3° Workshop SICOb – SID – SIO - 7 marzo 2014

L'integrazione tra terapia medica e chirurgica nel trattamento del paziente obeso diabetico

1°Corso SICOb – SID – SIO - 8 marzo 2014

Il management peri-operatorio del paziente obeso diabetico

Incontro Congiunto SICOb – SID – SIO 2014

Con il patrocinio di

Società Italiana dell'Obesità

S.I.C.OB.

PADOVA, 7/8 marzo

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di Medicina Legale
Ex Ospedale Militare

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Dott. Roberto Fabris - Dott. Mirto Foletto
Centro per lo Studio e la Terapia Integrata dell'Obesità

Terapia farmacologica nel paziente obeso-diabetico: Terapia dell'ipertensione arteriosa

Marco Rossato

Università degli Studi di Padova
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Clinica Medica 3
Direttore: Prof. Roberto VETTOR

Terapia farmacologica nel paziente obeso-diabetico

Terapia dell'ipertensione arteriosa

> Terapia dell'ipertensione nel soggetto obeso/diabetico

- Terapia dell'ipertensione nel soggetto obeso/diabetico post-chirurgia bariatrica

Obesità
Definizione (WHO)

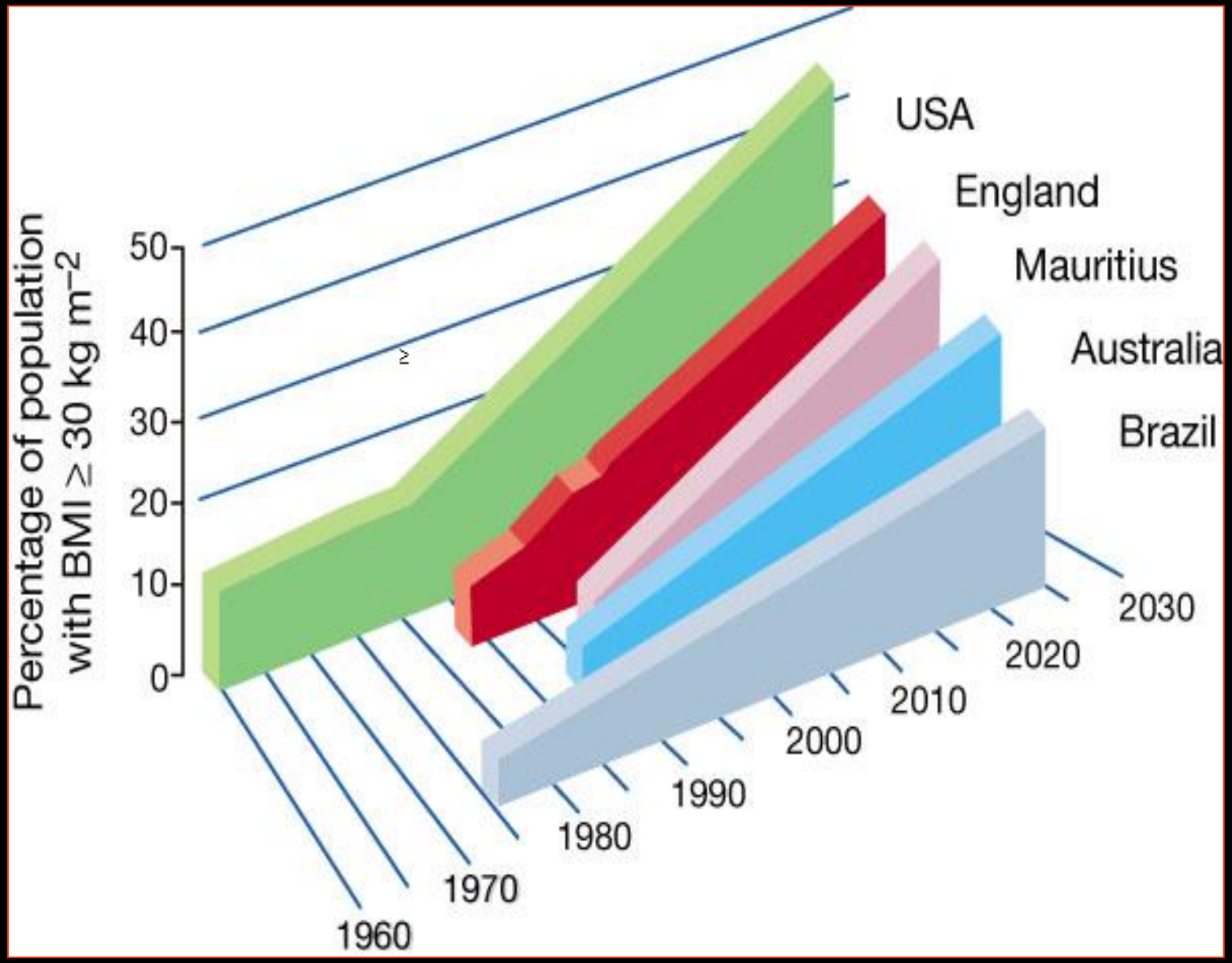
Condizione caratterizzata da eccessivo peso corporeo per accumulo di tessuto adiposo, in misura tale da influire negativamente sullo stato di salute.

Classificazione	*BMI (kg/m^2)*	*Rischio di co-morbilità*
Sottopeso	*<18.5*	*Basso (altre problematiche cliniche)*
Normale	*18.5-24.9*	*Nella media*
Sovrappeso	*25-29.9*	*Lieve*
Obesità I	*30-34.9*	*Moderato*
Obesità II	*35-39.9*	*Grave*
Obesità III	*≥ 40*	*Molto grave*

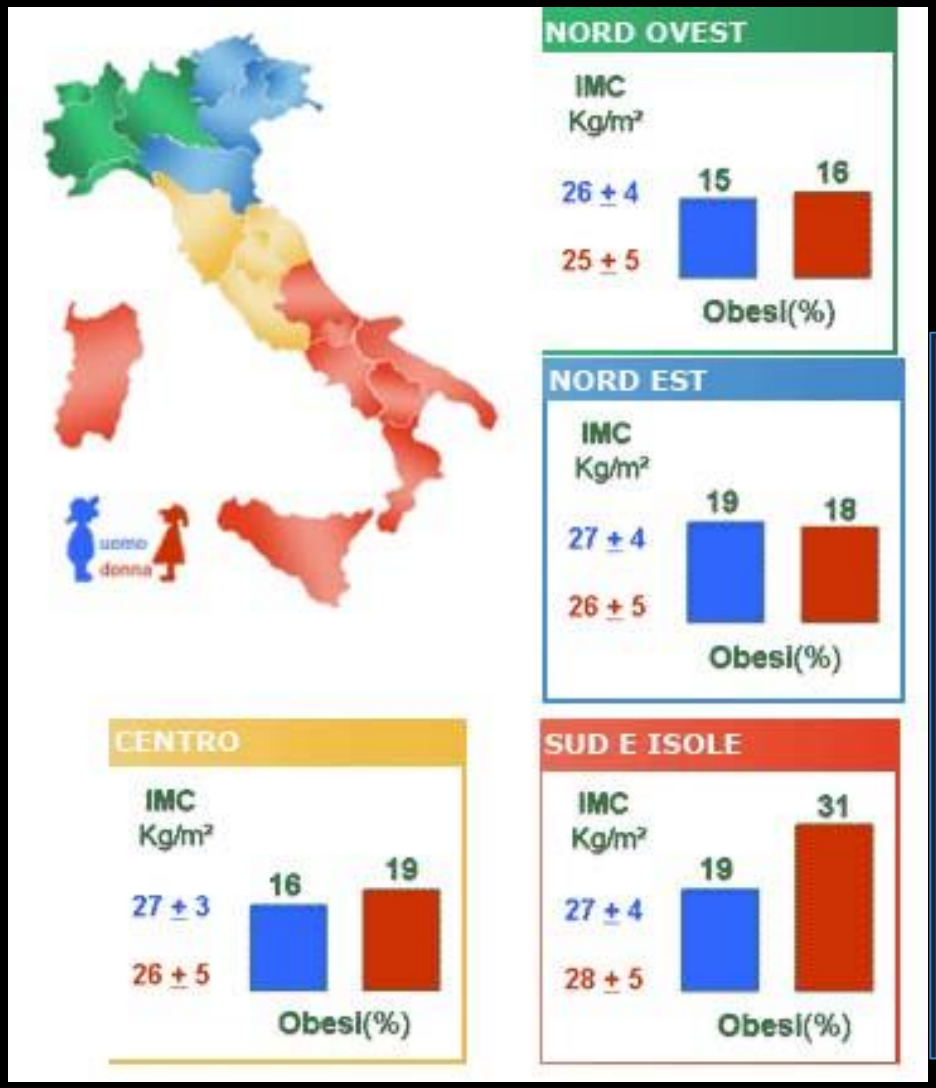
Valori pressori arteriosi che definiscono l'ipertensione

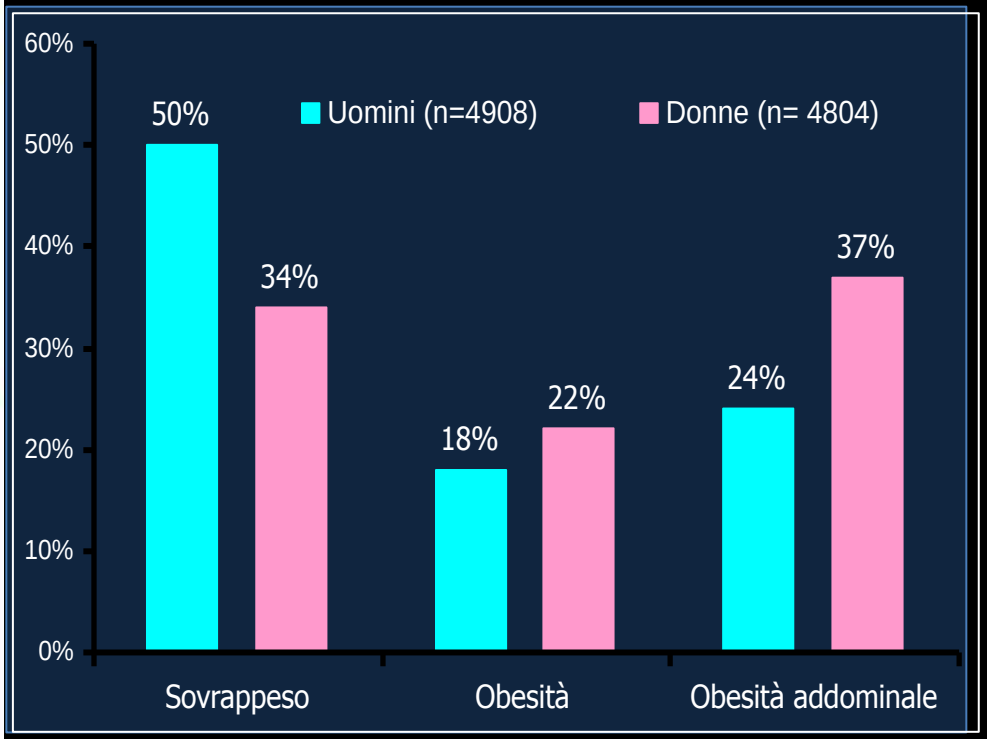
Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Office BP	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake)	≥135	and/or	≥85
Nighttime (or asleep)	≥120	and/or	≥70
24-h	≥130	and/or	≥80
Home BP	≥135	and/or	≥85

Prevalenza dell'obesità (BMI≥30 kg m^{-2}) 1960-2025



Epidemiologia dell'obesità/sovrappeso in Italia





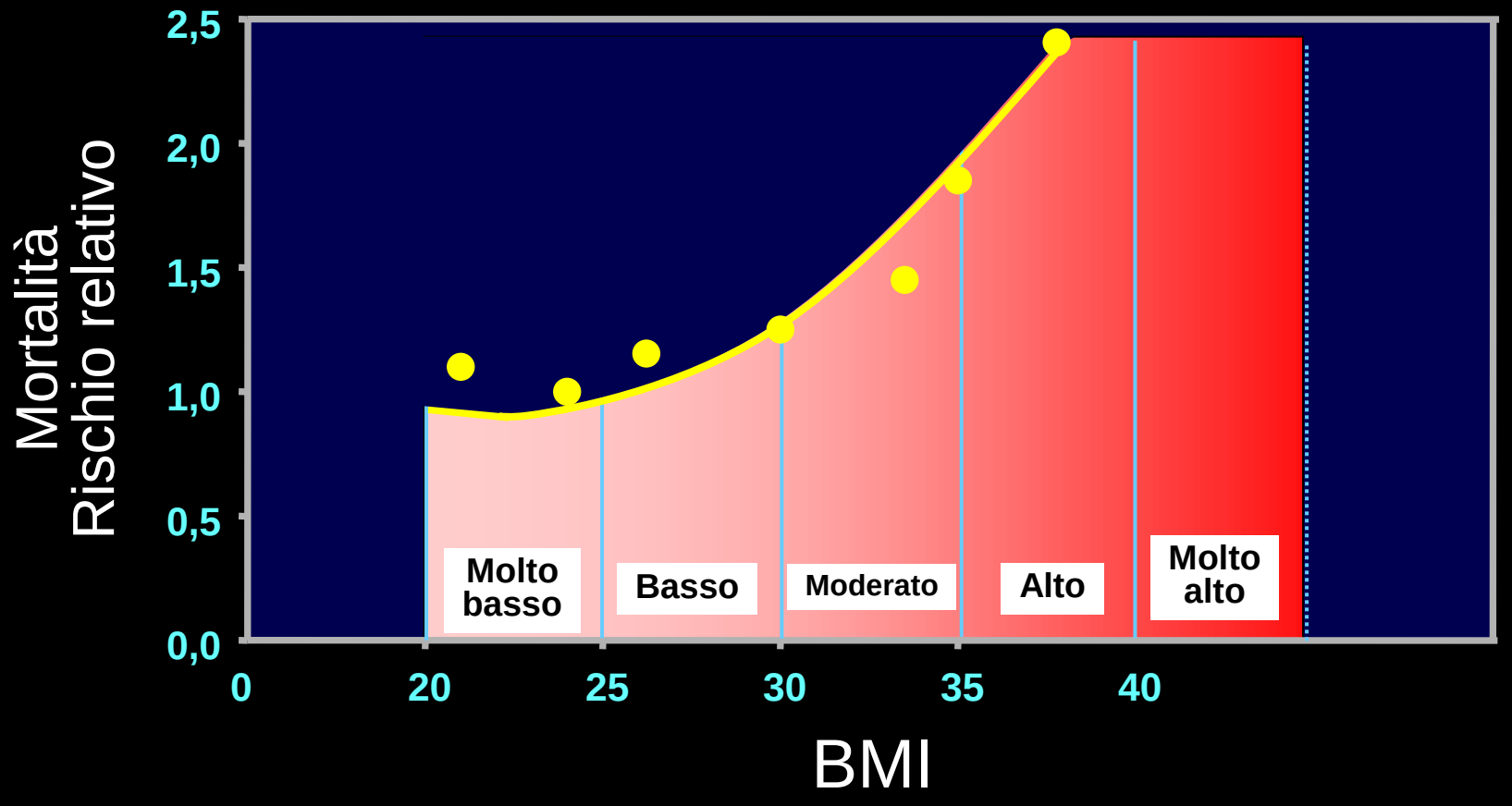
Conseguenze dell'obesità sullo stato di salute: le conosciamo da molto più tempo di quanto si pensi...

"la morte improvvisa è più frequente nei soggetti obesi che nei soggetti magri"

Ippocrate

cited in Bray, G.A. Endocrinol Metab Clin N. Amer 32 (2003) 787-804

Relazione tra mortalità e BMI

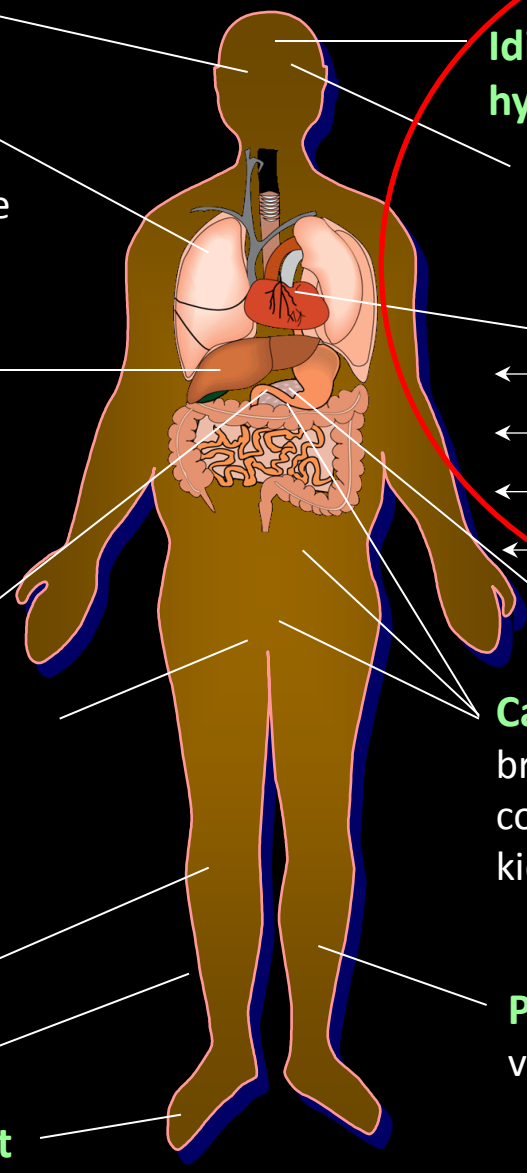


Bray, J Clin Endocrinol Metab, 1999

L’OBESO “VISCERALE” ha una più alta probabilità di sviluppare malattie come:

- diabete mellito di tipo 2 (NIDDM)
- dislipidemie
- ipertensione arteriosa
- iperuricemia
- cardiopatia ischemica e ictus
- disturbi respiratori (apnea notturna)
- patologie epatiche
- colecistopatie
- alcune forme di neoplasia

Medical Complications of Obesity



Cataracts

Pulmonary disease
abnormal function
obstructive sleep apnea
hypoventilation syndrome

Nonalcoholic fatty liver disease
steatosis
steatohepatitis
cirrhosis

Gall bladder disease

Gynecologic abnormalities
abnormal menses
infertility
polycystic ovarian syndrome

Osteoarthritis

Skin

Gout

Idiopathic intracranial hypertension

Stroke

Coronary heart disease

Diabetes

Dyslipidemia

Hypertension

Kidney disease

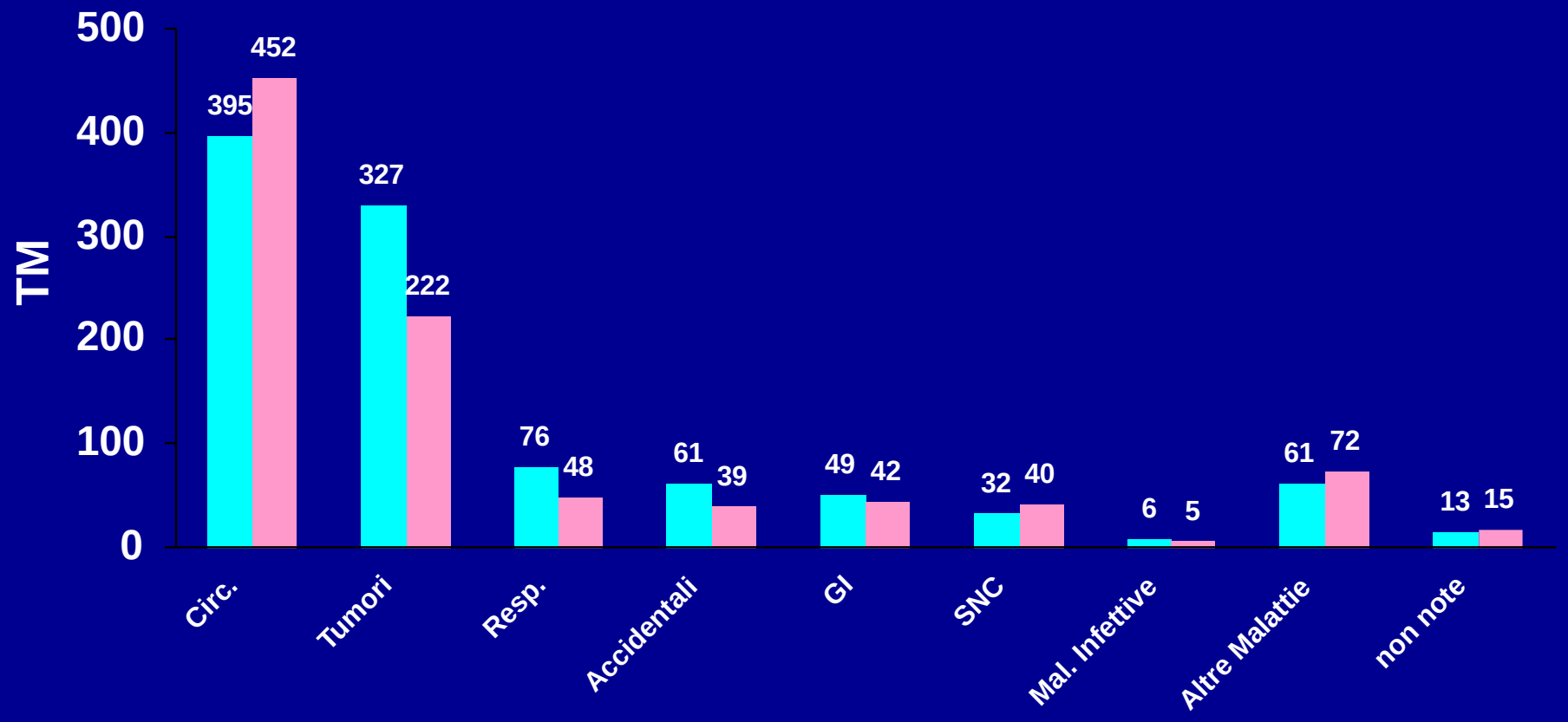
Severe pancreatitis

Cancer
breast, uterus, cervix
colon, esophagus, pancreas
kidney, prostate

Phlebitis
venous stasis

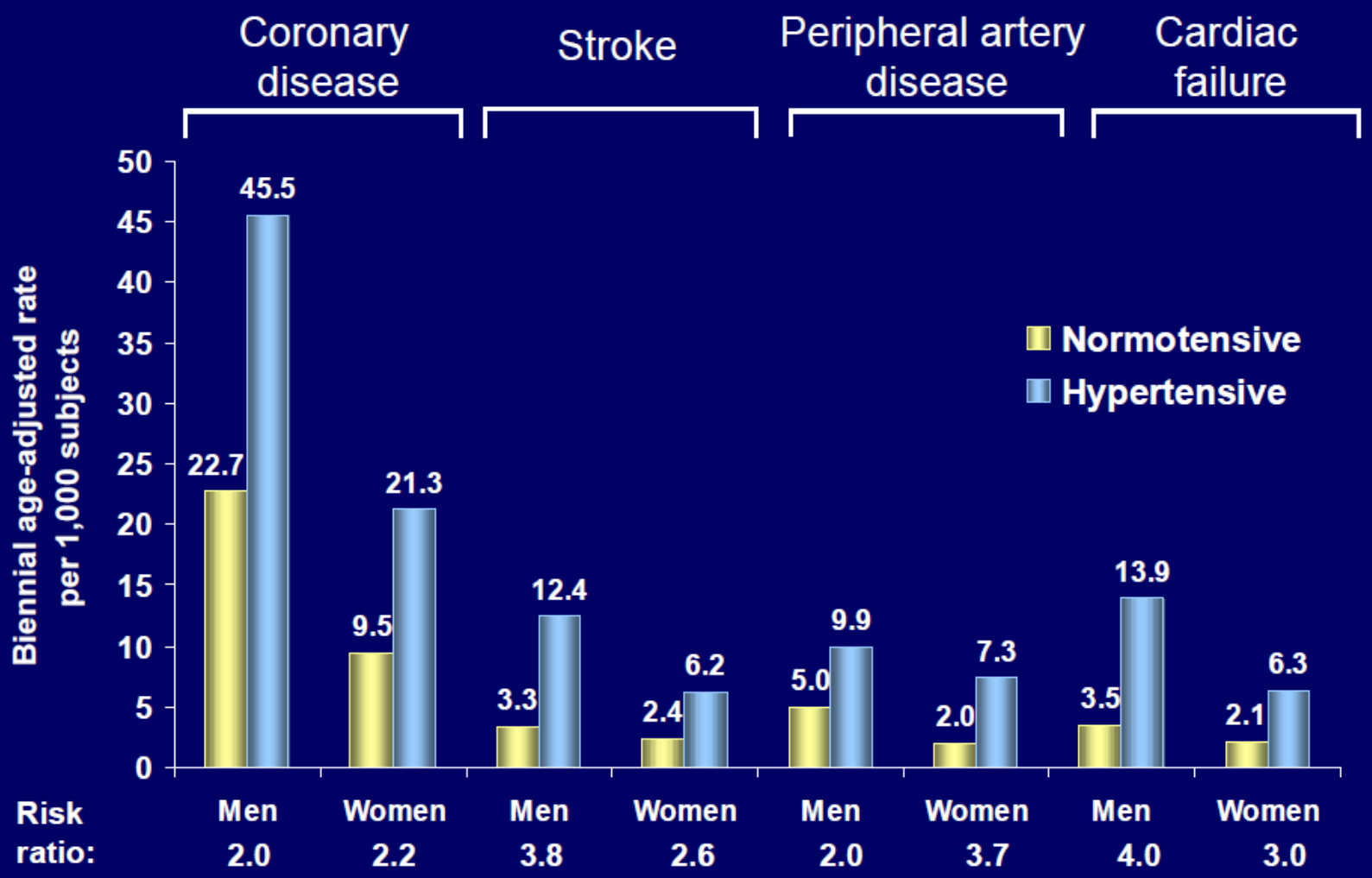
La malattia cardiovascolare resta la principale causa di morte

Tasso di mortalità (TM)
per 100.000 abitanti in Italia nel 1997



Annuario Statistico Italiano 2001 - ISTAT

Hypertension: A risk factor for cardiovascular disease



Kannel WB. *JAMA* 1996;275:1571-1576

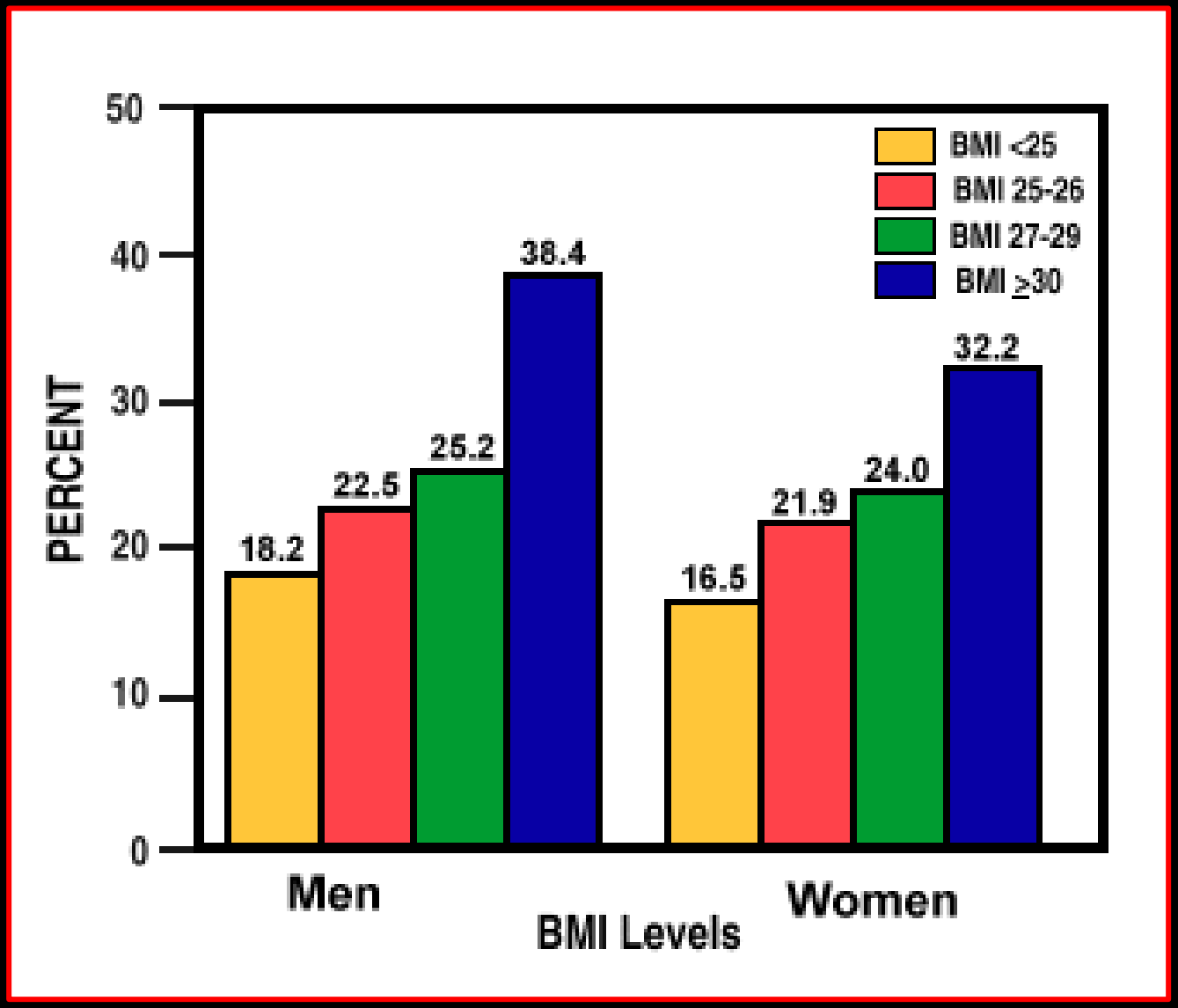
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

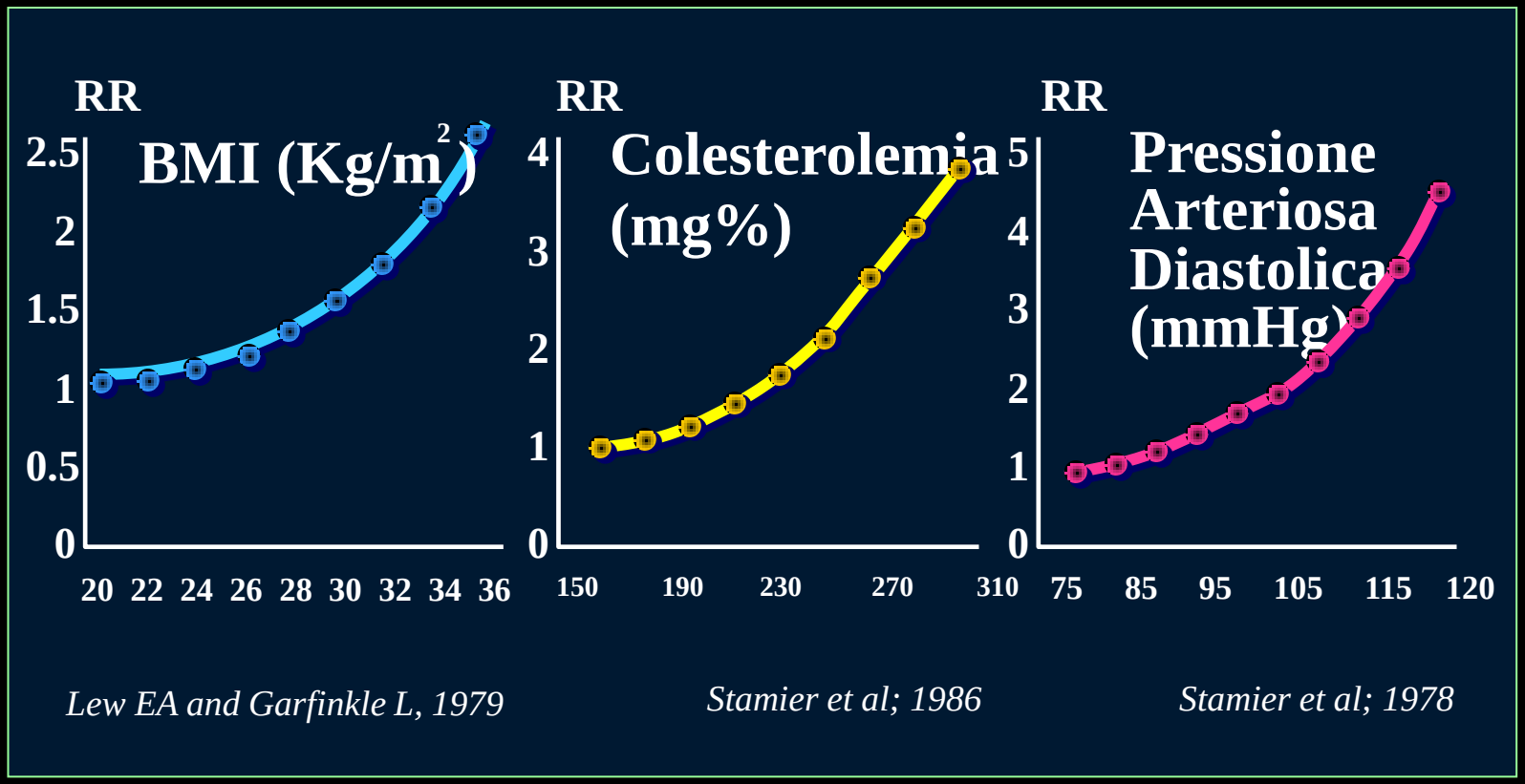
Heart Disease and Stroke Statistics—2009 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee

- Epidemiological data unequivocally support the link between body weight and blood pressure.
- Indeed, greater body weight is one of the major risk factors for high blood pressure.
- Recent data from NHANES indicate that the prevalence of hypertension among obese individuals, (BMI $\geq$ 30 kg/m2), is 42.5% compared with 27.8% for overweight individuals (BMI 25.0-29.9 kg/m2) and 15.3% for those with BMI < 25 kg/m2.

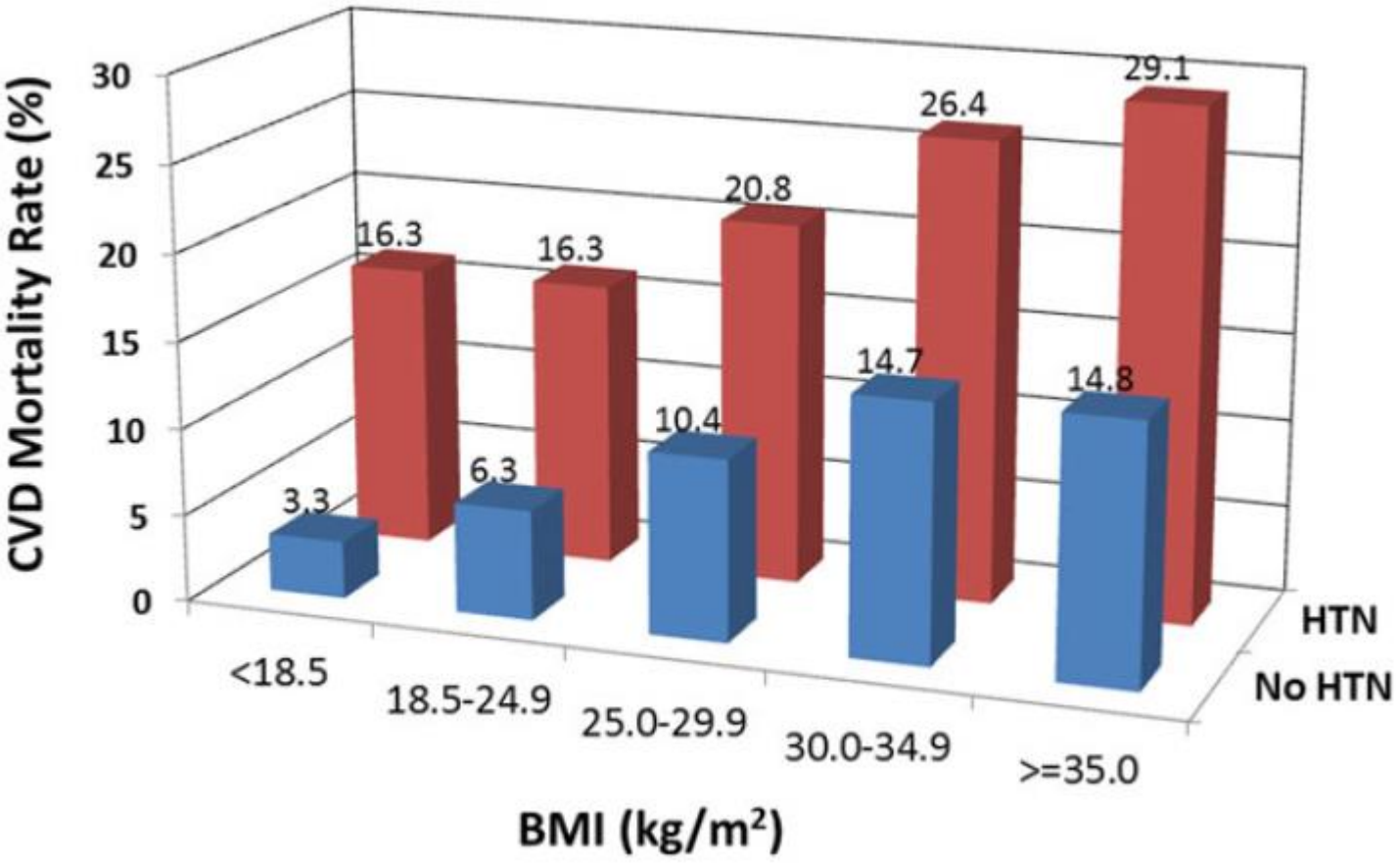
BMI and Prevalence of Hypertension



Associazione con il rischio di mortalità (RR): Confronto tra l'effetto del BMI, della colesterolemia e della pressione arteriosa diastolica



Thirty-two year rates of death due to cardiovascular disease in participants of the Chicago Heart Association Detection Project in Industry cohort, stratified by baseline body mass index (BMI) and hypertension (HTN) status



Pathogenesis of Obesity-Related Hypertension

Central (abdominal) obesity
- Insulin resistance (hyperinsulinemia)
- ↑ Leptin levels

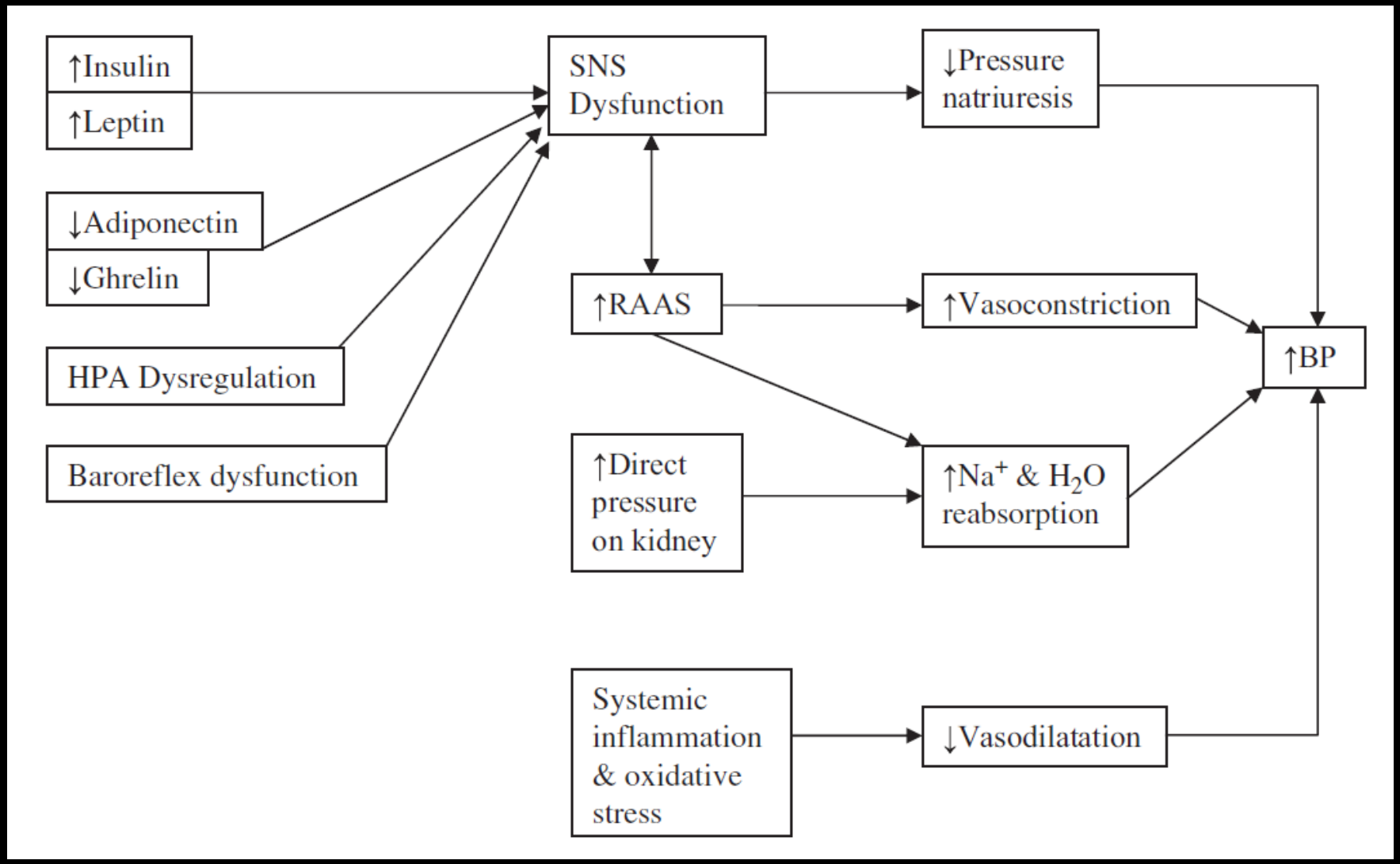
↑ Sympathetic nervous system (SNS) activity
- Insulin
- Leptin

↑ Renin-angiotensin-aldosterone system activity
- SNS stimulation of renin release
- ↑ Angiotensinogen from intra-abdominal adipocytes
- ↑ Aldosterone production (in excess of angiotensin stimulation)

Salt sensitivity (↑ renal sodium reabsorption)
- SNS
- Insulin
- Angiotensin (all)
- Aldosterone
- Intra-renal blood flow redistribution

Obesity | VOLUME 21 | NUMBER 1 | JANUARY 2013

Mechanisms by which obesity induces hypertension



Fattori Fisiopatologici

dell’ipertensione arteriosa associata all’obesità

Eccesso di varianti geniche ipertensivanti e/o deficit di varianti genetiche ipotensivanti
Eccessivo introito di sale con la dieta e deficit escretorio renale
Interazione tra fattori genetici e dieta nello sviluppo dell’ipertensione arteriosa nell’obeso iperteso
Deficit del sistema natriuretico basato sui peptidi natriuretici cardiaci
Inappropriata accentuazione dell’attività del sistema renina-angiotensina-aldosterone
Aumentata attività del sistema nervoso simpatico e possibile ruolo della leptina
Insulino-resistenza ed iperinsulinemia
“Disfunzione adipocitaria” e infiammazione cronica basso grado

?

Terapia dell'ipertensione arteriosa nel soggetto obeso

Prevenzione delle complicanze obesita'

Developmental Origins of Obesity-Related Hypertension

The childhood origins of obesity-related hypertension

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors

Markus Juonala, M.D., Ph.D., Costan G. Magnussen, Ph.D.,
Gerald S. Berenson, M.D., Alison Venn, Ph.D., Trudy L. Burns, M.P.H., Ph.D.,
Matthew A. Sabin, M.D., Ph.D., Sathanur R. Srinivasan, Ph.D.,
Stephen R. Daniels, M.D., Ph.D., Patricia H. Davis, M.D., Wei Chen, M.D., Ph.D.,
Cong Sun, M.D., Ph.D., Michael Cheung, M.D., Ph.D.,
Jorma S.A. Viikari, M.D., Ph.D., Terence Dwyer, M.D., M.P.H.,
and Olli T. Raitakari, M.D., Ph.D.

*…**Overweight or obese children who were obese as adults had increased risks of type 2 diabetes, hypertension, dyslipidemia, and carotid-artery atherosclerosis**.*
The risks of these outcomes among overweight or obese children who became nonobese by adulthood were similar to those among persons who were never obese…

N Engl J Med 365;20, november 17, 2011

Table 2. Relative Risks of High-Risk Outcomes in Adulthood among Participants in Four Cohort Studies Who Were Overweight or Obese in Childhood.*

Outcome	Bogalusa	Muscatine	CDAH	YFS	Male Subjects†	Female Subjects†	All Subjects†
Type 2 diabetes							
Relative risk (95% CI)	2.2 (1.3–3.8)	3.4 (1.6–7.1)	0.5 (0.1–3.5)	2.6 (1.2–5.8)	3.8 (2.1–6.9)	1.8 (1.1–3.0)	2.4 (1.6–3.6)
P value	0.006	0.002	0.46	0.02	<0.001	0.02	<0.001
Hypertension							
Relative risk (95% CI)	2.0 (1.3–2.8)	2.3 (1.4–3.9)	1.5 (1.0–2.2)	1.8 (1.4–2.3)	1.8 (1.5–2.2)	1.7 (1.3–2.4)	1.8 (1.5–2.1)
P value	<0.001	0.001	0.03	<0.001	<0.001	<0.001	<0.001
High-risk LDL cholesterol							
Relative risk (95% CI)	1.8 (1.3–2.6)	1.3 (0.7–2.4)	1.6 (1.1–2.3)	1.2 (0.8–1.7)	1.2 (0.9–1.6)	2.0 (1.4–2.7)	1.4 (1.2–1.8)
P value	0.001	0.39	0.02	0.31	0.18	<0.001	<0.001
High-risk HDL cholesterol							
Relative risk (95% CI)	1.5 (1.2–1.9)	1.3 (1.1–1.6)	1.4 (1.0–1.9)	1.6 (1.2–2.0)	1.2 (1.0–1.5)	1.8 (1.4–2.3)	1.4 (1.2–1.6)
P value	0.001	0.004	0.06	0.001	0.03	<0.001	<0.001
High-risk triglycerides							
Relative risk (95% CI)	1.8 (1.2–2.7)	1.8 (1.2–2.5)	1.8 (1.2–2.6)	1.5 (1.1–2.0)	1.6 (1.3–2.1)	1.6 (1.1–2.3)	1.6 (1.3–1.9)
P value	0.009	0.002	0.007	0.01	<0.001	0.02	<0.001
High-risk carotid-artery intima–media thickness‡							
Relative risk (95% CI)	2.5 (1.5–4.1)	1.4 (0.9–2.2)	1.0 (0.7–1.3)	1.5 (1.1–2.1)	1.3 (1.0–1.7)	1.3 (1.0–1.7)	1.3 (1.1–1.6)
P value	0.001	0.14	0.98	0.007	0.05	0.06	0.007

Terapia dell'ipertensione arteriosa nel soggetto obeso

Prevenzione delle complicanze obesita'

The New England
Journal of Medicine

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VOLUME 336 APRIL 17, 1997 NUMBER 16

A CLINICAL TRIAL OF THE EFFECTS OF DIETARY PATTERNS ON BLOOD PRESSURE

LAWRENCE J. APPEL, M.D., M.P.H., THOMAS J. MOORE, M.D., EVA OBARZANEK, PH.D., WILLIAM M. VOLLMER, PH.D., LAURA P. SVETKEY, M.D., M.H.S., FRANK M. SACKS, M.D., GEORGE A. BRAY, M.D., THOMAS M. VOGT, M.D., M.P.H., JEFFREY A. CUTLER, M.D., MARLENE M. WINDHAUSER, PH.D., R.D., PAO-HWA LIN, PH.D., AND NJERI KARANJA, PH.D., FOR THE DASH COLLABORATIVE RESEARCH GROUP*

…A diet rich in fruits, vegetables, and low-fat dairy foods and with reduced saturated and total fat can substantially lower blood pressure.
This diet offers an additional nutritional approach to preventing and treating hypertension…

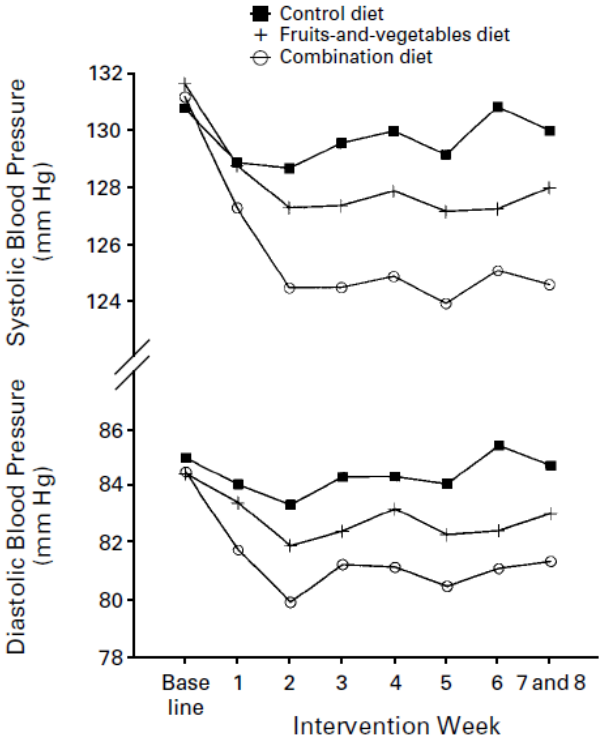


Figure 1. Mean Systolic and Diastolic Blood Pressures at Base Line and during Each Intervention Week, According to Diet, for 379 Subjects with Complete Sets of Weekly Blood-Pressure Measurements.

Lifestyle Changes in the Management of Obesity-Related Hypertension

Systematic reviews consistently report a decrease in SBP of about 1 mm Hg per kg of weight loss with follow-up of 2 to 3 years.

There is attenuation in the longer-term, with a decrease of about 6 mm Hg in SBP per 10 kg of weight loss.

Intervention programs appropriate for obesity-hypertension combine diet, physical activity, and behavioral modification and aim to achieve longterm change in health-related behaviors.

Low-Salt Diets

- Salt sensitivity is commonly associated with obesity. Salt restriction decreases the risk of hypertension with or without weight loss as well as reducing the incidence of CV events.
- In the Hypertension Prevention Trial, participants with DBP 78 to 89 mm Hg were followed for 3 years after being randomized to one of five groups: control, decreased energy intake, decreased sodium intake, decreased sodium and energy intake, or decreased sodium and increased potassium intake.
- BP decreased in all groups of intervention, with the greatest decrease in patients assigned to reduced energy only.
- The groups with reduced sodium intake had a significantly lower rate of hypertension.

Arch Intern Med. 1990;150:153-62

Physical Activity

Aerobic exercise can reduce weight and BP, but when exercise is the only intervention, weight losses are small, with an estimated change of 1.6 kg in moderate-intensity programs continued for 6 to 12 months.

In a meta-analysis that included assessment of ambulatory BP it was reported that in studies lasting 4 to 52 weeks, with physical activity as the only intervention, aerobic exercise reduced BP by 3/2.4 mm Hg.
The change affected daytime (3.3/3.5 mm Hg) but not nighttime (0.6/1.0 mm Hg) BP. *Clin Exp Pharmacol Physiol. 2006.*

The effect on BP was independent of the estimated weight loss of 1.2 kg. However, when aerobic exercise is combined with calorie restriction for weight control, the effects on ambulatory BP can be substantial . *J Hypertens. 1996.*

Alcohol

The pressor effect of alcohol has been established in clinical trials, with an estimated increase in SBP of 1 mm per 10 g of alcohol .
Paradoxically, drinking alcohol at low to moderate levels is associated with lower risk of atherosclerotic disease.

Alcohol provides 29 kJ/g and, although weight gain from excess intake might be expected, meta-analysis has not shown a consistent relationship between alcohol and weight gain.

In US adults, however, increased alcohol intake was associated with greater long-term weight gain. Moderation of heavier daily alcohol intake to no more than one standard drink in women and two standard drinks in men appears prudent, with potential benefits for both weight gain and BP.

In a factorial trial of independent and combined effects of alcohol moderation and weight reduction in overweight and obese hypertensive drinkers, effects on BP were additive over a 3-month period, with the combined modalities achieving a 14/9 mm Hg BP reduction compared with controls who maintained usual weight and drinking habits. *Hypertension. 1992.*

Smoking

Although smokers tend to have lower body weight, they may gain weight because of clustering of adverse health behaviors .

Smoking increases BP acutely, with an associated rise in arterial stiffness that lasts longer in hypertensive men.

There is an important window of opportunity for lifestyle programs to prevent the weight gain (and BP rise) often seen with smoking cessation.

N Engl J Med. 2011

Trattamento dell'ipertensione arteriosa

Classe di rischio del Paziente facendo riferimento alle Linee guida ESH/ESC

	Pressione arteriosa (mmHg)				
Altri fattori di rischio, danno d'organo o riscontro di patologia concomitante	Normale PAS 120-129 o PAD 80-84	Normale alta PAS 130-139 o PAD 85-89	Grado 1 PAS 140-159 o PAD 90-99	Grado 2 PAS 160-179 o PAD 100-109	Grado 3 PAS $\geq$ 180 o PAD $\geq$ 110
Nessun altro fattore di rischio aggiunto	Rischio nella media	Rischio nella media	Rischio aggiunto basso	Rischio aggiunto moderato	Rischio aggiunto elevato
1-2 fattori di rischio	Rischio aggiunto basso	Rischio aggiunto basso	Rischio aggiunto moderato	Rischio aggiunto moderato	Rischio aggiunto molto elevato
3 o più fattori di rischio, SM, danno d'organo o diabete	Rischio aggiunto moderato	Rischio aggiunto elevato	Rischio aggiunto elevato	Rischio aggiunto elevato	Rischio aggiunto molto elevato
Malattia CV o renale	Rischio aggiunto molto elevato	Rischio aggiunto molto elevato	Rischio aggiunto molto elevato	Rischio aggiunto molto elevato	Rischio aggiunto molto elevato

Trattamento dell'ipertensione arteriosa in relazione alla classe di rischio del paziente facendo riferimento alle linee guida ESH/ESC

	Pressione arteriosa (mmHg)				
Altri fattori di rischio, danno d'organo o malattie concomitanti	Normale PAS 120-129 o PAD 80-84	Normale elevata PAS 130-139 o PAD 84-89	Ipertensione di grado 1 PAS 140-159 o PAD 90-09	Ipertensione di grado 2 PAS 140-159 o PAD 90-99	Ipertensione di grado 3 PAS ≥180 o PAD ≥110
Nessun altro fattore di rischio	Nessun intervento	Nessun intervento	Cambiamento dello stile di vita per alcuni mesi e poi terapia farmacologica se PA non controllata	Cambiamento dello stile di vita per alcune settimane,poi terapia farmacologica se PA non controllata	Cambiamento dello stile di vita e terapia farmacologica immediata
1-2 fattori di rischio	Cambiamento dello stile di vita	Cambiamento dello stile di vita	Cambiamento dello stile di vita per alcune settimane,poi terapia farmacologica se PA non controllata	Cambiamento dello stile di vita per alcune settimane,poi terapia farmacologica se PA non controllata	Cambiamento dello stile di vita e terapia farmacologica immediata
≥3 fattori di rischio, sindrome metabolica o danno d'organo	Cambiamento dello stile di vita	Cambiamento stile di vita + eventuale terapia farmacologica	Cambiamento dello stile di vita + terapia farmacologica	Cambiamento dello stile di vita + terapia farmacologica	Cambiamento dello stile di vita e terapia farmacologica immediata
Diabete	Cambiamento dello stile di vita	Cambiamento stile di vita + terapia farmacologica			
Patologie cardiovascolari o nefropatia	Cambiamento dello stile di vita e terapia farmacologica immediata	Cambiamento dello stile di vita e terapia farmacologica immediata	Cambiamento dello stile di vita e terapia farmacologica immediata	Cambiamento dello stile di vita e terapia farmacologica immediata	Cambiamento dello stile di vita e terapia farmacologica immediata

Treatment of Hypertension in the Obese
BP Thresholds and Targets

As in individuals with diabetes and chronic kidney disease, many authorities have recommended lower target BPs for obese individuals.

This recommendation is partially due to the constellation of risk factors associated with obesity and the metabolic syndrome, and is also attributed to the fact that hypertension in obese patients has proven more difficult to control than hypertension in the nonobese population. In fact, even modest weight loss increases the likelihood of achieving goal BPs.

Although logical, there is no strong evidence to support lowering BP much beyond the defined 140/90 mm Hg threshold .

Terapia anti-ipertensiva nel soggetto obeso iperteso

Come riportato dalle Linee Guida ESH/ESC del 2013 la maggioranza degli studi clinici controllati hanno dimostrato che la riduzione significativa dell'incidenza degli eventi cardiovascolari, nei soggetti affetti da ipertensione arteriosa, dipendono essenzialmente dalla riduzione degli elevati valori pressori di per sé, dal raggiungimento del target pressorio e solo in parte dal tipo di farmaco impiegato.

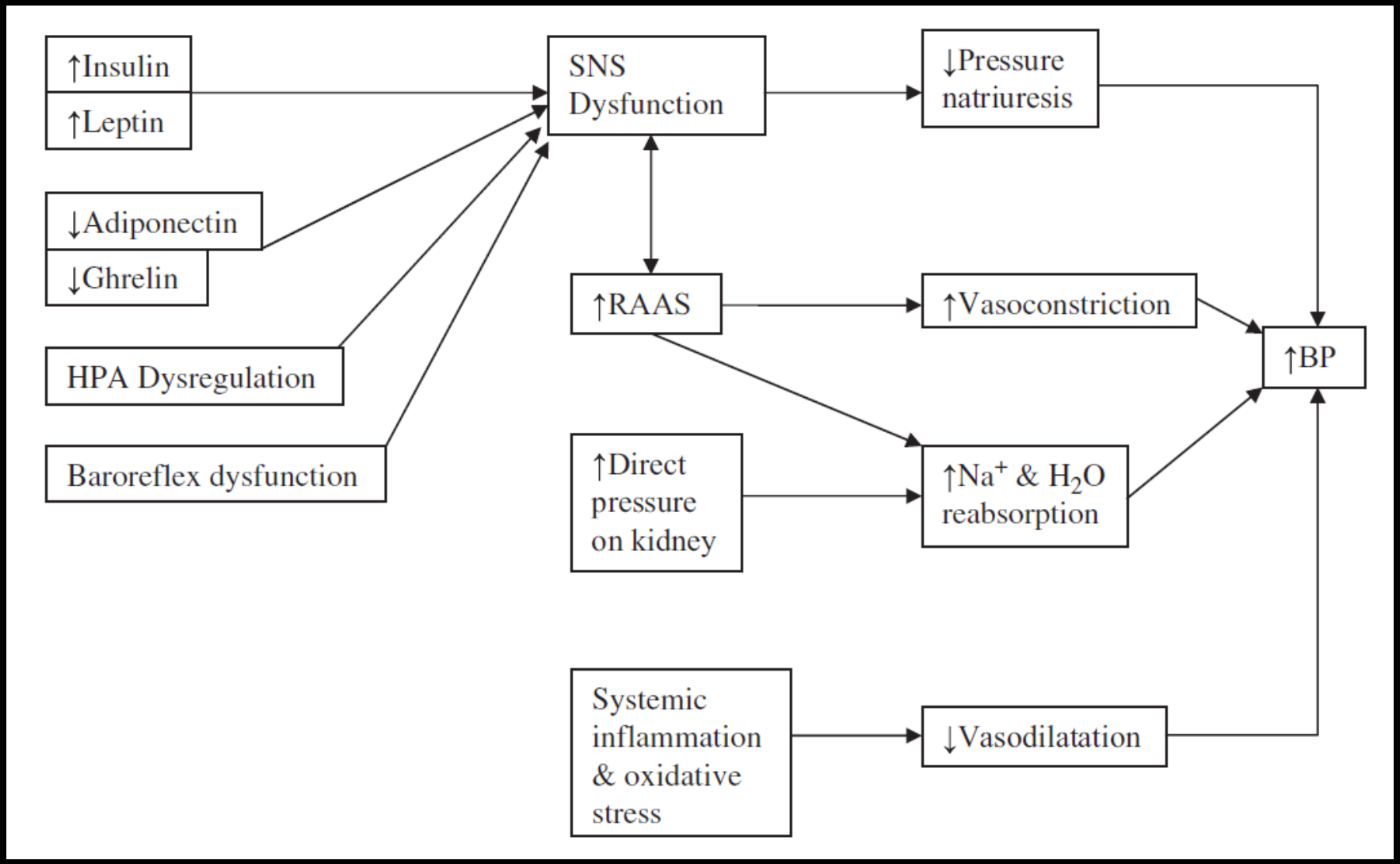
Ne deriva che i farmaci maggiormente usati a nostra disposizione quali i diuretici tiazidici (TZ) e tiazidico-simili, i beta-bloccanti (BB), i calcio antagonisti (CCB), gli ACE inibitori (ACEI) e i bloccanti recettoriali dell'angiotensina II (ARB o sartani), sono tutti farmaci dotati di un'efficacia antipertensiva ben documentata.

Antihypertensive Agents

More than 100 medications are available for the direct treatment of hypertension, acting on a variety of systems throughout the body.

Although there is no evidence based on longitudinal outcome studies in obese patients, recommendations for the use of specific antihypertensive agents in an obese population have emerged.

Mechanisms by which obesity induces hypertension



Anti-hypertensive Agents in Obesity

Target: $\leq$140/90

Renin-angiotensin-aldosterone system inhibition

- Angiotensin-converting enzyme inhibitors; angiotensin receptor blockers

Diuretics

- Low-dose thiazide or thiazide-like agent
- Loop diuretics (if required)
- Potassium–sparing agents

Avoid β-blockers except for specific cardiac indication

All agents potentiated by weight loss

RAAS Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), b-blockers, calcium channel blockers (CCBs), and thiazide diuretics are all effective in lowering BP in most obese patients. Although lowering BP is of paramount importance, studies suggest that antagonizing the RAAS system has special significance in obese patients .

As noted above, angiotensin is overexpressed in obesity, directly contributing to obesity-related hypertension, making the case to consider ACE inhibitors/ARBs as first-line agents. In comparison to ARBs or ACE inhibitors, b-blocker- and thiazide-based regimens increase insulin resistance and are associated with an increase in new cases of diabetes.

In contrast, regimens based on RAAS inhibition are associated with significantly fewer cases of new diabetes. This is of particular importance in the obese population, a group at heightened risk for the development of type 2 diabetes.

In addition, ACE inhibitors and ARBs have not been associated with weight gain or insulin resistance and provide renal protection in diabetes, a highly prevalent disease among obese persons.

Diuretics

Although thiazide diuretics are often recommended as first-line agents for the treatment of hypertension, their known dose-related side effects, which include dyslipidemia and insulin resistance, are undesirable in obese populations prone to the metabolic syndrome and type 2 diabetes.

This causes a therapeutic dilemma since obesity-related hypertension is salt-sensitive and diuretics will be required to control BP in most cases.

Many experts recommend low-dose thiazides (12.5 to 25 mg of hydrochlorothiazide or equivalent agent) along with close lipid and glucose monitoring.

If greater diuretic effect is required to control BP, the use of loop diuretics and/or the addition of potassium-sparing agents such as spironolactone, eplerenone, or amiloride should be considered, given the importance of aldosterone in obesity-related hypertension.

β-blockers

β-blockers have been shown to cause insulin resistance and have been closely associated with weight gain and higher body weights, as well as decreased diet-induced thermogenesis and fat oxidation rate.

The use of β-blockers should be limited to obese patients with specific CV indications such as postmyocardial infarction and heart failure. When β-blockers are indicated, agents with a vasodilating component such as carvedilol and nebivolol appear to have less weight gain potential and less of an impact on carbohydrate and lipid metabolism.

Although appropriate in heart failure, the protective effect of these agents with vasodilator effects postmyocardial infarction has not been definitively established

Calcium channel blockers

Calcium channel blockers are also effective in the treatment of obesity related hypertension and have not been associated with weight gain or adverse changes in lipids.

Treatment of resistant hypertension in obese patients

Data on how to treat obese patients with resistant arterial hypertension are scarce. In these patients, adding the mineralocorticoid antagonist spironolactone may be useful (in doses of 25 – 100 mg/day).

Remarkably, higher waist circumference has been associated with better response to spironolactone. These findings point to the special role of aldosterone in obesity- associated hypertension. Direct renin inhibition (aliskiren) may be an effective alternative treatment approach in obese hypertensive patients. However, the medication should be used with caution, particularly in combination with other renin – angiotensin system inhibitors or renal disease.

Recently, a large outcomes study testing aliskiren in combination with either angiotensin receptor blockade or angiotensin-converting enzyme inhibition in high-risk patients with diabetes mellitus was prematurely discontinued due to severe adverse effects.

Treatment of resistant hypertension in obese patients

Given the important role of the sympathetic nervous system in the pathogenesis of obesity-associated arterial hypertension and insulin resistance, central sympatholytic drugs are another treatment option for patients not responding to or not tolerating first-line antihypertensive drugs.

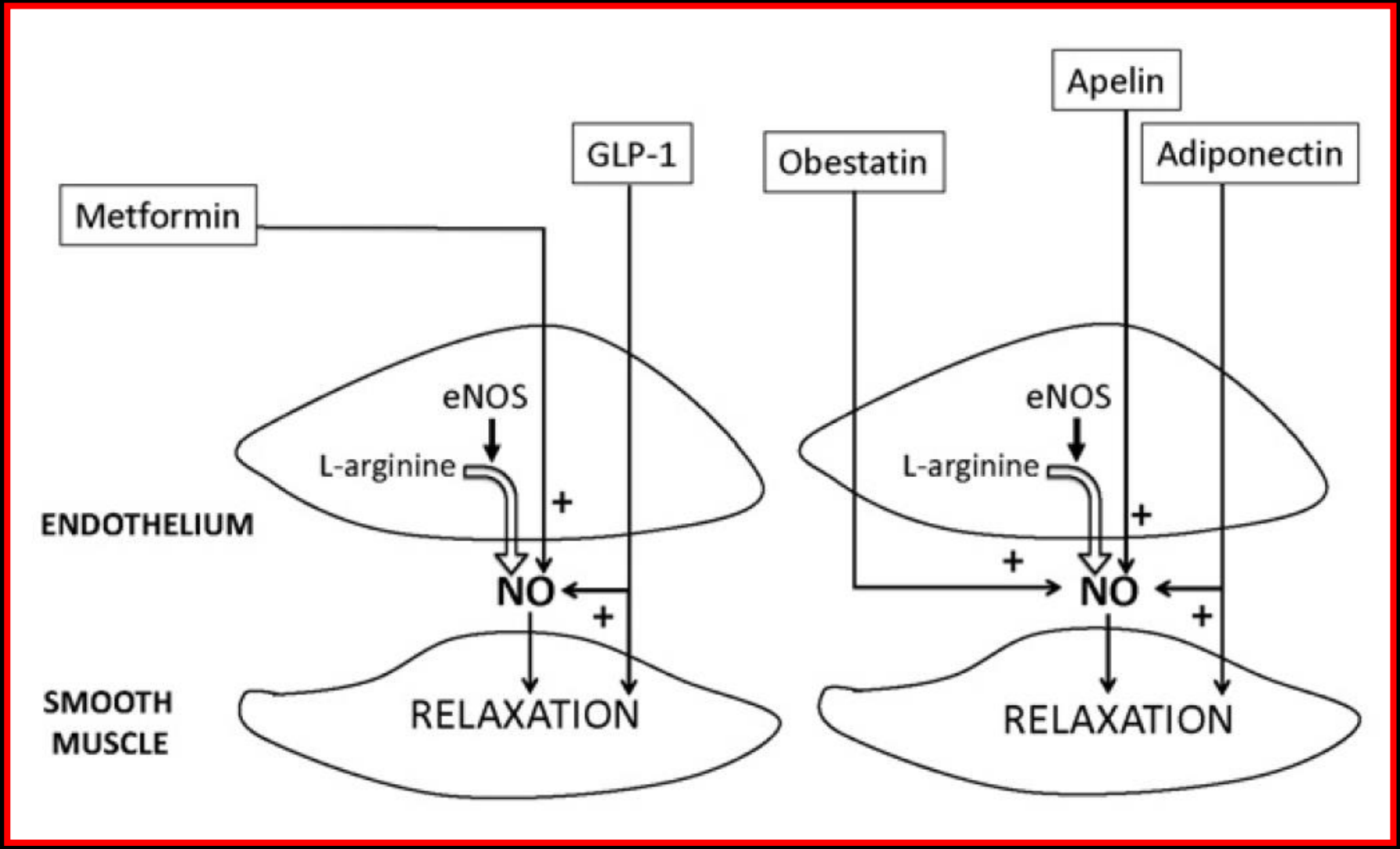
Treatment of resistant hypertension in obese patients

Renal sympathetic denervation through a novel catheter-based approach substantially reduced blood pressure in patients with treatment-resistant arterial hypertension with an average BMI of 31kg/m. The response may be mediated in part through ablation of renal afferent nerves decreasing centrally generated sympathetic activity. Renal sympathetic denervation may also improve glucose metabolism.

Another device-based approach is electrical baroreflex activation. The treatment requires surgical implantation of a pacemaker device and electrodes located at the level of the carotid sinus. Baroreflex activation therapy reduces blood pressure through sympathetic inhibition.

In a recent controlled clinical trial including treatment-resistant hypertensive patients with an average BMI of 32.4kg/m2, baroreflex activation therapy did not increase the proportion of patients achieving an at least 10 mmHg reduction in systolic blood pressure at month 6 (primary endpoint). However, the treatment increased the likelihood of achieving blood pressure control and showed promising effects on long-term blood pressure control. Clearly, both treatments need to be tested in larger clinical trials with hard endpoints.

Potential targets of drug treatments to improve vascular reactivity in patients with diabesity



Bariatric drugs

- Approved medications
  - Orlistat (Alli): causes fat malabsorption
  - Acarbose: causes sucrose malabsorption
  - Phenteramine (approved for short-term use only)
    - ↓ Appetite
    - ↑ Energy expenditure
  - Lorcaserin
    - ↓ Apetite
- Medications for diabetes that cause weight loss
  - Metformin (insulin sensitizer that ↓ hepatic glucose output and ↓ glucose absorption)
  - Incretin-based agents that ↑ insulin and ↓ glucagon secretion
    - GLP1 agonists: exenatide, liguratide
    - DPP-4 inhibitors: sitagliptin; saxagliptin; linagliptin
  - Pramlinatide (amytin congener)
    - Suppresses appetite: delays gastric emptying; increases satiety
- Combination agents
  - Phentermine/topiramate (Qnexa, Qsymia)
  - Naltrexone/bupropion (investigational)

Bariatric surgery

Bariatric surgeries affect or restrict the flow of food through the gastrointestinal tract. Restrictive surgical procedures, such as laparoscopic-adjustable gastric banding (LAGB), induce earlier satiety by decreasing the volume of the stomach. The Roux-en-Y gastric bypass (RYGB) involves both restriction of the stomach and bypass of the small bowel. The sleeve gastrectomy, in which the fundus of the stomach is removed, is becoming increasingly popular. However, RYGB and LAGB remain the most broadly used surgical treatments for morbid obesity and associated conditions, including obesity-related hypertension .

In an extensive meta-analysis of 136 studies, Buchwald and colleagues evaluated the impact of bariatric surgery on weight loss and obesity-related comorbidities including diabetes and hypertension.

The mean percentage of excess weight loss was 61.2% for all patients. Diabetes resolved in 76.8% of patients and resolved or improved in 86.0%, whereas hypertension resolved in 61.7% of patients and resolved or improved in 78.5%.

Annales Pharmaceutiques Françaises (2012) xxx, xxx–xxx

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THEMATIC SESSION: DIABESITY AND CARDIO-CEREBROVASCULAR DISEASES

Drug treatments to restore vascular function and diabesity☆

Restauration pharmacologique de la fonction vasculaire et diabésité

C. Cardillo*

Department of Internal Medicine, Catholic University Medical School, Rome, Italy

…In recent years, surgeons have been unexpectedly challenging physicians in the treatment of diabesity….

Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes

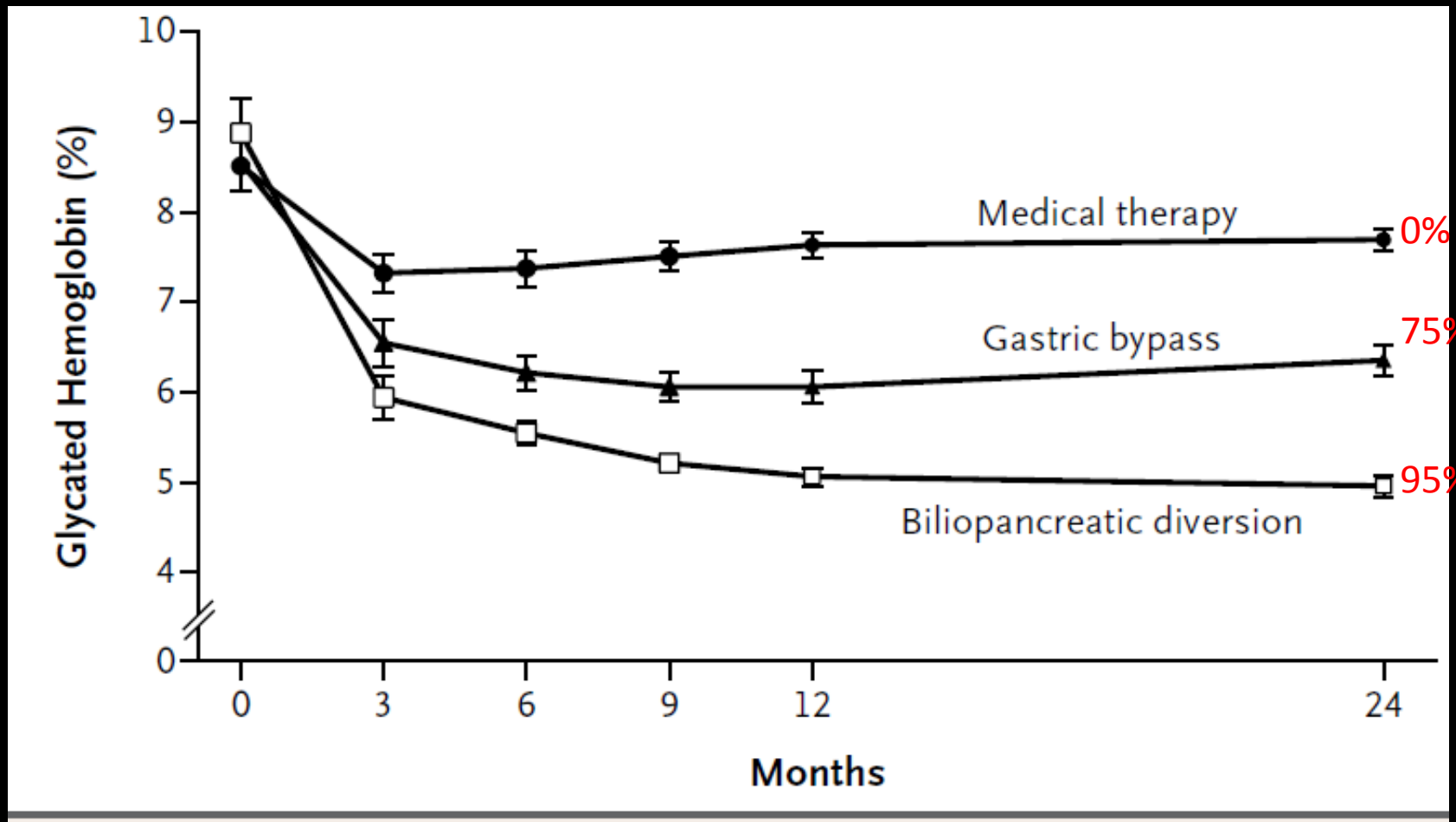


Figure 2. Glycated Hemoglobin Levels during 2 Years of Follow-up.

Mingrone et al, NEJM, 2012

Can Diabetes Be Surgically Cured?

Long-Term Metabolic Effects of Bariatric Surgery in Obese Patients with Type 2 Diabetes Mellitus

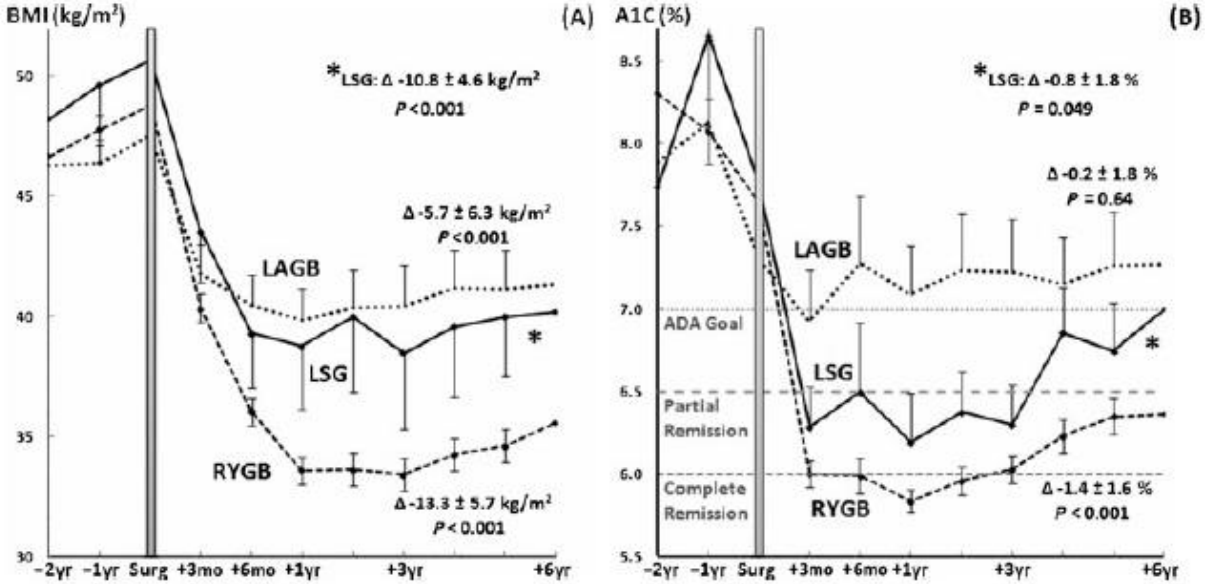


FIGURE 1. Changes in BMI (A) and A1C (B) according to procedure type. Δ: Mean ± SD at the last follow-up point—baseline at time of surgery.

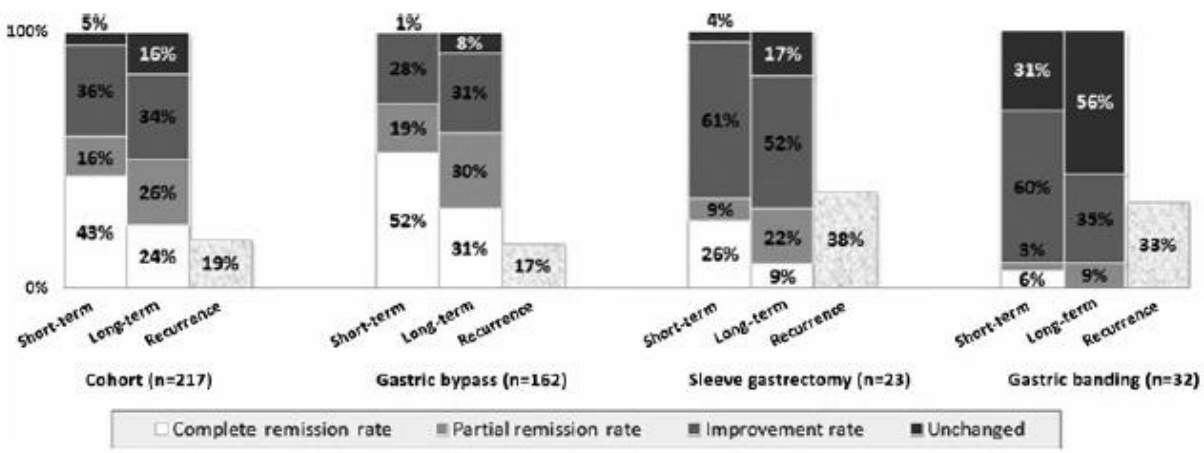


FIGURE 2. Short- and long-term diabetes remission and recurrence rates according to procedure type.

Brethauer et al., 2013

Blood Pressure, 2012; Early Online: 1–7

informa
healthcare

REVIEW ARTICLE

Obesity-related hypertension and its remission following gastric bypass surgery – A review of the mechanisms and predictive factors

SIMON TIMOTHY ADAMS, MOHAMED SALHAB, ZEIAD IHSAN HUSSAIN, GLENN V. MILLER & STEPHEN H. LEVESON

Department of General Surgery, York Hospital, Wigginton Road, York YO318HE, UK

REVIEW

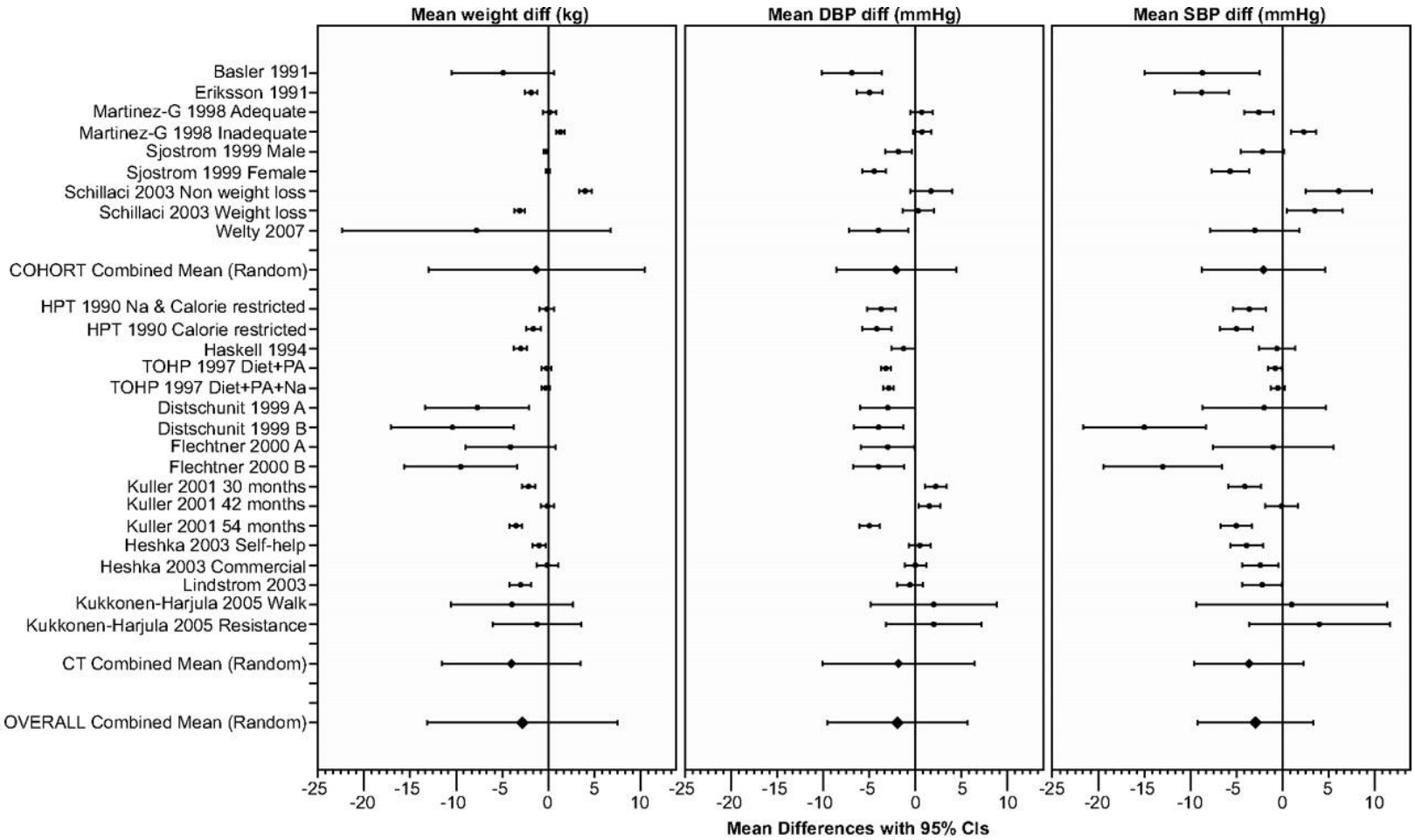
Bariatric Surgery

A Systematic Review and Meta-analysis

…Effective weight loss was achieved in morbidly obese patients after undergoing bariatric surgery.
A substantial majority of patients with diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea experienced complete resolution or improvement…

Buchwald H et al, JAMA, 2004

Figure. Forest plot of mean differences in weight and diastolic and systolic blood pressure at follow-up of at least 2 years.



Refer to Supplementary Tables S1 and S2 for specific details of each sub-group
Random: Random Effect model (heterogeneity): PA: physical activity; Na: sodium restricted

Aucott L et al. Hypertension 2009;54:756-762

American Heart Association.

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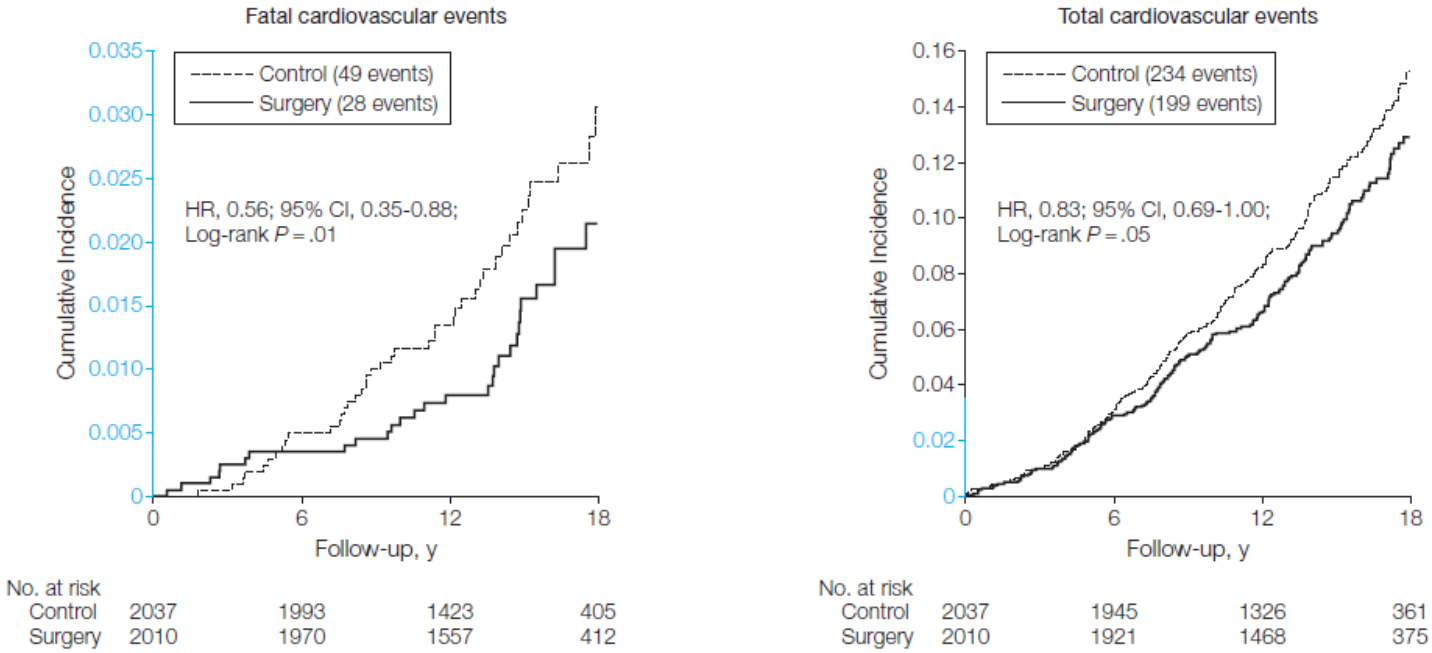
Bariatric Surgery and Long-term Cardiovascular Events

Figure 2. Kaplan-Meier Unadjusted Cumulative Incidence of Fatal and Total Cardiovascular Events in the Control and Surgery Groups of the Swedish Obese Subjects Study



The combined end point of myocardial infarction and stroke, whichever came first, with fatal cardiovascular events and total (fatal and nonfatal) cardiovascular events are shown. The incidence data are based on observations until December 31, 2009. Follow-up time is truncated at 18 years, because number of persons at risk beyond this point was low. All persons are included in the calculation of hazard ratios (HRs). The incidence rates per 1000 person-years for fatal cardiovascular events were 0.9 (95% CI, 0.6-1.3) in the surgery group and 1.7 (95% CI, 1.3-2.2) in the control group; and for total cardiovascular events, 6.9 (95% CI, 6.0-8.0) and 8.3 (95% CI, 7.3-9.4), respectively. Y-axis regions shown in blue indicate range from 0 to 0.035.

Factors associated with the resolution of hypertension following Roux-en-Y gastric bypass

Resolution of hypertension	
Positive correlation	Negative correlation
↓age	↓weight loss Afro-Caribbean ethnicity ↑Duration of hypertension Concomitant diabetes mellitus

Frontline Pharmacist

Hypertension and diabetes mellitus medication management in sleeve gastrectomy patients

…Patients experience progressive and drastic reduction of the dose of anti-hypertensive agents after sleeve gastrectomy…

Bland CM, Am J Health-Syst Pharma, 2013

Treatment of hypertension in obese patients after bariatric surgery (1)

….Literature regarding medication adjustment strategies and outcomes for bariatric patients is limited, especially for sleeve gastrectomy patients. Hypoglycemia in the acute postoperative period is well described for RYGB patients while data for sleeve gastrectomy patients are limited. Hypotension is also a concern, as many patients take multiple antihypertensives preoperatively and have limited fluid intake in the immediate postoperative period. Patients in the early postoperative period have difficulty adhering to fluid goals, which increases the risk for dehydration and hypotension…..

Bland CM, Am J Health-Syst Pharma, 2013

Treatment of hypertension in obese patients after bariatric surgery (2)

…When adjustments to antihypertensive medications are necessary, diuretics should be the first medication class to be withheld to limit volume depletion and hypotension after surgery.

Beta-blockers were continued after surgery for perioperative b-blockade….

Bland CM, Am J Health-Syst Pharma, 2013

L'IPERTENSIONE ARTERIOSA NEL PAZIENTE OBESO

Raccomandazioni Congiunte
della Società Italiana Ipertensione Arteriosa (SIIA)
e della Società Italiana Obesità (SIO)
2014

Riccardo Sarzani, Cesare Cuspidi, Maurizio Castellano, Ferruccio Galletti, Anna Maria Grandi, Lelio Morricone, Fabrizio Pasanisi, Marco Rossato, Guido Salvetti

a nome dei comitati direttivi della SIIA e della SIO

Conclusions

- Obesity-related hypertension is an important public health issue.
- As the prevalence of obesity increases, the prevalence of hypertension with its associated CV risk will increase as well.
- While primary and even primordial prevention is the long-term goal for diminishing the prevalence of obesity, control of both obesity and hypertension in the population at risk is the overriding current challenge.
- Treating hypertension in the obese requires addressing the obesity as part of the therapeutic plan.
- Lifestyle management is required in every case, with a focus on weight loss and risk reduction. Some have likened the treatment of obesity with caloric restriction alone to the treatment of hypertension with sodium restriction: it works if extreme enough, but it is not a feasible long-term strategy.
- In most patients, additional therapies including medications, aggressive diet counseling and behavioral techniques, and sometimes bariatric surgery will be required.

…bariatric surgery cannot be considered a universal panacea due to some serious shortcomings, such as the requirement for specialist surgeons and a not-inconsiderable perioperative mortality, are driving researchers to investigate the prospects for new treatments to provide the desired effects without operative risks….

Cardillo C, Ann Pharm Fr, 2012

Timeo chirurgos et dona ferentes !

Prof. Antonio Girolami, 1984, CdL M&C, III-IV a, Patologia Speciale Medica

Pieter Claesz. Soutman (1593/1601) - Laocoön and his sons being strangled by serpents

Non timeo chirurgos quia dona ferentes …nonnumquam !

2014,Incontro Congiunto SICOb – SID - SIO

Pieter Claesz. Soutman (1593/1601) - Laocoön and his sons being strangled by serpents

Obesity and Stroke

- Hypertension and Stroke
- Obesity and Hypertension Prevalence
  - 35% of obese have hpt
  - 17% of desirable BMI have hpt
- Diagnostic Criteria
  - systolic BP > 140 or
  - diastolic BP > 90

Hypertension

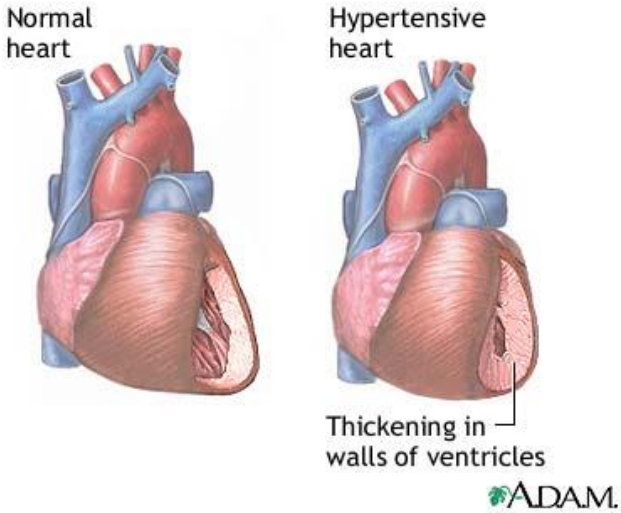
The Dangers

Failure to find and treat HTN is serious, as untreated HTN can cause:

- The heart to get larger, which may lead to heart failure.
- Small bulges (aneurysms) to form in blood vessels.
- Blood vessels in the kidney to narrow, which may lead to kidney failure.
- Arteries in the body to harden faster, especially those in the heart, brain, kidneys, and legs. This can cause a heart attack, stroke, kidney failure, or can lead to amputation of part of the extremities.
- Blood vessels in the eye to burst or bleed. This may cause vision changes and can result in blindness.

Hypertension

- Blood pressure is often increased in overweight individuals.
- Estimates suggest that control of overweight would eliminate 48% of the hypertension in Caucasians and 28% in African Americans.
- Overweight and hypertension interact with cardiac function, leading to thickening of the ventricular wall and larger heart volume, and thus to a greater likelihood of cardiac failure.



J La State Med Soc .2005; 157 (1): S42-49.

STRATIFICAZIONE DEL RISCHIO

ESH-ESC 2003

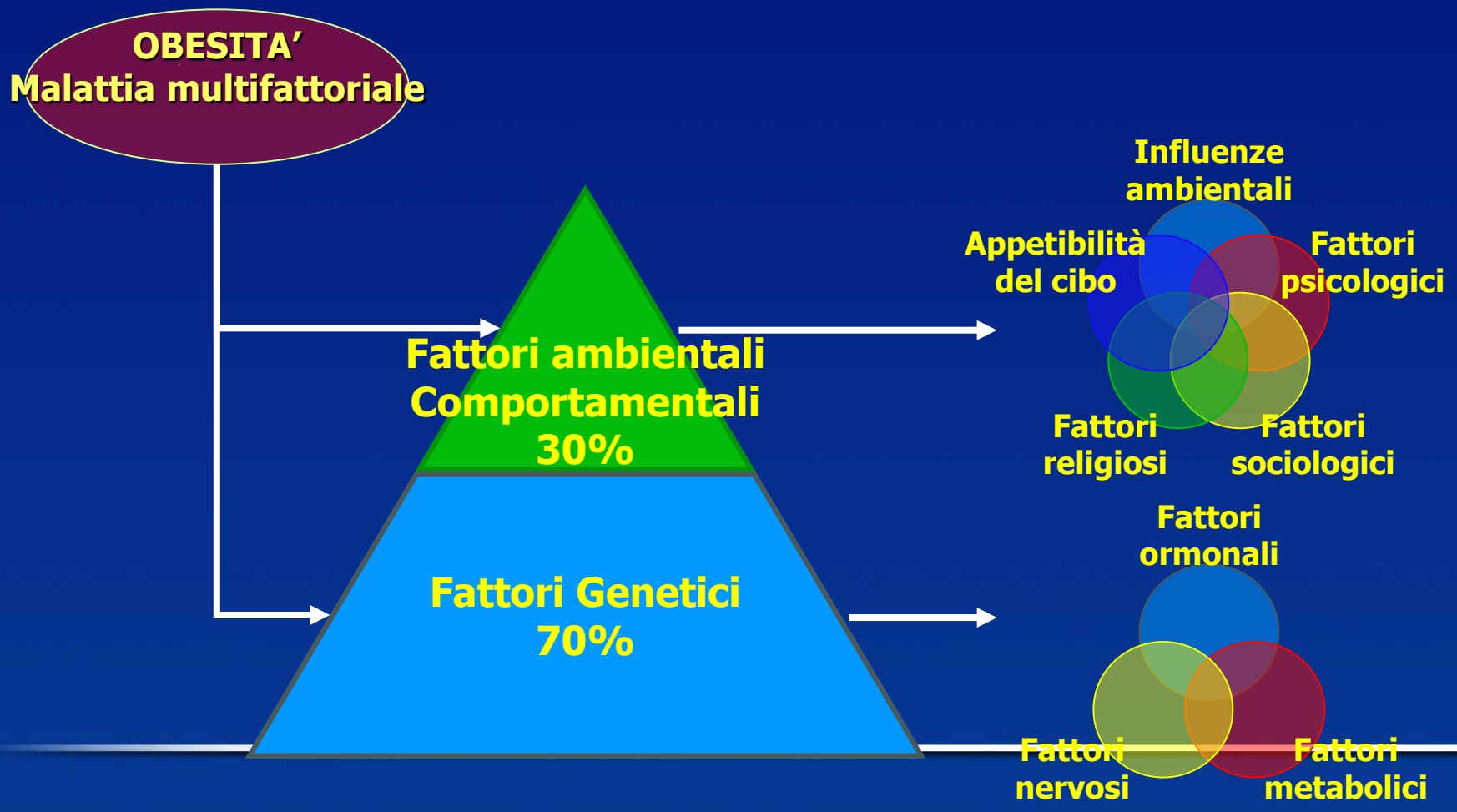
Altri fattori di rischio o riscontro di malattia	PRESSIONE ARTERIOSA				
	Normale PAS 120-129 PAD 80-84	Normale-alta PAS 130-139 PAD 85-89	Grado I PAS 140-159 PAD 90-99	Grado II PAS 160-179 PAD 100-109	Grado III PAS ≧ 180 PAD ≧ 110
I. Nessun fattore di rischio aggiunto	RISCHIO NELLA MEDIA	RISCHIO NELLA MEDIA	RISCHIO AGGIUNTIVO BASSO	RISCHIO AGGIUNTIVO MODERATO	RISCHIO AGGIUNTIVO ELEVATO
II. 1-2 fattori di rischio	RISCHIO AGGIUNTIVO BASSO	RISCHIO AGGIUNTIVO BASSO	RISCHIO AGGIUNTIVO MODERATO	RISCHIO AGGIUNTIVO MODERATO	RISCHIO AGGIUNTIVO MOLTO ELEVATO
III. 3 o piu' fattori di rischio o TOD o diabete	RISCHIO AGGIUNTIVO MODERATO	RISCHIO AGGIUNTIVO ELEVATO	RISCHIO AGGIUNTIVO ELEVATO	RISCHIO AGGIUNTIVO ELEVATO	RISCHIO AGGIUNTIVO MOLTO ELEVATO
IV. CCA	RISCHIO AGGIUNTIVO ELEVATO	RISCHIO AGGIUNTIVO MOLTO ELEVATO	RISCHIO AGGIUNTIVO MOLTO ELEVATO	RISCHIO AGGIUNTIVO MOLTO ELEVATO	RISCHIO AGGIUNTIVO MOLTO ELEVATO

TOD: danno d'organo bersaglio – CCA: condizioni cliniche associate – AGG.: aggiuntivo alla pressione

J Hypertension 2003,21:1011-1053

PRESSIONE ARTERIOSA NORMALE: < 140/90 MM HG

Eziopatogenesi dell'Obesità



Low-Salt Diets

Salt sensitivity is commonly associated with obesity. Salt restriction decreases the risk of hypertension with or without weight loss as well as reducing the incidence of CV events. In the **Hypertension Prevention Trial**, participants with DBP 78 to 89 mm Hg were followed for 3 years after being randomized to one of five groups: control, decreased energy intake, decreased sodium intake, decreased sodium and energy intake, or decreased sodium and increased potassium intake. BP decreased in all groups, with the greatest decrease in patients assigned to reduced energy only. The groups with reduced sodium intake had a significantly lower rate of hypertension. *Arch Intern Med. 1990.*

In the **Trials of Hypertension Prevention (TOHP) phase I study**, (135) participants with high normal BP were randomized to one of four groups for 18 months: control, weight loss, sodium restriction, or stress management. In the weight reduction group, weight decreased by 3.9 kg and BP by 2.9/2.3 mm Hg. Sodium restriction resulted in a decrease in BP of 1.7/2.9 mm Hg. Seven years later, the odds ratio for hypertension among 181 participants was lower by 77% with weight loss and 35% with sodium restriction. *Am J Clin Nutr. 1997*.

Phase II of TOHP examined the effects of weight loss, sodium restriction, or both on BP and the incidence of hypertension (136(137). At 6, 18, and 36 months, weight loss favored the weight reduction intervention over usual care, although weight loss was attenuated over time, and change in BP showed a similar pattern. In the sodium reduction group, a decrease in BP was greater at each time point and also became attenuated with time, from 5.1/4.4 mm Hg at 6 months to 0.7/3.0 mm Hg at 3 years. *Ann Intern Med. 2001.*

The **Trial of Nonpharmacologic Interventions in the Elderly (TONE)** study (138) investigated weight loss and salt restriction and the need for antihypertensive drugs in treated hypertensive patients during follow-up to a median of 29 months. Weight reduction, sodium restriction, and the combination of both were compared with usual care in obese participants. The relative hazard ratio was 0.60 for reduced sodium alone, 0.64 for weight loss alone, and 0.47 for the combined intervention. The within-groups rate of adverse events was similar. *Arch Intern Med 2001*

Long-Term Effects of Lifestyle

Although limited data are available, a few interventions and meta-analyses report long-term benefits associated with improvements in lifestyle, especially in at-risk populations.

In 10- to 15-year follow-up of prehypertensive adults who took part in the TONE studies, the risk of a CV event was lower by 25% to 30% in those who had been assigned to the salt-restricted group.

In adults at risk for diabetes, a program of diet and physical activity reduced the risk of diabetes by 58%, with size of the decrease related to the extent of change in lifestyle.

In adults with impaired glucose tolerance, a program of diet and physical activity was more effective for the prevention of diabetes than either metformin or usual care, with respective incidence rates per 100 person-years of 4.8, 7.8, and 11.

Treatment of Hypertension in the Obese
BP Thresholds and Targets (1)

As hypertension progresses, the risk of death from ischemic heart disease or stroke (beginning with a normal BP of 115/75 mm Hg) doubles with each increment of 20 mm Hg in SBP or 10 mm Hg in DBP across the entire BP range from 115/75 mm Hg to 185/115 mm Hg.

Individuals in the general population with a SBP of 120 to 139 mm Hg or a DBP of 80 to 89 mm Hg are considered prehypertensive and require lifestyle modification to prevent CVD. Patients with prehypertension are at twice the risk of developing hypertension as those with normal BP.

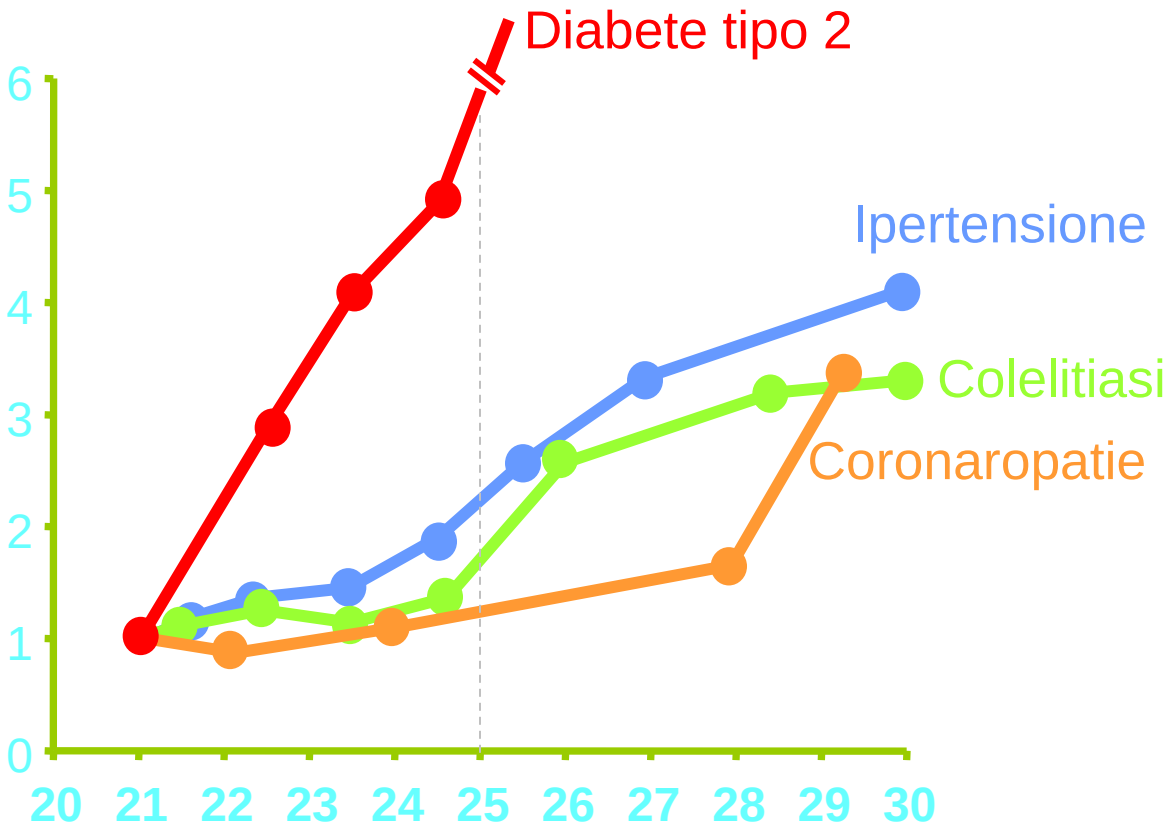
Stage 1 hypertension is defined as SBP between 140 and 159 mm Hg or DBP between 90 and 99 mm Hg.

Stage 2 hypertension is defined as SBP 160 mm Hg or DBP 100 mm Hg.

To reduce the incidence of CV and renal complications, target BPs for the general population should be <140/90 mm Hg and for patients with established diabetes or chronic kidney disease <130/80 mm Hg, but there is limited evidence in support of this lower threshold.

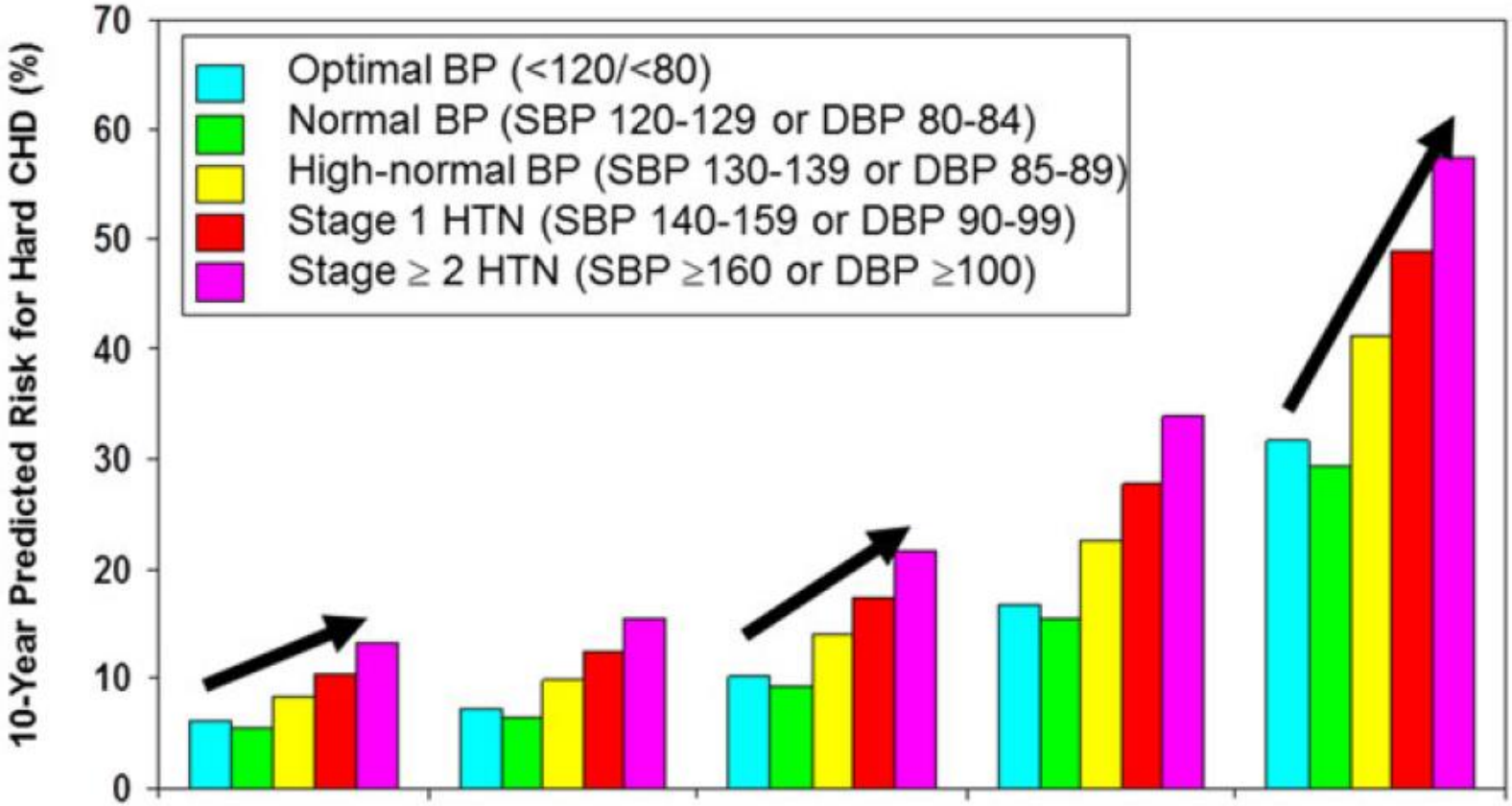
Relazione tra BMI e rischio relativo di:

DIABETE TIPO 2, IPERTENSIONE, COLELITIASI E CORONAROPATIE



Willet et al, N Engl J Med, 1999

Predicted 10-year risk for hard coronary heart disease events for a 50-year-old man with selected levels of risk factors and blood pressure (BP) stages



Total Chol	200	250	250	250	250
HDL-Chol	50	50	35	35	35
Diabetes	-	-	-	+	+
Smoking	-	-	-	-	+