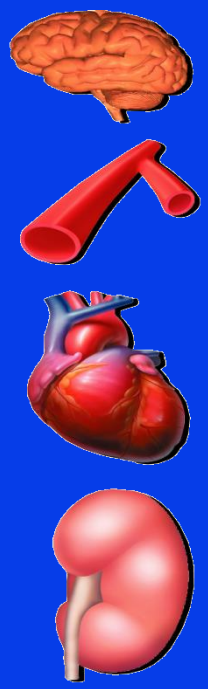
Corso Interattivo Teorico-Pratico sulla Valutazione del Danno Vascolare

Fattori di rischio e danno vascolare:meccanismi fisiopatologici

D.Monizzi

Coordinatore Cardiologia Ambulatoriale ASP Crotone

Continuum sistemico



Plaque rupture and thrombosis

Sudden Cardiac death

Myocardial Infarction
Stroke

Reduction of Contractility

Dilatation and Remodelling

GFR, S.Creatinine
Microalbuminuria, Proteinuria
Aldosterone release
Glomerular sclerosis

Terminal Heart Failure
Esrd

Ischemia

Vasoconstriction
Vascular hypertrophy
Endothelial dysfunction

Atherosclerosis

Risk Factors

Hypertension
Lipid disorders
Hyperinsulinemia
Diabetes
Smoking …

Modified from Dzau and Braunwald

The risk of a vulnerable patient is affected by vulnerable plaque and/or vulnerable blood and/or vulnerable myocardium

Naghavi, M. et al. Circulation 2003;108:1664-1672

Circulation

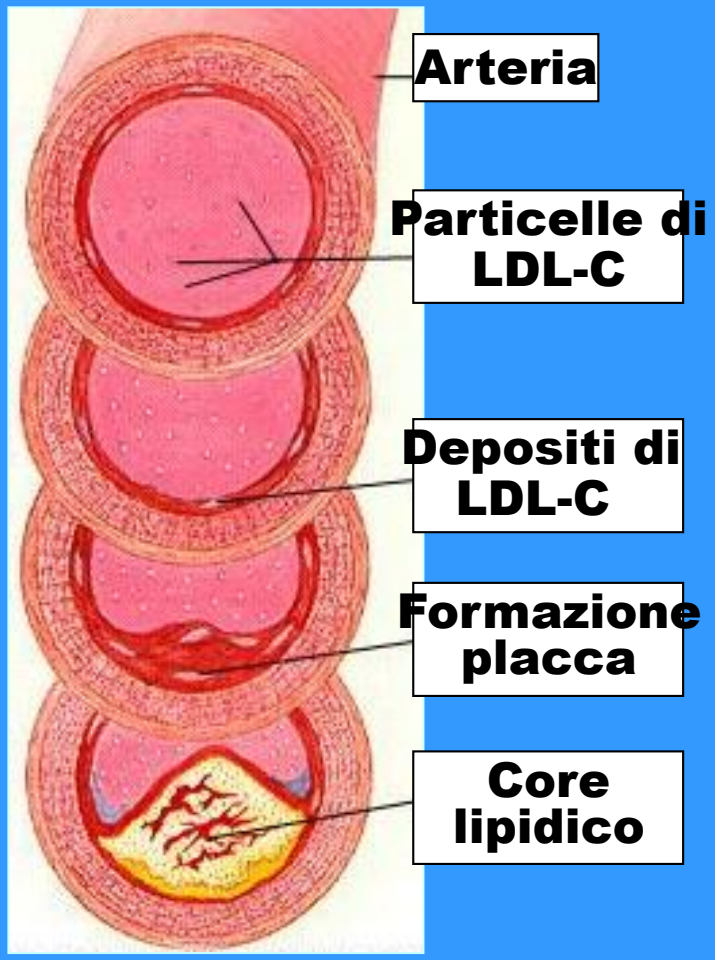
Naghavi et Al. Circulation 2003

American Heart Association
Learn and Live

Copyright ©2003 American Heart Association

Fisiopatologia della Placca Ateromasica

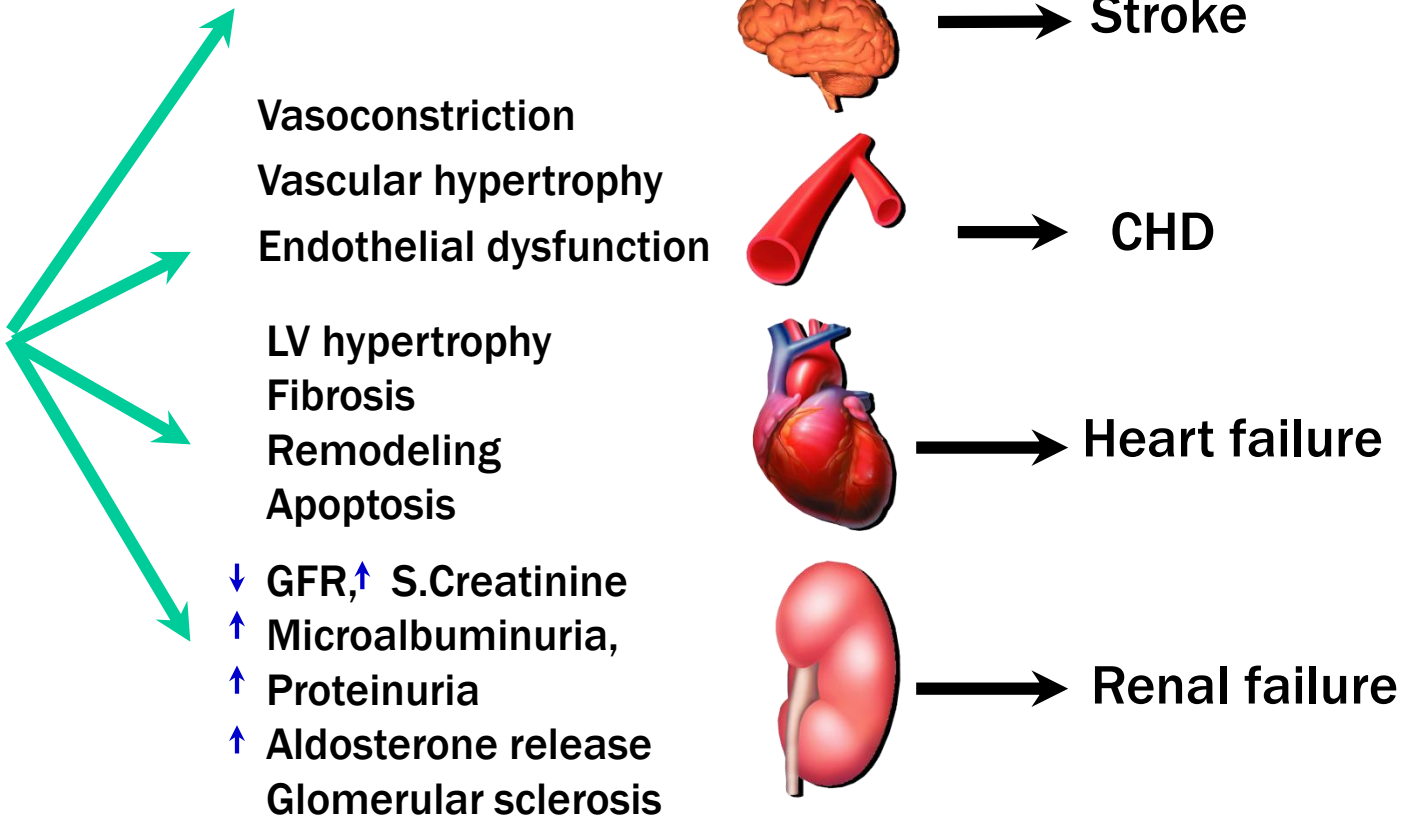
Ateroma: la genesi e lo sviluppo



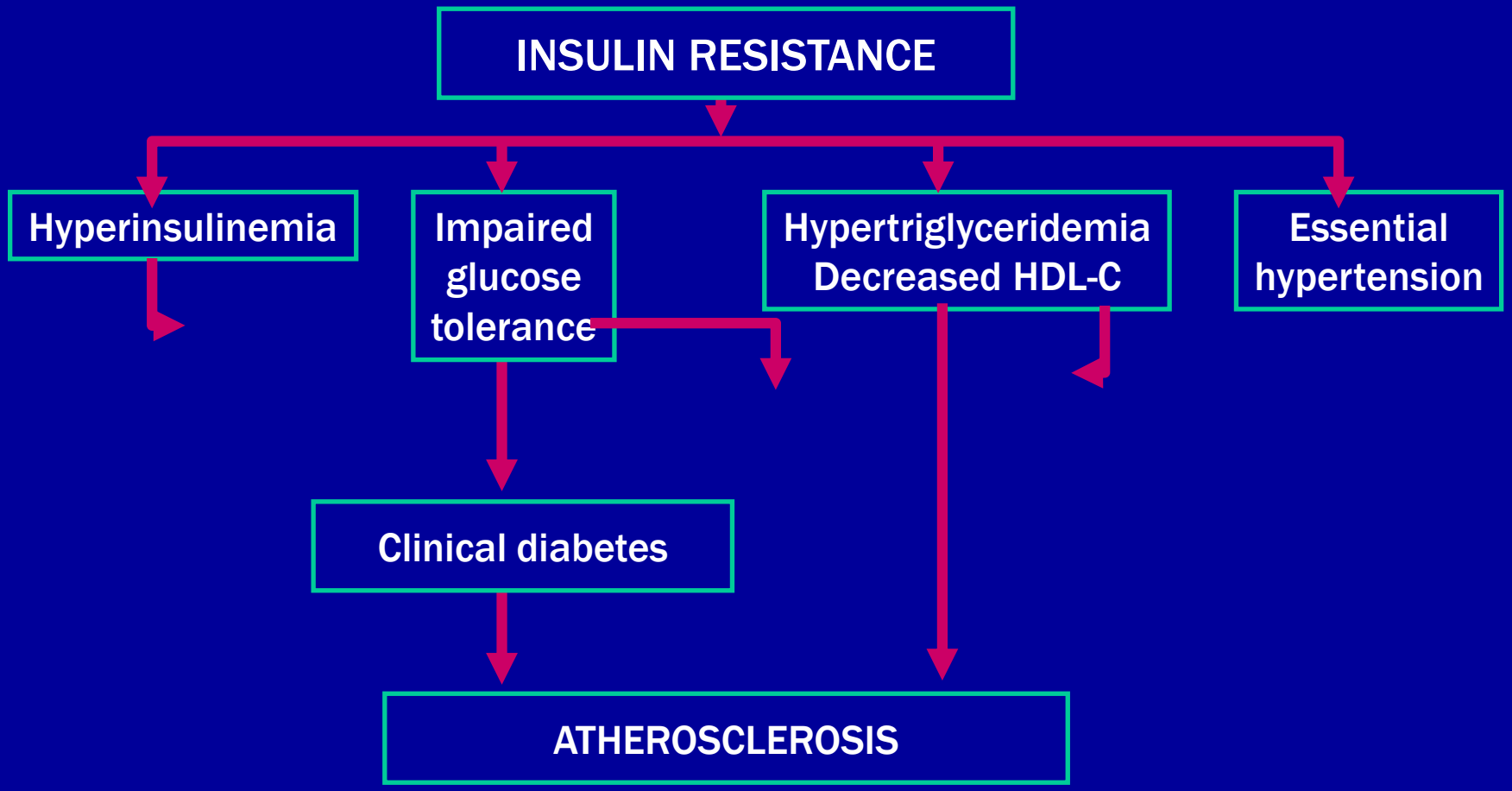
Si puo' ipotizzare un comune denominatore?

Risk factors

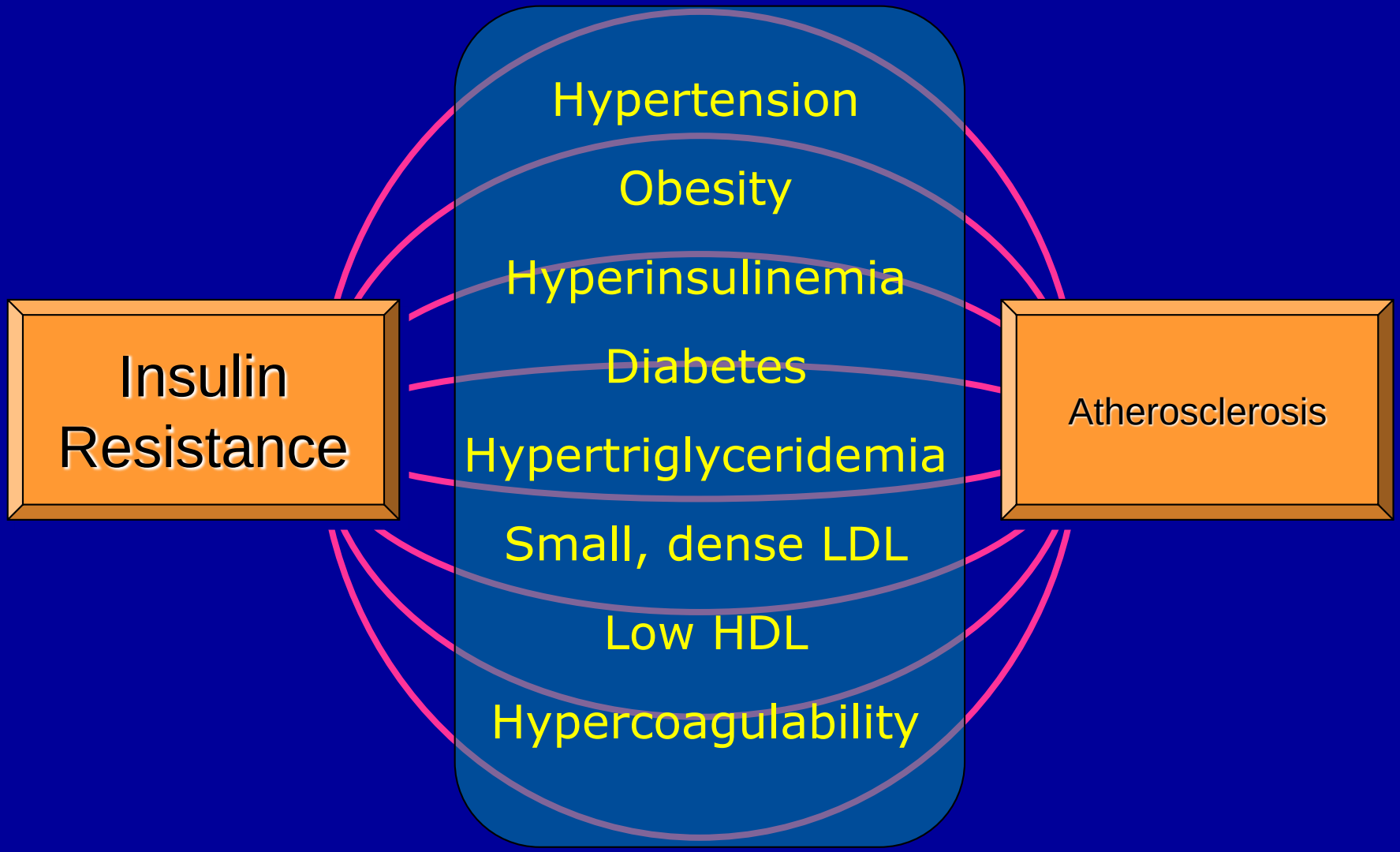
????????????

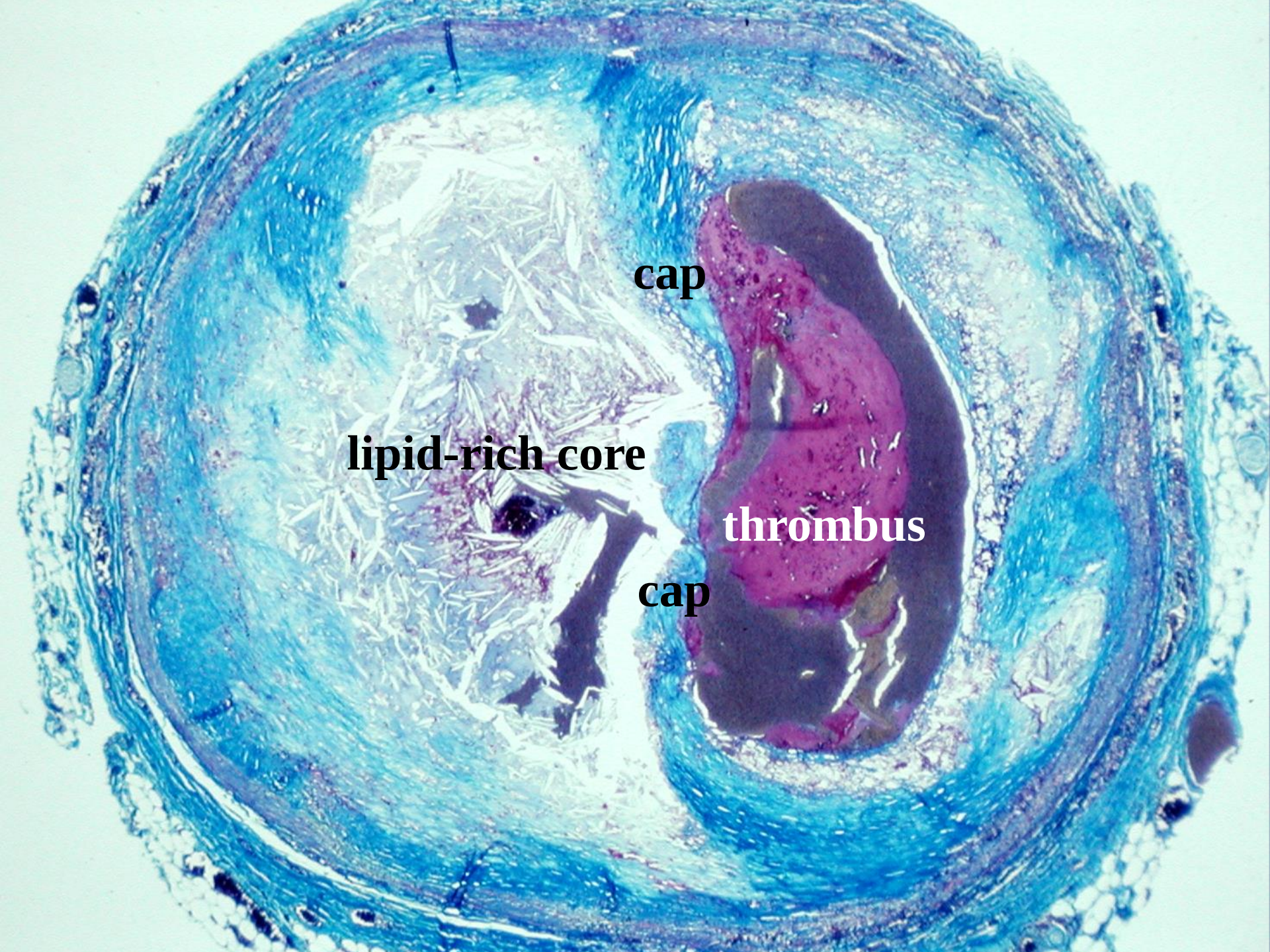


Insulin Resistance and Atherosclerosis: Posited Relationships

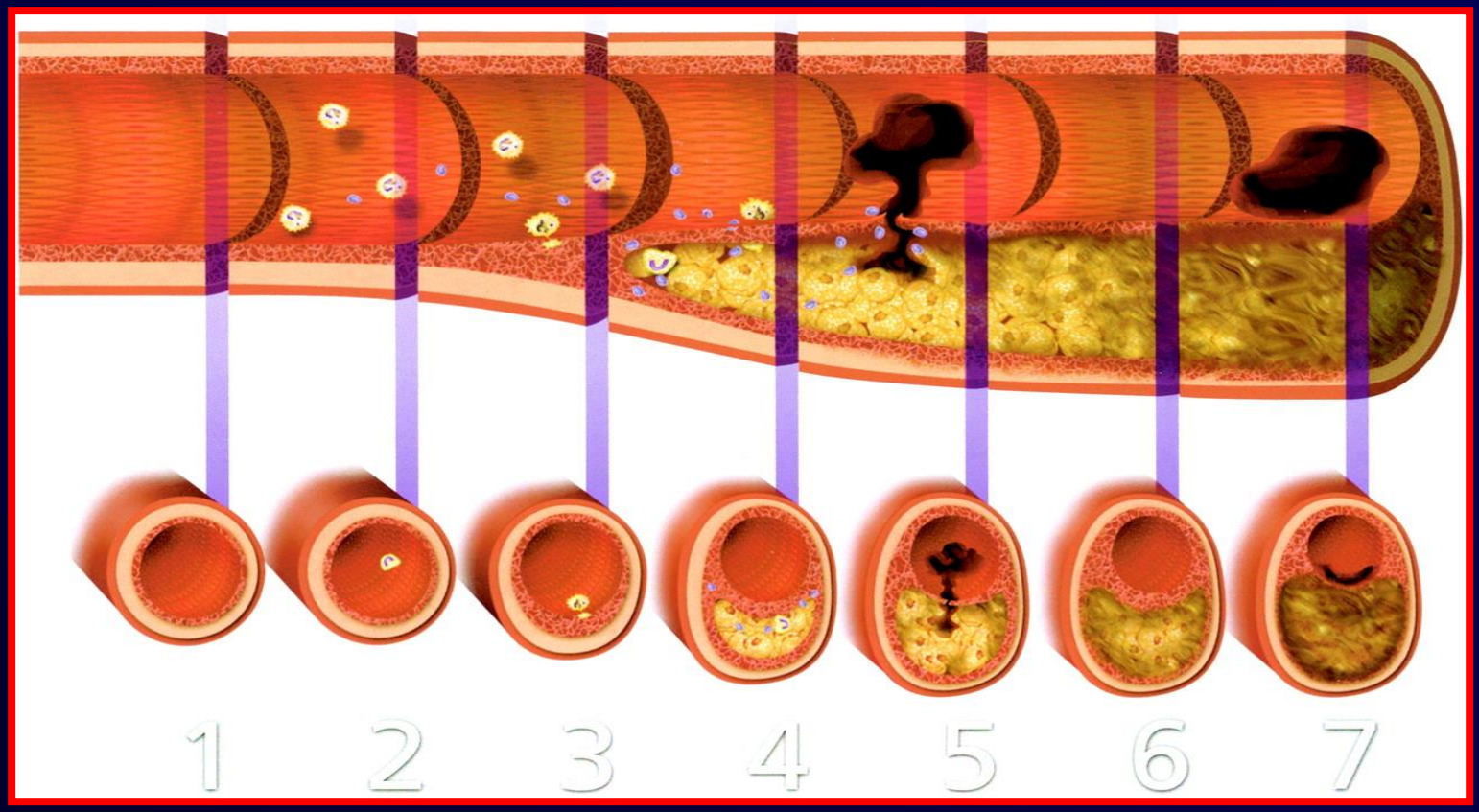


Interrelation Between Atherosclerosis and Insulin Resistance

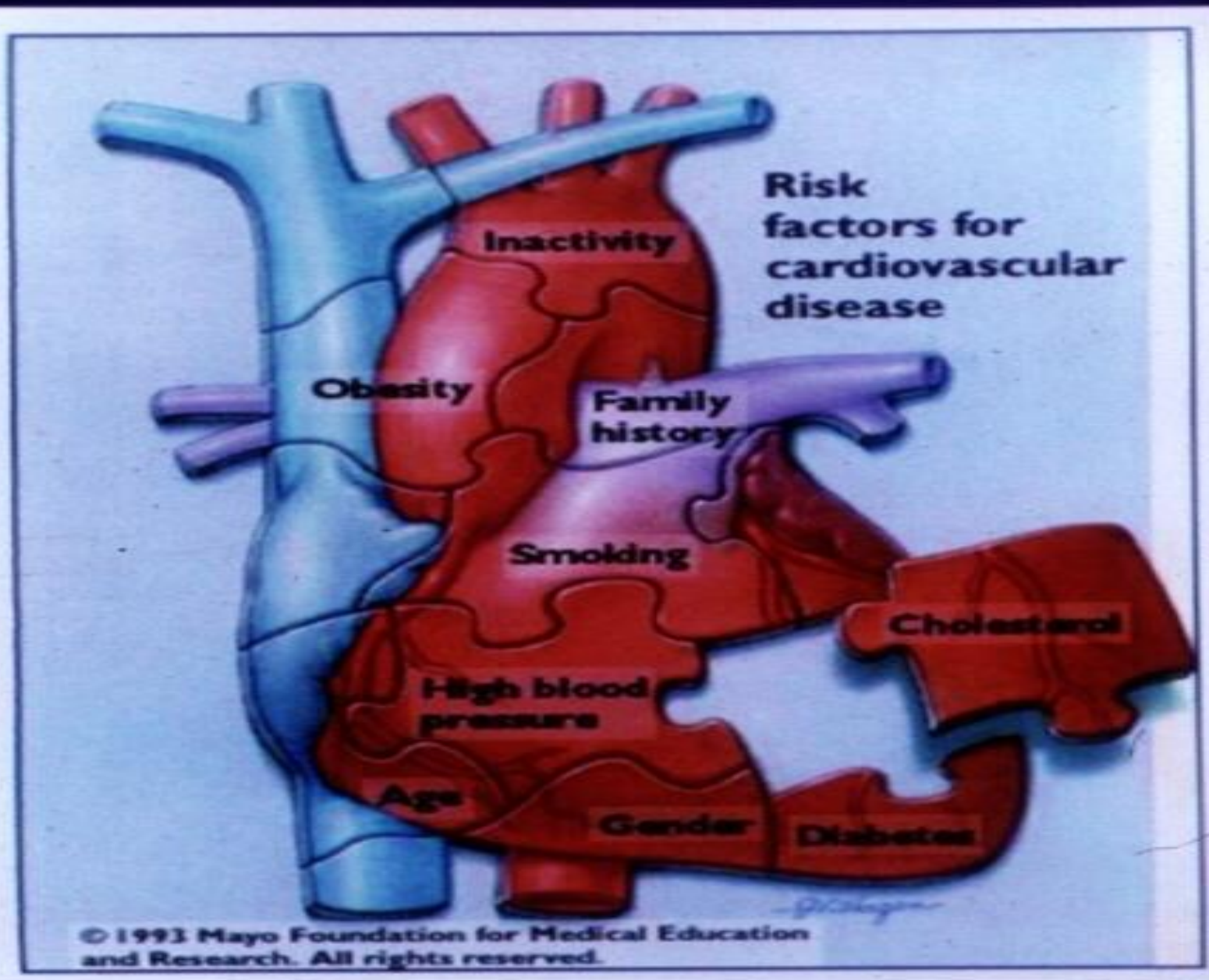



cap
lipid-rich core
thrombus
cap

Aterosclerosi e Malattia vascolare



P. Libby . Circulation. **2001;104:365-372**


Risk factors for cardiovascular disease
Inactivity
Obesity
Family history
Smoking
Cholesterol
High blood pressure
Age
Gender
Diabetes
© 1993 Mayo Foundation for Medical Education and Research. All rights reserved.

FATTORI DI RISCHIO CARDIOVASCOLARI

IPERTENSIONE

FUMO

OBESITA **(BMI>30 Kg/mq)**

INATTIVITA' FISICA

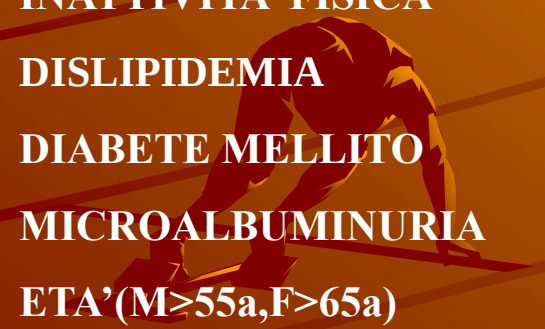
DISLIPIDEMIA

DIABETE MELLITO

MICROALBUMINURIA

ETA'(M≥55a,F>65a)

FAMILIARITA' PER CAD(M<55a,F<65a)



LIVELLI DI PAS E PAD

ABITUDINE AL FUMO

OBESITA'CENTR.(CV M=> 102 cm,W=>88 cm)

PROTEINA C REATTIVA

DISLIPIDEMIA

ETA'(M>55a,F>65a)

FAMILIARITA'PER CAD(M<55 a,F<65 a)

“NUOVI” FATTORI DI RISCHIO

ACCERTATI

*OMOCISTEINA

*PCR

*SINDROME METABOLICA

*OBESITA’

*FATTORI TROMBOGENI

*FATTORI EMORRAGICI

*MICROALBUMINURIA

*FREQUENZA CARDIACA

POSSIBILI

°ATTIVAZIONE SRA

°DISFUNZIONE ENDOTELIALE

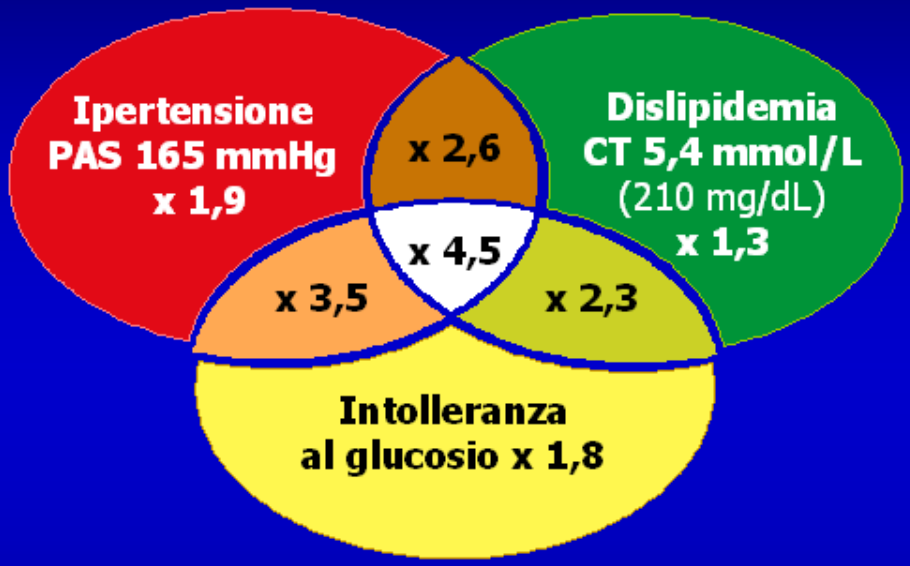
°ATTIVAZIONE SNS

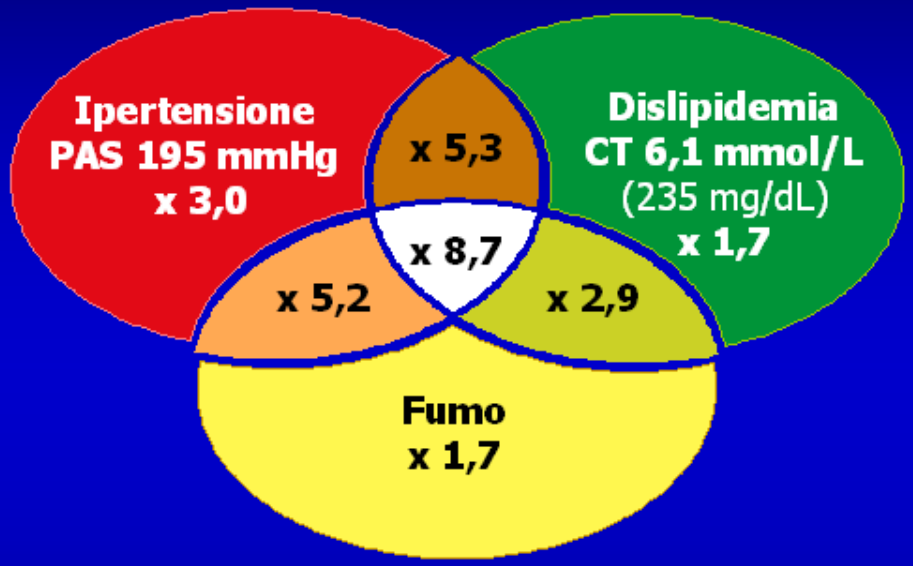
SINDROME APNEE NOTTURNE

°INSULINO-RESISTENZA

°PPARs
(peroxisome proliferator activated receptors)

Il rischio CV globale





Il rischio indicato è stato confrontato al rischio di un uomo di 40 anni non fumatore con CT 4,7 mmol/L (185 mg/dL), PAS 120 mmHg, e nessuna intolleranza al glucosio, ECG-LVH negativo, la cui probabilità di sviluppare una CVD è di 15/1000 (1,5%) in 8 anni

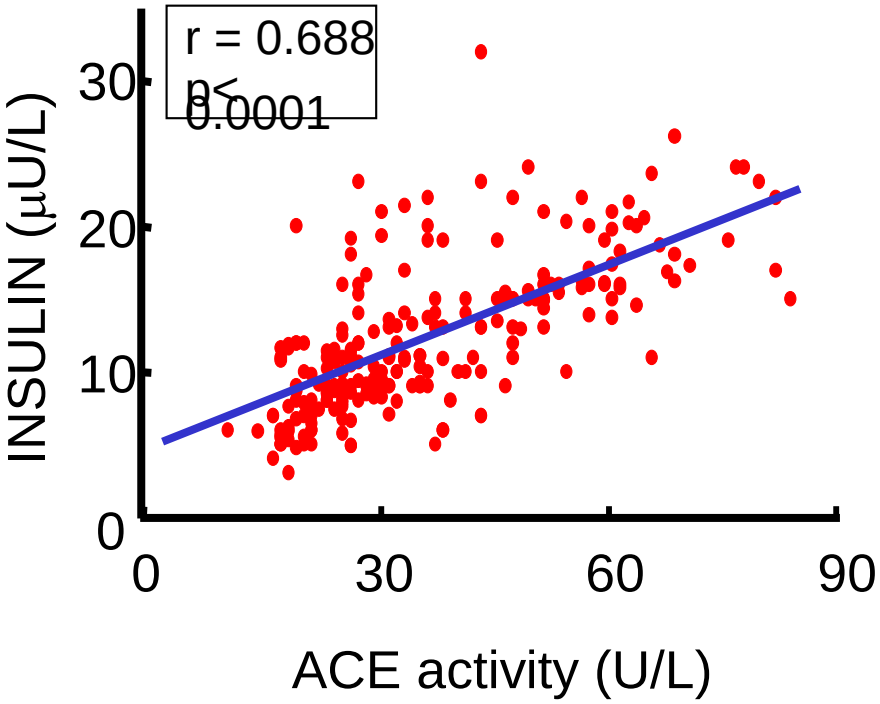
Kannel WB, In: Genest J et al., eds. Hypertension: Physiopathology and Treatment. New York, NY: McGraw Hill, 1977;888-910

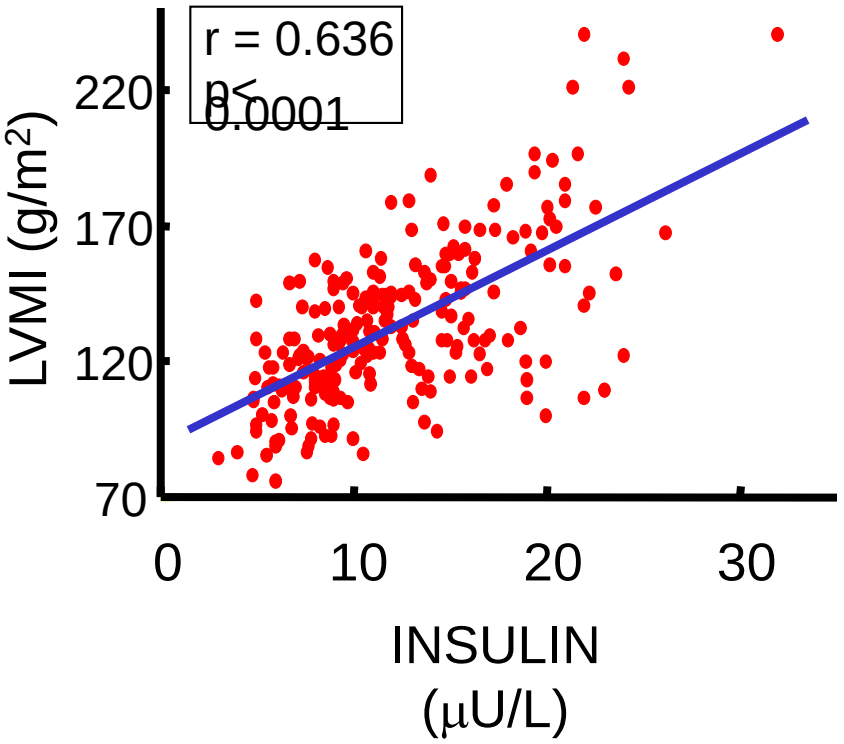
RISCHIO DI MALATTIA CORONARICA A 10 ANNI

(STUDIO FRAMINGHAM)

PAS	120	160	160	160	160	160	160
Colesterolo	220	220	260	260	260	260	260
Colesterolo HDL	50	50	50	35	35	35	35
Diabete	-	-	-	-	+	+	+
Sigarette	-	-	-	-	-	+	+
IVS all'ECG	-	-	-	-	-	-	+

Relationship Between ACE Activity, Fasting Insulin and LVM in Hypertensives





F Perticone et al, *J Clin Endocrinol Metab* 2001

Mechanisms of the Prognostic Value of LV Hypertrophy

Age, Sex, BP,
Smoking, Obesity,
SNS activity, Insulin,
IGF-1, Na,
Blood Viscosity, RAAS
Genetic factors, Lipids

Systolic dysfunction
Diastolic Dysfunction

Congestive Heart Failure

LVH

Progression of Atherosclerotic Lesions

↓ Coronary Flow Reserve

↑ Myocardial Oxygen Consumption

Prognostic Impact

Myocardial Ischemia

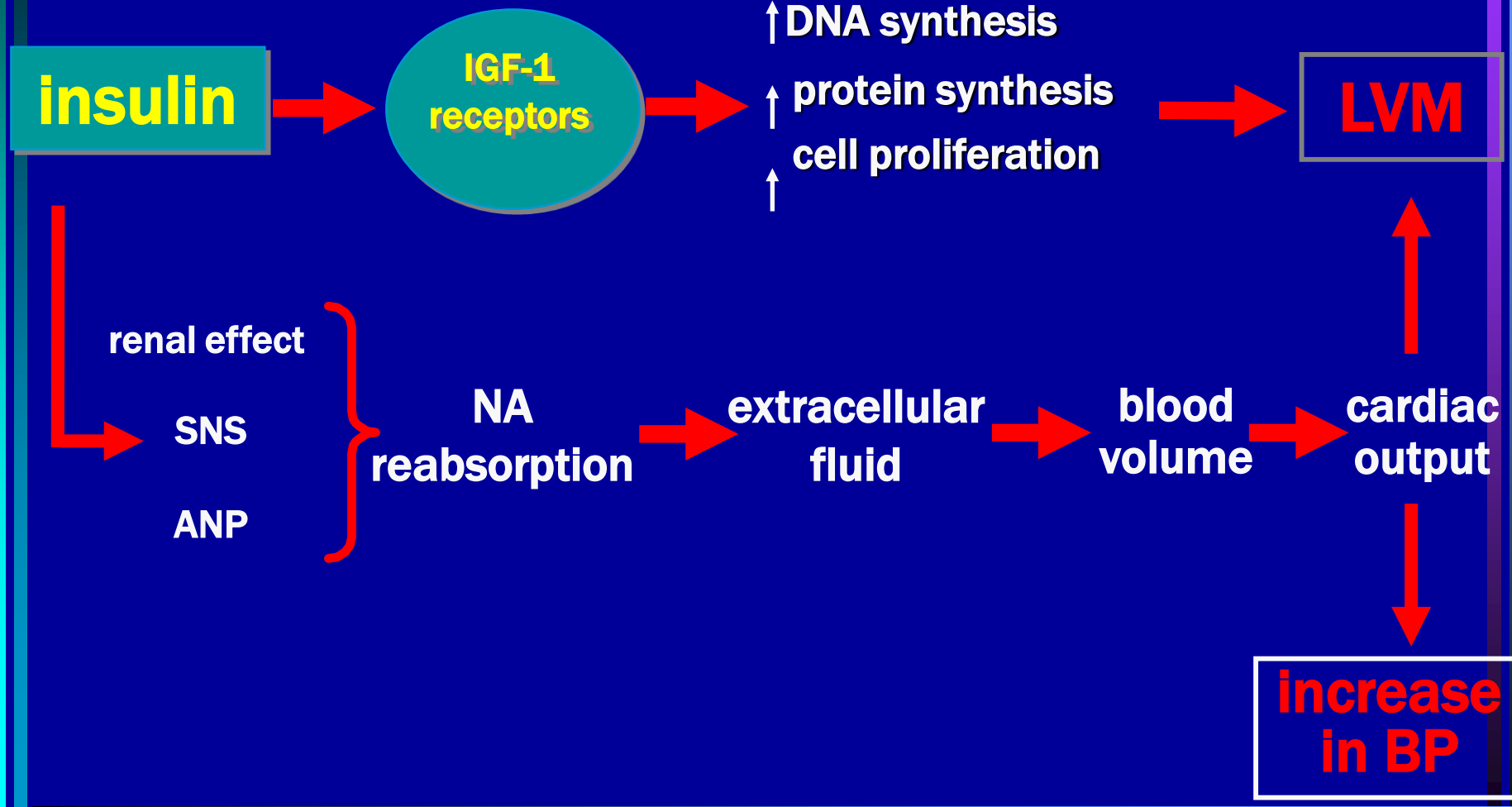
Plaque damage & thrombosis

Arrhythmias

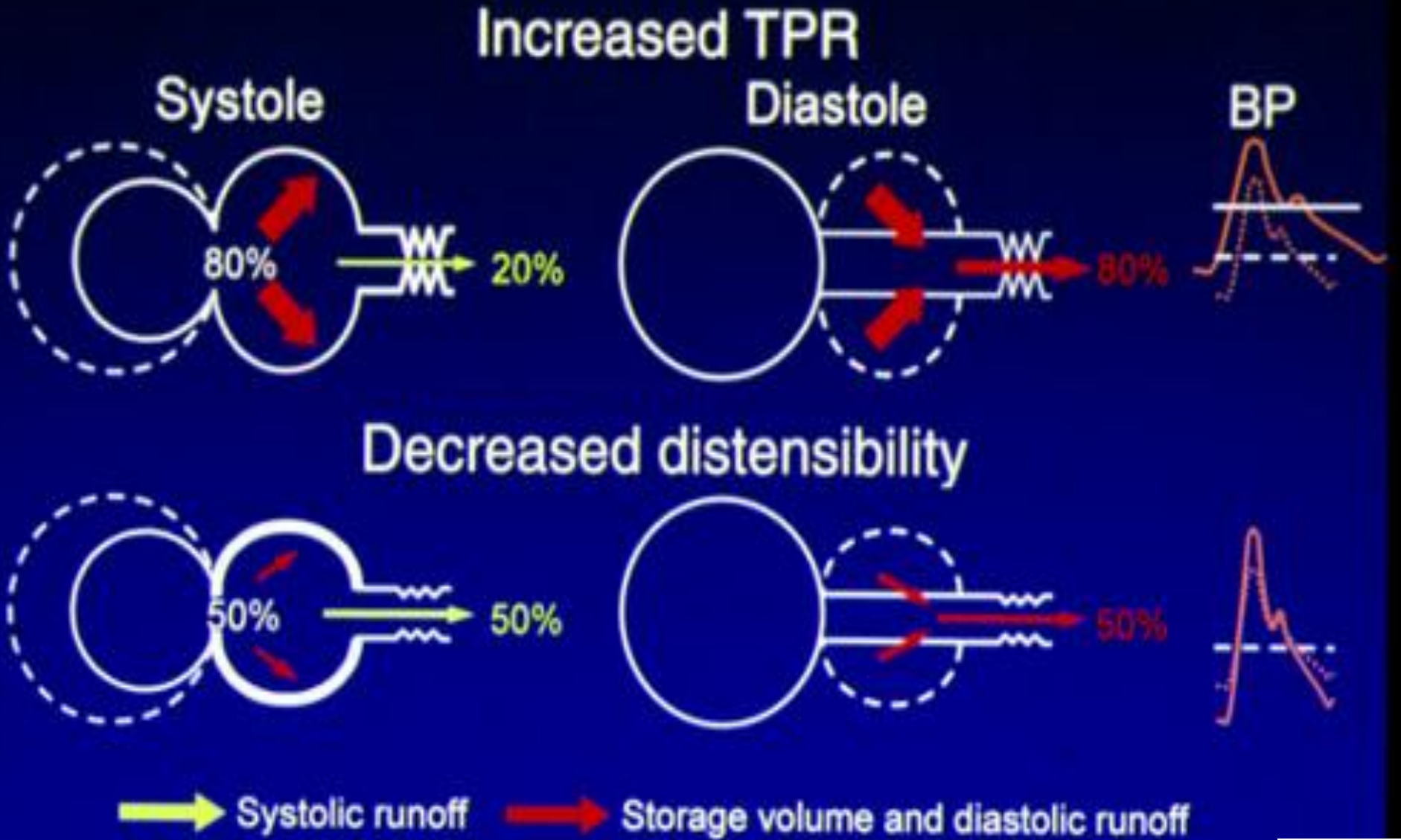
Angina

Stroke **Sudden Cardiac Death** **Myocardial Infarction**

Hemodynamic and Proliferative Effects of Insulin



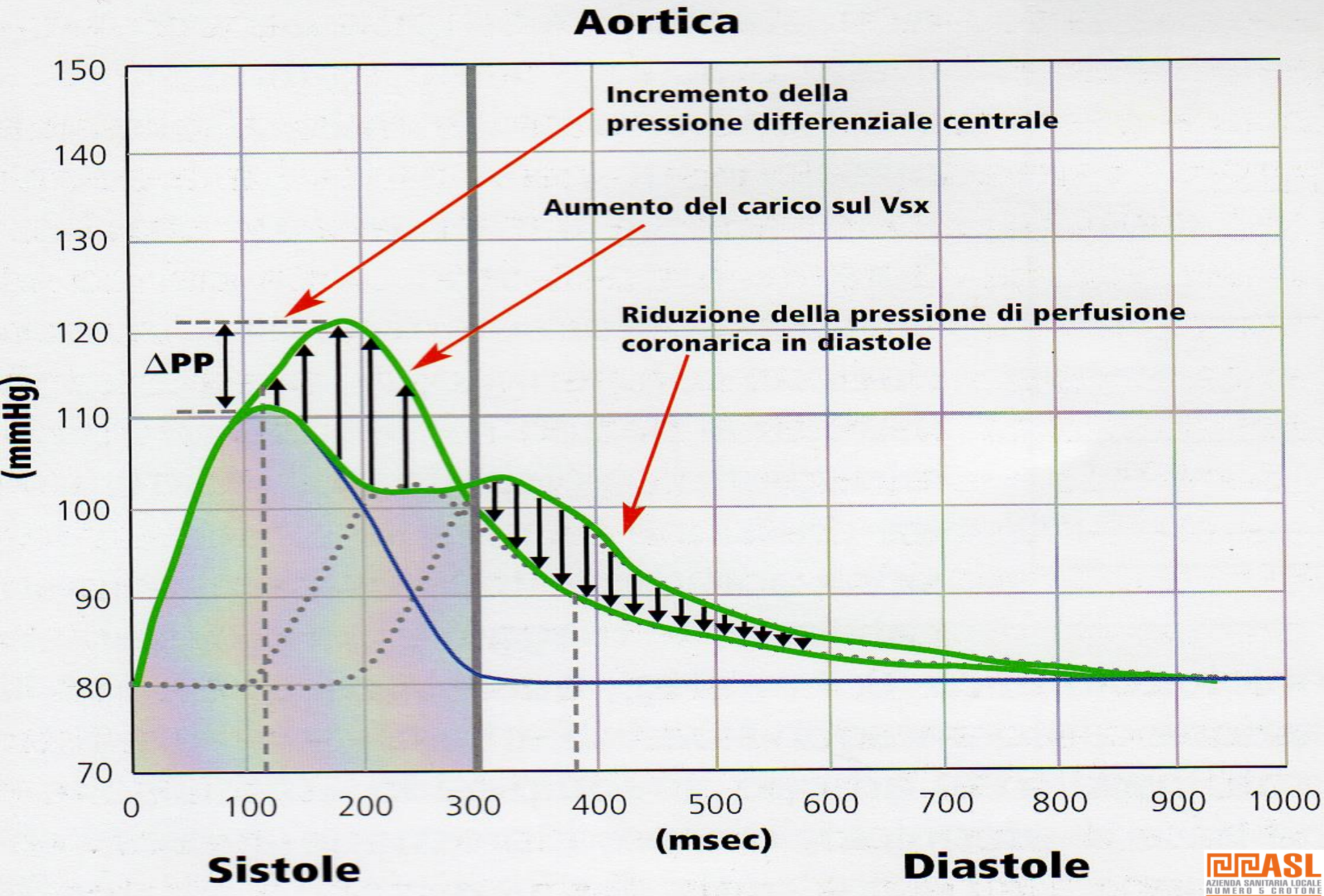
ARTERIES AS CUSHIONS



Soggetti a rischio Alto/Molto alto

- **PAS almeno 180mmHg e/o diastolica almeno 110mmHg**
- **PA Sistolica >160mmHg con PA diastolica bassa (<70 mmHg)**
- **Diabete mellito**
- **Sindrome Metabolica**
- **3 fattori di rischio cardiovascolare**
- ***Uno o più dei seguenti danni d'organo subclinici:***
- **– Ipertrofia ventricolara Sin all'ECG (particolarmente sovraccarico) o all'ecocardio (particolarmente concentrica)**
- **– Evidenza Ultrasonografica di ispessimento o placche carotidee**
- **– Aumentata rigidità vascolare**
- **– Moderato aumento della creatinina sierica**
- **– VFG calcolato ridotto**
- **– Microalbuminuria o proteinuria**
- **– Malattie cardiovascolari o renali conclamate**

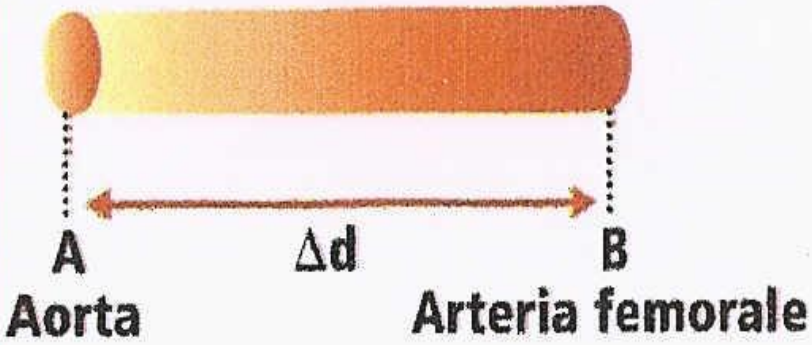
IMPATTO DELL'ONDA PRECOCE DI RIFLESSIONE

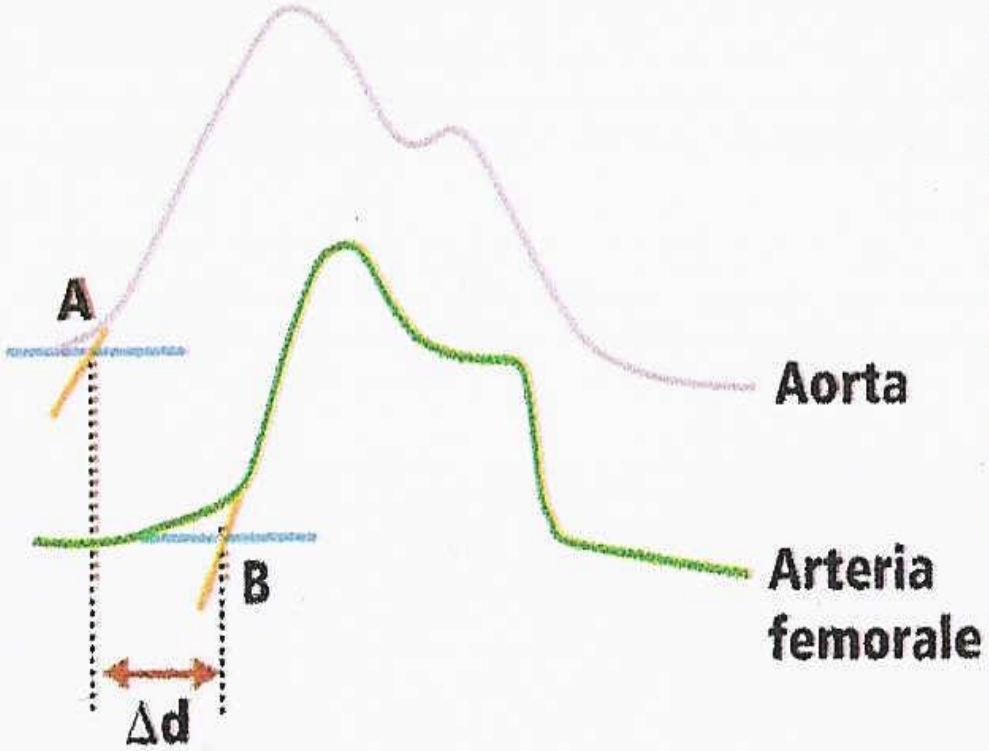


ASL
AZIENDA SANITARIA LOCALE
NUMERO 5 CROTONE
MagnaGrecia

PWV (Pulse Wave Velocity): Misurazione dell'onda di polso

Pulse pen





PWV= Distanza (Δd) / Tempo di ritardo = (ΔT m/sec)

Linee Guida ESH-ESC 2007: fattori che influenzano la prognosi nel paziente iperteso (in rosso le novità 2007)

Fattori di rischio cardiovascolare per la stratificazione

- PAS/PAD
- **PA differenziale nell'anziano**
- Uomo >55 anni
- Donna >65 anni
- Fumo
- Colesterolo totale >190 (250) mg/d; o C-LDL >115(155) mg/dL
- C-HDL U < 40 U o D <46 (48) mg/dL
- Familiarità per MCV precoci
- Obesità addominale (U ≥ 102 e D ≥88 cm)
- Proteina C reattiva (≥ 1 mg/dL)

Danno d'organo

- Ipertrofia ventricolare sinistra (LVMI U ≥125 e D ≥110 g/m^2)
- Evidenza ecografica di IMT carotideo ≥0.9 mm o placca
- lieve ↑ creatininemia (U 1,3-1,5 mg/dL o D 1,2-1,4 mg/dL)
- ridotto VFG (<60 ml/min)
- Microalbuminuria (30-300 mg/24 ore; albumina/creatinina U ≥ 22 e D ≥31 mg/g; U ≥2,5 e D ≥3,5 mg/mmol)
- **Velocità onda sfigmica carotido-femorale > 12 m/s**
- **Indice PA caviglia/braccio <0.9**

Diabete Mellito

- Glucosio plasmatico a digiuno (> 126 mg/dL)
- Glucosio plasmatico postprandiale (> 198 mg/dL)
- test tolleranza glucosio alterato
- Glucosio plasmatico a digiuno (102-125 mg/dL)

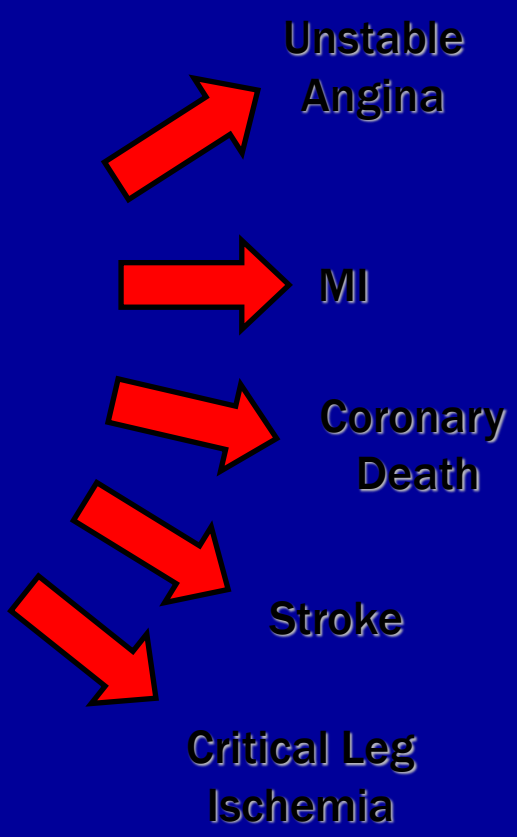
Condizioni cliniche associate

- Ictus, TIA, emorragia cerebrale
- IMA, angina, rivascolarizzazione coronarica, scompenso
- Nefropatia diabetica, insufficienza renale, proteinuria (>300 mg/24 ore)
- Vasculopatia periferica
- Retinopatia ipertensiva avanzata: emorragie, essudati e papilledema

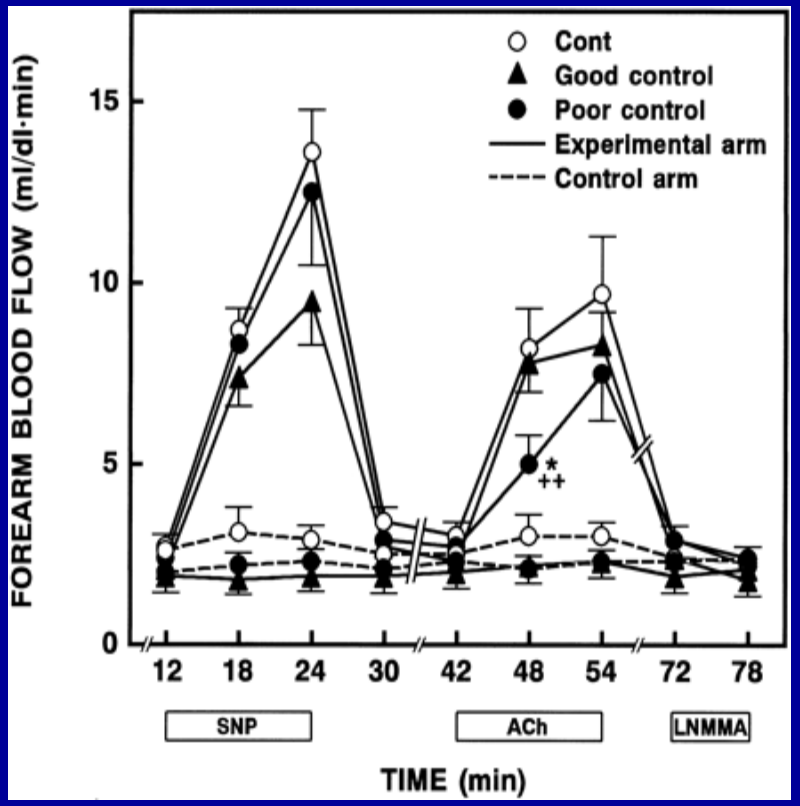
J Hypertension 2003, 21: 1011-53

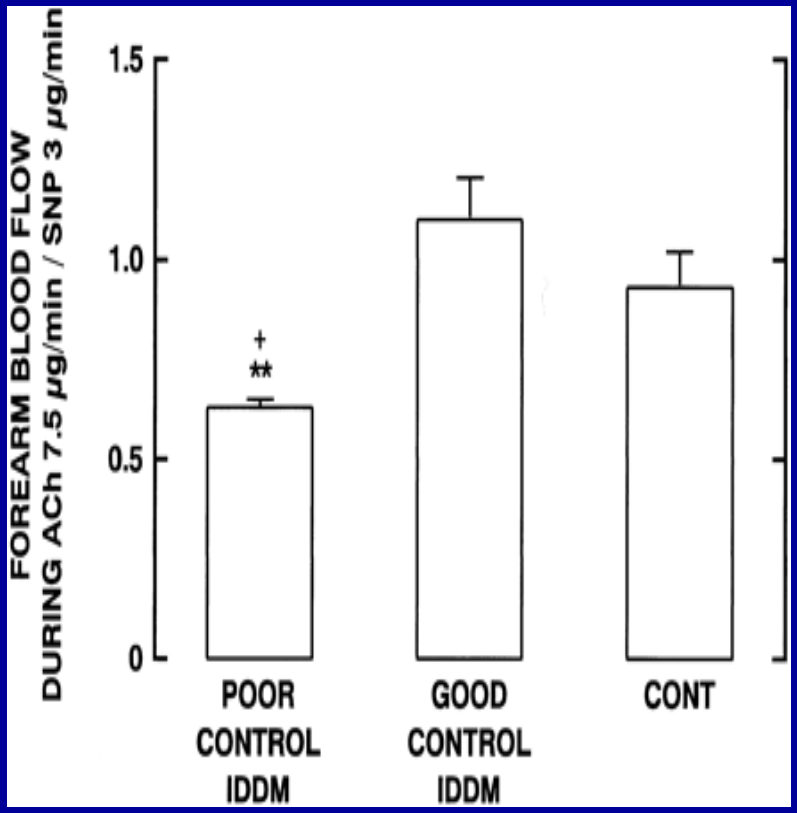
Diabetes Timeline

iperglicemia

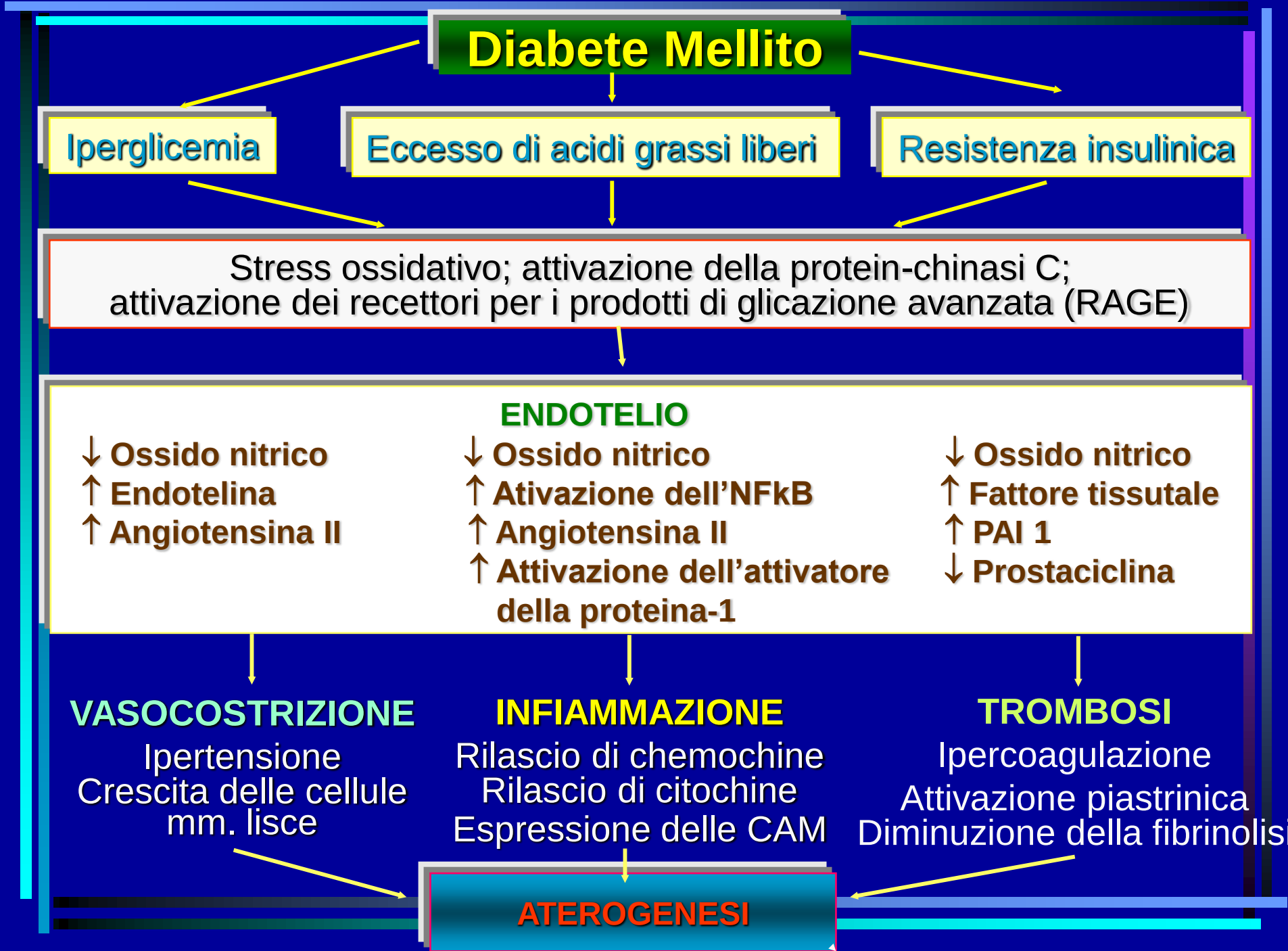


Diabetes Mellitus and Endothelial Function

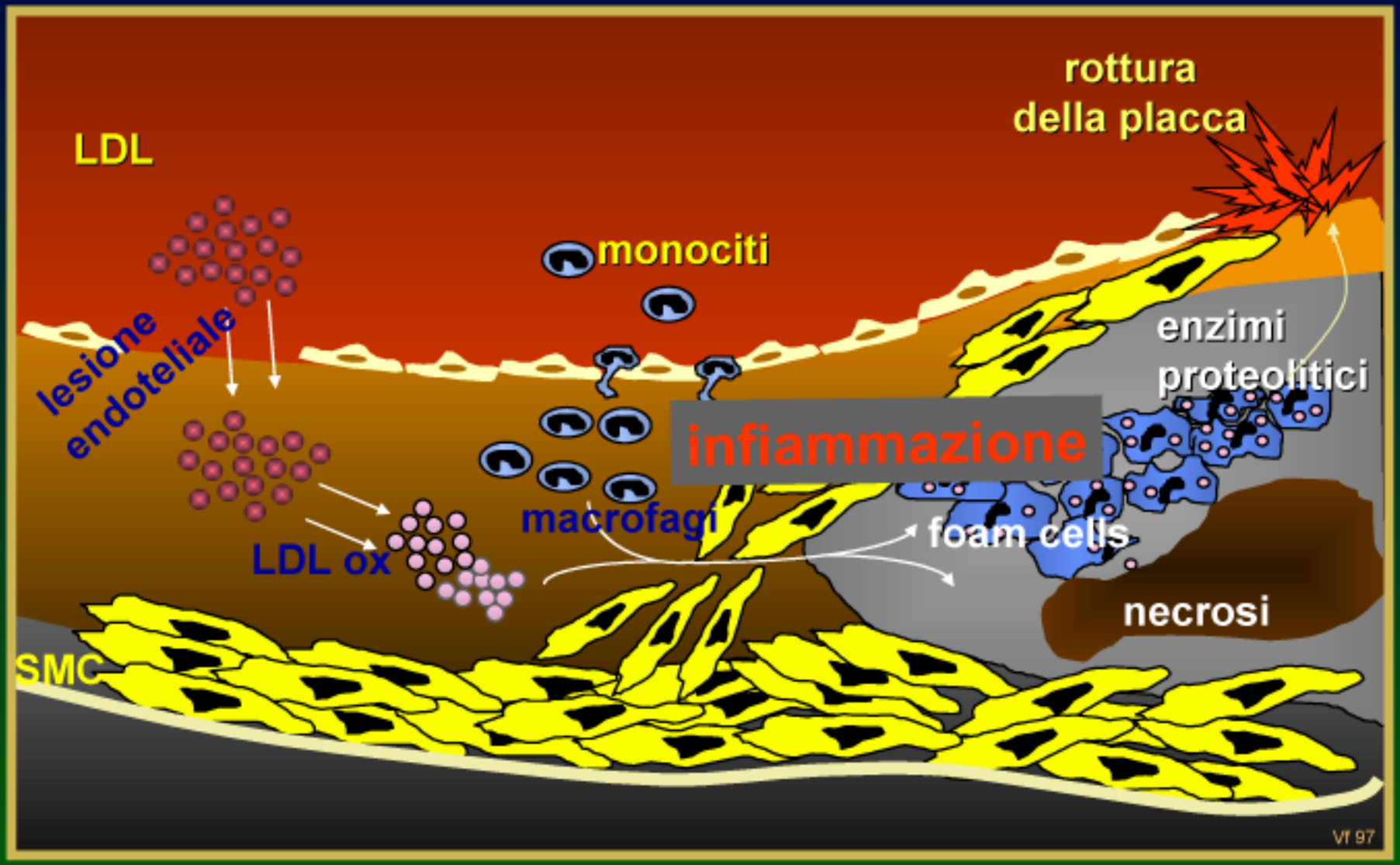




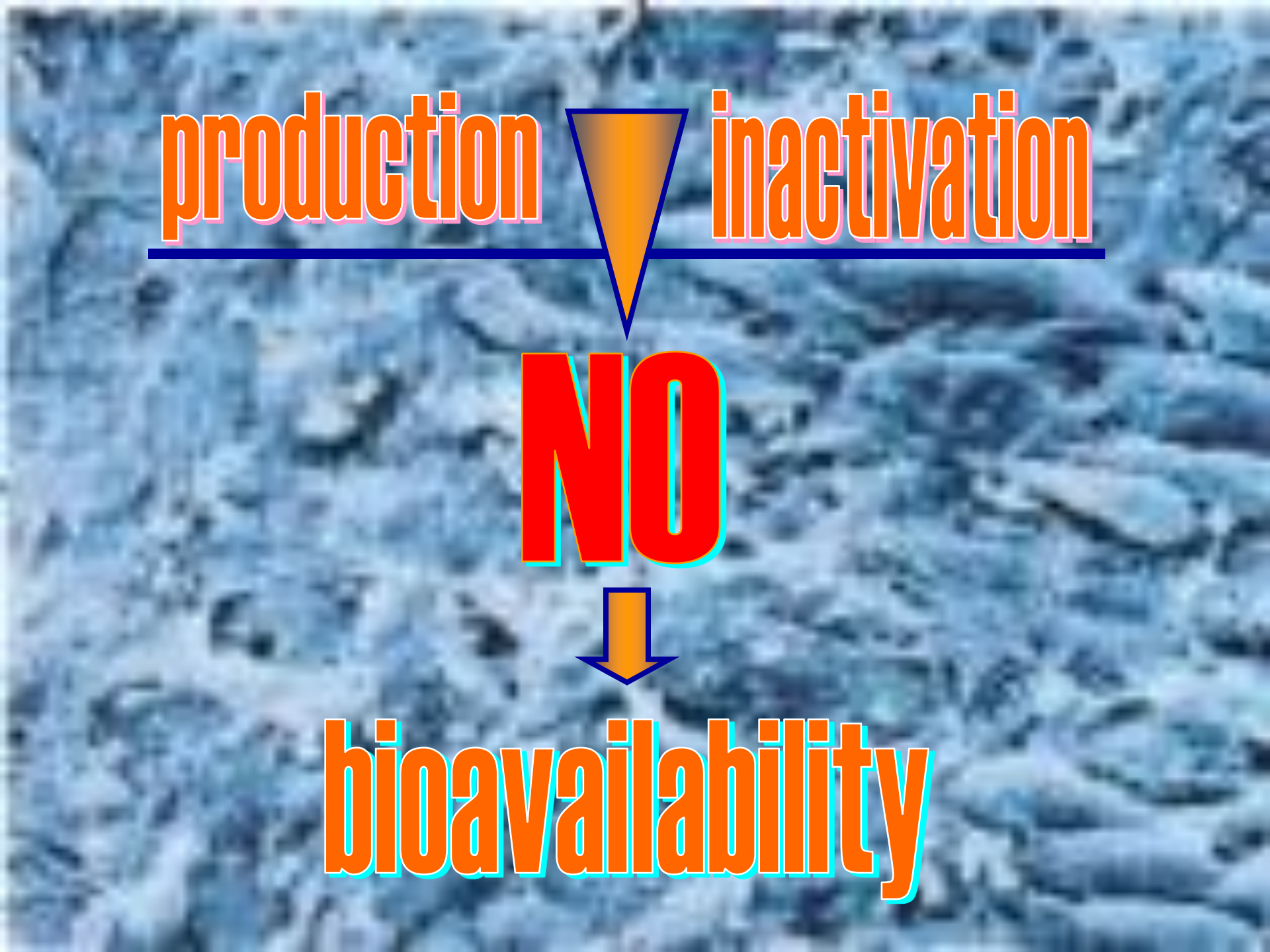
Makimatila S et al, *Circulation* ,1996


Diabete Mellito
Iperglicemia
Eccesso di acidi grassi liberi
Resistenza insulinica
Stress ossidativo; attivazione della protein-chinasi C;
attivazione dei recettori per i prodotti di glicazione avanzata (RAGE)
ENDOTELIO
↓ Ossido nitrico
↑ Endotelina
↑ Angiotensina II
↓ Ossido nitrico
↑ Ativazione dell'NFkB
↑ Angiotensina II
↑ Attivazione dell'attivatore della proteina-1
↓ Ossido nitrico
↑ Fattore tissutale
↑ PAI 1
↓ Prostaciclina
VASOCOSTRIZIONE
Ipertensione
Crescita delle cellule mm. lisce
INFIAMMAZIONE
Rilascio di chemochine
Rilascio di citochine
Espressione delle CAM
TROMBOSI
Ipercoagulazione
Attivazione piastrinica
Diminuzione della fibrinolisi
ATEROGENESI

la placca aterosclerotica: un processo flogistico continuo



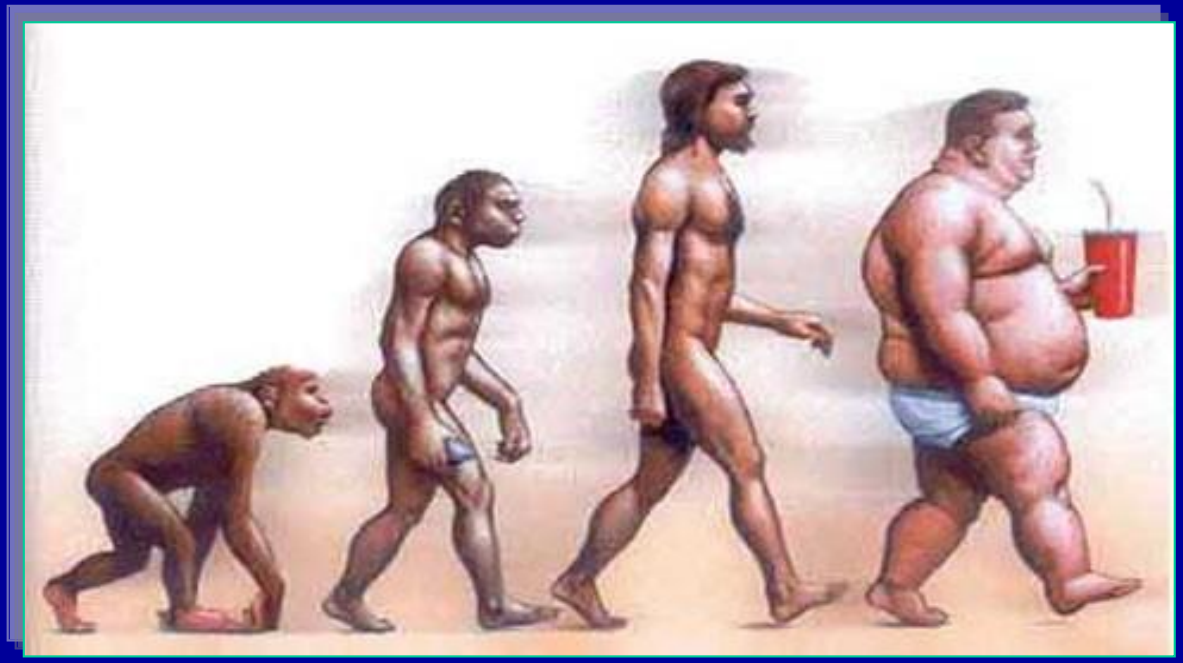
NON SOLO COLESTEROLO

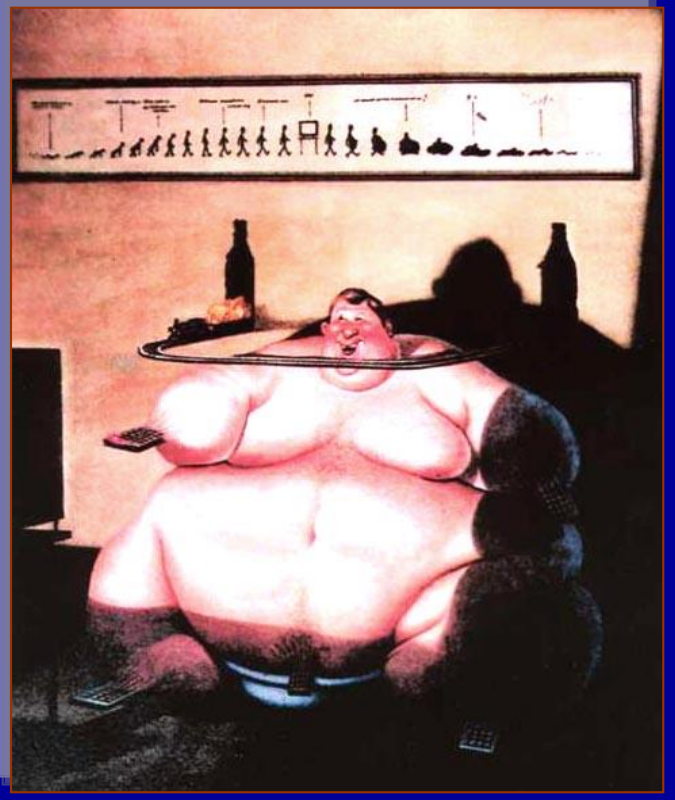

production
inactivation
NO
bioavailability

DAL RISCHIO CARDIOVASCOLARE GLOBALE AL RISCHIO CARDIOMETABOLICO

FATTORI TRADIZIONALI

FATTORI EMERGENTI





Homo sapiens

Lardopitecus

Homo sapiens sapiens televisivus

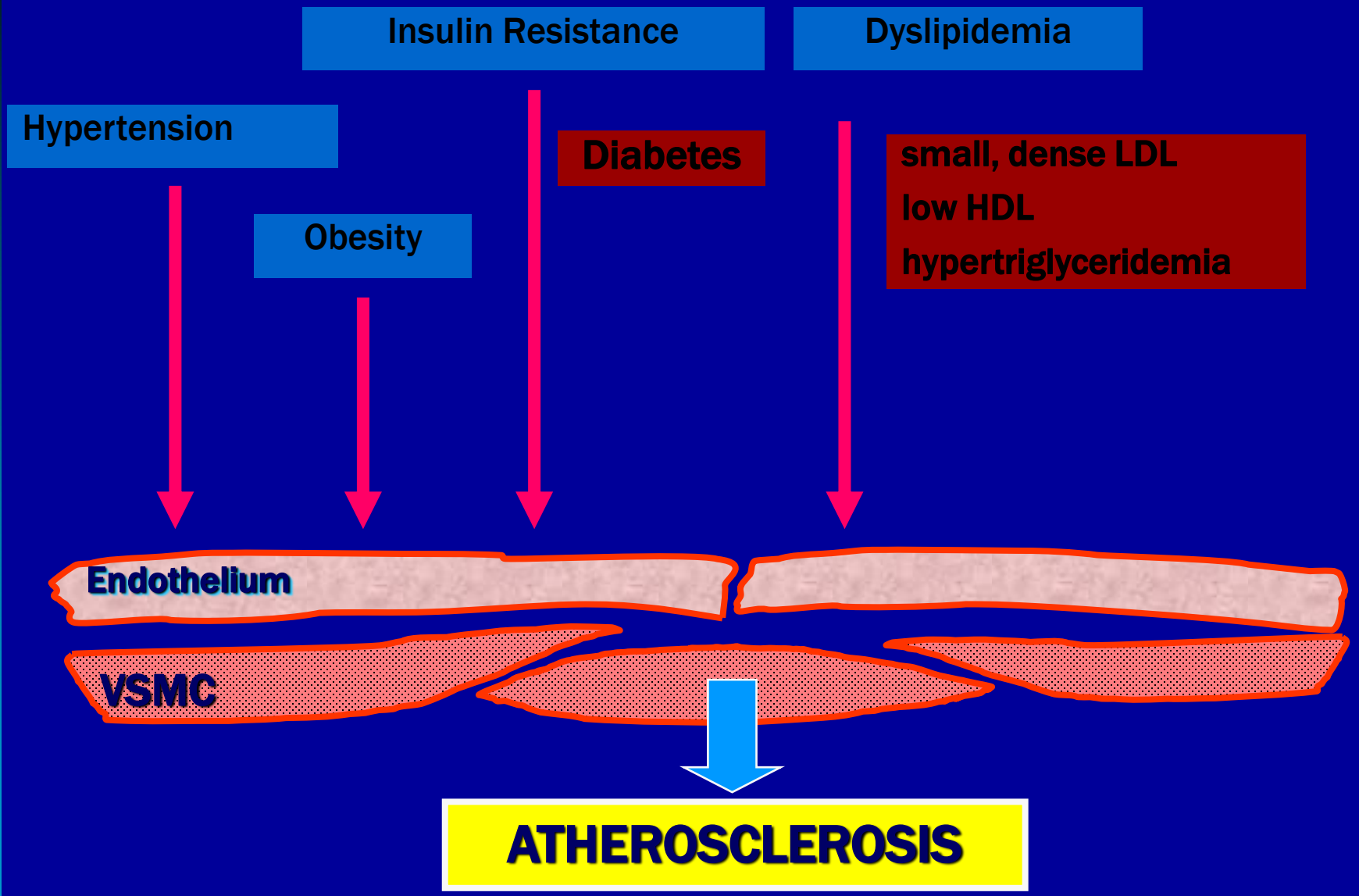
25 milioni di anni

50 anni

Ipotesi eziopatogenetiche
Sindrome metabolica

- Pima Indians,trasmigrati in Arizona
- Egiptian sand rat
- Aborigeni australiani
- Indiani Tarahunara

Cardiovascular Dysmetabolic Syndrome

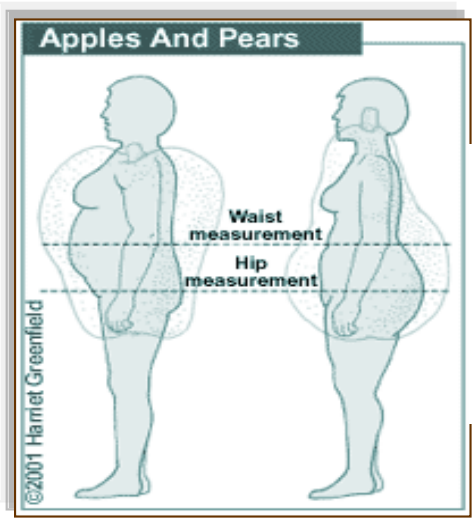


Circonferenza-Vita:
Indicatore del Tessuto Adiposo Viscerale

DONNA	UOMO
>88 cm	>102 cm

Forma
"a mela"
(Obesità Androide)

Adiposità intra-addominale



Forma
"a pera"
(Obesità Ginoide)

Grasso sottocutaneo

IDF 2005 Criteri per SM	
DONNA *	UOMO*
≥80 cm	≥94 cm

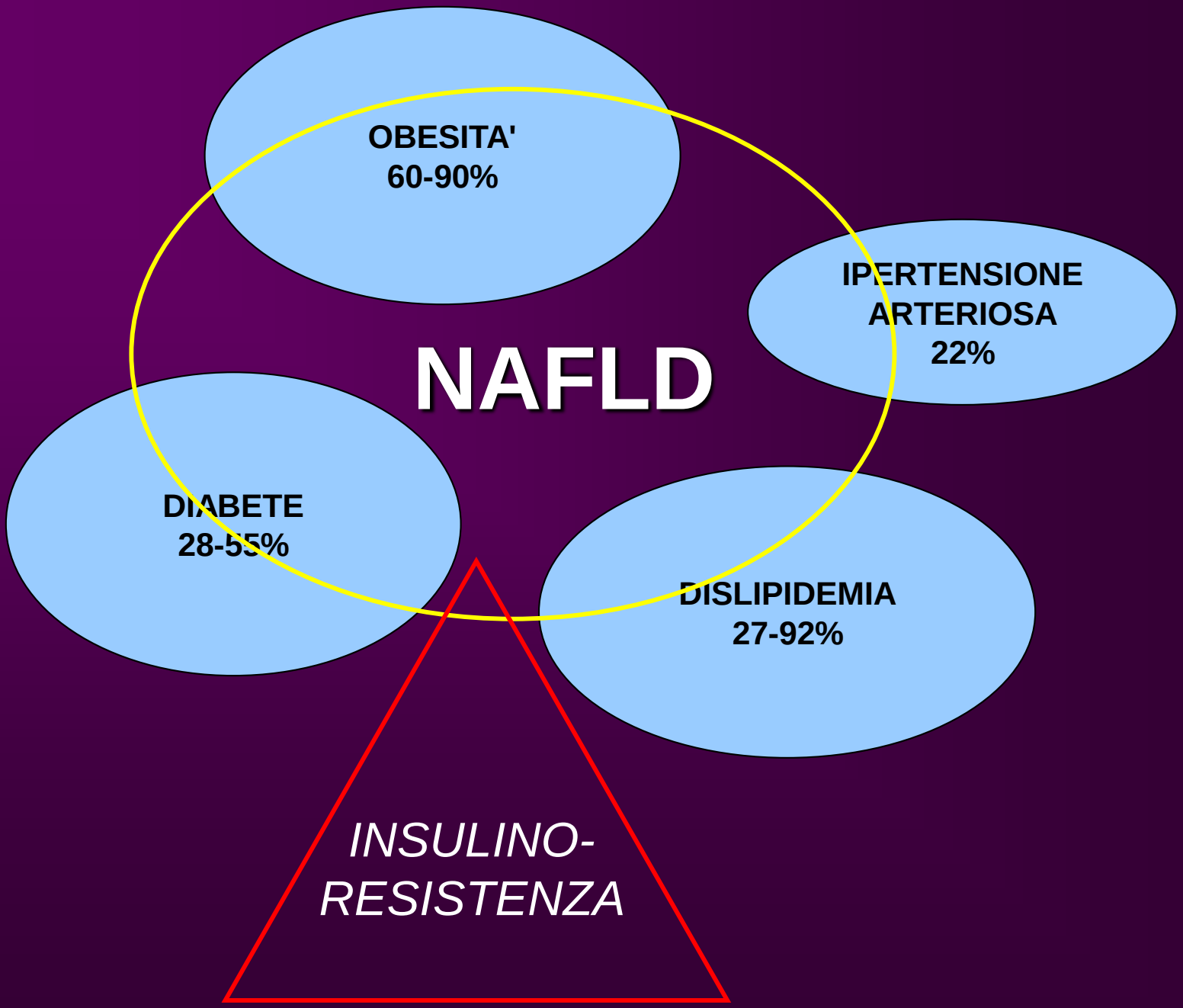
Donna	Uomo	Rischio
< 80 cm	< 94 cm	Normale
80-88 cm	95-102 cm	Moderato
> 88 cm	> 102 cm	Elevato

* Popolazione caucasica (Nord America ed Europa)

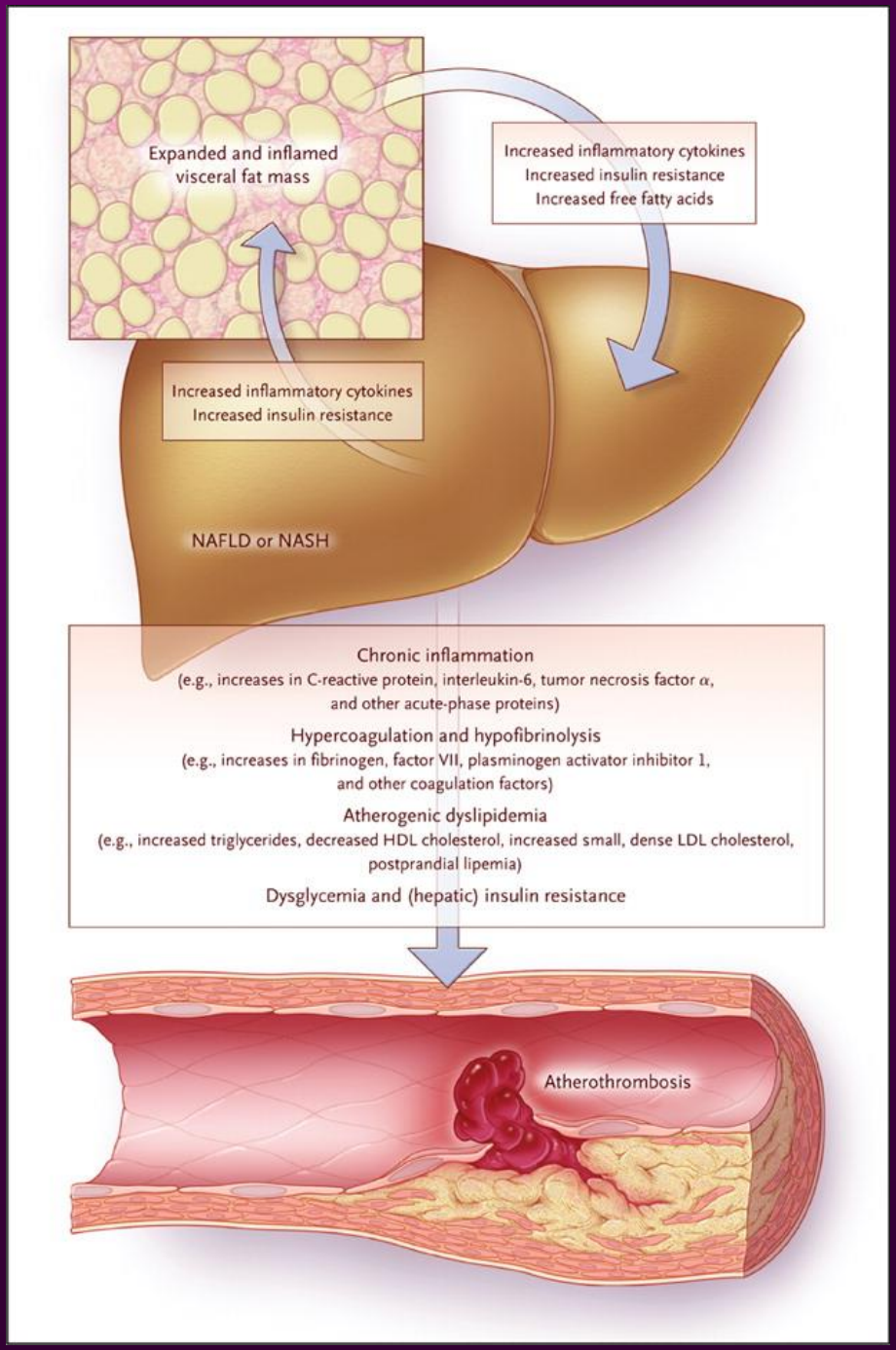
Asia
Uomini: 90 cm
Donne: 80 cm

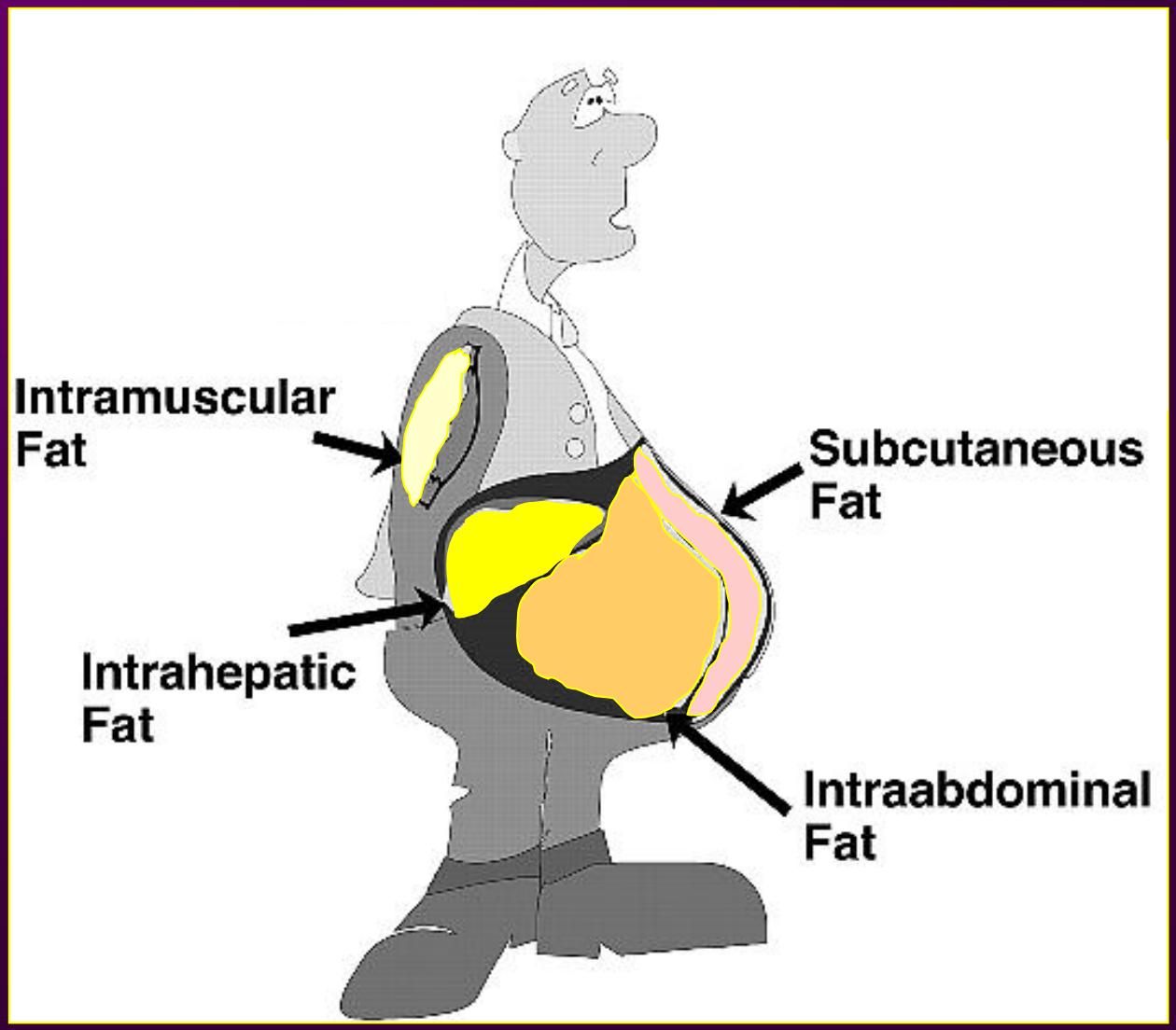
Rapporto vita/fianchi
Donne>0.80 = Rischio aumentato
Uomini >0.95 = Rischio aumentato

ACSM 2005

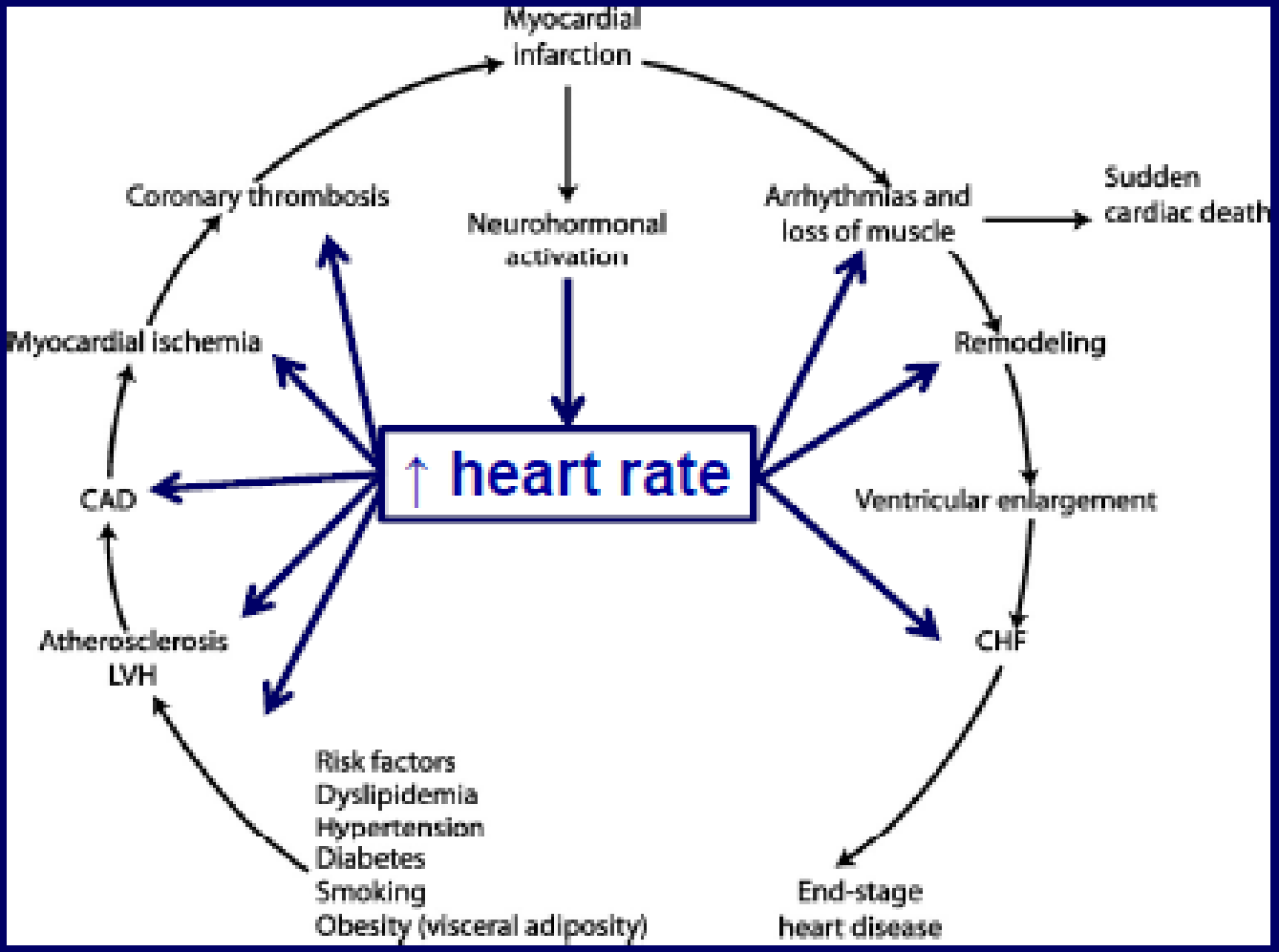


Tarquini et al GIC in press


Expanded and inflamed visceral fat mass
Increased inflammatory cytokines
Increased insulin resistance
Increased free fatty acids
Increased inflammatory cytokines
Increased insulin resistance
NAFLD or NASH
Chronic inflammation
(e.g., increases in C-reactive protein, interleukin-6, tumor necrosis factor α, and other acute-phase proteins)
Hypercoagulation and hypofibrinolysis
(e.g., increases in fibrinogen, factor VII, plasminogen activator inhibitor 1, and other coagulation factors)
Atherogenic dyslipidemia
(e.g., increased triglycerides, decreased HDL cholesterol, increased small, dense LDL cholesterol, postprandial lipemia)
Dysglycemia and (hepatic) insulin resistance
Atherothrombosis


Intramuscular Fat
Subcutaneous Fat
Intrahepatic Fat
Intraabdominal Fat

The Cardiovascular Disease Continuum Validated: Clinical evidence of improved patient outcome

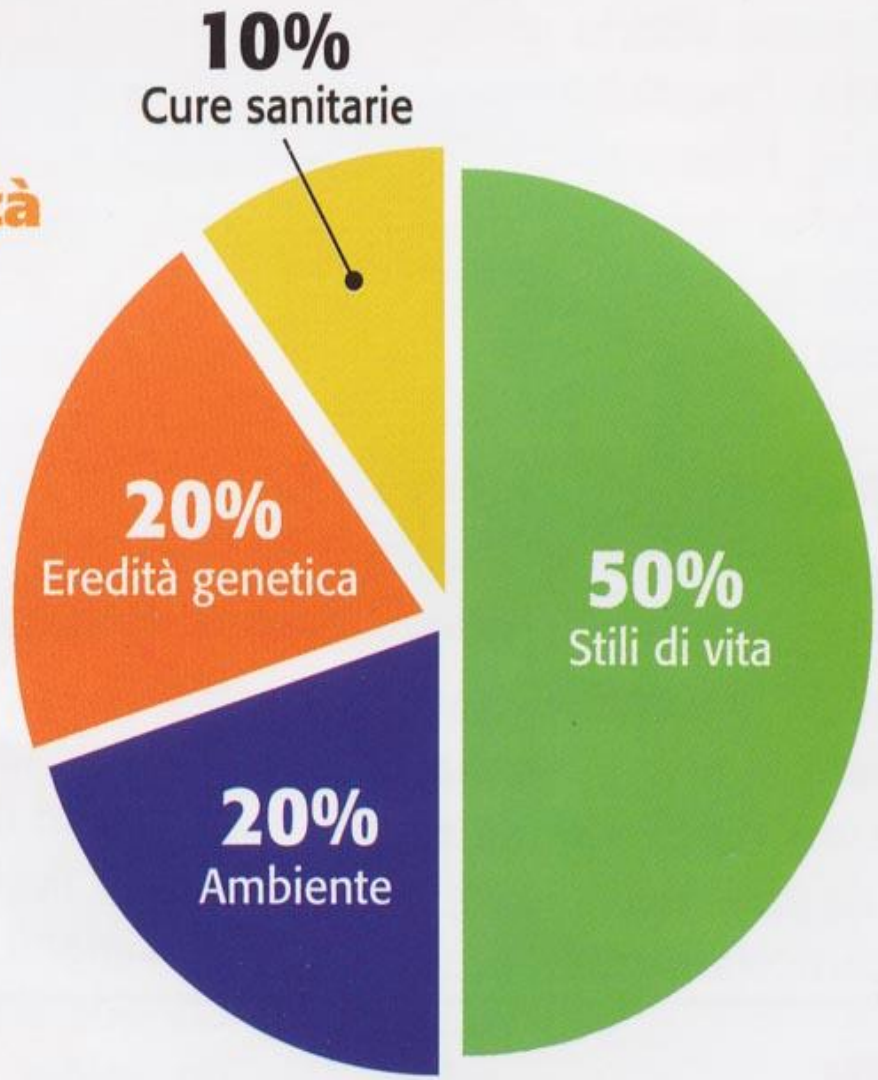


Dzau, V. J. et al. Circulation 2006;114:2850-2870

Heart Rate: the "*timepiece*" of life: *why*?

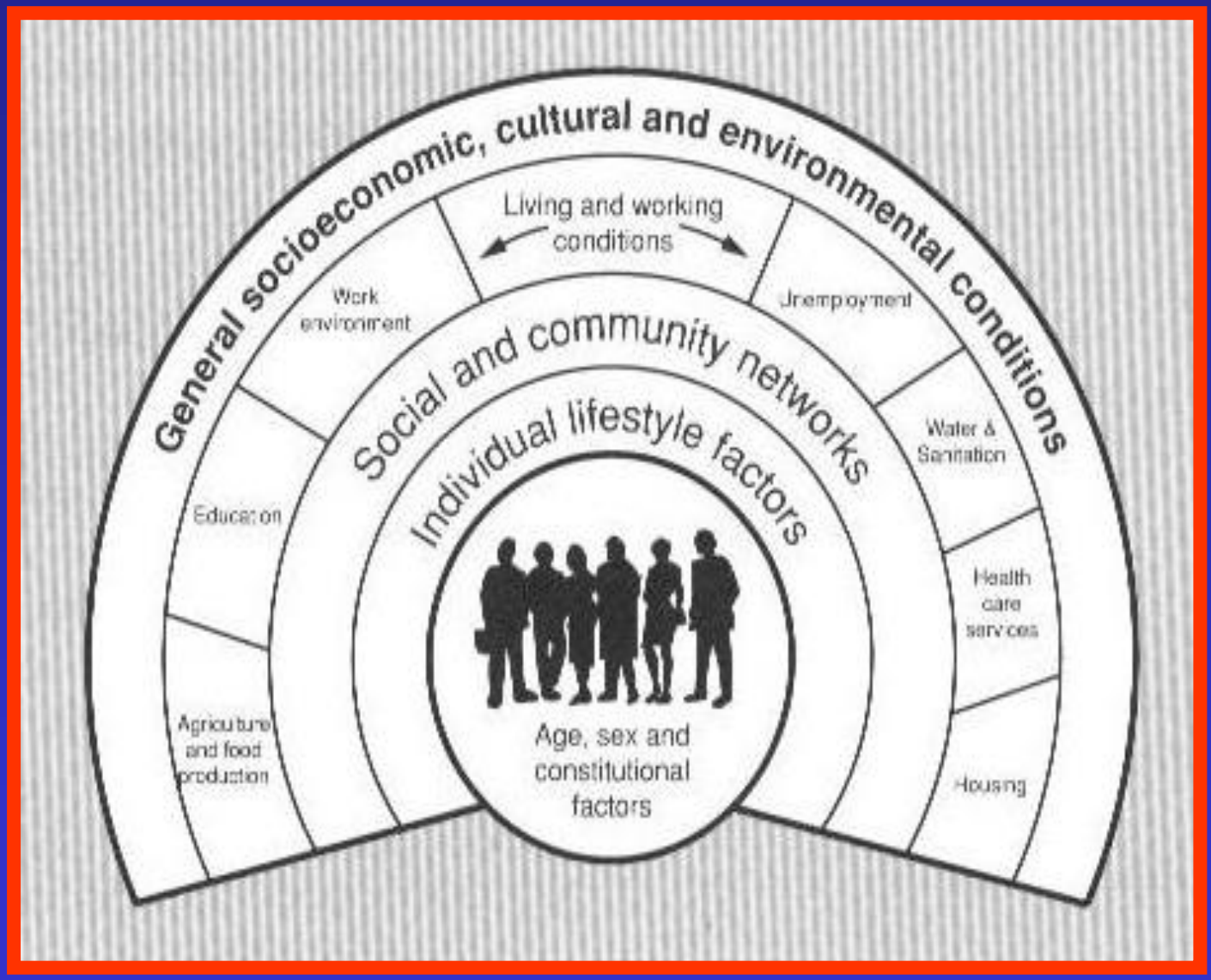
- HR controls endothelial "shear stress", NO release and vessel stiffness
- Increase in HR causes dilation, improves organ perfusion and energy delivery
- HR *reflects/determins*? body needs
- HR is the language between "centre" and "periphery"

Elementi che incidono sulla longevità



Bodura 1995

The Main Determinants of Health



From Dahlgren G and Whitehead M, 1991

Il genotipo

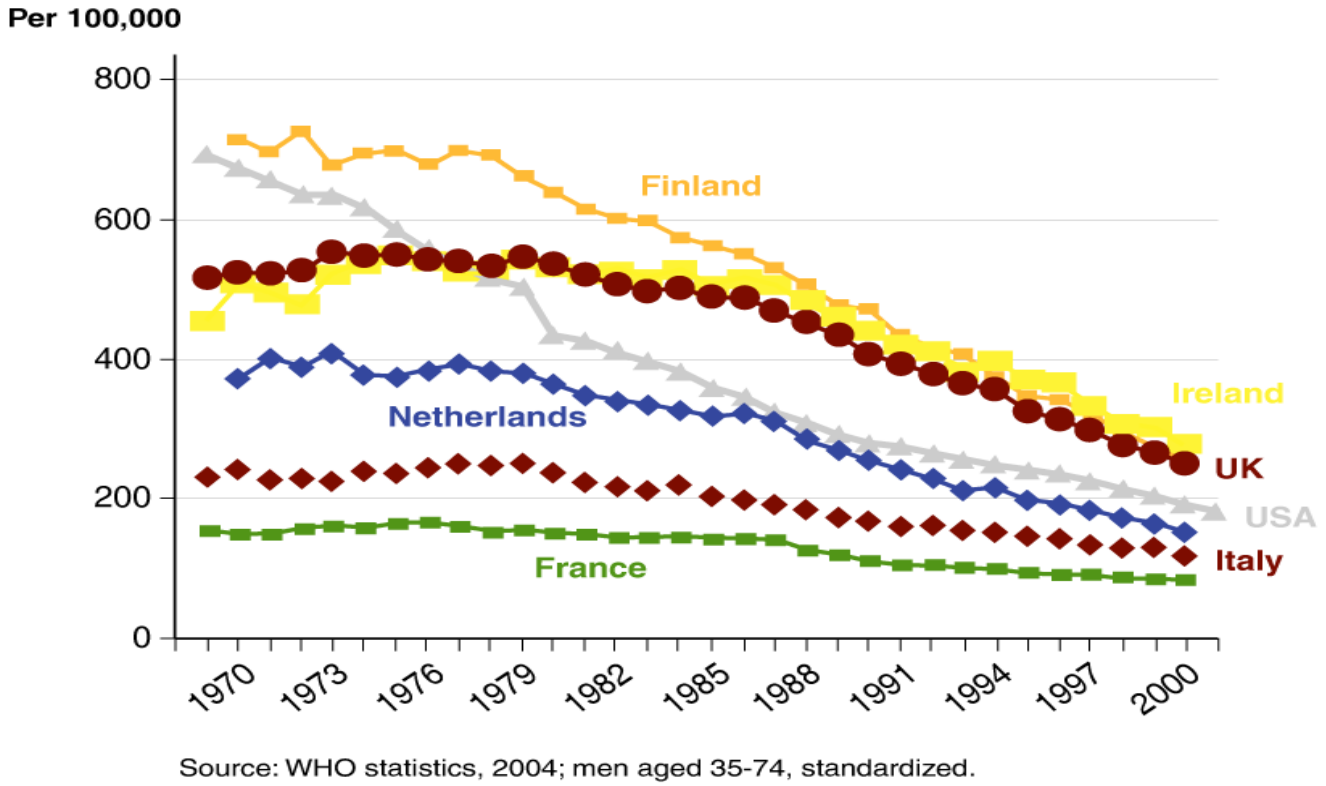
notipo (con un livello di rischio)

La condizione latente

La malattia manifesta

FIGURA 5.2 • La catena della causalità. Ogni tappa può essere condizionata da fattori promotori ed inibitori.

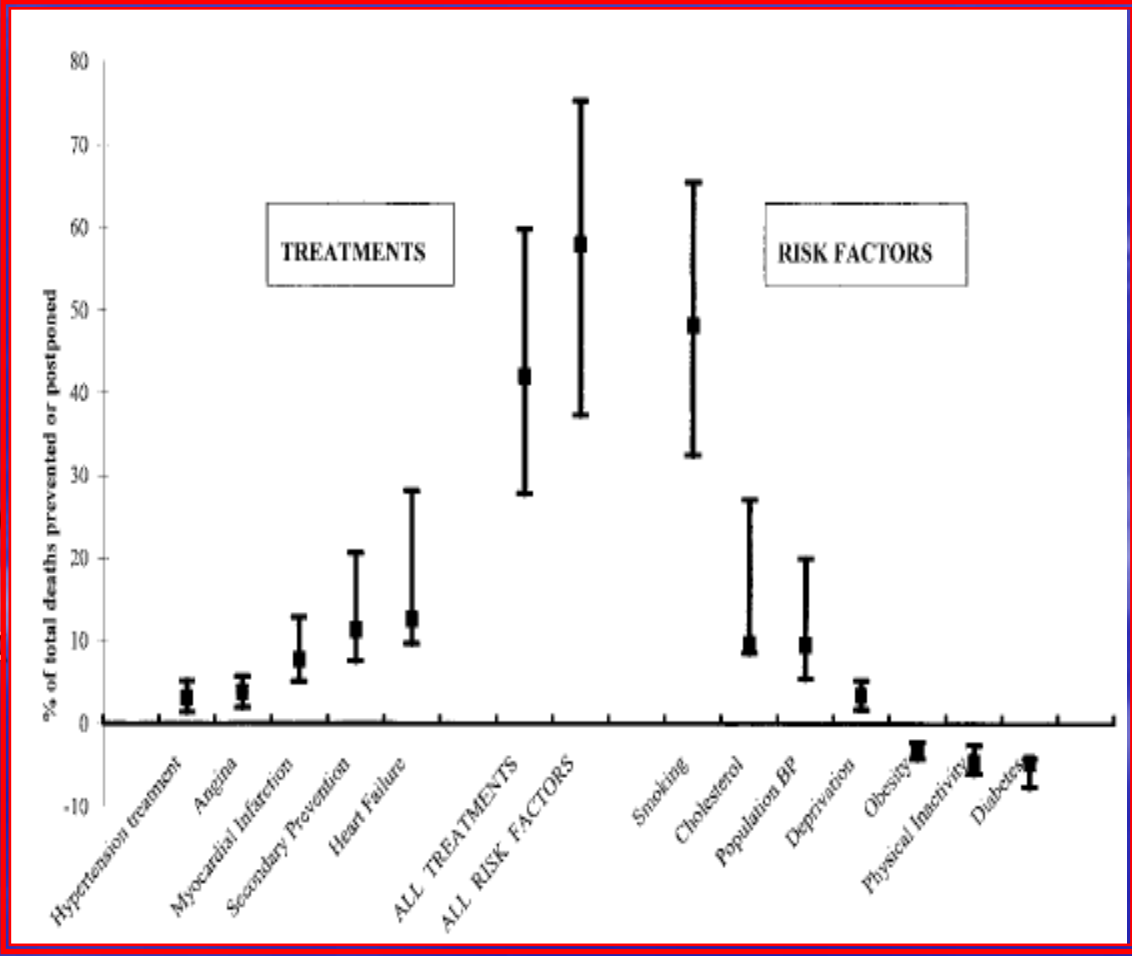
International CHD Mortality Trends in Men: 1968-2003



Source: WHO statistics, 2004; men aged 35-74, standardized.

Decline in Coronary Heart Disease Mortality

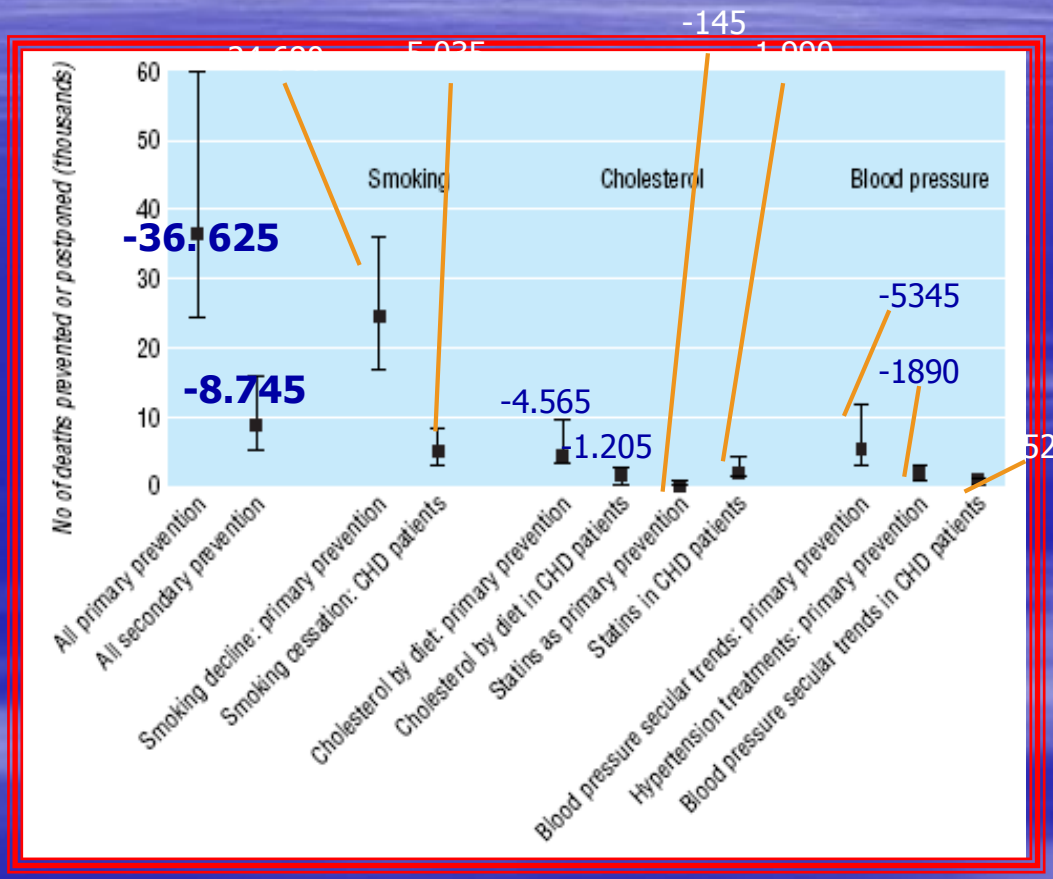
- Between 1981 and 2000, coronary heart disease mortality rates in England and Wales decreased by 62% in men and 45% in women: 68.230 fewer deaths in 2000.
- Some 42% of this decrease was attributed to treatments in individuals and 58% to population risk factor reductions



(Unal, *Circulation* 2004)

Better Primary Prevention

- Compared with secondary prevention, primary prevention achieved a fourfold larger reduction in deaths.
- Future CHD policies should prioritise population-wide tobacco control and healthier diets.



(Unal, *BMJ* 2005)

EUROASPIRE III: A SURVEY ON THE LIFESTYLE, RISK FACTORS AND USE OF CARDIOPROTECTIVE DRUG THERAPIES IN CORONARY PATIENTS FROM 22 EUROPEAN COUNTRIES

Kotseva K, Wood D, Backer GD, et al.

Eur J Cardiovasc Prev Rehabil, pubblicato on line il 12 marzo 2009

Fattori di rischio nelle survey EUROASPIRE

Fattori di rischio	EUROASPIRE I (%)	EUROASPIRE II (%)	EUROASPIRE III (%)
Fumo	20,3	21,2	18,2
Sovrappeso e obesità	76,8	79,9	82,7
Obesità	25,0	32,6	38,0
Ipertensione	58,1	58,3	60,9
Elevata coletsterolemia	94,5	76,7	46,2
Diabete mellito	17,4	20,1	28,0

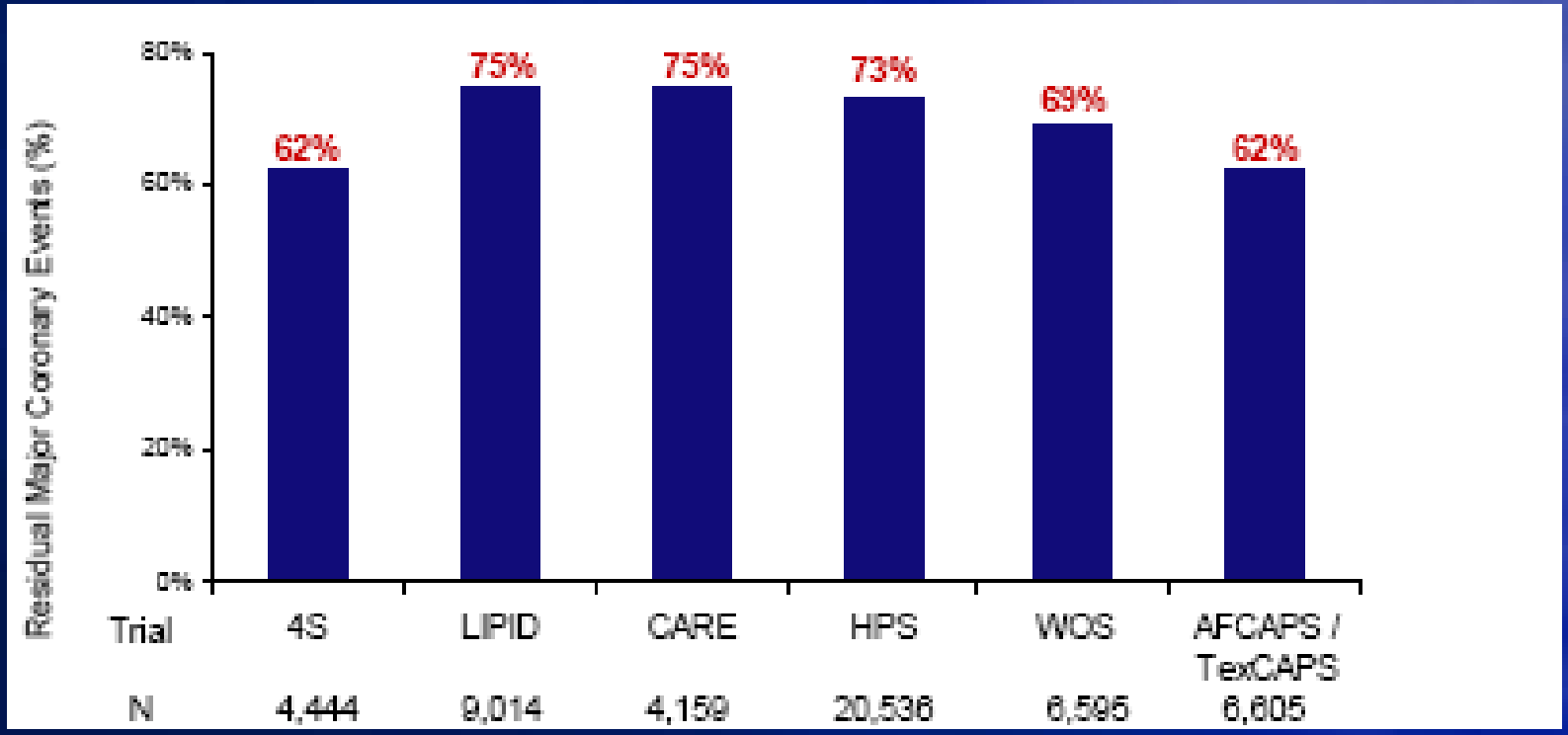
Terapia con farmaci cardioprotettivi nelle survey EUROASPIRE

Terapie	EUROASPIRE I (%)	EUROASPIRE II (%)	EUROASPIRE III (%)
Terapia antipiastrinica	80,8	83,6	93,2
Beta-bloccanti	56,0	69,0	85,5
Farmaci antipertensivi	84,5	90,6	96,8
Farmaci ipolipemizzanti	32,2	62,7	88,8

Sovrastima della terapia farmacologica?

- *Riduzione di rischio relativo mortalità dopo IMA:* -15% aspirina, -23% BB, 20% ACE-I, -22% statine e -26% RC.
- In un P trattato già con aspirina, l'aggiunta di un BB può ridurre solo il rischio **residuo** (1 – 0.15: 0.85); la successiva somministrazione di un ACE-I riduce il **rimanente** rischio 1 – [(1 – 0.15) X (1 – 0.23)].
  La riduzione del rischio relativo è del 34% invece che della semplice somma (106%).

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



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

“forgotten majority”

Peter Libby JACC 2005

Problem 1 - Inaccurate Individualized Assessment of Cardiovascular Risk

Who Has More Cardiovascular Risk Factors?

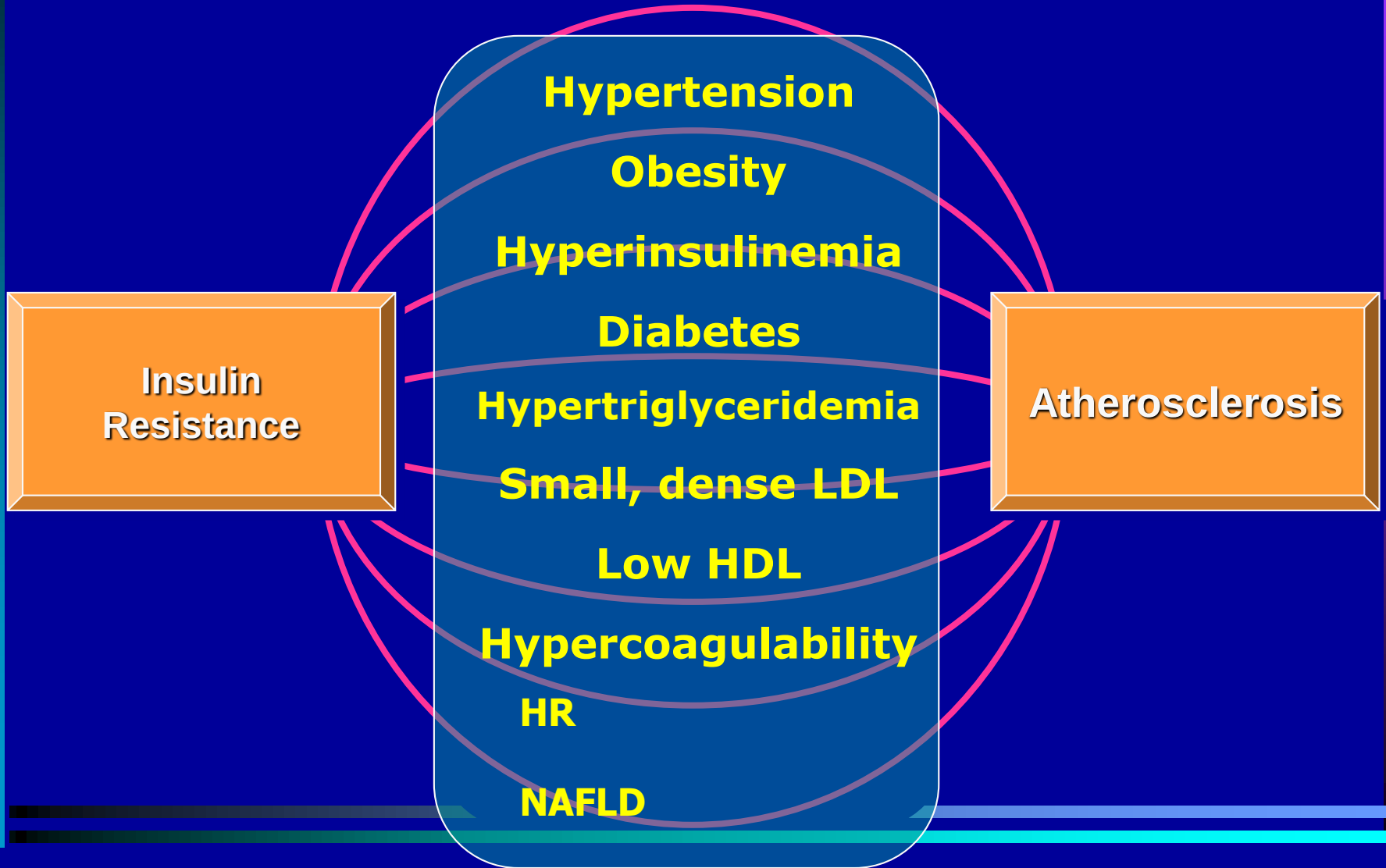
Sir Winston Churchill, 91 ✝

- Overweight
- Not Fit
- Heavy Smoker

Jim Fixx, 53 ✝♥

- Not Overweight
- Very Fit
- Non-Smoker

Interrelation Between Atherosclerosis and Insulin Resistance



Si puo' ipotizzare un comune denominatore?

Risk factors

Insulinoresistenza
NO
RAAS

Genetica

Atherosclerosis → Stroke

Vasoconstriction
Vascular hypertrophy
Endothelial dysfunction → CHD

LV hypertrophy
Fibrosis
Remodeling
Apoptosis → Heart failure

↓ GFR, ↑ S.Creatinine
↑ Microalbuminuria,
↑ Proteinuria
↑ Aldosterone release
Glomerular sclerosis → Renal failure


CRIME SCENE

Si puo' ipotizzare un comune denominatore?

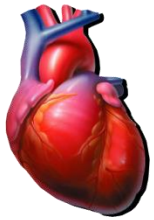
Risk factors

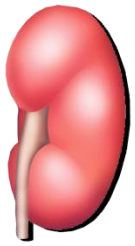
Insulinoresistenza
NO
RAAS

Genetica

Atherosclerosis →  → **Stroke**

Vasoconstriction
Vascular hypertrophy
Endothelial dysfunction →  → **CHD**

LV hypertrophy
Fibrosis
Remodeling
Apoptosis →  → **Heart failure**

↓ **GFR,** ↑ **S.Creatinine**
↑ **Microalbuminuria,**
↑ **Proteinuria**
↑ **Aldosterone release**
Glomerular sclerosis →  → **Renal failure**

Meccanismi acceleratori rallentatori!?

Problem 1 - Inaccurate Individualized Assessment of Cardiovascular Risk

Who Has More Cardiovascular Risk Factors?

Sir Winston Churchill, 91 ✝

- Overweight
- Not Fit
- Heavy Smoker

Jim Fixx, 53 ✝♥

- Not Overweight
- Very Fit
- Non-Smoker

“forgotten majority”

Peter Libby JACC 2005

European guidelines on CVD prevention

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.

Il Canone di Medicina Interna dell'Imperatore Giallo

上医医未病之病
中医医将病之病
下医医已病之病
——黄帝内经

Il medico superiore previene le malattie;
Il medico mediocre cura le malattie incombenti;
Il medico inferiore tratta le malattie completamente manifeste.

Neijn di Huang Di
(2695-2589 a.c.)