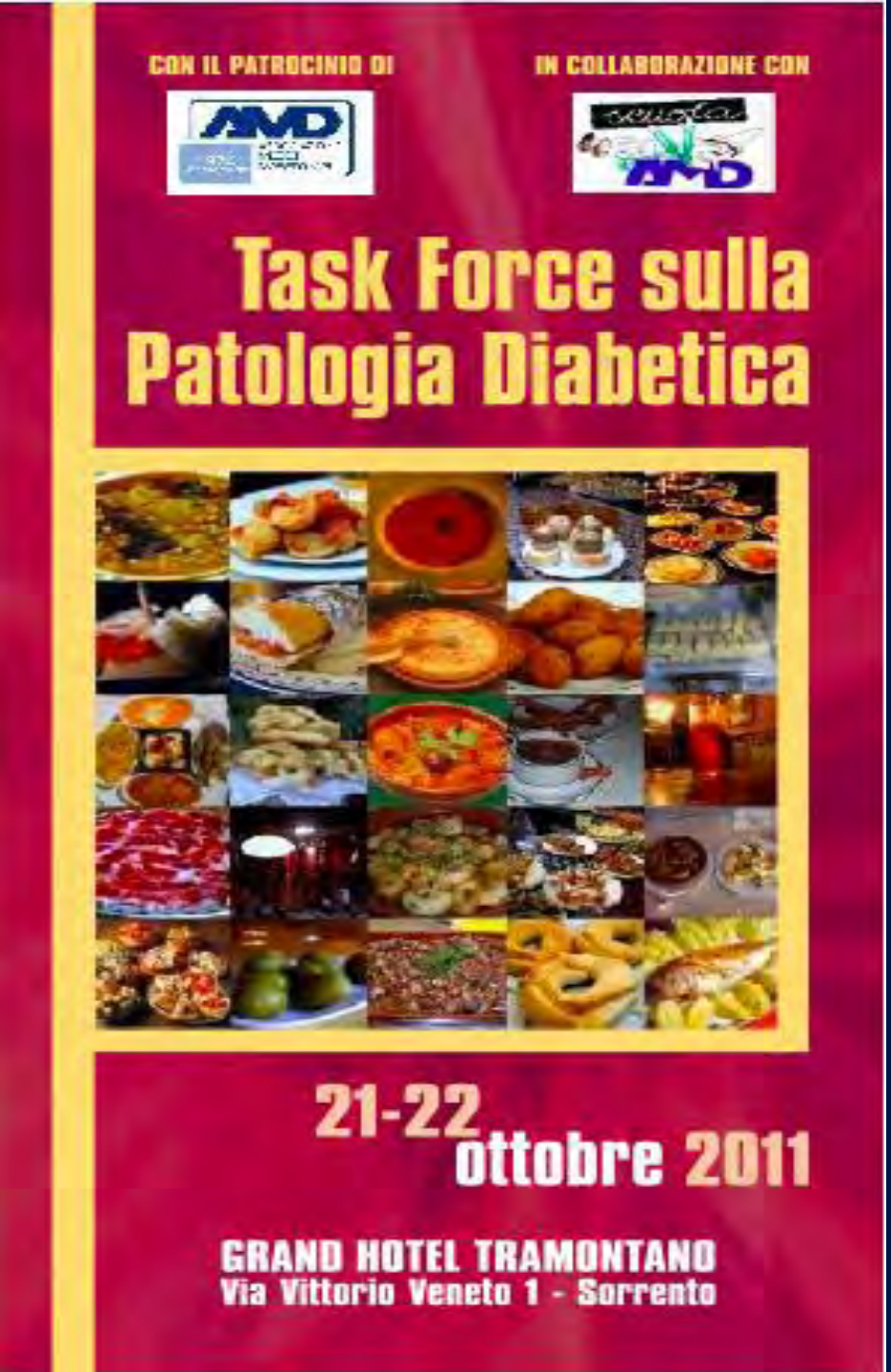
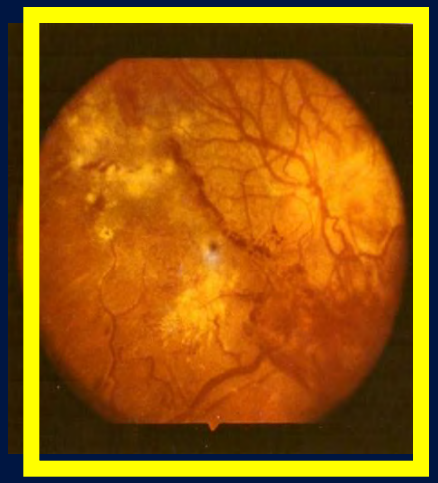


Fattori di Rischio Emergenti

Giuseppe Memoli

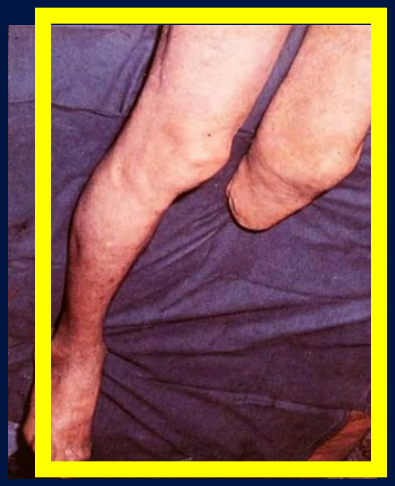
Diabete: "MALATTIA DA PRIMATO"



Prima causa
di cecità

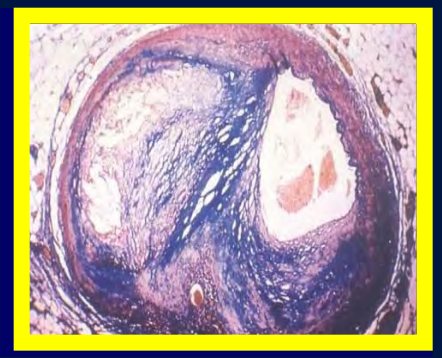
Prima causa
di insufficienza
renale & dialisi

Diabete



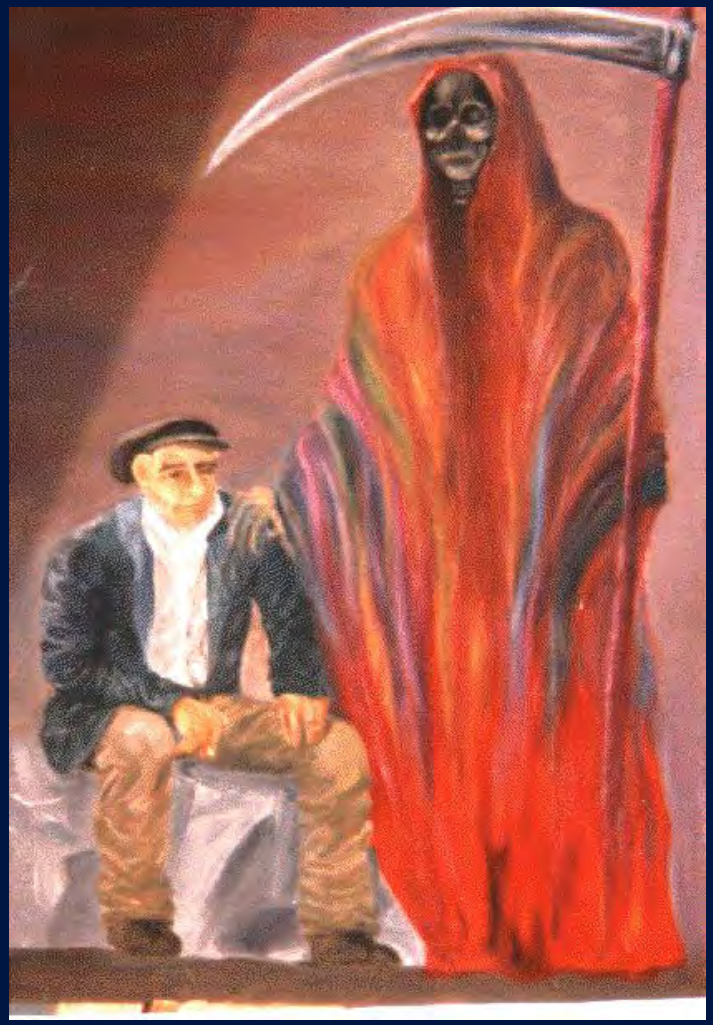
Prima causa
di amputazione
non traumatica

Concausa
nel 40-50%
di
infarti e ictus

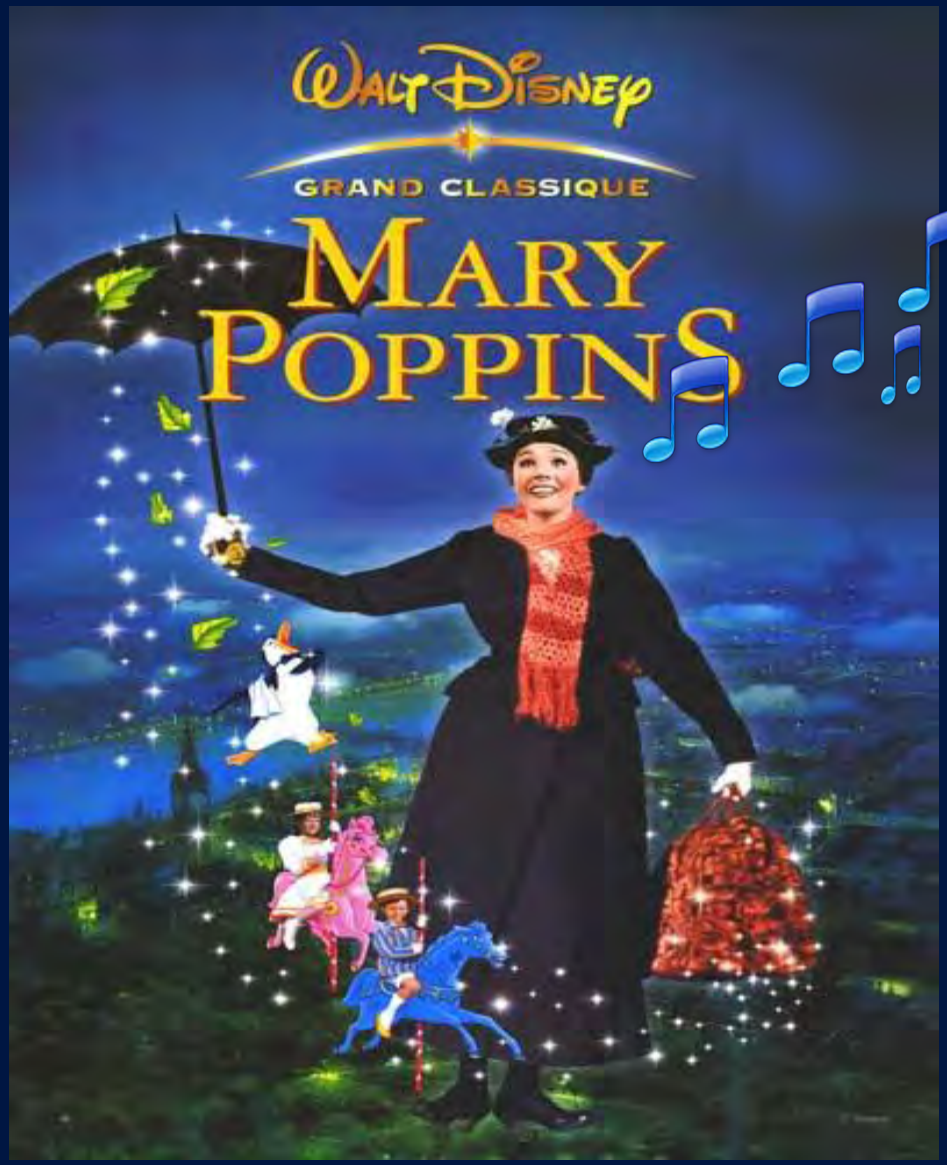


Gabriel García Márquez

Cronaca di una morte annunciata

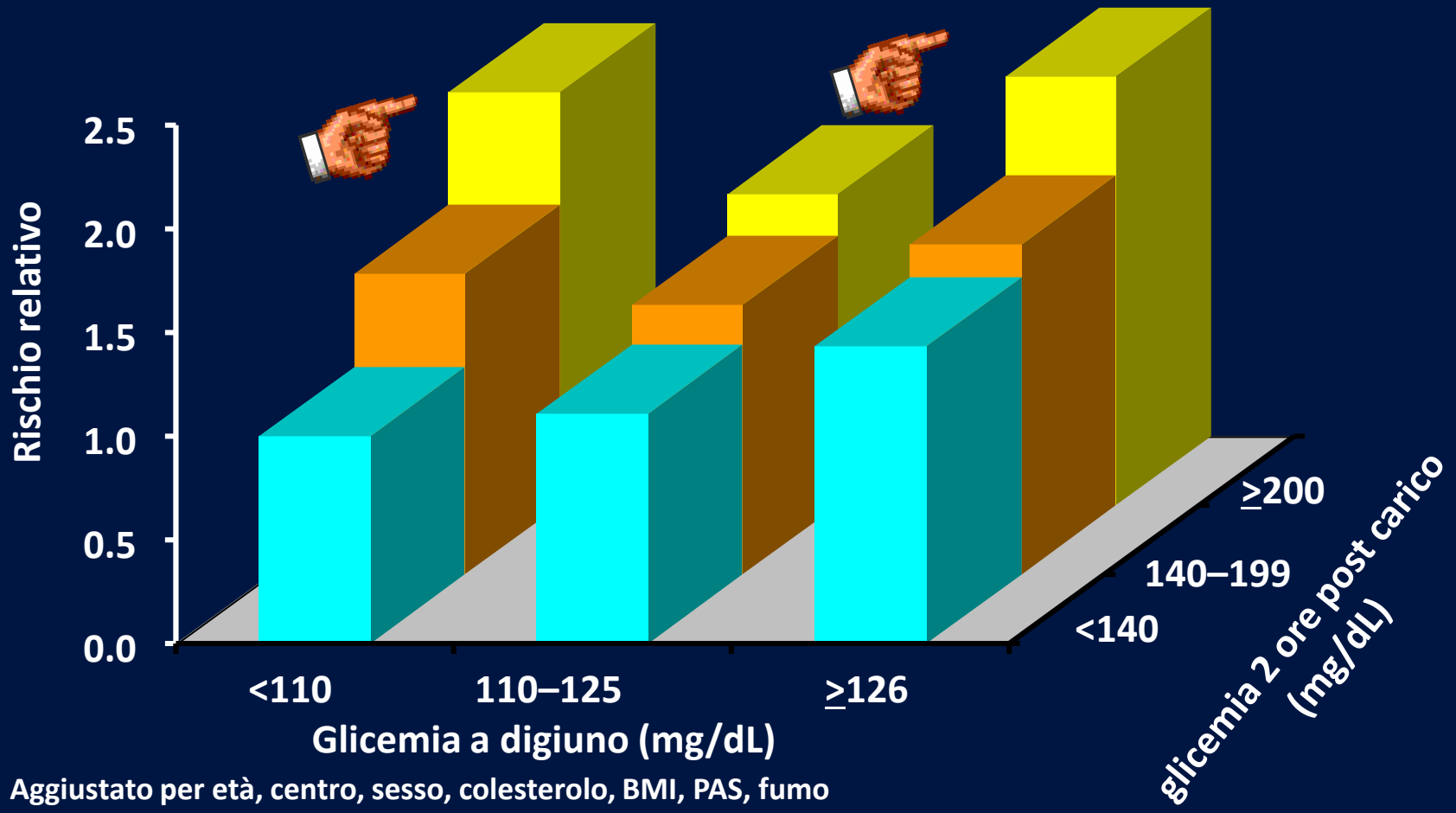


Il 75-78% dei pazienti con diabete mellito tipo 2 soccombe per malattie cardiovascolari



Basta un poco di zucchero e…

Studio DECODE: rischio relativo di mortalità cardiovascolare secondo la categoria diagnostica



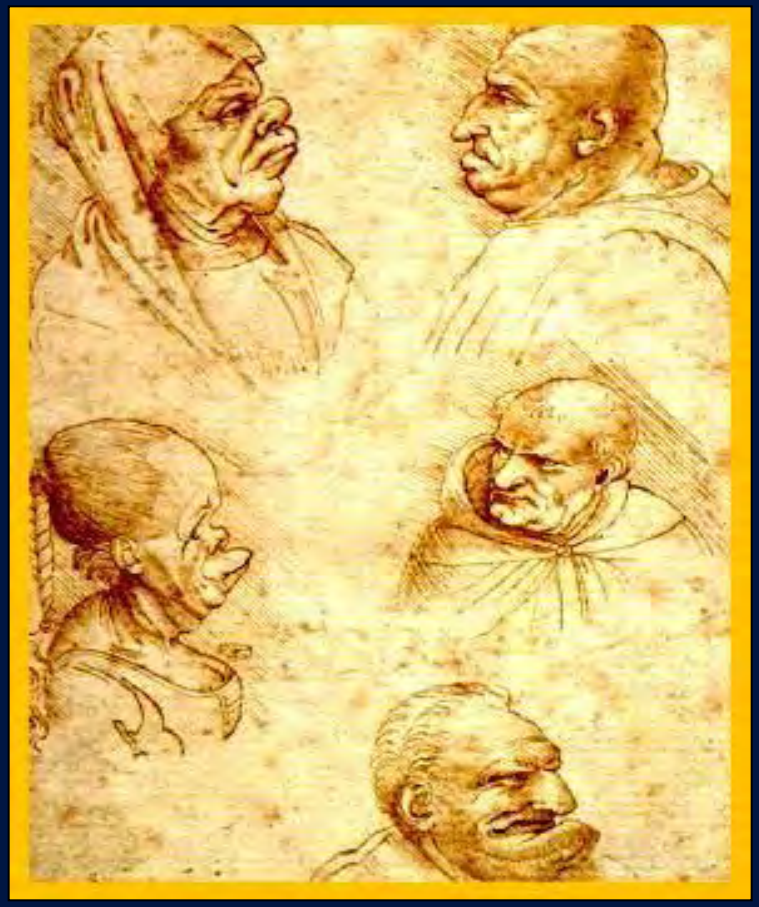
Aggiustato per età, centro, sesso, colesterolo, BMI, PAS, fumo

Adattato da DECODE Study Group. *Lancet* 1999;354:617–621.

COSTANTE AGGREGAZIONE CON ALTRI FATTORI DI RISCHIO CARDIOVASCOLARE

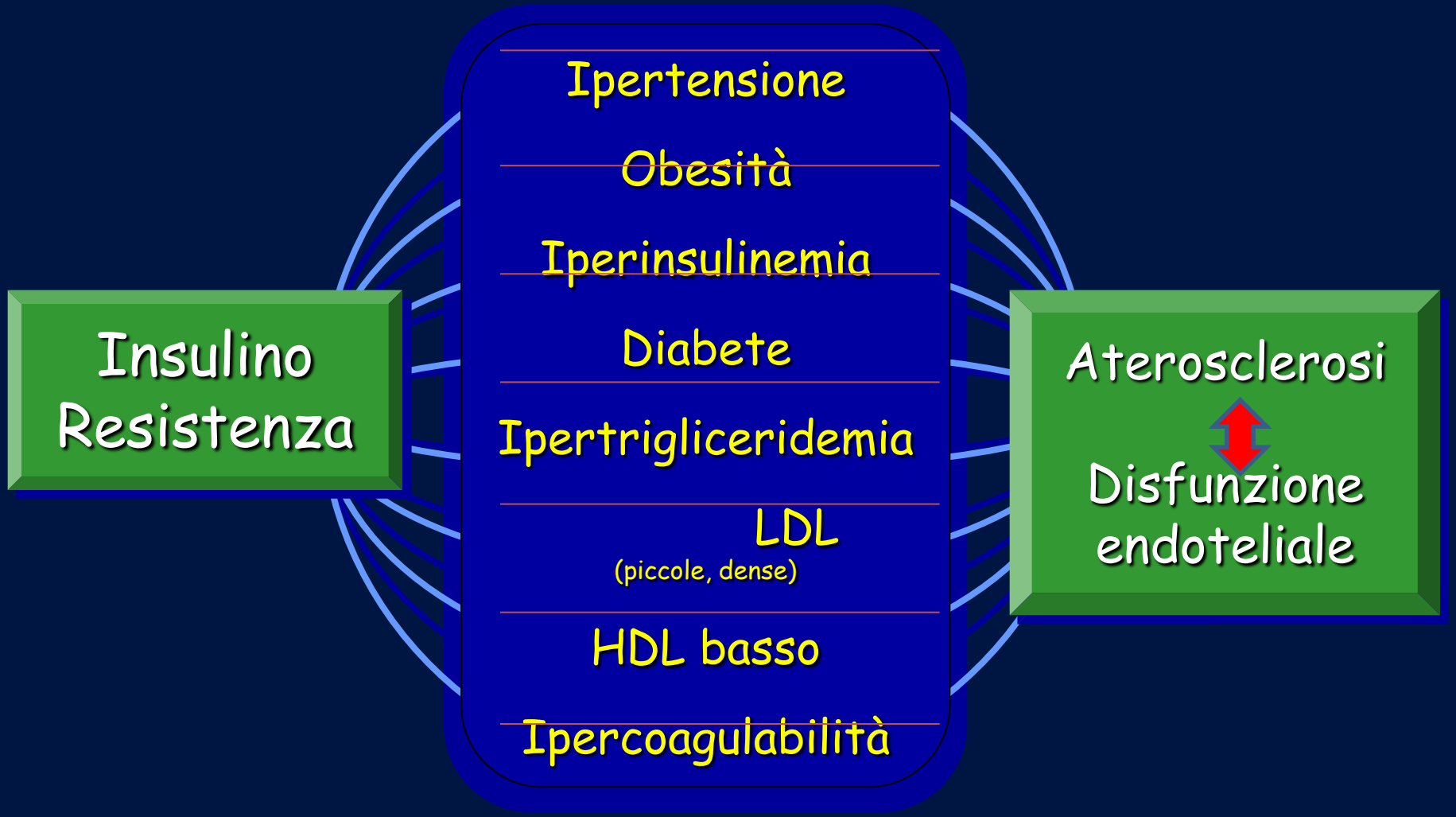
OVVERO

" I CATTIVI COMPAGNI E LE RELAZIONI PERICOLOSE"

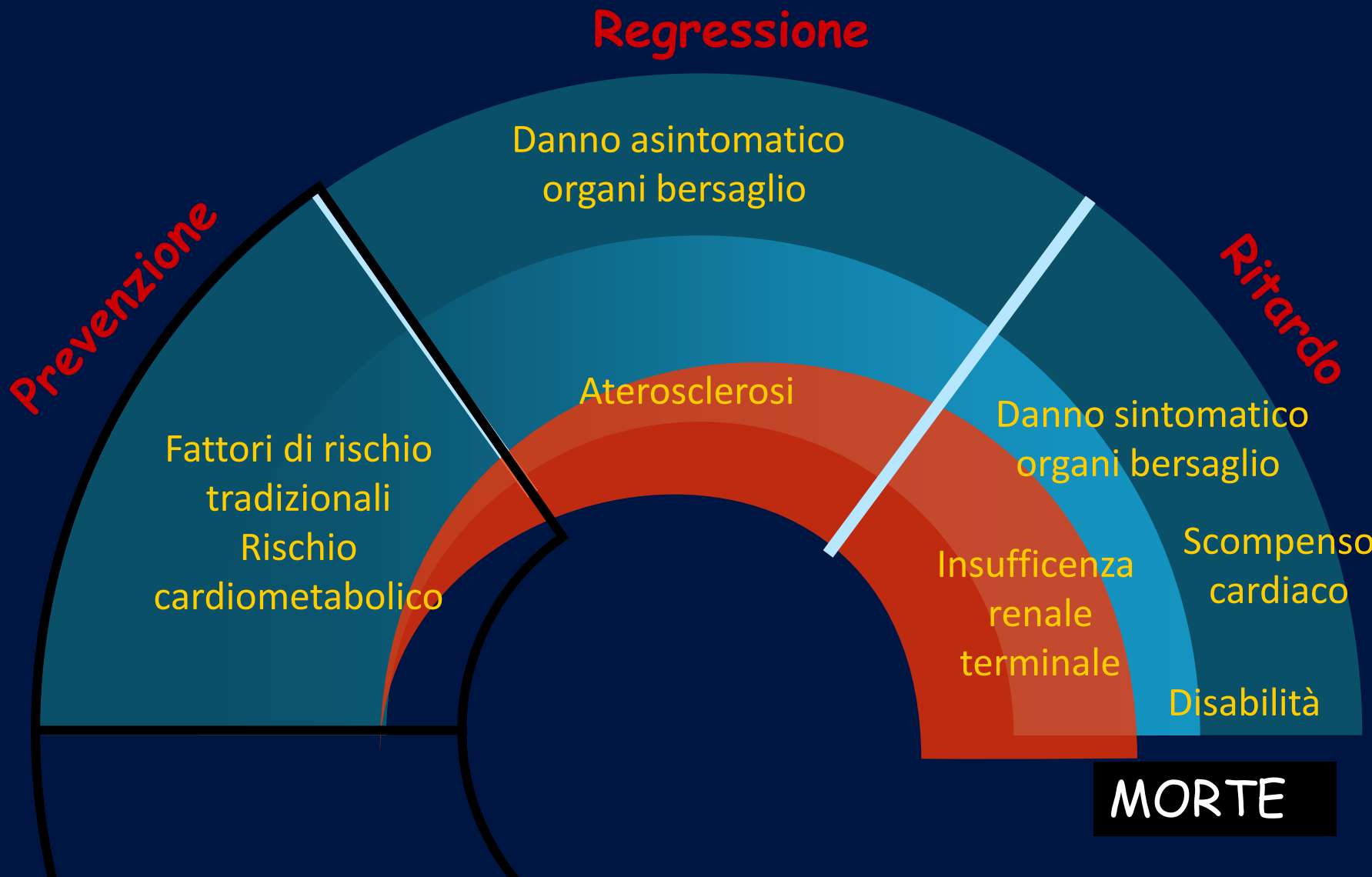


- IPERTENSIONE ARTERIOSA
- OBESITA'
- IPERLIPIDEMIA
- ALTERAZIONI DELLA COAGULAZIONE E DELLA FIBRINOLISI
- IPERINSULINEMIA - INSULINORESISTENZA

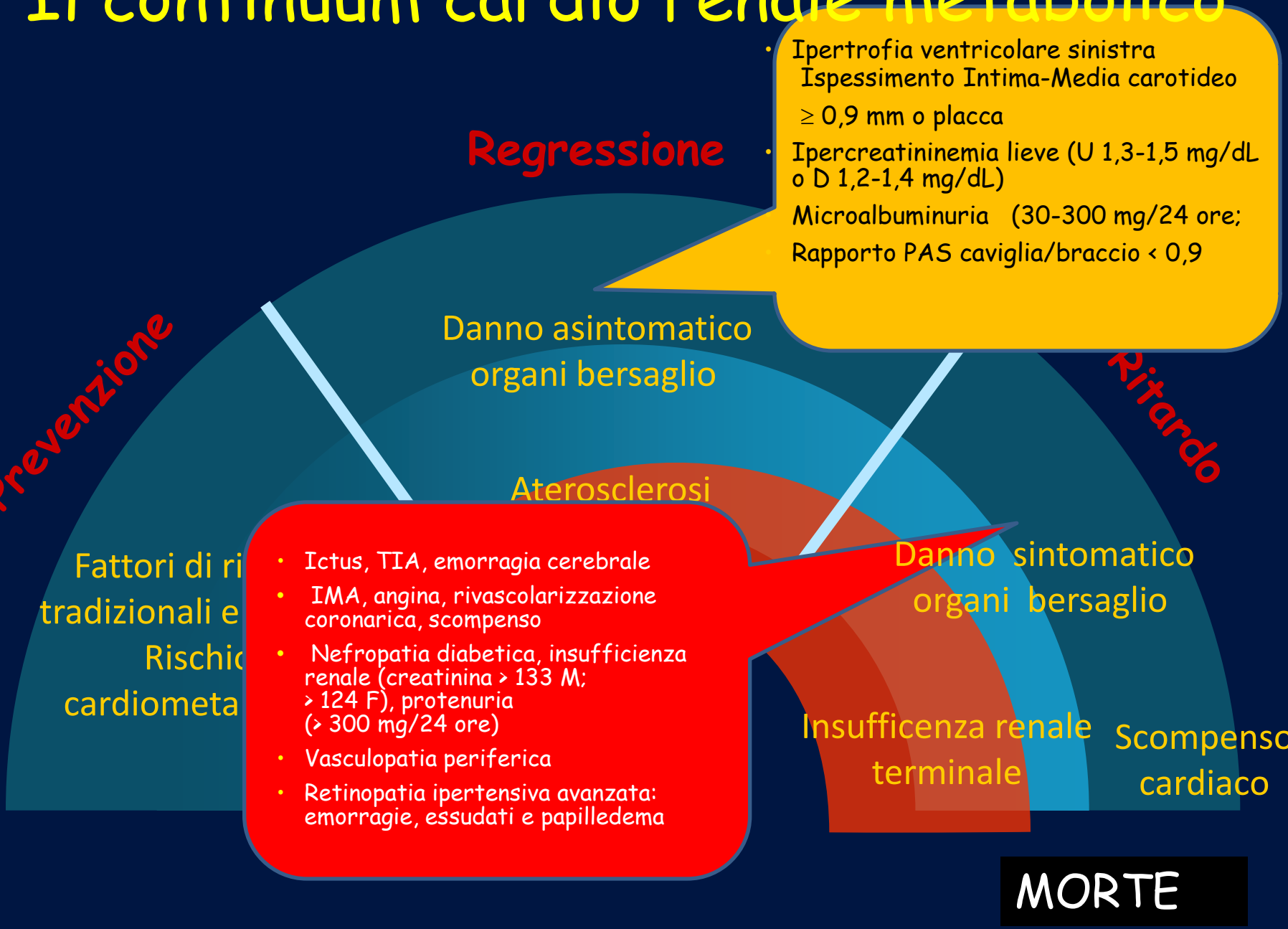
I legami tra Aterosclerosi e Insulino-Resistenza



Il continuum cardio renale metabolico



Il continuum cardio renale metabolico



INTERHEART Yusuf S et al Lancet 2004; 364: 937-952

- "Nove fattori di rischio, facilmente misurabili, "spiegano" oltre il 90% degli infarti miocardici"

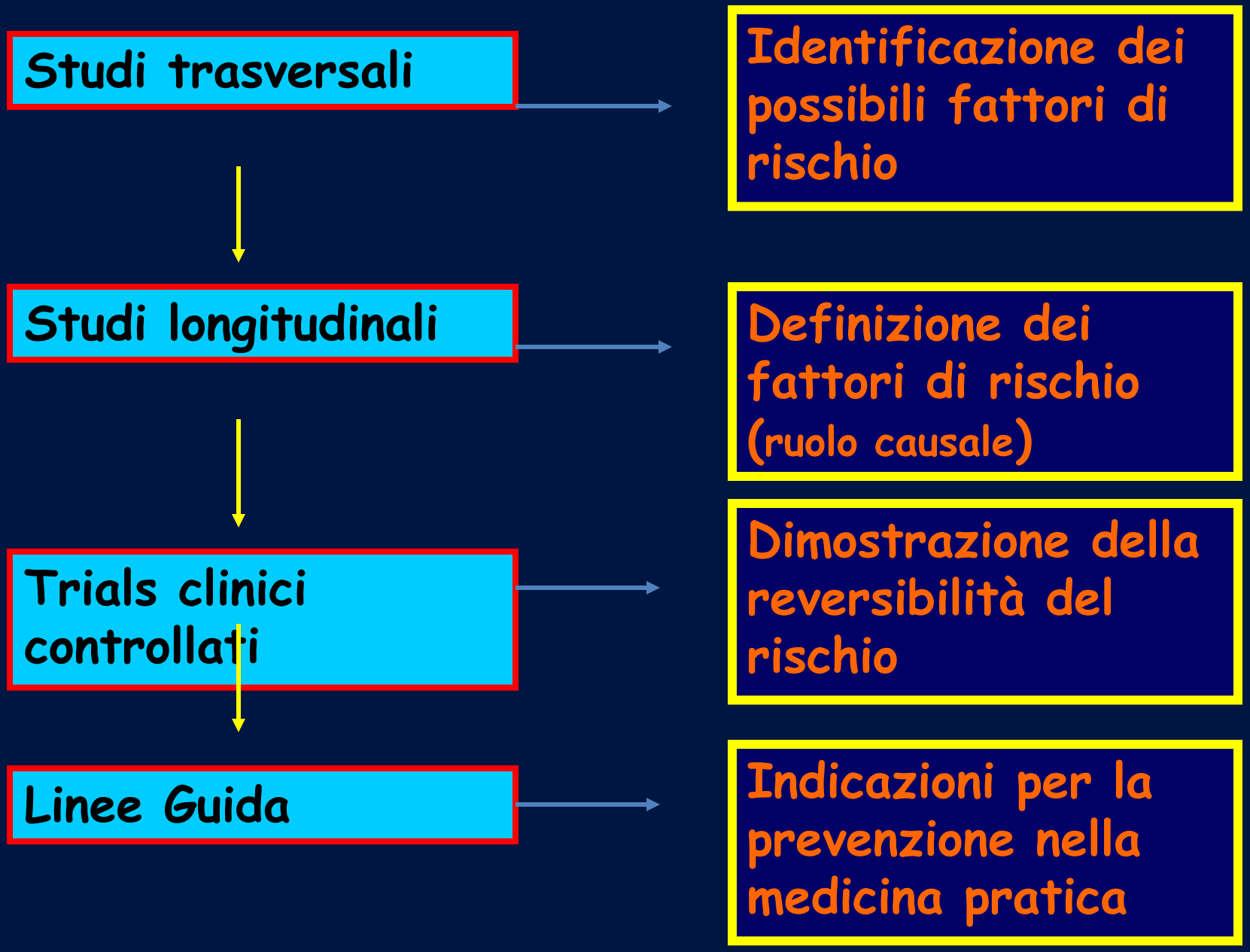
•Questi fattori sono:

- Fumo
- Ipertensione
- Diabete
- Dislipidemia
- Obesità addominale
- Stress
- Inattività fisica
- Scarsa assunzione di frutta e verdura
- Assunzione di alcol

- **L'associazione di più fattori di rischio moltiplica la probabilità di infarto**

Chi presenta tutti i nove fattori ha una probabilità di infarto che è più di 330 volte superiore a quella di chi non ne ha nessuno

L'American Heart Association ha recentemente definito che un marker di rischio dovrebbe dimostrare che è indipendente da altri fattori in più studi di coorte prospettici, che la sua valutazione porta vantaggi clinici sugli esiti del paziente, che è facilmente misurabile con metodi standardizzati e che è economico


Studi trasversali
Identificazione dei possibili fattori di rischio
Studi longitudinali
Definizione dei fattori di rischio (ruolo causale)
Trials clinici controllati
Dimostrazione della reversibilità del rischio
Linee Guida
Indicazioni per la prevenzione nella medicina pratica

Aforisma di Cochrane

Prima di farvi fare un esame decidete che cosa farete se

a)è positivo e *b)* è negativo.

Se la risposta è la stessa, non fate l'esame.

Arthur Bloch

DOMANDA

ABBIAMO DI ALTRI FATTORI DI RISCHIO O MARKERS PER IDENTIFICARE IL RISCHIO CARDIOVASCOLARE DEI NOSTRI PAZIENTI ?

Microalbuminuria, hsPCR, ICAM, VCAM,

E selectina, vWF, trombomodulina, PAI1,

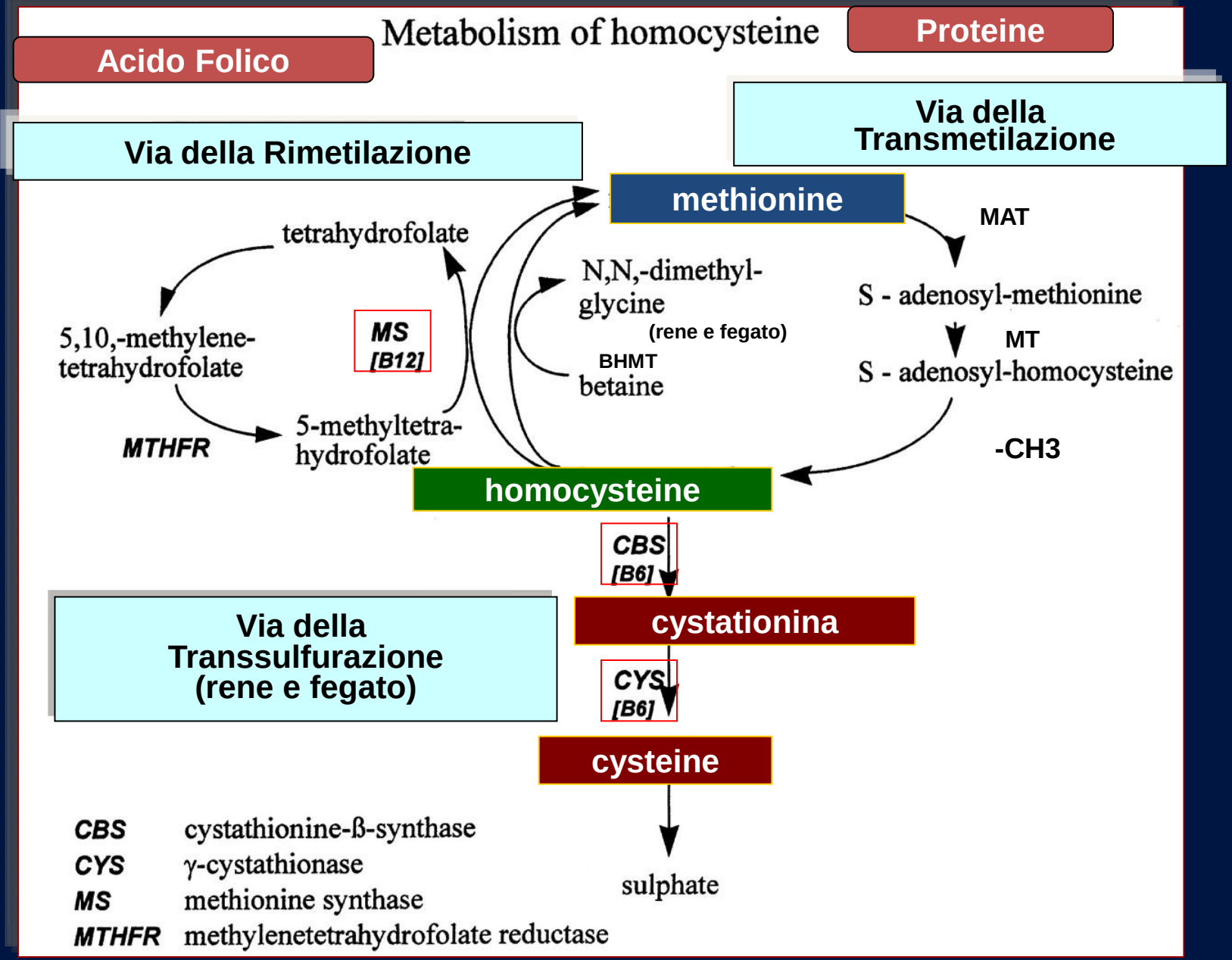
lipoproteina (a), fibrinogeno, ipovitaminosi D, HbA1c, stress ossidativo, Angiotensina, EPC, NT-proBNP,leptina, TNFa, conta leucociti, iperomocisteinemia,iperuricemia, polimorfirmi genetici, agenti infettivi (Chamydia P, H. Pylori) ispessimento mio intimale, Ipertrofia ventricolare sinistra, ABI, pressione arteriosa centrale, Ca score, D.E. malattia paradontale ecc…

1. Iperomocisteinemia
2. Fibrinogeno
3. Hs PCR
4. Lipoproteina (a)

1º

Iperomocisteinemia

Metabolismo dell'Omocisteina



Martí-Carvajal AJ et al, Cochrane Database Syst Rev 2009; (4): CD006612

Homocysteine lowering interventions for preventing cardiovascular events.

Results from available published trials suggest that there is no evidence to support the use of HLI to prevent cardiovascular events.

Clarke R et al.

Effects of Lowering Homocysteine Levels With B Vitamins on Cardiovascular Disease, Cancer, and Cause-Specific Mortality. *Arch Intern Med.* 2010; 170(18):1622-1631

Meta-analisi che ha coinvolto più di 37.000 individui a rischio per patologia cardiovascolare per verificare se il trattamento suppletivo con folati volto a ridurre i valori di iperomocisteinemia fosse in grado di ridurre anche il rischio cardiovascolare.

La supplementazione con acido folico ha determinato una riduzione media dei livelli di omocisteinemia del 25%; nonostante ciò gli individui che l'avevano ottenuta non hanno mostrato significativi risultati in termine di riduzione del RR sia per le patologie cardiovascolari nel loro insieme (OR 1.01) e sia per la scomposizione in patologia coronarica (1.03) o cerebro-vascolare (0.96), come pure per la mortalità globale. Anche l'incidenza di cancro o la mortalità per cancro non erano influenzate dalla supplementazione vitaminica. L'iperomocisteinemia pare quindi essere un marker, ma non la causa di un aumentato rischio cardiovascolare ed il suo trattamento non pare necessario.

2º

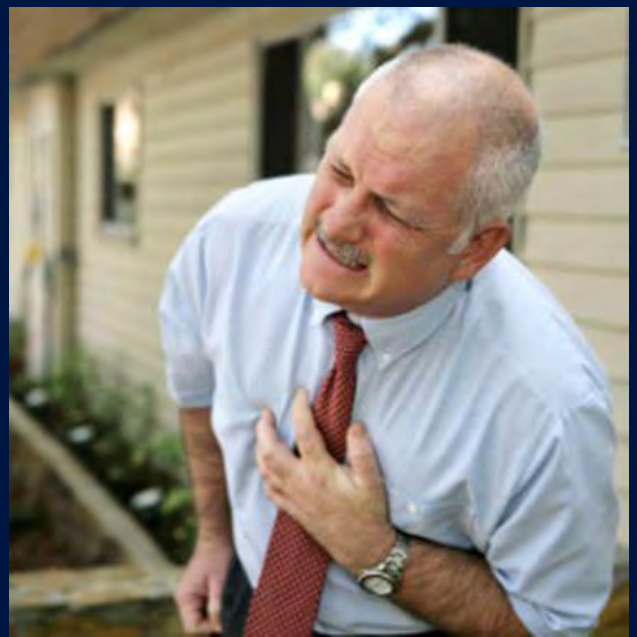
Fibrinogeno

Clinical Chemistry 56:5
781–788 (2010)

γ′ Fibrinogen: Evaluation of a New Assay for Study of Associations with Cardiovascular Disease

Rehana S. Lovely,[1] Steven C. Kazmierczak,[2] Joseph M. Massaro,[3] Ralph B. D'Agostino, Sr.,[4] Christopher J. O'Donnell,[5] and David H. Farrell[2*]

In conclusion, γ′ fibrinogen shows promise as a marker for cardiovascular disease. The addition of this marker to other established risk factors such as high- sensitivity CRP (hsCRP) (28) and cholesterol may pro- vide additive predictive value for assessment of risk of adverse cardiac events.



3º

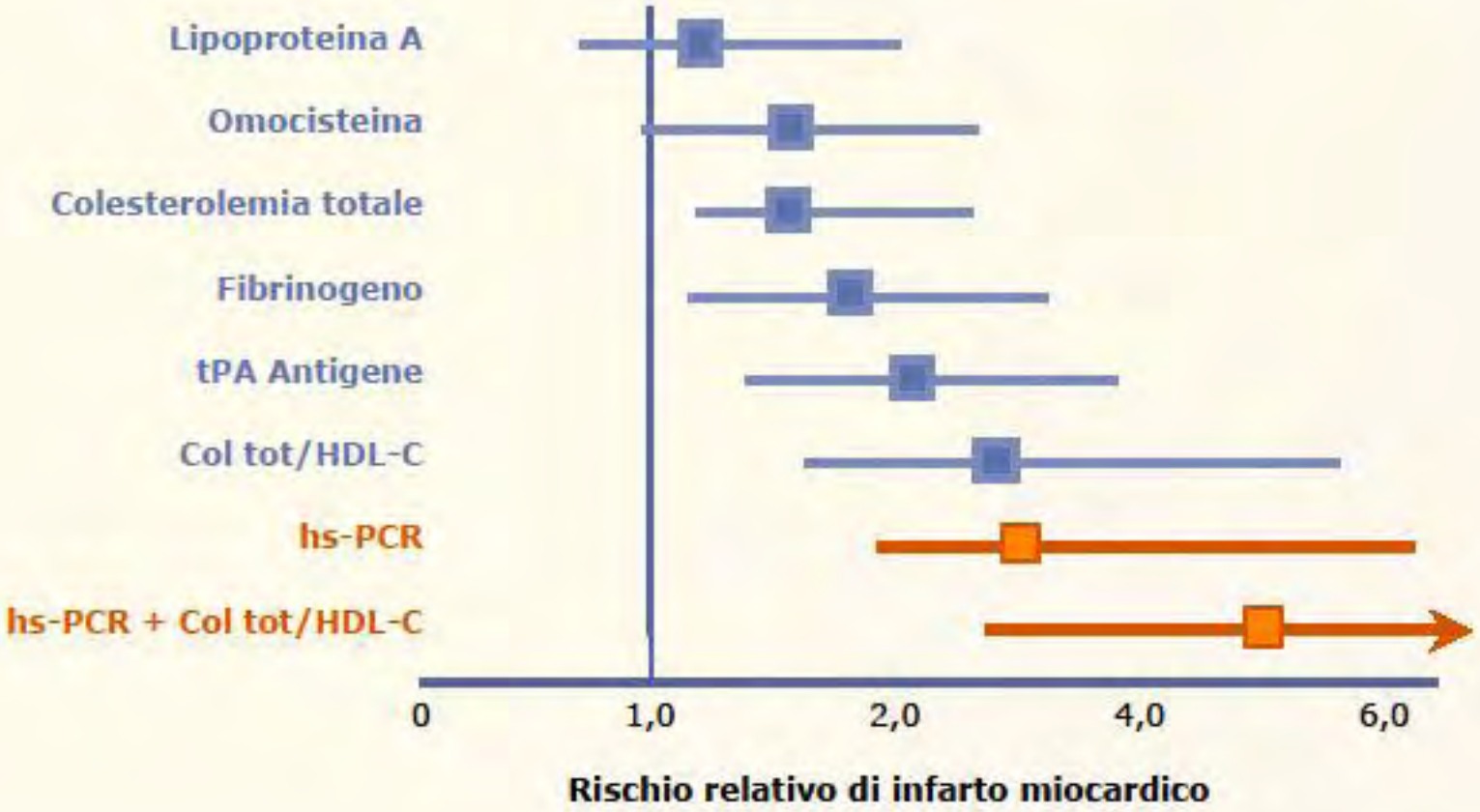
Proteina C Reattiva

PCR e hs-PCR

- La PCR è una proteina della fase acuta dell'infiammazione prodotta dal fegato in risposta alla produzione di citochine (IL-6, IL-1, tumor necrosis factor) in concomitanza con danno tissutale, infiammazione o infezione
- I test di misurazione standard della PCR permettono di misurare livelli aumentati fino a 1.000 volte in risposta ad infezioni o danni tissutali ma non possono valutare adeguatamente i valori nel range di normalità
- I metodi di misura della PCR ad alta sensibilità (hs-PCR), come il Dade Behring, permettono di rilevare le variazioni dei livelli di PCR all'interno dei limiti di normalità, in grado di predire il rischio di futuri eventi cardiovascolari

Rischio di futuro infarto miocardico in uomini apparentemente sani di mezza età

Physician's Health Study



Ridker PM et al. Ann Intern Med 1999;130:933-937

Table 2. Major Clinical Studies Evaluating the Role of CRP in Atherosclerosis

Study	Patient Population (n)/ Study Design	Results
Women's Health Study [1]	Apparently healthy postmenopausal women (366)/ prospective population-based study	hsCRP was additive to LDL cholesterol and the Framingham risk score in predicting cardiovascular events in healthy American women
Rotterdam Study [54]	Asymptomatic men and women≥55 years without history of coronary heart disease (6347)/ prospective population-based study	hsCRP was strongly and independently associated with heart failure in men, whereas this association was weaker in women
Cardiovascular Health Study [55]	Asymptomatic healthy men and women ≥65 years (4641)/ prospective population-based study	CRP alleles associated with higher hsCRP levels conferred an increased risk of heart disease
CARE [62]	Patients following an acute myocardial infarction (391)/ randomized to pravastatin (40 mg/day) *vs.* placebo	Patients with elevated hsCRP levels at baseline exhibited an increased risk of recurrent coronary events [relative risk (RR)=1.77, p=0.02]
REVERSAL [63]	Patients with angiographically documented coronary artery disease (502)/ randomized to atorvastatin 80 mg/day *vs.* pravastatin 40 mg/day	Lowering hsCRP levels in addition to LDL cholesterol in patients with coronary artery disease attenuated atherosclerotic lesion progression
PROVE IT [64, 65]	Patients following an acute coronary syndrome (3745)/ randomized to atorvastatin 80 mg/day *vs.* pravastatin 40 mg/day	Patients with hsCRP levels <2 mg/L had fewer recurrent events, regardless of LDL cholesterol level achieved by statin therapy
MIRACL [68, 69]	Patients after unstable angina or non Q-wave myocardial infraction (2402)/ randomized to atorvastatin 80 mg/day *vs.* placebo	Lowering hsCRP levels in atorvastatin group (34% lower in atorvastatin group compared with placebo) resulted in 16% relative reduction in primary endpoints
PEACE [75]	Patients with stable coronary disease (3771)/ randomized to trandolapril *vs.* placebo	hsCRP >1 mg/L was a significant predictor of adverse cardiovascular events independently of baseline characteristics and treatment
A to Z [83]	Patients with acute coronary syndrome (4497)/randomized to simvastatin 40 mg/day for 1 month followed by 80 mg/day *vs.* placebo for 4 months followed by simvastatin 20 mg/day	No risk reduction during the first 4 months, probably because of the small reduction in hsCRP levels in this period
JUPITER [55]	Asymptomatic individuals with LDL cholesterol <130 mg/dL and hsCRP ≥2 mg/L (15,000)/ randomized to rosuvastatin 20 mg/day *vs.* placebo	Stopped early (29 March 2008) due to positive results
CORONA [86]	Patients ≥60 years old with NYHA II, III, IV ischemic, systolic heart failure (5011)/ randomized to rosuvastatin 10 mg/day *vs.* placebo	Despite the greater reduction in hsCRP compared with placebo (-31.6% *vs.* +5.5%, p<0.001), rosuvastatin did not reduce the primary outcome

Endothelial Function Testing as a Biomarker of Vascular Disease

Subodh Verma, MD, PhD; Michael R. Buchanan, PhD; Todd J. Anderson, MD

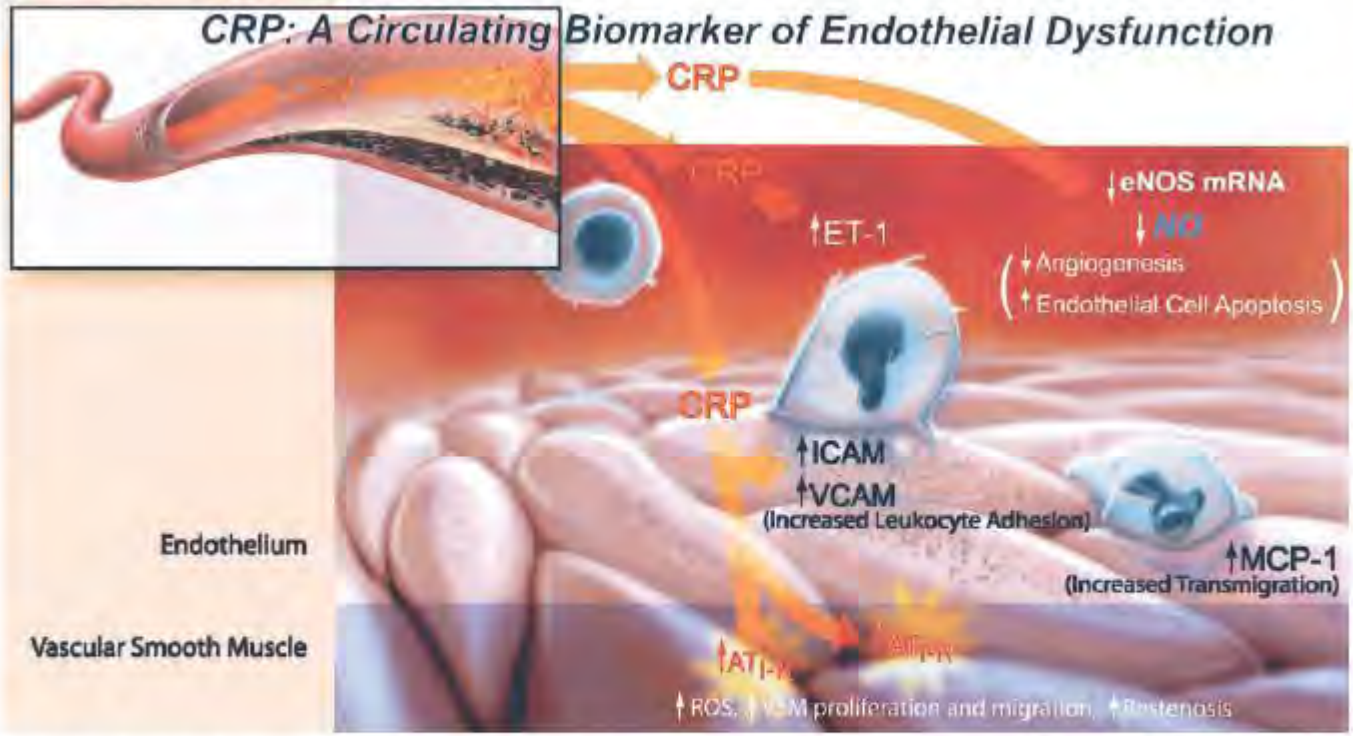


Figure 2. The mechanistic basis of the predictive value of CRP may be its ability to incite endothelial dysfunction. CRP can decrease eNOS mRNA,[16] augment endothelin-1 (ET-1),[15] and upregulate diverse adhesion molecules and chemoattractant chemokines, uncovering a proinflammatory and proatherosclerotic phenotype. Preliminary observations also suggest that CRP upregulates the nuclear factor–κB signaling in endothelial cells while attenuating endothelial progenitor cell survival and differentiation (Verma et al, unpublished observations, 2003). Also, the proatherogenic effects of CRP are augmented in the hyperglycemic milieu.[21,25] Also, CRP has been demonstrated to potently upregulate angiotensin type 1 ($AT_{1\text{-}R}$) receptor in vascular smooth muscle cells in vivo and in vitro, augmenting vascular smooth muscle (VSM) proliferation and migration, reactive oxygen species (ROS) production, and restenosis.[20] CRP therefore seems to function as an important circulating marker of endothelial dysfunction. ICAM indicates intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; and MCP, monocyte chemoattractant protein.

BMJ

BMJ 2011;342:d548

RESEARCH

Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data

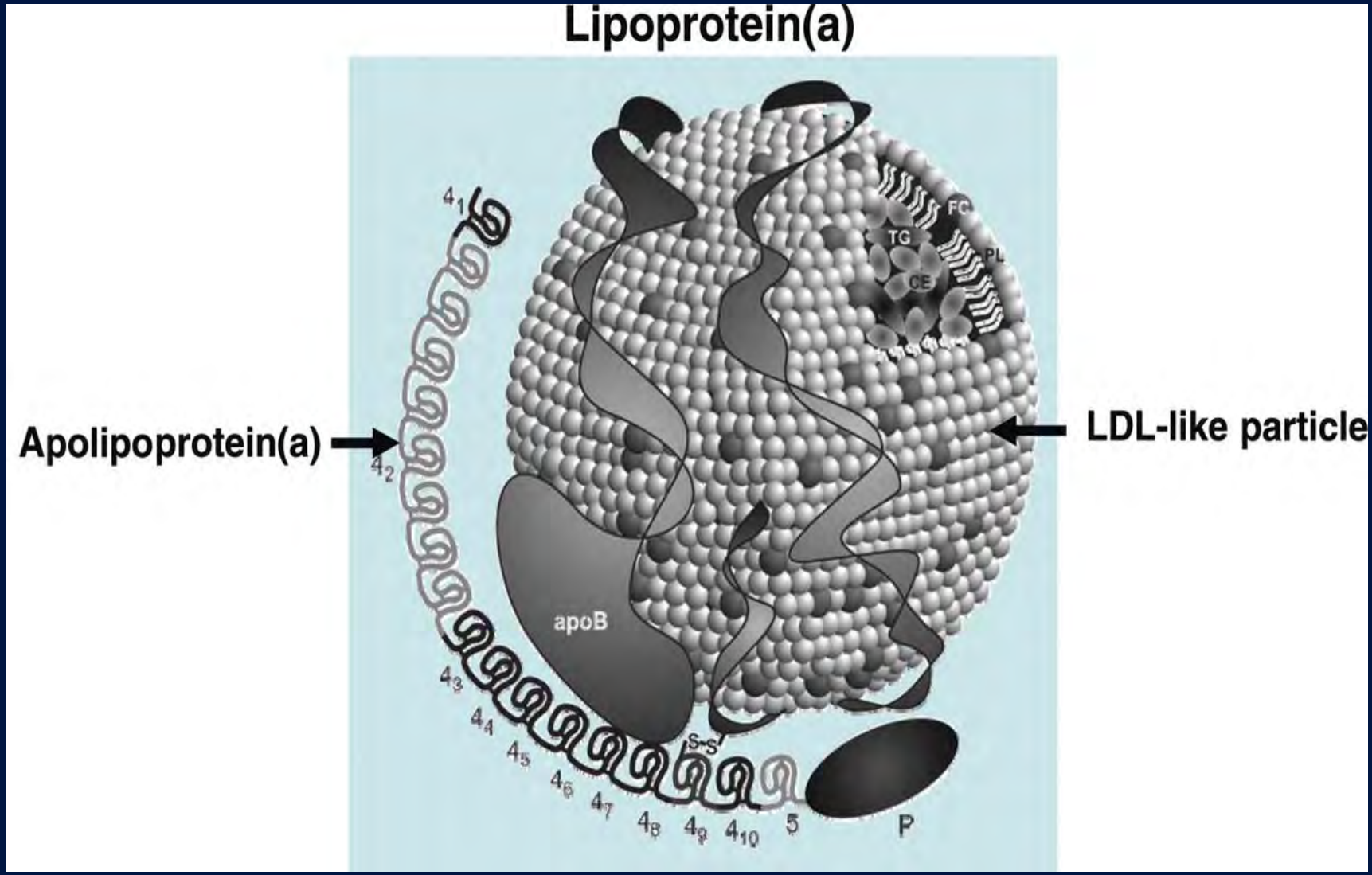
C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC)

E' improbabile che la concentrazione di proteina C-reattiva rappresenti un fattore causale nella malattia coronarica

4º

Lipoproteina (a)

Lipoprotein(a) consists of an LDL-like particle to which apolipoprotein(a) is covalently linked.



Nordestgaard B G et al. Eur Heart J 2010;eurheartj.ehq386

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Variants Associated with Lp(a) Lipoprotein Level and Coronary Disease

Robert Clarke, F.R.C.P., John F. Peden, Ph.D., Jemma C. Hopewell, Ph.D., Theodosios Kyriakou, Ph.D., Anuj Goel, M.Sc., Simon C. Heath, Ph.D., Sarah Parish, D.Phil., Simona Barlera, M.S., Maria Grazia Franzosi, Ph.D., Stephan Rust, Ph.D., Derrick Bennett, Ph.D., Angela Silveira, Ph.D., Anders Malarstig, Ph.D., Fiona R. Green, Ph.D., Mark Lathrop, Ph.D., Bruna Gigante, M.D., Karin Leander, Ph.D., Ulf de Faire, M.D., Udo Seedorf, Ph.D., Anders Hamsten, F.R.C.P., Rory Collins, F.R.C.P., Hugh Watkins, F.R.C.P., and Martin Farrall, F.R.C.Path., for the PROCARDIS Consortium*

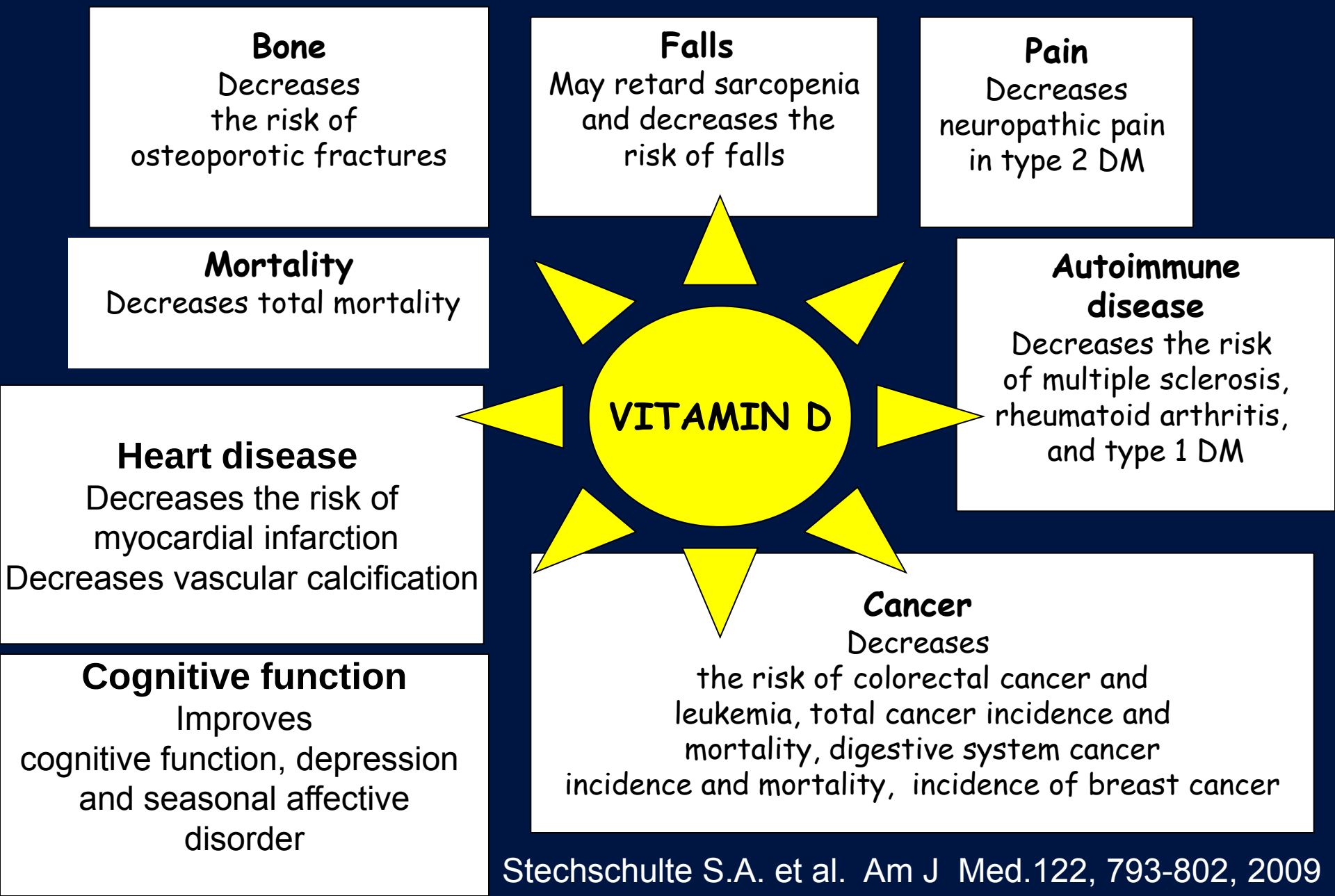
CONCLUSIONS

We identified two LPA variants that were strongly associated with both an increased level of Lp(a) lipoprotein and an increased risk of coronary disease. Our findings provide support for a causal role of Lp(a) lipoprotein in coronary disease.

5º

Ipovitaminosi D

ATTUALI E POTENZIALI RUOLI DELLA VIT. D



Stechschulte S.A. et al. Am J Med.122, 793-802, 2009

Cells with evidence for cytosolic or nuclear and/or membrane-bound vitamin D receptors (from Nemere & Farach-Carson, 1998; Norman, 1998, DeLuca & Cantorna, 2001)

Cell type

Neurons	Intestinal cells
Placenta	Muscle cells
Skin fibroblasts	Osteoblasts
Chondrocytes	Distal renal cells
Colon enterocytes	Parathyroid cells
Liver cells	Islet cells, pancreas
Prostate cells	Epidermal cells
Ovarian cells	Circulating monocytes
Keratinocytes of skin	Transformed B-cells
Endocrine cells, stomach	Activated T-cells
Aortic endothelial cells	Adipose tissue
Pituitary cells	

DEFINIZIONE DI IPOVITAMINOSI D

Deficiency	Insufficiency	Preferred range	Intoxication
<20 ng/ml	20-29 ng/ml	30-60 ng/ml	>150 ng/ml

Le concentrazioni in nmol/L possono essere convertite in ng/ml moltiplicando per 0.4.

Le concentrazioni in ng/ml possono esere convertite in mol/L moltiplicando per 2.496

Eur J Nutr (2008) 47:87–91
DOI 10.1007/s00394-008-0700-4

ORIGINAL CONTRIBUTION

Steinar Konradsen
Harald Ag
Fedon Lindberg
Sofie Hexeberg
Rolf Jorde

Serum 1,25-dihydroxy vitamin D is inversely associated with body mass index

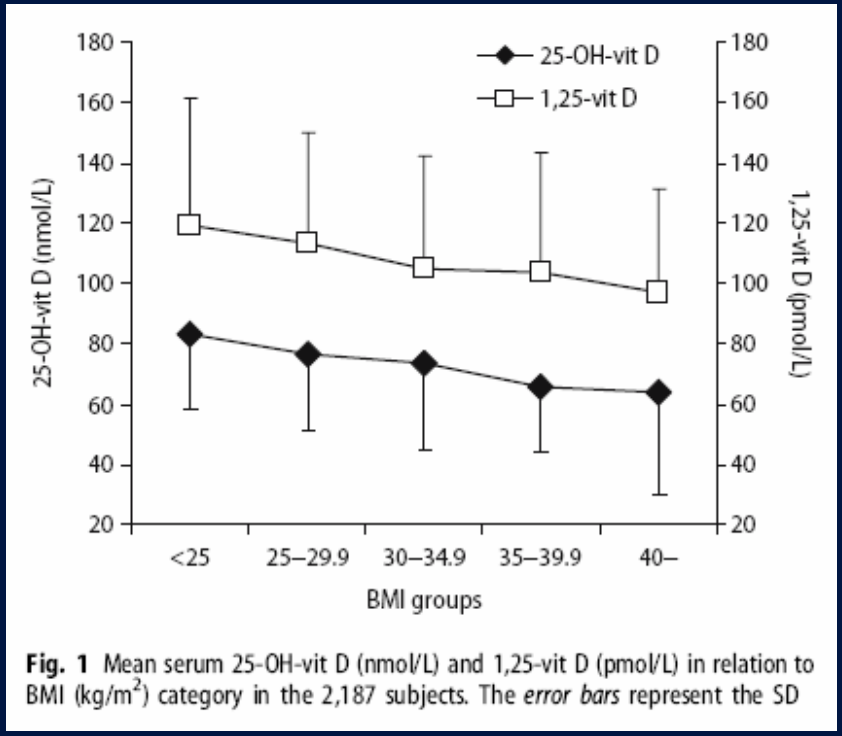


Fig. 1 Mean serum 25-OH-vit D (nmol/L) and 1,25-vit D (pmol/L) in relation to BMI (kg/m^2) category in the 2,187 subjects. The *error bars* represent the SD

Vitamin D and Risk of Hypertension

Plasma 25-Hydroxyvitamin D Levels and Risk of Incident Hypertension

John P. Forman, Edward Giovannucci, Michelle D. Holmes, Heike A. Bischoff-Ferrari, Shelley S. Tworoger, Walter C. Willett, Gary C. Curhan

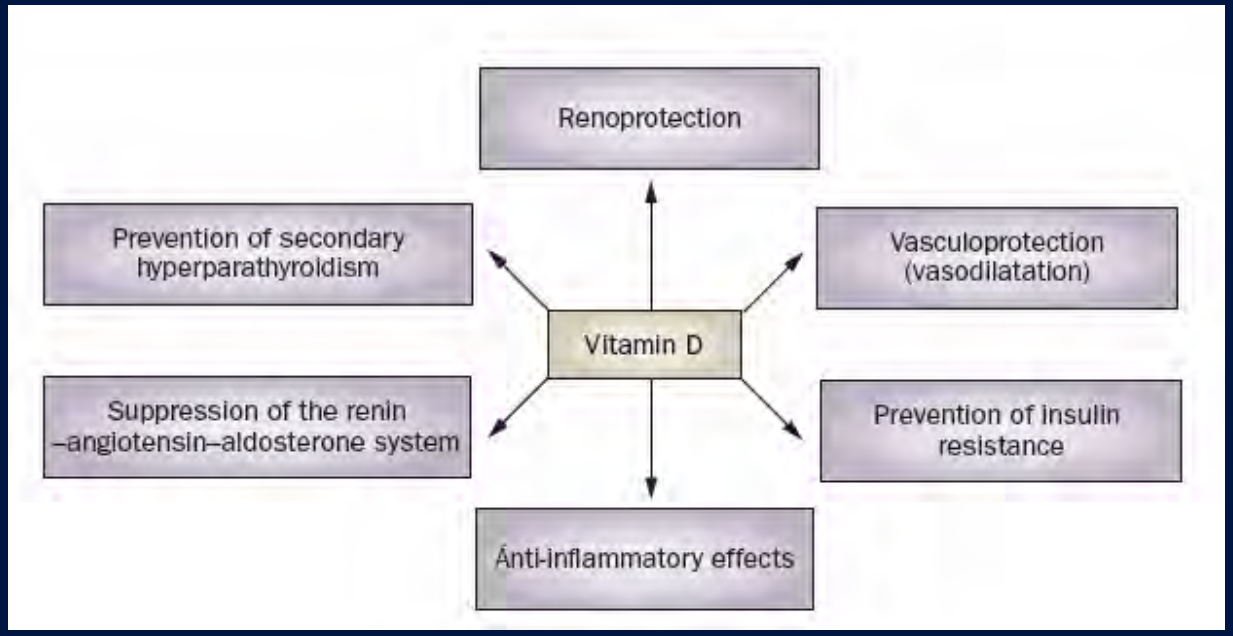
TABLE 2. Measured Plasma 25(OH)D and 4-Year Multivariable Adjusted Relative Risk of Incident Hypertension in Men and Women

	Measured Plasma 25(OH)D, ng/mL		
Statistic	≥30	15–29	<15
Men			
Person-years	865	1295	122
No. of cases	22	33	6
Multivariable RR (95% CI)	1.0 (reference)	1.12 (0.51 to 2.48)	6.13 (1.00 to 37.8)
Women			
Person-years	2207	2317	335
No. of cases	58	60	11
Multivariable RR (95% CI)	1.0 (reference)	0.85 (0.53 to 1.34)	2.67 (1.05 to 6.79)

Multivariable models adjusted for age, BMI, physical activity (all as continuous variables), as well as race, and (in women) menopausal status.

Hypertension 49:1063-1069, 2007

Hypothetical associations of vitamin D insufficiency with hypertension, diabetes mellitus and CVD



Pilz, S. et al. Nat. Rev. Cardiol. 6:621–630, 2009

Deficit di vitamina D e Diabete

Sono trascorsi circa tre decenni dai primi studi, condotti su animali, che collegano la vitamina D con il metabolismo dell'Insulina.

Da allora, le pubblicazioni sulla vitamina D e diabete sono state tantissime

Vitamin D Deficiency Inhibits Pancreatic Secretion of Insulin

Abstract. *The effect of a vitamin D deficiency on insulin and glucagon release was determined in the isolated perfused rat pancreas by radioimmunoassay of the secreted proteins. During a 30-minute period of perfusion with glucose and arginine, pancreases from vitamin D–deficient rats exhibited a 48 percent reduction in insulin secretion compared to that for pancreases from vitamin D–deficient rats that had been replenished with vitamin D. Vitamin D status had no effect on pancreatic glucagon secretion. This result, along with the previously demonstrated presence in the pancreas of a vitamin D–dependent calcium-binding protein and cytosol receptor for the hormonal form of vitamin D, 1,25-dihydroxyvitamin D_3, indicates an important role for vitamin D in the endocrine functioning of the pancreas.*

Vitamin D_3 is essential in higher animals to effect normal calcium and phosphorus homeostasis (*1*). This is accomplished by an endocrine system that regulates the sequential metabolism of vitamin D_3 by the liver and kidney into its two principal biologically active metabolites, 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$] (*1*, *2*) and 24,25-dihy-

vitamin D_3 and 1,25-$(OH)_2D_3$ (*1*) and of receptors for 1,25-$(OH)_2D_3$ have been documented in the parathyroid gland (*12*), bone (*13*), and kidney (*14*), but the presence of a vitamin D–dependent CaBP in the pancreas was unexpected. We have, however, reported the presence in the chick pancreas of a protein receptor for 1,25-$(OH)_2D_3$ (*14*) homolo-

stricted cages to San Francisco, where they were fed the same vitamin D–deficient diet and were given free access to water.

At approximately 72, 48, and 24 hours prior to perfusion, the restrained unanesthetized rats were given either 0.2 ml of ethanol (95 percent) (D-deficient animals) or 0.2 ml of a solution (95 percent ethanol and 1,2-propanediol, 1:1 by volume) containing 200 I.U. (5.0 μg) of vitamin D_3 (D-replete animals). Just before the pancreas was removed, arterial blood was collected, heparinized, chilled in ice, centrifuged, and stored at −20°C until it was assayed for calcium, phosphorus, magnesium, and 25-$(OH)D_3$. The serum concentrations of calcium, phosphorus, and 25-$(OH)D_3$ reported in Table 1 are typical for vitamin D–deficient and replete rats (*1*). Although body weights and pancreas

ent animals, tistically sig- insulin and essed by the Fanska (*16*). sources of albumin in odified prepa- nach, spleen, m were re- as and proxi- sed in vitro er biocarbo- the following a+, 142; K+, $H_2PO_4^-$, 1.5; O_4^{2+}, 1.2. The

20 30

alin and gluca- (●) D-replete

823

Endocrinology

THE ENDOCRINE SOCIETY

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Endocrinology, doi:10.1210/endo-104-5-1495
Endocrinology Vol. 104, No. 5 1495-1503

Studies on the Mode of Action of Calciferol. XIII. Development of a Radioimmunoassay for Vitamin DDependent Chick Intestinal Calcium-Binding Protein and Tissue Distribution*

SYLVIA CHRISTAKOS, ERNEST J. FRIEDLANDER, BRAD R. FRANDSEN and ANTHONY W. NORMAN†

Department of Biochemistry, University of California Riverside, California 92521

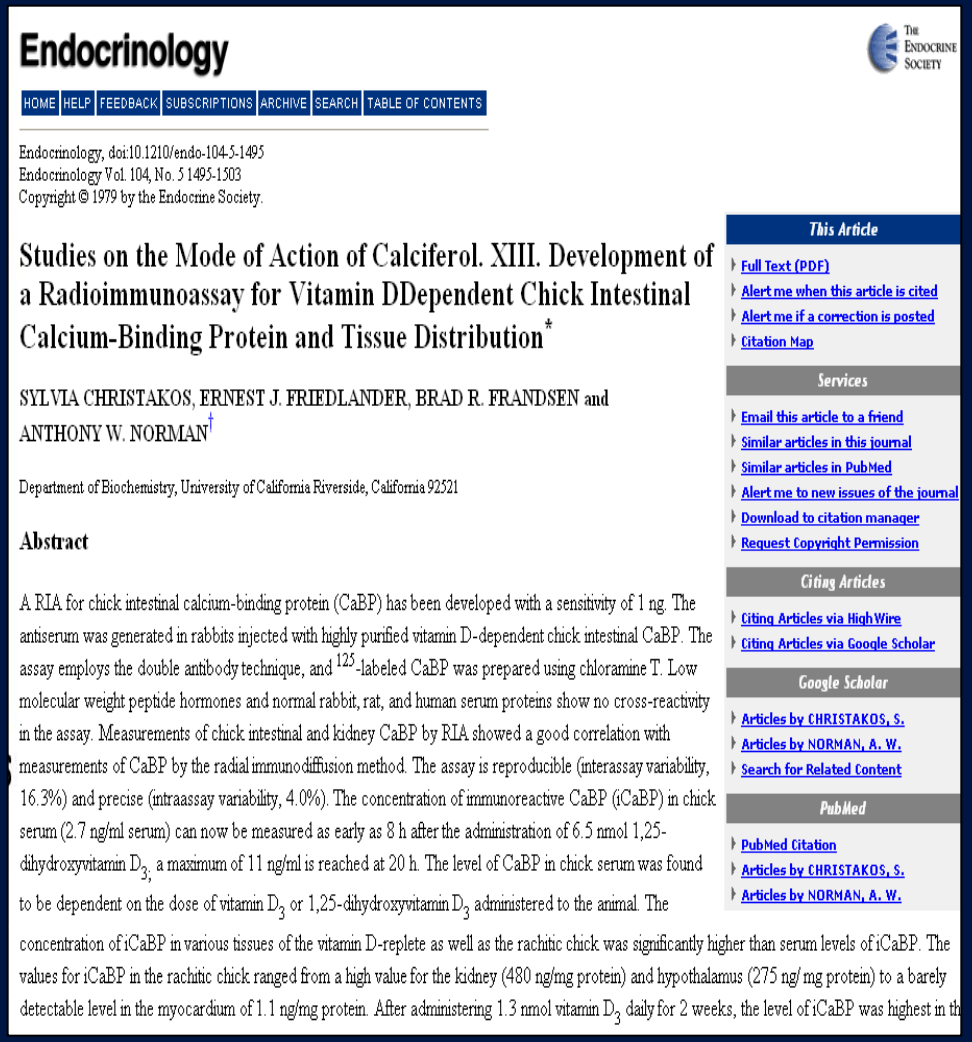
Abstract

A RIA for chick intestinal calcium-binding protein (CaBP) has been developed with a sensitivity of 1 ng. The antiserum was generated in rabbits injected with highly purified vitamin D-dependent chick intestinal CaBP. The assay employs the double antibody technique, and ^{125}-labeled CaBP was prepared using chloramine T. Low molecular weight peptide hormones and normal rabbit, rat, and human serum proteins show no cross-reactivity in the assay. Measurements of chick intestinal and kidney CaBP by RIA showed a good correlation with measurements of CaBP by the radial immunodiffusion method. The assay is reproducible (interassay variability, 16.3%) and precise (intraassay variability, 4.0%). The concentration of immunoreactive CaBP (iCaBP) in chick serum (2.7 ng/ml serum) can now be measured as early as 8 h after the administration of 6.5 nmol 1,25-dihydroxyvitamin D_3; a maximum of 11 ng/ml is reached at 20 h. The level of CaBP in chick serum was found to be dependent on the dose of vitamin D_3 or 1,25-dihydroxyvitamin D_3 administered to the animal. The concentration of iCaBP in various tissues of the vitamin D-replete as well as the rachitic chick was significantly higher than serum levels of iCaBP. The values for iCaBP in the rachitic chick ranged from a high value for the kidney (480 ng/mg protein) and hypothalamus (275 ng/mg protein) to a barely detectable level in the myocardium of 1.1 ng/mg protein. After administering 1.3 nmol vitamin D_3 daily for 2 weeks, the level of iCaBP was highest in th

Primo studio che identifica la presenza di un

Recettore Pancreatico

del metabolita attivo (1,25-diidrossivitamina D) della vitamina D



Endocrinology

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Endocrinology, doi:10.1210/endo-104-5-1495
Endocrinology Vol. 104, No. 5 1495-1503

Studies on the Mode of Action of Calciferol. XIII. Development of a Radioimmunoassay for Vitamin DDependent Chick Intestinal Calcium-Binding Protein and Tissue Distribution*

SYLVIA CHRISTAKOS, ERNEST J. FRIEDLANDER, BRAD R. FRANDSEN and ANTHONY W. NORMAN†

Department of Biochemistry, University of California Riverside, California 92521

Abstract

A RIA for chick intestinal calcium-binding protein (CaBP) has been developed with a sensitivity of 1 ng. The antiserum was generated in rabbits injected with highly purified vitamin D-dependent chick intestinal CaBP. The assay employs the double antibody technique, and ^{125}-labeled CaBP was prepared using chloramine T. Low molecular weight peptide hormones and normal rabbit, rat, and human serum proteins show no cross-reactivity in the assay. Measurements of chick intestinal and kidney CaBP by RIA showed a good correlation with measurements of CaBP by the radial immunodiffusion method. The assay is reproducible (interassay variability, 16.3%) and precise (intraassay variability, 4.0%). The concentration of immunoreactive CaBP (iCaBP) in chick serum (2.7 ng/ml serum) can now be measured as early as 8 h after the administration of 6.5 nmol 1,25-dihydroxyvitamin D_3, a maximum of 11 ng/ml is reached at 20 h. The level of CaBP in chick serum was found to be dependent on the dose of vitamin D_3 or 1,25-dihydroxyvitamin D_3 administered to the animal. The concentration of iCaBP in various tissues of the vitamin D-replete as well as the rachitic chick was significantly higher than serum levels of iCaBP. The values for iCaBP in the rachitic chick ranged from a high value for the kidney (480 ng/mg protein) and hypothalamus (275 ng/ mg protein) to a barely detectable level in the myocardium of 1.1 ng/mg protein. After administering 1.3 nmol vitamin D_3 daily for 2 weeks, the level of iCaBP was highest in th

Christakos S, Friedlander EJ, Frandsen BR, Norman AW: Studies on the mode of action of calciferol. XIII. Development of a radioimmunoassay for vitamin D-dependent chick intestinal calcium-binding protein and tissue distribution. ***Endocrinology 104:1495****–1503,* ***1979***

…..e quello che ha dimostrato che

la Carenza di Vitamina D diminuisce la secrezione di Insulina

Vitamin D Deficiency Inhibits Pancreatic Secretion of Insulin

Abstract. *The effect of a vitamin D deficiency on insulin and glucagon release was determined in the isolated perfused rat pancreas by radioimmunoassay of the secreted proteins. During a 30-minute period of perfusion with glucose and arginine, pancreases from vitamin D–deficient rats exhibited a 48 percent reduction in insulin secretion compared to that for pancreases from vitamin D–deficient rats that had been replenished with vitamin D. Vitamin D status had no effect on pancreatic glucagon secretion. This result, along with the previously demonstrated presence in the pancreas of a vitamin D–dependent calcium-binding protein and cytosol receptor for the hormonal form of vitamin D, 1,25-dihydroxyvitamin D_3, indicates an important role for vitamin D in the endocrine functioning of the pancreas.*

Vitamin D_3 is essential in higher animals to effect normal calcium and phosphorus homeostasis (*1*). This is accomplished by an endocrine system that regulates the sequential metabolism of vitamin D_3 by the liver and kidney into its two principal biologically active metabolites, 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$] (*1*, *2*) and 24,25-dihydroxyvitamin D_3 [24,25-$(OH)_2D_3$] (*3*). The best documented biological actions of vitamin D_3 and its most active metabolite, 1,25$(OH)_2D_3$, are the stimulation of intestinal calcium absorption and the mobilization of bone calcium (*1*).

The mode of action of 1,25-$(OH)_2D_3$ in stimulating intestinal calcium absorption is believed to be analogous to that of other steroid hormones (*1*, *2*). Biochemical evidence supports the existence of a cytosol protein receptor for 1,25-$(OH)_2D_3$ in the intestine of the chick (*4*), rat (*5*), and man (*6*). This 1,25-$(OH)_2D_3$ steroid-receptor complex migrates to the nucleus of the cell and stimulates the biosynthesis of a number of messenger RNA molecules that code for proteins related to the generation of the biological response—including a calcium-binding protein (CaBP) (*7*). It is not yet clear whether CaBP in the intestine has an obligatory role in effecting the transepithelial transport of calcium ions across the cell or whether it is present for other reasons, which might include "protection" of the cell against the deleterious effects of high concentrations of intracellular Ca^{2+} occurring as a consequence of vitamin D–mediated intestinal calcium absorption. However, the presence of CaBP is totally dependent on the presence of 1,25-$(OH)_2D_3$ (*7*); the amount of CaBP in the chick intestine is exactly proportional to the amount of 1,25-$(OH)_2D_3$ localized in the intestinal mucosa (*8*).

By a sensitive and specific radioimmunoassay (*9*) with antibodies against highly purified chick intestinal CaBP (*10*), we have detected vitamin D–dependent CaBP in the chick bone (*11*), kidney, intestine, and pancreas (*9*). The actions of vitamin D_3 and 1,25-$(OH)_2D_3$ (*1*) and of receptors for 1,25-$(OH)_2D_3$ have been documented in the parathyroid gland (*12*), bone (*13*), and kidney (*14*), but the presence of a vitamin D–dependent CaBP in the pancreas was unexpected. We have, however, reported the presence in the chick pancreas of a protein receptor for 1,25-$(OH)_2D_3$ (*14*) homologous to the 1,25-$(OH)_2D_3$ receptors previously described in the chick intestine (*4*), parathyroid gland (*12*), and bone (*13*).

The presence in the chick pancreas of cytosol receptors for 1,25-$(OH)_2D_3$ as well as CaBP is evidence of a hitherto unappreciated role of vitamin D and its metabolites in pancreatic endocrine and exocrine function. We now describe our initial efforts to determine whether vitamin D deficiency has any effect on the endocrine function of the rat pancreas.

Weanling rats (Holzman, Madison, Wis.) were raised on a standard vitamin D–deficient nonrachitogenic diet (*15*) in a room devoid of ultraviolet light. After 12 weeks the rats were shipped in light-restricted cages to San Francisco, where they were fed the same vitamin D–deficient diet and were given free access to water.

At approximately 72, 48, and 24 hours prior to perfusion, the restrained unanesthetized rats were given either 0.2 ml of ethanol (95 percent) (D-deficient animals) or 0.2 ml of a solution (95 percent ethanol and 1,2-propanediol, 1:1 by volume) containing 200 I.U. (5.0 μg) of vitamin D_3 (D-replete animals). Just before the pancreas was removed, arterial blood was collected, heparinized, chilled in ice, centrifuged, and stored at −20°C until it was assayed for calcium, phosphorus, magnesium, and 25-$(OH)D_3$. The serum concentrations of calcium, phosphorus, and 25-$(OH)D_3$ reported in Table 1 are typical for vitamin D–deficient and replete rats (*1*). Although body weights and pancreas weights tended to be slightly greater in D-replete than in D-deficient animals, the differences were not statistically significant. The secretion of insulin and glucagon in vitro was assessed by the technique of Grodsky and Fanska (*16*). To exclude extrapancreatic sources of glucagon and to conserve the albumin in the perfusate, we used a modified preparation (*17*) in which the stomach, spleen, and most of the duodenum were removed. Briefly, the pancreas and proximal duodenum were perfused in vitro with a modified Krebs-Ringer biocarbonate buffer (*p*H 7.4) with the following millimolar composition: Na^+, 142; K^+, 5.9; Ca^{2+}, 2.35; Mg^{2+}, 1.22; $H_2PO_4^-$, 1.5; HCO_3^-, 29; Cl^-, 119, and SO_4^{2+}, 1.2. The

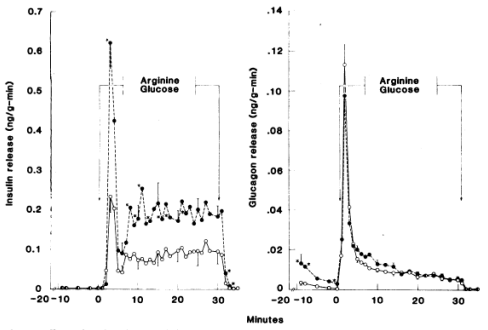


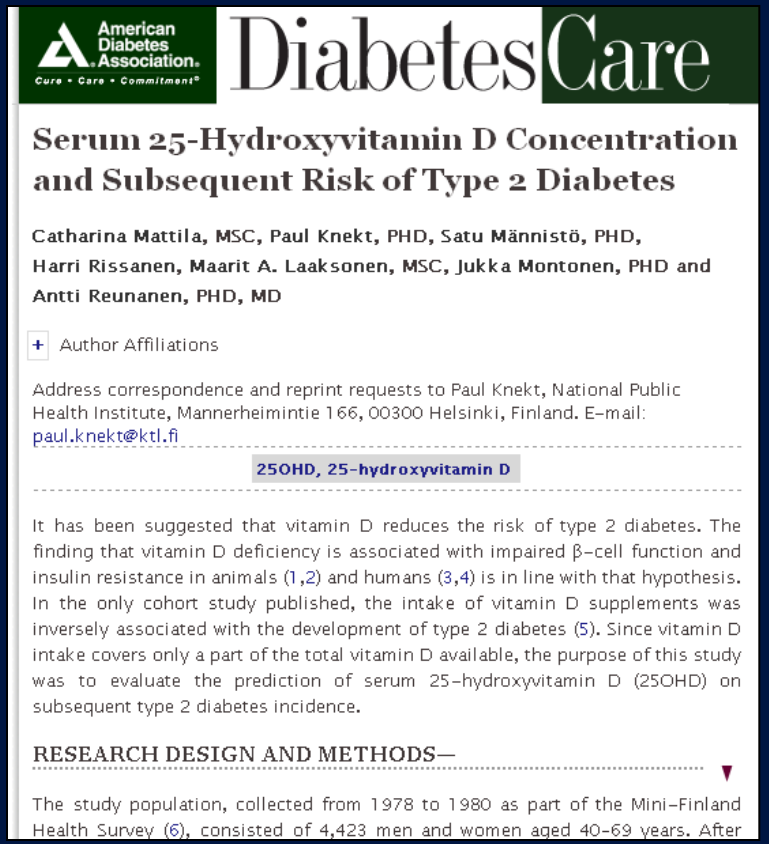
Fig. 1. Effect of a vitamin D deficiency on glucose-plus-arginine–stimulated insulin and glucagon release from the isolated perfused rat pancreas; (○) D-deficient (N = 7) and (●) D-replete (N = 5) animals.

0036-8075/80/0815-0823$00.50/0

Norman AW, Frankel JB, Heldt AM, Grodsky GM: Vitamin D deficiency inhibits pancreatic secretion of insulin. ***Science 209:823–825, 1980***

Gli studi di coorte forniscono i dati più attendibili che mettono in relazione la carenza di vitamina D e rischio di diabete:

Ulteriori conferme vengono dal seguente studio finlandese, che dimostra una associazione inversa tra livelli iniziali di 25 OH D e Diabete tipo 2



American Diabetes Association. Cure • Care • Commitment®

Diabetes Care

Serum 25-Hydroxyvitamin D Concentration and Subsequent Risk of Type 2 Diabetes

Catharina Mattila, MSC, Paul Knekt, PHD, Satu Männistö, PHD, Harri Rissanen, Maarit A. Laaksonen, MSC, Jukka Montonen, PHD and Antti Reunanen, PHD, MD

+ Author Affiliations

Address correspondence and reprint requests to Paul Knekt, National Public Health Institute, Mannerheimintie 166, 00300 Helsinki, Finland. E-mail: paul.knekt@ktl.fi

25OHD, 25-hydroxyvitamin D

It has been suggested that vitamin D reduces the risk of type 2 diabetes. The finding that vitamin D deficiency is associated with impaired β-cell function and insulin resistance in animals (1,2) and humans (3,4) is in line with that hypothesis. In the only cohort study published, the intake of vitamin D supplements was inversely associated with the development of type 2 diabetes (5). Since vitamin D intake covers only a part of the total vitamin D available, the purpose of this study was to evaluate the prediction of serum 25-hydroxyvitamin D (25OHD) on subsequent type 2 diabetes incidence.

RESEARCH DESIGN AND METHODS—

The study population, collected from 1978 to 1980 as part of the Mini-Finland Health Survey (6), consisted of 4,423 men and women aged 40-69 years. After

•Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes Mattila C et al

•*Diabetes Care* 2007; 30: 2569–2570

THE LANCET

2010; 376(9752):1543-51

Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial

SPECIAL FEATURE

Editorial

25-OH Vitamin D: Is It the Universal Panacea for Metabolic Syndrome and Type 2 Diabetes?

Kwame Osei

Division of Endocrinology, Diabetes, and Metabolism, and Diabetes Research Center, The Ohio State University, Columbus, Ohio 43210

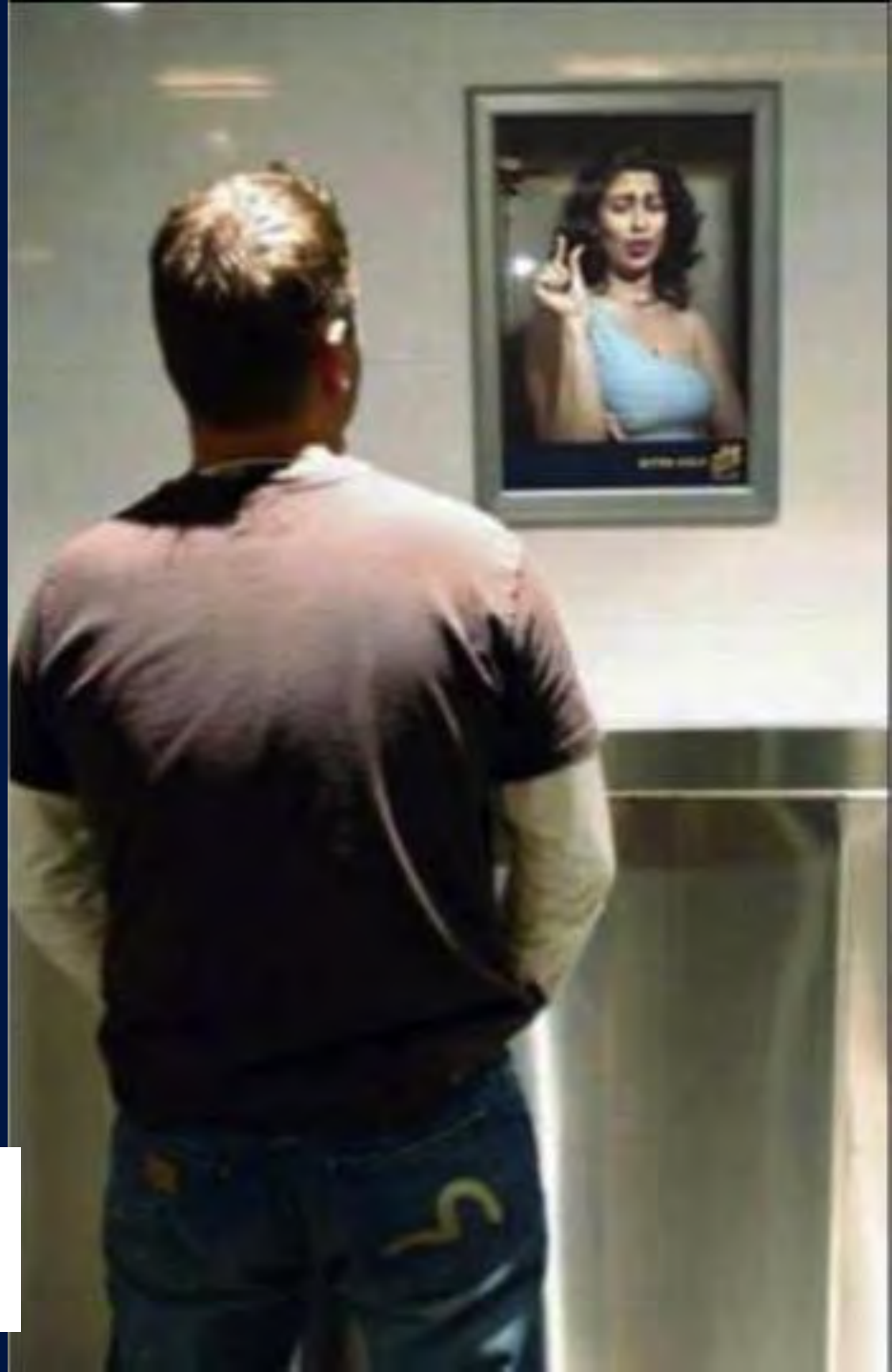
K. Osei, J Clin Endocrinol Metab, 95:4220-4222, 2010

RELAZIONE TRA IPOVITAMINOSI D E' DOCUMENTATA PER:

- INSULINO RESISTENZA
- SINDROME METABOLICA
- OBESITA'
- DISLIPIDEMIA
- DIABETE TIPO 2
- IPERTENSIONE
- MORTALITA' E MORBILITA' CARDIOVASCOLARE

IN STUDI OSSERVAZIONALI TRASVERSALI E OSSERVAZIONALI

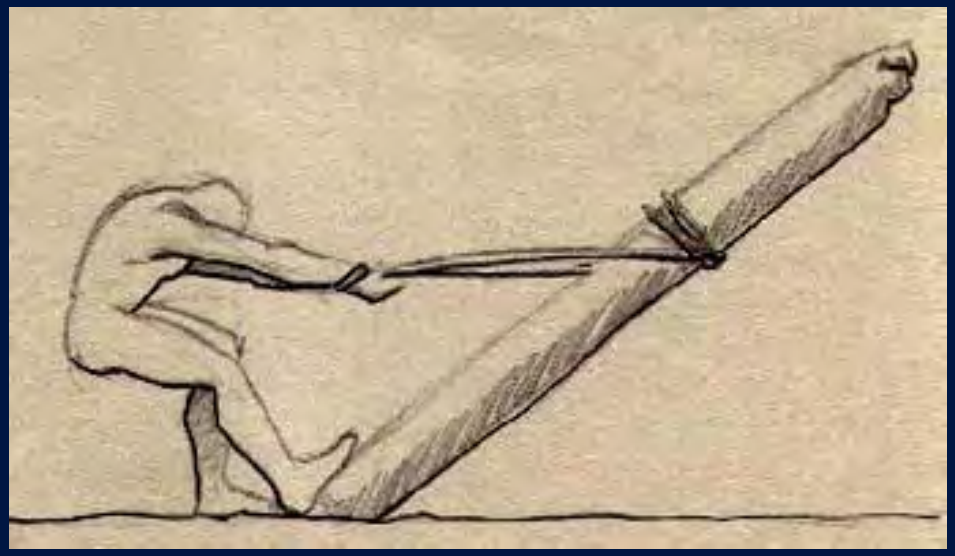
STUDI RANDOMIZZATI E CONTROLLATI MOLTO PICCOLI ED INCONSISTENTI



6º

Disfunzione erettile

Disfunzione erettile



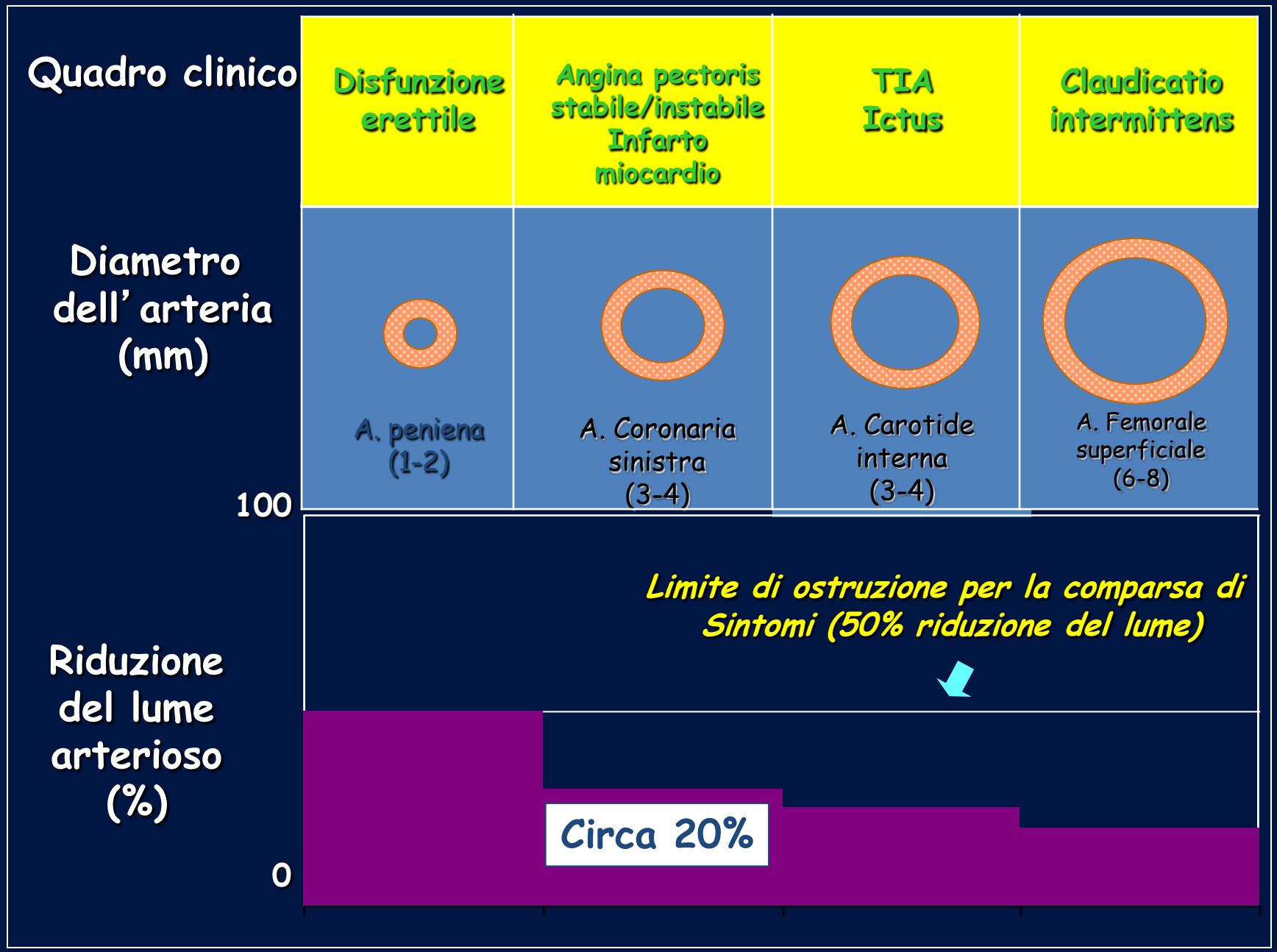
Disfunzione endoteliale

LA DISFUNZIONE ERETTILE COME POTENZIALE INDICATORE DI UNA PATOLOGIA VASCOLARE PIU' GENERALIZZATA

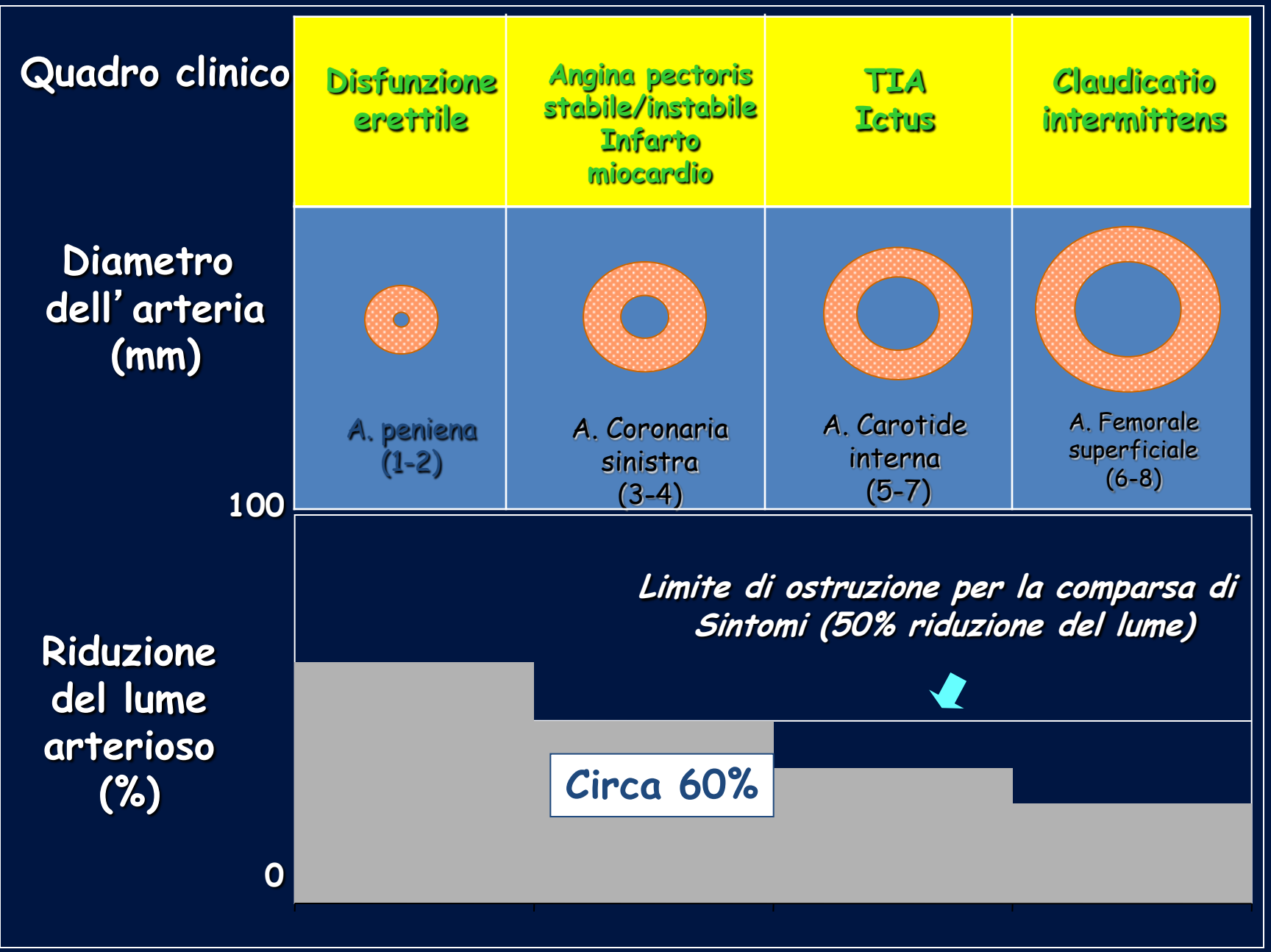
European Urology 2003; 44: 352-371

- "La patologia vascolare sistemica?"
  P.Montorsi, F.Montorsi, C.C. Schulman
- "La disfunzione erettile è associata a un' alta prevalenza di iperlipidemia e a un rischio elevato di cardiopatia coronarica"
  T.Roumeguerè, E.Wespes,Y.Carpentier, PHoffman, C.C. Schulman
- "Rischio di cardiopatia coronarica in pazienti di sesso maschile con disfunzione erettile"
  T.G.W. Speel, H.van Langen , E.J.H.Meuleman

disfunzione erettile è la punta di un iceberg di una



Montorsi P. *Italian Journal of Andrology* 2003: 16 - 18



Montorsi P. *Italian Journal of Andrology* 2003: 16 - 18

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ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.08.058

Does Erectile Dysfunction Contribute to Cardiovascular Disease Risk Prediction Beyond the Framingham Risk Score?

Andre B. Araujo, PhD,* Susan A. Hall, PhD,* Peter Ganz, MD,† Gretchen R. Chiu, MS,*
Raymond C. Rosen, PhD,* Varant Kupelian, PhD,* Thomas G. Travison, PhD,*
John B. McKinlay, PhD*

Watertown, Massachusetts, and San Francisco, California

JACC

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Vol. 51, No. 21, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.10.069

Erectile Dysfunction as a Predictor of Cardiovascular Events and Death in Diabetic Patients With Angiographically Proven Asymptomatic Coronary Artery Disease

A Potential Protective Role for Statins and 5-Phosphodiesterase Inhibitors

Carmine Gazzaruso, MD, PHD,* Sebastiano B. Solerte, MD,† Arturo Pujia, MD,§ Adriana Coppola, RN, MS,* Monia Vezzoli, MD,* Fabrizio Salvucci, MD,* Cinzia Valenti, MD,* Andrea Giustina, MD,‖ Adriana Garzaniti, MD‡

Vigevano, Pavia, Catanzaro, and Brescia, Italy

Conclusions Our data first show that ED is a powerful predictor of cardiovascular morbidity and mortality in diabetic patients with silent CAD and that the treatment with statins and 5-PDE inhibitors might reduce the occurrence of MACE among CAD diabetic patients with ED. (J Am Coll Cardiol 2008;51:2040–4) © 2008 by the American College of Cardiology Foundation

J Am Coll Cardiol. 2010 Nov 30;56(23):1908-13.

Erectile dysfunction and later cardiovascular disease in men with type 2 diabetes: prospective cohort study based on the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) trial.

Batty GD, Li Q, Czernichow S, Neal B, Zoungas S, Huxley R, Patel A, de Galan BE, Woodward M, Hamet P, Harrap SB, Poulter N, Chalmers J; ADVANCE Collaborative Group.

Conclusioni: nella coorte di uomini dello studio Advance con diabete tipo 2, la presenza di DE si associa ad un aumento significativo del rischio cardiovascolare

CONSENSUS:
SCREENING E TERAPIA DELLA CARDIOPATIA ISCHEMICA NEL PAZIENTE DIABETICO

SID AMD ANMCO ARC SIC SISA

Il medico è responsabile

di ciò che il paziente tace:

avrebbe dovuto chiederglielo

Ippocrate

DOMANDA:

“Ha notato negli ultimi 6 mesi modifiche rilevanti nei rapporti sessuali?”

IPERTENSIONE ARTERIOSA

Aspetti critici della interpretazione dei valori pressori

Gerarchia dei predittori di infarto fatale o non-fatale nel T2DM

(UKPDS: observational study *BMJ* 1998;316:823-828)

1. LDL colesterolo
2. Pressione arteriosa diastolica
3. Fumo di sigaretta
4. HDL colesterolo
5. HbA_1c

Target di PA nel diabetico

- **<130/80** (pz tipo 1 e 2)
- **<120/75** (nefropatico con > 1 gr di proteinuria)

Annals of Internal Medicine | ARTICLE

Dogma Disputed: Can Aggressively Lowering Blood Pressure in Hypertensive Patients with Coronary Artery Disease Be Dangerous?

Franz H. Messerli, MD; Giuseppe Mancia, MD; C. Richard Conti, MD; Ann C. Hewkin, MSc; Stuart Kupfer, MD; Annette Champion, MBA; Rainer Kolloch, MD; Athanase Benetos, MD; and Carl J. Pepine, MD

Background: Because coronary perfusion occurs mainly during diastole, patients with coronary artery disease (CAD) could be at increased risk for coronary events if diastolic pressure falls below critical levels.

Objective: To determine whether low blood pressure could be associated with excess mortality and morbidity in this population.

Design: A secondary analysis of data from the International Verapamil-Trandolapril Study (INVEST), which was conducted from September 1997 to February 2003.

Setting: 862 sites in 14 countries.

Patients: 22 576 patients with hypertension and CAD.

Interventions: Patients from INVEST were randomly assigned to a verapamil sustained-release– or atenolol-based strategy; blood pressure control and outcomes were equivalent.

Measurements: An unadjusted quadratic proportional hazards model was used to evaluate the relationship between average on-treatment blood pressure and risk for the primary outcome (all-cause death, nonfatal stroke, and nonfatal myocardial infarction [MI]), all-cause death, total MI, and total stroke. A second model adjusted for differences in baseline covariates.

Results: The relationship between blood pressure and the primary outcome, all-cause death, and total MI was J-shaped, particularly for diastolic pressure, with a nadir at 119/84 mm Hg. After adjustment, the J-shaped relationship persisted between diastolic pressure and primary outcome. The MI–stroke ratio remained constant over a wide blood pressure range, but at a lower diastolic blood pressure, there were substantially more MIs than strokes. An interaction between decreased diastolic pressure and history of revascularization was observed; low diastolic pressure was associated with a relatively lower risk for the primary outcome in patients with revascularization than in those without revascularization.

Limitations: This is a post hoc analysis of hypertensive patients with CAD.

Conclusions: The risk for the primary outcome, all-cause death, and MI, but not stroke, progressively increased with low diastolic blood pressure. Excessive reduction in diastolic pressure should be avoided in patients with CAD who are being treated for hypertension.

Ann Intern Med. 2006;144:884-893. www.annals.org
For author affiliations, see end of text.
ClinicalTrial.gov identifier: NCT00133692.

The NEW ENGLAND JOURNAL of MEDICINE

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

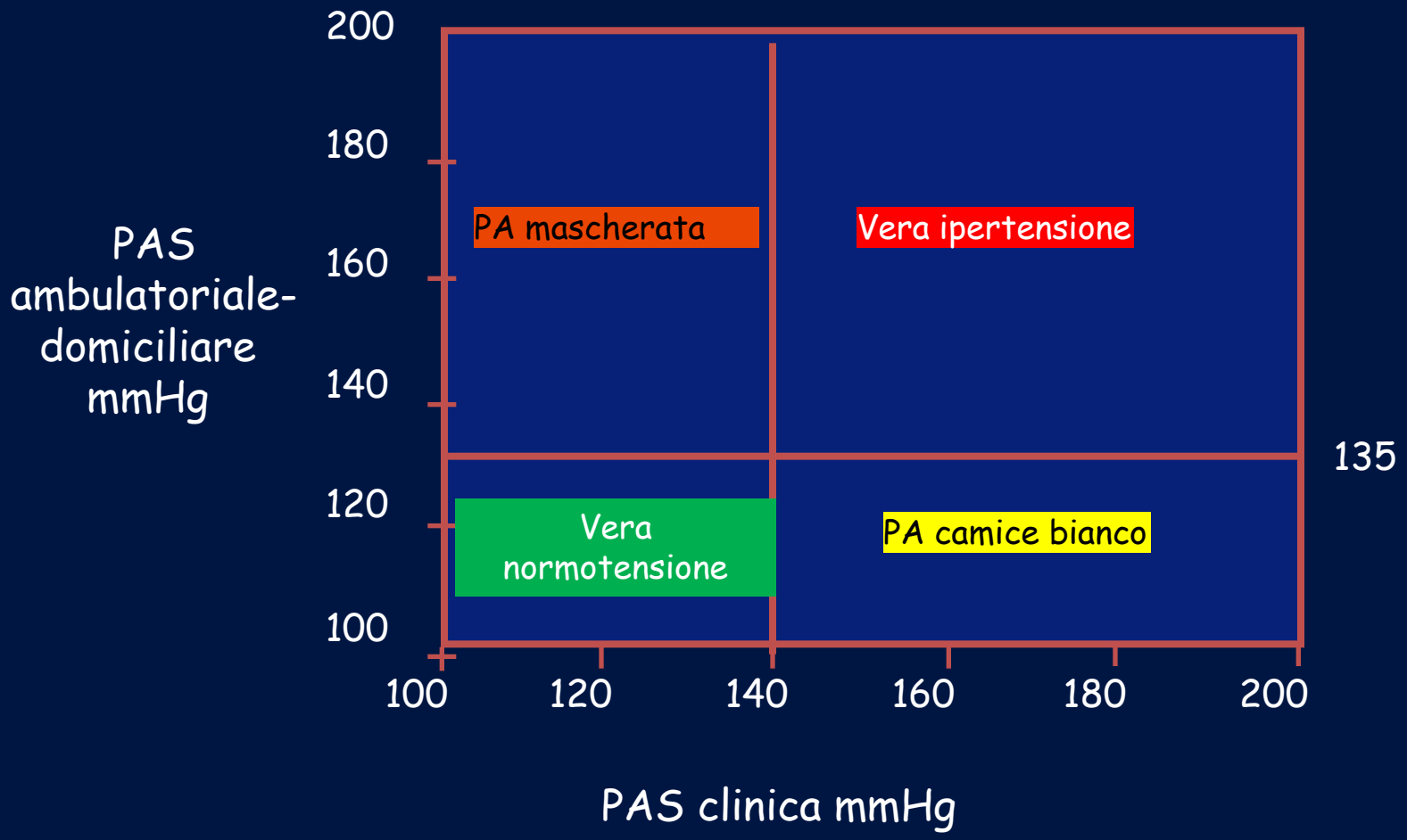
The ACCORD Study Group

Conclusions:

In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.

Published at www.nejm.org March 14, 2010
(10.1056/NEJMoa1001286)

LE MANIFESTAZIONI CLINICHE DELL'IPERTENSIONE ARTERIOSA



From Pickering, Hypertension 1992

Cutoff pressori clinici, domiciliari e delle 24 ore per la definizione di Ipertensione Arteriosa

Metodica di rilevazione	PAS (mmHg)	PAD (mmHg)
Sfigmomanometrica o clinica	140	90
Domiciliare	130-135	85
Holter pressorio 24h	125-130	80
Periodo diurno	130-135	85
Periodo notturno	120	70

Linee Guida ESH/ESC 2007

La pressione arteriosa media (PAM) =

Durante un ciclo cardiaco rappresenta la forza di spinta della perfusione periferica e può essere calcolata con la formula

$PAM = PAD + PP/3$

Oppure

$PAM = (PAS + 2\,PAD)/3$

La PA media è probabilmente più importante ai fini del rischio dell' ictus cerebrale

La pressione differenziale o di polso (Pulse Pressure)

PP= Pressione sistolica(PAS) – Pressione diastolica (PAD)

La PP superiore a 50-55 mmHg in soggetti di età superiore a 55 anni è predittiva di mortalità cardiovascolare

La PP è probabilmente più importante ai fini del rischio dell' infarto miocardico

7º

Pressione arteriosa centrale

Aortic stiffnes in an indipendent predictor predictor of all causes and cardiovascular mortality in hypertensive patients.
Hypertension 2001

Aortic stiffnes in an indipendent predictor of primary conorary events in hypertensive patients: a longitudinal study.
Hypertension 2002

Augmentation index is associated with cardiovascular risk.
Hypertension 2002

Differential impact of bllod pressure-lowering drugs on central aortic pressure and clinical outcomes: principals results of the Conduit Artery Function Evaluation (CAFE') Study
Circulation 2006

Rigidità arteriosa e rischio cardiovascolare

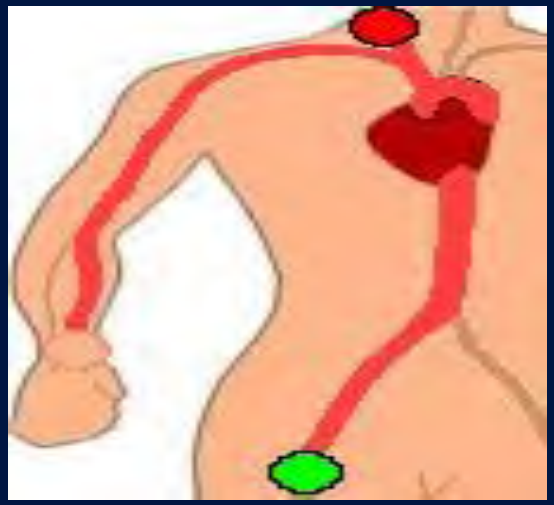
Valore predittivo della rigidità arteriosa ovvero della pressione arteriosa centrale per gli eventi CV

First author (year; country)	Events	Follow-up (years)	Type of patient (number)	Mean age at entry (years)
Aortic PWV – YES				
Blacher (1999;Fr)	CV mortality	6,0	ESRD (241)	51
Laurent (2001;Fr)	CV mortality	9,3	Hypertension (1980)	50
Meaume (2001;Fr)	CV mortality	2,5	Elderly (>70) (141)	87
Shoji (2001;Jp)	CV mortality	5,2	ESRD (265)	55
Boutouyrie (2002;Fr)	CHD events	5,7	Hypertension (1045)	51
Cruickshank (2002;GB)	All cause M.	10,7	Diabetes and MS (571)	51
Laurent (2003;Fr)	Fatal strokes	7,9	Hypertension (1715)	51
Sutton-Tyrrell (2005;USA)	CV events	4,6	Elderly (2488)	74

By Laurent S

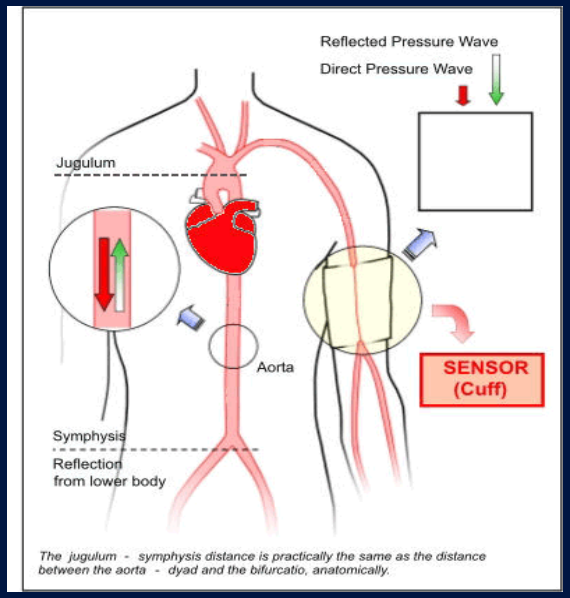
La velocità dell'onda di polso (PWV)

- è il rapporto tra lo spazio percorso o il punto di riflessione (D) ed il tempo di propagazione dell'onda sfigmica tra le due sedi di registrazione o il tempo di ritardo tra l'onda incidente e l'onda riflessa (t) secondo la formula:



Complior

$$PWV = \frac{D}{t} \quad (m/s)$$



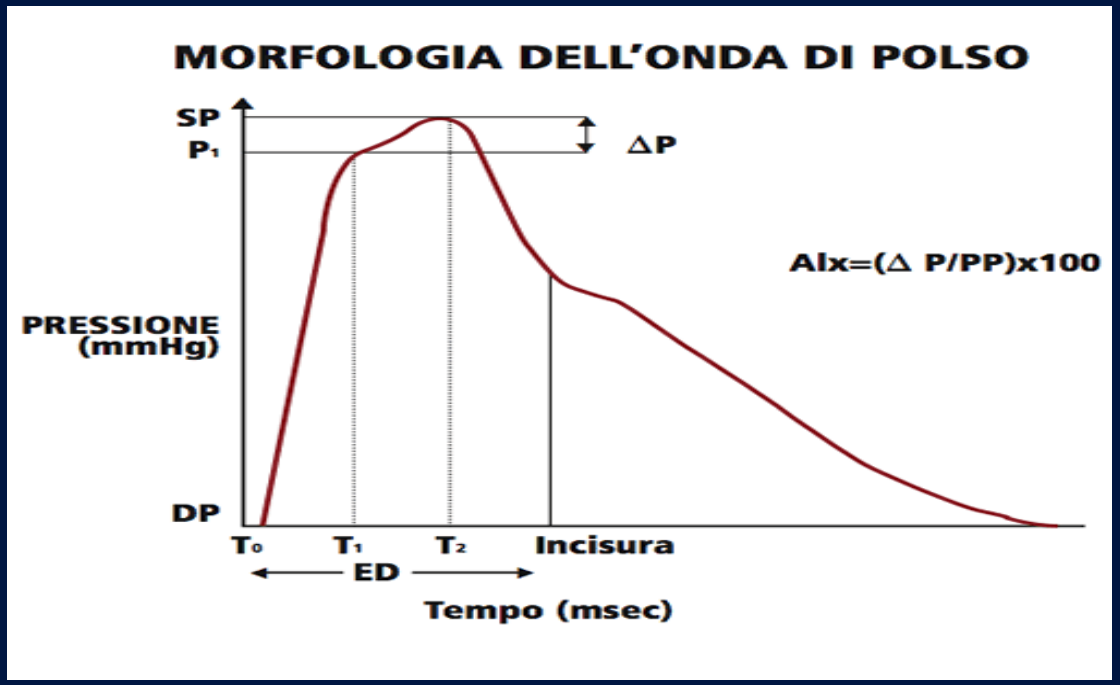
Tensiomed Arteriograph

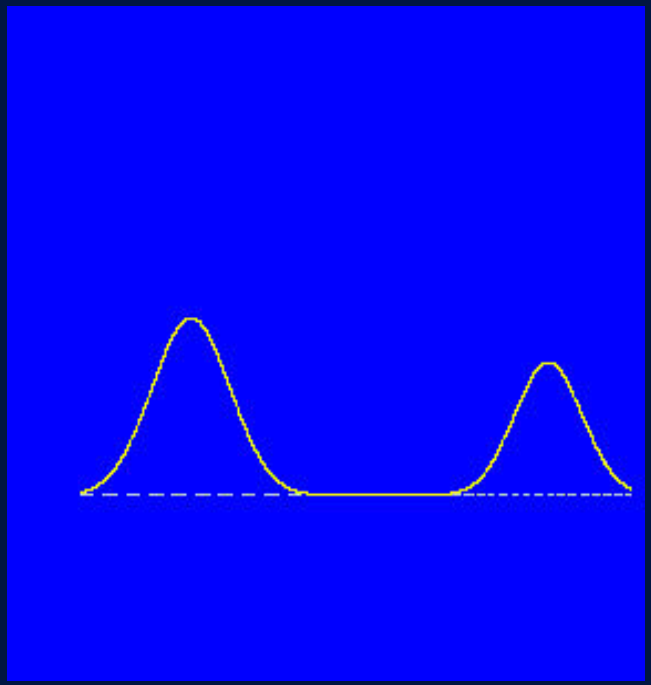
- La velocità dell'onda di polso è inversamente proporzionale alla distensibilità arteriosa.
- L'interpretazione della velocità dell'onda di polso è semplice: quando la rigidità arteriosa aumenta, la distensibilità diminuisce e la velocità dell'onda di polso aumenta.

THE AUGMENTATION INDEX (Aix)

E' DEFINITO COME LA DIFFERENZA TRA IL SECONDO (ONDA RIFLESSA) ED IL PRIMO PICCO (ONDA INCIDENTE) ED ESPRESSO COME PERCENTUALE DELLA PRESSIONE DIFFERENZIALE.

Augmentation index (Aix %) = (P2 – P1 / PP) x 100





ONDA DI POLSO: ONDA INCIDENTE + ONDA RIFLESSA

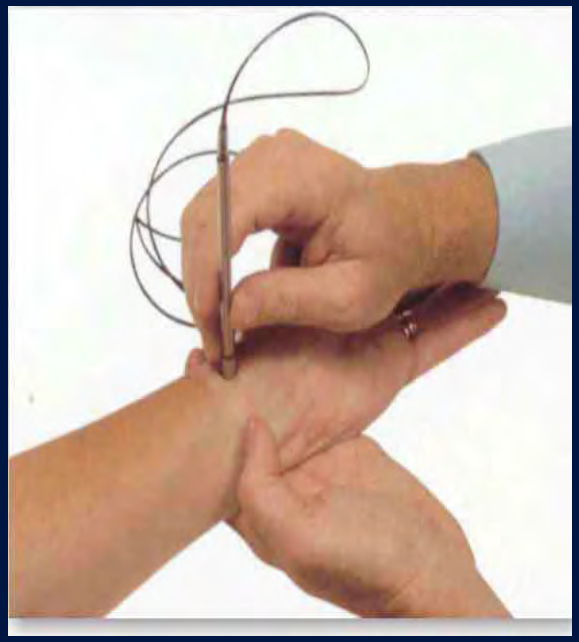
AIX È UN INDICE INDIRETTO DELLA RIGIDITA AORTICA, RAPPRESENTA L'EFFETTO DELL'ONDA RIFLESSA SULL'ONDA INCIDENTE A LIVELLO DELL'AORTA ASCENDENTE.

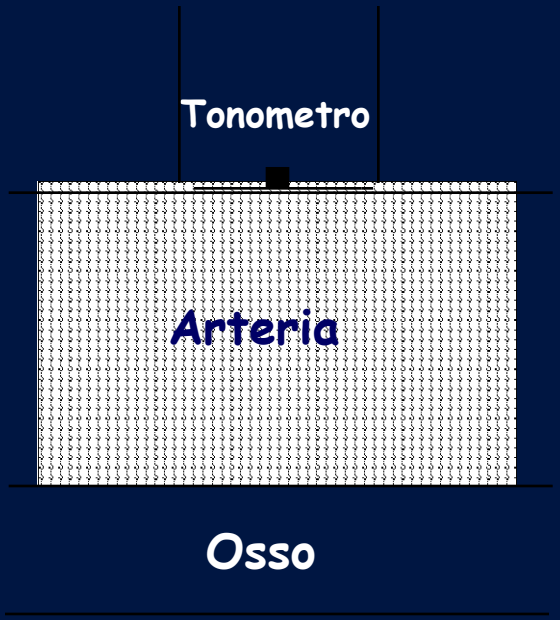
È UNA MISURA DEL CARICO ADDIZIONALE A CUI IL Vsx È SOTTOPOSTO A CAUSA DELL'ONDA DI RIFLESSIONE.

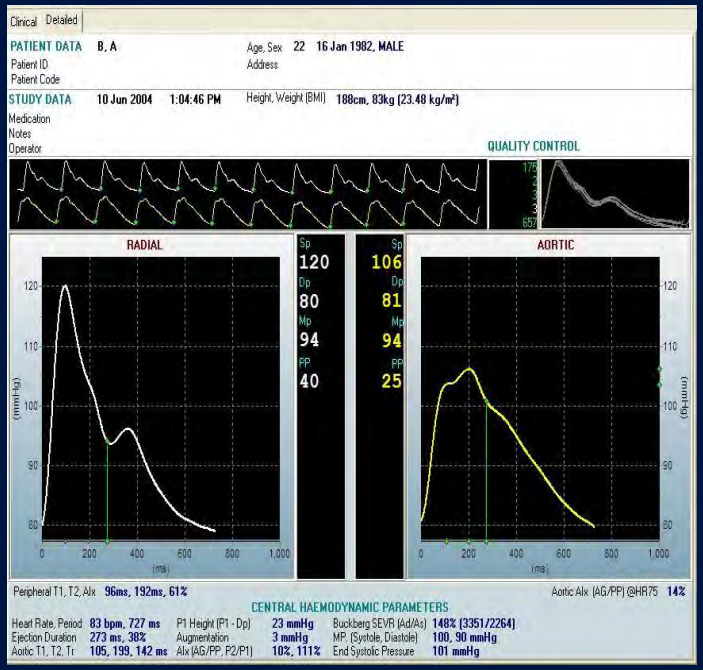
PULSE WAVE VELOCITY

Augmentation Index (Aix)

The SphygmoCor device







Il tonometro permette di rilevare la pressione di polso comprimendo una arteria superficiale, la radiale, sulle strutture ossee sottostanti **permettendo la misurazione del volume e della pressione del polso**.

Linee guida

Linee guida 2007 per il trattamento dell'ipertensione arteriosa

A cura del Comitato per la stesura delle Linee Guida della Società Europea di Ipertensione Arteriosa (ESH) e della Società Europea di Cardiologia (ESC)

Tabella 4. Fattibilità, significato prognostico e impatto economico di alcuni marker di danno d'organo (valutazione da 0 a 4+).

Marker	Valore predittivo per eventi CV	Fattibilità	Costo
Elettrocardiografia	++	++++	+
Ecocardiografia	+++	+++	++
Spessore medio-intimale carotideo	+++	+++	++
Distensibilità arteriosa (velocità dell'onda di polso)	+++	+	++
Indice pressorio arti inferiori/arti superiori	++	++	+
Contenuto di calcio a livello delle pareti coronariche	+	+	++++
Struttura del tessuto cardiaco/vascolare	?	+	++
Marker circolanti di collagene	?	+	++
Disfunzione endoteliale	++	+	+++
Lacune cerebrali/lesioni della sostanza bianca	?	++	++++
Stima della filtrazione glomerulare o della creatinina clearance	+++	++++	+
Microalbuminuria	+++	++++	+

CV = cardiovascolari.

PRIMUM
NON
NOCERE

I vecchi paradigmi della terapia del Diabete mellito tipo 2

Terapia aggressiva

Perseguire targets di quasi normalità

"Lower is better"

I nuovi paradigmi della terapia del Diabete mellito tipo 2

"Earlier is better"

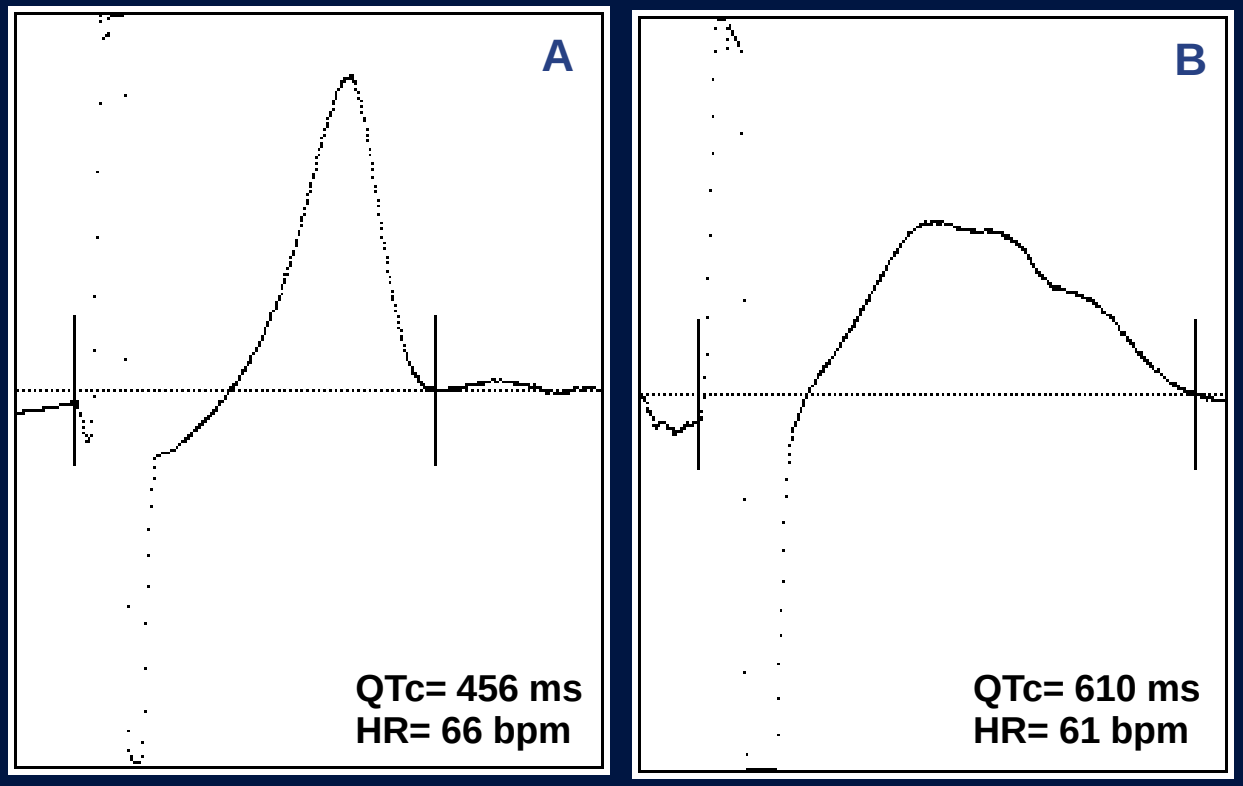
Terapia appropriata

Terapia personalizzata

POTENZIALI MECCANISMI CON CUI L'IPOGLICEMIA AUMENTA LA MORTALIà CARDIOVASCOLARE

- Aritmie cardiache da anormale ripolarizzazione cardiaca
- Incremento della tendenza alla trombosi e riduzione delle capacità di trombolisi
- Le catecolamine determinano
  - Aumento dela frequenza cardiaca
  - Ischemia miocardica silente
  - Angina e infarto del miocardio

Effect of experimental hypoglycaemia on QT interval



5.0mM 2.5mM

International Diabetes Monitor 2009; 21(6): 234-241.
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CONCLUSIONI

1. *Non vi sono ancora prove sufficienti per includere i fattori di rischio emergenti nella valutazione del rischio cardiovascolare*
2. *La corretta interpretazione dei principali fattori di rischio tradizionali può migliorare la predizione degli eventi cardiovascolari*

CONCLUSIONI

4. Devono essere corretti tutti fattori di rischio cardiovascolari con una terapia appropriata

5. La prevenzione delle ipoglicemie rappresenta il presupposto principale della cura del diabetico

TERAPIA PERSONALIZZATA

"La vita è uguale ad una scatola di cioccolatini,
non sai mai quello che ti capita"