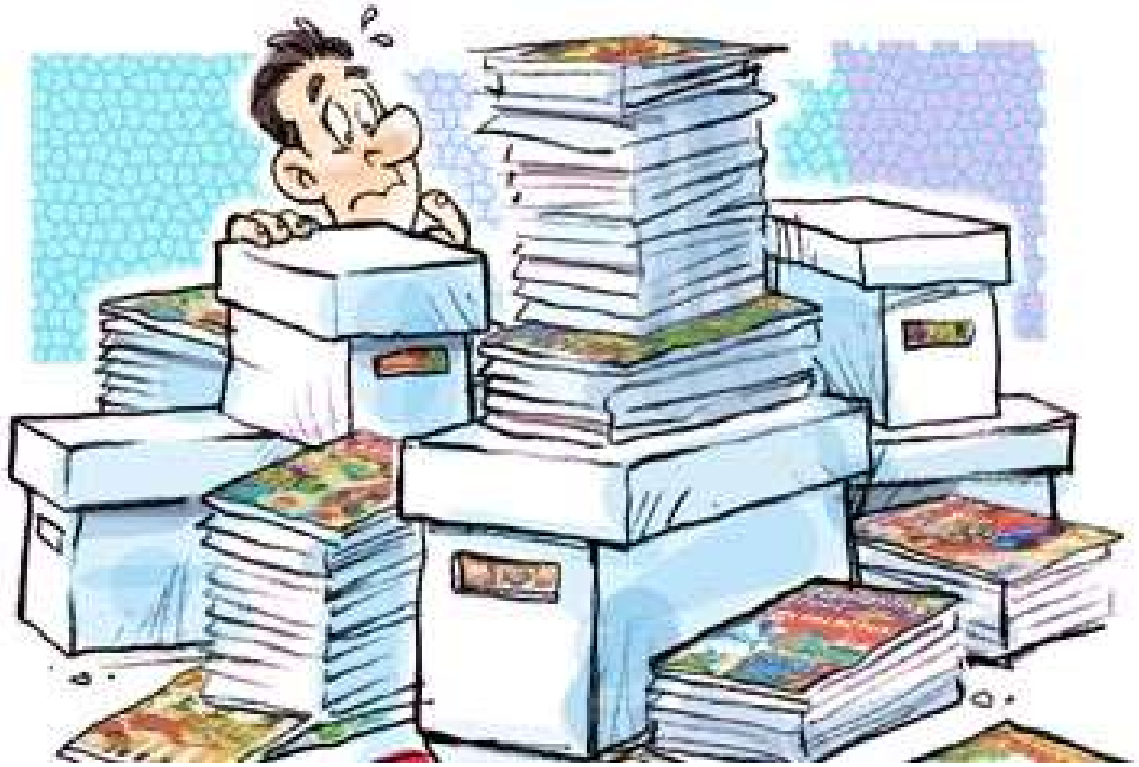
Evento ALDAI: «Prevenzione cardiovascolare»
Milano, 16 ottobre 2018

La prevenzione in ambito cardiovascolare oltre le linee guida: *dove siamo, cosa ci attende?*

Riccardo Bigi MD, PhD, EFESC
Centro Diagnostico Italiano, Milano



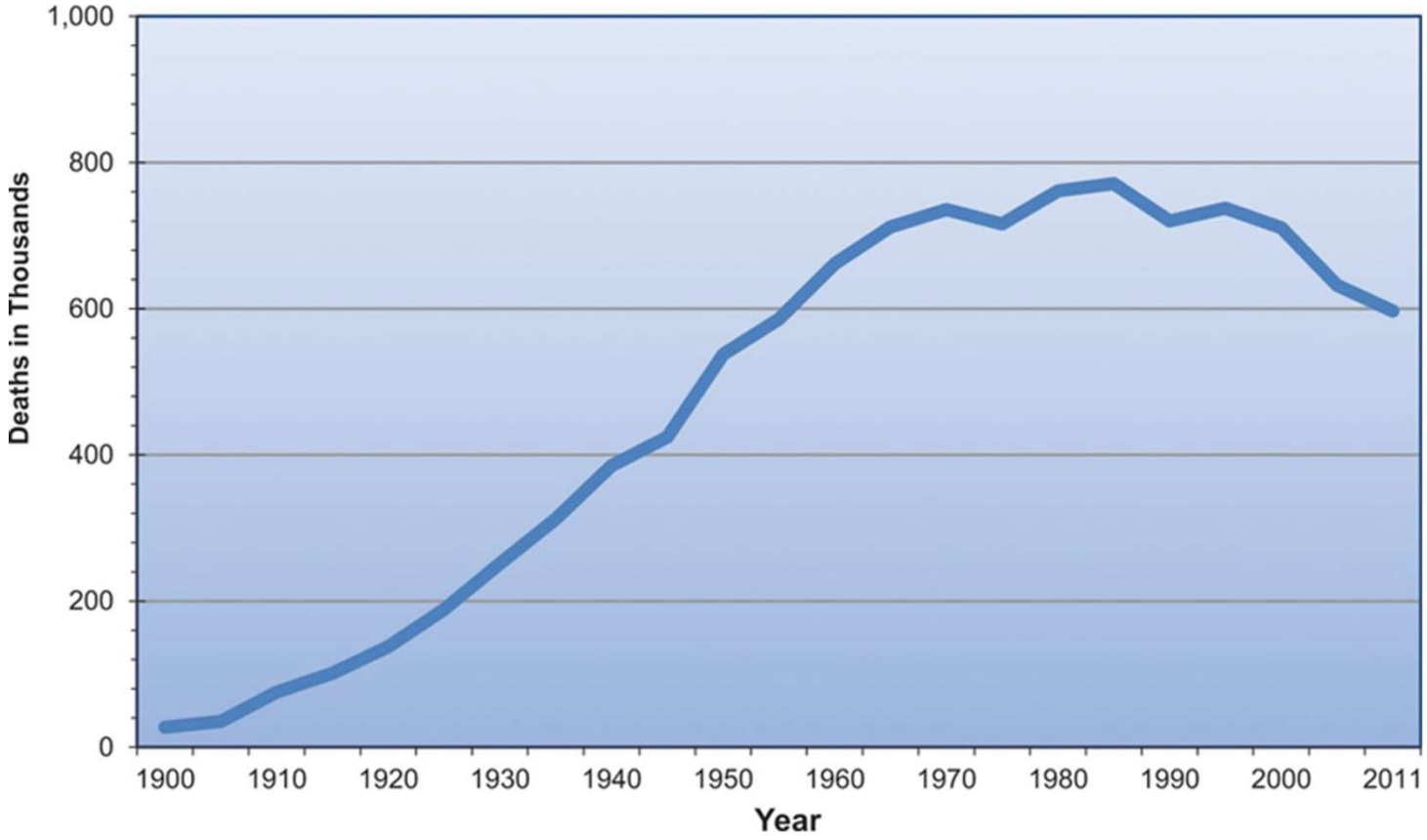
Le cose migliori della vita o sono illegali
o sono immorali o fanno ingrassare.

O. Wilde

Basi razionali della prevenzione CV

1. **Le malattie CV rappresentano la causa primaria di mortalità, morbidità e disabilità nei paesi avanzati**

Mortalità per malattie CV negli USA



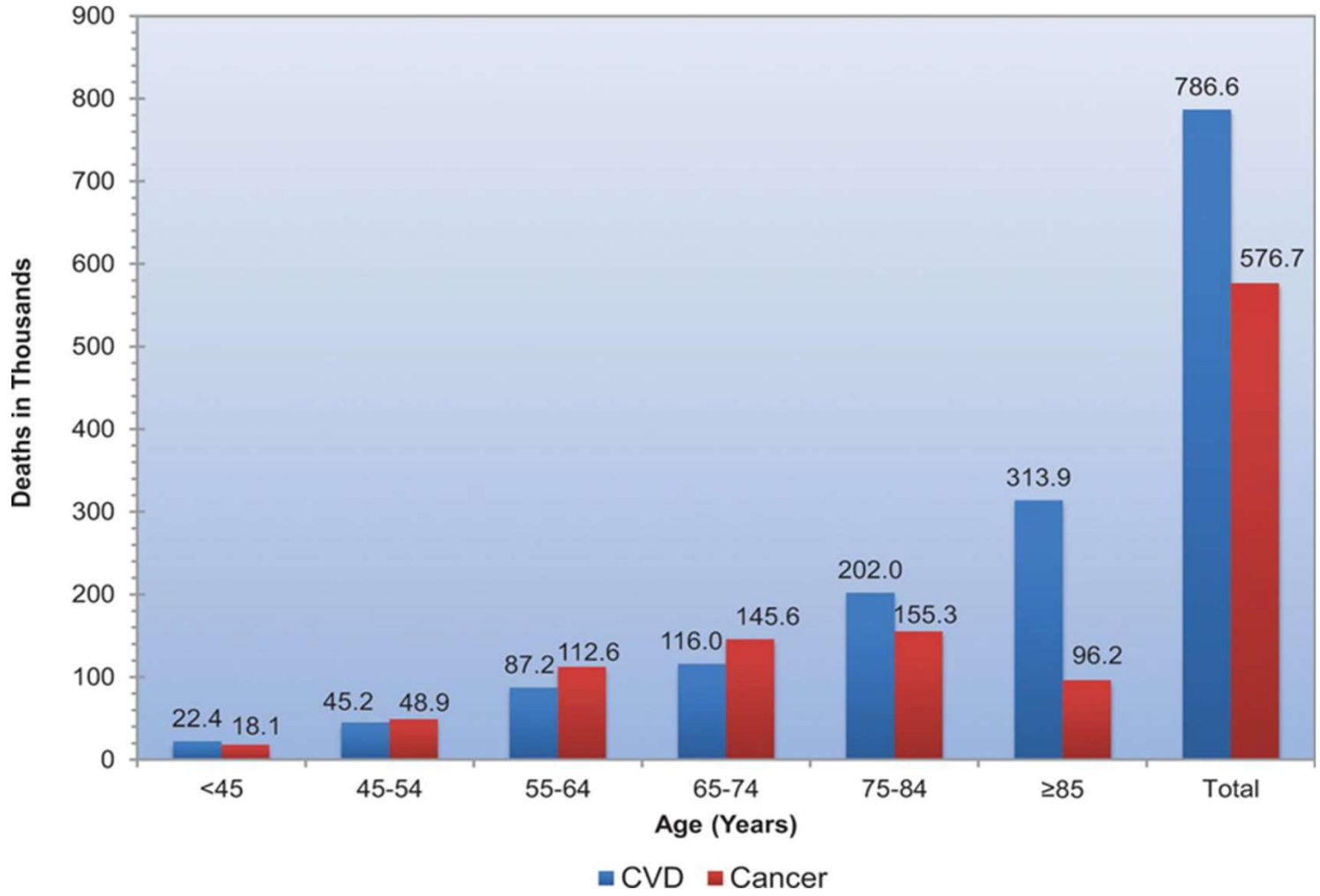
Mozaffarian D et al. Circulation. 2015;131:e29-e322

Mortalità per malattie CV

- Circa 735.000 americani subiscono un attacco cardiaco ogni anno. Per 525,000 di loro si tratta del primo episodio, mentre per 210,000 di una recidiva.
- Il 20% della popolazione americana è affetta da una patologia CV.
- In Europa, le malattie CV causano ogni anno oltre 4 milioni di decessi di cui circa 2 milioni nella sola UE.
- La patologia CV è causa del 47% della mortalità globale in Europa e del 40% di quella in UE.

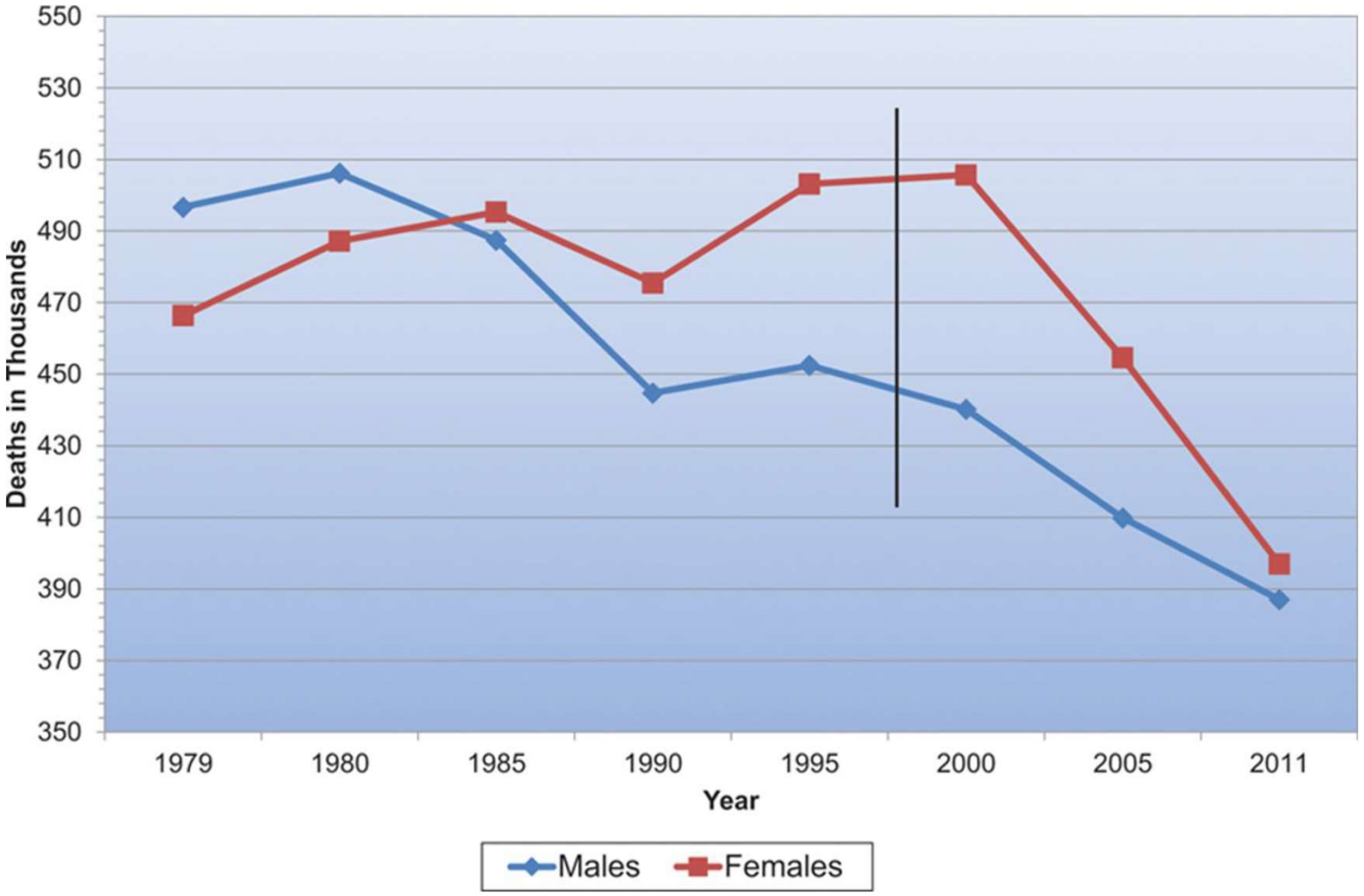
Mozaffarian D et al. Circulation. 2015;131:e29-e322

Confronto fra mortalità CV e per cancro in rapporto all'età



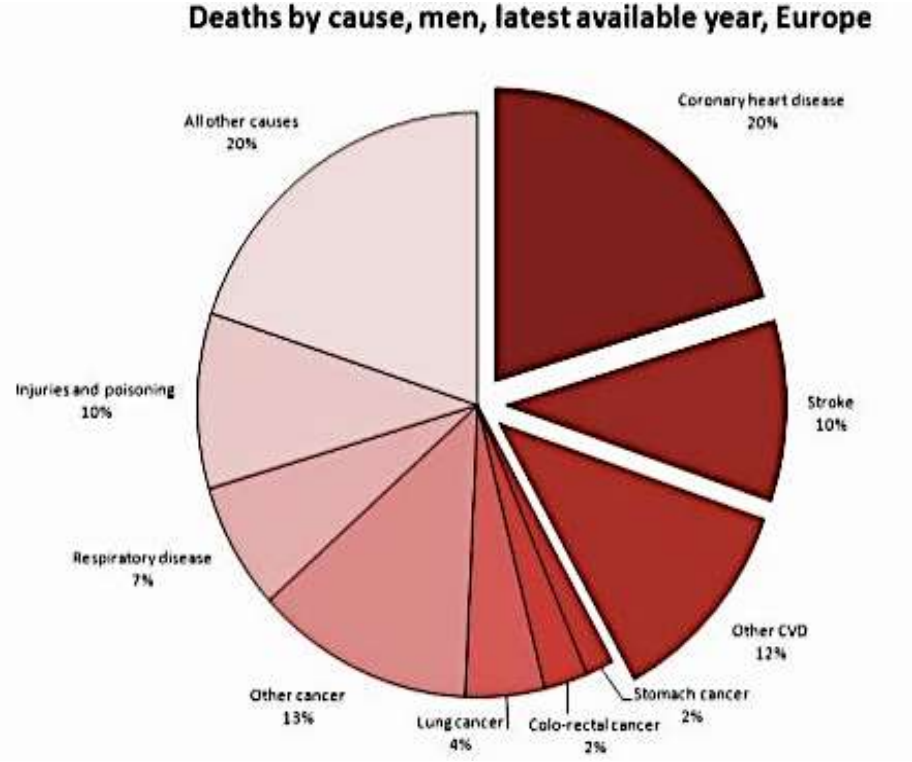
Mozaffarian D et al. Circulation. 2015;131:e29-e322

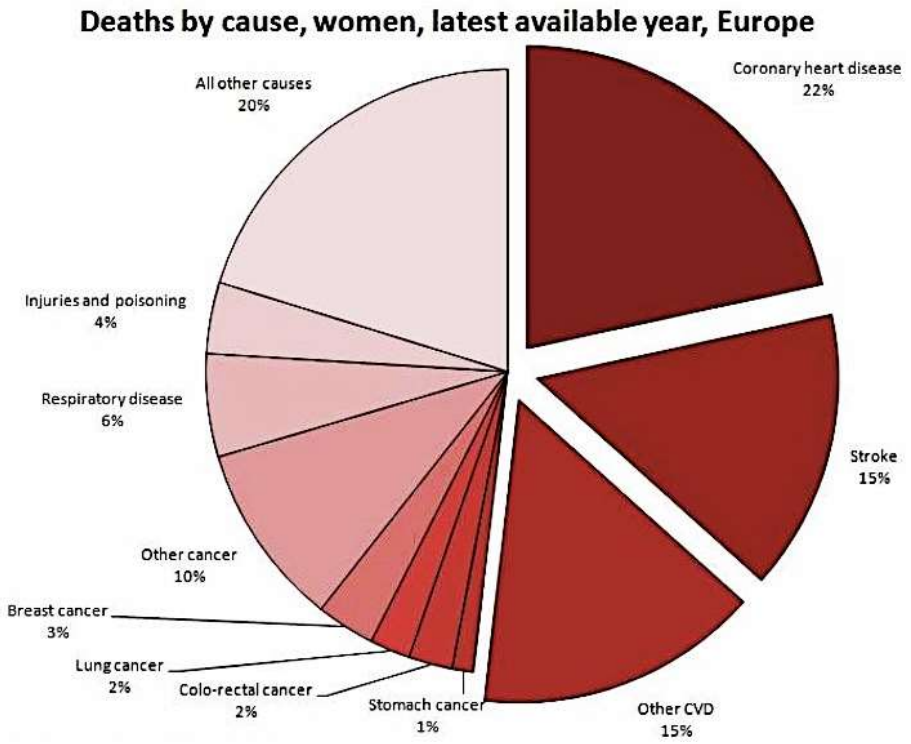
Andamento della mortalità CV per sesso negli USA



Mozaffarian D et al. Circulation. 2015;131:e29-e322

Cause di mortalità in Europa



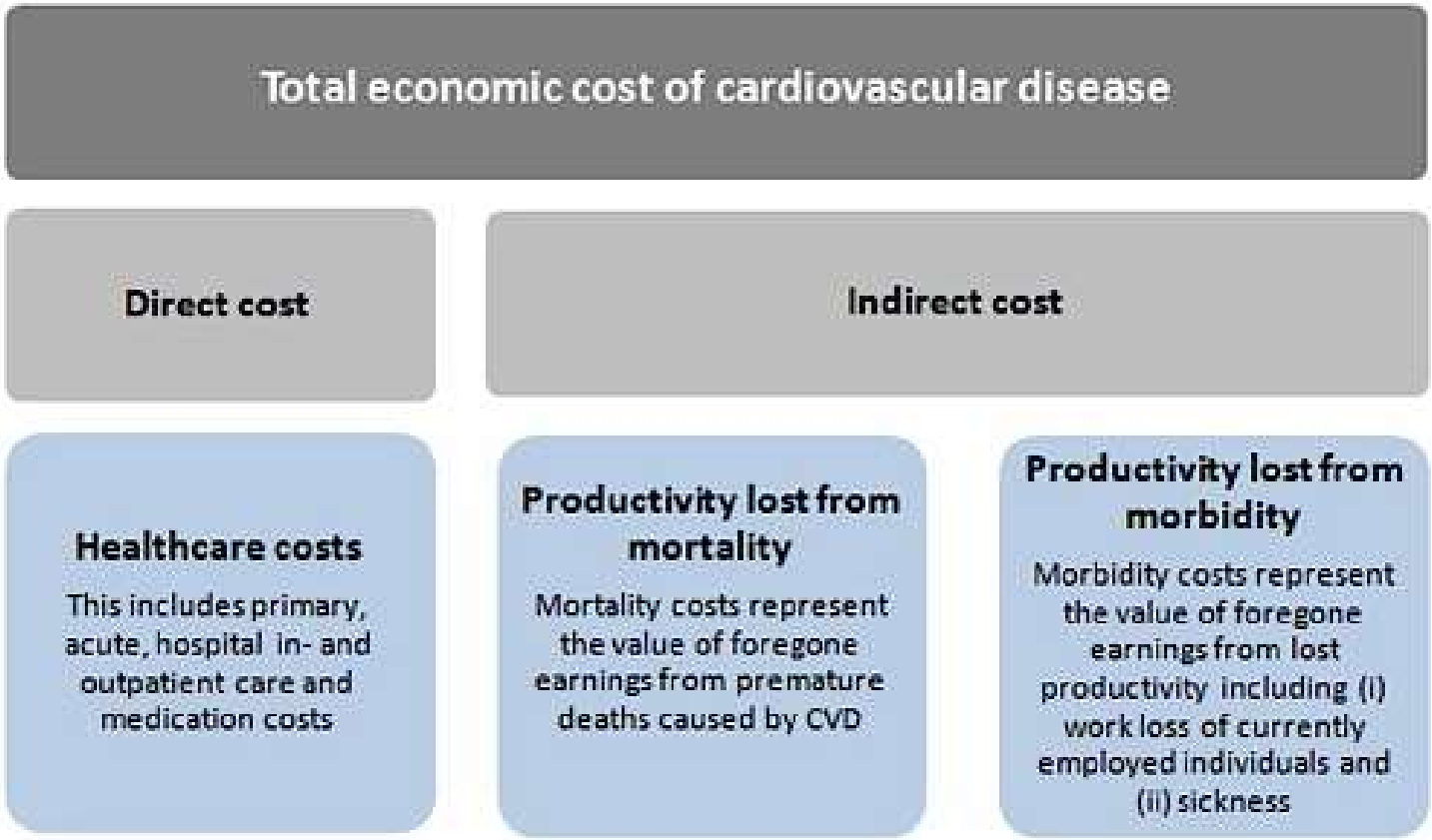


European Cardiovascular Disease Statistics 2012 ed., EuroHeart Survey II, ESC

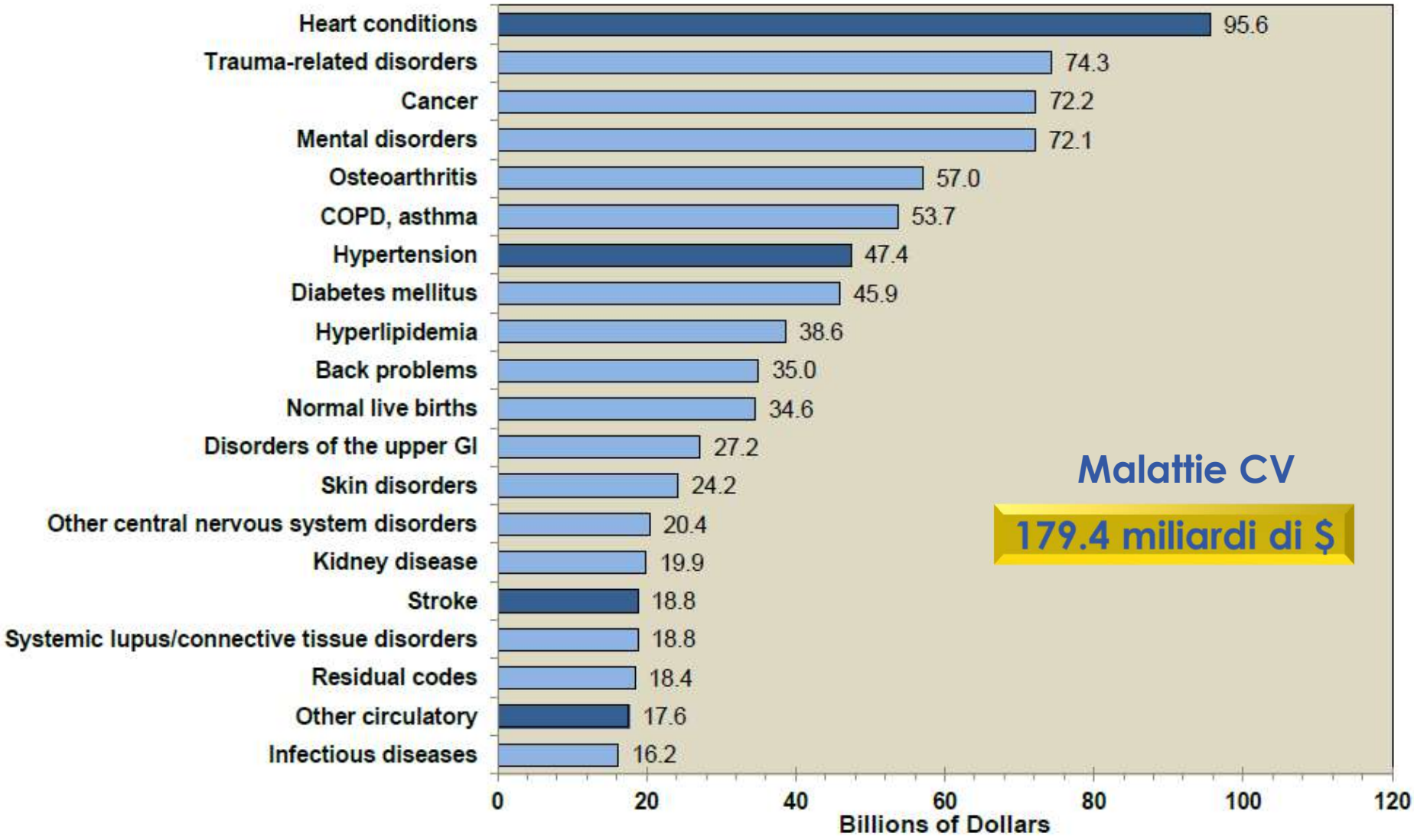
Basi razionali della prevenzione CV

2. **Le malattie CV rappresentano una fonte primaria di costi diretti ed indiretti per i sistemi sanitari**

Costi economici della patologia CV

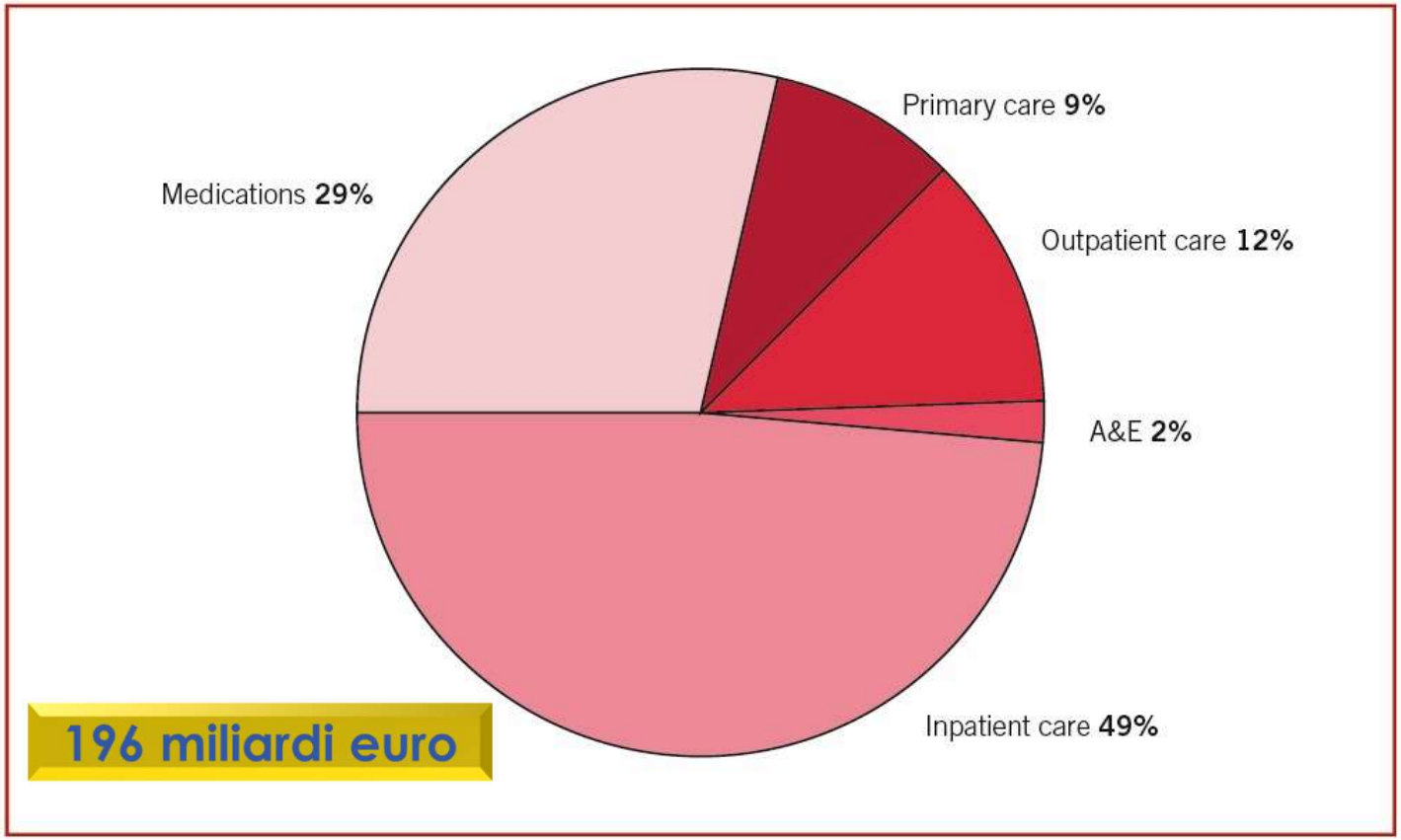


Costi diretti dell'assistenza sanitaria negli USA (miliardi di $)



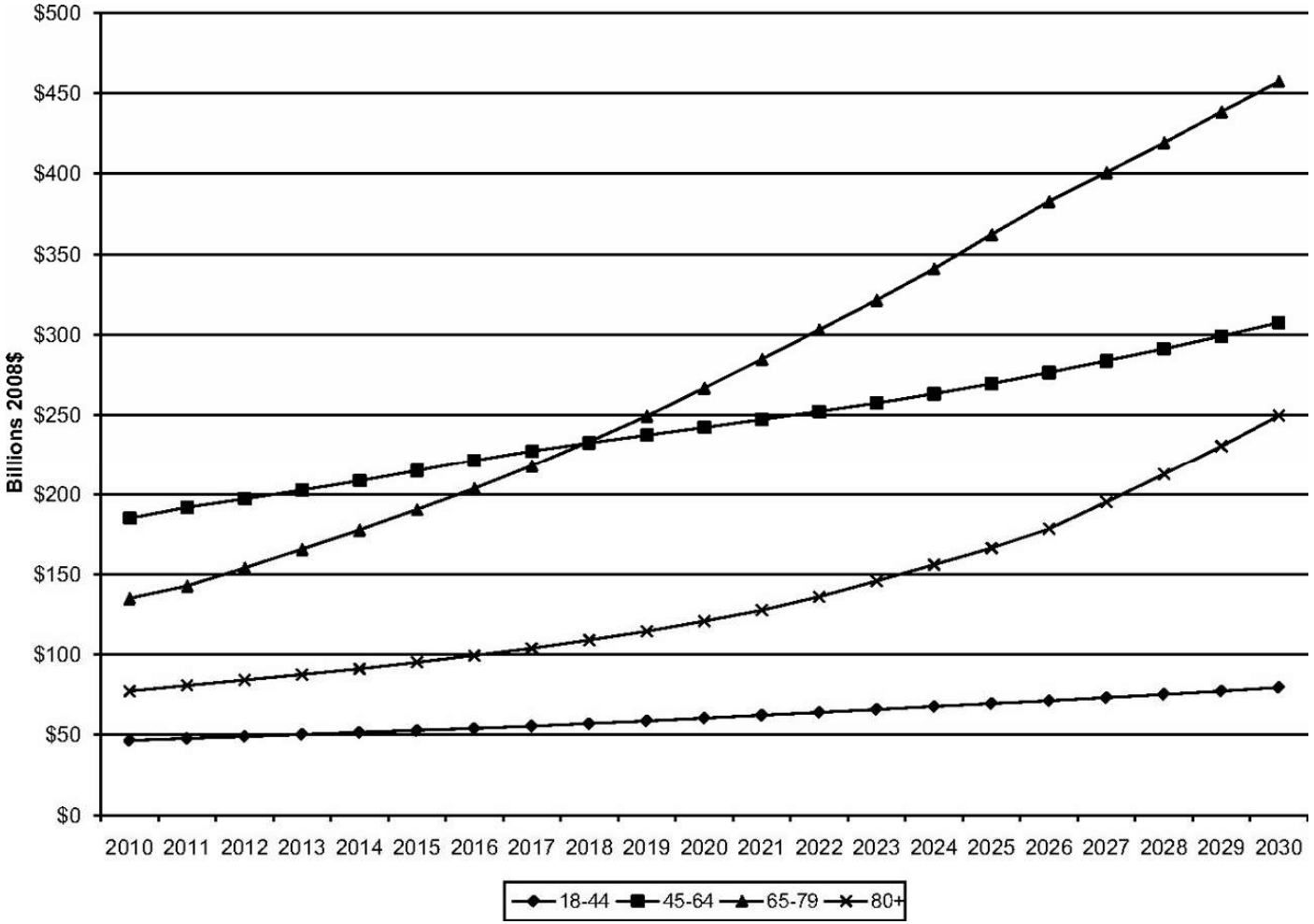
Go AS, Circulation. 2013;127:e6-e245

Ripartizione degli indici di spesa per malattie CV in EU



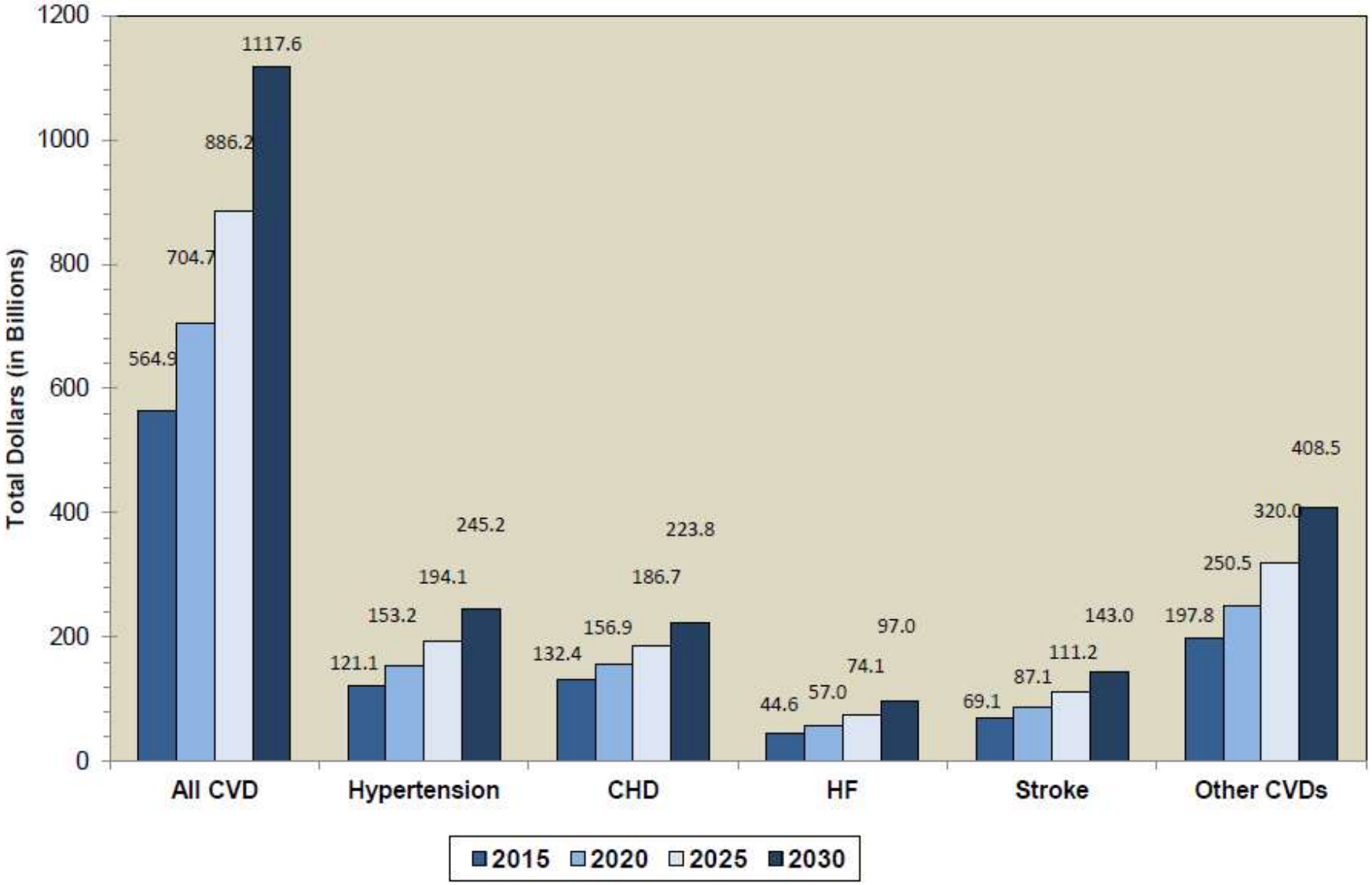
European Cardiovascular Disease Statistics 2012 ed., EuroHeart Survey II, ESC

Proiezioni dei costi per malattie CV negli USA (miliardi di $)



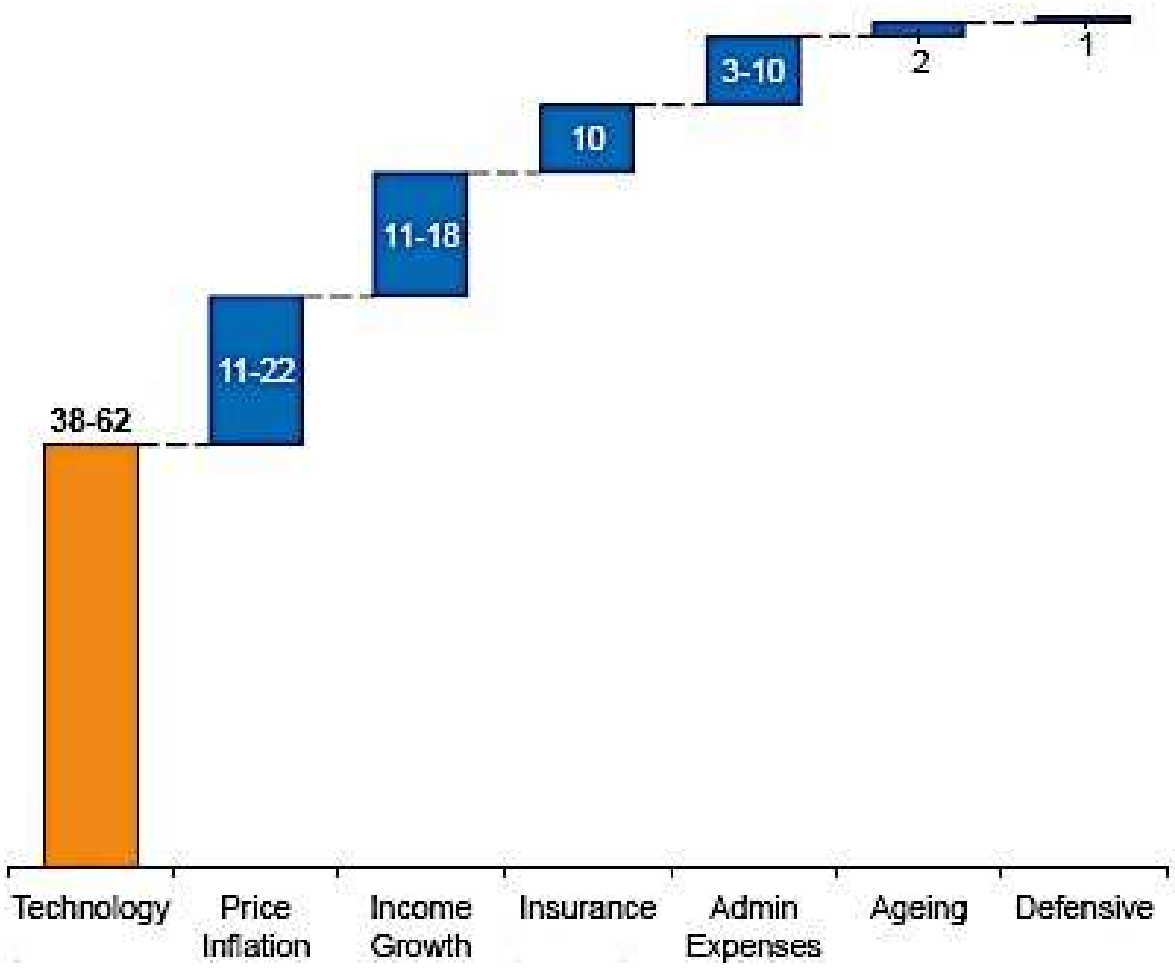
Heidenreich P, Circulation 2011; 123: 933-944

Proiezioni dei costi per malattie CV negli USA (miliardi di $)



Go AS, Circulation. 2013;127:e6-e245

Principali fattori di incremento dei costi



Source: Smith, Heffler and Freeland, 2000

CLINICAL PERSPECTIVE

Prediction of Lifetime Risk for Cardiovascular Disease by Risk Factor Burden at 50 Years of Age

Donald M. *Circulation. 2006;113:791-798*

- Despite 4 decades of declining mortality, CVD remains by far the leading cause of morbidity and mortality in developed countries and it is soon to be the leading cause of morbidity and mortality in the developing world
- Recent data suggest disturbing increases in the prevalence of CVD risk factors such as diabetes, obesity, and the metabolic syndrome which may reverse downward trends in CVD mortality
- In the face of the enormous public health burden imposed by CVD, renewed ***efforts are needed to promote prevention***

Basi razionali della prevenzione CV

3. Le malattie CV possono essere un killer silente

Il killer silente

- Il rischio di sviluppare nel corso della vita una patologia CV sintomatica nei 50enni arruolati nel Framingham Heart Study era pari al 52% fra gli uomini e al 39% fra le donne

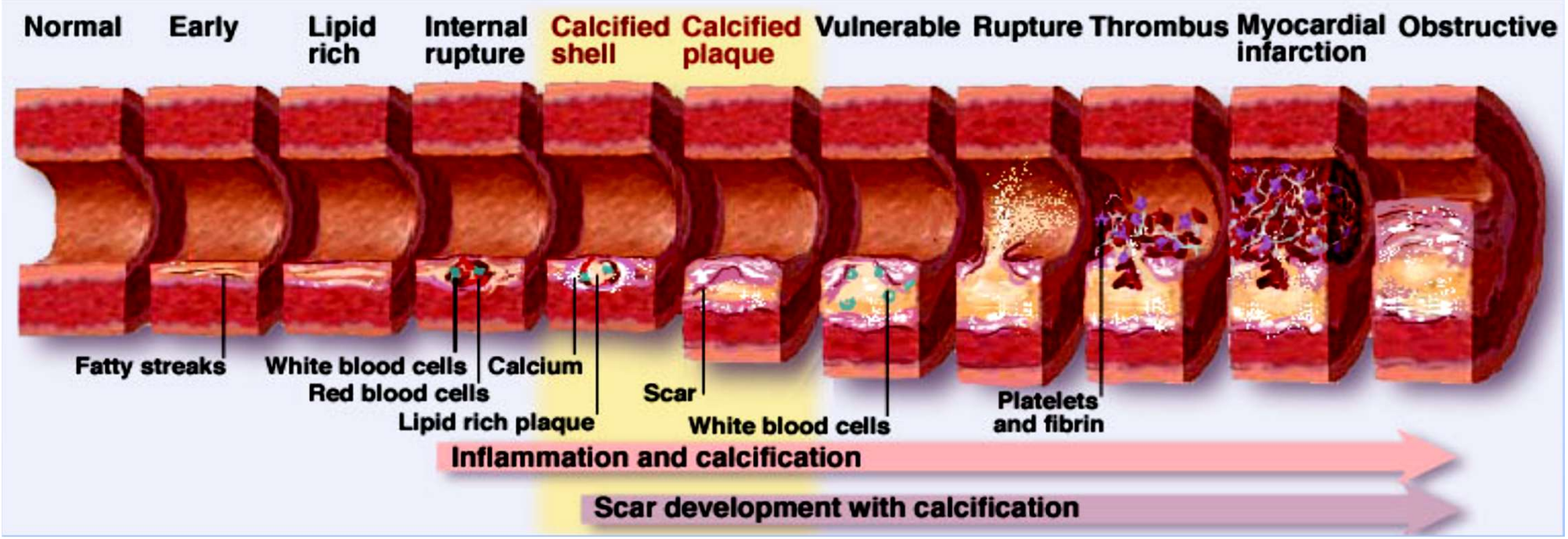
- Nel 30% - 50% dei casi, la patologia esordiva con un evento catastrofico, come ictus, infarto miocardico o morte improvvisa

Pasternak RC, Circulation 2006;113:791-798

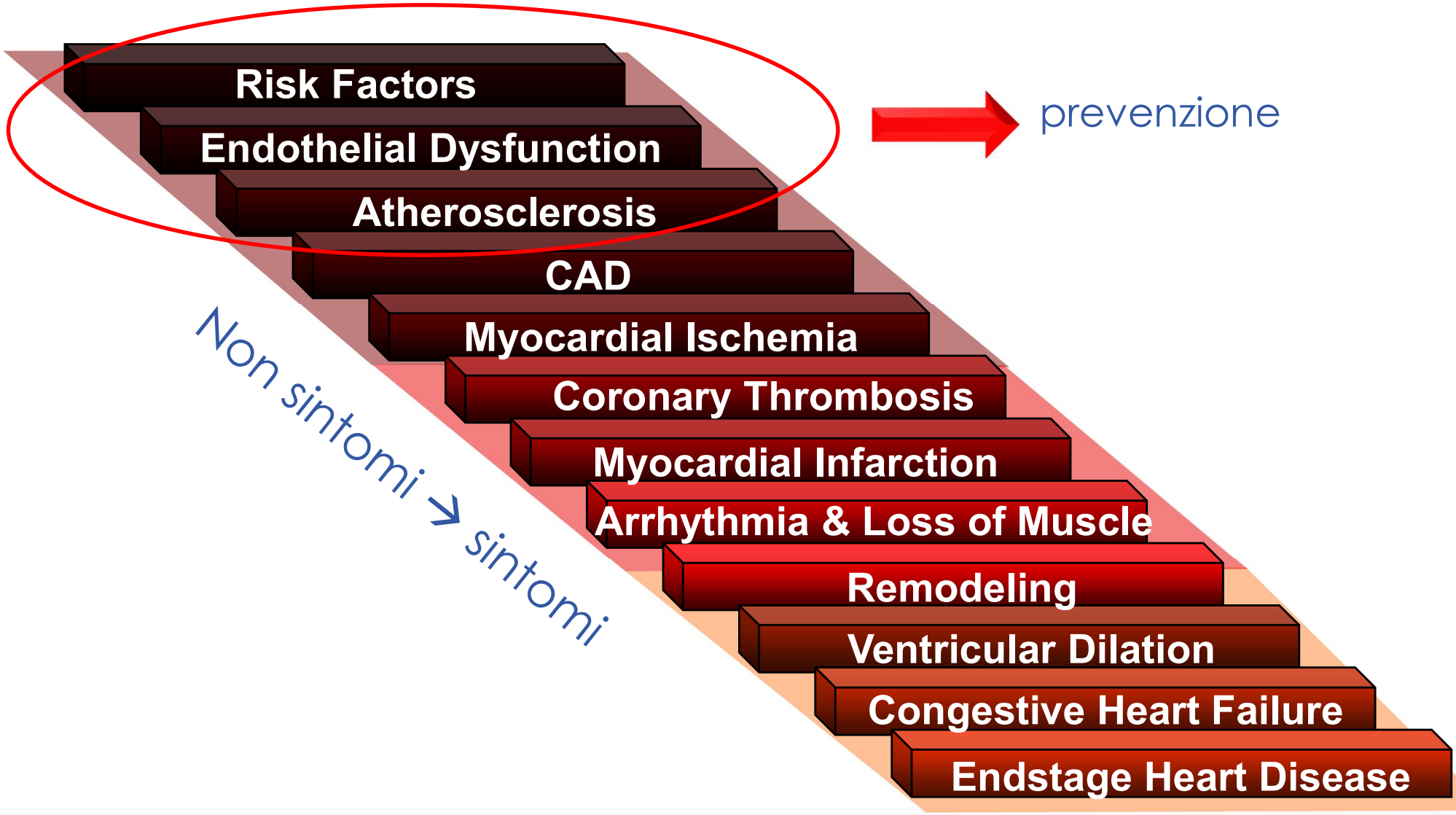
Basi razionali della prevenzione CV

4. Le malattie CV hanno carattere progressivo

Evoluzione della patologia aterosclerotica



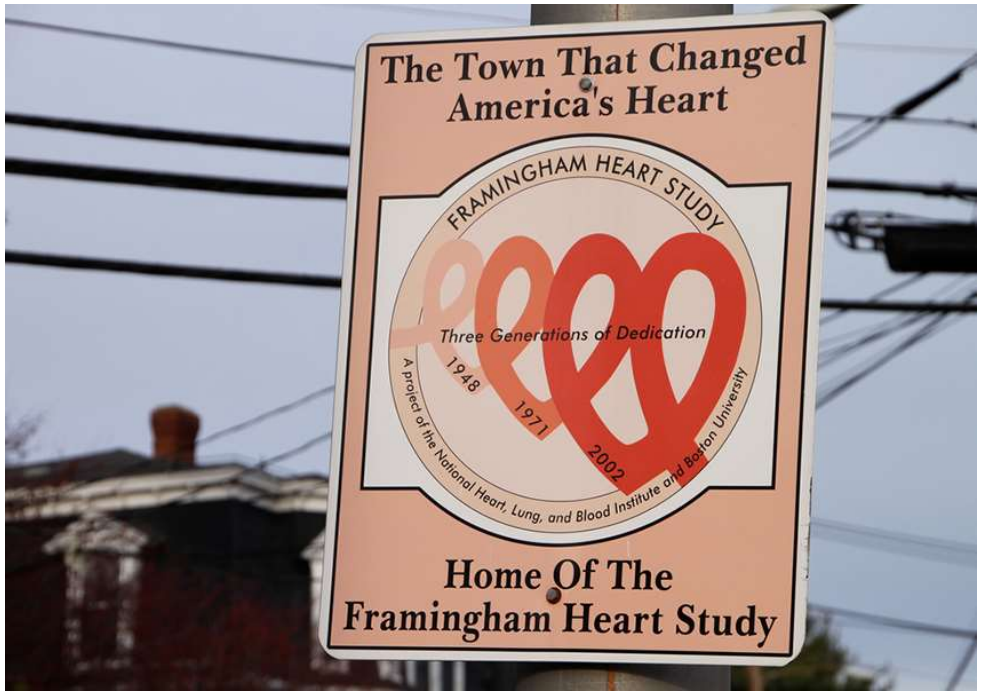
Sviluppo progressivo di malattia CV



Strategia di lotta ai fattori di rischio

Moriyama IM et al. J Chronic Dis. 1958;7:401-412

Observation on possible factors responsible for the sex and race trends in cardiovascular-renal mortality in the United States


The Town That Changed America's Heart
FRAMINGHAM HEART STUDY
Three Generations of Dedication
1948
1971
2002
A project of the National Heart, Lung, and Blood Institute and Boston University
Home Of The Framingham Heart Study

Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study

*Salim Yusuf, Steven Hawken, Stephanie Ôunpuu, Tony Dans, Alvaro Avezum, Fernando Lanas, Matthew McQueen, Andrzej Budaj, Prem Pais, John Varigos, Liu Lisheng, on behalf of the INTERHEART Study Investigators**

Lancet 2004; 364: 937–52

Published online
September 3, 2004
http://image.thelancet.com/extras/04art8001web.pdf

See **Comment** page 912

*Listed at end of report.

Population Health Research Institute, Hamilton General Hospital, 237 Barton Street East, Hamilton, Ontario, Canada L8L 2X2
(Prof S Yusuf DPhil, S Ôunpuu PhD, S Hawken MSc, T Dans MD, A Avezum MD, F Lanas MD, M McQueen FRCP, A Budaj MD, P Pais MD, J Varigos BSc, L Lisheng MD)

Correspondence to:
Prof Salim Yusuf
yusufs@mcmaster.ca

Summary

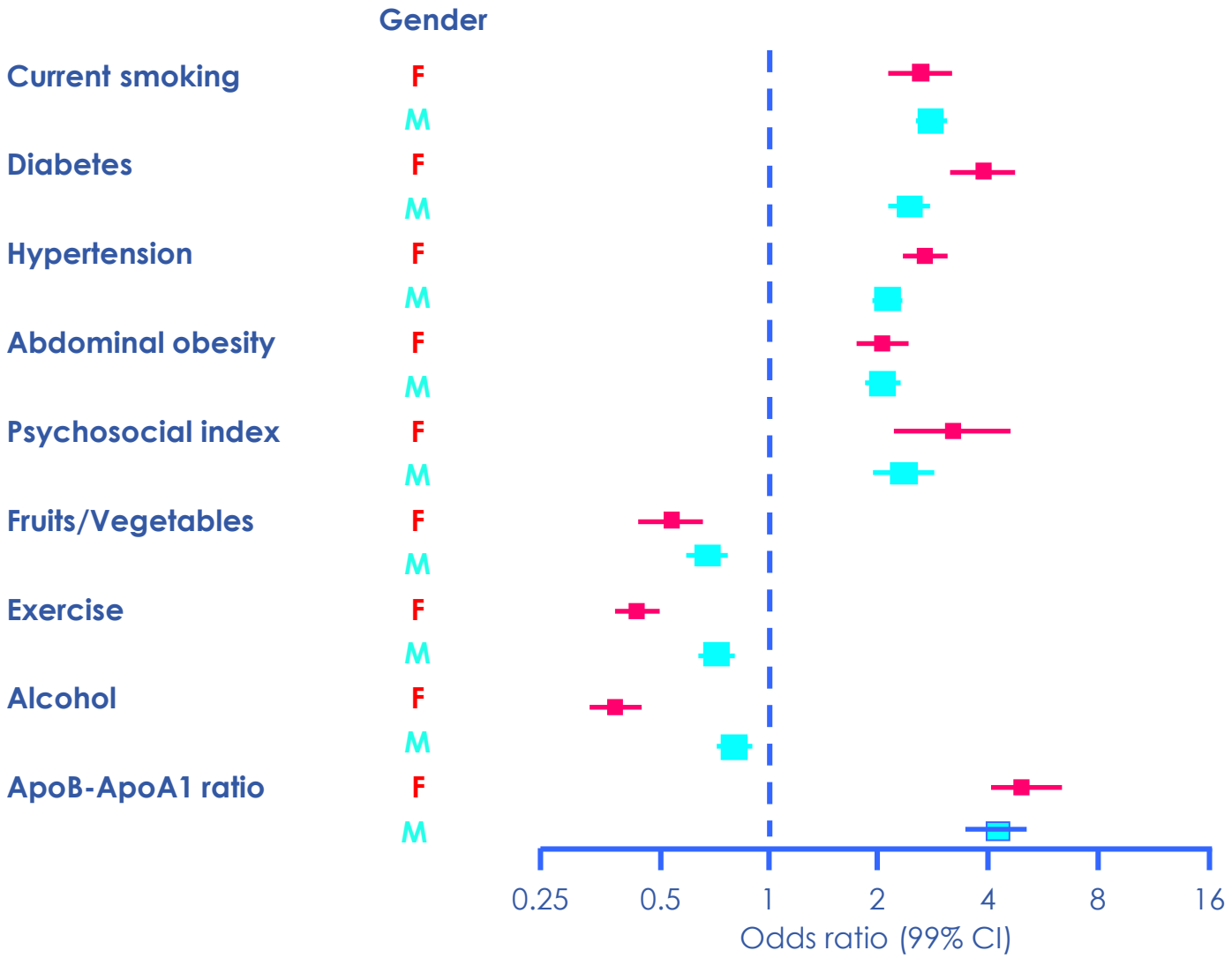
Background Although more than 80% of the global burden of cardiovascular disease occurs in low-income and middle-income countries, knowledge of the importance of risk factors is largely derived from developed countries. Therefore, the effect of such factors on risk of coronary heart disease in most regions of the world is unknown.

Methods We established a standardised case-control study of acute myocardial infarction in 52 countries, representing every inhabited continent. 15 152 cases and 14 820 controls were enrolled. The relation of smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins (Apo), and psychosocial factors to myocardial infarction are reported here. Odds ratios and their 99% CIs for the association of risk factors to myocardial infarction and their population attributable risks (PAR) were calculated.

Findings Smoking (odds ratio 2·87 for current *vs* never, PAR 35·7% for current and former *vs* never), raised ApoB/ApoA1 ratio (3·25 for top *vs* lowest quintile, PAR 49·2% for top four quintiles *vs* lowest quintile), history of hypertension (1·91, PAR 17·9%), diabetes (2·37, PAR 9·9%), abdominal obesity (1·12 for top *vs* lowest tertile and 1·62 for middle *vs* lowest tertile, PAR 20·1% for top two tertiles *vs* lowest tertile), psychosocial factors (2·67, PAR 32·5%), daily consumption of fruits and vegetables (0·70, PAR 13·7% for lack of daily consumption), regular alcohol consumption (0·91, PAR 6·7%), and regular physical activity (0·86, PAR 12·2%), were all significantly related to acute myocardial infarction ($p<0·0001$ for all risk factors and $p=0·03$ for alcohol). These associations were noted in men and women, old and young, and in all regions of the world. Collectively, these nine risk factors accounted for 90% of the PAR in men and 94% in women.

Interpretation Abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity account for most of the risk of myocardial infarction worldwide in both sexes and at all ages in all regions. This finding suggests that approaches to prevention can be based on similar principles worldwide and have the potential to prevent most premature cases of myocardial infarction.

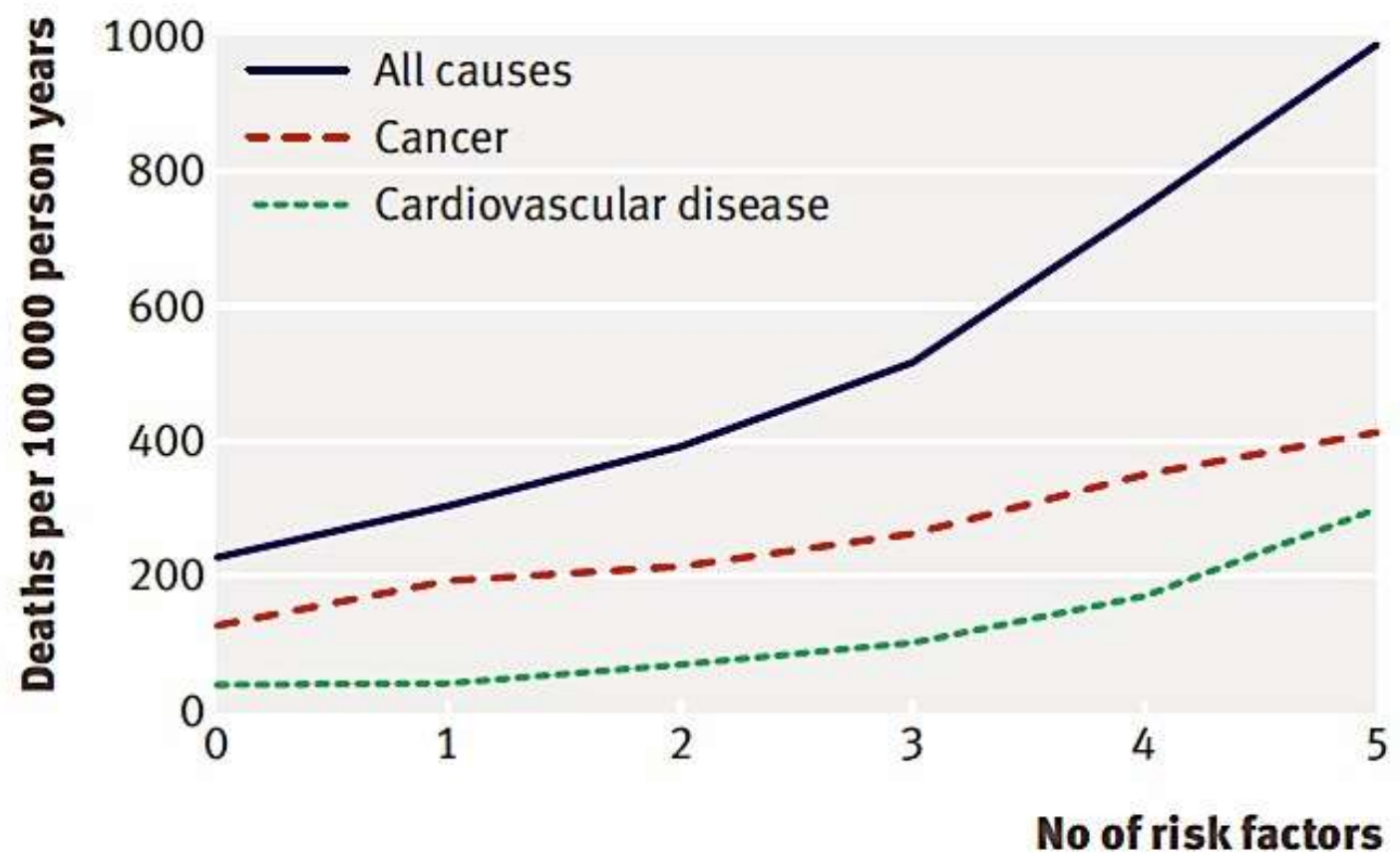
INTERHEART: Association of risk factors with acute MI



Adjusted for age, sex, geographic region
Note: odds ratio plotted on a doubling scale

Yusuf S et al. *Lancet*. 2004;364:937-52.

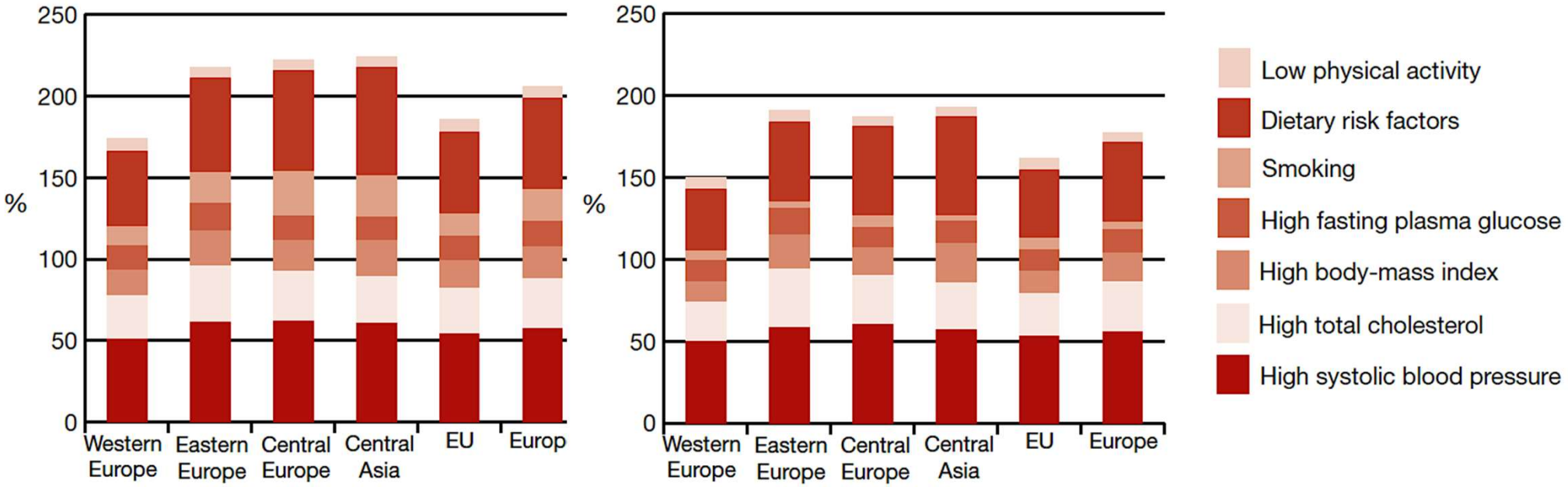
Relazione fra fattori di rischio e mortalità standardizzata per età



24 yrs. F.U

Van Damm RM, BMJ 2008;337:a1440

% di decessi per malattie CV attribuibile ai singoli fattori di rischio



Maschi **Femmine**

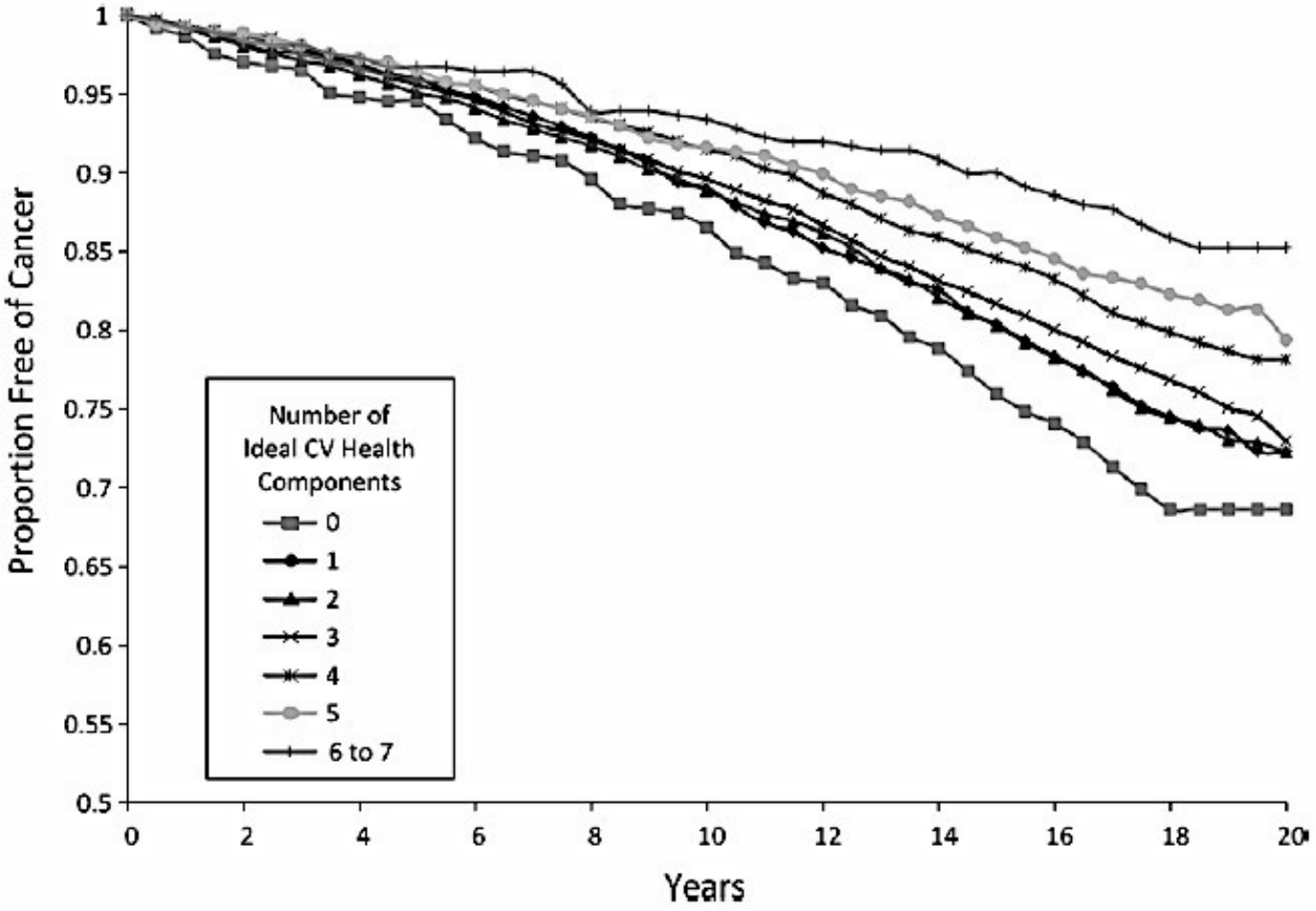
Wilkins E, et Al. (2017). European Cardiovascular Disease Statistics 2017. European Heart Network, Brussels.

Indicatori ideali di salute (ARIC) 1987-2006

- never smoking or quitting >12 months ago;
- BMI <25 kg/ m2;
- 4–5 components of a healthy diet score;
- ≥75 minutes/week of vigorous physical activity [or 150 minutes/week of moderate or moderate + vigorous activity]
- untreated total cholesterol <200 mg/dL,
- untreated blood pressure <120 mmHg systolic and 80 mmHg diastolic
- untreated fasting serum glucose <100 mg/dL

Rasmussen-Torvik LJ, Circulation 2013;127:1270-1275

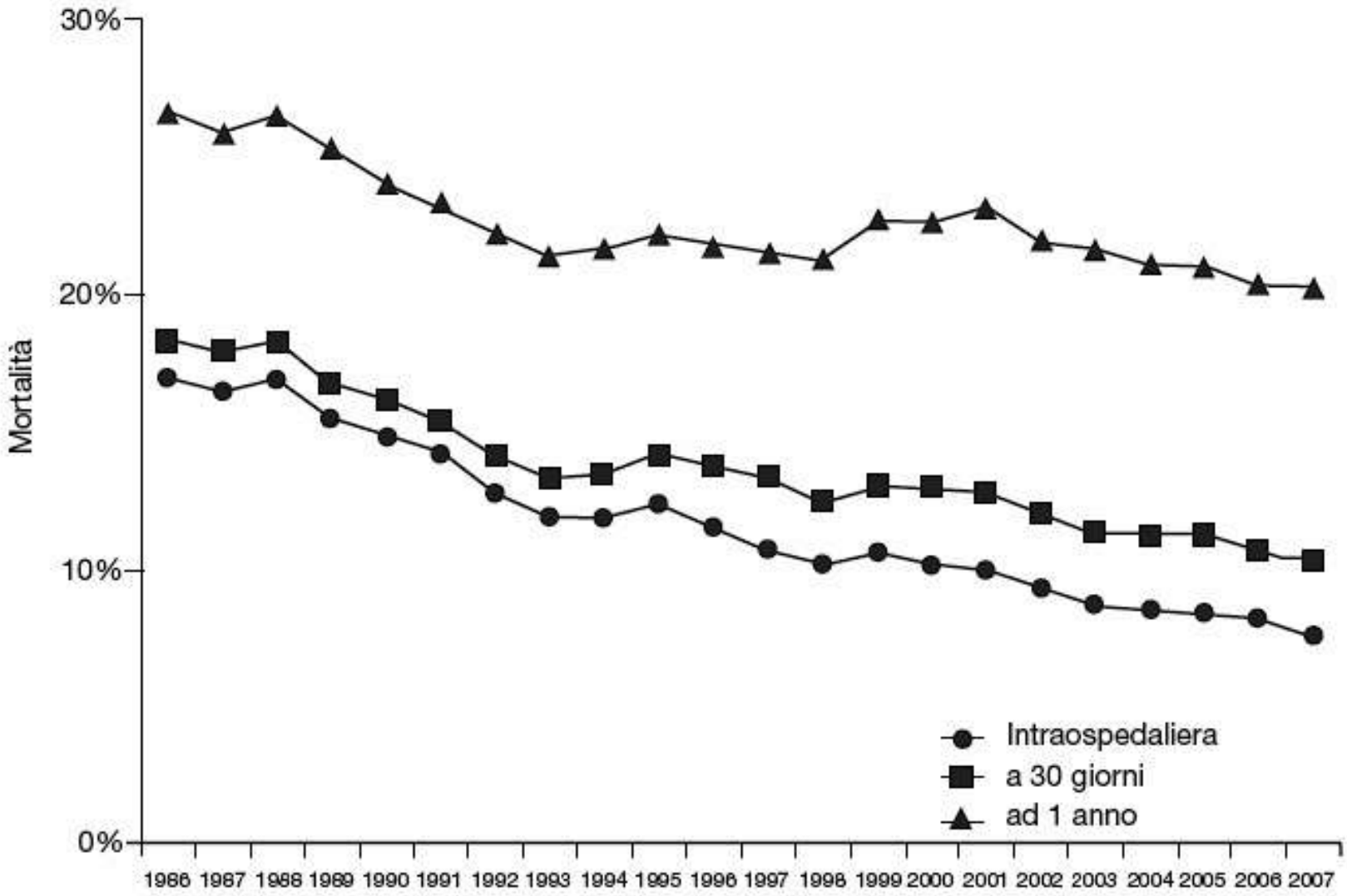
Curve di sopravvivenza per incidenza di cancro in rapporto agli indicatori di salute (ARIC) 1987-2006



Rasmussen-Torvik LJ, Circulation 2013;127:1270-1275

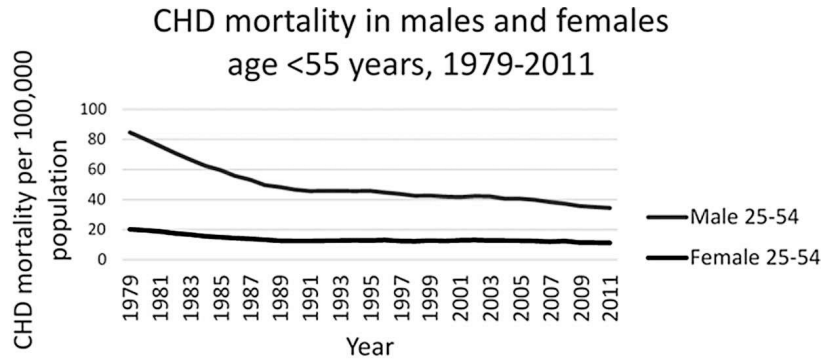
Bisogna cercare di rendere le cose il più semplici possibile, ma non più semplici di quel che sia possibile

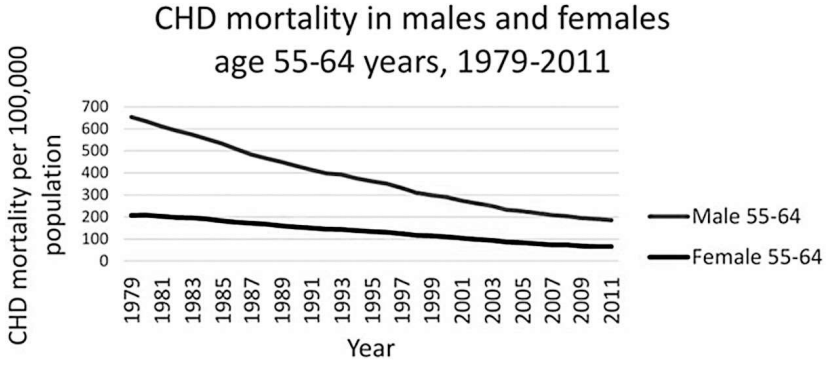
Albert Einstein

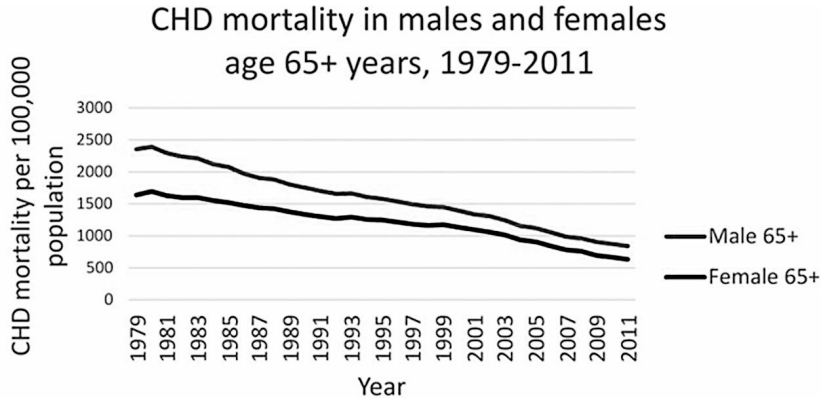


Kostis WJ, Circ Cardiovasc Qual Outcomes 2010; 3:581-589

Trends in age-specific CHD mortality rates in US, 1979 to 2011







Kobina A. Wilmot et al.
Circulation 2015;132:997-1002

Fattori di rischio e Suscettibilità

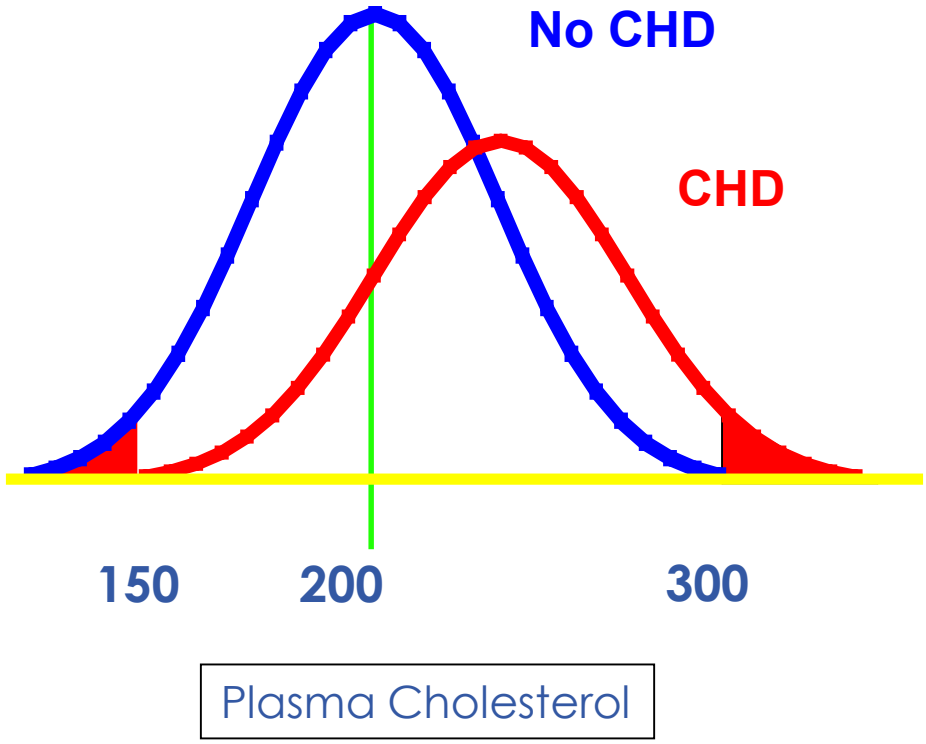
Sir Winston Churchill, 91 ✝

Jim Fixx, 53 ✝♥

Limiti del ruolo del LDL colesterolo nella cardiopatia ischemica

Framingham Heart Study - 26 anni di FU

- Esiste un significativo overlap fra I livelli di LDL colesterolo fra le popolazioni con e senza C.I.
- L' 80% of dei pazienti con IM presentavano valori di LDL colesterolo simili a quelli dei soggetti senza IM



Castelli W, Atherosclerosis 1996; 124: S1-S9

CLINICAL GUIDELINES | Annals of Internal Medicine

Emerging Risk Factors for Coronary Heart Disease: A Summary of Systematic Reviews Conducted for the U.S. Preventive Services Task Force

Mark Helfand, MD, MPH; David I. Buckley, MD, MPH; Michele Freeman, MPH; Rongwei Fu, PhD; Kevin Rogers, MD; Craig Fleming, MD; and Linda L. Humphrey, MD, MPH

Ankle-brachial index
C-reactive protein
Carotid intima media thickness
Electron beam computed tomography
Fasting glucose
Homocysteine
Lipoprotein(a)
Periodontal disease
White blood cell count

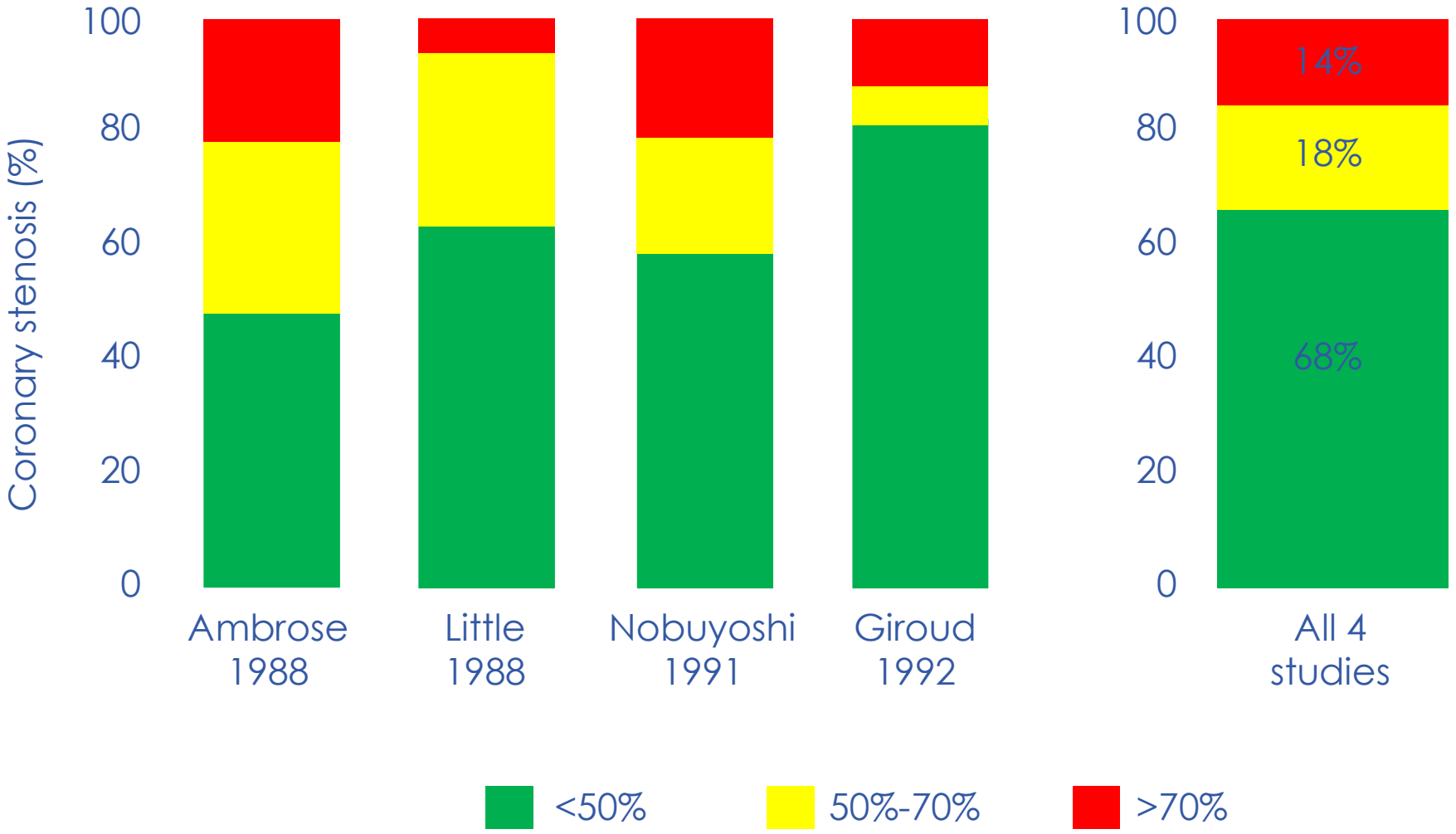
Conclusion: The current evidence does not support the routine use of any of the 9 risk factors for further risk stratification of intermediate-risk persons.

Ann Int Med 2009;151:496-507

Potenziali fattori di rischio addizionali

Angiotensin-converting enzyme genotype,
ApoE genotype
Apolipoproteins A1 and B
Cystatin C
D-dimer
Electrocardiogram findings
Exercise treadmill testing
Factors V, VII, and VIII
Fibrinogen
Fibrinopeptide A
Heart rate
High-density lipoprotein subtypes
Infectious agents: Cytomegalovirus, Chlamydia pneumonia, Helicobacter pylori, Herpes viruses
Insulin resistance
Interleukins (e.g., IL-6)
Lipoprotein-associated phospholipase A(2)
Metabolic syndrome
Microalbuminuria
Oxidized LDL
PAI-1 genotype
Physical inactivity
Plasminogen activator inhibitor 1 (PAI-1)
Platelet activity
Platelet aggregation
Platelet size and volume
Prothrombin fragment 1 + 2
Pulse pressure
Remnant lipoproteins
Serum amyloid A
Soluble CD40 ligand
Tissue-plasminogen activator
Vascular and cellular adhesion molecules
von Willebrand factor antigen
Waist-to-hip ratio

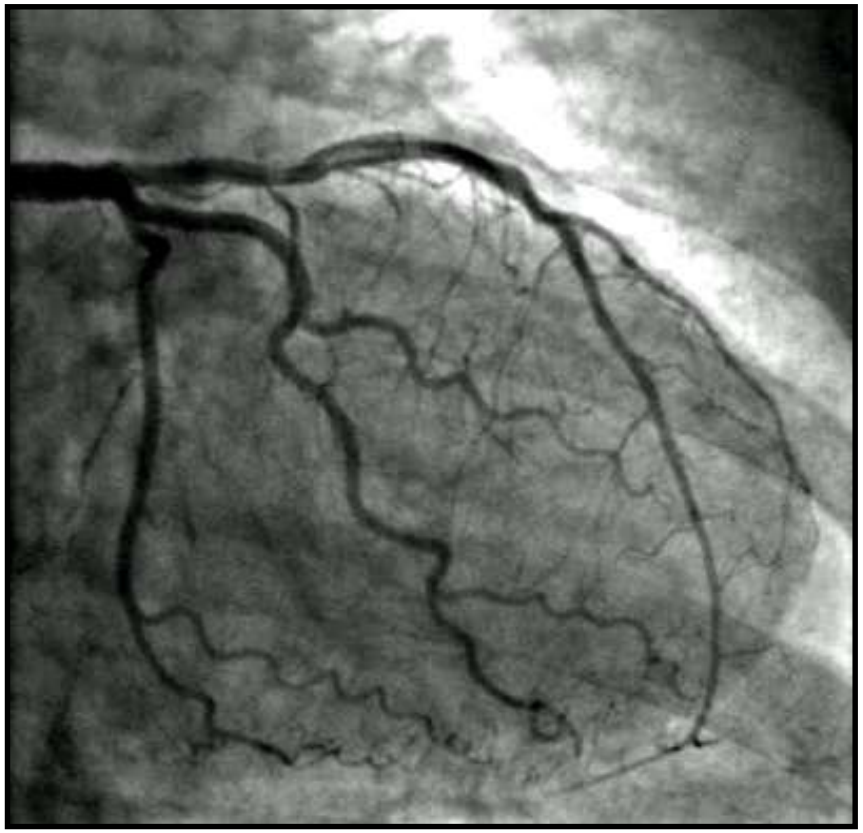
Coronary stenosis severity prior to MI



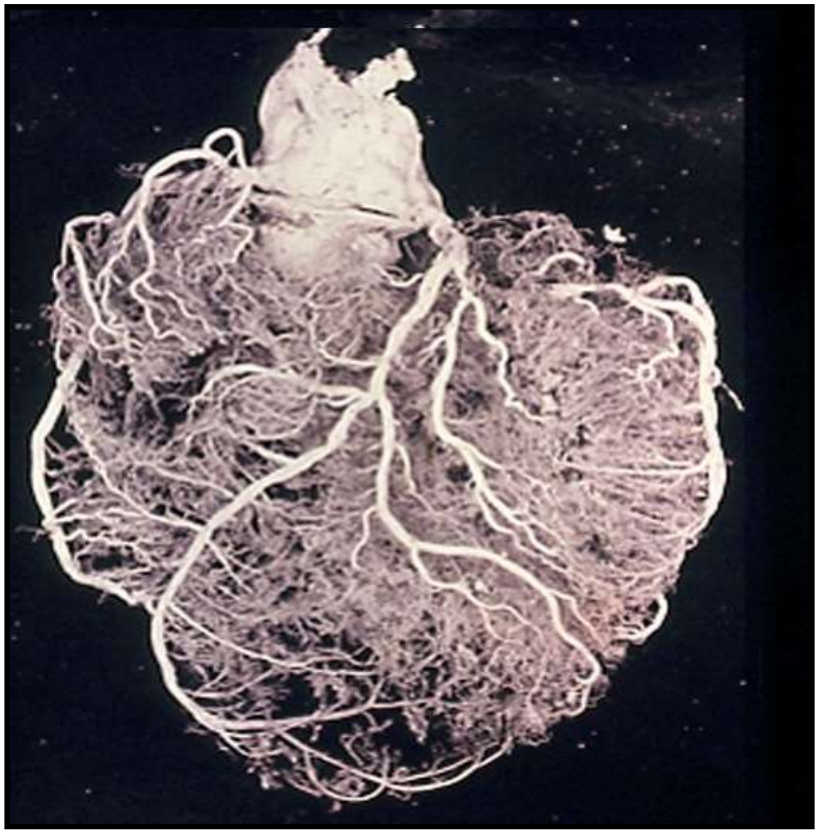
Falk E, et al. Circulation. 1995;92:657-671

Anatomic approach: limitations

Diameter >100 micron

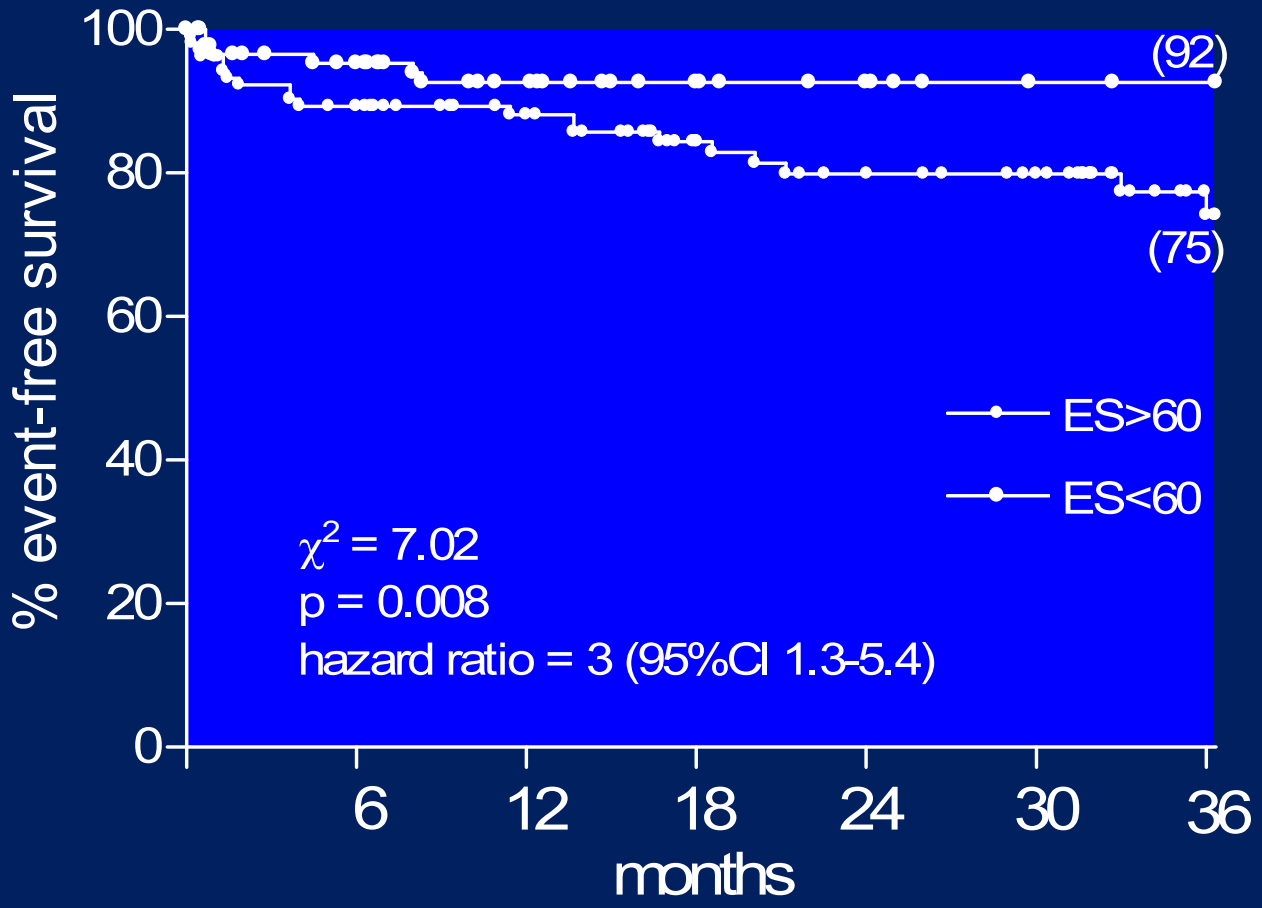


Diameter 20-350 micron



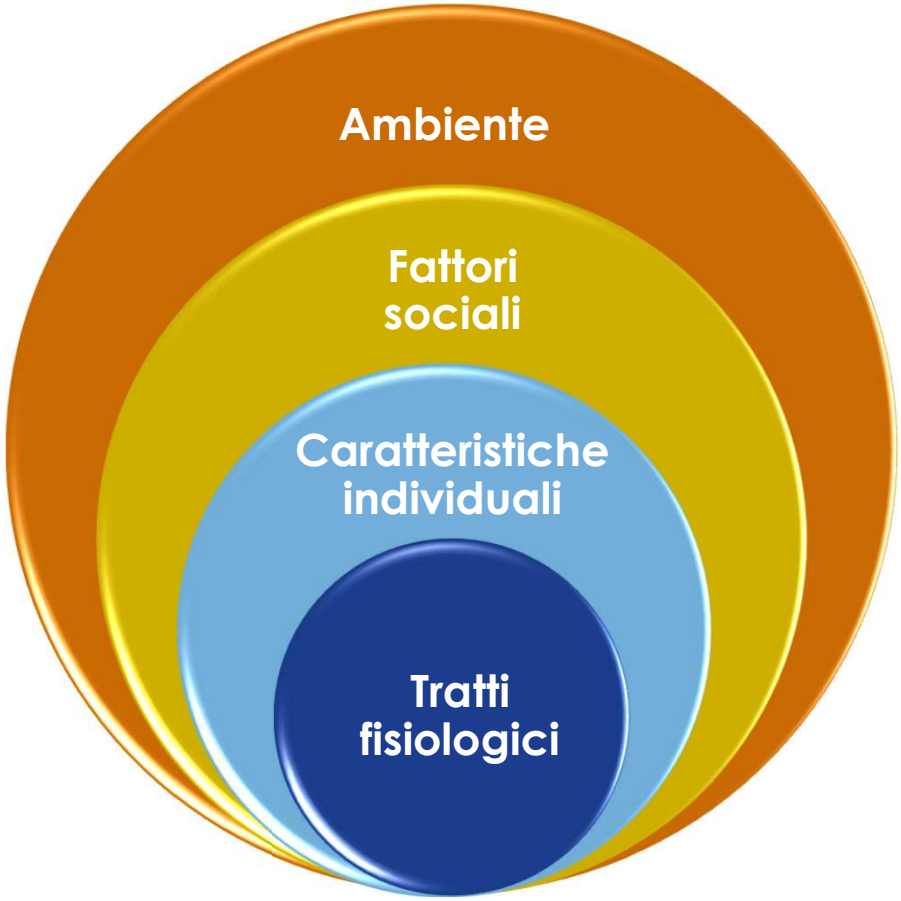
Baroldi G, Bigi R, Cortigiani L. Cardiovascular Ultrasound 2005, 3:6 doi:10.1186/1476-7120-3-6

Prognostic and clinical correlates of angiographically diffuse non-obstructive coronary lesions

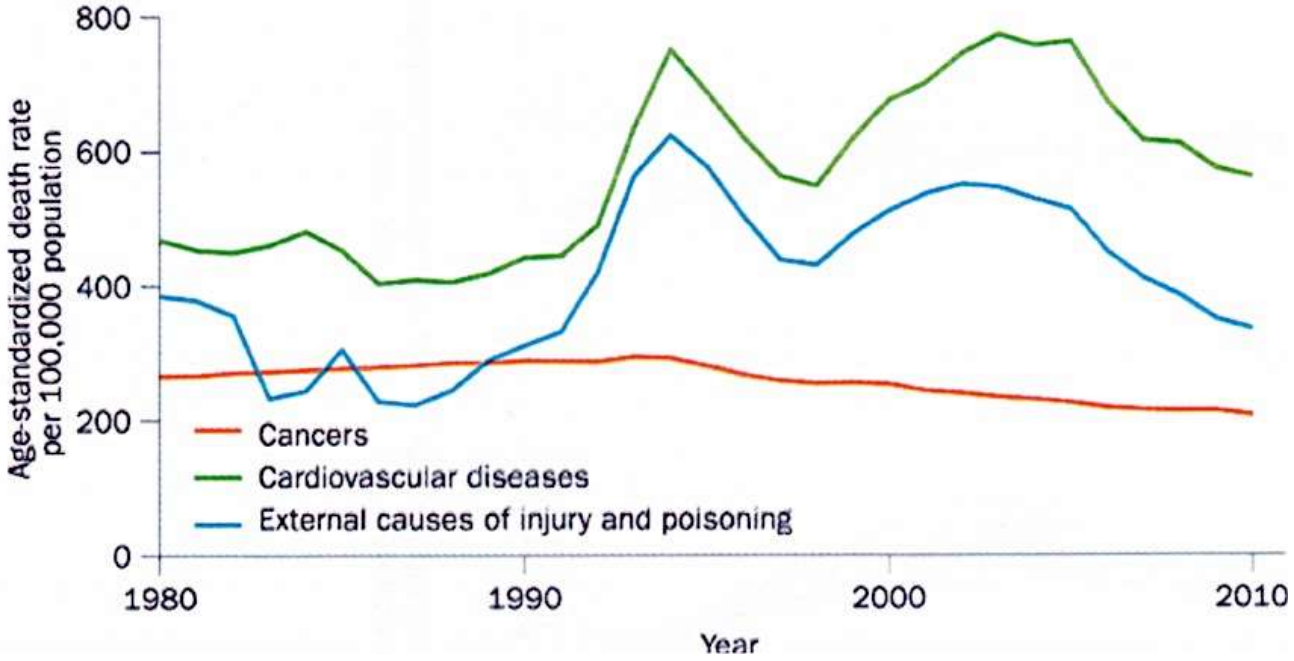


Bigi R, Heart 2003;99:1009-1013

Eterogeneità e complessità dell'origine della patologia CV



Trends dei tassi di mortalità fra 25-64 anni in Russia, 1980-2010

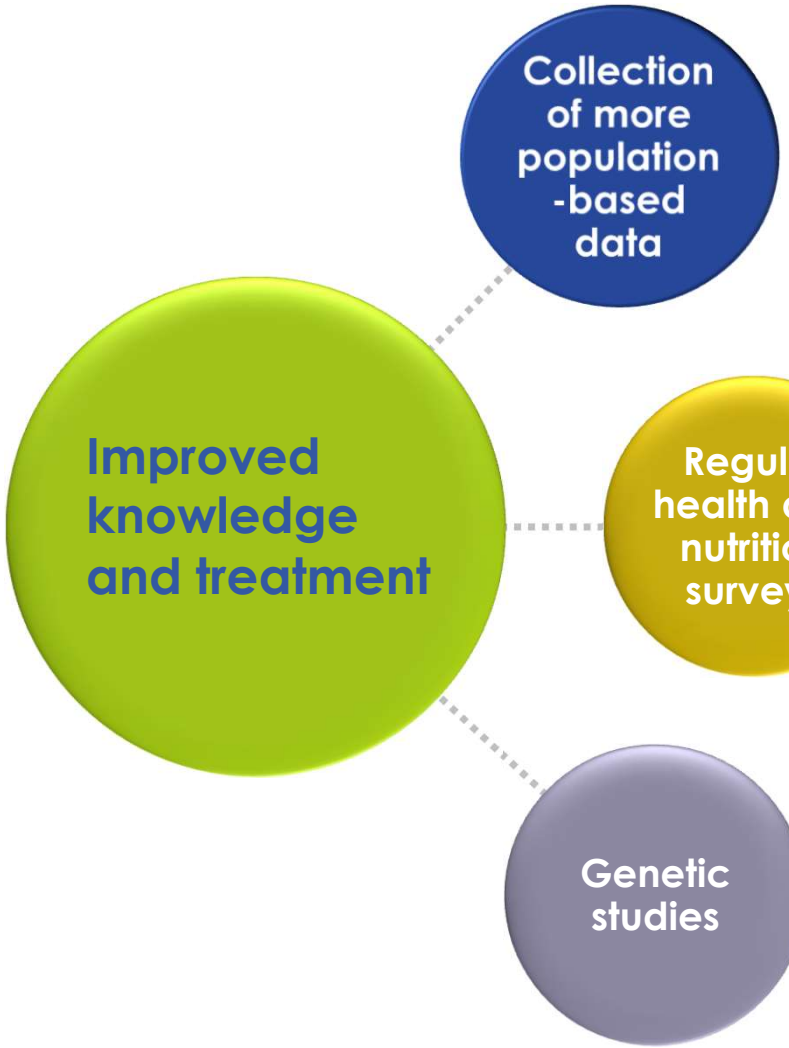


Ezzati M, Nat Rev Cardiol 2015;12:508-530

Aspetti critici attuali della prevenzione e cura delle malattie CV

- Necessità di riduzione dei costi
- Insufficiente rapporto costo/efficacia
- Eccesso di utilizzo di risorse
- Elevati tassi di re-ospedalizzazione e mortalità

Prospettive future



- To improve the understanding of long-term changes in CVD mortality across different countries
- Role of new risk factors and link between CVD and other major causes of death
- To identify genetic determinants of CV traits and disease

FUTURE OF CARDIOLOGY

INVASIVE

3D PRINTING

NANOTECHNOLOGY

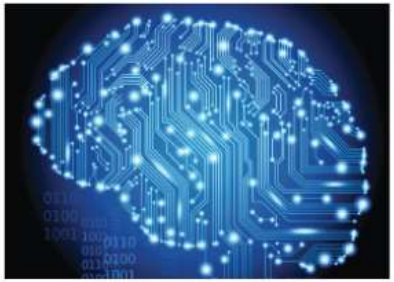
TISSUE ENGINEERING

PREVENTIVE

EMR

GENOMICS

ARTIFICIAL INTELLIGENCE



SENSORS

VARIABILITA' GENETICA

Il genoma umano è costituito da circa 3 miliardi di coppie di basi di DNA alloggiate in 23 coppie di cromosomi che formano da 20.000 a 25.000 geni

	Framingham	SCORE	ASSIGN	QRISK	PROCAM
Popolazione (tipo)	generale (Framingham)	12 studi in paesi europei	generale (Scozia)	database dei medici di MG	impiegati
Selezione	volontari	casuale + coorti occupazionali	casuale	consecutiva	volontari
Evento previsto (outcome)	ogni evento CV a 10 anni	mortalità CV a 10 anni	ogni evento CV a 10 anni	ogni evento CV a 10 anni	2 scores separati per ogni evento CV e per soli eventi cerebrovascolari a 10 anni
Età	30-75	40-65	30-74	20-75	40-79
Variabili incluse	sesso. età, colesterolo, HDL, PA, fumo, diabete, terapia antipertensiva	sesso. età, colesterolo totale o rapporto tot/HDL, PA, fumo	sesso. età, colesterolo tot, HDL, PA, fumo, diabete, deprivazione sociale, familiarità	sesso. età, colesterolo tot/HDL, PA, fumo, diabete, deprivazione sociale, terapia antipertensiva, familiarità, BMI, etnicità, FA, malattie croniche	età, sesso, LDL, HDL, diabete, fumo, ipertensione
Formato	in origine fogli per calcolo, in seguito carte a colori, calcolatore online o portatile	carte a colori, versione elettronica	calcolatore online	calcolatore online, software dedicato	fogli di calcolo, calcolatore online
Raccomandazione in linee guida	National Cholesterol Education Program (USA)	Linee guida europee per la prevenzione CV	Scottish Itercollegiate Guidelines Network	National Institute for Health and Clinical Excellence (UK)	International Task Force for Prevention of Coronary Disease
Sito Web	www.nhlbi.nih.gov/guidelines/cholesterol/index/htm	www.HeartScore.org	www.assign-score.com	www.qrisk.co.uk	www.chd-taskforce.com/calculator

Personalized Medicine: Definition

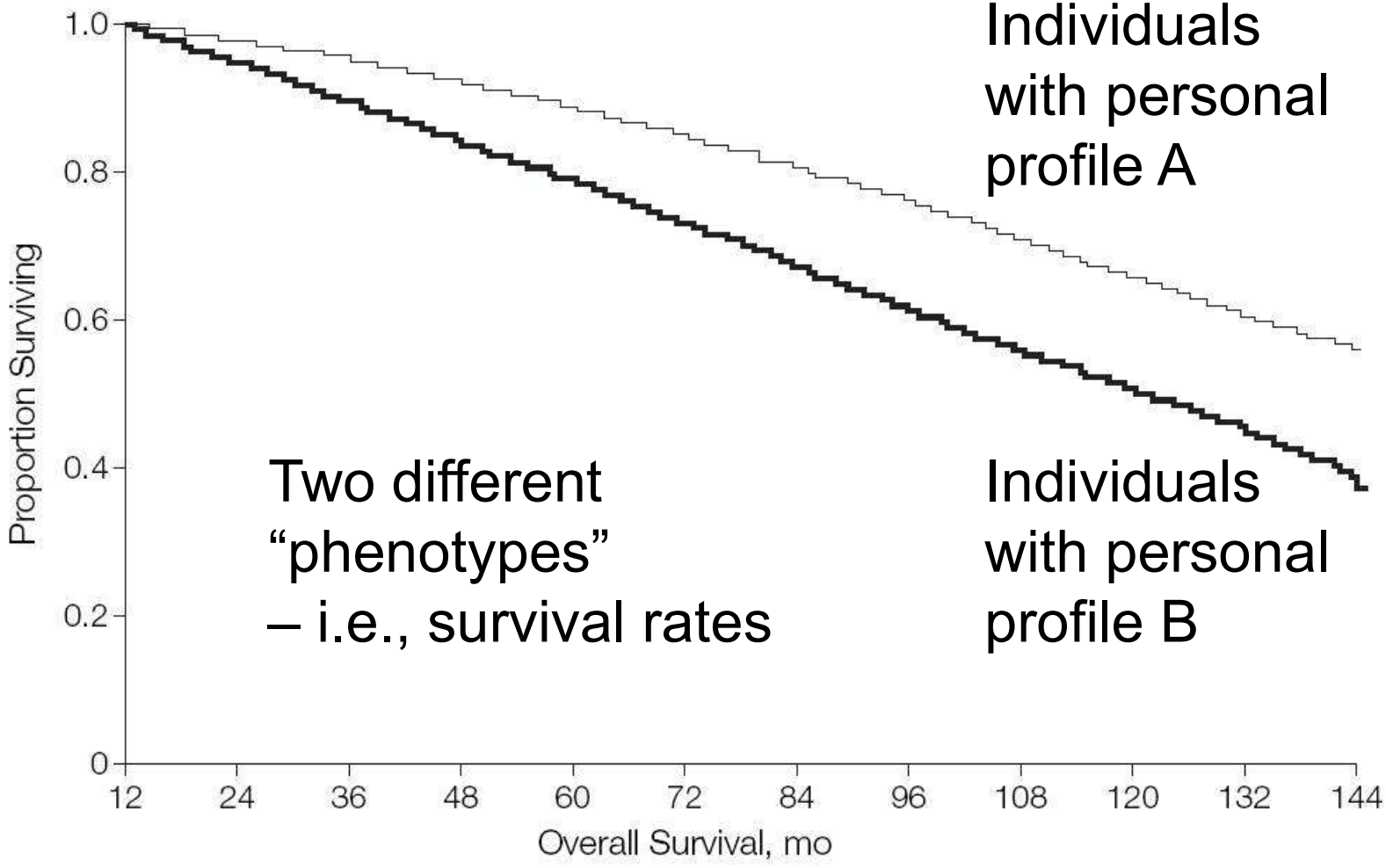
"Personalized medicine is the use of diagnostic and screening methods to better manage the individual patient's disease or predisposition toward a disease….

"Personalized medicine will enable risk assessment, diagnosis, prevention, and therapy specifically tailored to the unique characteristics of the individual, thus enhancing the quality of life and public health."

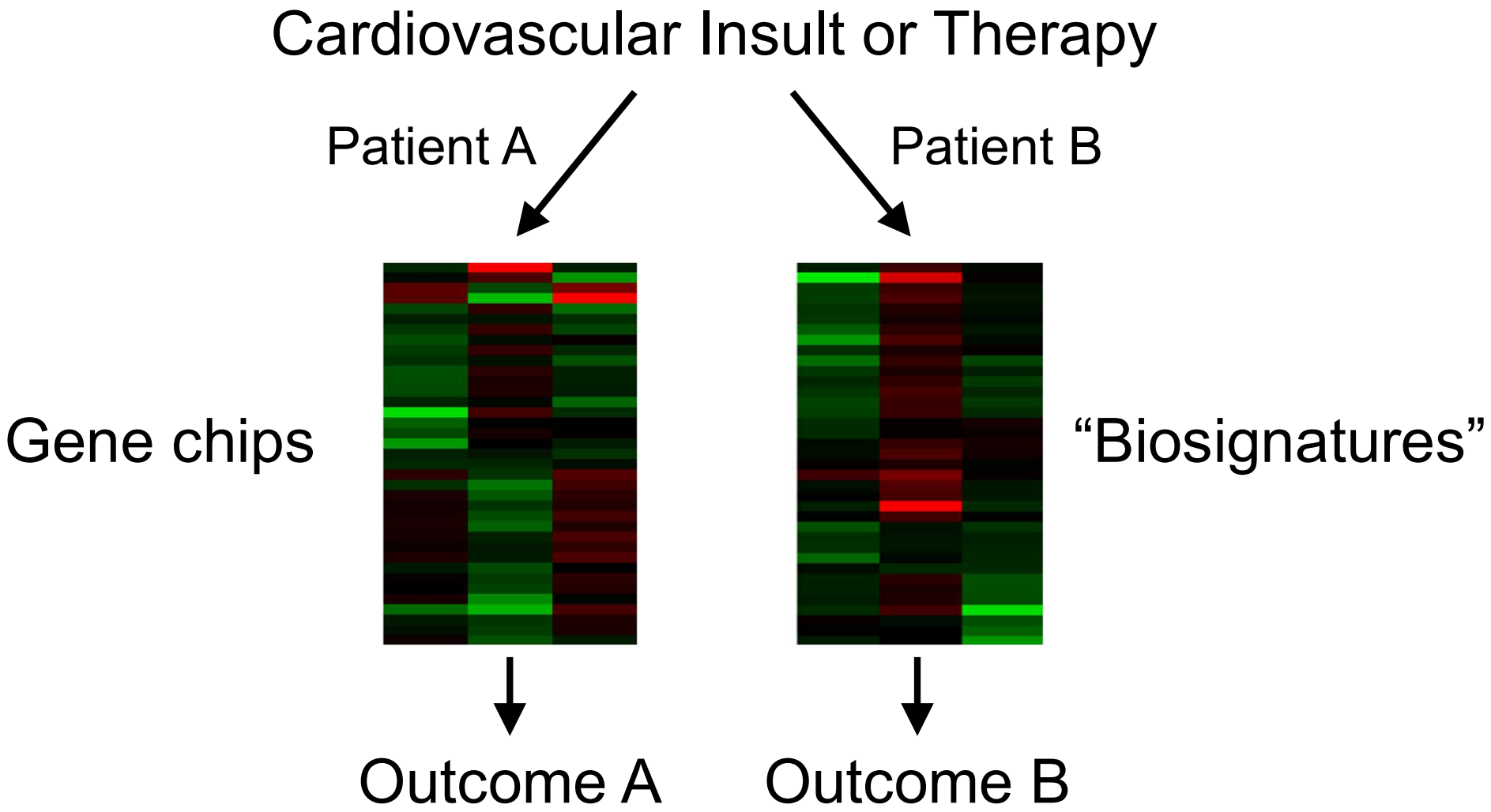
– NHLBI Strategic Planning, Theme #10

AMERICAN COLLEGE of CARDIOLOGY

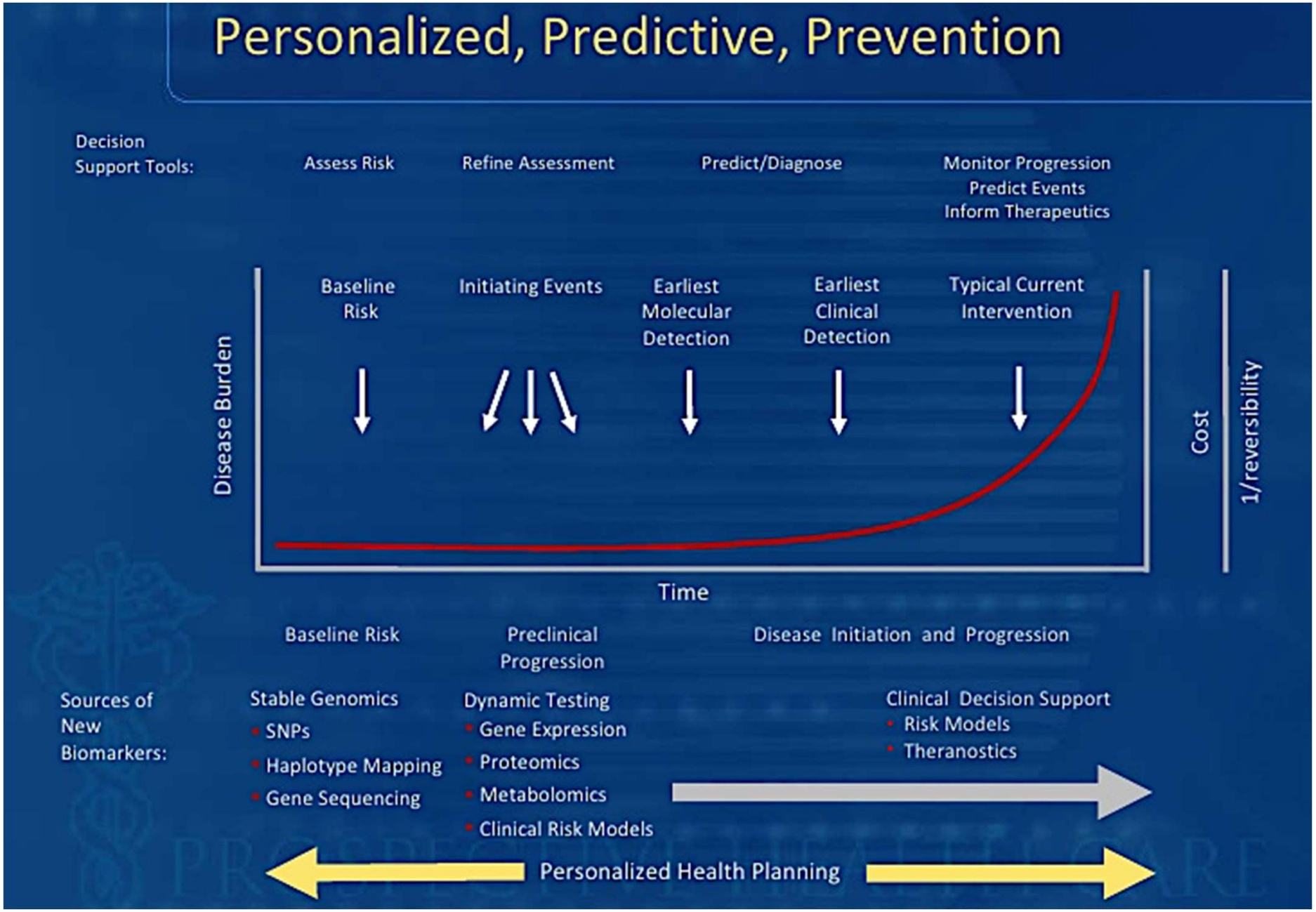
The Challenge

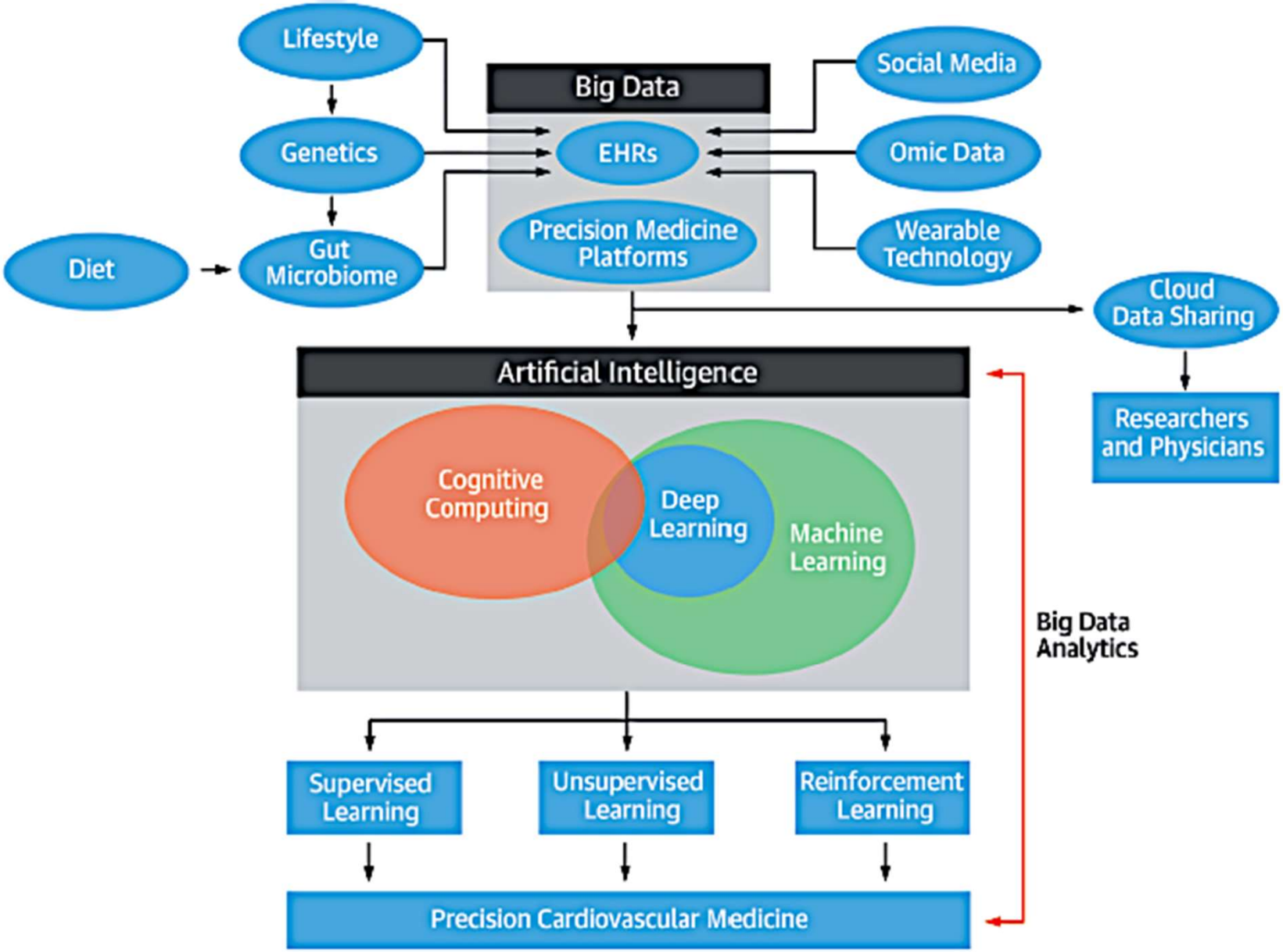


Concept of "Biosignature"



Personalized, Predictive, Prevention





Krittanawong, C. et al. J Am Coll Cardiol. 2017;69(21):2657-64.

Ipotesi

Conferma sperimentale

"If it were not for the great variability among individuals, medicine might as well be a science and not an art"

Sir William Osler, 1892