

A SMARTool project workshop

# CAD RISK PREDICTION AND STRATIFICATION: THE ICT APPROACH

## Omics and coronary atherosclerosis

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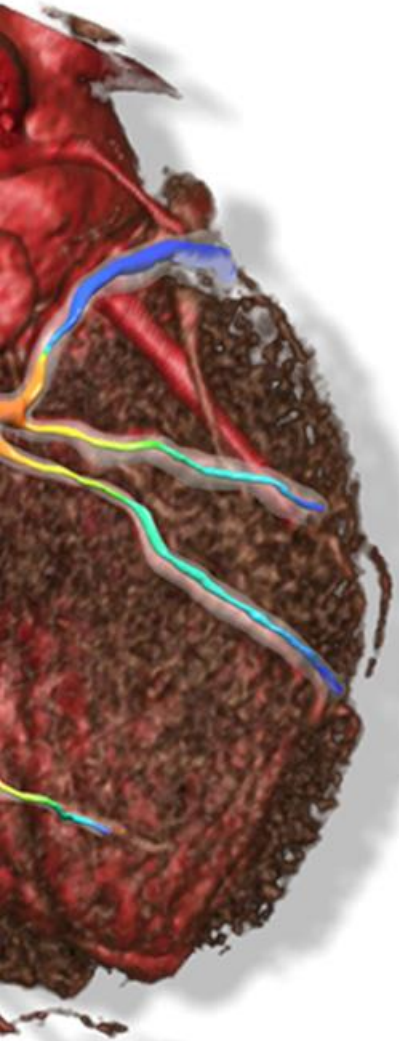
Centro Scienze dell'Invecchiamento e Medicina  
Traslazionale CESI-Met

Università "G. d'Annunzio" Chieti

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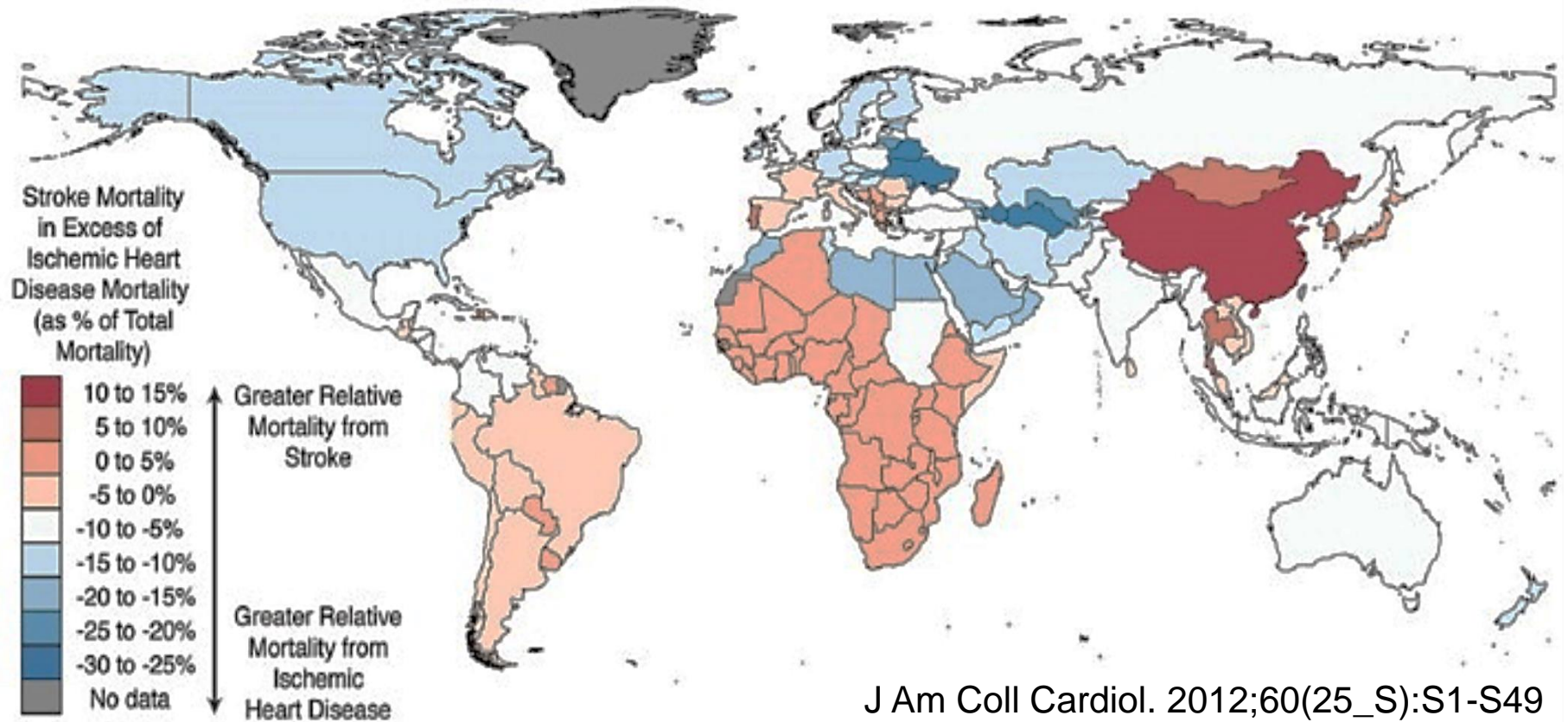
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Horizon 2020  
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# Geographic Distribution of Relative Mortality From Stroke and Coronary Heart Disease

Despite aggressive strategies are now available to reduce CV risk factors, the risk of cardiovascular events around the world remains substantial



# Coronary Artery Disease

- Chronic inflammatory process in arterial walls , which ends with the accumulation of atheromatous plaques in the walls of the coronary arteries.
- Chronic atherosclerosis may lead to:
  - Stenosis and claudication
  - Plaque rupture and thrombosis
  - Clinical manifestations of CAD: myocardial infarction (MI), unstable or sudden cardiac death in ~50% of individuals with the pathology



# Subclinical coronary atherosclerosis

- **Prevalence:** 36% in women and 38.7% in men > 65 years
- **Increased prevalence** in specific subgroups of patients: postmenopausal women, women with a family history of premature CHD, European Americans as compared with African Americans, persons with metabolic disorders (diabetes)
- **There is association between the presence of asymptomatic atherosclerosis and risk of cardiovascular events**

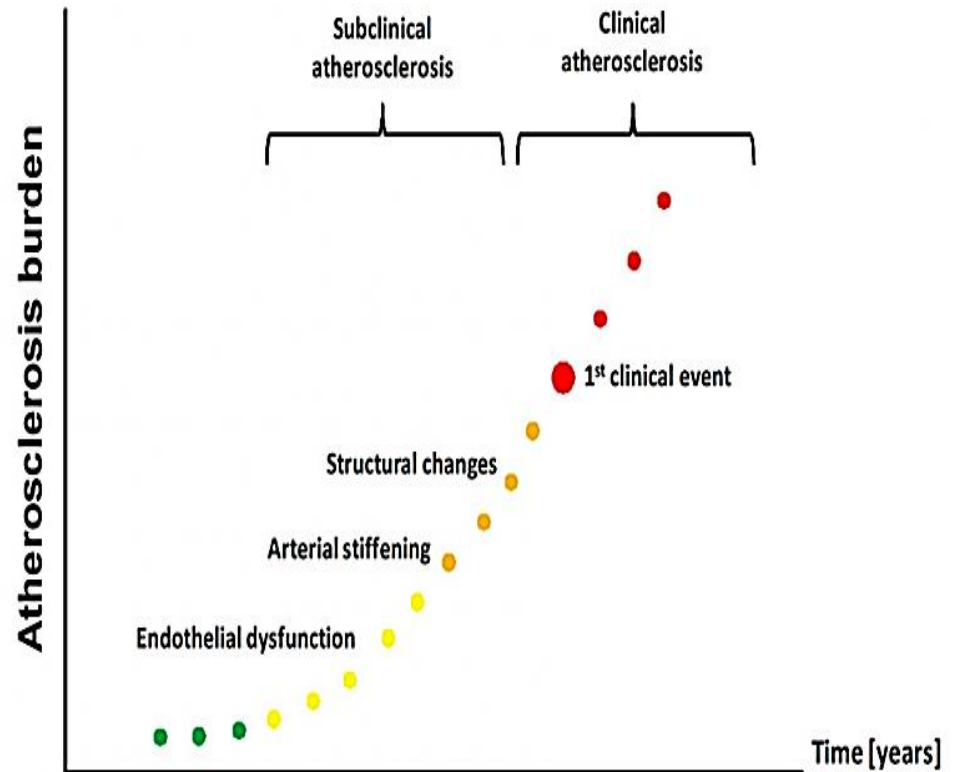
# What is subclinical coronary atherosclerosis

- Atherosclerotic lesions without manifestation of disease
- Subclinical atherosclerosis is characterized by:

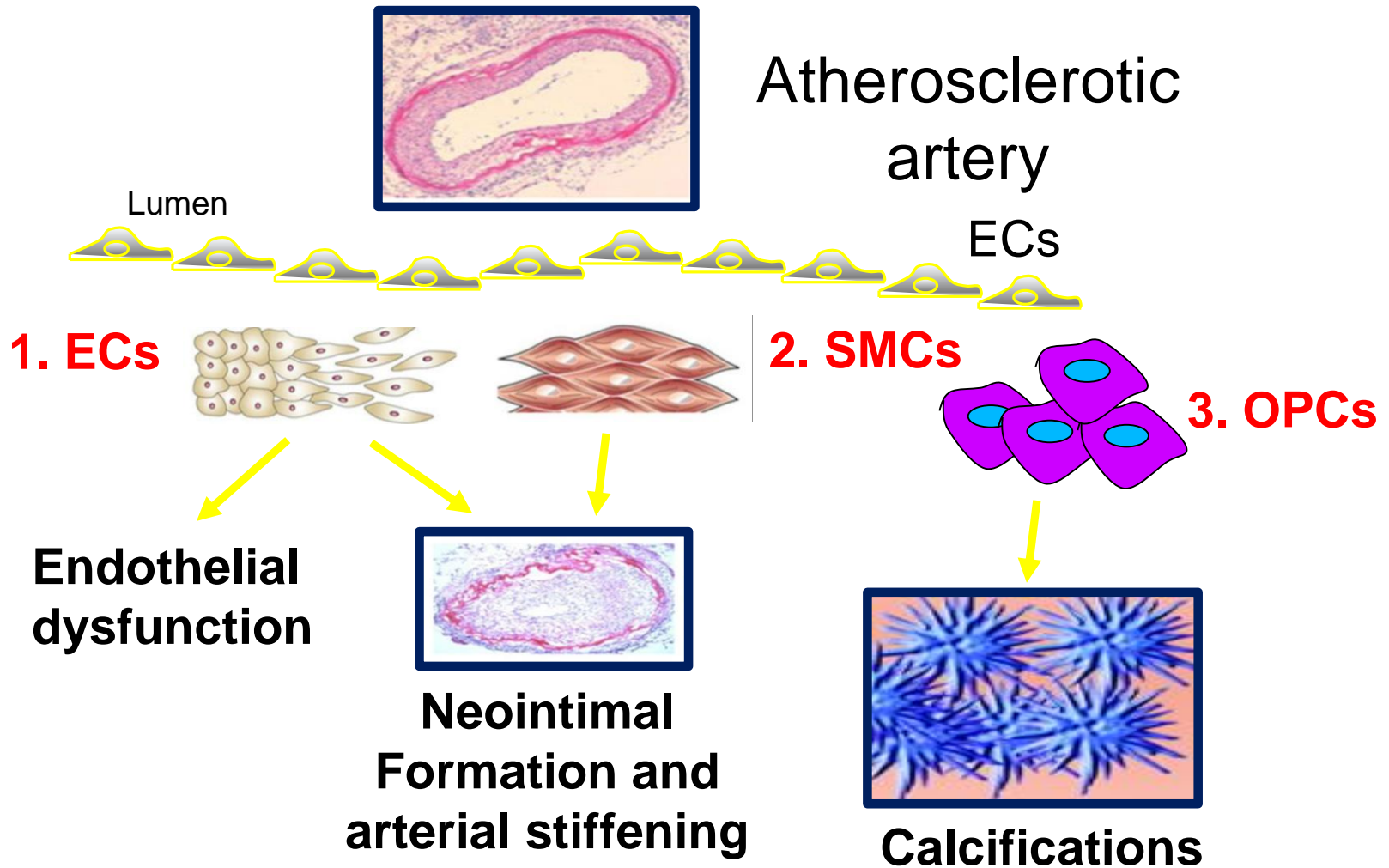
1. Endothelial dysfunction
2. Arterial stiffening
3. Calcium deposition in the tunica media and intima of large and medium-size arteries

**Coronary arteries:** intimal calcified nodules, which contribute to destabilize the plaque

**Peripheral arteries:** medial calcification and arterial stiffening

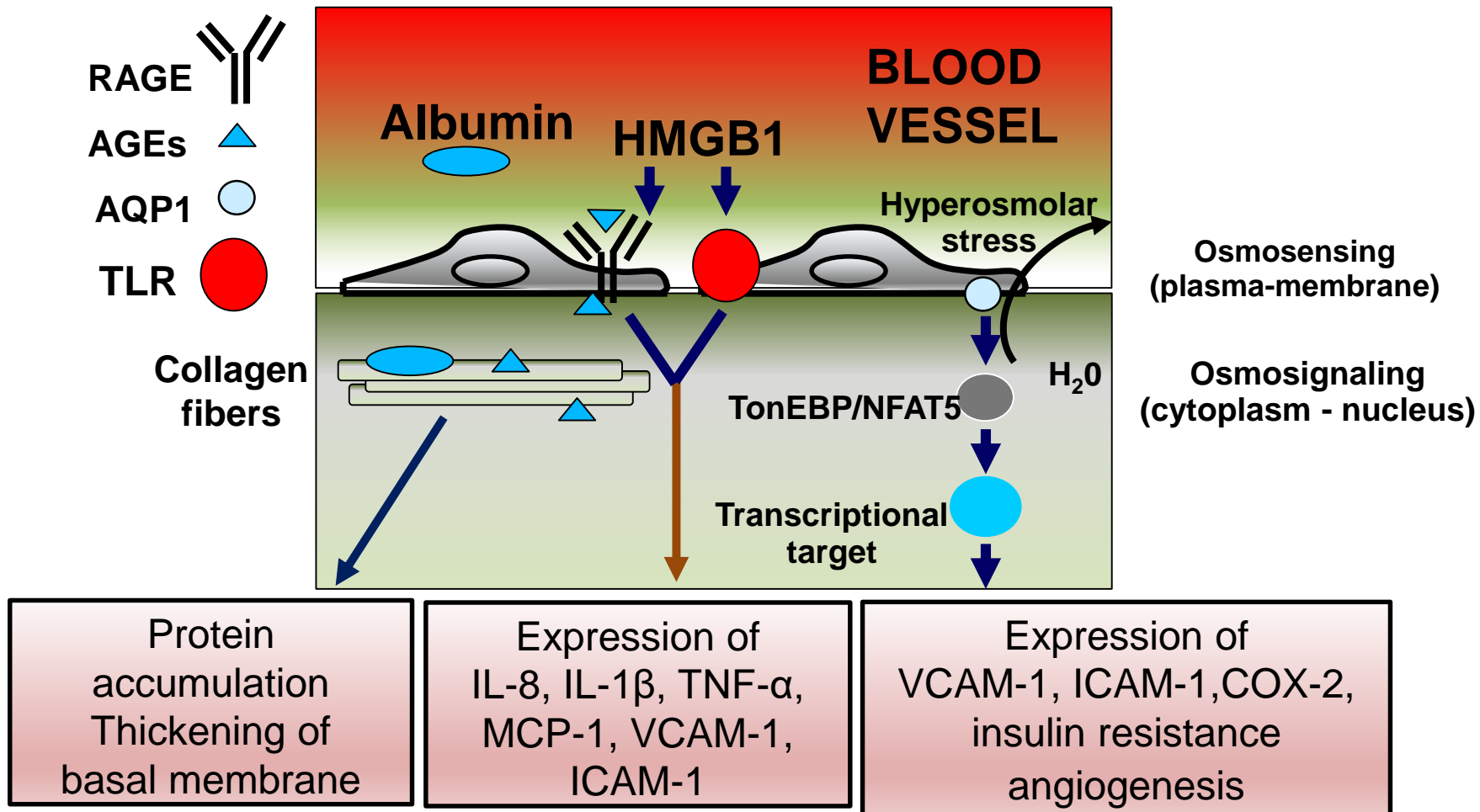


# Cellular targets of coronary atherosclerosis



Madonna, De Caterina et al Vasc Pharm 2018

# Molecular targets of coronary atherosclerosis in diabetes



Madonna, De Caterina et al Vasc Pharm 2018

# Assessment of subclinical atherosclerosis

- Cardiovascular risk assessment
- Detection of subclinical atherosclerosis



# When do I assess cardiovascular risk and how?

- The person is a middle aged smoker
- There is abdominal obesity
- One or more risk factors such as blood pressure, lipids or glucose is raised
- There is a family history of premature cardiovascular disease or of other risk factors
- There are symptoms suggestive of cardiovascular disease

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Systematic CV risk assessment is recommended in individuals at increased CV risk, i.e. with family history of premature CVD, familial hyperlipidaemia, major CV risk factors (such as smoking, high BP, DM or raised lipid levels) or comorbidities increasing CV risk.	I	C
It is recommended to repeat CV risk assessment every 5 years, and more often for individuals with risks close to thresholds mandating treatment.	I	C
Systematic CV risk assessment may be considered in men >40 years of age and in women >50 years of age or post-menopausal with no known CV risk factors.	IIb	C
Systematic CV risk assessment in men <40 of age and women <50 years of age with no known CV risk factors is not recommended.	III	C

ESC Guidelines. Eur Heart J 2016

# Detection of subclinical atherosclerosis

ECG

Echocardiogra

Scintigraphy

B-mode

MRI-Angiography

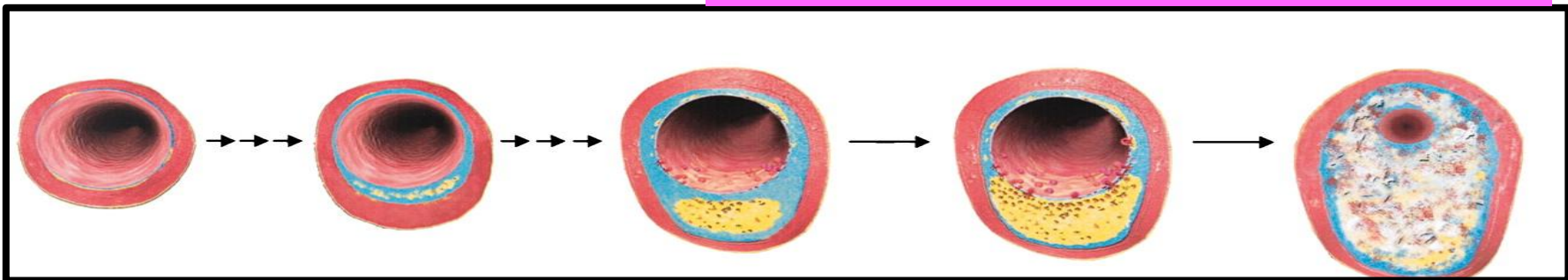
Electron bean CT/Contrast-enhanced multislice CT

IVUS

Coronary Angiography

Non-invasive methods

Invasive methods



Erbel et al HERZ. 2007



# Hyperglycemia, insulin resistance and hyperinsulinemia

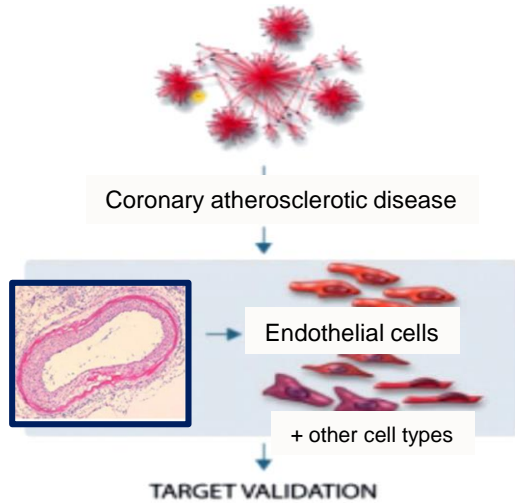
- Are associated with higher prevalence of atherosclerosis
- Are predictors of future cardiovascular events
- Are key players of atherosclerosis
- **Are associated with higher levels of surrogate subclinical atherosclerosis markers such as carotid intima-media thickness and coronary artery calcium score**

**Need for novel targets of  
subclinical coronary atherosclerosis,  
especially in high risk patients such as  
those with diabetes**

**Unbiased omics approach  
for target identification?**

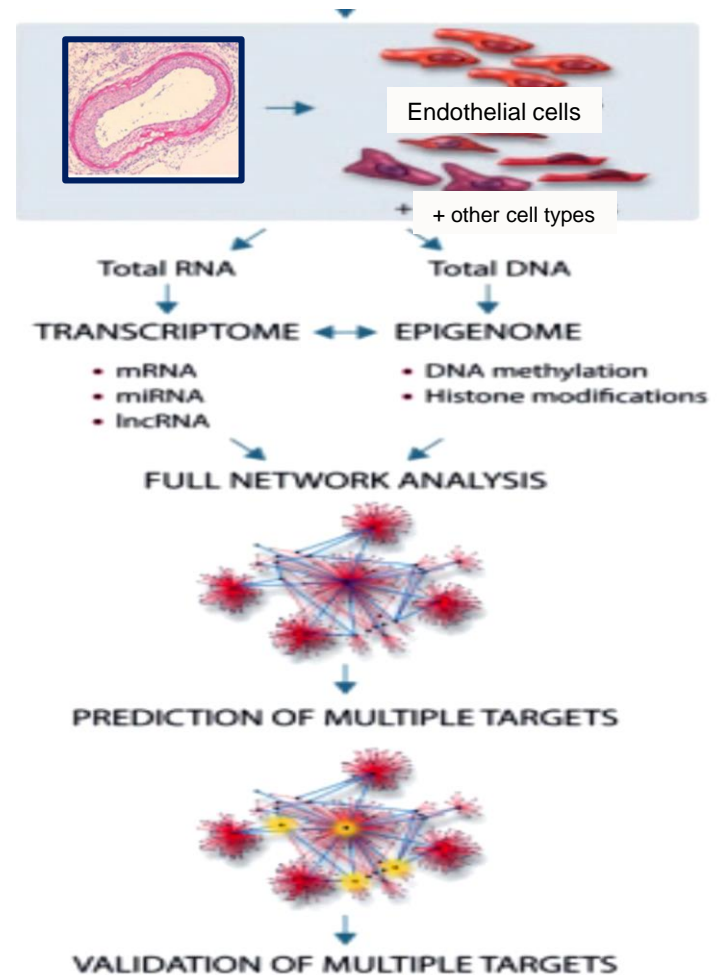
# Hypothesis-driven approach

## Biased target selection



# Unbiased «fishing» approach

## Coronary atherosclerosis



Cardiovascular Research (2017) 113, 725–736  
doi:10.1093/cvr/cvx070

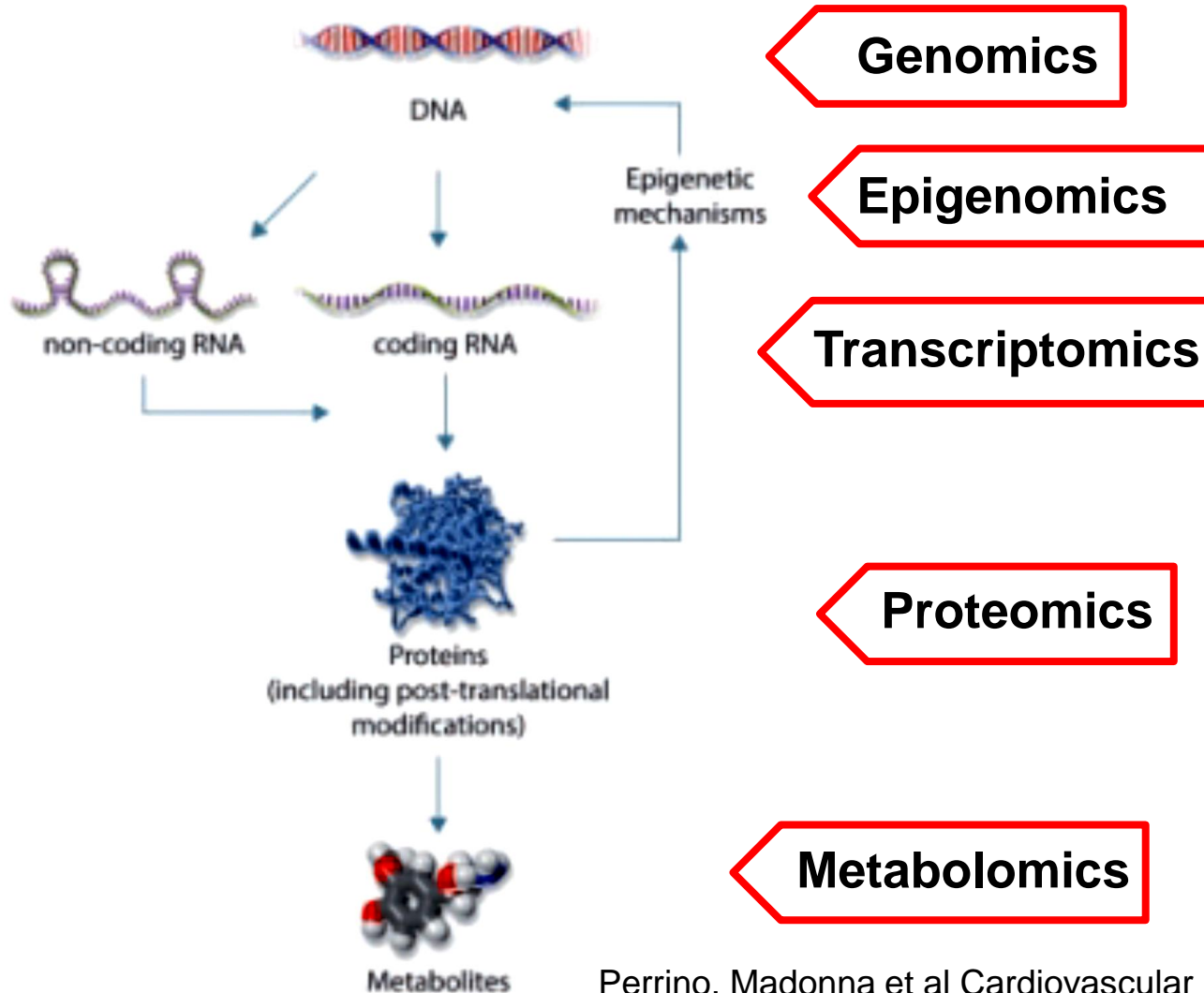
## Epigenomic and transcriptomic approaches in the post-genomic era: path to novel targets for diagnosis and therapy of the ischaemic heart? Position Paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart

Cinzia Perrino<sup>1</sup>, Albert-Laszlo Barabasi<sup>2,3,4,5</sup>, Gianluigi Condorelli<sup>6,7</sup>, Sean Michael Davidson<sup>8</sup>, Leon De Windt<sup>9</sup>, Stefanie Dimmeler<sup>10,11</sup>, Felix Benedikt Engel<sup>12</sup>, Derek John Hausenloy<sup>13,14,15,16,17,18</sup>, Joseph Addison Hill<sup>19</sup>, Linda Wilhelmina Van Laake<sup>20,21</sup>, Sandrine Lecour<sup>22</sup>, Jonathan Leor<sup>23,24</sup>, Rosalinda Madonna<sup>25,26</sup>, Manuel Mayr<sup>27</sup>, Fabrice Prunier<sup>28</sup>, Joost Petrus Gerardus Sluijter<sup>29</sup>, Rainer Schulz<sup>30</sup>, Thomas Thum<sup>31</sup>, Kirsti Ytrehus<sup>32</sup>, and Péter Ferdinandy<sup>33,34,35,40</sup>

Perrino, Madonna et al Cardiovascular Research 2017



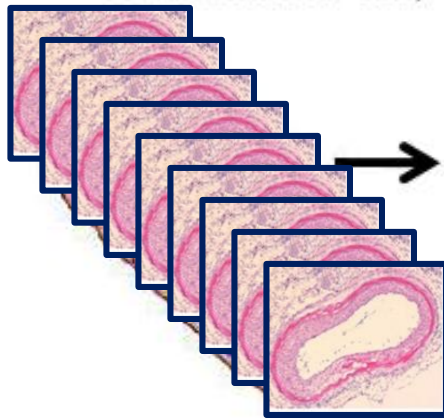
# OMICS tools for detection of subclinical atherosclerosis



Perrino, Madonna et al Cardiovascular Research 2017

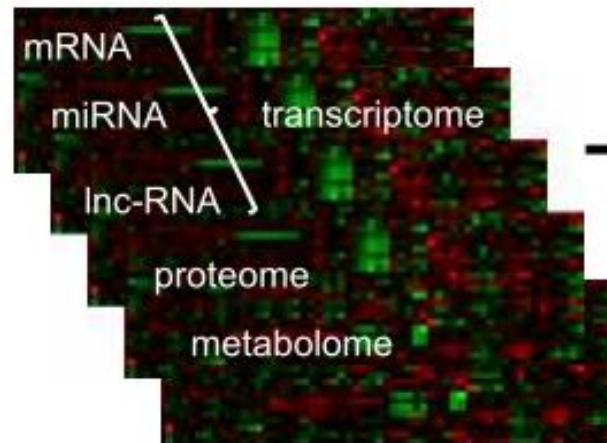
# Unbiased multi-omics for target finding

Multiple translational experimental interventions (ischemia, conditioning, comorbidity, comedications, etc.)



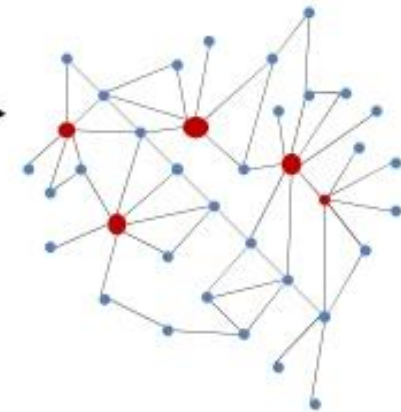
**Endothelial cell specific sampling**

Integrated „omics“



**Open access omics data**

Network analysis



**User friendly Bioinformatic tools**

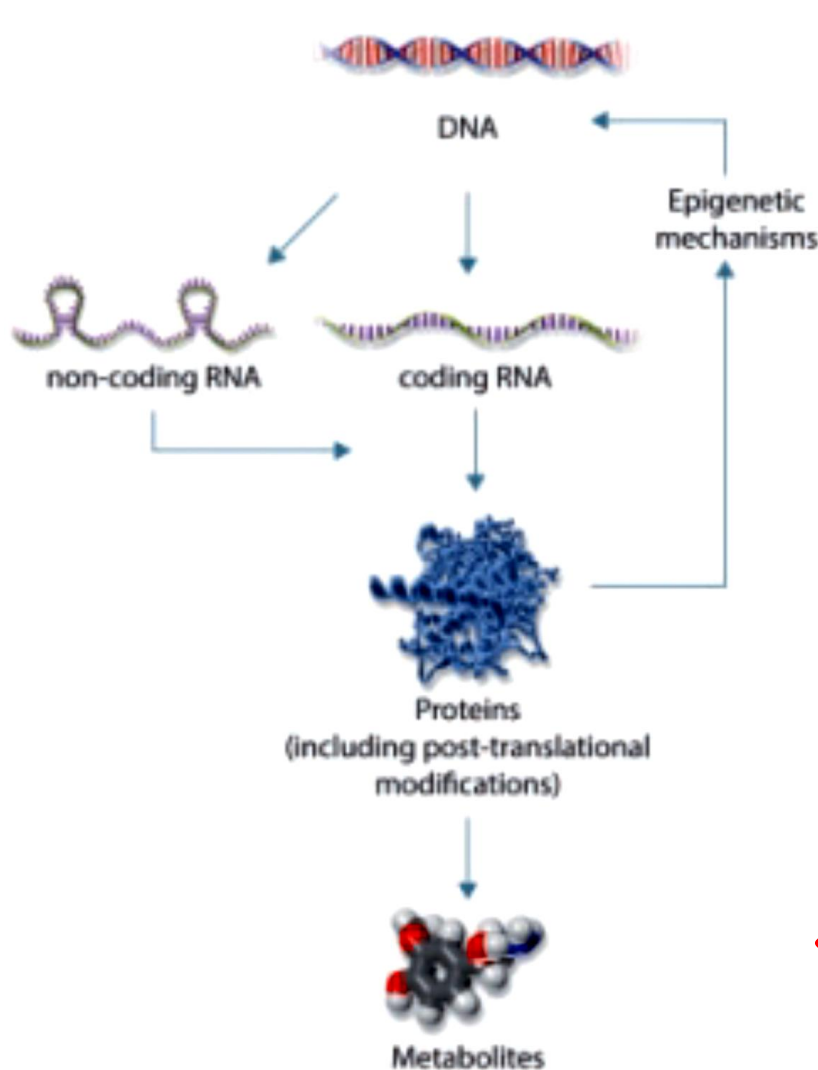
Perrino, Madonna et al Cardiovascular Research 2017

# Take home messages

The “omics” approach may offer novel and promising tools to detect endothelial genes and signaling pathways modulated by high glucose and hyperosmolar stress, with more robust and predictable approach to early detection of subclinical coronary atherosclerosis in high risk diabetic patients



# Drawbacks...



**Genomics**  
(therapeutic value?)

**Epigenomics**  
(no data so far)

**Transcriptomics**

**Proteomics**  
(technical problems)

**Metabolomics**  
(technical difficulties)

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