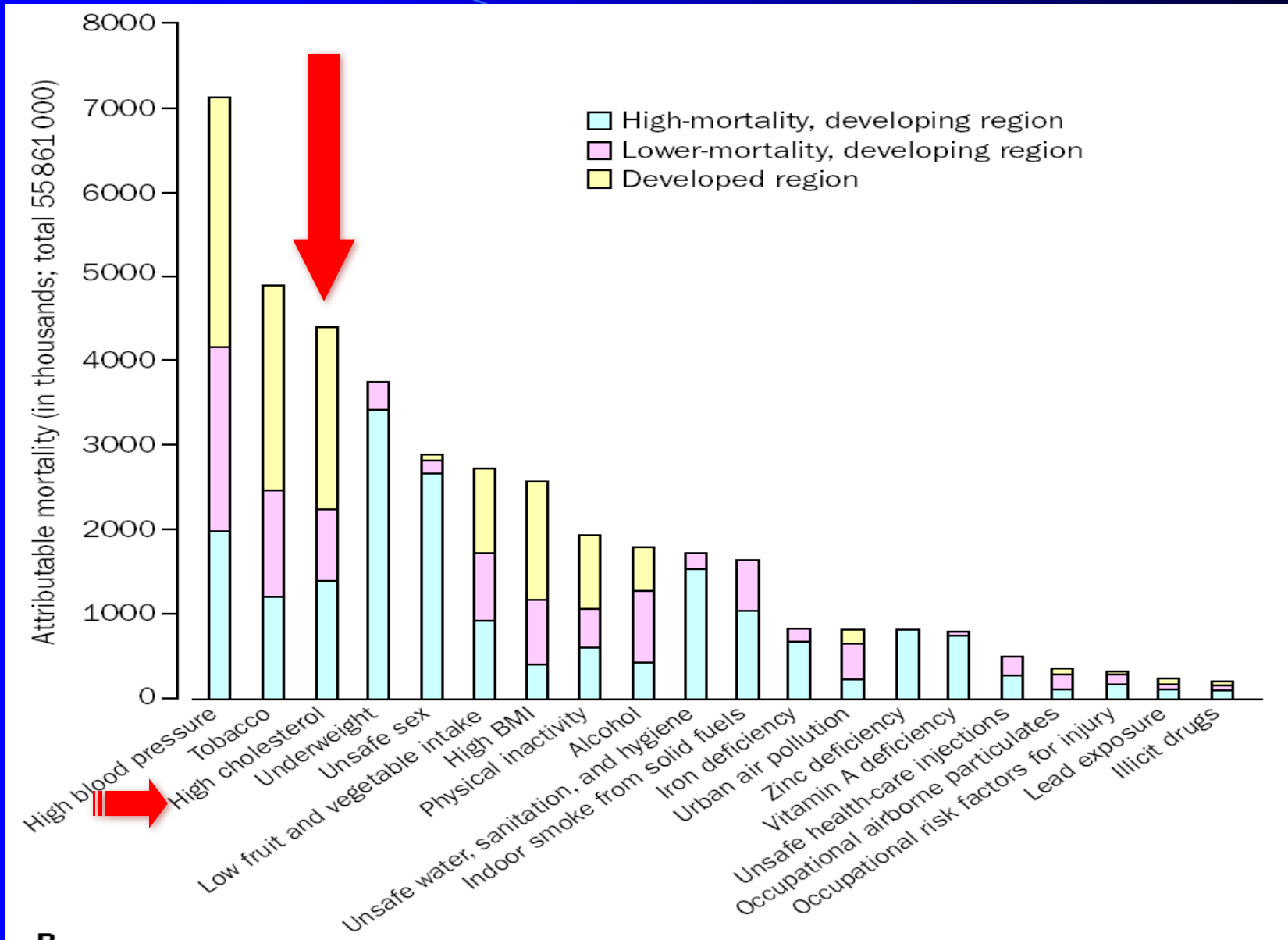




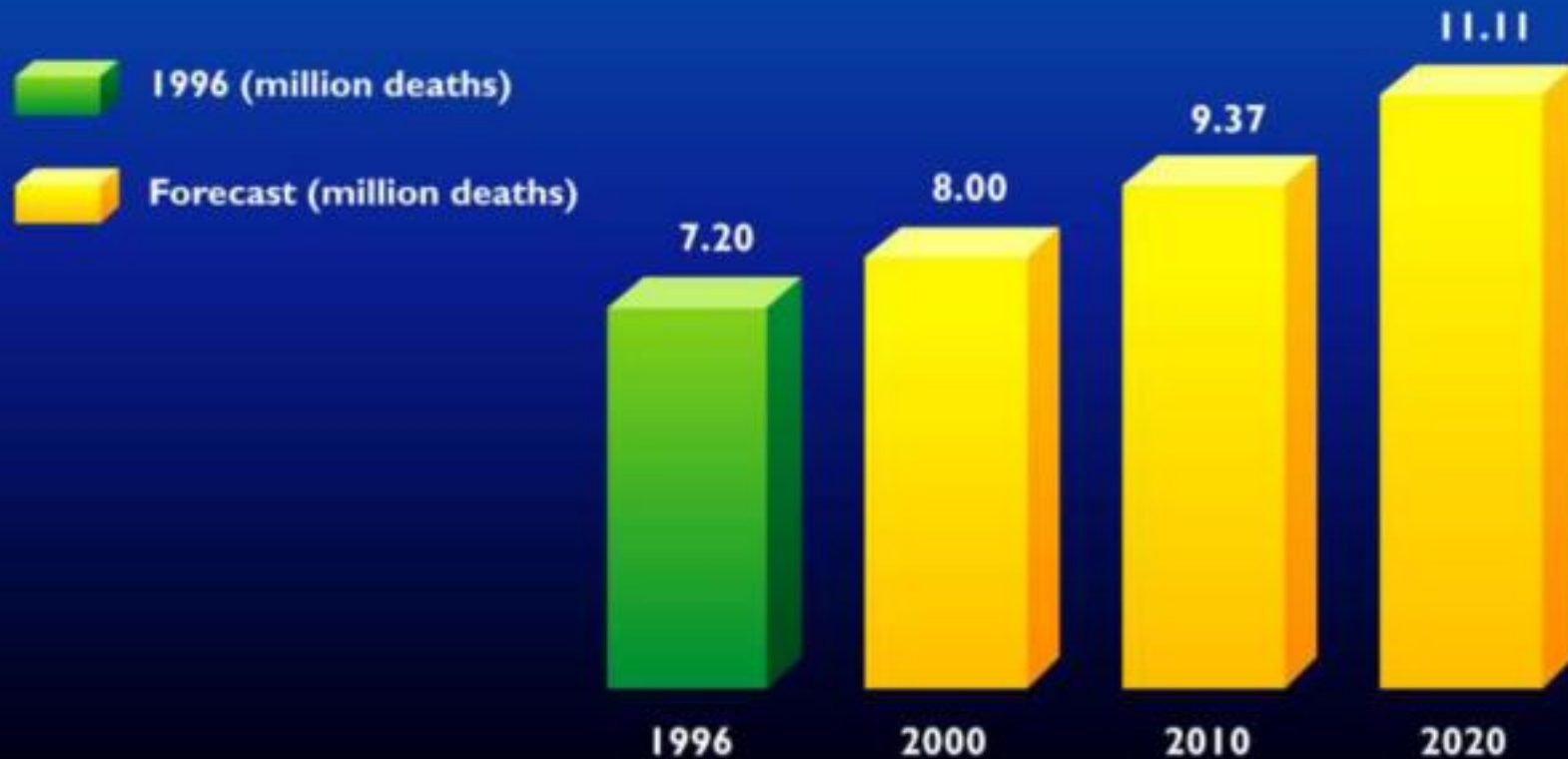
Domenico Monizzi
Cardiologia Territoriale ASP Crotona



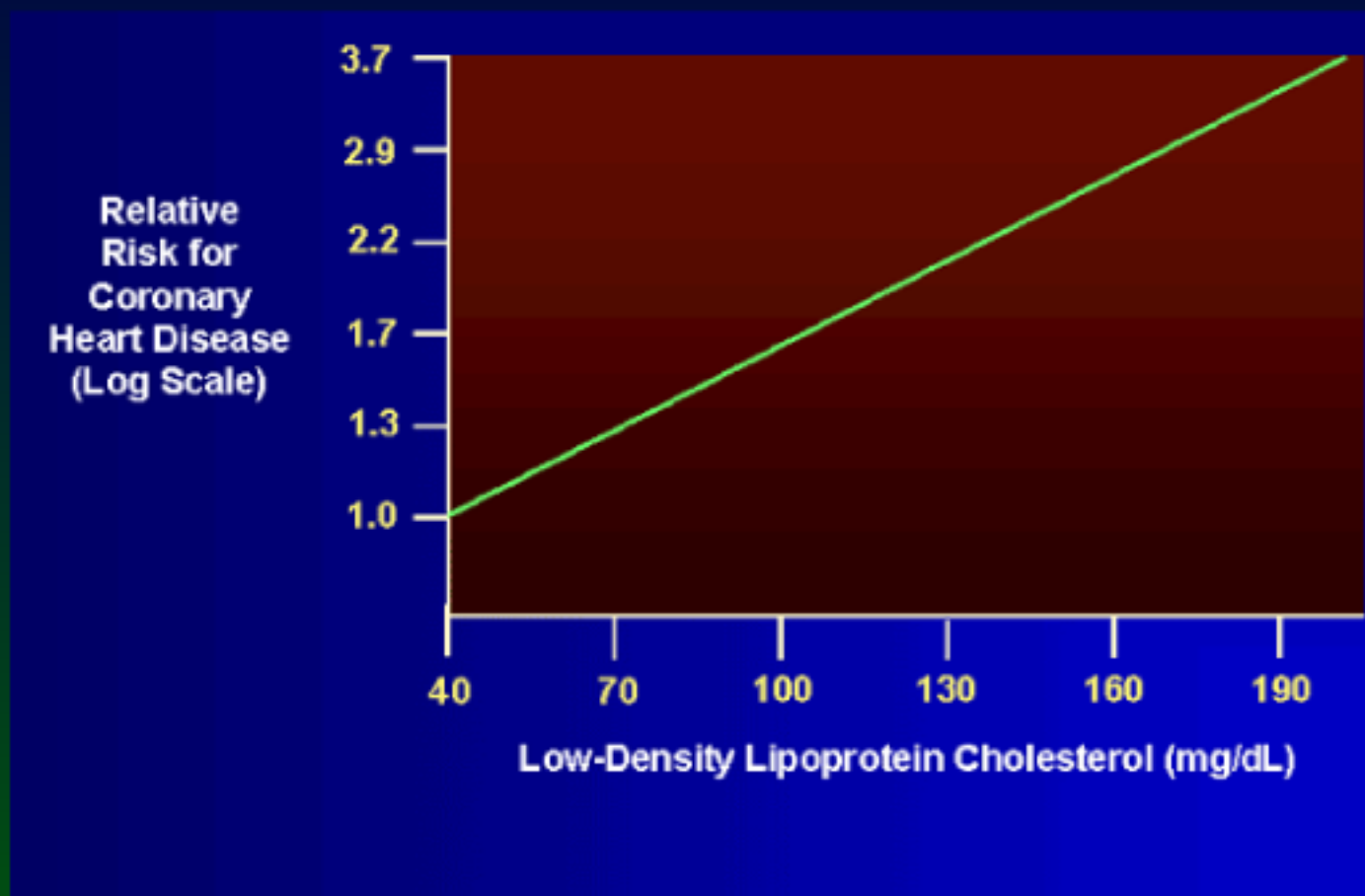
Mortalità dovuta ai principali fattori di rischio globali



Mortalità per coronaropatia



Livelli di C-LDL e rischio di coronaropatia



Recent Clinical Trials and NCEP ATP III

Grundy SM et al. JACC Vol. 44, No. 3, 2004



Colesterolo LDL



- **La riduzione del colesterolo LDL deve essere il primo obiettivo della terapia per la prevenzione degli eventi cardiovascolari**

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MARCH 8, 2004

VOL. 350 NO. 9

PROVE-IT Conclusioni

Lo Studio indica che pazienti recentemente ricoverati per una SCA traggono beneficio da una riduzione precoce e duratura del C-LDL a livelli significativamente minori rispetto agli attuali obiettivi di trattamento.



Primary Study Objective

Evaluate benefit of Simva/ezetimibe vs. simvastatin alone in subjects post ACS to ↓ Major CV events:

1° of: CV death, MI, stroke, UA, Revasc (>30 days)

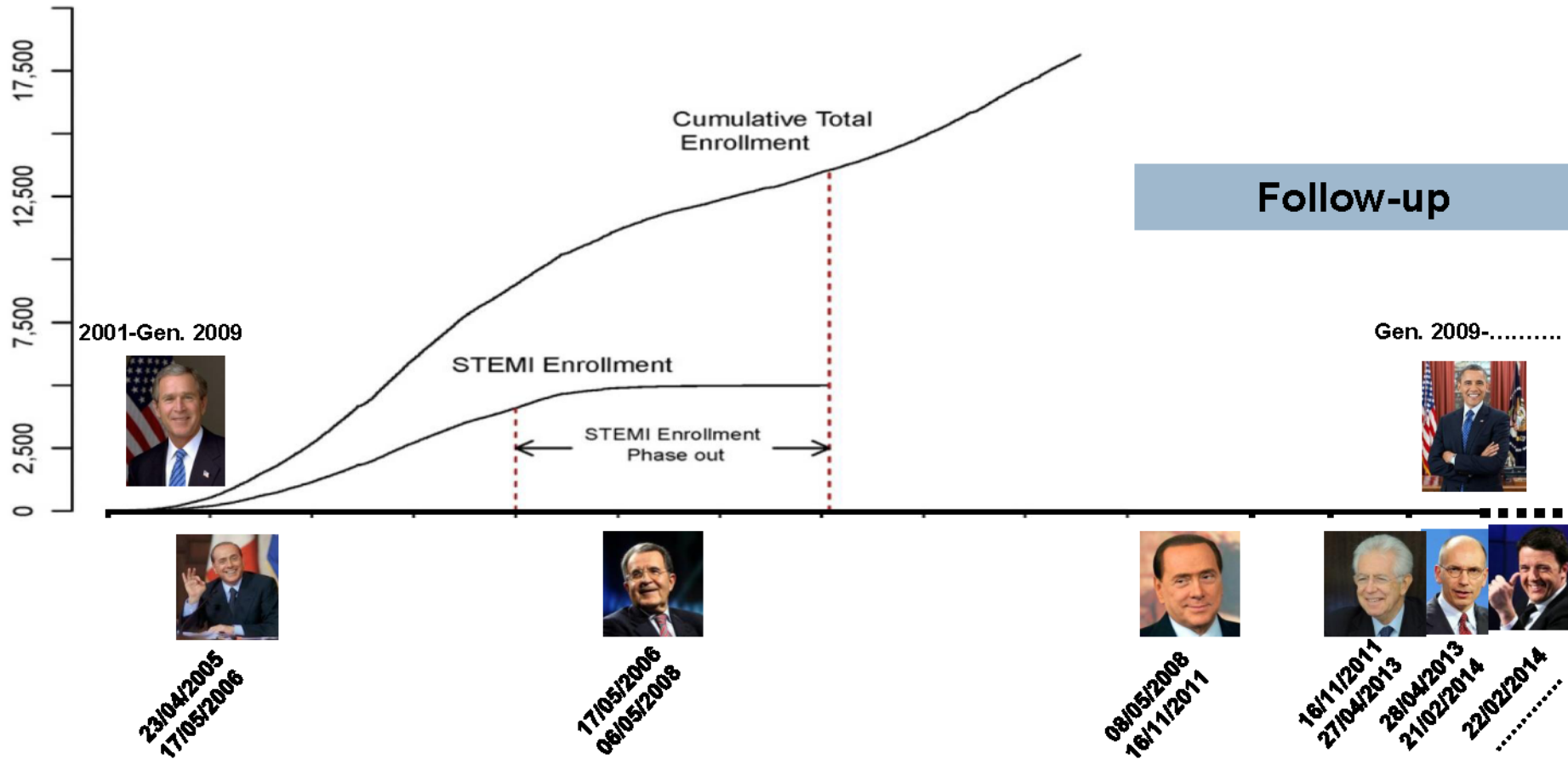
Does lowering LDL further with ezetimibe added to background statin reduce cardiovascular events?

Large CV Trials



Trial	Total N	# Endpoints	1° Endpoints
GUSTO-1	41,021	2848	Death
ALLHAT	33,357	2956	CHD Death/MI
ISIS-4	58,050	4319	Death
ISIS-3	41,299	4321	Death
COMMIT	45,852	4431	Death
HPS	20,536	4628	CHD Death/MI/Stroke/Revasc
		2835	Death
IMPROVE-IT	18,144	5314	CV Death, MI, UA, Stroke, Coronary revasc

Cronologia dello Studio IMPROVE-IT



Follow-up

Study Design

Patients stabilized post ACS ≤ 10 days:

LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM

**2.6mM

N=18,144

Standard Medical & Interventional Therapy

**Simvastatin
40 mg**

*Uptitrated to
Simva 80 mg
if LDL-C > 79
(adapted per
FDA label 2011)*

**Ezetimibe / Simvastatin
10 / 40 mg**

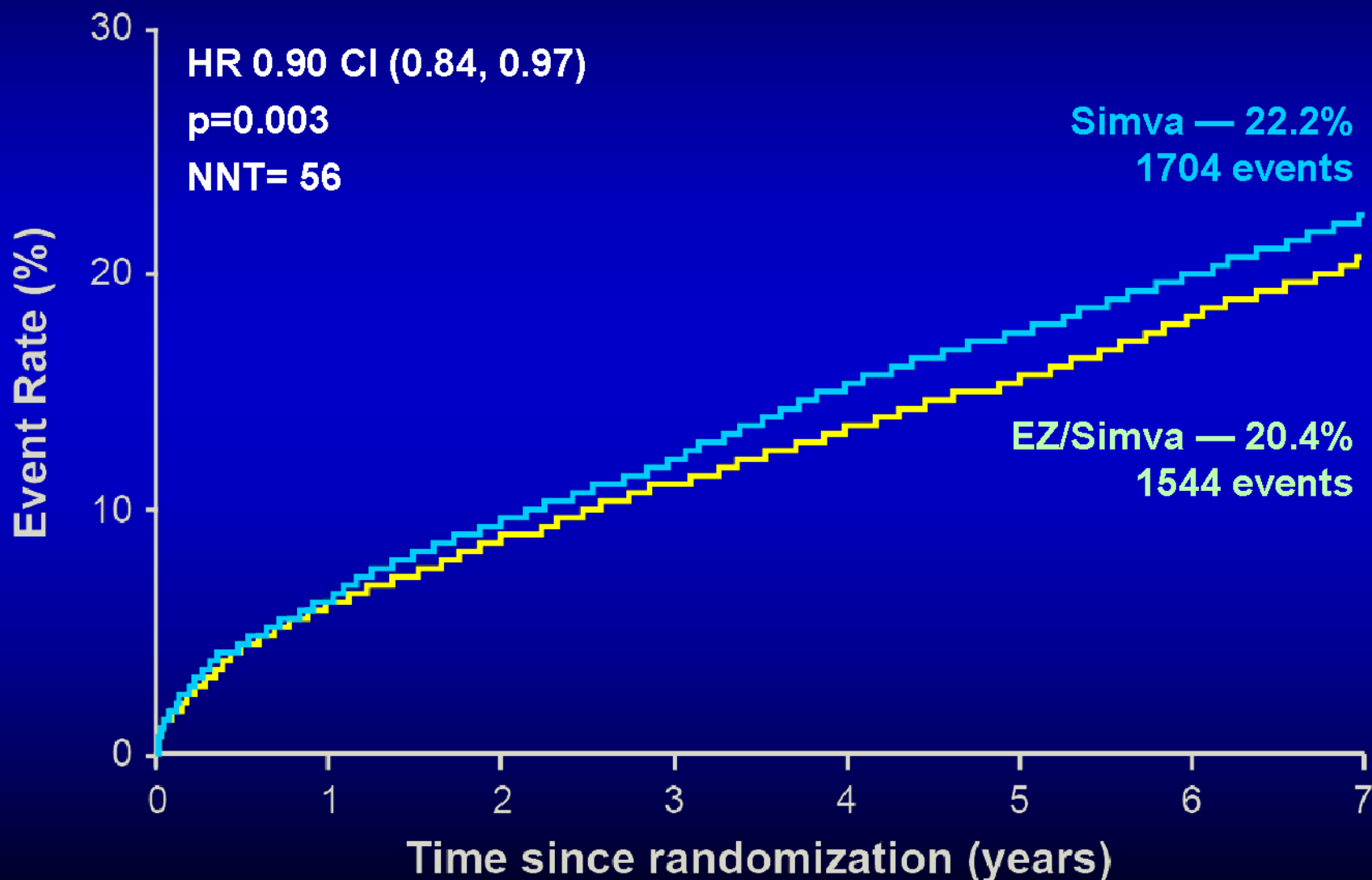
Follow-up Visit Day 30, every 4 months

*90% power to detect
~9% difference*

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

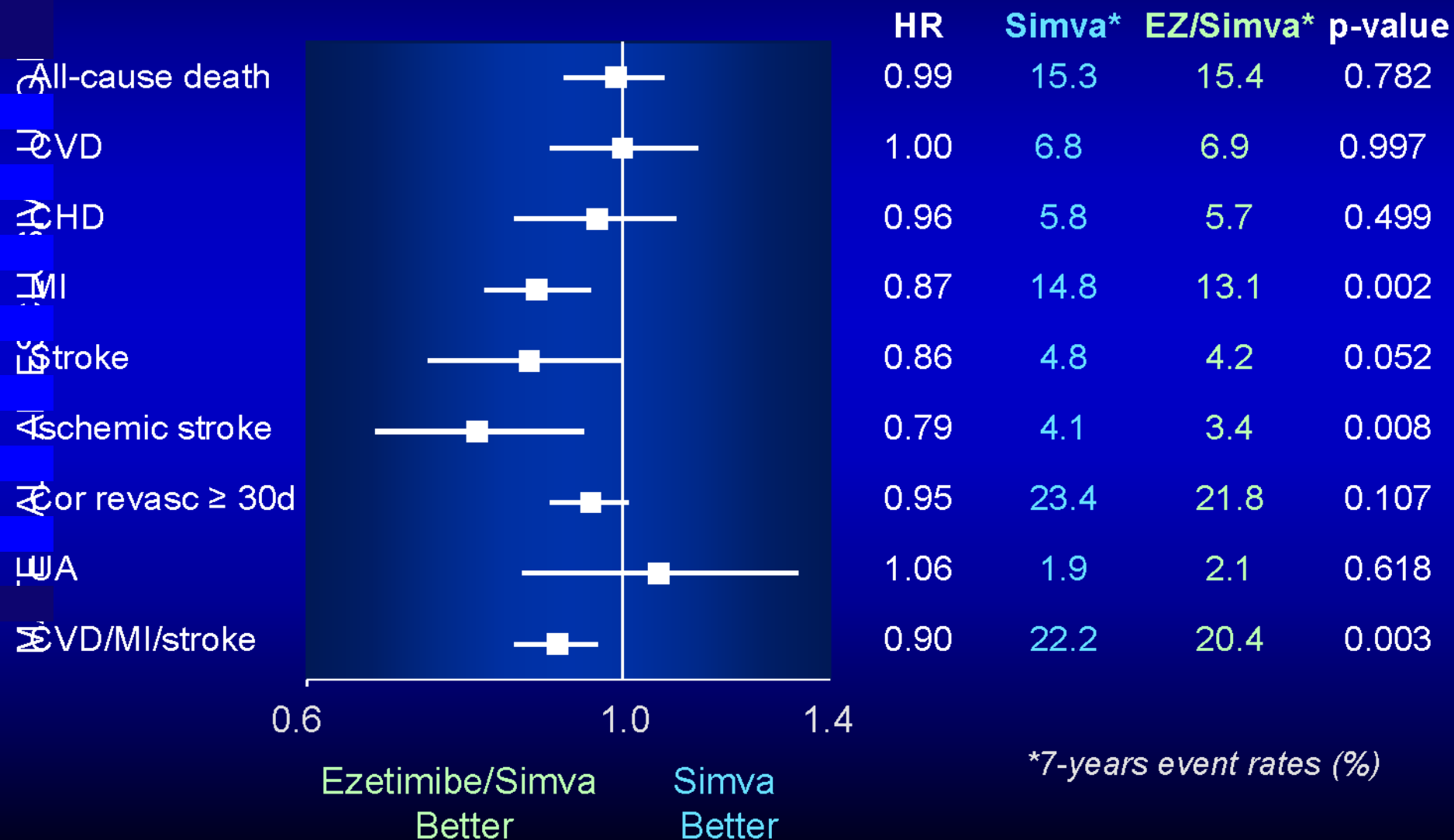
Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

CV Death, Non-fatal MI or Non-fatal Stroke



7-year event rates

Individual Cardiovascular Endpoints and CVD/MI/Stroke



Conclusions

⑩ **IMPROVE-IT**: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:

✔ **YES:** Non-statin lowering LDL-C with ezetimibe reduces cardiovascular events

✔ **YES:** Even Lower is Even Better
(achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)

✔ **YES:** Confirms ezetimibe safety profile

➡ ⑩ **Reaffirms the LDL hypothesis**, that reducing LDL-C prevents cardiovascular events

➡ ⑩ Results could be considered for future guidelines

TODAY

Thanksgiving

PLUS Dating A

- Halliburton announced a deal to buy oil-field services rival Baker Hughes for \$35 billion, but the merger could face resistance from regulators. **B1**
- Deutsche Bank said it was sharply reducing trading in credit-default swaps, the derivatives blamed for accelerating the 2008 financial crisis. **C1**
- Global investors flocked to buy shares in Chinese firms on the first day of a Hong Kong-Shanghai trading link. **C1**
- Merck's Zetia proved effective at cutting risk of heart attacks, strokes and other heart problems in a major trial. **B3**
- The S&P 500 eked out a record, rising 1.50 points to 2041.32. The Dow edged up 13.01 points to 17647.75. **C6**
- Madoff investors will recover nearly \$500 million from two investment funds under a new settlement. **C2**
- An HSBC unit was accused of helping wealthy Belgians



Source: Dealogic Photos: Agence France-Presse/Getty Images (Allergan); Bloomberg (Halliburton)

LARGEST ANNOUNCED DEALS IN 2014

Buyer/Target	Deal Value
Actavis/Allergan (Monday)	\$66 billion
AT&T/DirectTV	\$49 billion
Comcast/Time Warner Cable	\$42 billion
Medtronic/Covidien	\$39 billion
Kinder Morgan/El Paso Partners	\$35 billion
Halliburton/Baker Hughes	\$35 billion

Stock Surge Fueled

Year's Mergers Tallu Tops \$3 Trillion. With J

THE WALL STREET JOURNAL

TUESDAY, NOVEMBER 18, 2014 - VOL. CCLXIV NO. 119

WSJ.com

13.01 0.1% NASDAQ 4671.00 ▼ 0.4% NIKKEI 16973.80 ▼ 3.0% STOXX 600 337.25 ▲ 0.5% 10-YR. TREAS. ▼ 6/32, yield 2.340% OIL \$75.64 ▼ \$0.18 GOLD \$1,183.00 ▼ \$2.00 EURO

at's

Big Year for Big Mergers

Recent tie-ups have pushed the value of merger activity for 2014



Jap

pheric quarters of the old former East. "Poor but sexy" became the city slogan.

"Twenty-five years ago, there was the expectation that a reunified Berlin would become the economic engine of the new Germany, a great metropolis," recalled Peter Schneider, a novelist and the author of "Berlin Now."

"There was even talk of 10 million inhabitants," he said. "In-

Potsdamer Platz in 1962, left, isolated by the Berlin Wall, and this year, after efforts to develop it.

stead of going up, the population dropped."

A friend recently took me to where he lived in East Berlin before the wall fell. He still sees the wall in his mind every day, he told me, when he drives across the city. But he could not find where it had blocked off the

street just yards from his old apartment. Almost all traces of it are gone now, obliterated in the rush to wipe clean the historical slate.

Few Germans thought about preserving significant parts of the wall in 1989, as a cautionary tale. Today, many Berliners re-

gret the haste with which it was demolished and sold in bits and pieces.

"It's horrible, how we deleted it," lamented Simon Schaffer, who runs Factory, a Berlin incubator for start-ups, recently opened in a refurbished brewery

Continued on Page A11

NATIONAL A12-16

Alternative to Statins

A six-year study of 18,000 people found that another drug was also highly successful at lowering LDL cholesterol, offering hope to millions at risk of heart attacks.

PAGE A13

INTERNATIONAL A4-11

Merkel Assails Russia

Chancellor Angela Merkel of Germany, abandoning a traditionally cautious tone, castigated Russia for its actions in Ukraine and for threatening to spread conflict across Europe.

PAGE A10

ARTS C1-7

Two Lives Entwined

The Broadway revival of "Side Show" reintroduces audiences to conjoined twins who became vaudeville stars. Charles Isherwood reviews.

PAGE C1

The New York Times

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Print"

No. 56,689

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TUESDAY, NOVEMBER 18, 2014

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Printe

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HEAL
RECA
AS

POWE

The lower, the better

**Più basso il colesterolo-LDL,
meno eventi cardiovascolari**

Obiettivo

**Identificare
i soggetti a rischio
alto**

Ridurre il Colesterolo LDL
per ridurre gli eventi cardiovascolari

- **Target di C-LDL diversi** per livelli di rischio coronarico diversi, e **tanto più bassi** quanto più **elevato** è il rischio
- **Treat to Target: tanto maggiore è il rischio coronarico assoluto tanto più evidente è il beneficio**

**LDL colesterolo:
quanto abbassarlo?**

Linee guida EAS/ESC 2011

Atherosclerosis 217S (2011) S1–S44



ELSEVIER

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis



Review

ESC/EAS Guidelines for the management of dyslipidaemias

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)^{☆,☆☆}

Authors/Task Force Members: Alberico L. Catapano (EAS Chairperson) (Italy)^{*}, Željko Reiner (ESC Chairperson) (Croatia)^{**}, Guy De Backer (Belgium), Ian Graham (Ireland), Marja-Riitta Taskinen (Finland), Olov Wiklund (Sweden), Stefan Agewall (Norway), Eduardo Alegria (Spain), M. John Chapman (France), Paul Durrington (UK), Serap Erdine (Turkey), Julian Halcox (UK), Richard Hobbs (UK), John Kjekshus (Norway), Pasquale Perrone Filardi (Italy), Gabriele Riccardi (Italy), Robert F. Storey (UK), David Wood (UK)

TARGET per LDL-C secondo diverse linee guida

<i>RCVG a 10 anni</i>	<i>TARGET NCEP ^[1]</i>	<i>TARGET ESC ^[2]</i>
<i>0-5 %</i>	<i>< 160 mg/dL</i>	<i>< 115 mg/dL</i>
<i>5-10 %</i>	<i>< 160 mg/dL</i>	<i>< 115 mg/dL</i>
<i>10-15 %</i>	<i>< 130 mg/dL</i>	<i>< 100-115 mg/dL</i>
<i>15-20%</i>	<i>< 130 (100) mg/dL</i>	<i>< 100 (80) mg/dL</i>
<i>> 20%</i>	<i>< 100 (70) mg/dL</i>	<i>< 100 (80) mg/dL</i>

^[1] Grundy SM et al. *Circulation* 2004; 110:227-239.

^[2] Fourth Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2007;28:2375-2414.



AACE Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS' GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF ATHEROSCLEROSIS

Paul S. Jellinger, MD, MACE; Donald A. Smith, MD, FACE;

Adi E. Mehta, MD, FRCP(C), FACE; Om Ganda, MD, FACE;

Yehuda Handelsman, MD, FACP, FACE; Helena W. Rodbard, MD, FACP, MACE;

Mark D. Shepherd, MD, FACE; John A. Seibel, MD, MACE;

the AACE Task Force for Management of Dyslipidemia and Prevention of Atherosclerosis

Coronary artery disease risk categories and low-density lipoprotein treatment goals

Risk category	Risk factors ^a /10-year risk ^b	LDL-C treatment goal
Very high risk	Established or recent hospitalization for coronary, carotid, and peripheral vascular disease or diabetes plus 1 or more additional risk factor(s)	<70 mg/dL
High risk	≥2 risk factors and 10-year risk >20% or CHD risk equivalents ^c , including diabetes with no other risk factors	<100 mg/dL
Moderately high risk	≥2 risk factors and 10-year risk 10%-20%	<130 mg/dL
Moderate risk	≥2 risk factors and 10-year risk <10%	<130 mg/dL
Low risk	≤1 risk factor	<160 mg/dL

Abbreviations: CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.

^a Major independent risk factors are high low-density lipoprotein cholesterol, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low high-density lipoprotein cholesterol (<40 mg/dL), family history of coronary artery disease (in male first-degree relative younger than 55 years; in female first-degree relative younger than 65 years), and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high high-density lipoprotein cholesterol (≥60 mg/dL) (10 [EL 4], 11 [EL 4]).

^b Framingham risk scoring is applied to determine 10-year risk (10 [EL 4]).

^c Coronary artery disease risk equivalents include diabetes and clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease).

NOTA 13 APRILE 2013: stratificazione del rischio cardiovascolare

- Il rischio “**moderato**” (in ESC score 2- 5%) è stato **differenziato** nelle categorie di “**medio**” (score 2-3%- target C-LDL **<130 mg/dl**) e “**moderato**” (score 4-5%-target C-LDL **<115 mg/dl**)
- **Rischio alto- target C-LDL < 100 mg/dl:**
pazienti con score ≥ 5 e $< 10\%$ di rischio a 10 anni di CV fatale, pazienti con dislipidemie familiari, ipertensione severa, pazienti diabetici senza fattori di rischio CV e senza danno d'organo, pazienti con IRC moderata (FG 30-59 ml/min)
- **Rischio molto alto- target C-LDL < 70 mg/dl:**
pazienti con score $\geq 10\%$ di rischio a 10 anni di CV fatale, pazienti con malattia coronarica, stroke ischemico, arteriopatie periferiche, pregresso IM, bypass aorto-coronarico, pazienti diabetici con più fattori di rischio e/o markers di danno d'organo (come microalbuminuria) e i pazienti con IRC grave (FG 29-15 ml/min)



Goals

- ⑩ **IMPROVE-IT**: First large trial evaluating clinical efficacy of combination EZ/Simba vs. simvastatin (i.e., the addition of ezetimibe to statin therapy):
 - Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?
 - “Is (Even) Lower (Even) Better?” (estimated mean LDL-C ~50 vs. 65mg/dL)
 - Safety of ezetimibe

Ma queste Linee Guida
vengono applicate
nella pratica clinica
di tutti i giorni ?

Sistemi di comunicazione efficaci: la lettera di dimissione

- la diagnosi
- i fattori di rischio
- l'esito degli esami
- la condizione di rischio del paziente
- la dieta suggerita ...
- l'attività fisica consigliata con indicazione di f.c. allenante e modalità di esecuzione
- il profilo psicologico del paziente
- la terapia suggerita
- il calendario dei prossimi appuntamenti



Problema: Il target

- Mancato raggiungimento del target terapeutico in un'elevata quota di pazienti ad alto rischio cardiovascolare
- Scarsa consapevolezza della correlazione tra riduzione del rischio cardiovascolare e obiettivi terapeutici suggeriti dalle Linee Guida
- Mancato monitoraggio dell'efficacia del trattamento ipocolesterolemizzante

Problema: Il trattamento

- Scarsa propensione allo screening dei principali fattori di rischio
- Tendenza ad insistere con la correzione dello stile di vita anche quando è del tutto evidente che il paziente non può - non vuole - non riesce ad attuarli
- Mancato trattamento di un'elevata quota di pazienti ad alto rischio cardiovascolare

Terapia ipolipemizzante : perche' non si raggiunge il target

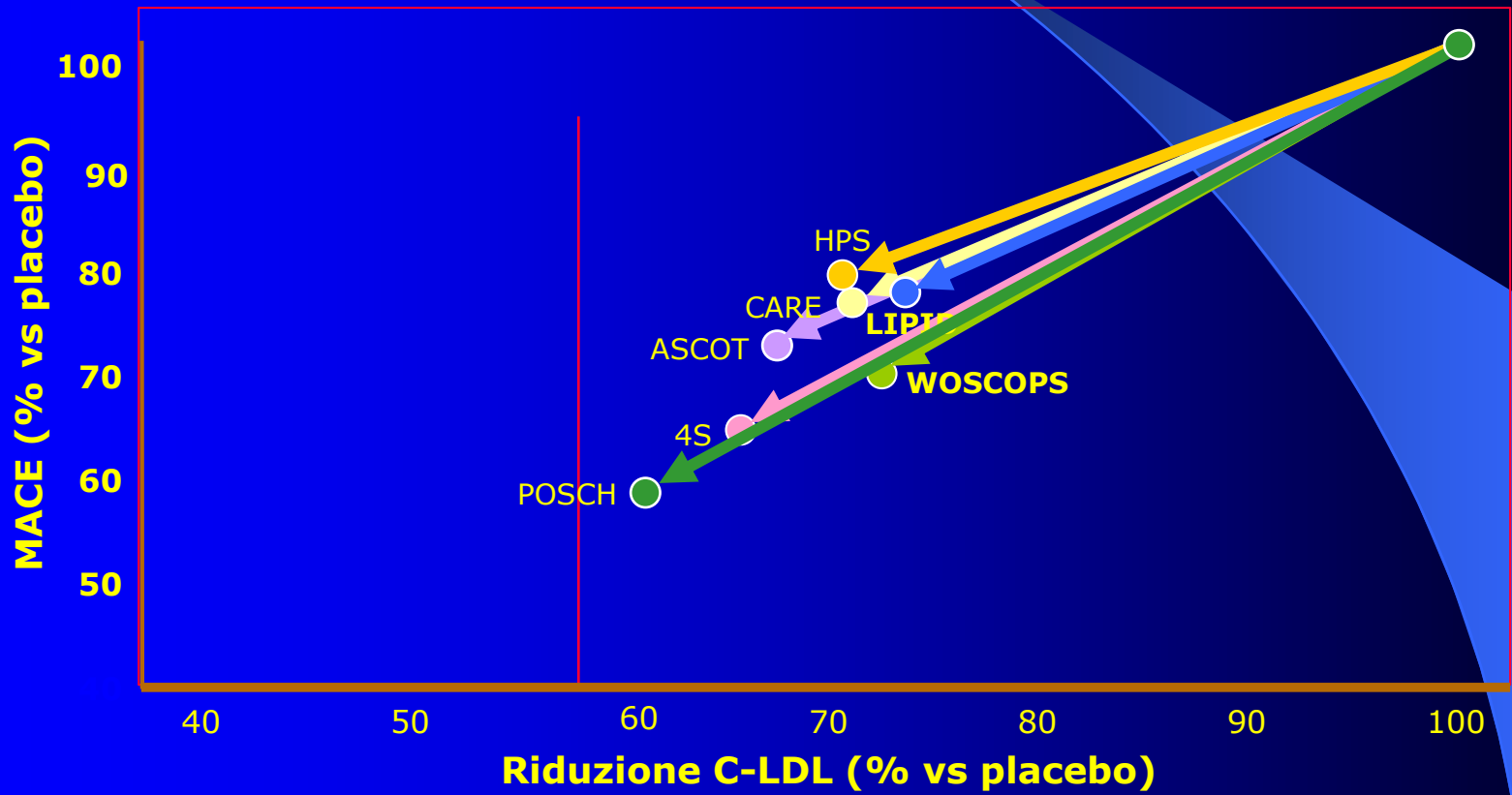
Atteggiamento

- **Apatia del paziente : scarsa compliance**
- **Apatia del medico : timidezza prescrittiva
inerzia terapeutica**



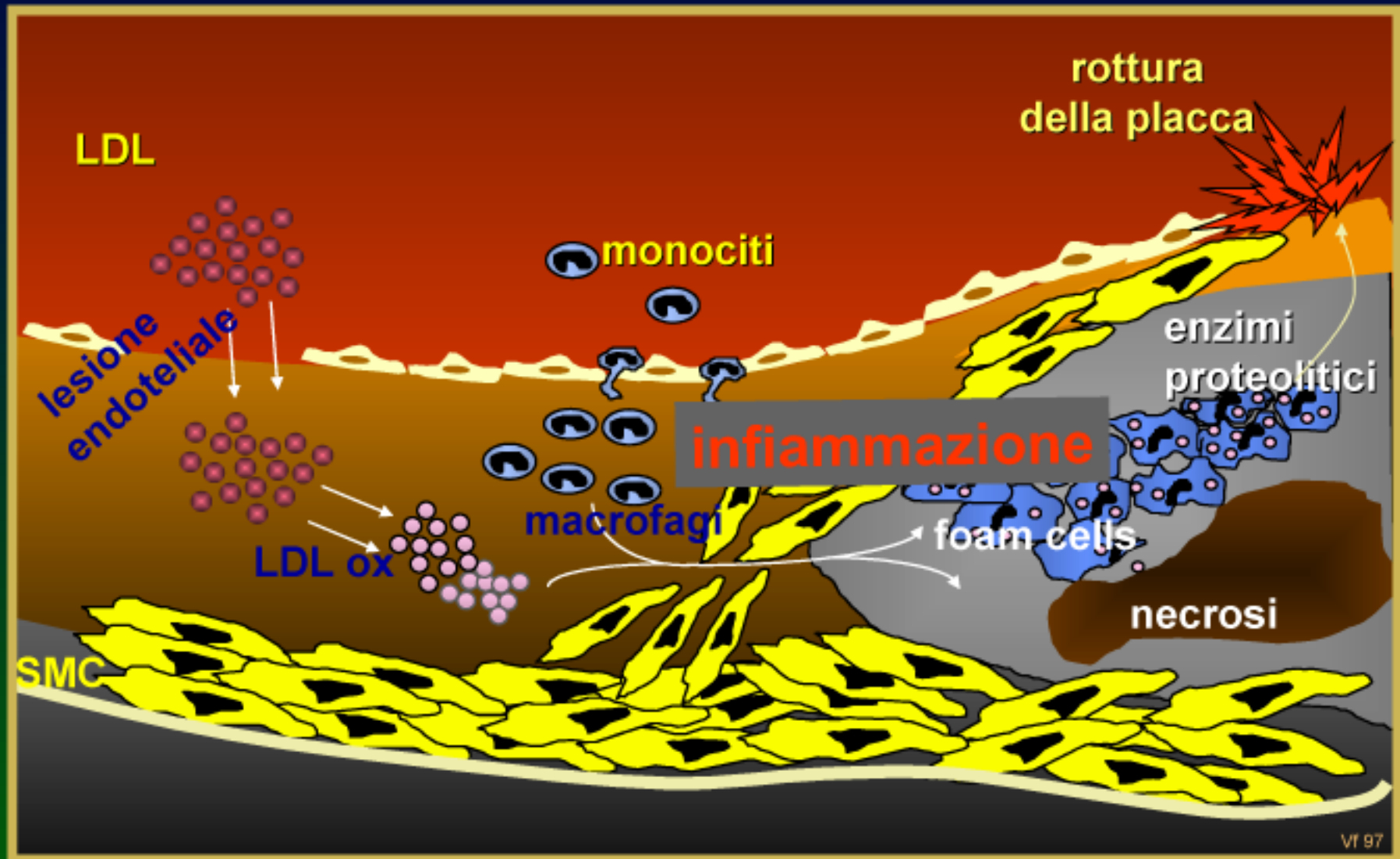
Terapie inadeguate

Interventi di maggiore efficacia su C-LDL sembrano ridurre in modo maggiore gli eventi



cardiovascolari maggiori

la placca aterosclerotica: un processo flogistico continuo



NON SOLO COLESTEROLO



Table 5
**Major Coronary Artery Disease Risk Factors (10 [EL 4], 11 [EL 4],
 12 [EL 4], 13 [EL 4], 14 [EL 2], 15 [EL 4], 16 [EL 2], 17 [EL 4],
 18 [EL 2], 19 [EL 2], 20 [EL 4], 21 [EL 3])**

Major risk factors	Additional risk factors	Nontraditional risk factors
Advancing age ^{a,d}	Obesity, abdominal obesity ^{c,d}	Elevated lipoprotein (a)
High total serum cholesterol level ^{a,b,d}	Family history of hyperlipidemia ^d	Elevated clotting factors
High non-HDL-C ^d	Small, dense LDL-C ^d	Inflammation markers (hsCRP; Lp-PLA₂)
High LDL-C ^{a,d}	↑ Apo B ^d	Hyperhomocysteinemia
Low HDL-C ^{a,d,e}	↑ LDL particle number	Apo E4 isoform
Diabetes mellitus ^{a,b,c,d}	Fasting/postprandial hypertriglyceridemia ^d	Elevated uric acid
Hypertension ^{a,b,c,d}	PCOS ^d	
Cigarette smoking ^{a,b,c,d}	Dyslipidemic triad ^f	
Family history of CAD ^{a,d,g}		

Abbreviations: apo, apolipoprotein; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, highly sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp-PLA₂, lipoprotein-associated phospholipase A₂; PCOS, polycystic ovary syndrome.

^a Risk factors identified in the Framingham Heart study.

^b Risk factors identified in the MRFIT study (Multiple Risk Factor Intervention Trial).

^c Risk factors identified in the INTERHEART study.

^d Risk factors identified in guidelines and position statements (National Cholesterol Education Program Adult Treatment Panel III, American Association of Clinical Endocrinologists Polycystic Ovary Syndrome Position Statement, American Association of Clinical Endocrinologists Insulin Resistance Syndrome Position Statement, American Diabetes Association Standards of Care 2009, American Diabetes Association/American College of Cardiology Consensus Statement on Lipoprotein Management in Patients with Cardiometabolic Risk).

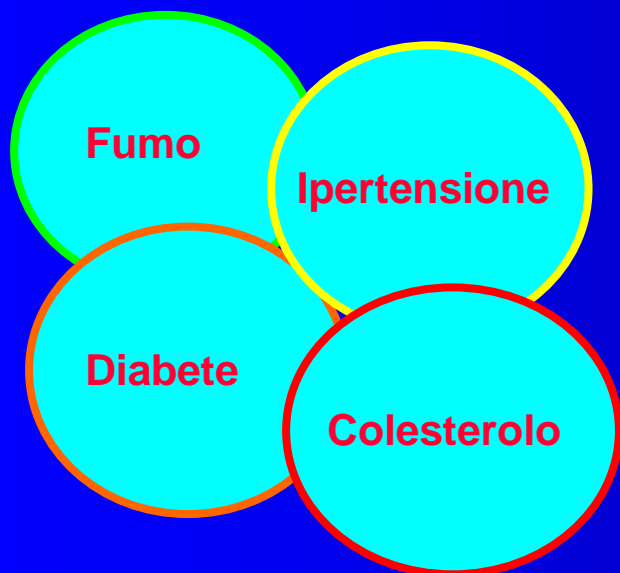
^e Elevated high-density lipoprotein cholesterol is a negative risk factor.

^f Hypertriglyceridemia; low high-density lipoprotein cholesterol; and small, dense low-density lipoprotein cholesterol.

^g Definite myocardial infarction or sudden death before age 55 years in father or other male first-degree relative or before

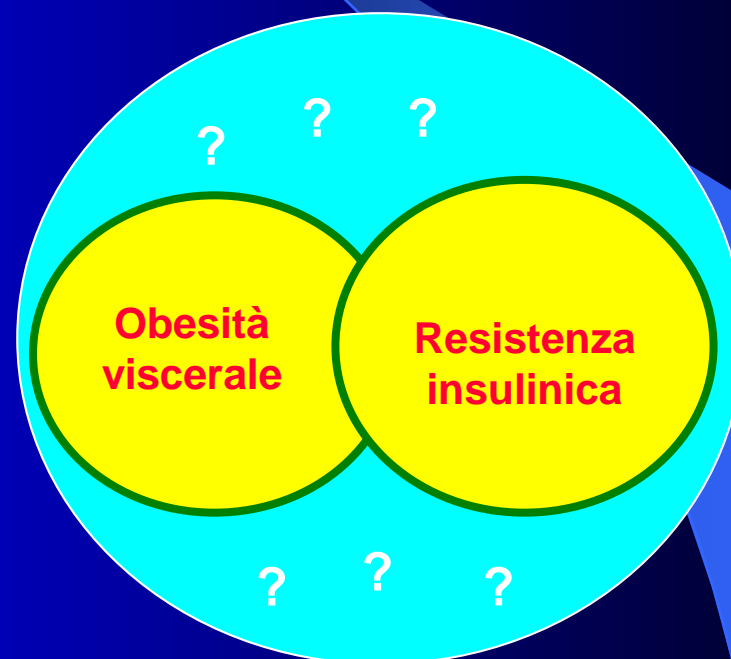
DAL RISCHIO CARDIOVASCOLARE GLOBALE AL RISCHIO CARDIOMETABOLICO

FATTORI TRADIZIONALI



+

FATTORI EMERGENTI



Obiettivi per il controllo del rischio cardiometabolico globale:

- Colesterolo LDL
- Adiposità viscerale e complicanze metaboliche correlate (sindrome metabolica)

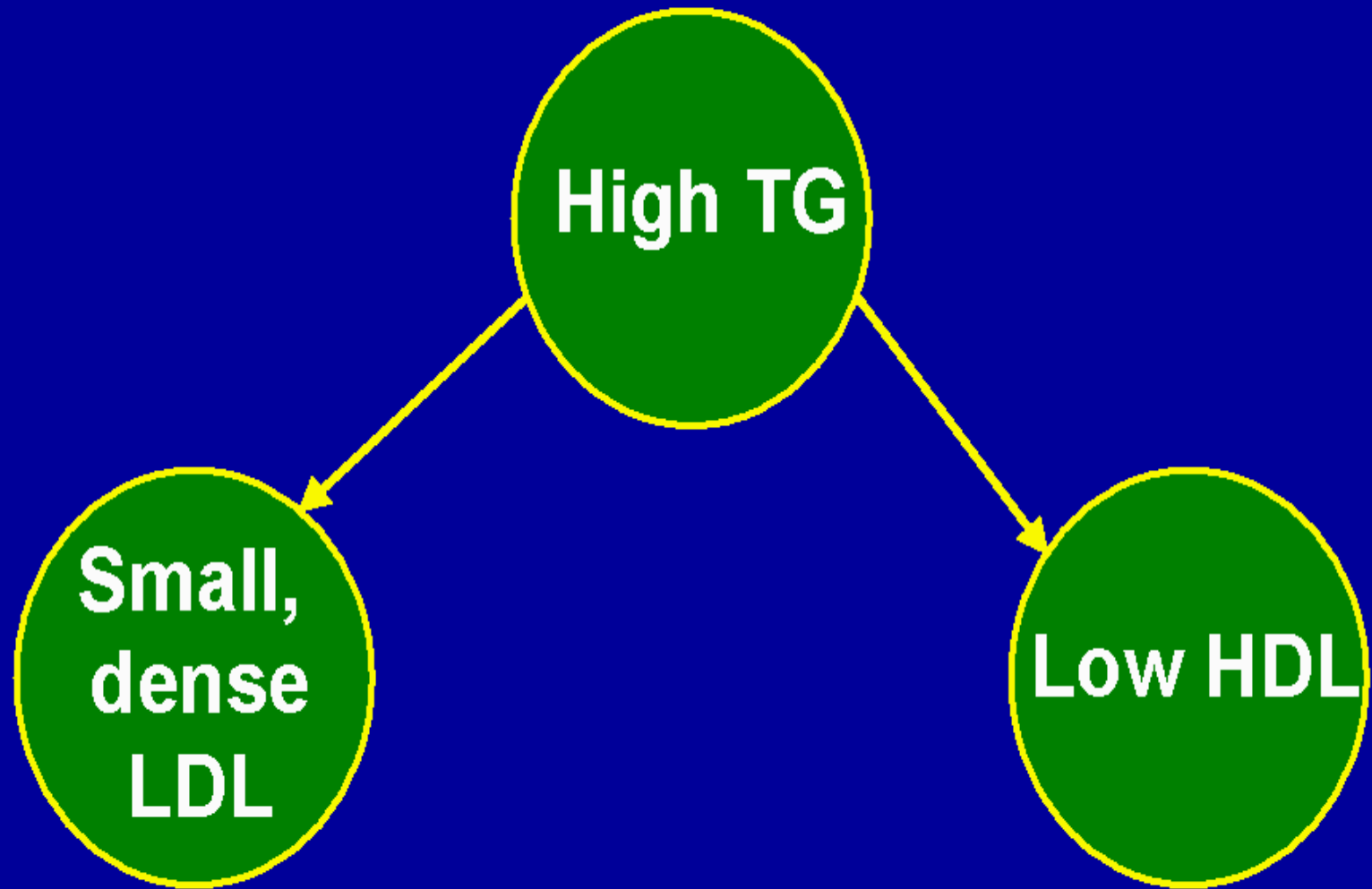
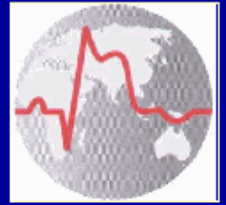
Metabolic syndrome (Syndrome X)

- Central obesity
- High blood pressure
- High triglycerides
- Low HDL-cholesterol
- Insulin resistance

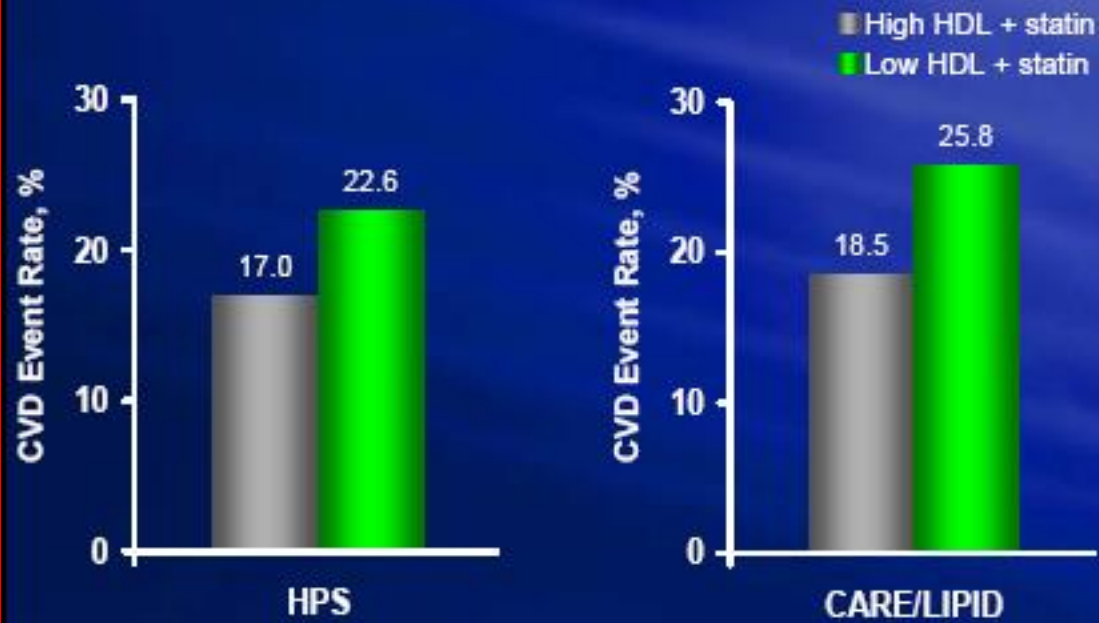




The Lipid Triad

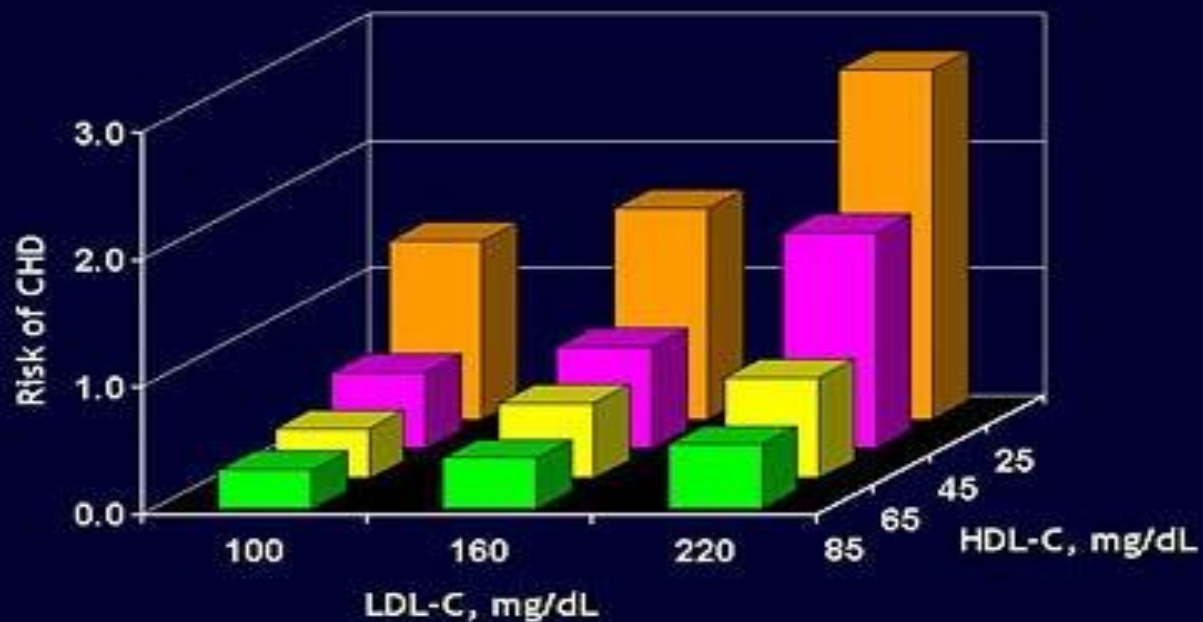


Statin Therapy Does Not Eliminate the CVD Risk Associated With Low HDL-C Level



HPS Collaborative Group. *Lancet*. 2002;360:7-22.
Sacks FM, et al. *Circulation*. 2000;102:1893-1900.

Low HDL-C: Independent Predictor of CHD Risk Even When LDL-C Is Low



Gordon T et al. *Am J Med*. 1977;62:707-714.

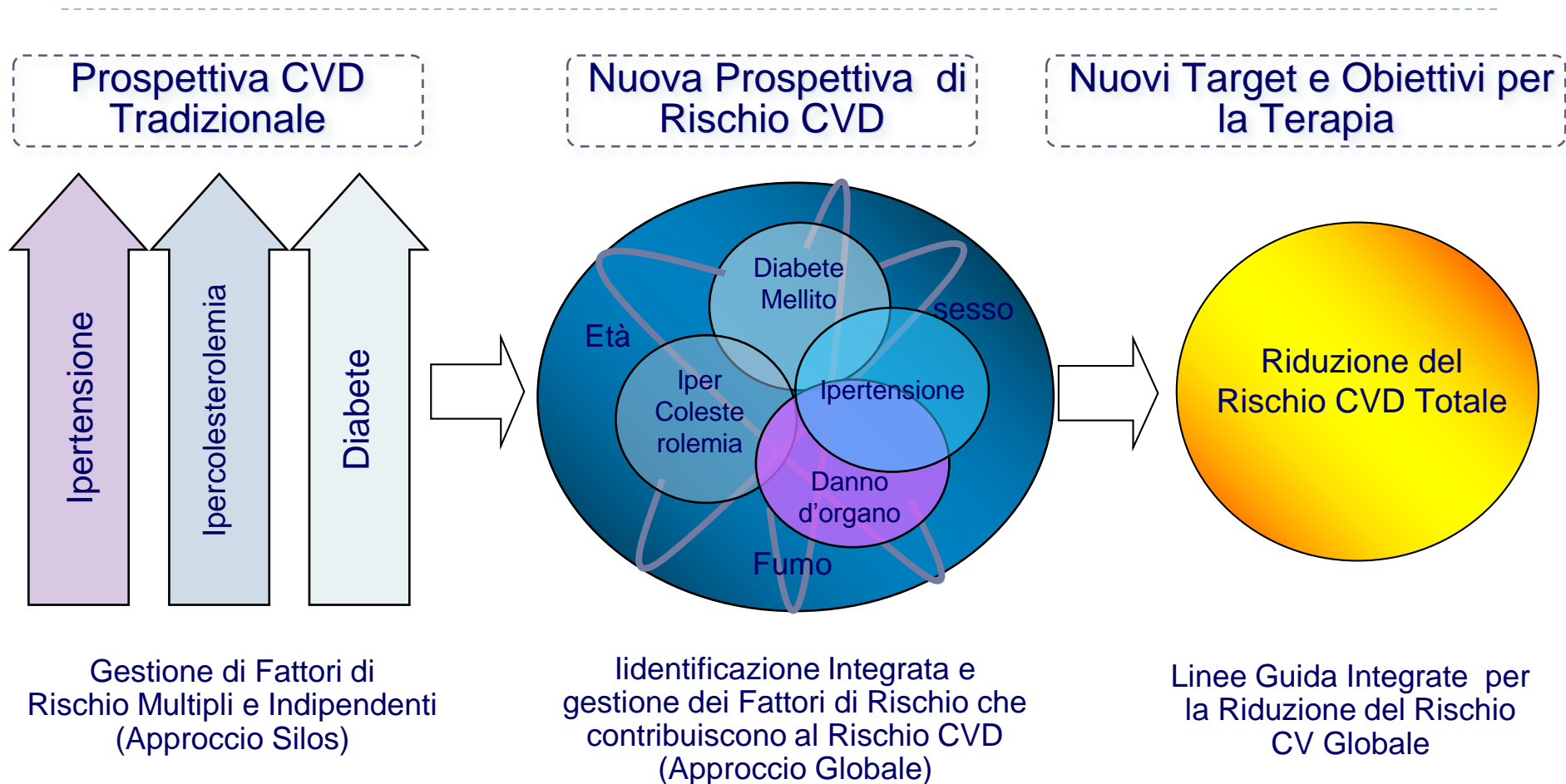
CONCLUSIONI

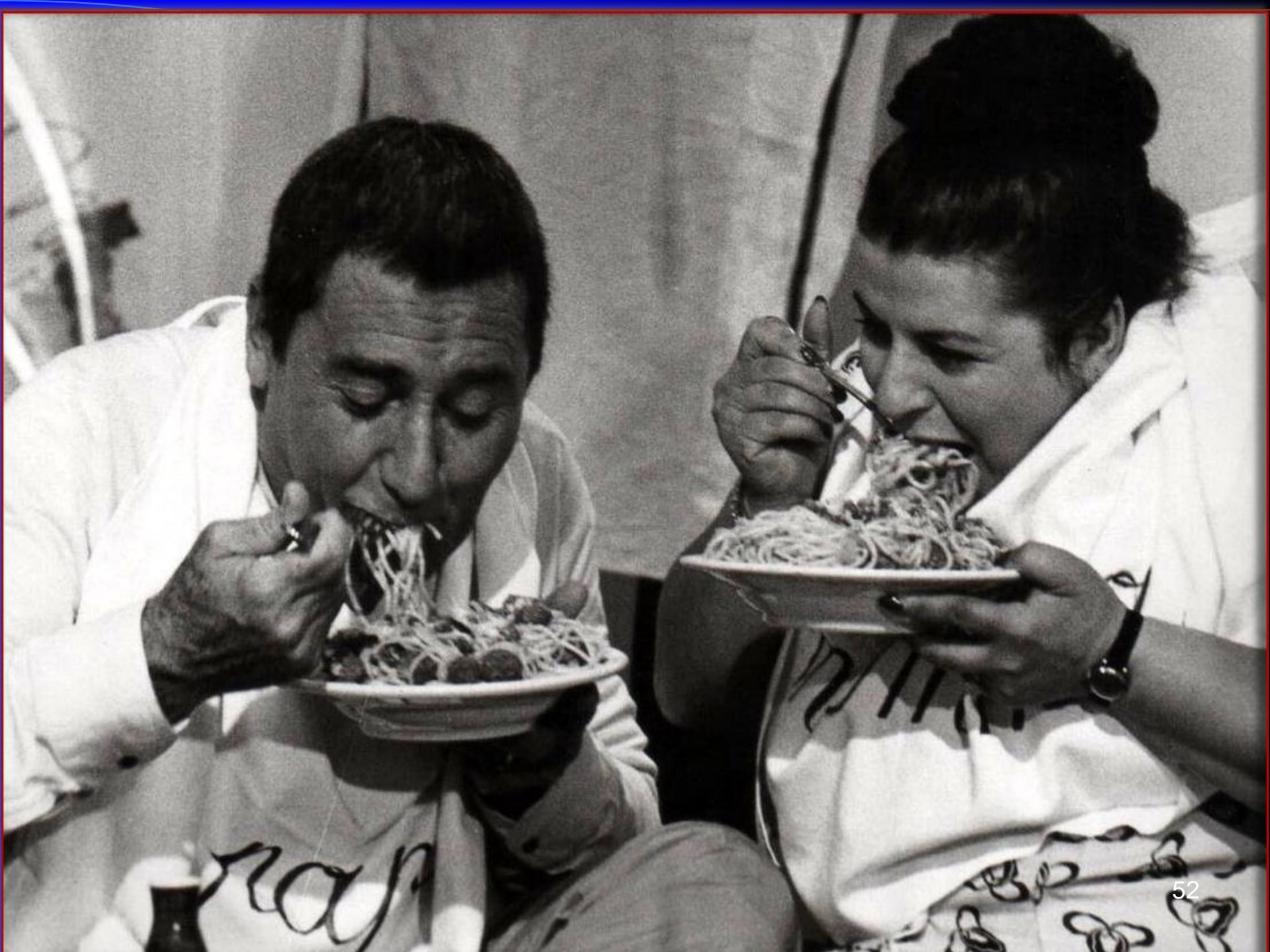
Identificare i pazienti con la malattia cardiovascolare o a rischio globale elevato e quelli con la sindrome metabolica.

Usare le statine con i dosaggi dimostrati efficaci nei trials

Ezetemibe si e' rivelata efficace ,sicura nel ridurre LDL e gli eventi cardiovascolari.

Moderna Strategia per la prevenzione CVD





***Cio che accade prima non e'
necessariamente l'inizio***

Henning Mankell

Who Has More Cardiovascular Risk Factors?

Sir Winston Churchill, 91 ♀



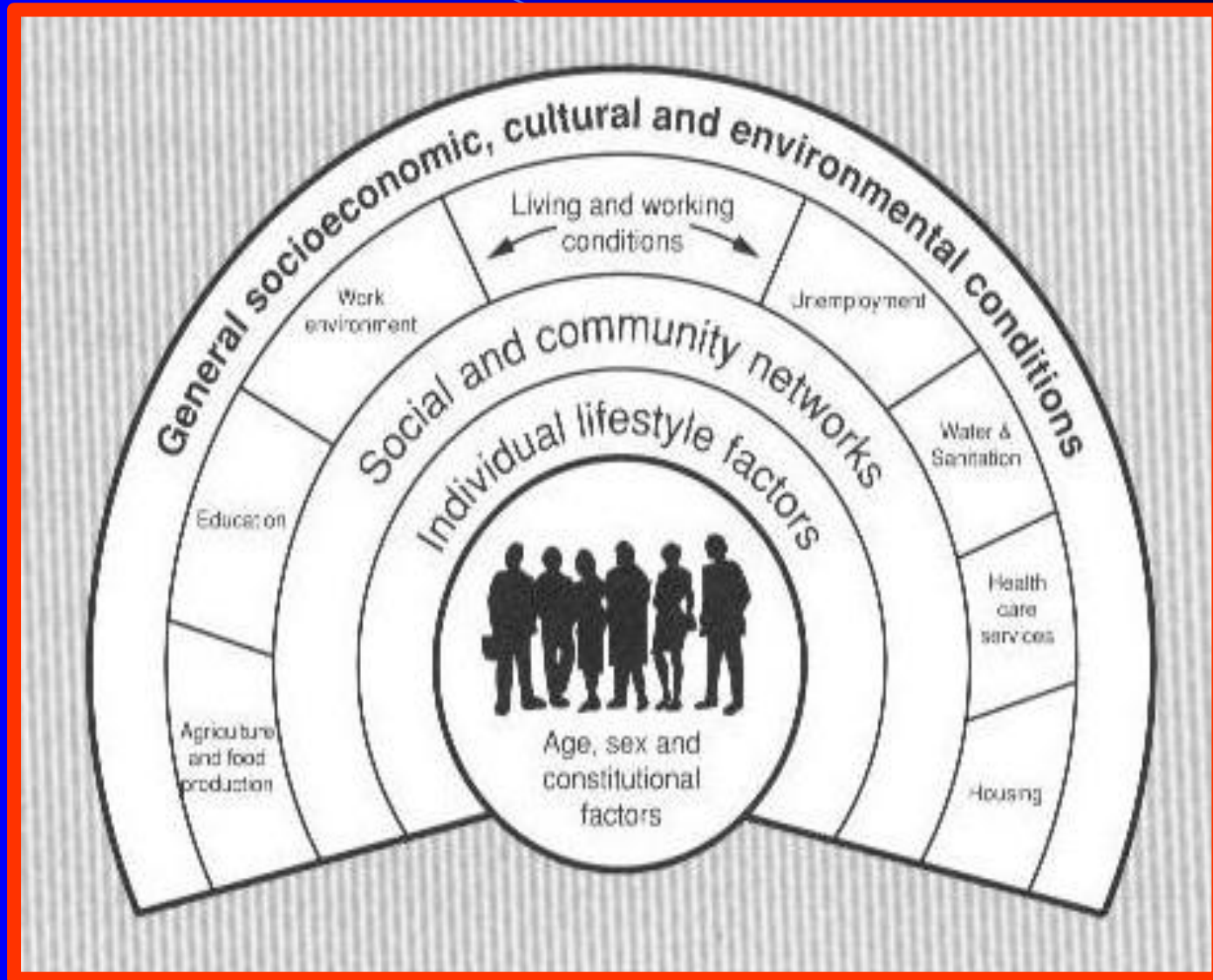
- Overweight
- Not Fit
- Heavy Smoker

Jim Fixx, 53 ♀ ♥



- Not Overweight
- Very Fit
- Non-Smoker

The Main Determinants of Health

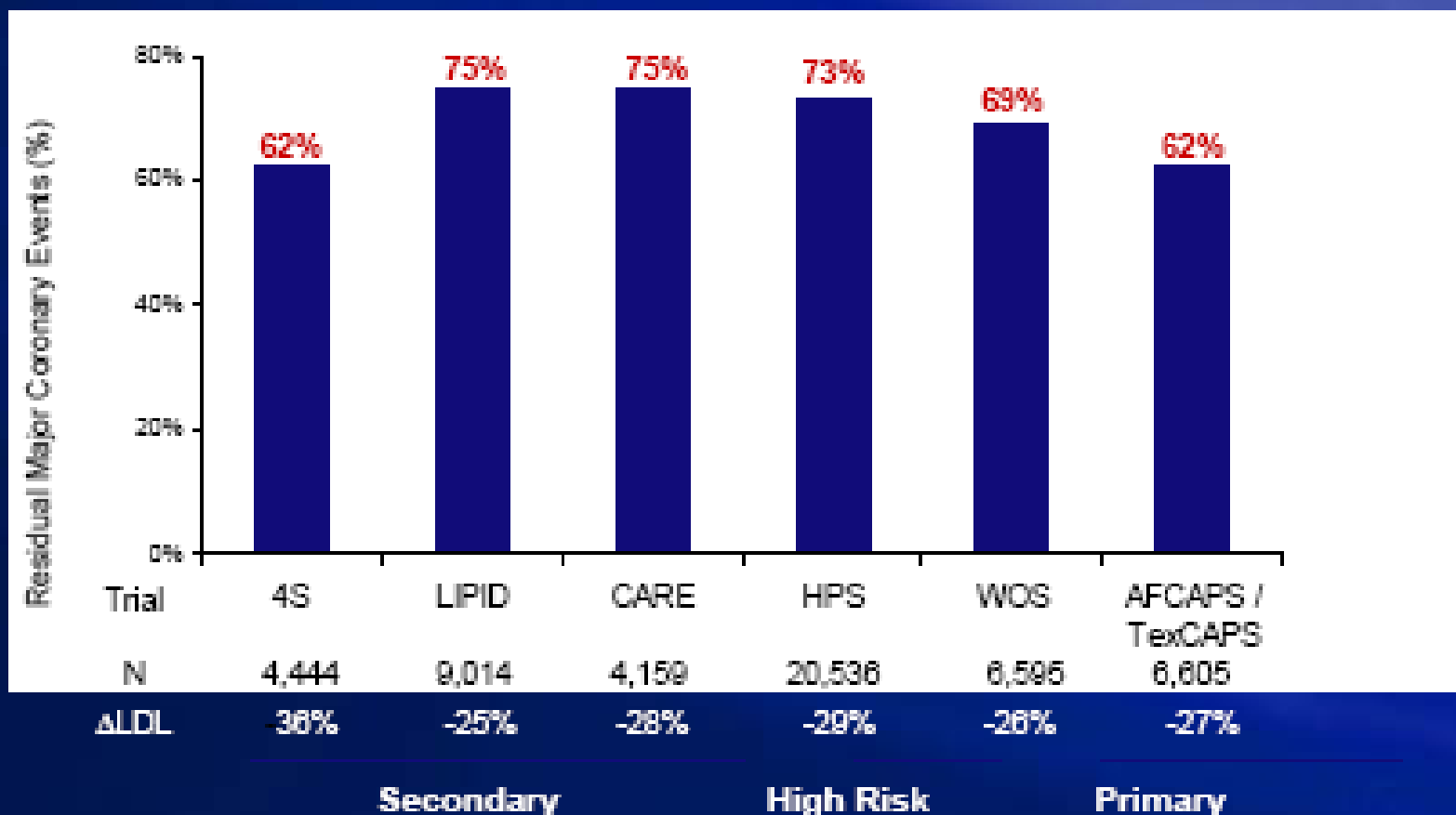


From Dahlgren G and Whitehead M, 1991

“forgotten majority”

Peter Libby JACC 2005

The Forgotten Majority: Residual Burden of CV Events Remains High in the Statin “Megatrials”



Source: Libby P. *J Am Coll Cardiol*. 2005;46:1225.

AUTOPOIESI: SISTEMI CONSERVATIVI

- Nei sistemi biologici viventi autopoietici (es., sistema nervoso, sistema immunitario, circolatorio..), se ci fosse una malattia(placca aterosclerotica...), l'autopoiesi continuerebbe a funzionare. L'**organizzazione** rimarrebbe intatta, essa è stabile, continua, sempre attiva, è un **sistema conservativo, diverso da individuo ad individuo.**

- Nei sistemi biologici con macro-interazioni c'è una **"mente"** sintesi di un sistema autopoietico che si basa su un'unità composita (es., **sistema psico – neuro – endocrino - immunitario**) diversa da soggetto a soggetto, tanto che oggi si parla sempre di piu' di **“medicina personalizzata”**.

MEDICINA PERSONALIZZATA

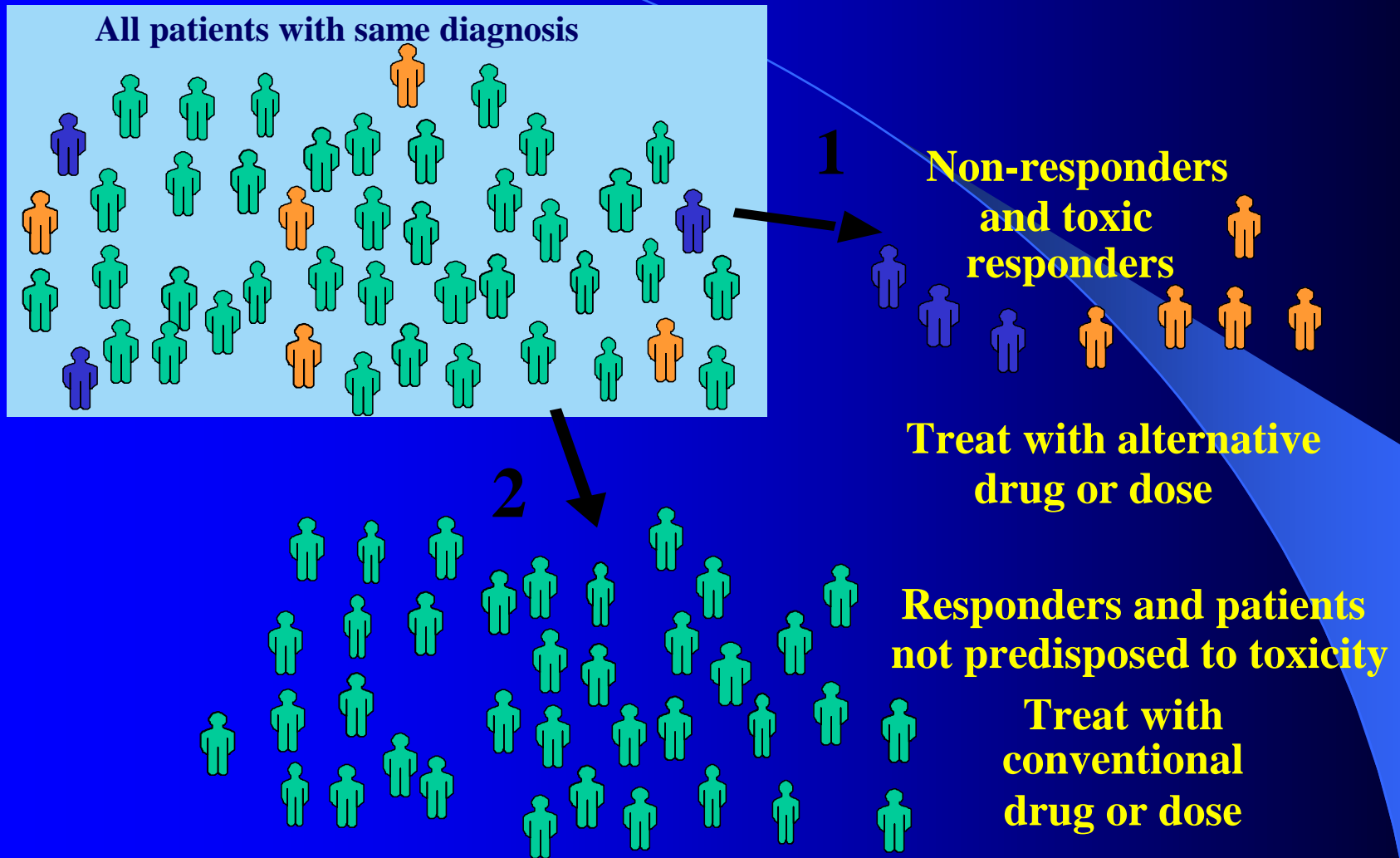
- **La medicina personalizzata: ritagliare il trattamento terapeutico sulla base del profilo genetico. Le varianti genetiche sono comuni ma possono avere un impatto notevole su come l'organismo metabolizza i farmaci ed in senso lato una terapia. (Mayo Clinic)**

MEDICINA PREDITTIVA

Deriva dall'interazione tra tecniche di laboratorio, analisi statistica, calcolo delle probabilità, identificazione dei fattori di rischio genetici ed ambientali di malattia, al fine di **pronosticare la probabile storia clinica del *singolo individuo* in qualsiasi momento o di **rallentarne lo sviluppo**, suggerendo stili di vita e/o terapie personalizzate.**

INCENTRATA SUL SINGOLO PAZIENTE

Il potenziale della farmacogenomica: Medicina predittiva e terapia personalizzata



“Il farmaco giusto alla dose giusta per il paziente giusto”

PATIENTS CAN RESPOND DIFFERENTLY TO THE SAME MEDICINE

HYPERTENSION DRUGS
ACE Inhibitors

10-30%



HEART FAILURE DRUGS
Beta Blockers

15-25%



ANTI-DEPRESSANTS

20-50%



CHOLESTEROL DRUGS
Statins

30-70%



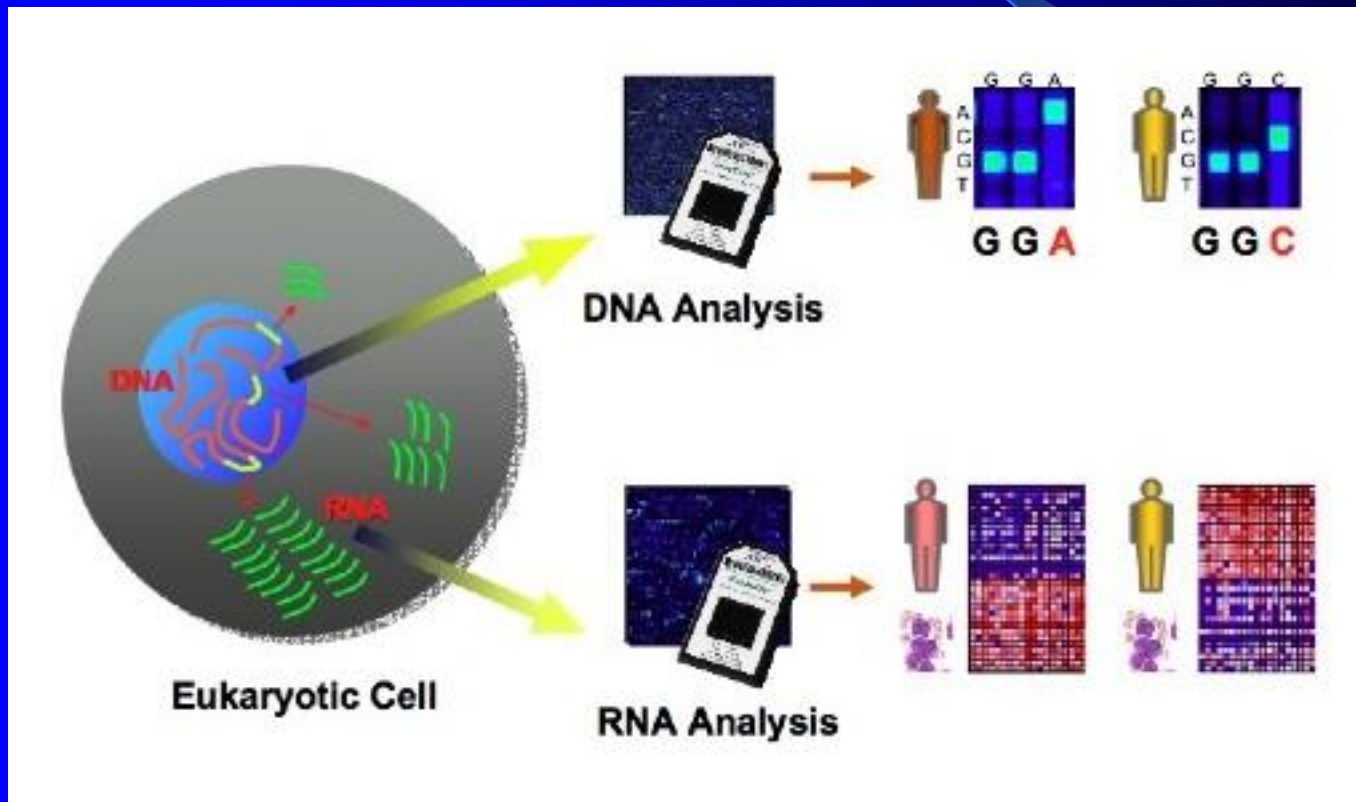
ASTHMA DRUGS
Beta-2-agonists

40-70%



Percentage of the patient population for which any particular drug is ineffective

Analisi dell'informazione genetica (Genomica)



Costo di ogni singolo test: meno di mille euro

**E' aspettativa diffusa che
la Sequenza del Genoma Umano
fornira' conoscenze e strumenti per:**

L'inizio di una nuova era della Medicina

POST-GENOMICA
MEDICINA MOLECOLARE

- prevenzione,***
- diagnostica***
- terapie personalizzate***

•La gestione di questa fase di transizione è complessa e richiede *modelli organizzativi nuovi* che rispettino l'esigenza di contemporaneità e connessione tra

Scienza di base ,

Sviluppo tecnologico,

Ricerca clinica + farmaceutica

ed Attività assistenziale.

Number for health

"0 3 5 140 5 3 0"

0 = no smoking

3 = walking 3 km/day

5 = eating 5 portions of fruit/vegetables per day

140 = blood pressure < 140 mm Hg

5 = cholesterol < 5 mmol/L

3 = LDL cholesterol < 3 mmol/L

0 = avoidance of overweight and diabetes

European Guidelines on CVD Prevention, 2007.

***Cio che accade prima non e'
necessariamente l'inizio***

Henning Mankell