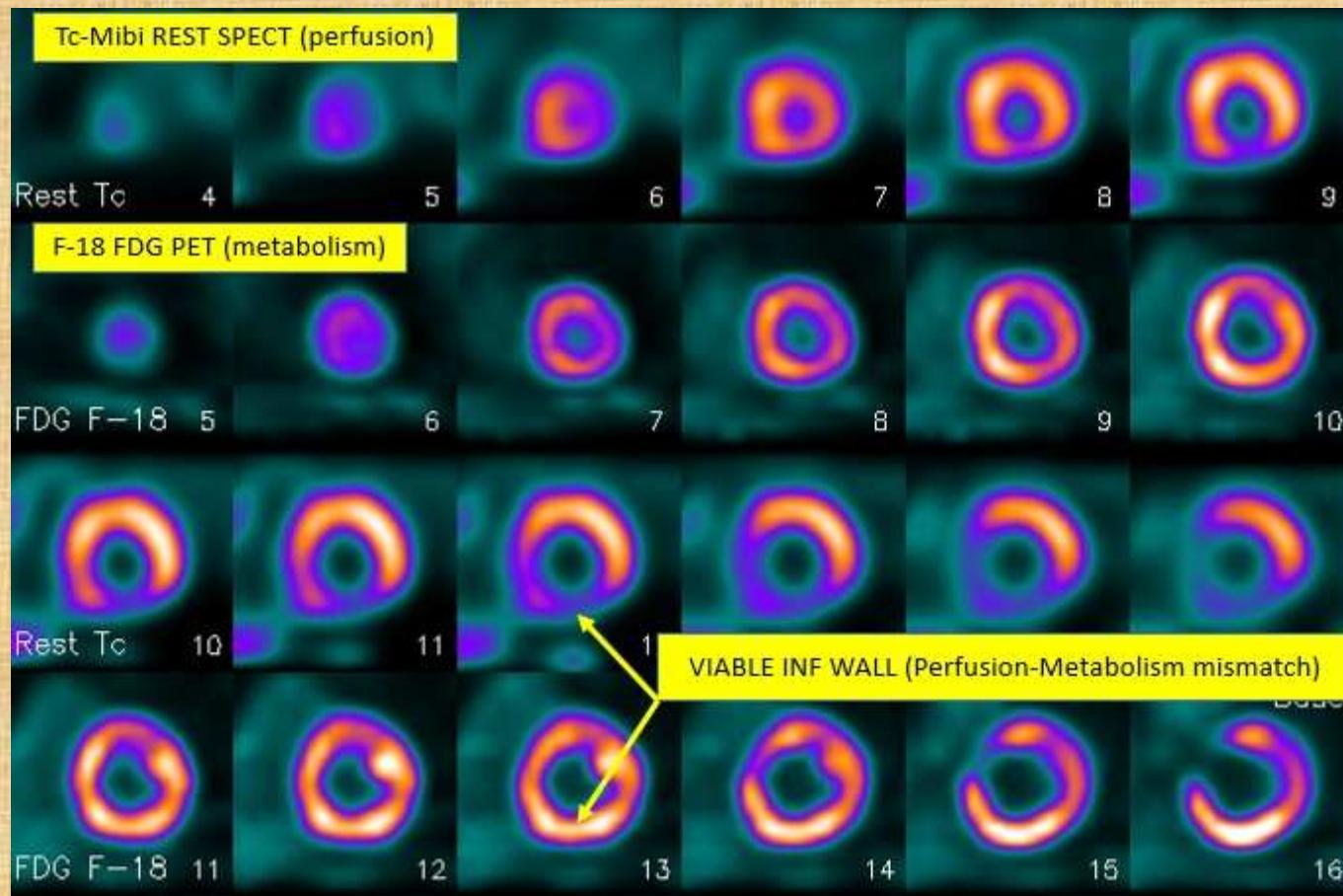


**MICROBUBBLE CONTRAST AGENTS (differ in their SHELL & Gas Core)**

# PET Stress + PET Rest



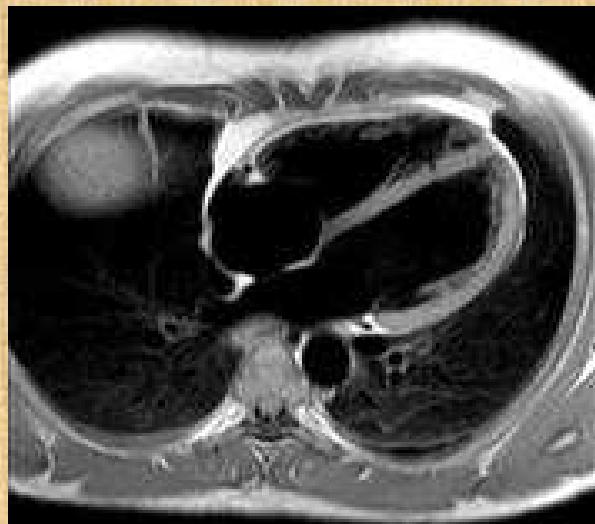
# PET-SPECT fused



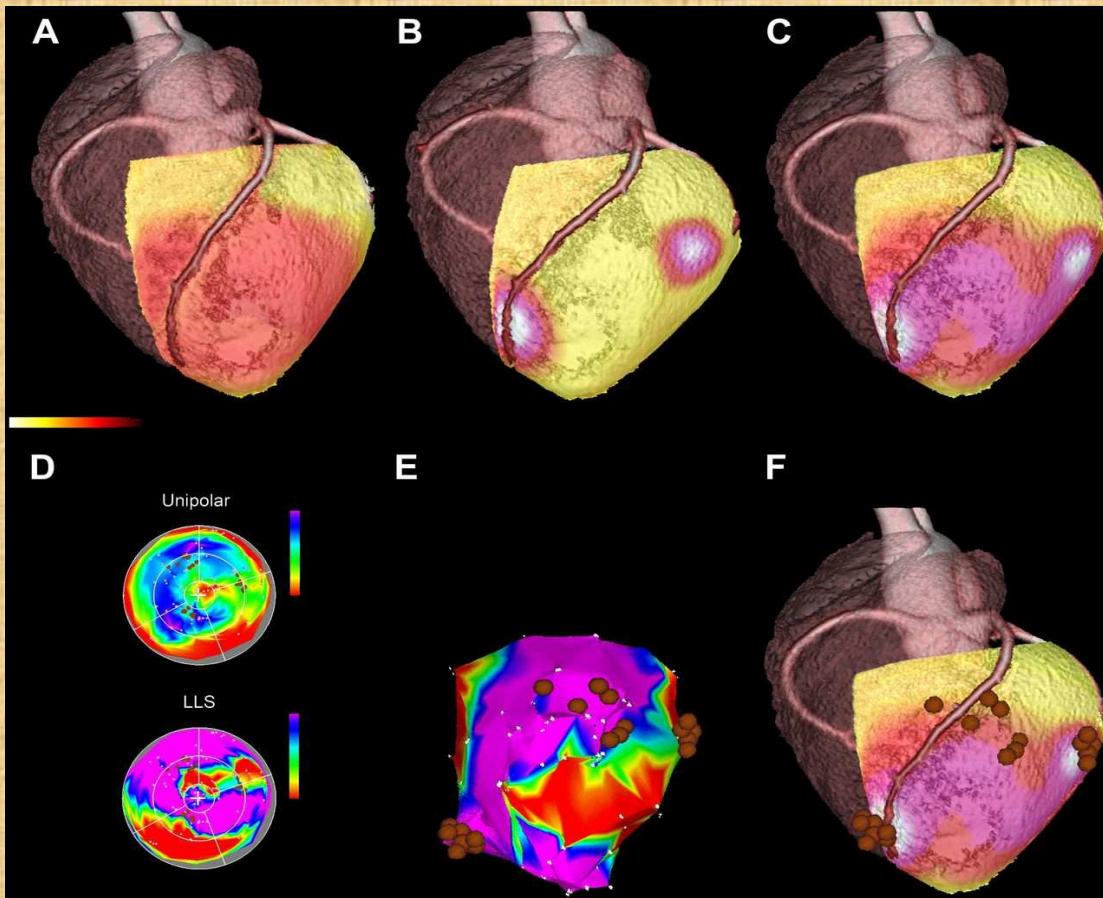
# Cardiac MRI

3T MRI

Black-blood MRI



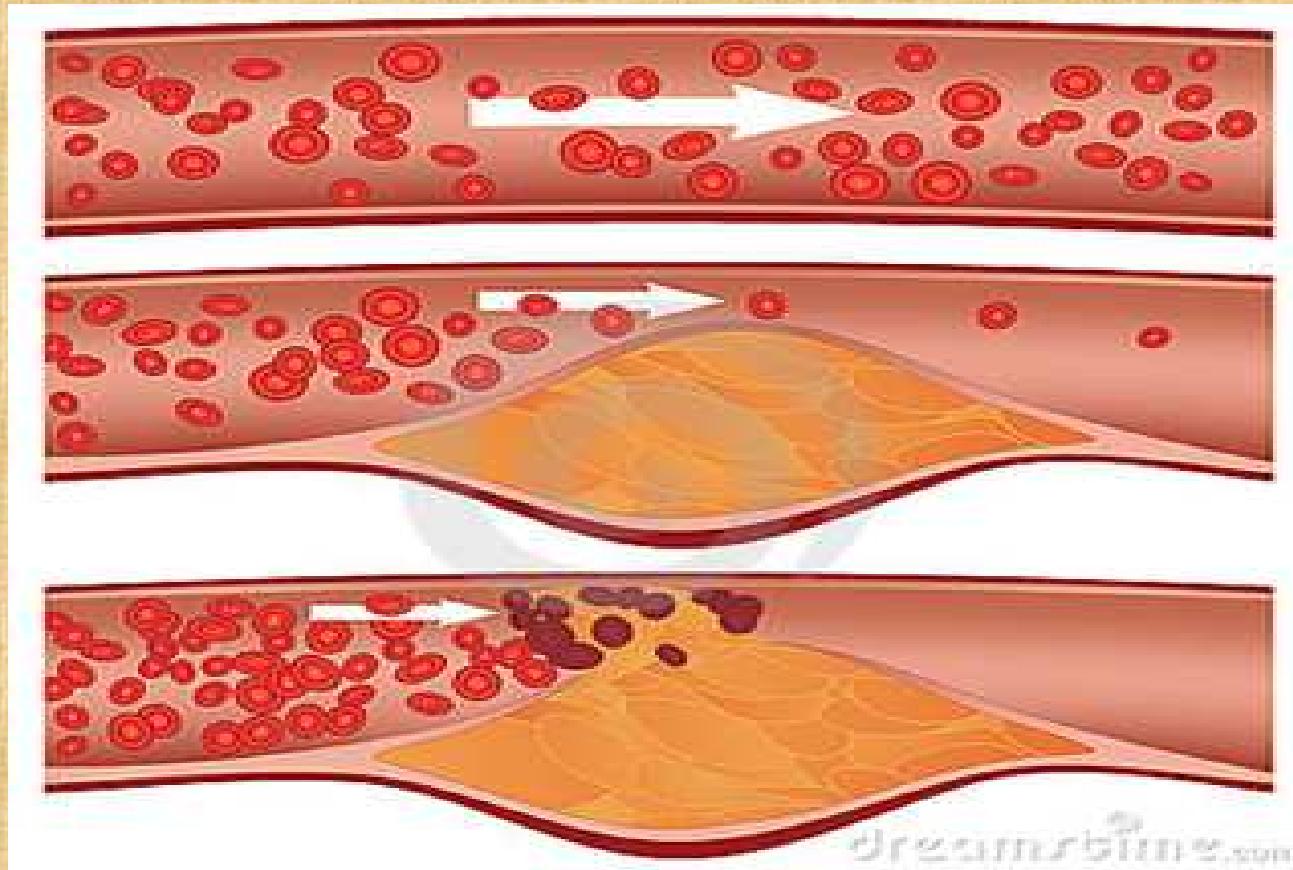
# Superparamagnetic iron oxide (SPIO)



ferumoxide

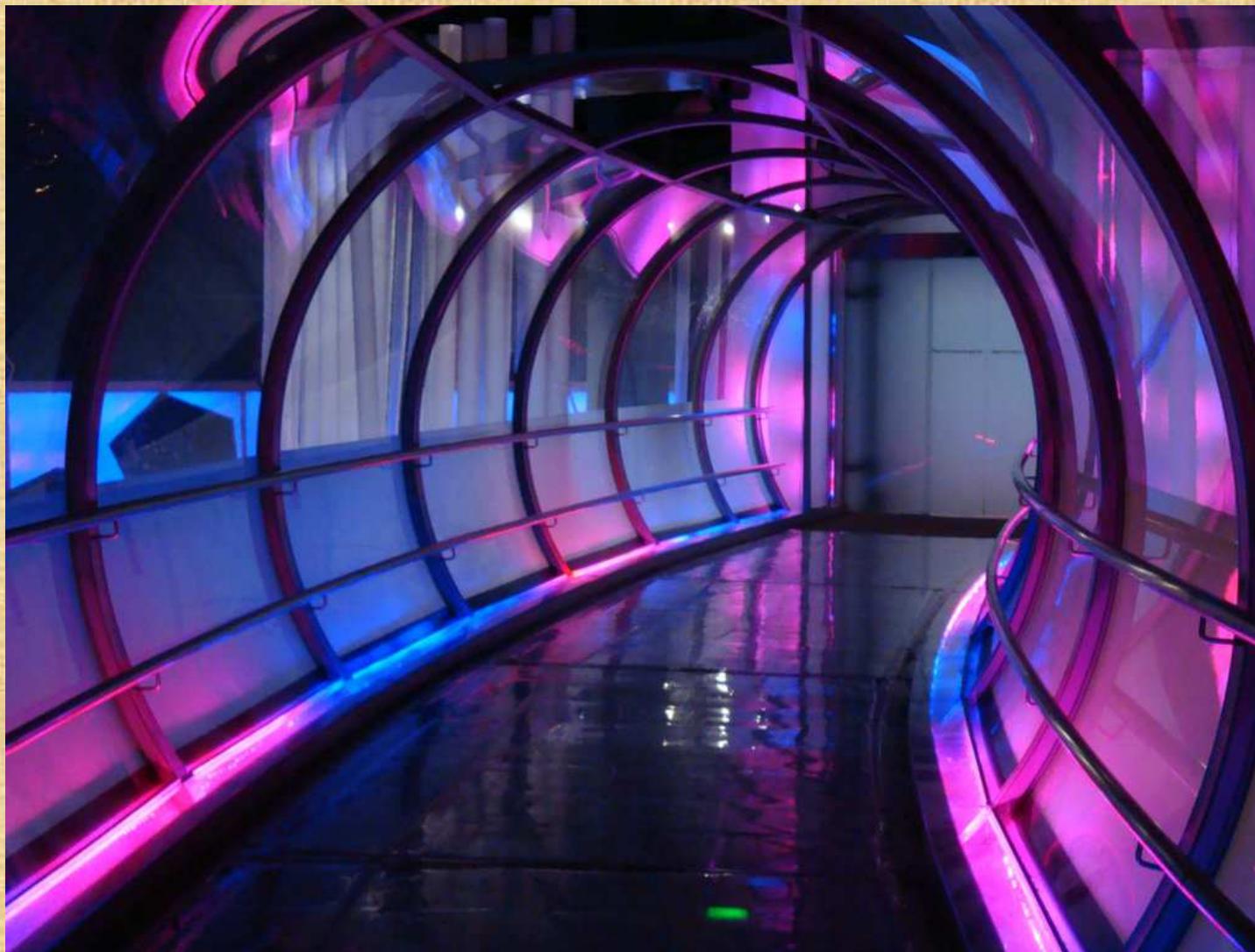
ferucarbotran

# Raman spectroscopy



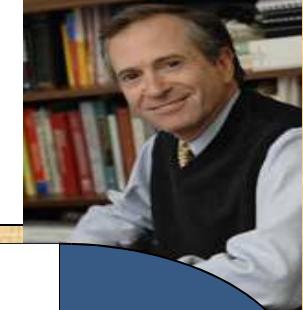
Brennan et al, Circulation. 1997, 96: 99-105 // Chung et al, Clin Transl Sci, 2009

# GATEWAY TO THE FUTURE

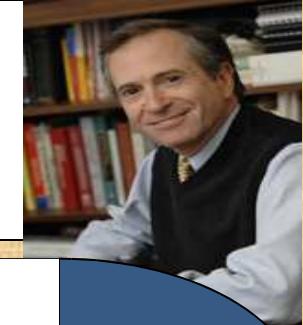
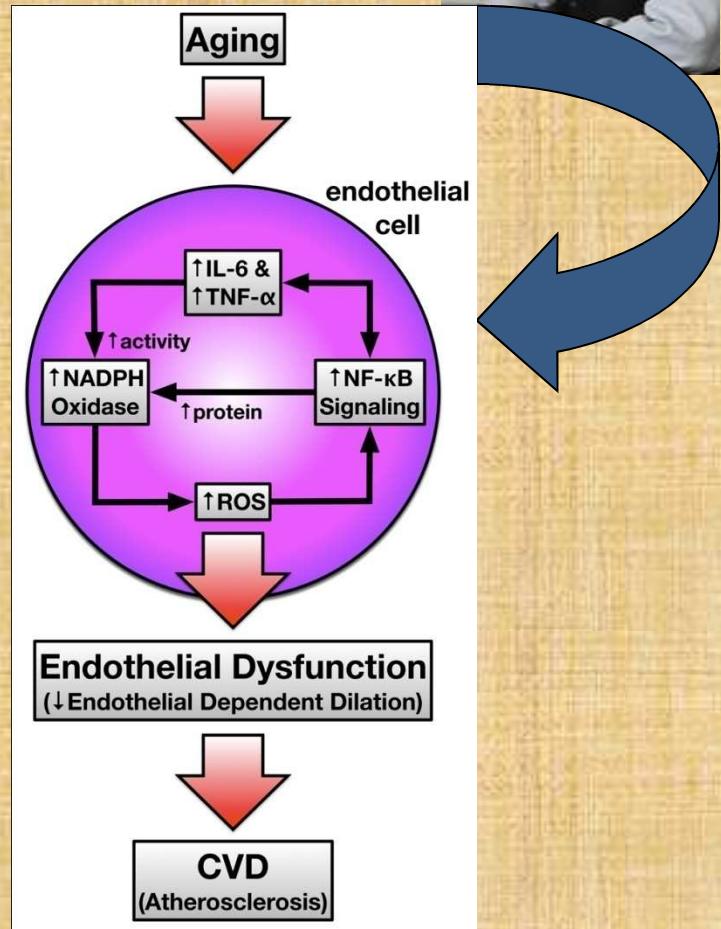
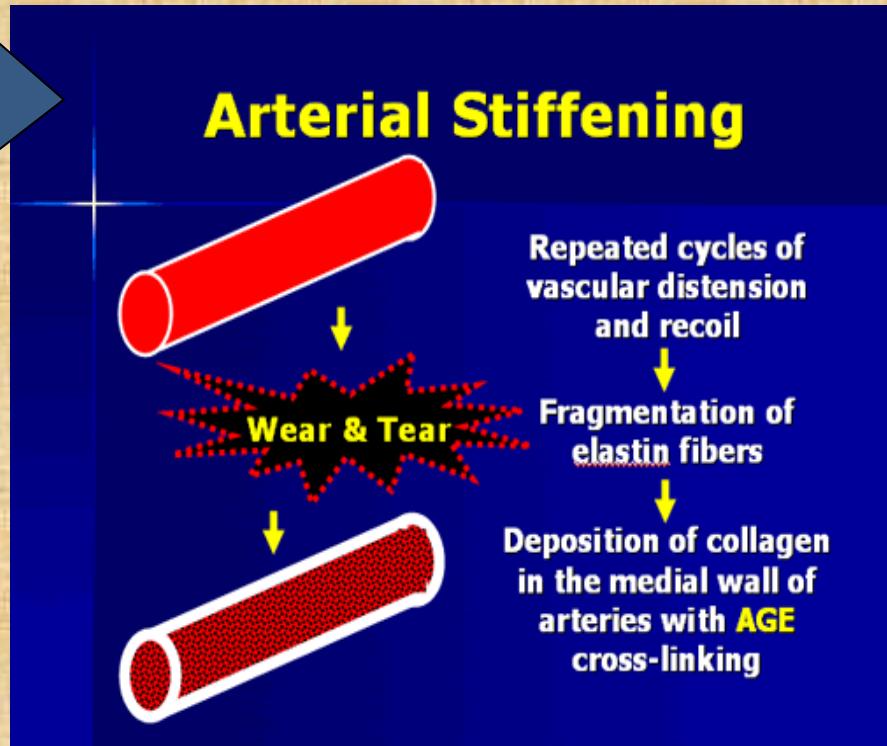
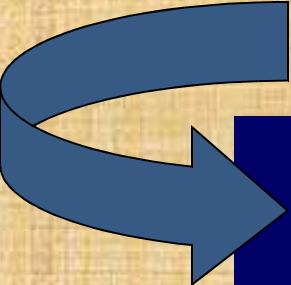




# *Overall vascular aging profile*



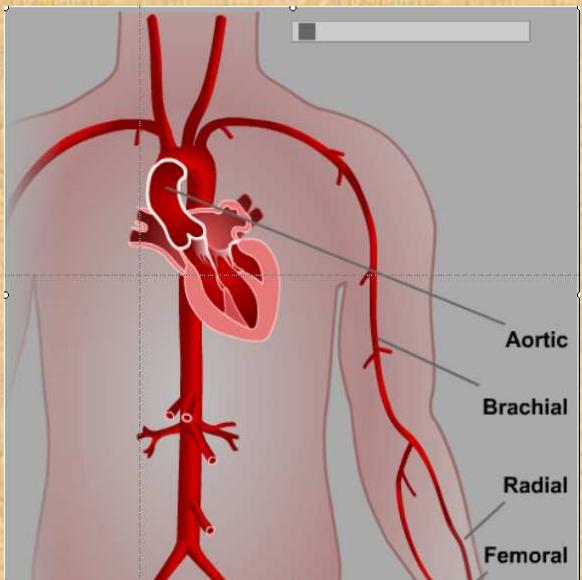
of a given individual



Lakatta EG & Levy D: Arterial and Cardiac Aging: Major Shareholders in Cardiovascular Disease Enterprises. Circulation. 2003 Jan 7;107(1):139-46.

## Endotelio y Adaptabilidad

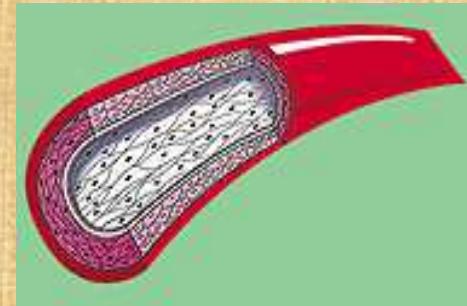
SphygmoCor



## Inflexibilidad vascular



## Envejecimiento



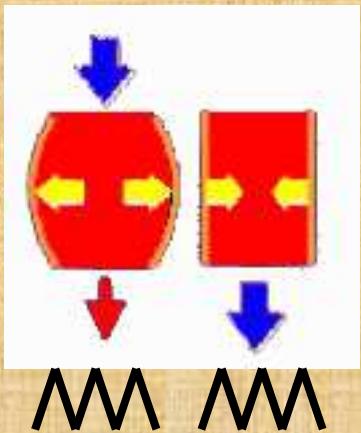
**Inflexibilidad  
Metabólica**

**Inflexibilidad  
Vascular**

## ARTERIA SANA

### Elasticidad

Sístole Diástole



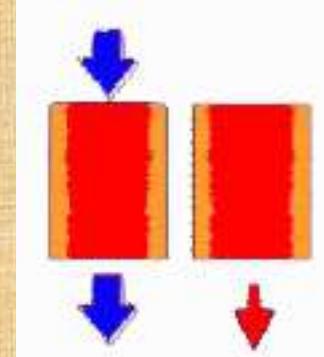
## RIGIDEZ ARTERIAL

Endurecimiento de las arterias

## ARTERIA ENFERMA

### Rigidez

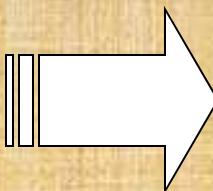
Sístole Diástole



- Edad (> 55 años)
  - envejecimiento vascular
- Hipertensión
- **Hiperglucemia (DM)**
- Colesterol
- Tabaco

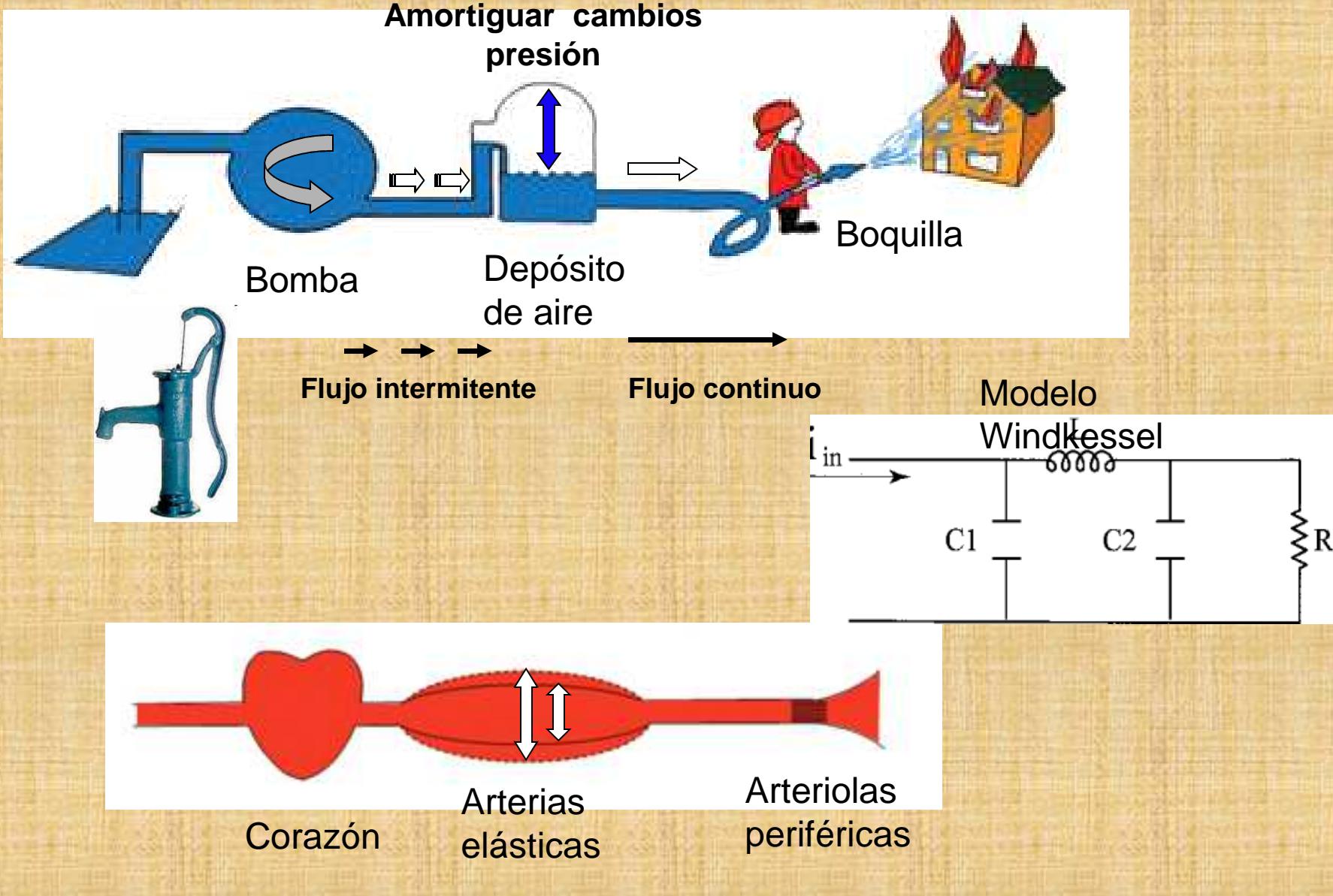
La diabetes provoca un envejecimiento prematuro del vaso

Arteriosclerosis  
Aterosclerosis



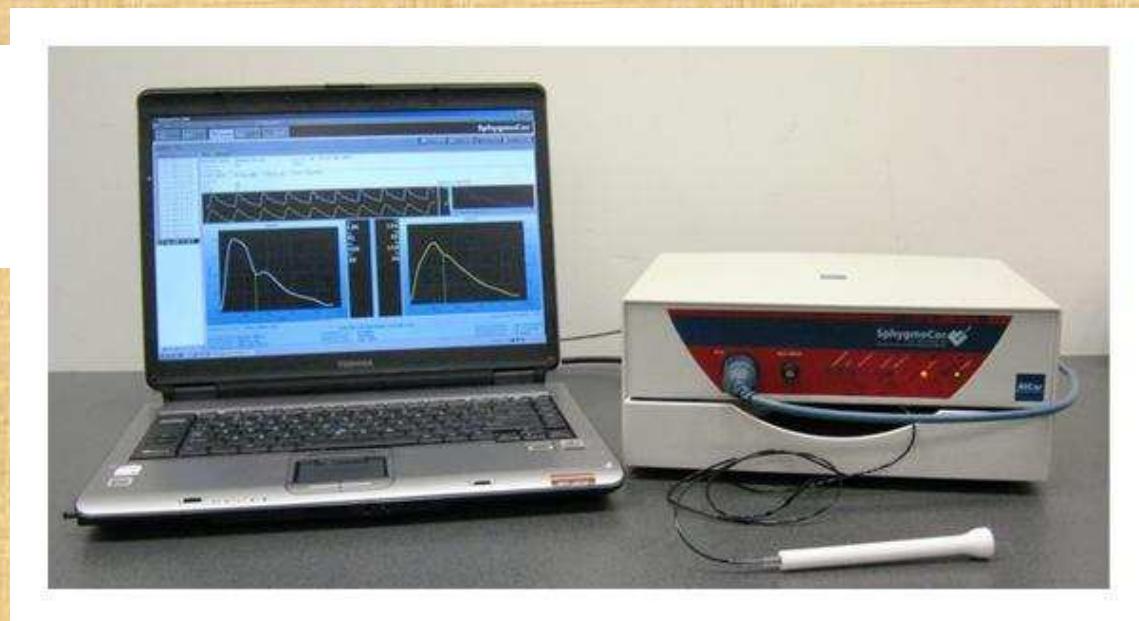
Insuficiencia cardiaca  
Infarto de miocardio  
Ictus

# Analogía del sistema cardiovascular: Modelo Windkessel (Stephen Hales)



## MEDIDA DE LA RIGIDEZ ARTERIAL

- Velocidad de la onda de pulso: PWV
- Análisis de la onda de pulso
- Índice de aumento (AIx)



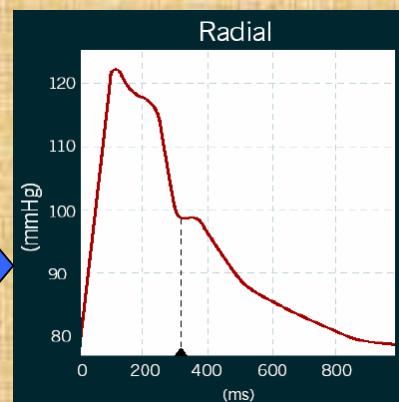
SphygmoCor device, AtCor Medical, Sydney, Australia





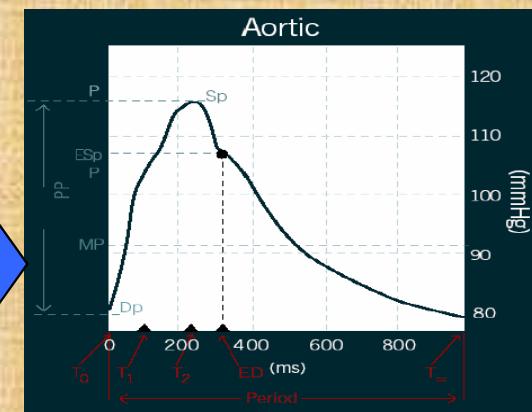
## ANALISIS ONDA DE PULSO

El **análisis de onda de pulso** nos va a permitir estudiar el comportamiento de las arterias centrales (aorta) mediante medidas obtenidas en arterias periféricas (radial). No invasiva.



Sensor tonométrico

Forma onda radial



Forma onda aórtica

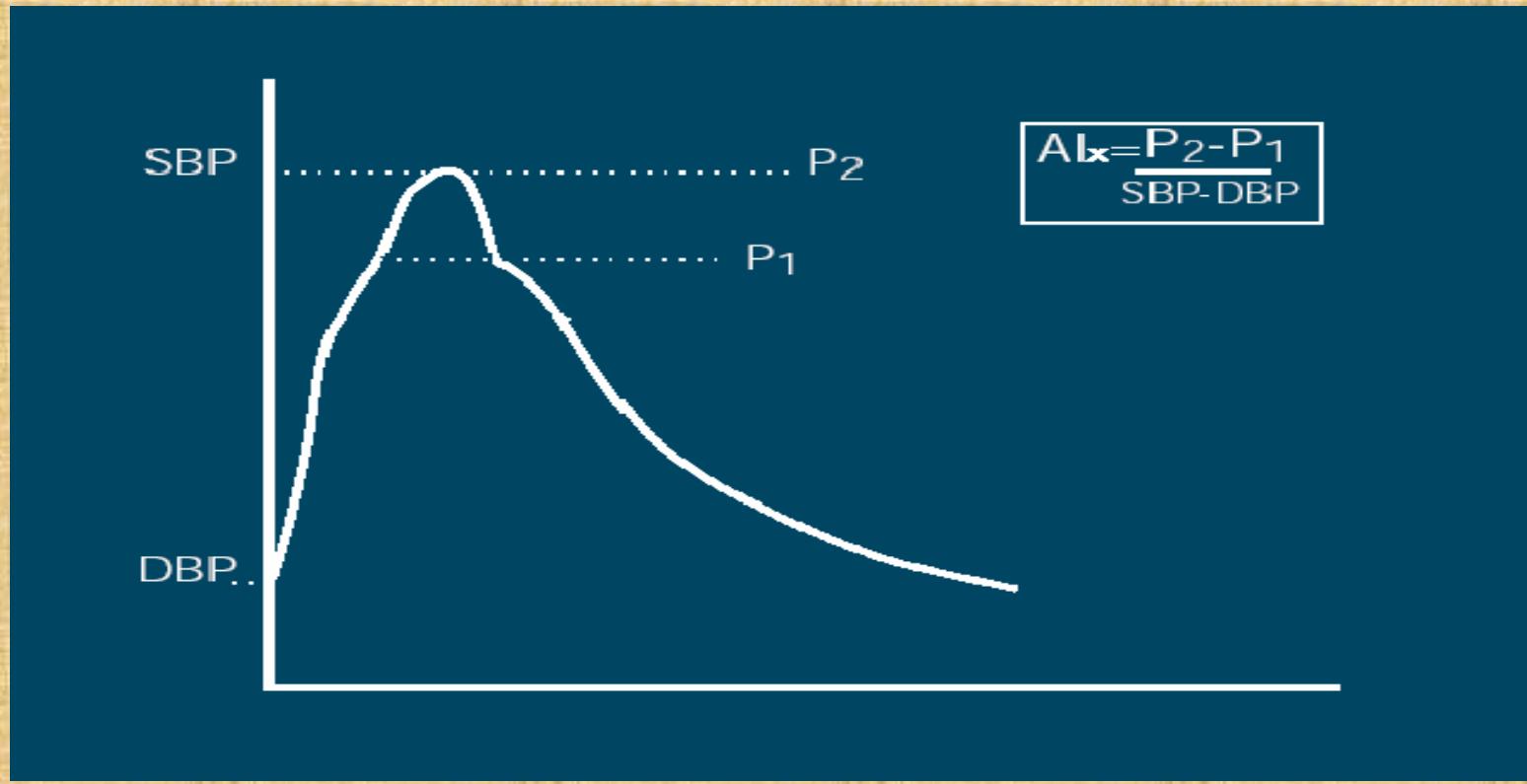
Derivar parámetros cardiovasculares centrales relacionados con la tensión arterial aórtica nos van a permitir cuantificar la rigidez arterial.



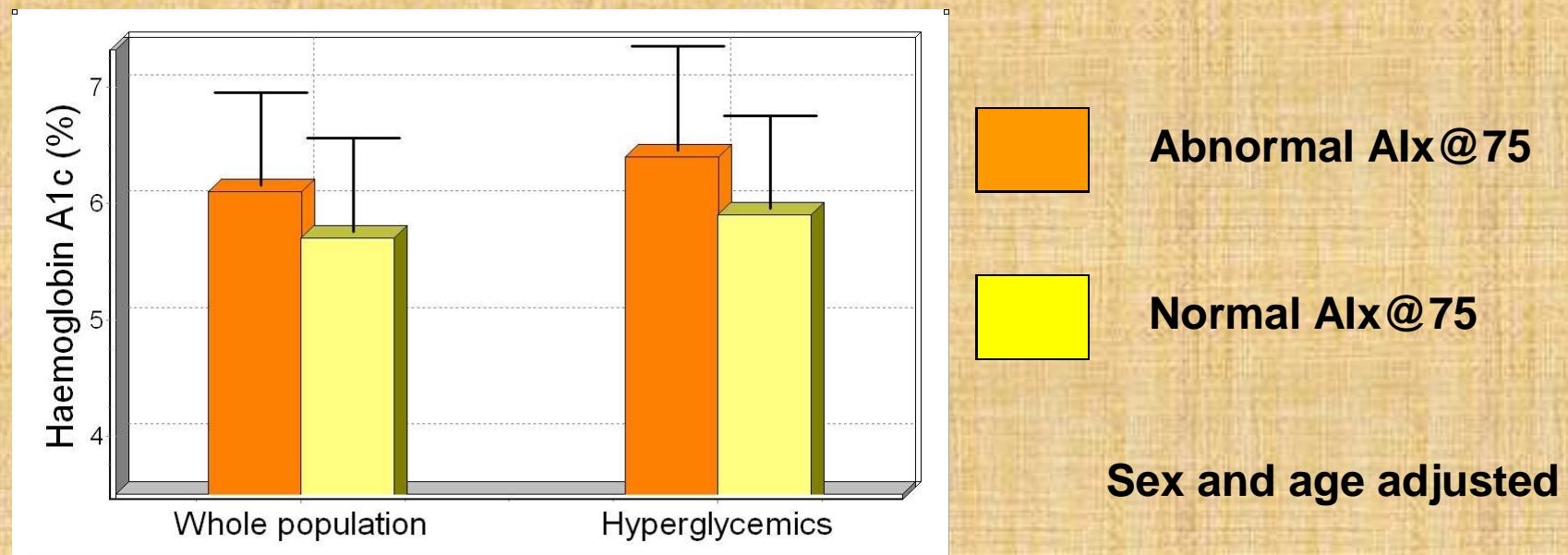
## ÍNDICE DE AUMENTO (AIx)

$$AIx (\%) = \frac{P_2 - P_1}{SBP - DBP} : \text{Incremento presión aórtica (mmHg)} \quad \times 100$$

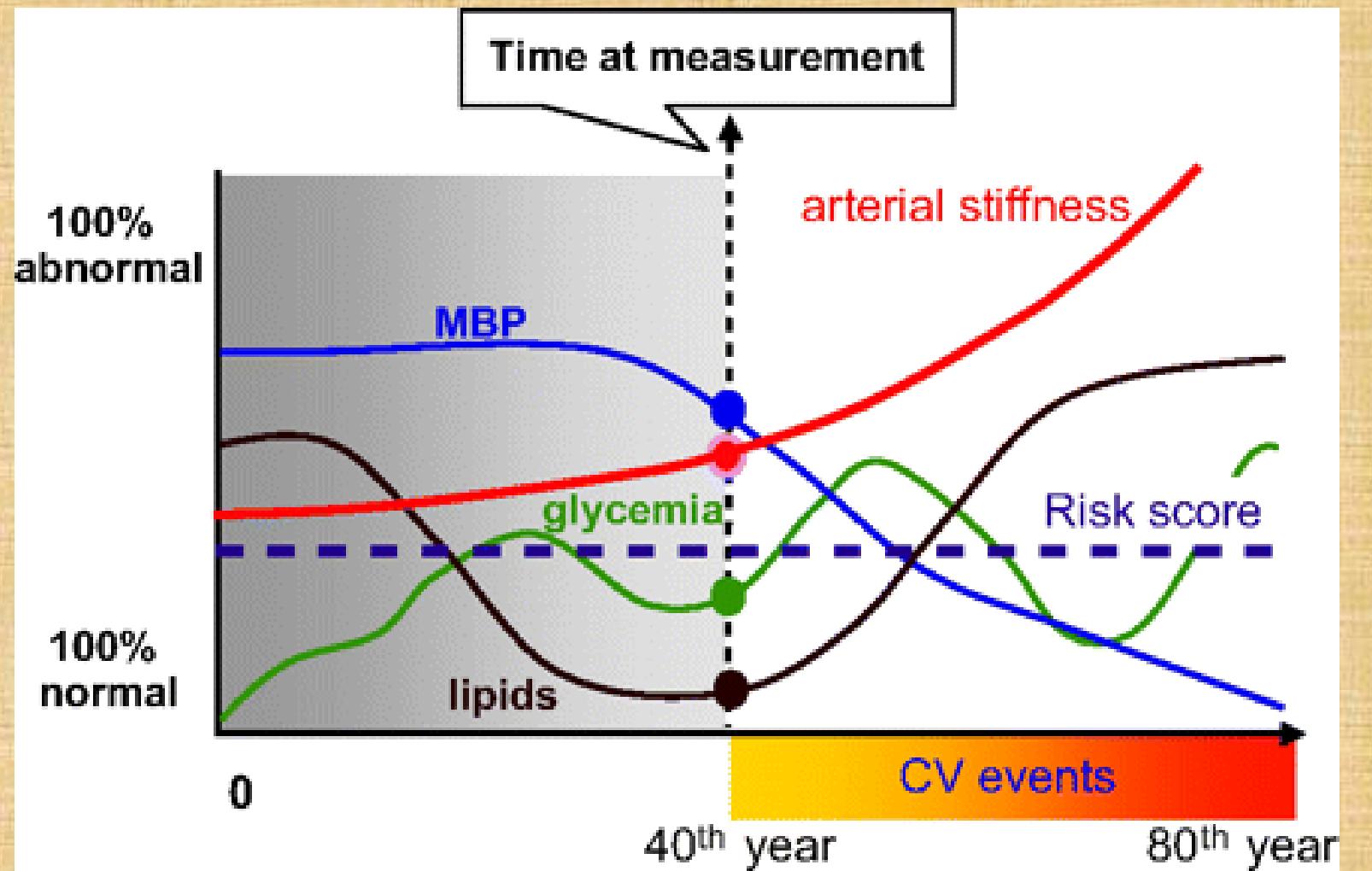
SBP –DBP: presión de pulso aórtica (mmHg)



<b>N</b>	<b>103 with moderate-high cv risk</b>
<b>Age mean (SD) [range]</b>	<b>59.6 (13.1) years [21, 81]</b>
<b>Gender</b>	<b>60% males / 40% females</b>
<b>Hypertension</b>	<b>72.8 %</b>
<b>Hyperglycemia (prediabetes/T2DM)</b>	<b>70.9 %</b>
<b>Coronary Heart Disease</b>	<b>9 %</b>
<b>Smoking</b>	<b>24.3 %</b>

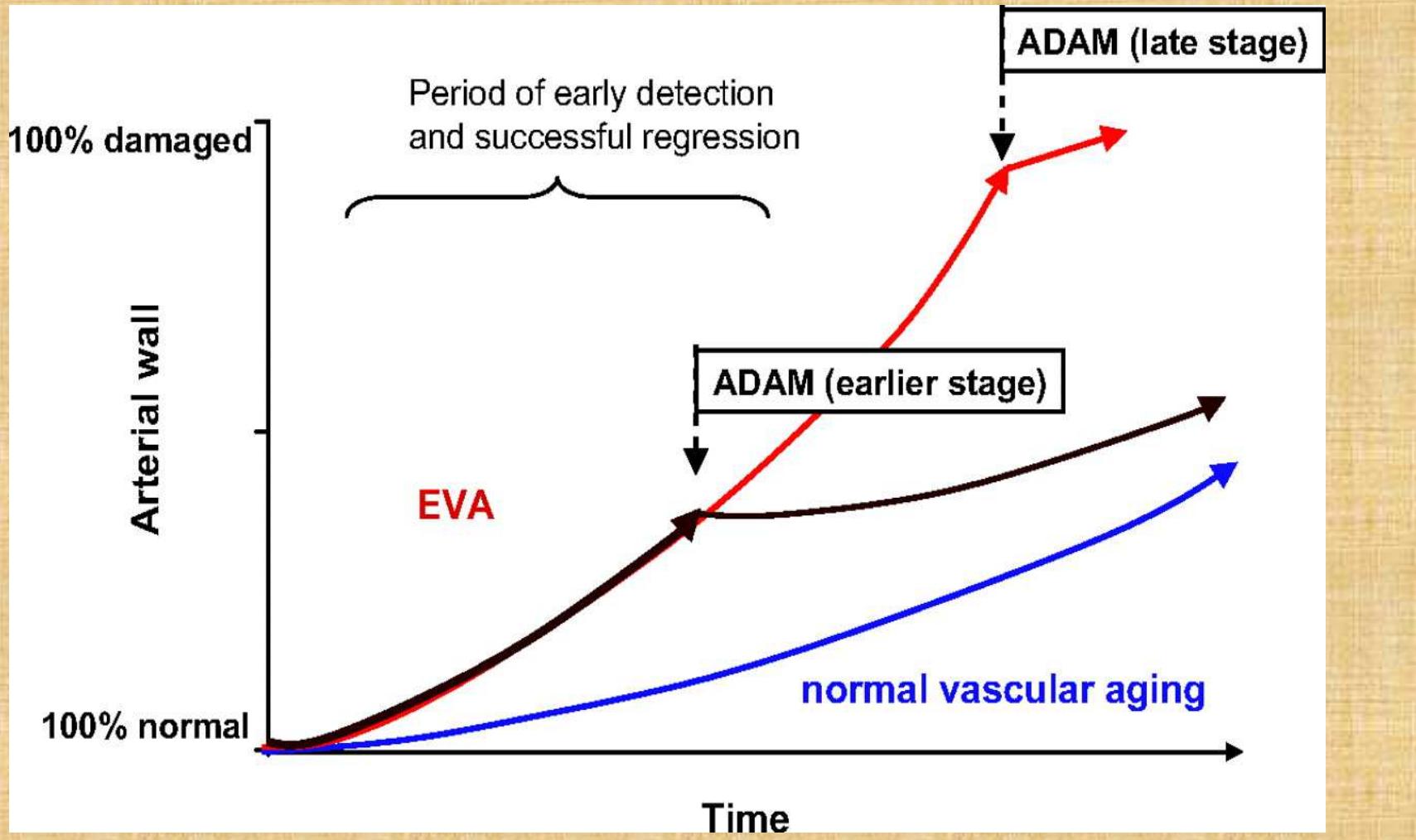


M. FABREGATE ET AL: CENTRAL SYSTOLIC BLOOD PRESSURE, PULSE WAVE VELOCITY AND ABNORMAL AUGMENTATION INDEX IN THE SHOWCASE OF VASCULAR SENESCENCE. SEMI -2012



EVA: Early Vascular Aging

Nilsson, PM, Boutouyrie, P & Laurent, S: A Tale of EVA and ADAM in CV Risk Assessment and Prevention. Hypertension. 2009; 54: 3-10



**ADAM: aggressive decrease of atherosclerosis modifiers**

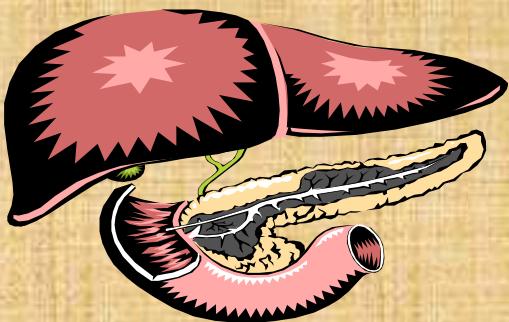
Nilsson, PM, Boutouyrie, P & Laurent, S: A Tale of EVA and ADAM in CV Risk Assessment and Prevention. Hypertension. 2009; 54: 3-10



140



250



1500



*Krogh-1929*

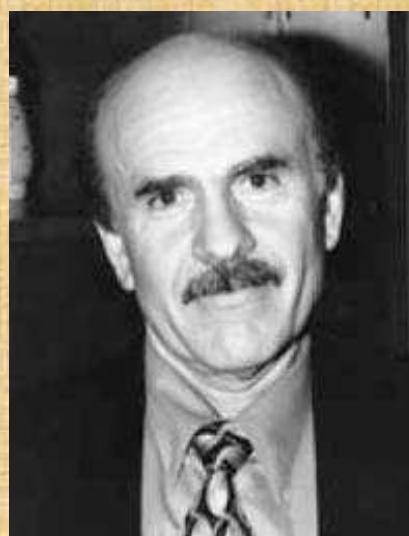


1300

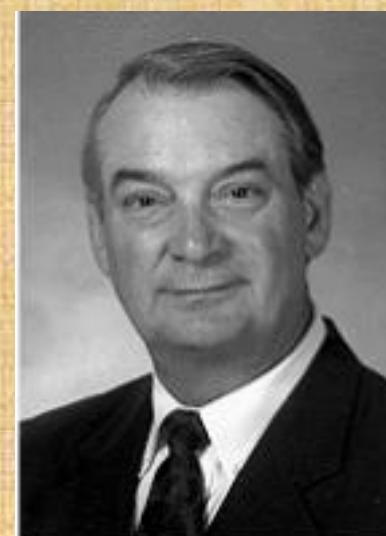
# Premios Nobel de Medicina 1998



Robert  
Furchtgott



Louis  
Ignarro



Ferid  
Murad

*Más de una década después de los premios Nobel se sigue reivindicando como el “barómetro” de la salud cardiovascular.*

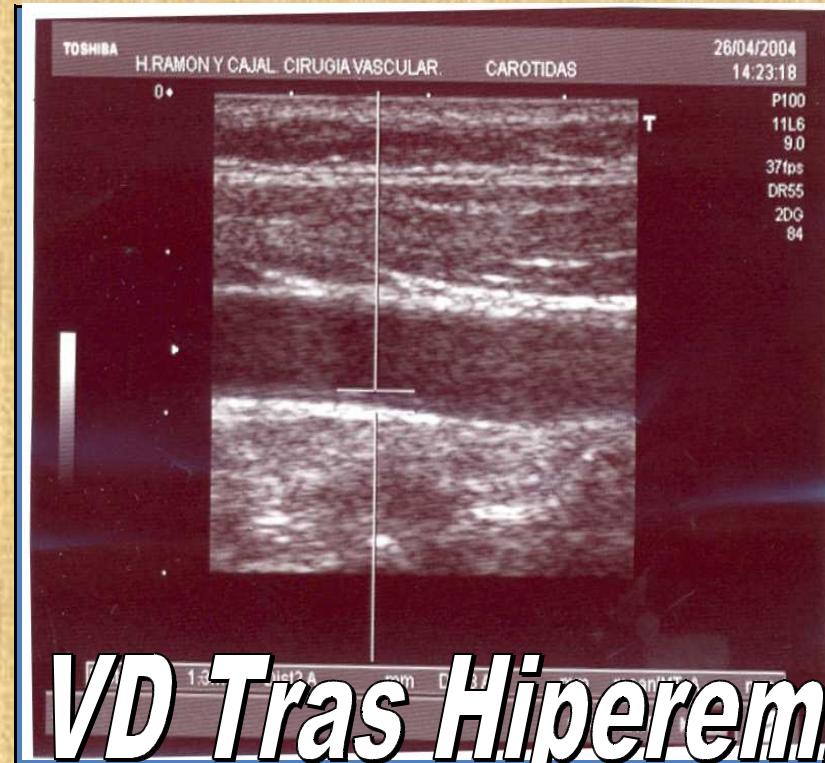


Hermann J & Lerman A. The Endothelium- The Cardiovascular **Health** Barometer. Herz, 2008, 33: 343-353. Division of Cardiovascular Diseases. Mayo Clinic Rochester.

# Disfunción endotelial por Doppler



*Situación basal*



*VD Tras Hiperemia*

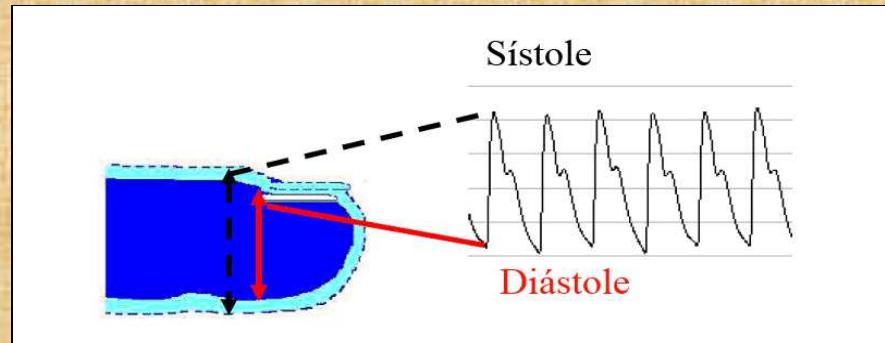
# EVALUACIÓN HEMODINÁMICA DE LA DISFUNCIÓN ENDOTELIAL

## Distintos métodos:

- Método Celermajer o “Flow Mediated Vasodilation” (FMD). Eco-Doppler.
- Flujometría láser-Doppler.
- Tonometría de amplitud del pulso digital: Análisis de la onda PAT (“Peripheral Arterial Tone”)

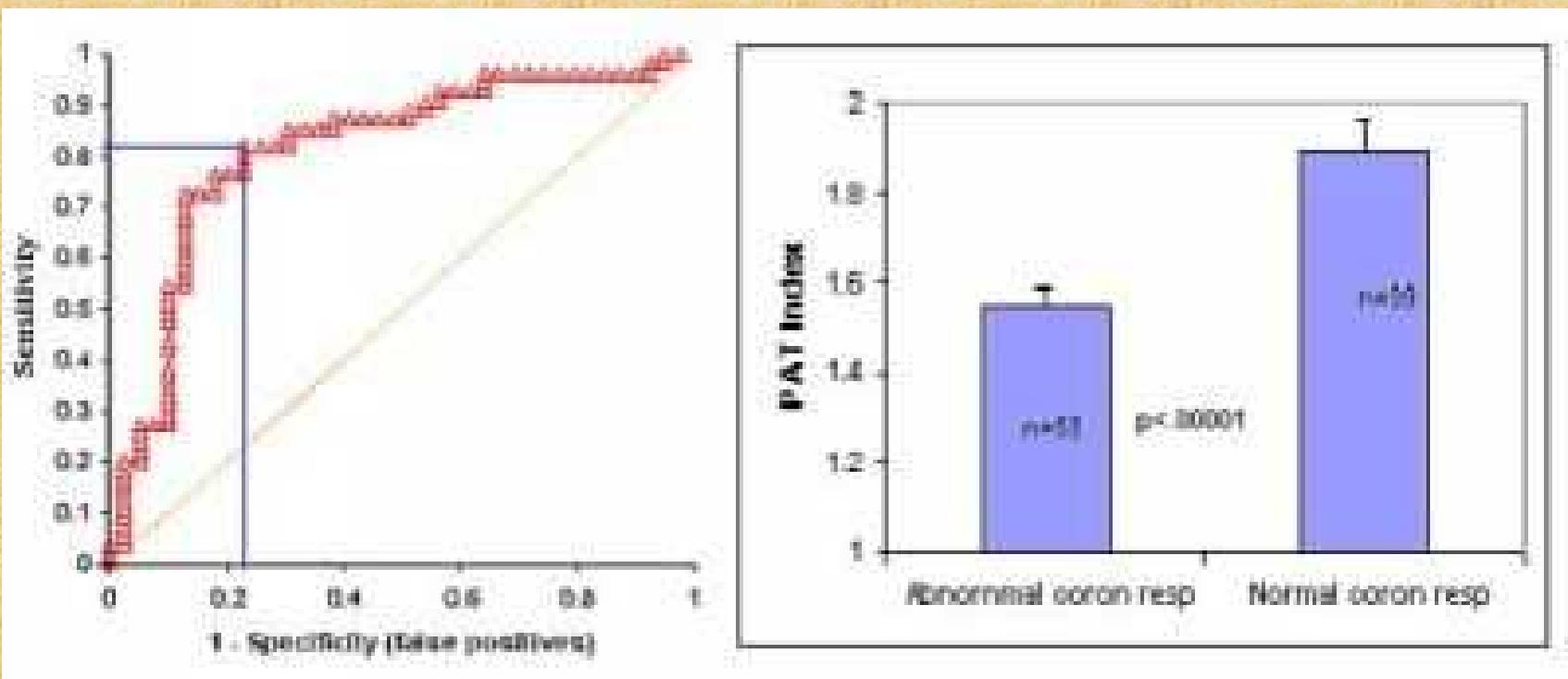


Endo-PAT (Itamar Medical, Cesarea, Israel)



## HIPEREMIA REACTIVA. ONDA PAT.





**PAT RH index yielded a sensitivity of 82% and a specificity of 77% compared to intra-coronary endothelial function tests.**

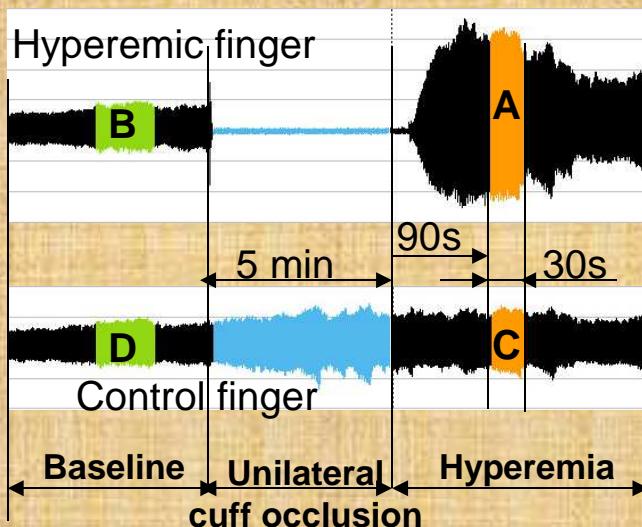
# Aims / Methods

## ► AIMS

### Microvascular Endothelial Dysfunction (ED)

- Haemodynamic and Metabolic Factors implicated?
- Related to arterial stiffness (Alx) and vascular inflammation (hs-CRP)?

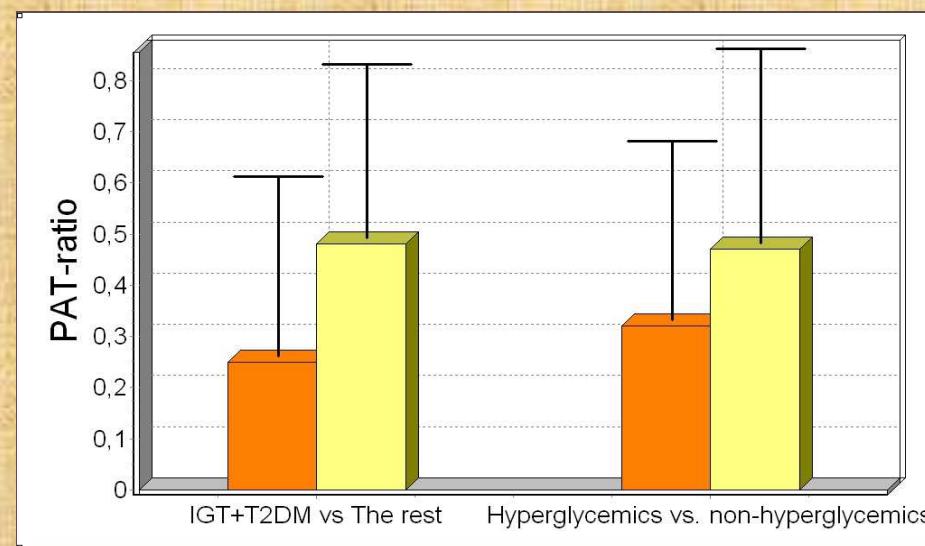
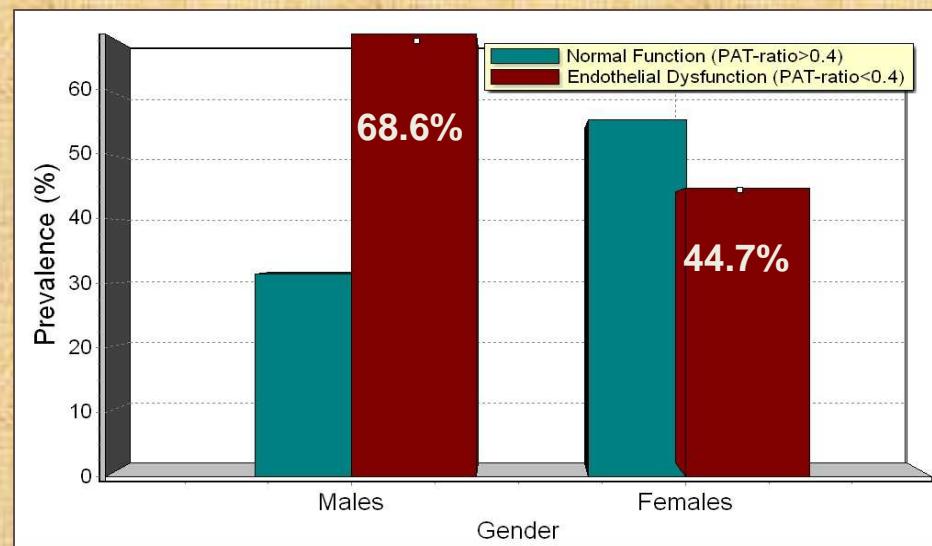
## ► METHODS



$$\text{PAT-ratio} = \ln [(A/B)/(C/D)]$$

- Endo-PAT2000 (Itamar Medical, Israel)
- PAT-ratio: 90- to 120-second postdeflation (according to Framingham HS, Hamburg et al. Circulation 2008).
- Cut-off point for ED: PAT-ratio < 0.4 (based on Rubinshtain et al. Eur Heart J, 2010)
- Augmentation Index of BP (Alx, %) ~ arterial stiffness.
- Serum biochemistry: Hitachi. Hemoglobin A1C (%): DCCT. High-sensitivity C-Reactive Protein (hs-CRP) (mg/L) and Apo-A1 (mg/dL): Nephelometry.
- Statistics: Mean (Standard deviation) [Range].  
Multivariate linear regression (age- and sex- adjusted).  
Student/Mann-Whitney. Chi-squared. p<0.05. SPSS v15.0.

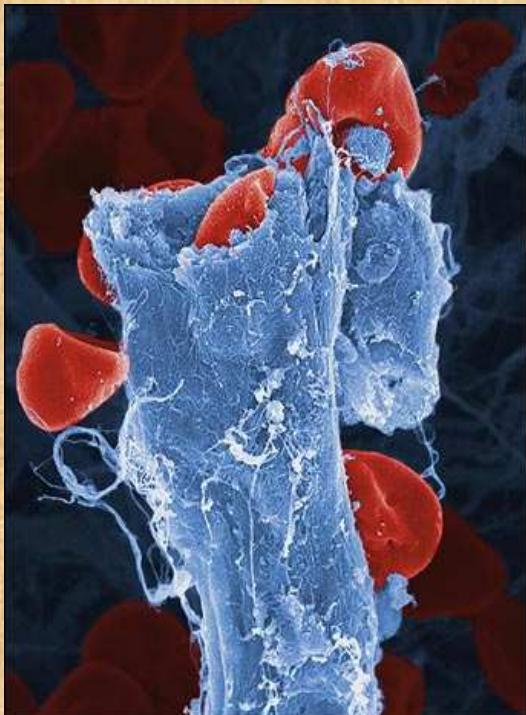
<b>Subjects</b>	<b>117 with moderate-high cv risk</b>	
<b>Age mean (SD) [range]</b>	<b>61.1 (12.2) years [32, 83]</b>	
<b>Gender</b>	<b>60% males / 40% females</b>	
<b>Hypertension</b>	<b>74.4 %</b>	
<b>Chronic hyperglycemia*</b> (prediabetes+ T2DM)	<b>70.1</b>	Prediabetes: 43.9 %
	<b>%</b>	T2DM: 56.1 %
<b>Coronary Heart Disease</b>	<b>12.8 %</b>	
<b>Smoking</b>	<b>17.1 %</b>	
<b>Metabolic Syndrome (2005 ATP-III criteria)</b>	<b>49.8 %</b>	



**M. FABREGATE ET AL. IMPACT OF HDL-CHOLESTEROL AND HYPERGLYCEMIC STATUS ON MICROVASCULAR ENDOTHELIAL DYSFUNCTION. SEMI-2012**

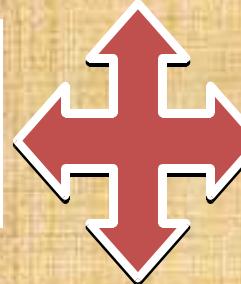
# El lugar de los biomarcadores

Endothelial Scanning  
“multimarker approach”



**VCAM/MCP-1**

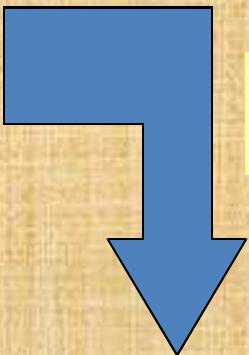
**PLA2**



**tPA/PAI-1**

**ADIPONECTINA  
/RESISTINA**

Role in Primary Prevention More Important



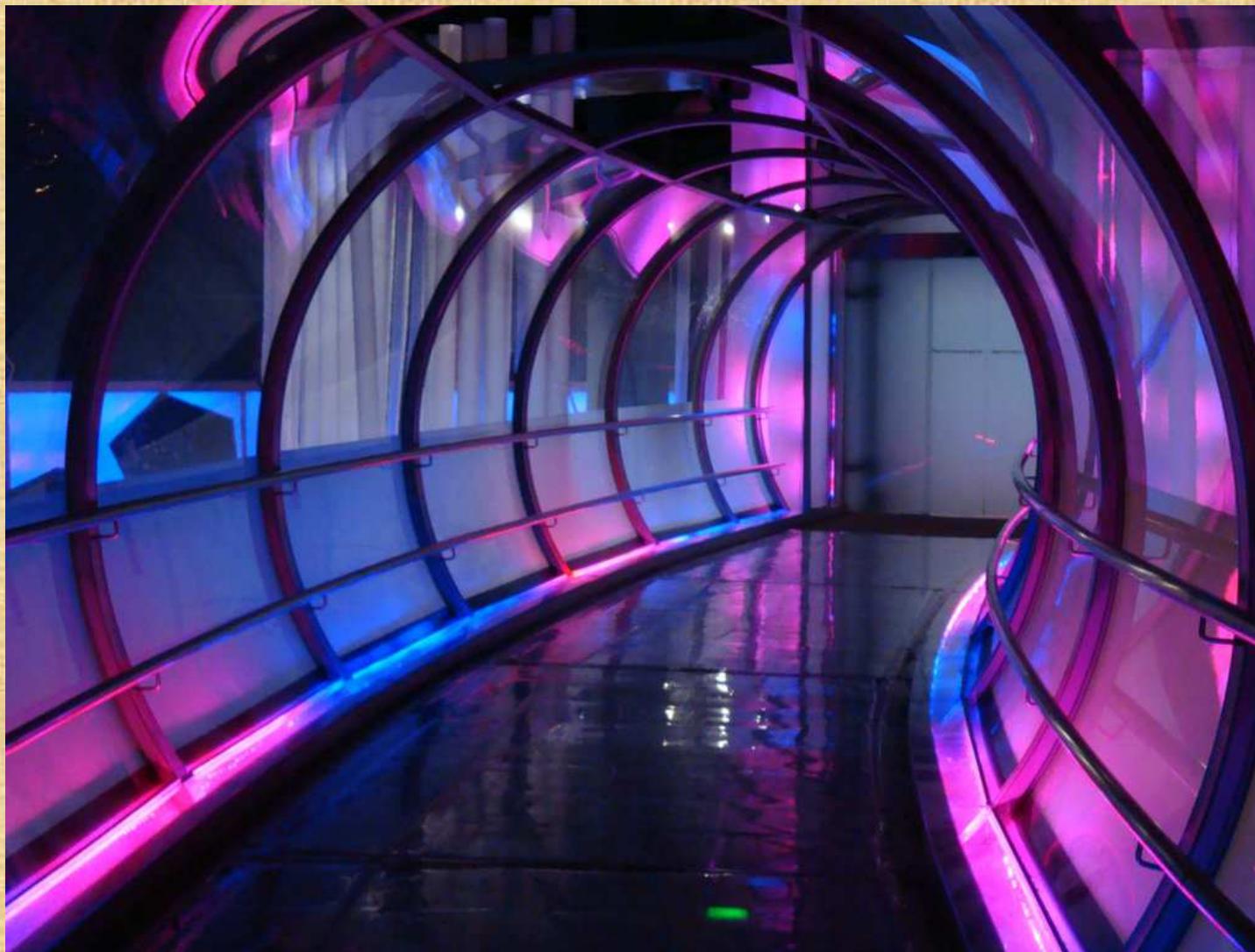
17 años



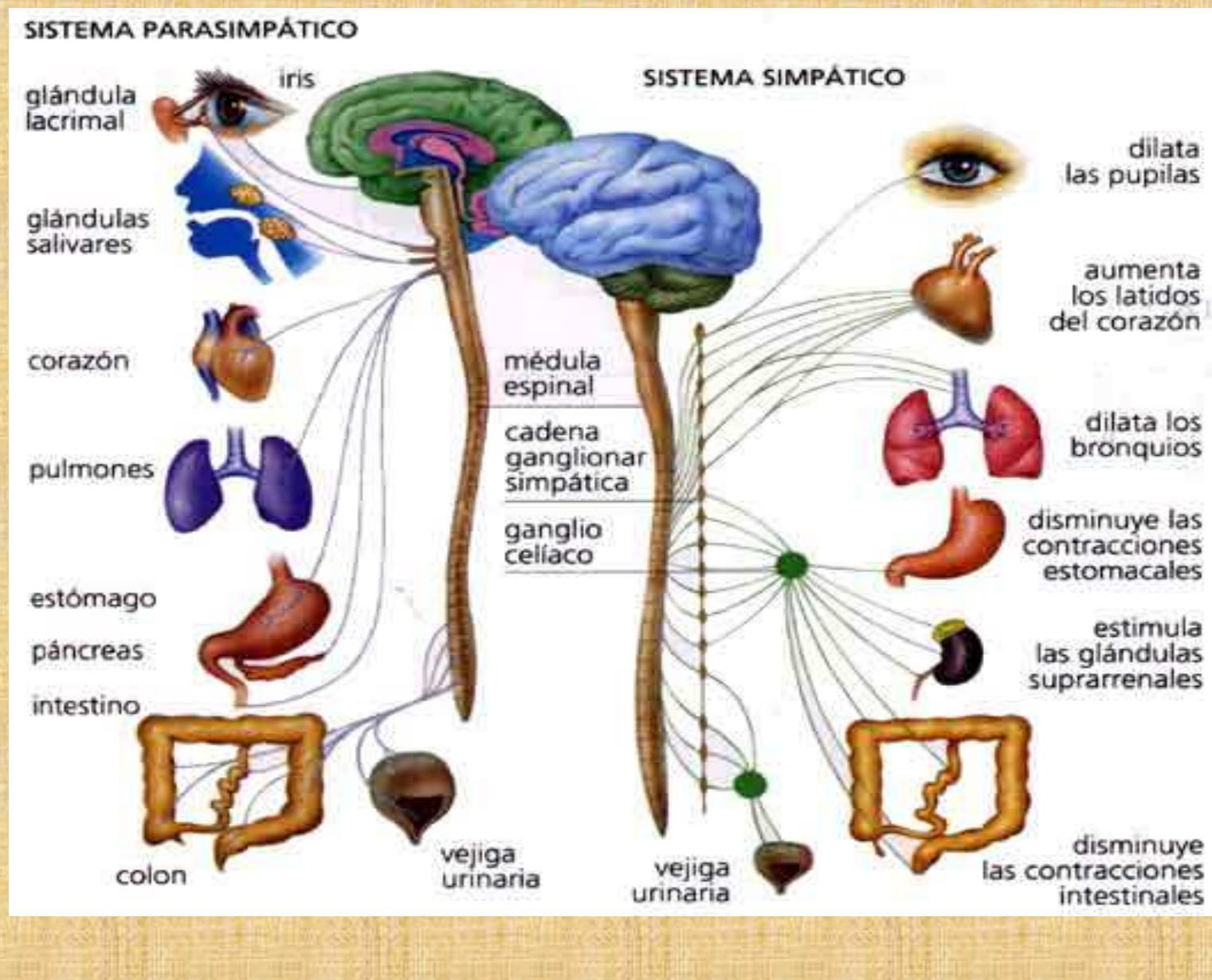
*"Endothelial dysfunction and low-grade inflammation explained 43% of the increase in CV mortality risk conferred by T2D"*

The Hoorn Study (Prof Coen Stehouwer, Univ. Hosp. Maastricht).  
Arteriosclerosis, Thrombosis and Vascular Biology. 2006; 26:1086-1095

# GATEWAY TO THE FUTURE



# SISTEMA NERVIOSO AUTÓNOMO (SNA)

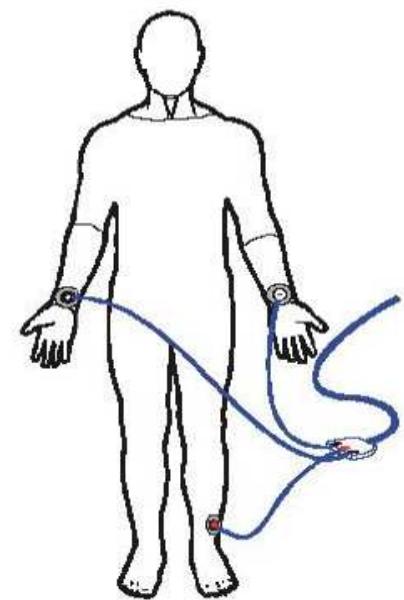


**CARDIAC AUTONOMIC AND SOMATIC  
NEUROPATHY IN DIABETIC PATIENTS  
WITH AND WITHOUT MICROANGIOPATHY**

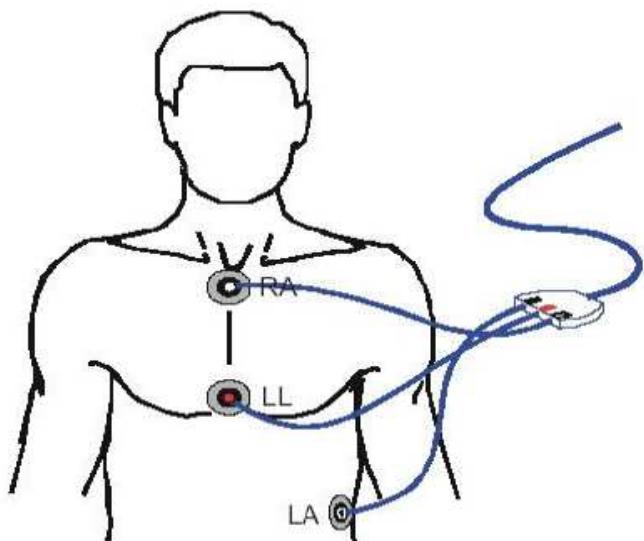
**J. Sabán, A. Tobaruela, C. Campos,  
A. Ordóñez, M. Castillo, M. Serrano-Ríos**

Service of Internal Medicine,  
Hospital Ramon Y Cajal, Madrid 28034, Spain

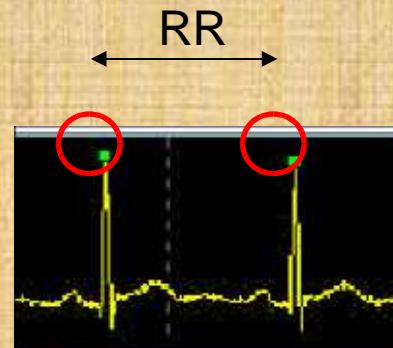
## VARIABILIDAD DE LA FRECUENCIA CARDIACA (HRV)



Electrodes on Peripheral Limbs



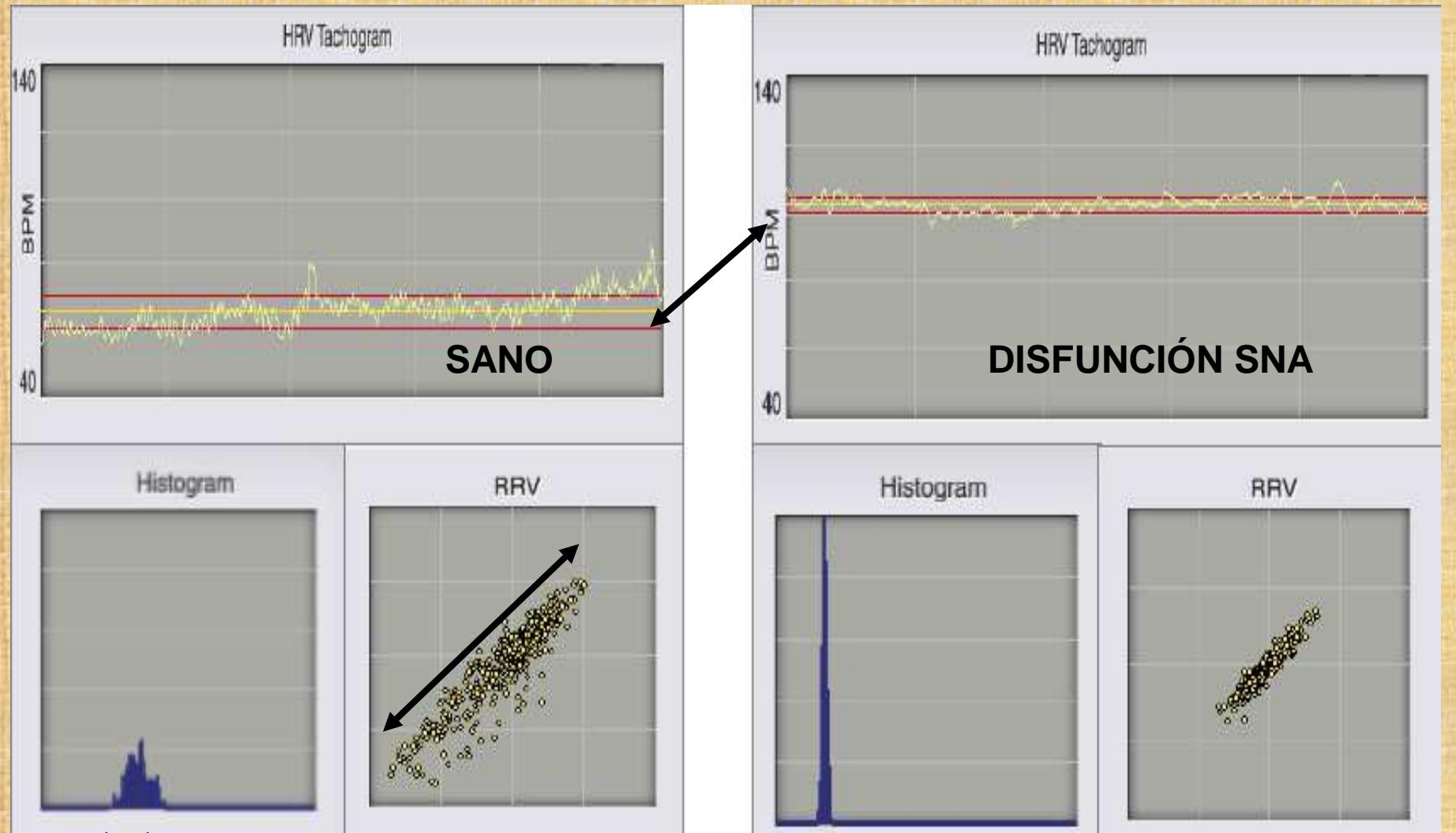
Electrodes on Chest



El análisis puede realizarse tanto en situación basal o estable, como en respuesta a las maniobras de Valsalva, bipedestación o respiración profunda.



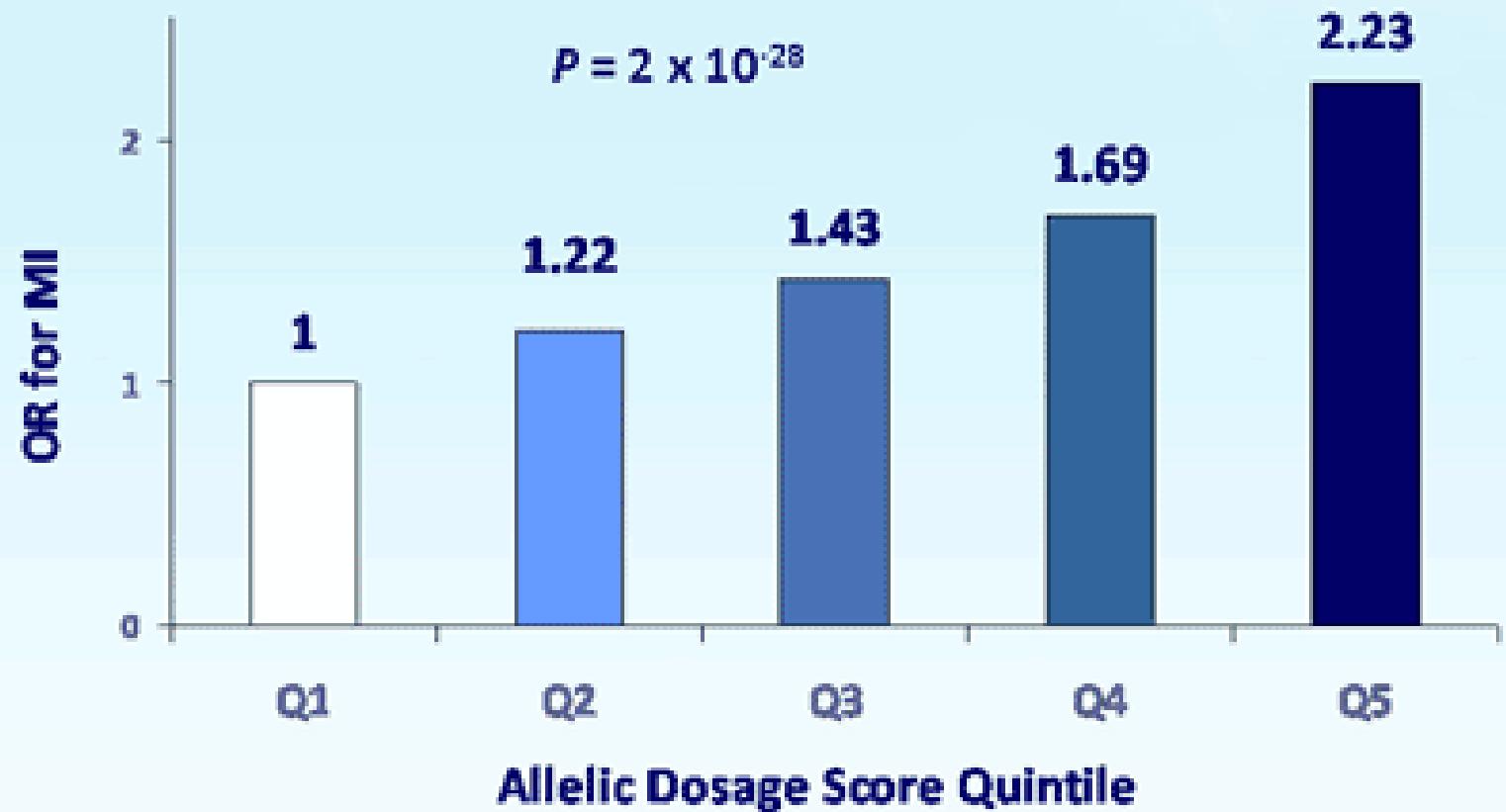
## ANALISIS DE HRV. SITUACIÓN BASAL. INTERPRETACIÓN



# GATEWAY TO THE FUTURE



# Genetic Risk Score



Risk score calculated by adding the number of risk alleles for the 9 validated SNPs

Myocardial Infarction Genetics Consortium, et al. *Nat Genet.* 2009;41:334-341.

Medscape CME

the  
heart.org  
10 years of online learning

# 9p21.3 in ARIC

9998 white individuals without prevalent CHD

Risk for incident coronary disease with carriage of 9p21.3: HR 1.20  $P = 3 \times 10^{-6}$

## Clinical Factors + 9p21.3

Clinical Factors	Clinical Factors + 9p21.3				Total Reclassified for Category
	Low (0%-5%)	Intermediate-Low (5%-10%)	Intermediate-High (10%-20%)	High (> 20%)	
Low (0%-5%)	4460 1.6%	157 (3.4%) 3.3%	0 0	0 0	157 (3.4%)
Intermediate-Low (5%-10%)	188 (6.8%) 2.7%	2429 8.0%	146 (5.3%) 11.4%	0 0	334 (12.1%)
Intermediate-High (10%-20%)	0 0	160 (8.0%) 11.5%	1741 (14.8%)	91 (4.6%) 21.2%	251 (12.6%)
High (> 20%)	0 0	0 0	66 (10.5%) 20.5%	560 30.0%	66 (10.5%)

Net reclassification index (NRI) 0.8%,  $P = .31$

Clinical NRI (for risk categories 5%-20%) 6.2%,  $P = .03$

Integrated discriminant index (IDI) .002,  $P < .015$

Brautbar A, et al. *Circ Cardiovasc Genet*. 2009;2:279-285.

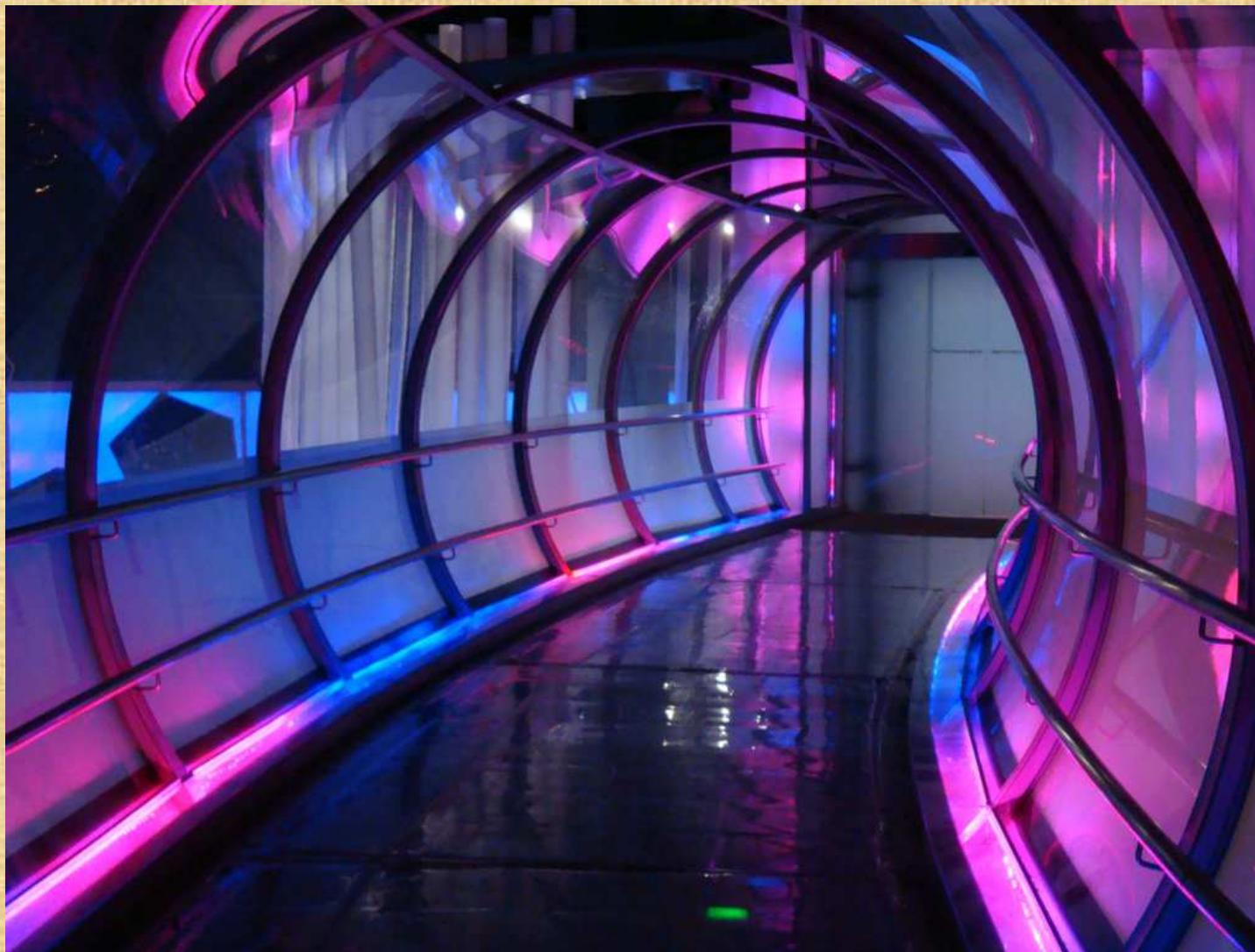
Medscape CME

the  
**heart**.org  
10 years of online education

# Unidad de Endotelio y Medicina CM. HRy Cajal.



# GATEWAY TO THE FUTURE



# **A simple urinary test: the key to solving the ongoing debate about the indications of aspirin in cardiovascular prevention?**

**Sanchez O., Fabregate R., Fabregate M., de la Torre N., Alonso A., Tello S., Fernandez A., Sanchez D., Saban-Ruiz J.**

*Endothelial Pathology Unit. Ramon y Cajal Hospital. Madrid. Spain.*

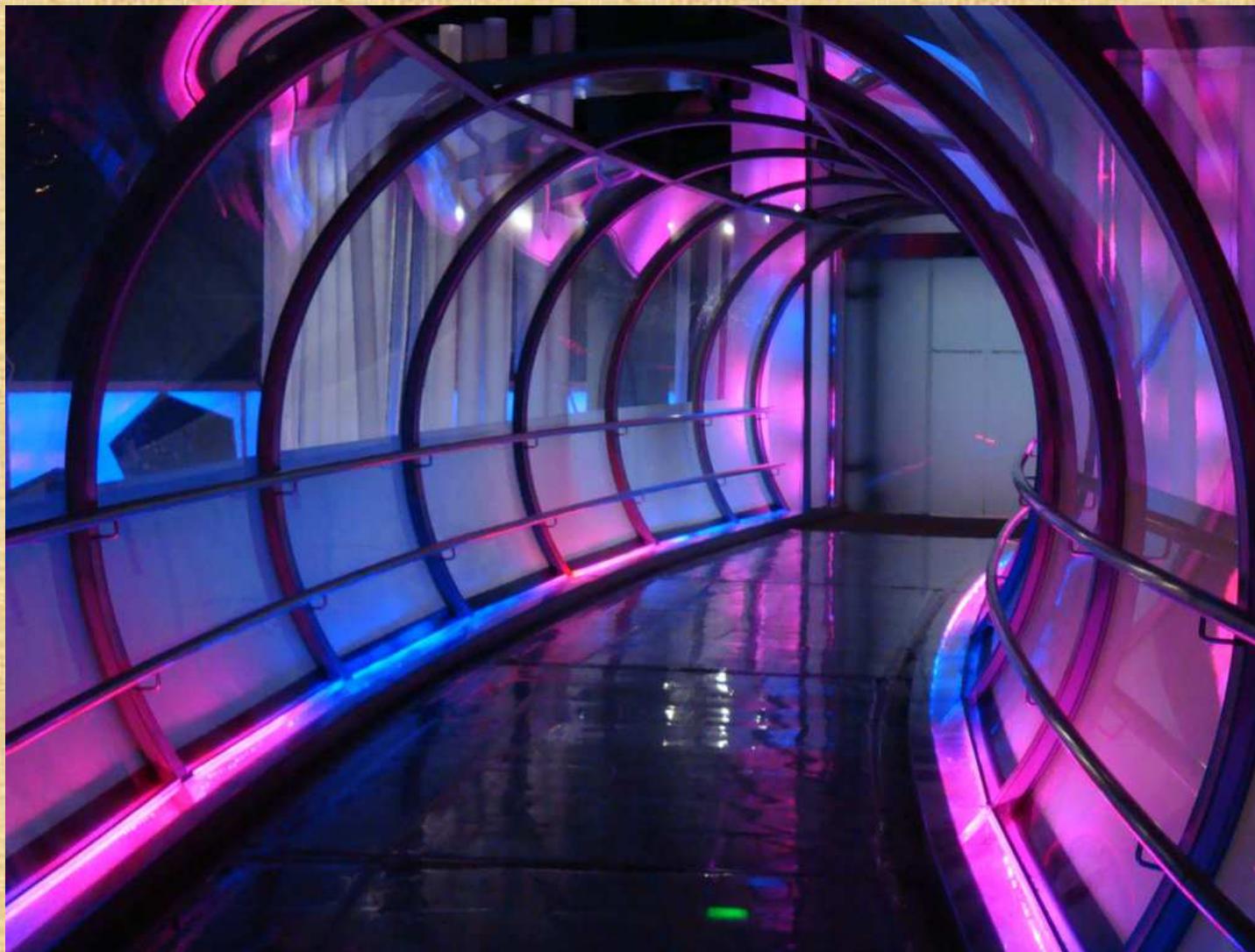
**Proceedings of the 8th ICCAD 2009,  
Medimond ed, pags: 397 - 400**

# Poor Response to Antiplatelet Drugs



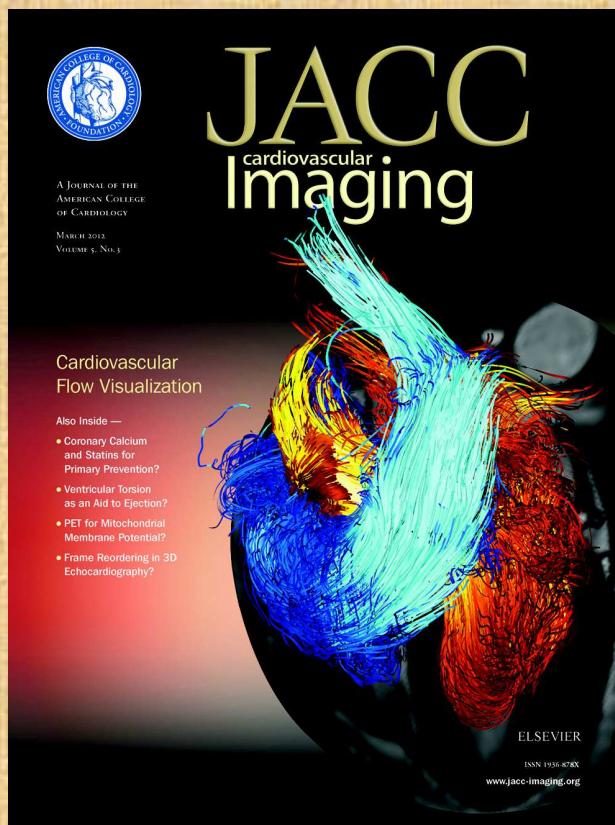
**Del Castillo-Carnevali HA, Barrios-Alonso V, Sabán-Ruiz J, Zamorano, JL  
Poor Response to Antiplatelet Drugs. An Important Issue in Drug- Eluting Stents.  
Curr Clin Pharmacol. 2013, 8: 340-349.**

# GATEWAY TO THE FUTURE



# Urge un análisis de costes

2010 ACCF/AHA Guideline for Assessment  
of Cardiovascular Risk in Asymptomatic  
Adults.



Journal of the American College of Cardiology Vol. 56, 2010

# Global Cost of Diabetes

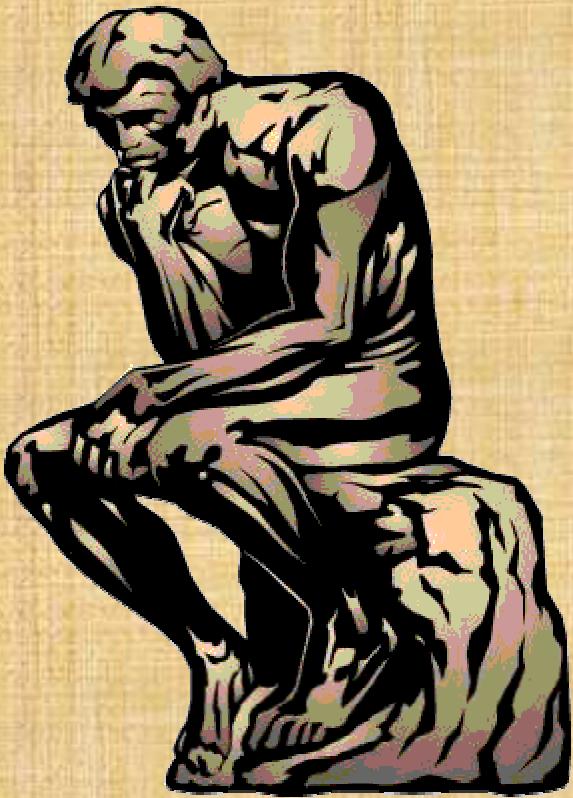
- In 2011, healthcare expenditures\* due to diabetes accounted for 11% of the total healthcare expenditures in the world.
- Estimated global healthcare expenditures to treat diabetes and prevent complications:
  - In 2011, about 465 billion ID<sup>†</sup>
  - By 2030, >654 billion ID
- Average spent per person with diabetes on treating and managing the disease in 2011: 1,366 ID

\*Include spending on diabetes by the healthcare system and by people living with diabetes.

<sup>†</sup>ID correct for differences in purchasing power.

ADA 2014 Standards of Medical Care in Diabetes  
Diabetes Care Vol 37, Suppl 1 Jan 2014 S14-80

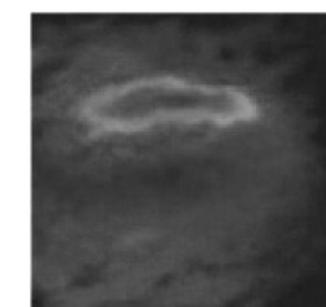
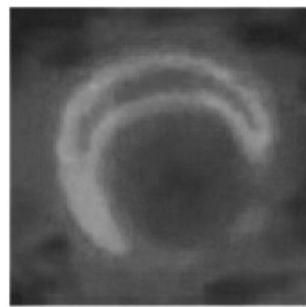
**CVD** is the major cause of morbidity and mortality for individuals with diabetes, and **the largest contributor to the direct and indirect costs of diabetes.**



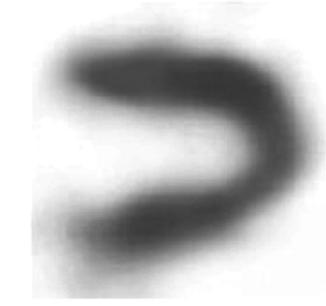
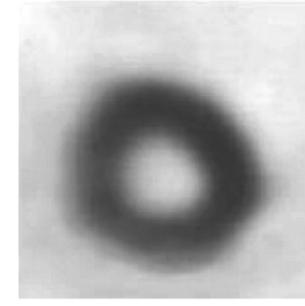
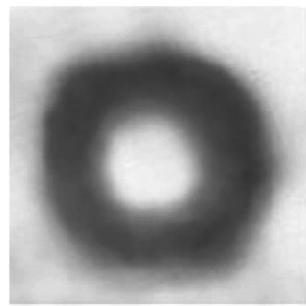
**¿Cuál es la diferencia entre PET y SPECT?**

	<b>Short axis (basal)</b>	<b>Short axis (apical)</b>	<b>Vertical long axis</b>
--	-------------------------------	--------------------------------	-------------------------------

**$^{18}\text{F}$ -FDG  
PET**



**$^{99\text{m}}\text{Tc}$ -MIBI  
SPECT**



**Patient 9**

# Molecular imaging (FDG-PET) in Vascular Inflammation

atherosclerotic plaque composition

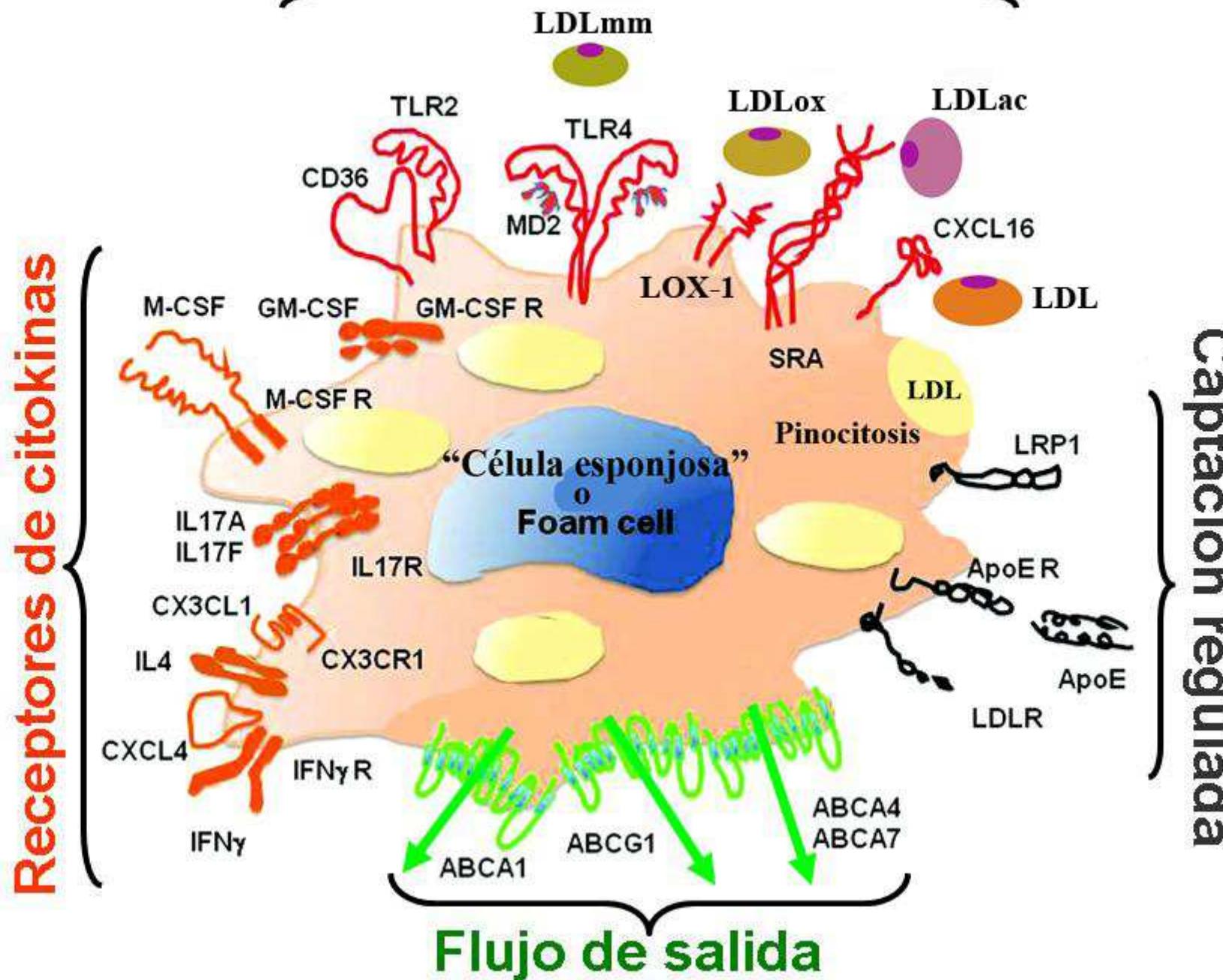
plaque vulnerability

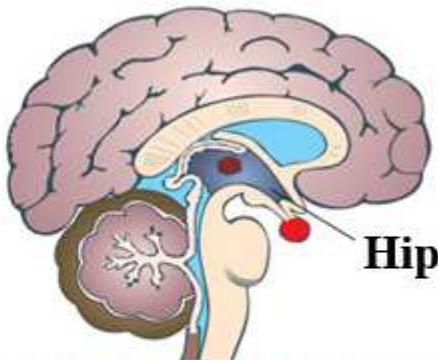
Vulnerable plaques have a large lipid-rich necrotic core, a thin-fibrous cap and numerous inflammatory cells.

**metabolically active macrophages**

Tahara et al. Molecular imaging of vascular inflammation. Curr Pharm Des. 2013 Jun 20. [Epub ahead of print]

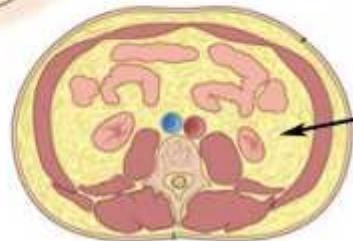
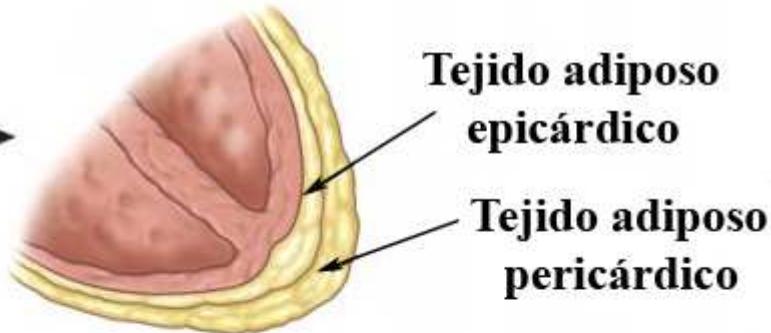
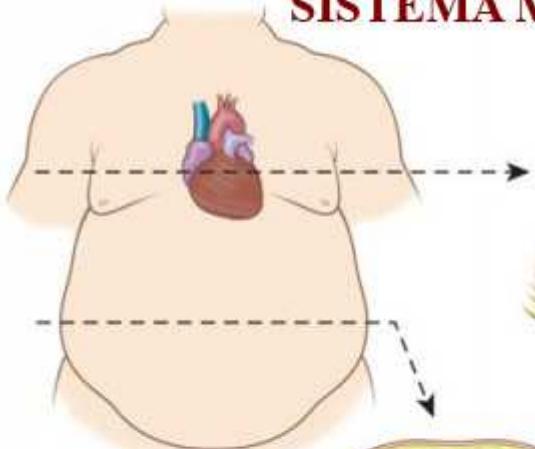
# Captación no regulada o “insaciable”





Hipotálogo

## SÍSTEMA MONOCITO-MACRÓFAGO

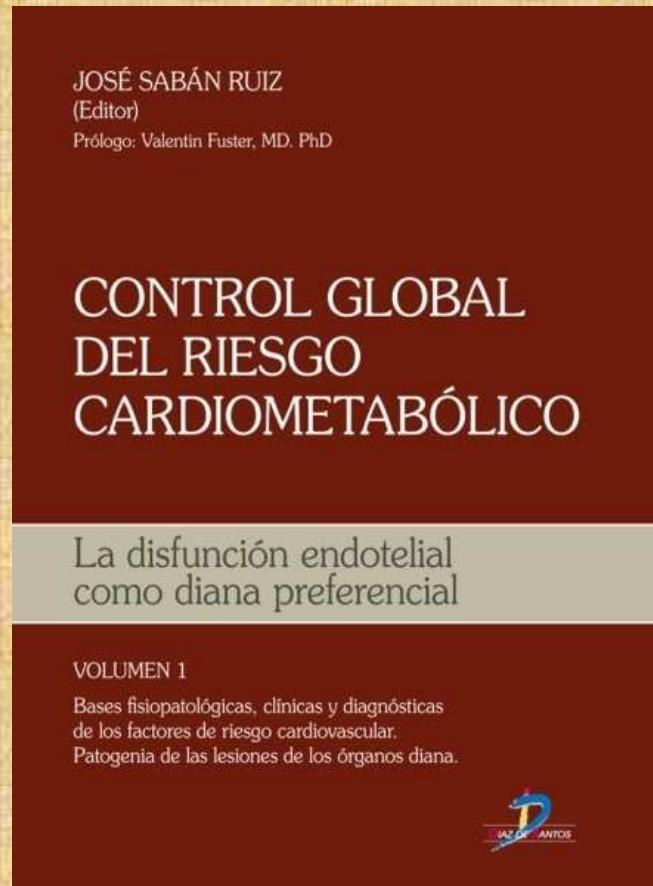


Grasa  
intraabdominal

**Todo esto y mucho más .....**

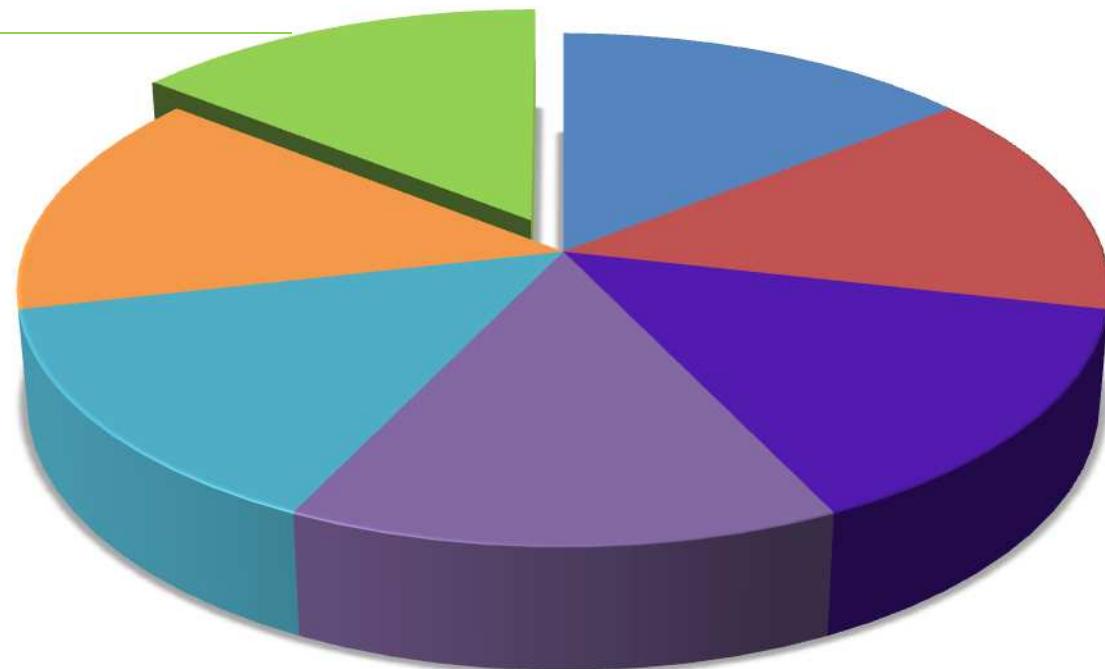


Janus, 153 BC



Editorial Díaz de Santos. Madrid.

# Conclusiones



Introducción

Corazón y vasos coronarios

Cerebrovascular y Arteriopatía periférica

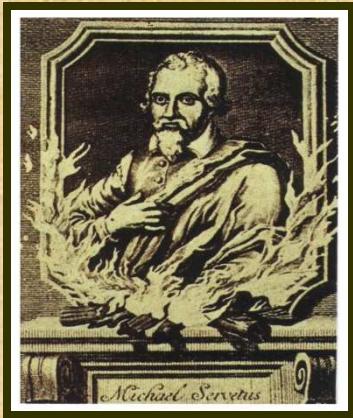
Valor predictivo coronario

Fitness CR

Perspectivas futuras

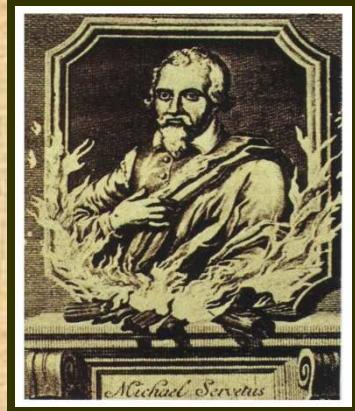
Conclusiones

# CONCLUSIONES



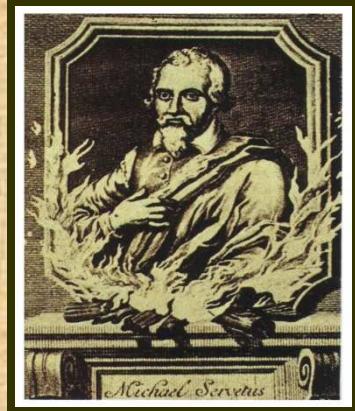
1. La verdadera tasa de enfermedad vascular asociada a la diabetes es desconocida.

# CONCLUSIONES



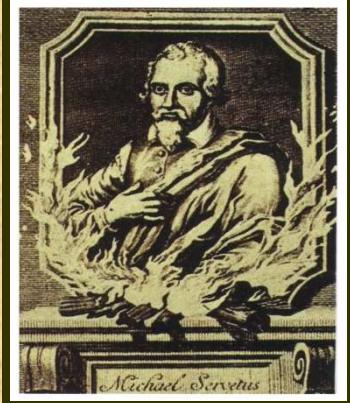
- 2- Los nuevos marcadores subclínicos como el IMT, ABI, disfunción VI post-estrés y CAC son mejores predictores de EC y de eventos que las escalas de riesgo.
- 3-La interpretación del ABI y del IMT no debe hacerse de la misma forma: mientras el ABI es un marcador dual de enfermedad local y coronaria, el IMT es fundamentalmente un predictor de EC

# CONCLUSIONES



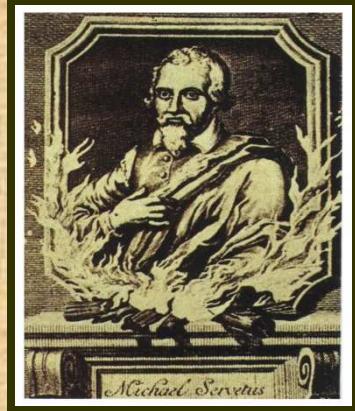
4- El fitness CR se erige como la técnica de exploración vascular más completa tanto en la población diabética como en la población prediabética y aquella con Síndrome Metabólico.

# CONCLUSIONES



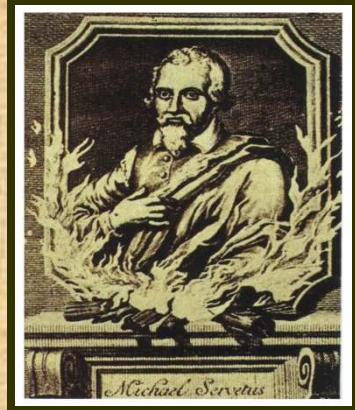
5- El futuro **a corto plazo** lo vemos en la exploración de la rigidez arterial, **a mediano plazo** en la evaluación de la disfunción endotelial por FMD o parámetros afines (ENDOPAT) y la función autonómica automatizada, **y a largo plazo** por Nuevas técnicas de imagen y una batería de Biomarcadores más específicos y sensibles que la PCR... además de la genética.

# CONCLUSIONES



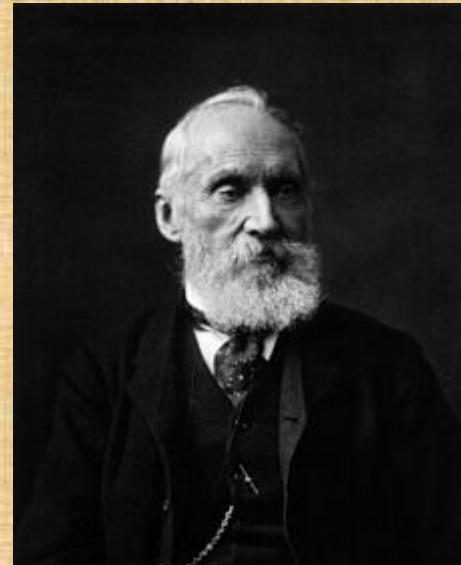
6- Hay que PREVENIR la enfermedad desde las fases tempranas, urge implementar estrategias de DIAGNÓSTICO PRECOZ y urge investigar NUEVOS TRATAMIENTOS que nos sirvan para frenar los mecanismos de activación, entre otros del Estrés de Retículo y del mTOR.

# CONCLUSIONES



- 7- Deberíamos incorporar a nuestro sistema sanitario de forma urgente economistas de la salud, si queremos resolver el actual galimatías en el que se ha convertido la enfermedad CV asociada al Status Hiperglucémico Crónico en general y no solo en el paciente diabético.

**¿Por qué medir?**



*“Lo que no se define, no se puede medir.  
Lo que no se mide, no se puede mejorar.  
Lo que no se mejora, se degrada siempre.”*

**William Thomson, primer barón Kelvin (1824-1907)**  
**Físico y matemático británico.**





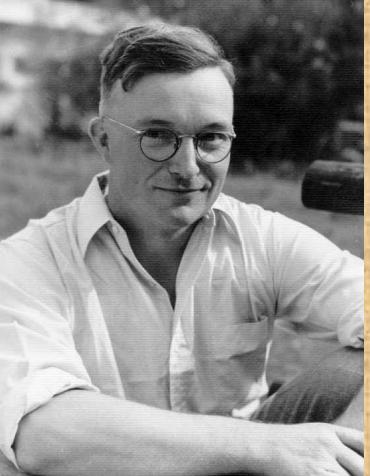
Thomas Sydenham

Siglo XVII

"A man is as old as his arteries"

"Un hombre tiene la edad  
de sus arterias"





**Endothelium : Its Development, Morphology, Function And Pathology / Rudolf Altschul**  
Altschul, Rudolf, 1901-1963  
New York : Macmillan, 1954  
157 p.

*It has been said that one is as old as one's arteries. In view of the supreme importance of endothelium in arterial function, I should like to modify... this statement by saying that one is as old as one's endothelium.<sup>1</sup>*

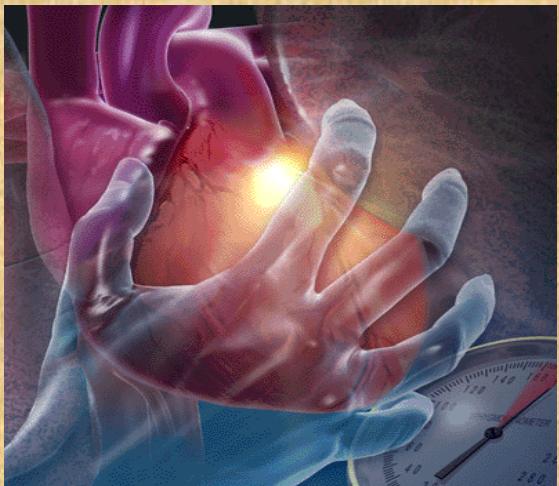
R. Altschul, 1954

## **DIAGNOSTICO ESPIRITUAL**

**Autor: Jose Antonio Izquierdo Monge\***

**Ya se corazón mío, estás dolido  
sin ganas de latir, triste y cansado  
de tanto desengaño recibido  
de tanto y tanto amar como has amado**

**Tu vida viejo amigo no termina  
acaso te me pares de repente  
reposes en la dulce paz divina  
y vuelvas a latir ya eternamente.**



*Versos Robados*



J. Sabán

Poesía

www.LibrosALCANA.com

## ASPIRINA

Autor: José Sabán Ruiz

Oh, droga milagrosa,  
benditos sean los asirios  
por rescatarte de los sauces y de los mirtos,  
tú que estás tan repleta de radicales acetilos,  
que combates lo mismo la fiebre que el dolor,  
como reconfortas al corazón malherido.

Protégeme de los efectos de la tensión,  
del maligno tabaco y del dulce *azucarillo*;  
pero cuando llegue mi momento,  
déjame yacer en paz, porque si por ti fuera,  
aquí no se muere ni Cristo.