Scientific session of the
Institut d'Investigació Sanitària de Palma (IdISPa)

The search for Biomarkers in coronary artery disease

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REGICOR 35 anys
Registre Gironí del Cor
www.regicor.org

IMIM
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Institut Hospital del Mar d'Investigacions Mèdiques

PROGRAMA HERACLES
Red de Investigación Cardiovascular

The problem

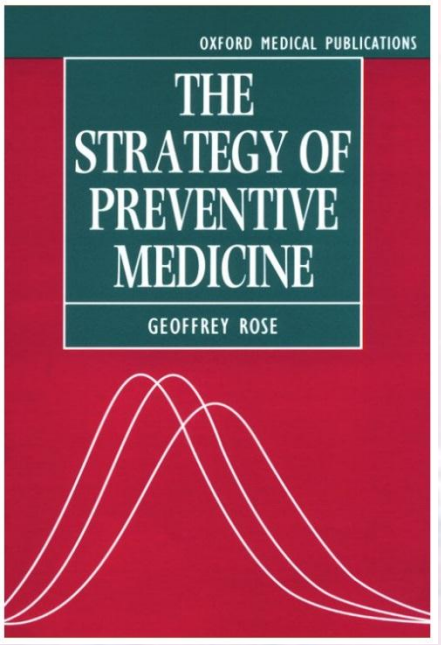
- Each year cardiovascular disease (CVD) causes over **4.3 million deaths** in Europe.
- CVD causes nearly **half of all deaths in Europe (48%)**.
- CVD is the main cause of the **disease burden** in Europe (**23%** of all the disease burden).
- Overall CVD is estimated to cost the EU economy **€192 billion a year**.

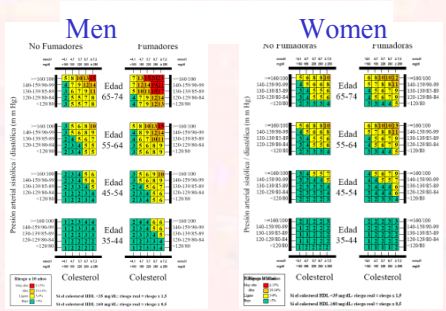
Justification of primary prevention of coronary heart disease

- Greatest cause of death in developed countries. In ~35% of cases its onset symptom is sudden death.

- Most cases are related to lifestyle & other modifiable factors, whose improvement results in reduced CHD incidence.

Modificación de la distribución poblacional de un factor de riesgo e incidencia de cardiopatía isquémica: el ejemplo del colesterol





Disease prevention

Screening

POPULATION Population individuals Patients Patients

Genetic Characteristics

Risk Factors

Disease

Reccurrences

Primordial prevention

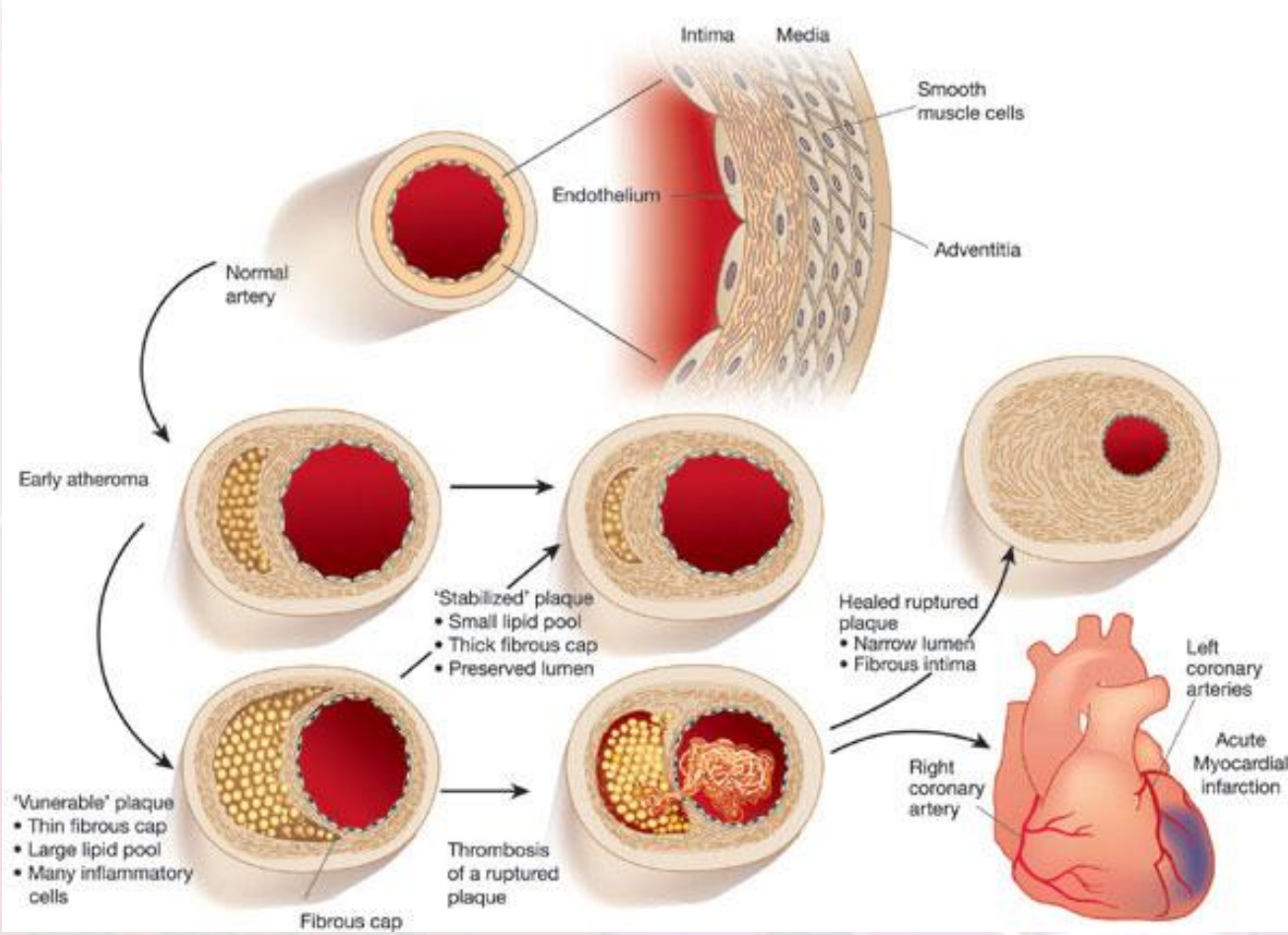
Primary Prevention

Secondary Prevention

Inappropriate Life Styles

Reto para el futuro

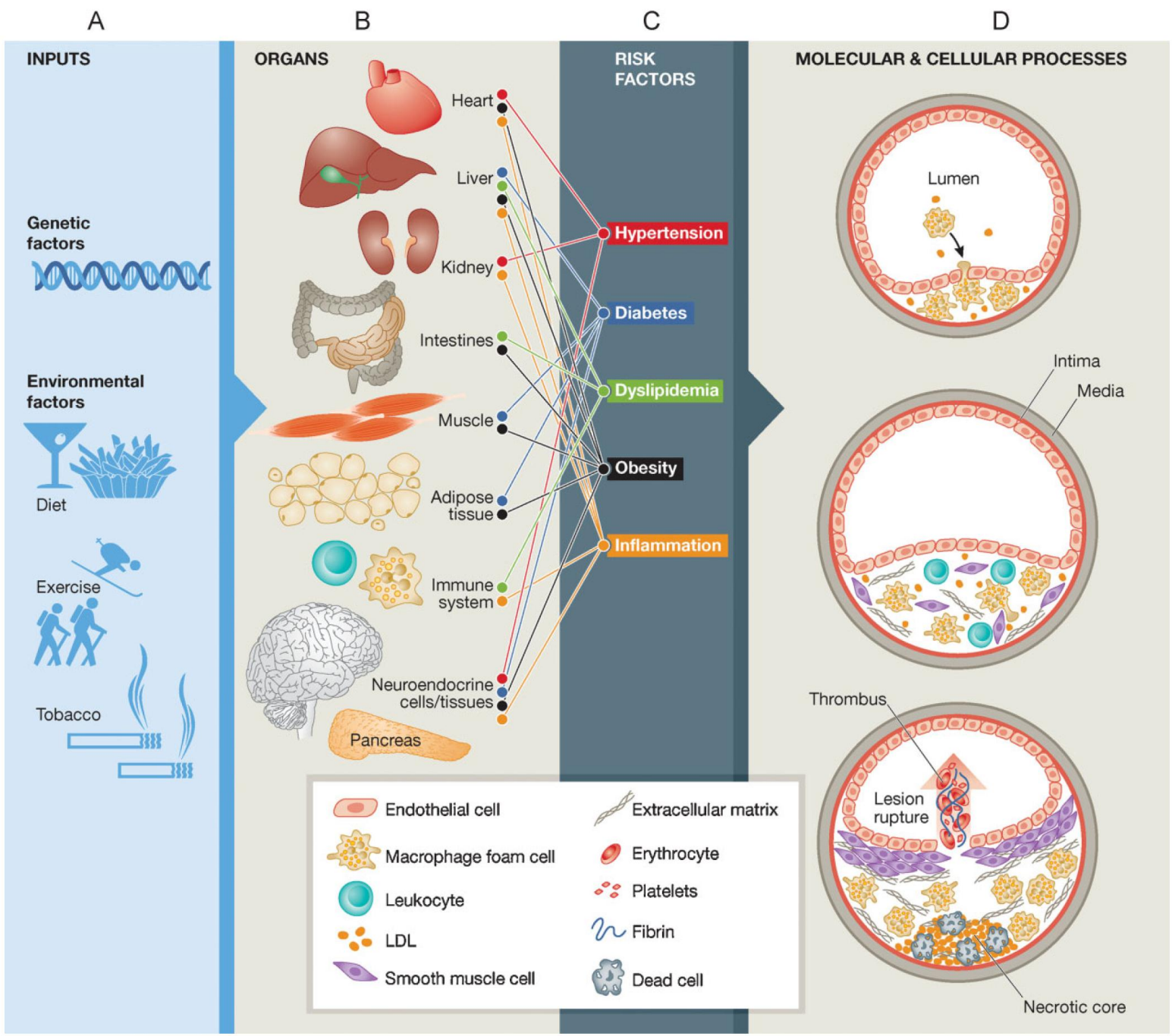
- Identificación pacientes con placas vulnerables (estenóticas o no) susceptibles de rotura



Potential use of biomarkers

- Diagnostic tests
  - To clarify etiology of symptoms
  - During acute phase of disease
- To assess risk
  - Risk of developing symptomatic disease: Primary prevention (10 years)
  - Prognosis of established diseases (days, months)

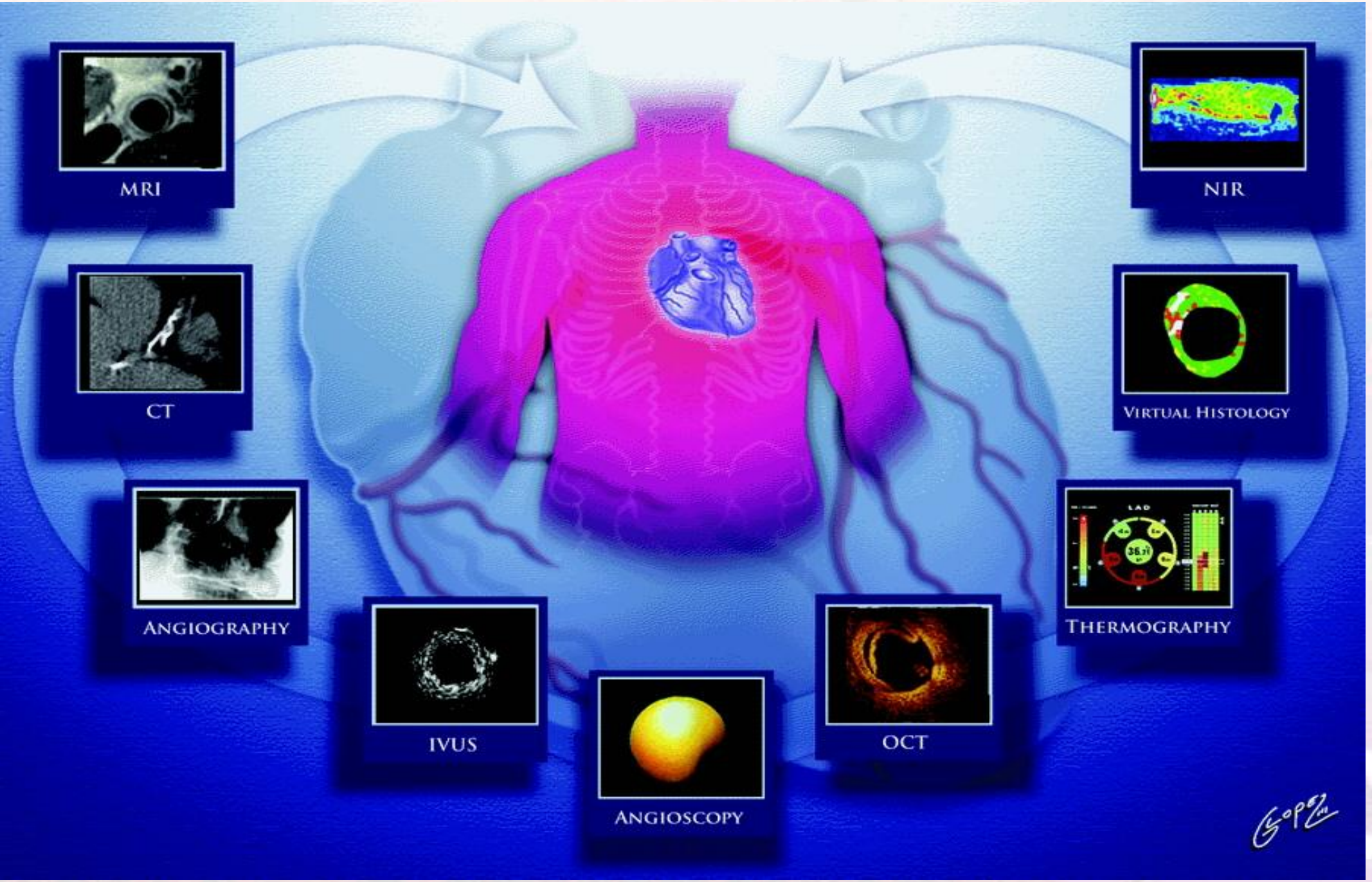
Ramsey EA et al. EMBO Mol Med 2010;2:79–89



gure 1. The pathophysiology of atherosclerosis involves interacting systems at multiple levels.

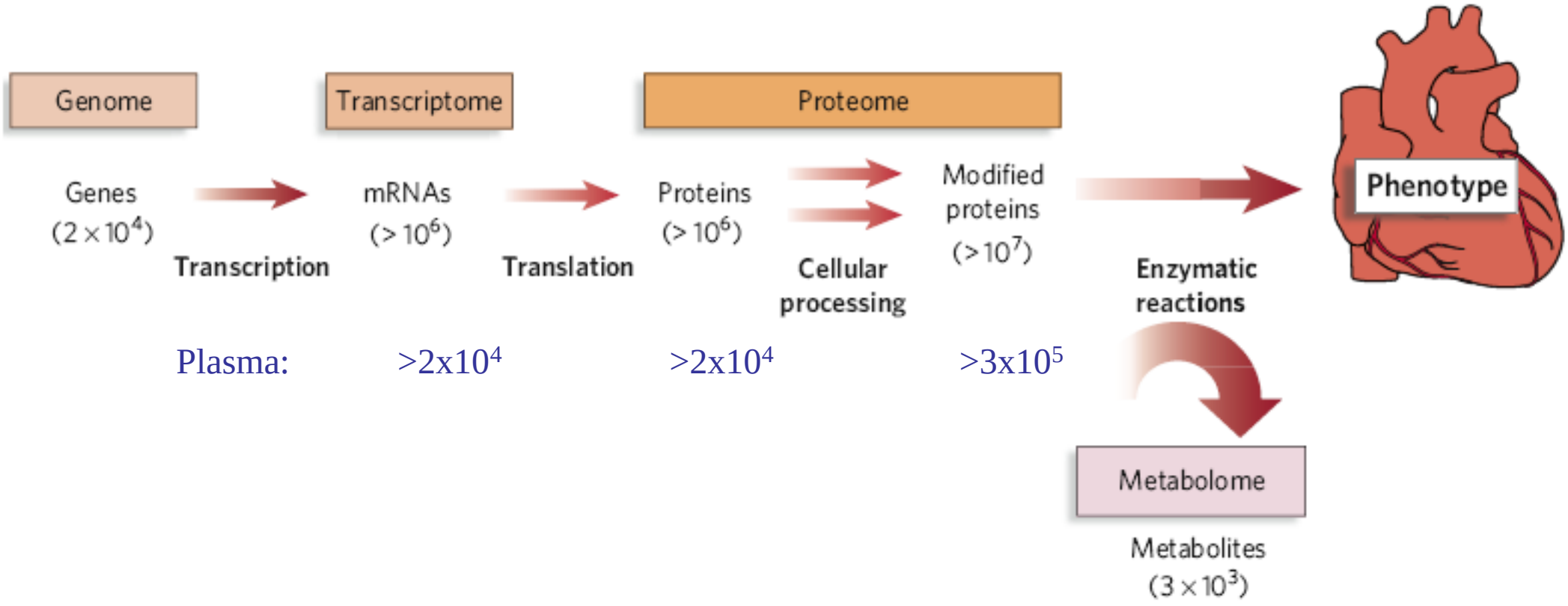
Types of biomarkers

- Life styles & cardiovascular risk factros
- Imaging
- Molecular
  - Biochemical
  - Genetic



Madjid M, et al ATVB 2004;24:1775-82.

Molecular Biomarkers



Anderson, N. L. *et al*. Mol. Cell. Proteomics 3, 311–326 (2004).

Potential biomarkers in CV diseases

The 22 more abundant proteins, including albumin & immunoglobulins, constitute 99% of the plasmatic proteome mass.

Many biologically interesting molecules circulate in very small concentrations:

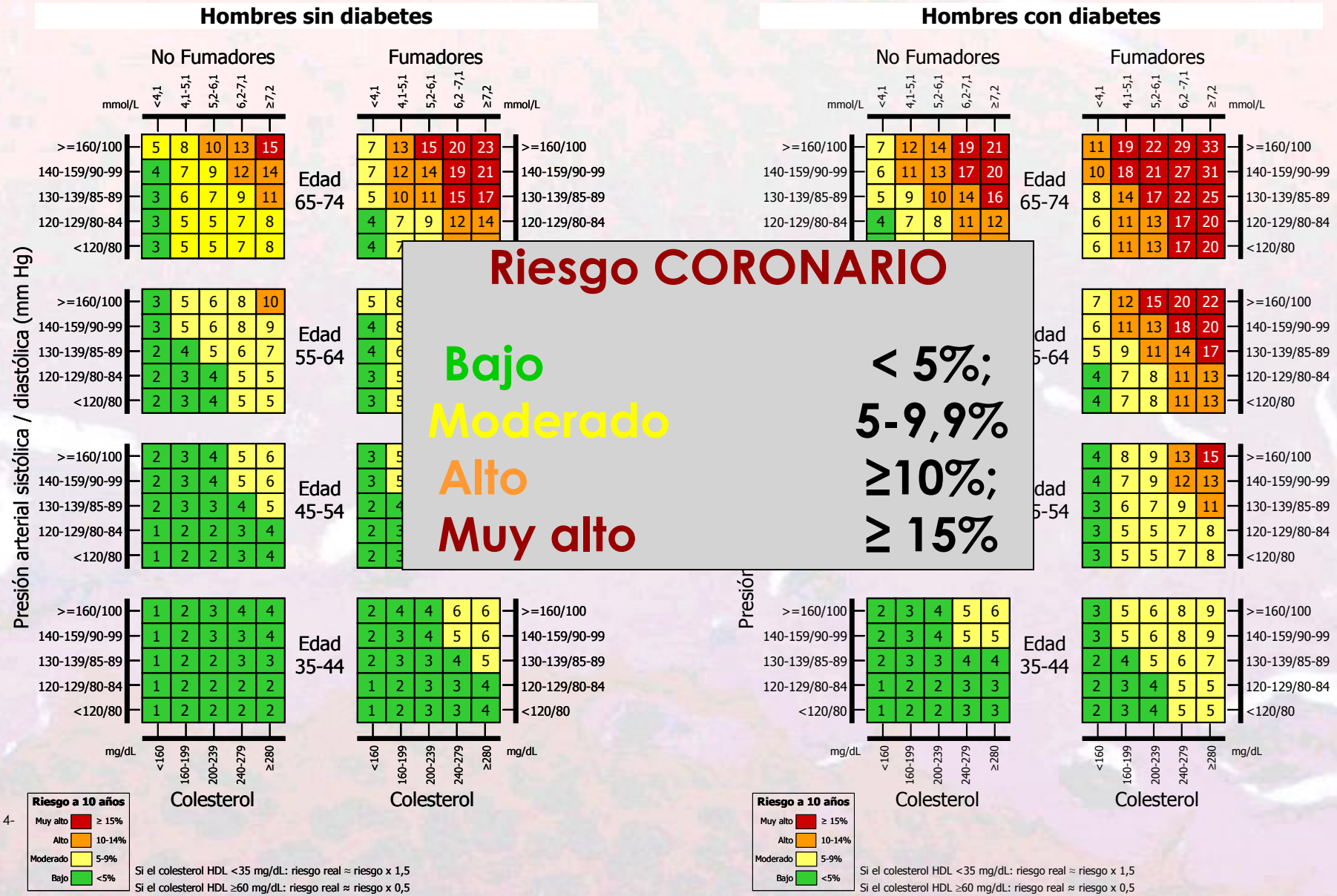
- Troponin: **nanomolar** (10^{-6}) concentration
- Insulin: **picomolar** (10^{-9}) concentration
- TNF: **femtomolar** (10^{-12}) concentration

Anderson, N. L. et al. The human plasma proteome: a nonredundant list developed by combination of four separate sources. Mol. Cell. Proteomics 3, 311–326 (2004).

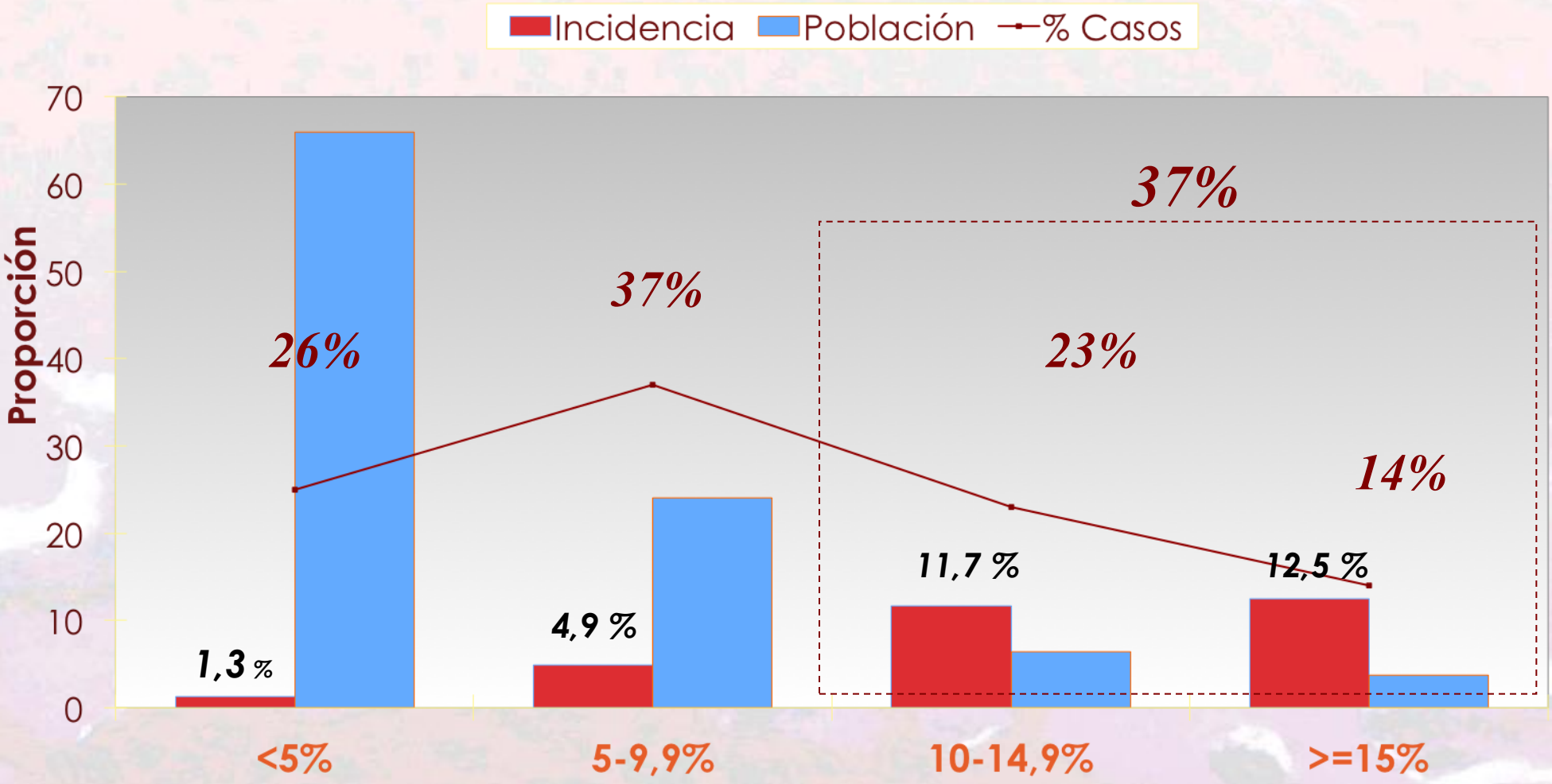
Cardiovascular risk functions

- Mathematical equations to estimate the probability of developing the disease in the future.
- This estimation is based on:
  - exposure to the different risk factors included in the function;
  - the effect size of the association between each risk factor and the disease;
  - the incidence rate of the disease in the population.

Riesgo REGICOR: Instrumento básico para el cribado poblacional

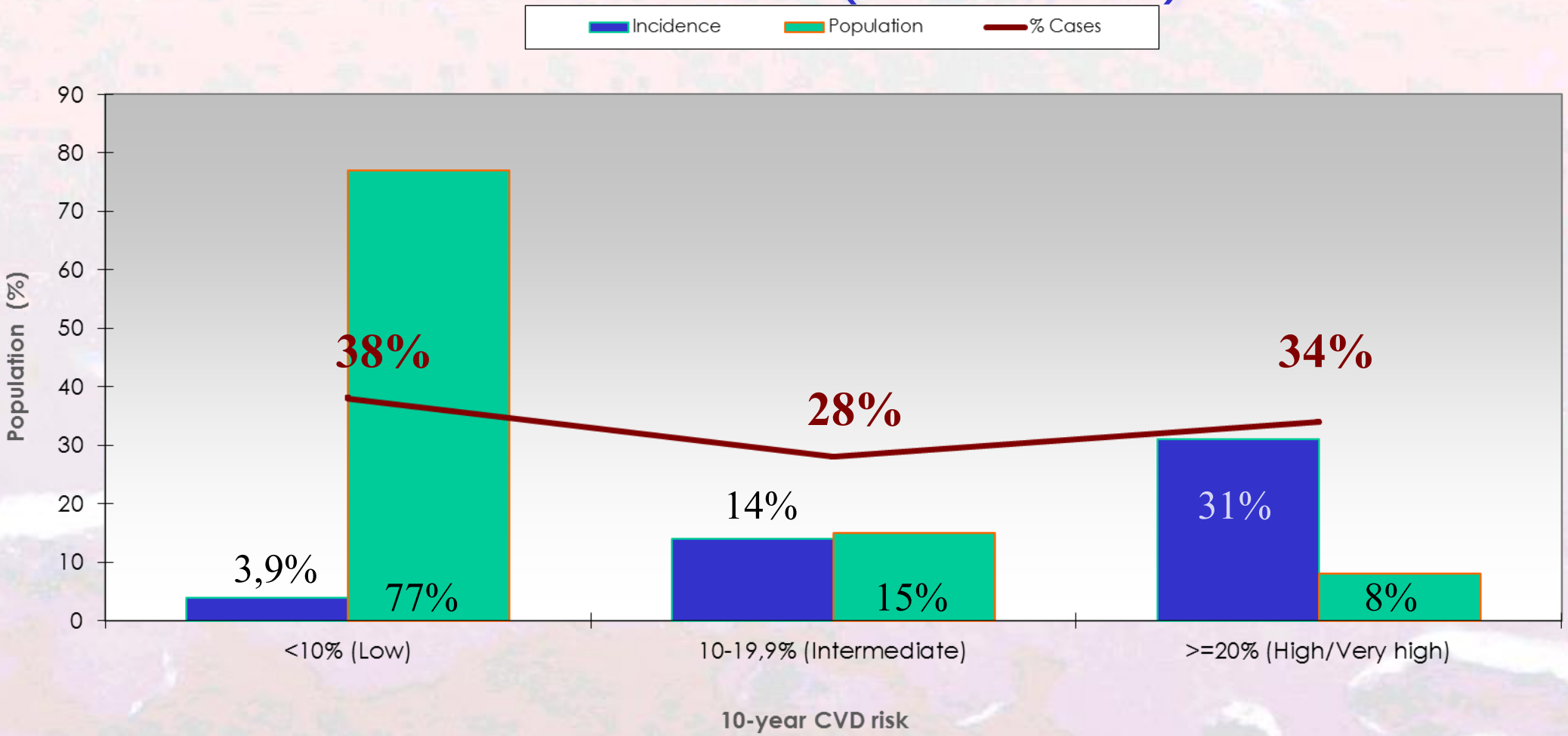


Riesgo coronario e incidencia de acontecimientos coronarios a 10 años en el estudio REGICOR (n=3724)

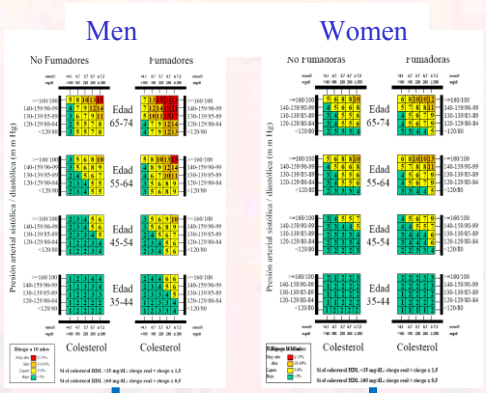


Marrugat J et al. Rev Esp Cardiol 2011; 64: 385-94

Coronary artery disease risk and 10-year CAD event incidence in the USA The Emerging Risk Factors Collaboration* (n=246,669)



The Emerging Risk Factors Collaboration. NEJM. 2012; 367: 1310-20.



CVD risk

Low

Moderate

High

?

Stimulate healthy lifestyles, appropriate weight and follow-up

RECLASSIFICATION

Intensive intervention on risk factors

Posibles factores para la reclasificación de candidatos a prevención CV primaria

- Proteína C reactiva -as > 1g/l, Lp(a) > 30 UI
- Historia familiar de ECV precoz,
- Obesidad (IMC > 30), o cintura > recomendaciones,
- Microalbuminuria o insuficiencia renal,
- Dieta inadecuada (cuestionario corta auto-administrado)
- Ejercicio insuficiente (cuestionario corta auto-administrado)
- Perfil genético adverso (predisposición/carga genética)

- Grosor de la íntima media Carotidea
- Indice tobillo brazo
- Calcio intracoronario

Enfermedad subclínica

Evaluación de un biomarcador

Prueba de concepto—Se asoci… de presentar la enfermedad?

Estudios de asociación, caso-control: OR

Validación prospectiva—Predice la … enfermedad en el seguimiento d…?

Estudios de cohorte poblacional: RR, estadígrafo c

Valor añadido—Mejora la capacidad predi… s funciones clásicas?

Estudios de cohorte poblacional: mejora estadígrafo c, reclasificación NRI

***Circulation* 2009;119;2408-2416;**

Evaluación de un biomarcador

Utilidad clínica—L[illegible]mplican cambi[illegible]

Acontecimientos clín[illegible] de acon[illegible]

Coste-efectividad—Está justifica[illegible]oste adicional de la determinación [illegible]biomarcador?

Estudios base poblacional: beneficio neto, curvas de decisión

Ensayo clínico: eficacia de la utilización del Biomarcador en la reducción de la incidencia

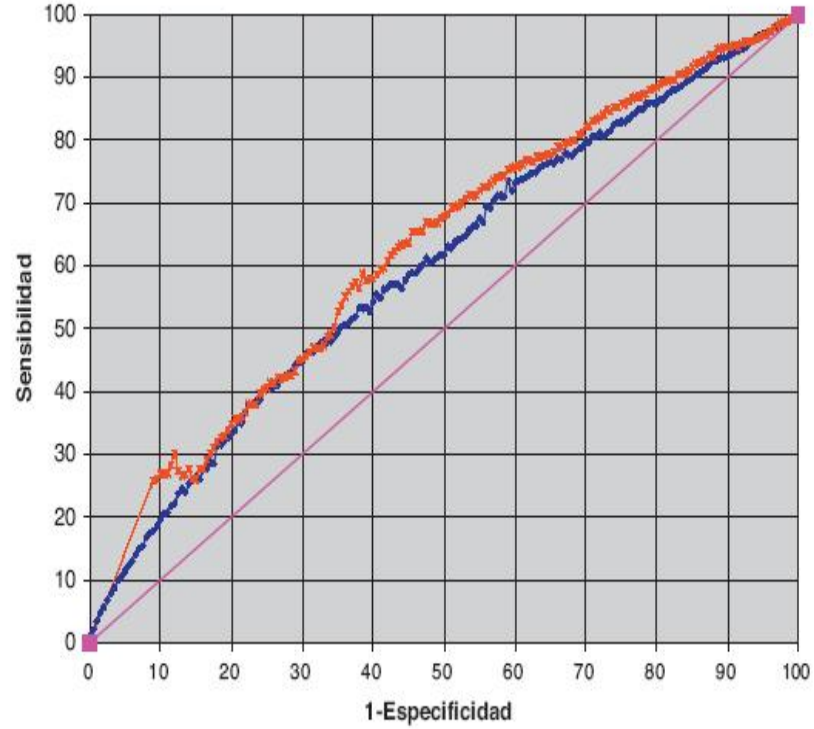
Estudios de coste-efectividad

***Circulation* 2009;119;2408-2416;**

Calcio intracor

Added value of CA
cardiovascular ev

Sanne A. E. Peters, Marina Bakker, He
Julius Center for Health Sciences and Prim



- Mejora estadígrafo c
  - Mejora del estadígrafc

- Mejora reclasificación (4 estudios)
  - NRI: 14 – 25%

Peters SAE et al. Eur J Clin Inv 2011 (DOI: 10.1111/J.1365-2362.2011.02555.x)

Some advantatges of determining the cardiovascular risk genotype over other biomarkers

Genetic characteristics :

- Does not change with age or sex
- Does not change with food
- Does not change with drugs
- Does not have intra-individual variability
- Need to be determined only once in life (or until new markers are found)
- Can be incorporated to CV risk functions

$$\text{prob}(\text{event}_i \mid \text{CRF}_{p,i}, \text{SNP}_{j,i}) = 1 - \widehat{S}^{\exp\left[\sum_{p=1}^{P}\beta_{\text{CRF}_p} * \text{CRF}_{p,i} + \sum_{j=1}^{J}\beta_{\text{SNP}_j} * \text{SNP}_{j,i} - \sum_{p=1}^{P}\beta_{\text{CRF}_p} * \overline{\text{CRF}_P} - \sum_{j=1}^{J}\beta_{\text{SNP}_j} * \overline{\text{SNP}_j}\right]}$$

REGICOR, Framingham, PROCAM, QRISK, SCORE

- Proof of concept—Do novel genetic markers, non associated with classical risk factors, differ between subjects with and without CHD?
  - In silico case-control study: on the Wellcome Trust Case Control Consortium public data

- Prospective validation—Incremental value:
  - Cohort studies:
    - REGICOR + Framingham
    - …

Hlatky MA et al. Circulation 2009;119:2408-16.

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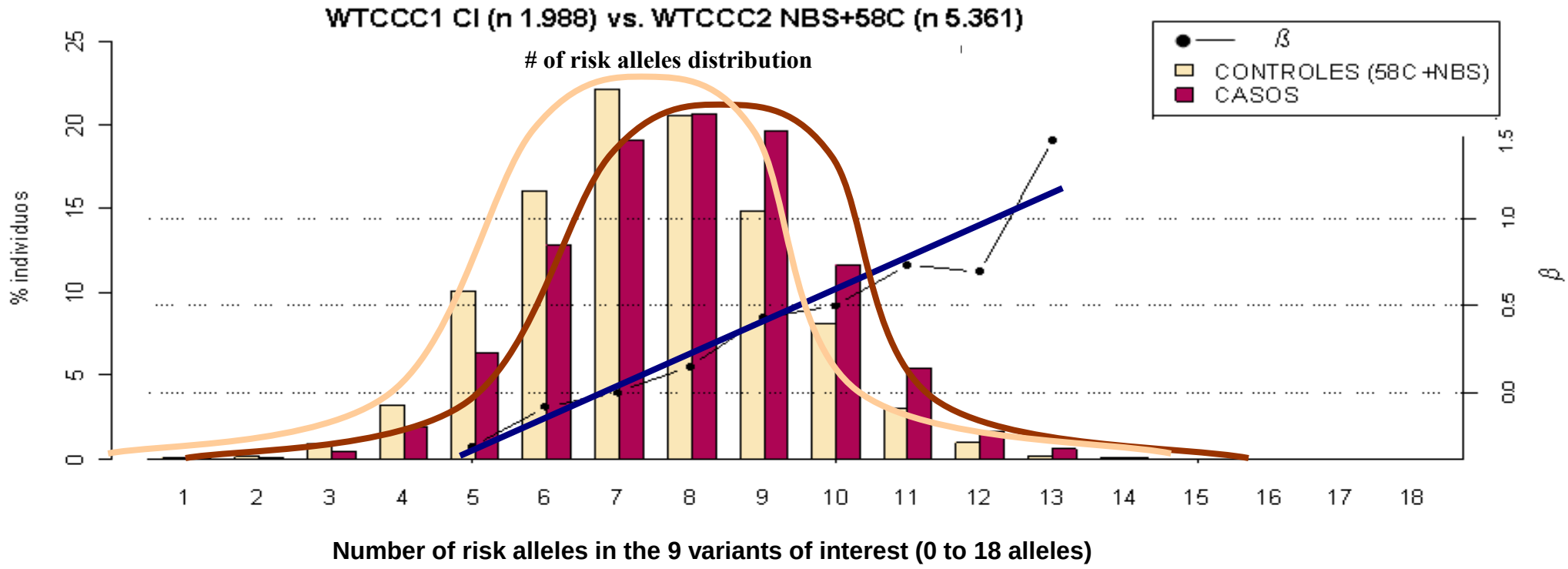
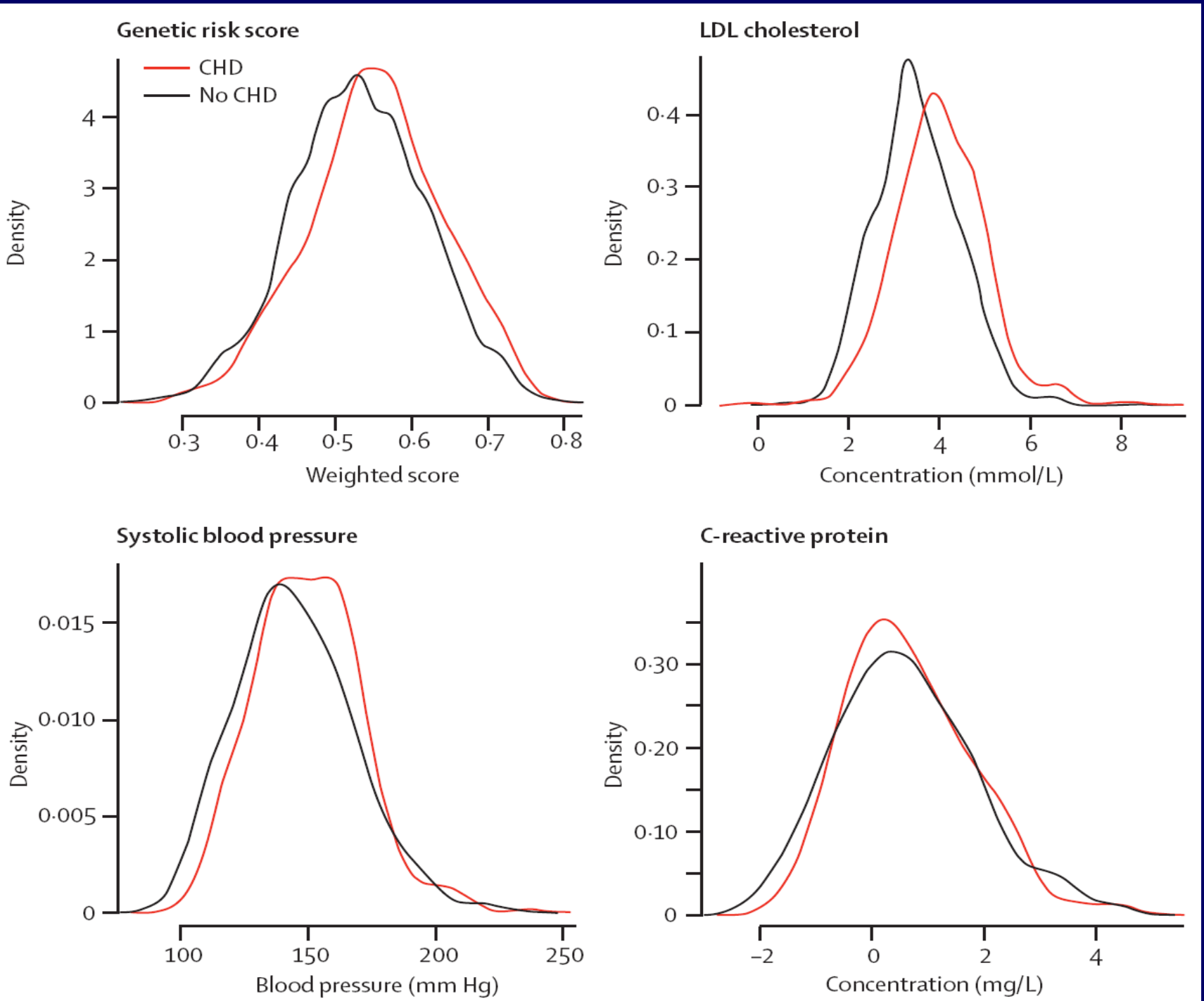
Distribution of the number of alleles in the Welcome Trust CHD cases and controls consortium



OR per allele = 1.18

Lluis-Ganella C. REC 2010;63(8):925-33



Ripatti S et al. Lancet 2010;376:1393–400

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Hlatky MA et al. Circulation 2009;119:2408-16.

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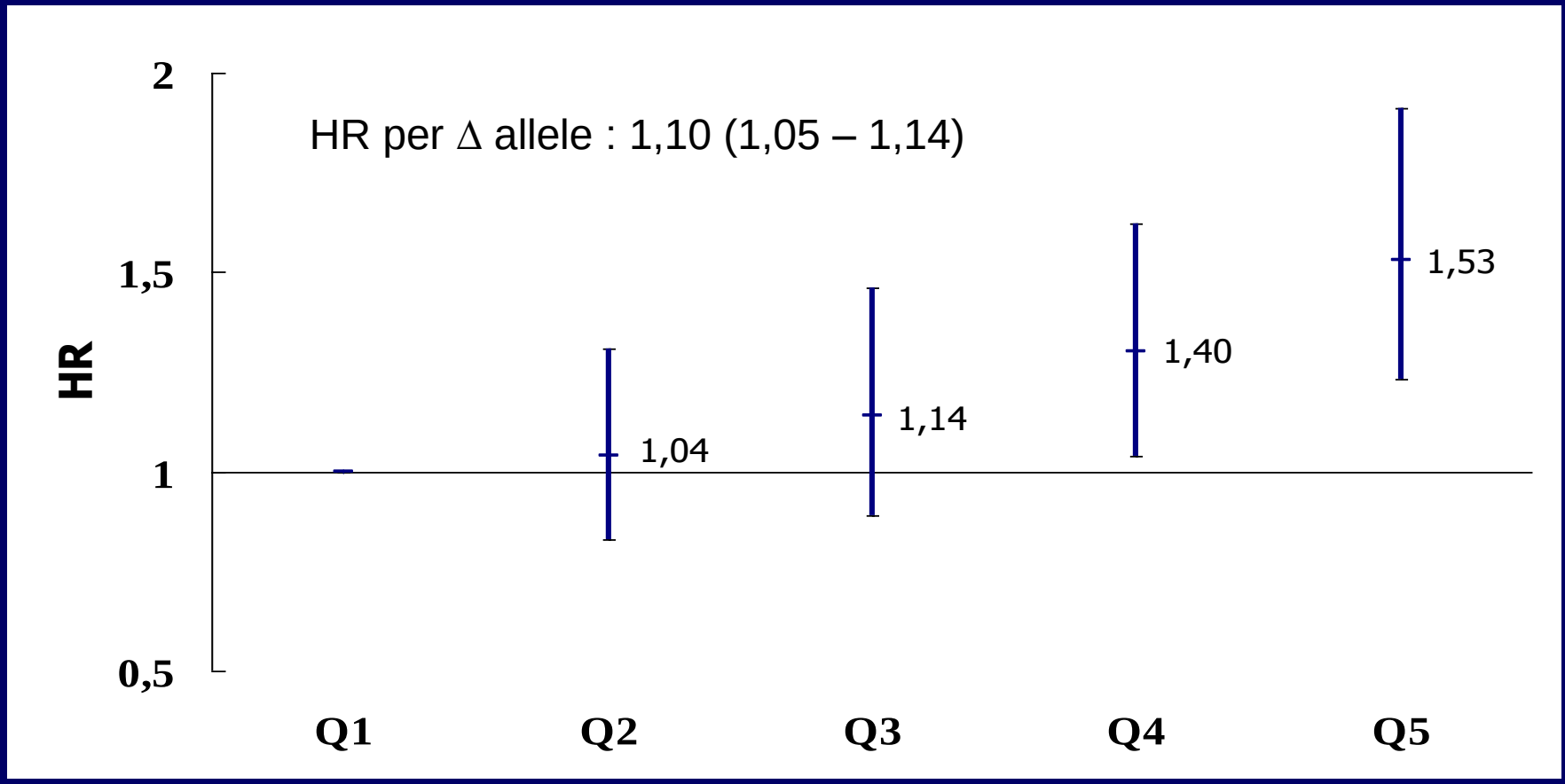
Quintiles of genetic risk score and 10-year CHD incidence Meta-analysis of the REGICOR, Spain & Framingham, US, separate cohorts (Preliminary results)



Coronary events

REGICOR

Classical risk factors + Genetic Score

Classical risk factors	Low risk	Intermediate-low risk	Intermediate-high risk	High risk
Cases				
Low risk	24	6	0	0
Intermediate-low risk	1	22	8	1
Intermediate-high risk	0	4	10	5
High risk	0	0	1	21
Non-cases				
Low risk	1415	105	1	0
Intermediate-low risk	115	339	64	9
Intermediate-high risk	0	36	69	30
High risk	0	5	20	40

Framingham

Classical risk factors + Genetic Score

Classical risk factors	Low risk	Intermediate-low risk	Intermediate-high risk	High risk
Cases				
Low risk	60	11	0	0
Intermediate-low risk	7	36	5	0
Intermediate-high risk	0	4	30	9
High risk	0	0	8	84
Non-cases				
Low risk	2014	50	0	0
Intermediate-low risk	57	444	49	1
Intermediate-high risk	0	47	207	30
High risk	0	0	34	350

	REGICOR-Spain		**FRAMINGHAM**		**Meta-analysis**	
	All	Interm Risk	All	Interm Risk	All	Interm Risk
NRI for CHD (%)	12	**25**	3	**14**	6	**17**

Life-time CV risk representation (35 to 74 y) by REGICOR risk function with CRF and with CAD genetics alone

$$\text{prob}(\text{event}_i \mid \text{CRF}_{p,i}, \text{SNP}_{j,i}) = 1 - S_0^{\exp\left[\sum_{p=1}^{P} \beta_{\text{CRF}_p} * \text{CRF}_{p,i} + \sum_{j=1}^{J} \beta_{\text{SNP}_j} * \text{SNP}_{j,i} - \sum_{p=1}^{P} \beta_{\text{CRF}_p} * \overline{\text{CRF}_p} - \sum_{j=1}^{J} \beta_{\text{SNP}_j} * \overline{\text{SNP}_j}\right]}$$

REGICOR, Framingham, PROCAM, QRISK, SCORE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P Solanas, I Ramió, M Piqué, M Sirera, B Camps

CHD/CVD screening

- Population — ✓**Risk charts: screening basic system**
- Individuals — ✓ **First level of Reclassification**
  - ✓Biomarkers
  - ✓Genetic predisposition
- Individuals — ✓**Second level of reclassification**
  - ✓Exercise test, ABI, C-IMT
  - ✓Non-invasive angiography
- Patients — ✓**Diagnostic Confirmation**
  - ✓Coronary angiography
- Patients — ✓**PCI / other revascularization**

Simplified figure for potential use of emerging risk factors and imaging techniques in CV primary prevention