

**GIMBE**<sup>®</sup>

Gruppo Italiano per la Medicina Basata sulle Evidenze

Evidence-Based Medicine Italian Group

*Workshop*  
**Decisioni Cliniche e  
Prove di Efficacia**

Seconda Edizione

*Riccione, 26-27 marzo 2004*



**Workshop Clinici Interattivi (5)**  
**Sindrome metabolica e  
rischio cardiovascolare**

**La strada passa sempre per il diabete?**

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Discussant

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# Scenario Clinico (1)

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- La signora Giovanna è un'impiegata alle poste di 42 anni, sposata con due gemelli, in buone condizioni generali.
- In sovrappeso dall'adolescenza, con pregressa diagnosi di sindrome dell'ovaio policistico, ha recentemente riscontrato una lieve iperglicemia a digiuno.
- 5 anni prima lieve diabete gestazionale (trattato con sola dieta), in corso di gravidanza gemellare ottenuta dopo stimolo farmacologico.

# Scenario Clinico (1)

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## Anamnesi familiare

- Madre obesa, ipertesa, dislipidemica (deceduta a 75 anni per ictus).
- Padre deceduto a 58 anni per infarto del miocardio.
- Familiarità per diabete tipo 2.

# Scenario Clinico (1)

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## Anamnesi fisiologica

- Menarca a 11 anni, con cicli successivi molto irregolari.
- Prolungata assunzione di estroprogestinici, interrotta 3 anni fa. Attualmente in amenorrea.
- Attività fisica scarsa, alimentazione regolare, fuma 10-15 sigarette al dì e non beve alcolici.

# Scenario Clinico (1)

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## Obiettivamente

- BMI 29.7. kg/m<sup>2</sup>, circonferenza vita 91 cm
- Irsutismo di grado lieve-moderato, lieve epatomegalia.
- PAO 135/88 mmHg.

# Dati di laboratorio (1)

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## Profilo metabolico basale

- Glicemia 112 mg/dl
- Colesterolo totale 221 mg/dl
- HDL-colesterolo 42 mg/dl
- Trigliceridi 187 mg/dl
- LDL-colesterolo 141 mg/dl
- Insulinemia 22 mU/l

## OGTT

- Glicemia 120 min 176 mg/dl

# Indagini strumentali (1)

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## **Ecografia addome e pelvi**

- Fegato lievemente ingrandito, steatosico; ovaie di volume lievemente aumentato, con multipli piccoli follicoli alla periferia.

## **ECG**

- Nella norma

## **Ecodoppler TSA**

- Lievi ispessimenti intimali bilaterali

# CLINICAL QUESTIONS





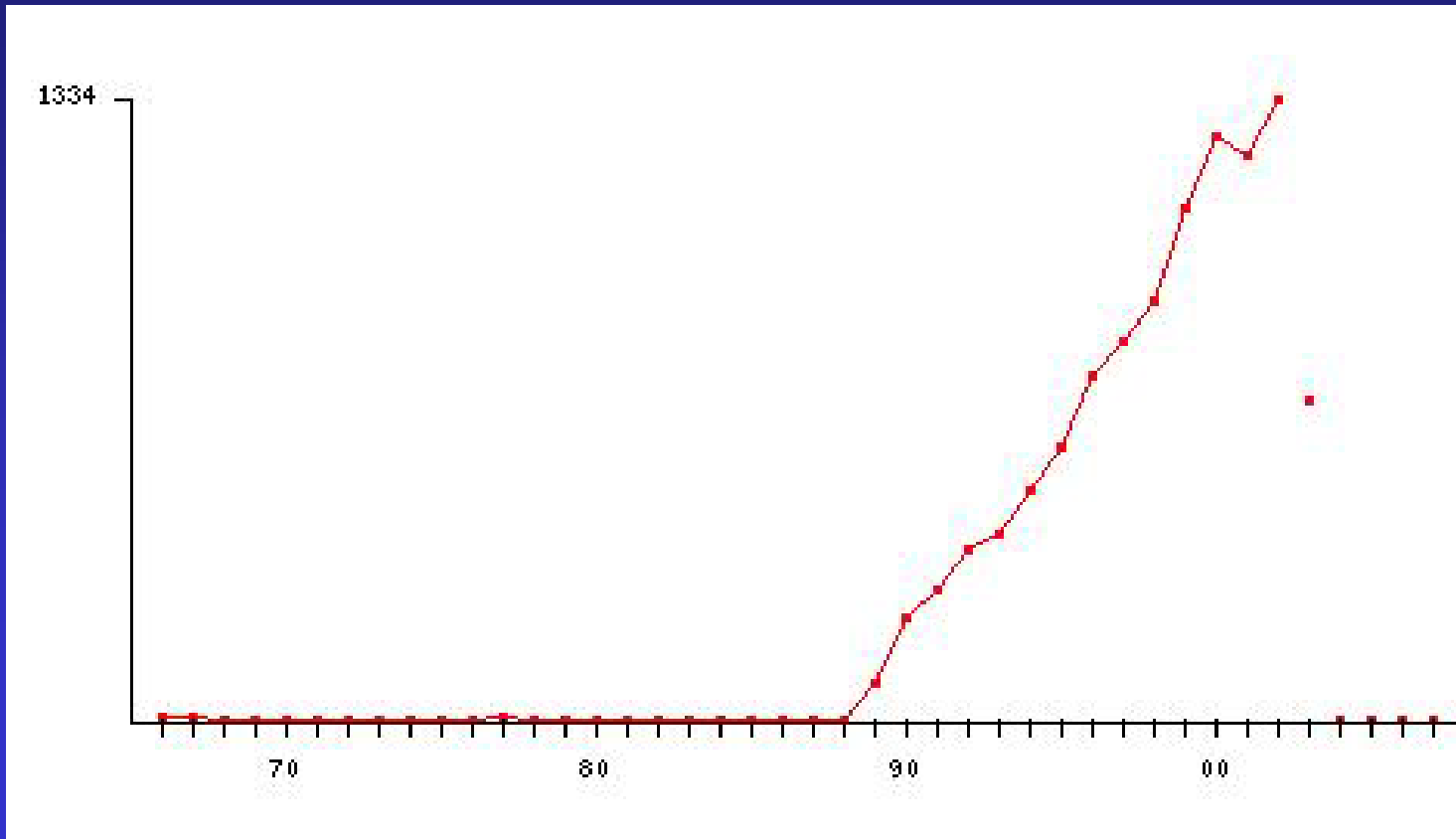
## 5. Sindrome Metabolica e rischio cardiovascolare.

### A. Quale tra i seguenti, non rientra tra i criteri diagnostici della sindrome metabolica?

1. Circonferenza addominale
2. Trigliceridi
3. LDL
4. HDL
5. Pressione arteriosa
6. Glicemia a digiuno

# MEDLINE

"Metabolic Syndrome X"[All] OR "Metabolic Syndrome"[ti]: 1210 articoli



# Metabolic Syndrome

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Two recent events have focused the attention of the medical community on the metabolic syndrome

1. The inclusion of the syndrome in the recently published ATP III guidelines
2. The creation of an ICD 9 diagnostic code (277.7) which makes reimbursement for treating the syndrome possible

*Hill JO, et al. Arch Intern Med 2003*

*Alexander CM*

**The Coming of Age of  
the Metabolic Syndrome**

*Diabetes Care, November 1, 2003*

*Davidson MB*

**Metabolic Syndrome/Insulin  
Resistance Syndrome/Pre-Diabetes.  
New section in Diabetes Care**

*Diabetes Care. 2003 Nov;26(11):3179*

# MEDLINE

"Metabolic Syndrome X"[All] OR "Metabolic Syndrome"[ti]: **1210 articoli**

- 464 Review, Editoriali, Lettere
- 46 Clinical trial
- 24 Randomized controlled trials

# Sindrome metabolica

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- **1983.** The clustering of the atherosclerotic risk factors that identify the metabolic syndrome was first recognized.
- **1988. Reaven** introduced the term syndrome X, with insulin resistance (IR) as a common denominator.
- **1988-1998.** Other **synonyms:** multiple metabolic syndrome, IR syndrome, deadly quartet, DROP syndrome (Dyslipidemia, iR, Obesity, and high blood Pressure).

# Sindrome metabolica

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- **1998.** The **WHO** recommended a unifying definition and chose the term metabolic syndrome, because current data did not establish IR as the cause of all components of the syndrome.
- **2001.** The **ATP III** (NIH) define the metabolic syndrome as a new secondary target for cardiovascular risk reduction therapy beyond LDL cholesterol lowering
- **2003.** Position statement of **ACE/AACE** (a back step?)



*American Heart Association  
National Heart, Lung, and Blood Institute.*

## **Definition of metabolic syndrome**

Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition.

*Circulation 2004;109:433-8.*

# Sindrome metabolica: quali criteri diagnostici?

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- **1988.** WHO
- **2001.** ATP III
- **2003.** ACE/AACE

# Sindrome metabolica: quali criteri diagnostici?

**TABLE 1. ATP III Clinical Identification of the Metabolic Syndrome**

Risk Factor	Defining Level
Abdominal obesity, given as waist circumference*†	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL‡

# Sindrome metabolica: quali criteri diagnostici?

**TABLE 2. WHO Clinical Criteria for Metabolic Syndrome\***

Insulin resistance, identified by 1 of the following:

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance
- or for those with normal fasting glucose levels ( $<110$  mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions

Plus any 2 of the following:

- Antihypertensive medication and/or high blood pressure ( $\geq 140$  mm Hg systolic or  $\geq 90$  mm Hg diastolic)
- Plasma triglycerides  $\geq 150$  mg/dL ( $\geq 1.7$  mmol/L)
- HDL cholesterol  $< 35$  mg/dL ( $< 0.9$  mmol/L) in men or  $< 39$  mg/dL (1.0 mmol/L) in women
- BMI  $> 30$  kg/m<sup>2</sup> and/or waist:hip ratio  $> 0.9$  in men,  $> 0.85$  in women
- Urinary albumin excretion rate  $\geq 20$   $\mu$ g/min or albumin:creatinine ratio  $\geq 30$  mg/g

NHLBI/AHA, 2004

# Sindrome metabolica: quali criteri diagnostici?

**TABLE 3. AACE Clinical Criteria for Diagnosis of the Insulin Resistance Syndrome\***

Risk Factor Components	Cutpoints for Abnormality
Overweight/obesity	BMI $\geq$ 25 kg/m <sup>2</sup>
Elevated triglycerides	$\geq$ 150 mg/dL (1.69 mmol/L)
Low HDL cholesterol	
Men	<40 mg/dL (1.04 mmol/L)
Women	<50 mg/dL (1.29 mmol/L)
Elevated blood pressure	$\geq$ 130/85 mm Hg
2-Hour postglucose challenge	>140 mg/dL
Fasting glucose	Between 110 and 126 mg/dL
Other risk factors	Family history of type 2 diabetes, hypertension, or CVD Polycystic ovary syndrome Sedentary lifestyle Advancing age Ethnic groups having high risk for type 2 diabetes or CVD

\*Diagnosis depends on clinical judgment based on risk factors.

NHLBI/AHA, 2004

# Sindrome metabolica: quali criteri diagnostici?

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- **1988. WHO**
  - Requires: glucose tolerance testing, insulin concentration measurements, microalbuminuria testing.
- **2001. NHBLI. ATP III**
  - Easier to use in clinical practice
- **2003. ACE/AACE.**
  - Hybrid (WHO, ATP III)
  - No defined number of risk factor is specified
  - Diagnosis is left to clinical judgment

*National Heart, Blood and Lung Institute*

**Third Report of the Expert Panel on  
Detection, Evaluation, and Treatment  
of High Blood Cholesterol in Adults  
(Adult Treatment Panel III)**

*JAMA 2001;285:2486-97*

# ATP III

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- 1. LDL cholesterol:** the primary target of therapy
2. Benefit beyond LDL lowering: the **metabolic syndrome** as a secondary target of therapy

*NHBLI. ATP III. JAMA 2001*



# Metabolic Syndrome

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- A constellation of lipid and non-lipid risk factors of metabolic origin, closely linked to a generalized metabolic disorder called insulin resistance
- The risk factors of the metabolic syndrome enhance risk for CHD at any given LDL cholesterol level.

*NHBLI. ATP III. JAMA 2001*

# Sindrome Metabolica: criteri ATP III

Diagnosis is made when 3 or more of the risk are present

Risk Factor	Defining Level
• Abdominal obesity* (waist circumference)†	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
• Triglycerides	≥150 mg/dL
• High-density lipoprotein cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
• Blood pressure	≥130/≥85 mm Hg
• Fasting glucose	≥110 mg/dL

*Ford ES, Giles WH.*

**A comparison of the prevalence of  
the metabolic syndrome using two  
proposed definitions**

*Diabetes Care 2003;26:575-81*

## RESULTS

- Among 8608 participants aged  $\geq 20$  years, the age-adjusted prevalence was 23.9% using the ATP III definition and 25.1% using the WHO definition.
- Among all participants, 86.2% were classified as either having or not having the metabolic syndrome under both definitions.

## CONCLUSIONS

- A universally accepted definition of the metabolic syndrome is needed.

**TABLE 4. Impact on Prevalence of Metabolic Syndrome if Impaired Glucose Tolerance Plus 2 or More Risk Factors Is Added to the National Cholesterol Education Program Definition\***

Demographic Characteristics	% Meeting Current National Cholesterol Education Program Definition	% Meeting Revised Definition
Overall	37.9	43.5
Race/ethnicity		
Non-Hispanic white	38.2	43.6
Non-Hispanic black	34.6	38.9
Mexican American	43.5	53.4
Other	35.9	43.1
Age group, y		
50–59	30.6	36.5
60–69	41.5	48.1
70–79	42.6	48.4
80+	43.3	43.3

\*Data derived from NHANES III. Data analysis provided by Dr Steven Haffner.

# Metabolic Syndrome

Risk Factor	Defining Level
• Abdominal obesity* (waist circumference)†	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
• Triglycerides	≥150 mg/dL
• High-density lipoprotein cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
• Blood pressure	≥130/≥85 mm Hg
• Fasting glucose	≥110 mg/dL

**Sig.ra Letizia**

**89 cm**

**187 mg/dL**

**42 mg/dL**

**135/88 mmHg**

**112 mg/dL**

# Issue of Oral Glucose Tolerance Test

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- Both WHO and AACE include IGT, detected by oral glucose tolerance test (OGTT) or 2-hour postglucose challenge, among the risk factors for metabolic syndrome.
- ATP III did not include it because of the added inconvenience and cost of OGTT in clinical practice.
- Its added value for CVD risk prediction appears small.
- Several conference participants suggested adding OGTT at the physician's discretion in nondiabetic patients with ATP III–defined metabolic syndrome or  $\geq 2$  metabolic risk factors

# Diagnosi

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## Sindrome metabolica

(discreta insulinoresistenza, sovrappeso, IGT, lieve dislipidemia, valori pressori borderline),  
in paziente con sindrome dell'ovaio policistico



## 5. Sindrome Metabolica e rischio cardiovascolare.

**B. Utilizzando i criteri ATP III, quale percentuale della popolazione generale, ritieni sia affetta da sindrome metabolica?**

1. < 10%
2. 11-20%
3. 21-30%
4. > 30%

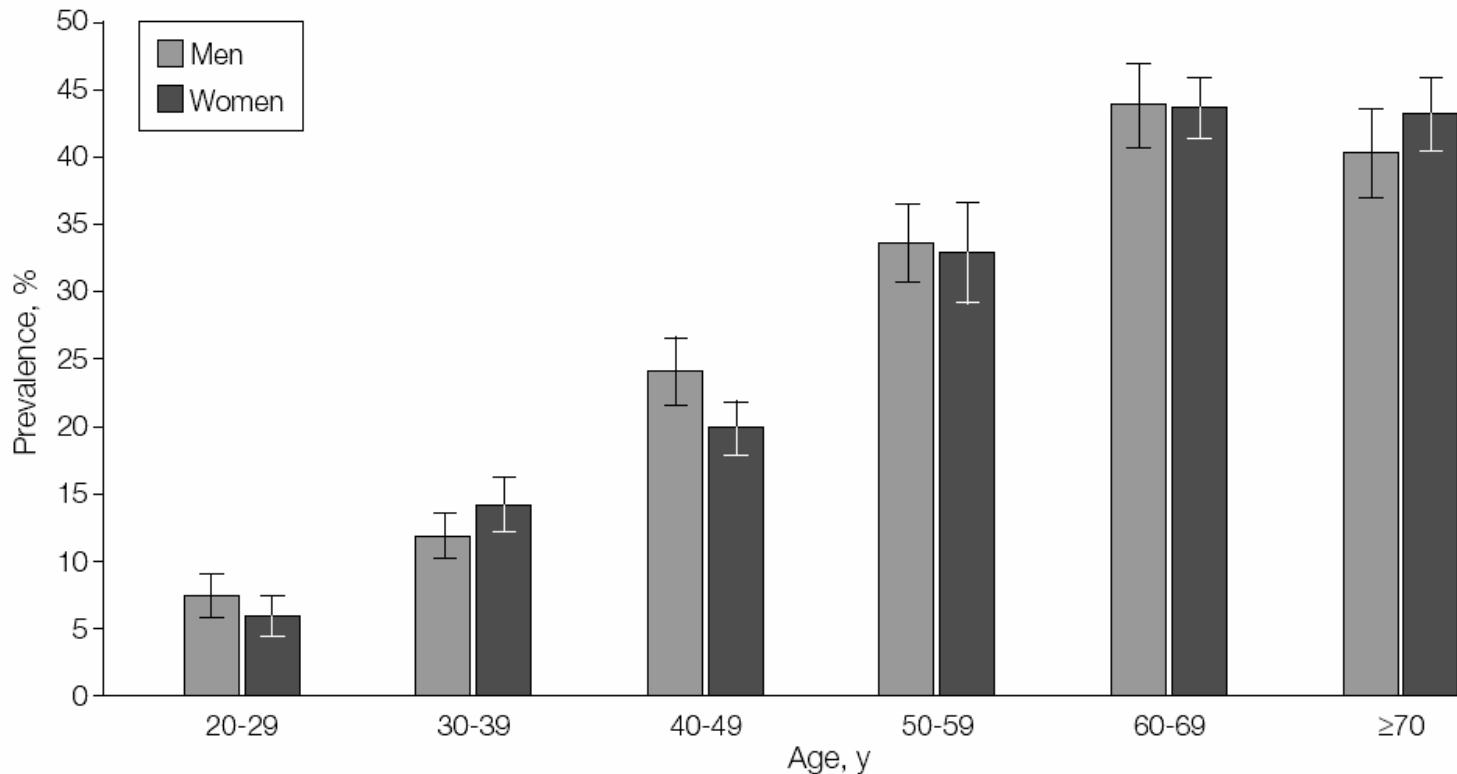
*Ford ES, Giles WH, Dietz WH.*

**Prevalence of the metabolic  
syndrome among US Adults.  
Findings from the third National Health  
and Nutrition Examination Survey**

*JAMA 2002;287:356-359*

# Age-adjusted prevalence of the MS= 23.7%

**Figure 1.** Age-Specific Prevalence of the Metabolic Syndrome Among 8814 US Adults Aged at Least 20 Years, by Sex, National Health and Nutrition Examination Survey III, 1988-1994



## C. Qual è il trattamento di prima scelta per la sig.ra Giovanna?

1. Estroprogestinici
2. Metformina
3. Modificazioni dello stile di vita
4. Antiandrogeni

# Sindrome metabolica: quali obiettivi terapeutici

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- 1. To reduce underlying causes (ie, obesity and physical inactivity)**
2. To treat associated risk factors (nonlipid and lipid)

*NHBLI. ATP III. JAMA 2001*

# Sindrome metabolica: la riduzione del peso

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- Weight reduction will enhance LDL lowering and reduce all of the risk factors of the metabolic syndrome.

**Weight reduction is a first-line therapy**

*NHBLI. ATP III. JAMA 2001*

# Sindrome metabolica: attività fisica

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## Regular physical activity

- reduces VLDL levels
- raises HDL cholesterol
- in some persons, lowers LDL levels
- can lower blood pressure
- reduce insulin resistance
- improve cardiovascular function

**Regular physical activity is a routine component  
in management of metabolic syndrome**

*NHBLI. ATP III. JAMA 2001*

Regardless of diagnostic criteria used, there is full agreement that **therapeutic lifestyle change**, with emphasis on weight reduction, **constitutes first-line therapy for metabolic syndrome.**



# Sindrome metabolica

## Riduzione del peso e attività fisica

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Dramatic evidence from recent prospective intervention studies showing that the combination of weight loss and increased physical activity can significantly decrease the development of type 2 diabetes in high-risk individuals.

- **Finnish Diabetes Prevention Study**. *May, 2001*
- **Diabetes Prevention Program Group**. *February, 2002*

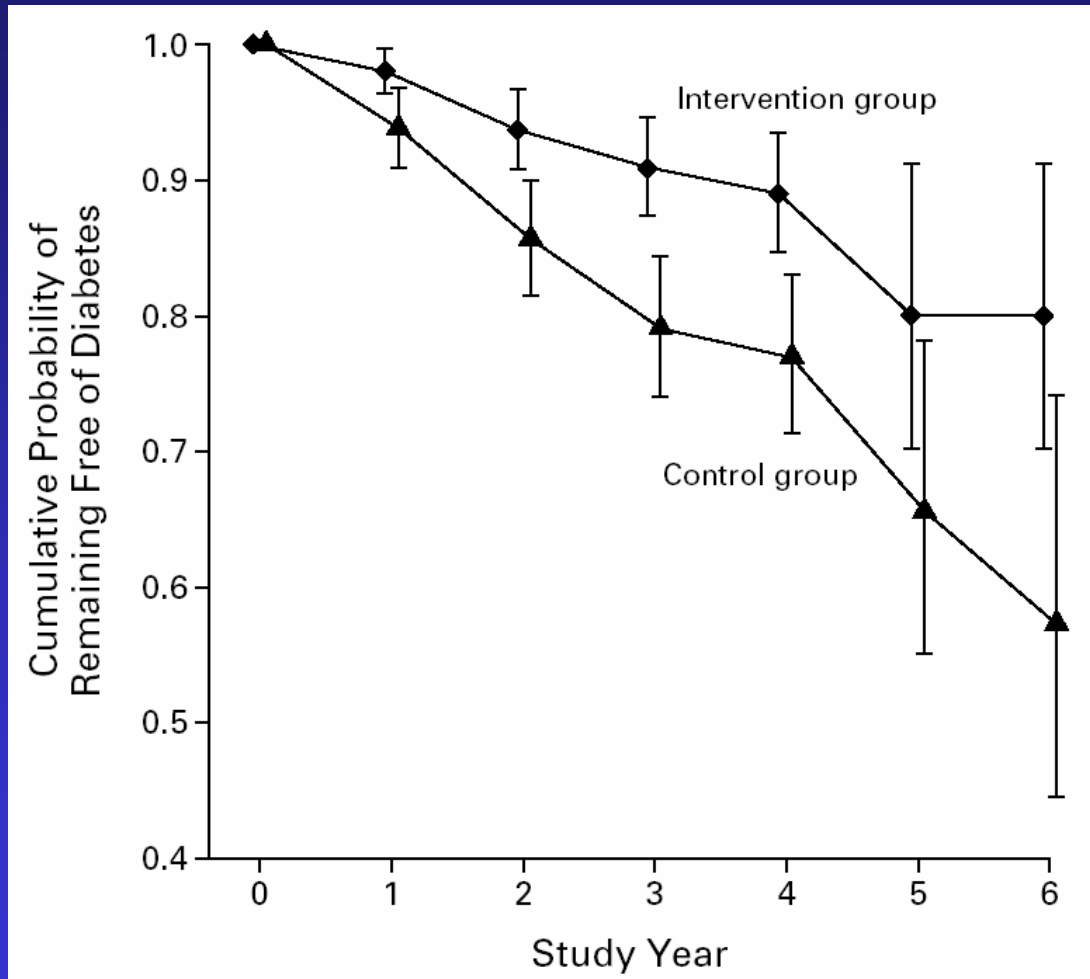
*ACE-AACE, 2003*

*Tuomilehto J, Lindstrom J, Eriksson JG, et al.*

**Prevention of type 2 diabetes by  
changes in lifestyle among subjects  
with impaired glucose tolerance**

*N Engl J Med 2001;344:1343-1350.*

# The Finnish Diabetes Prevention Study



*Tuomilehto J, et al  
N Engl J Med 2001*

# The Finnish Diabetes Prevention Study

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Lifestyle-intervention program vs control for the prevention of type 2 diabetes mellitus in patients with impaired glucose tolerance at a mean follow-up of 3.2 years

**NNT 8 (5 to 15)**

NNT= Numero necessario di pazienti da trattare per prevenire un evento (diabete)

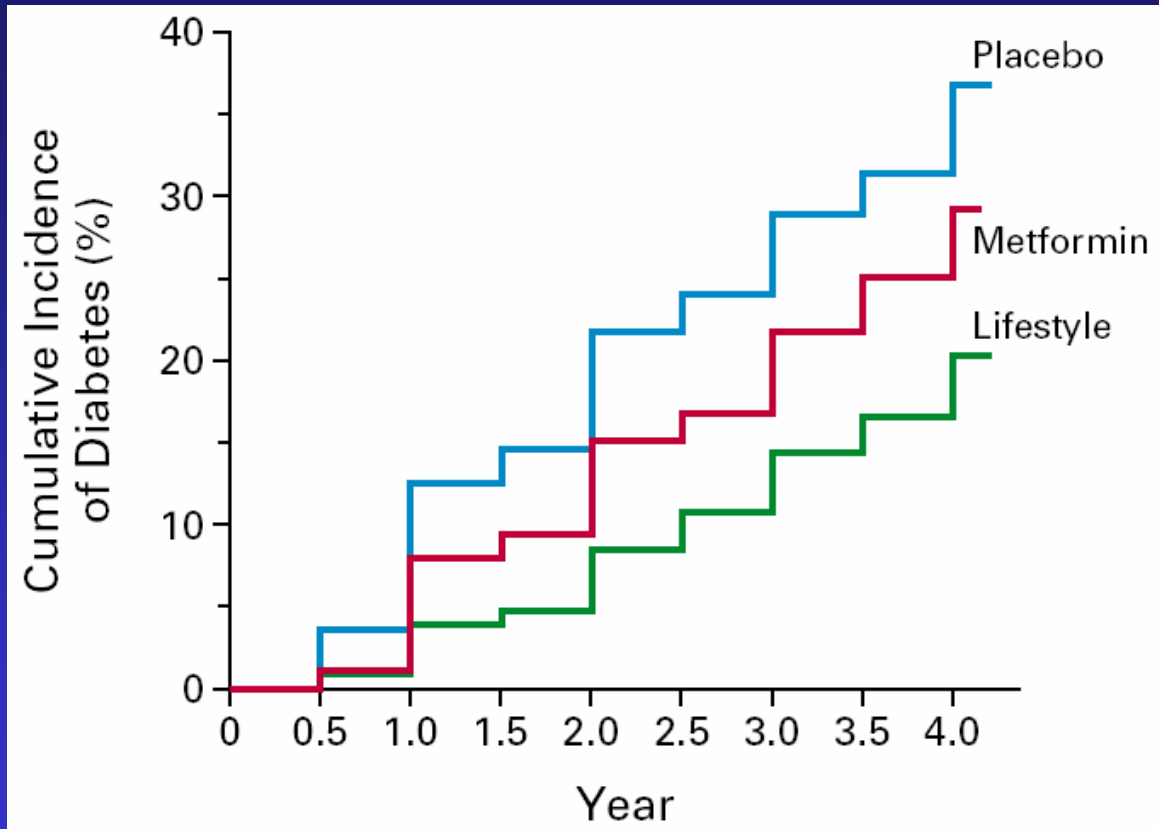
*Tuomilehto J, et al. N Engl J Med 2001*

*Knowler WC, Barrett-Connor E, Fowler SE, et al.*

**Reduction in the incidence of type 2  
diabetes with lifestyle intervention  
or metformin**

*N Engl J Med 2002;346:393-403.*

# The Diabetes Prevention Program Group



The study initially included a fourth intervention, troglitazone, which was discontinued because of the drug's potential liver toxicity.

*Knowler WC, et al. N Engl J Med 2002*

# The Diabetes Prevention Program Group

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Intensive life-style intervention (ILI) or metformin plus standard lifestyle vs placebo plus standard lifestyle for prevention of type 2 diabetes at 3 years

## NNT

- ILI vs placebo                      NNT 7 (6 to 10)
- Metformin vs placebo              NNT 14 (9 to 34)

NNT= Numero necessario di pazienti da trattare per prevenire un evento (diabete)

*Knowler WC, et al. N Engl J Med 2002*

**Explanatory  
RCTs**

Condizioni  
sperimentali  
ideali

*Validità interna  
(efficacy)*

*Applicabilità clinica  
(effectiveness)*

**Pragmatic  
RCTs**

Setting  
assistenziali  
reali



# The Diabetes Prevention Program Group

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- Modest weight loss (5%-7%) and modest increases in physical activity (~150 min/wk) can have substantial benefits in preventing diabetes.

# Decisione clinica (1)

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- La paziente viene istruita su come modificare il suo stile di vita:
  - Dieta bilanciata moderatamente ipocalorica
  - Programma di attività fisica moderata: 30 minuti al dì per 5 giorni alla settimana.
  - Abolizione del fumo.
- Controllo ambulatoriale dopo 4 settimane.

## Scenario Clinico (2)

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- La paziente si presenta regolarmente ai controlli, ma non smette di fumare.
- Dopo iniziale calo ponderale di 5.5 Kg in due mesi, con miglioramento di glicemia e trigliceridi, il peso riprende a salire lentamente, tornando al livello di partenza dopo 8 mesi.
- I ripetuti tentativi di ottenere una migliore compliance alle prescrizioni comportamentali danno risultati transitori.
- La signora Giovanna rimane amenorroica.

## Dati di laboratorio (2)

	<b>Baseline</b>	<b>1 anno</b>
<b>BMI</b>	29.7	<b>30.9</b>
<b>Glicemia</b>	112	<b>120</b>
<b>HbA1c</b>	-	<b>6.1</b>
<b>Colesterolo tot.</b>	221	<b>225</b>
<b>Colesterolo HDL</b>	42	<b>41</b>
<b>Colesterolo LDL</b>	141	<b>143</b>
<b>Trigliceridi</b>	187	<b>205</b>
<b>Uricemia</b>	6.0	<b>6.7</b>
<b>PAO</b>	135/88	<b>135/90</b>

# CLINICAL QUESTIONS



## 5. Sindrome Metabolica e rischio cardiovascolare.

**D. Quale trattamento farmacologico, in relazione alle prove di efficacia disponibili, ritenete più appropriato?**

1. Nessuno\*
2. Estroprogestinici
3. Metformina
4. Ipolipemizzanti

\*mantenere solo le modificazioni dello stile di vita

## Decisione clinica (2)

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- Si prescrive metformina (500 mg alla sera, poi 500 mg x 2), ma il farmaco viene sospeso dopo 3 settimane per pirosi e disturbi dell'alvo.
- La paziente mantiene le prescrizioni comportamentali, ma il calo ponderale è ancora modesto e fugace.
- Il fumo viene sospeso, ma solo transitoriamente.
- Per l'amenorrea, dopo esame ginecologico, viene prescritta terapia ciclica con soli progestinici (nomegestrolo, 1cp 5mg per 10gg/mese), con ripresa delle mestruazioni.
- Dopo alcuni mesi, la paziente viene persa al follow-up.

# The Diabetes Prevention Program Group

**TABLE 3. ADVERSE EVENTS.**

EVENT	PLACEBO	METFORMIN	LIFESTYLE
Gastrointestinal symptoms (no. of events/ 100 person-yr)*	30.7	77.8†	12.9†
Musculoskeletal symptoms (no. of events/ 100 person-yr)‡	21.1	20.0	24.1†
Hospitalization			
One or more admissions (% of participants)	16.1	15.9	15.6
Rate (no. of admissions/100 person-yr)	7.9	8.4	8.0
Median stay (days)	3	3	3
Deaths (no./100 person-yr)	0.16	0.20	0.10

\*Gastrointestinal symptoms included diarrhea, flatulence, nausea, and vomiting.



# CLINICAL QUESTIONS



## 5. Sindrome Metabolica e rischio cardiovascolare.

**E. Ritenete che il rischio cardiovascolare della sig.ra Giovanna avrebbe giustificato un trattamento farmacologico?**

1. Anti-ipertensivi
2. Ipolipemizzanti
3. 1 + 2
4. Nessun trattamento\*

\*mantenere solo le modificazioni dello stile di vita

# Sindrome metabolica: quali obiettivi terapeutici

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1. To reduce underlying causes (ie, obesity and physical inactivity)
2. **To treat associated risk factors (non-lipid and lipid)**

*NHBLI. ATP III. JAMA 2001*

**The ATP III does not specify whether subjects with the metabolic syndrome should receive more intense therapy for underlying conditions (ie, hypertension, lipid disorders)**

# Sindrome metabolica: quali obiettivi terapeutici

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## 1. Behavioral

- Weight loss
- Increased physical activity

## 2. Pharmacological (treat underlying conditions)

- Lipid disorders
- Hypertension
- Diabetes

## 3. Treat insulin resistance in non-diabetic subjects

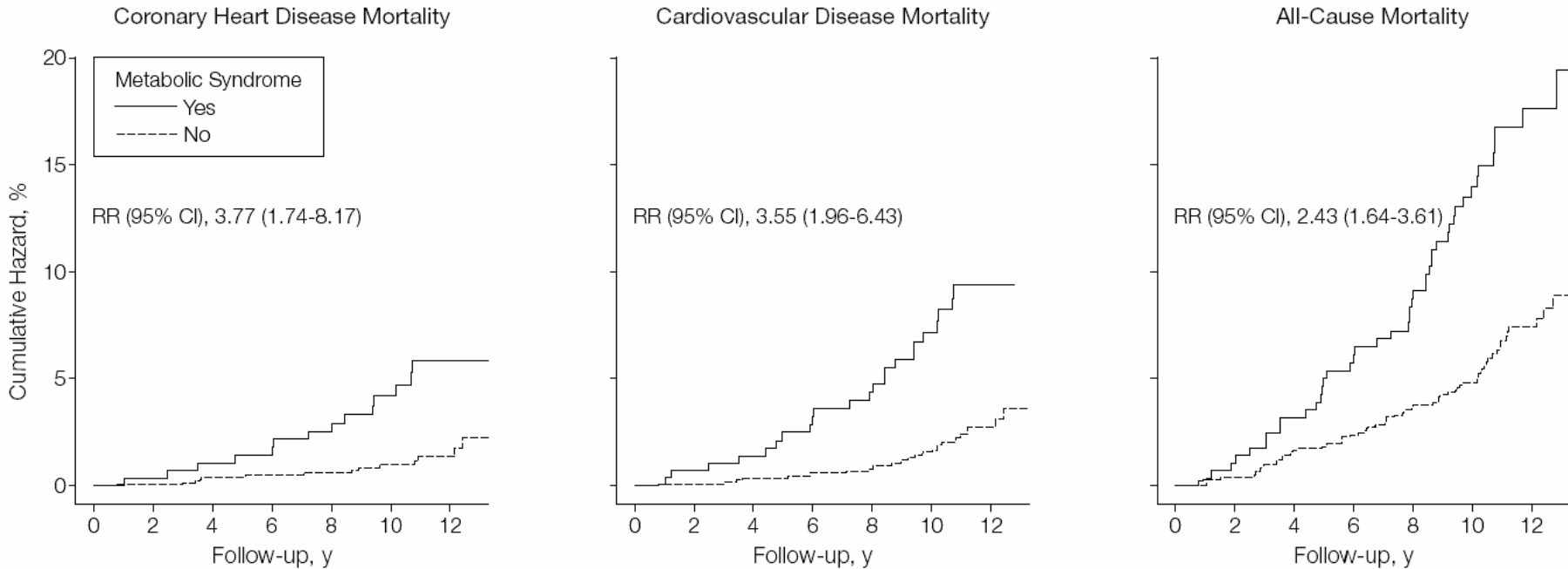
*Haffner S, et al. Circulation 2003*

*Lakka HM, Laaksonen DE, Lakka TA, et al.*

**The metabolic syndrome and  
total and cardiovascular disease  
mortality in middle-aged men**

*JAMA 2002;288:2709-16*

# Sindrome metabolica: il rischio cardiovascolare

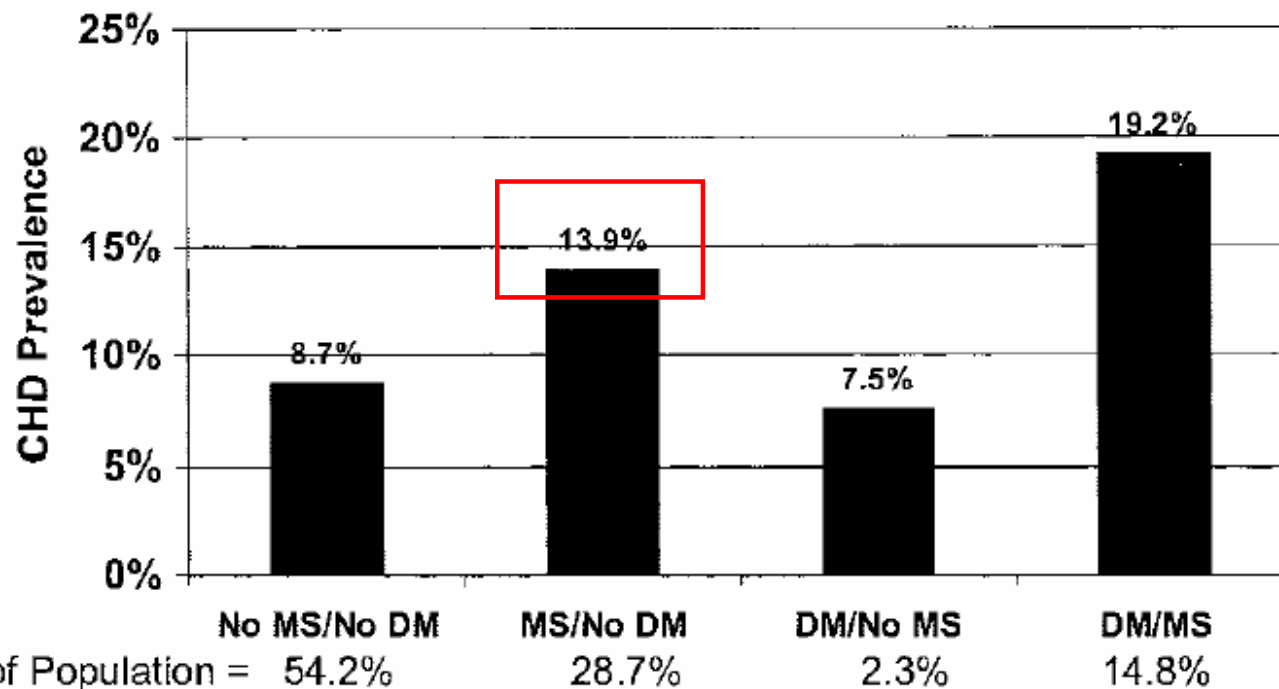


Cardiovascular disease and all-cause mortality are increased in men with the metabolic syndrome, even in the absence of baseline CVD and diabetes.

*Alexander CM, Landsman PB, Teutsch SM, et al.*

**NCEP-defined metabolic syndrome,  
diabetes mellitus, and prevalence  
of coronary heart disease among  
NHANES III participants age 50 years  
and older**

*Diabetes 2003;52:1210-214*



Age-adjusted prevalence of coronary heart disease in the US population >50 years of age categorized by presence of metabolic syndrome (MS) and diabetes mellitus (DM). Combinations of metabolic syndrome and diabetes mellitus status are shown.<sup>15</sup>



# Sindrome metabolica: il rischio cardiovascolare

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Although these results need to be replicated in other populations, particularly in prospective studies, suggest that **subjects with the NCEP-defined metabolic syndrome have an intermediate risk of CHD** and are not equivalent in risk to subjects with only CHD or type 2 diabetes.

*Haffner S, et al. Circulation 2003*

# Sindrome metabolica: quali obiettivi terapeutici

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## 2. Pharmacological (treat underlying conditions)

- Lipid disorders
- Hypertension
- Diabetes

Should the treatment of these disorders be “more aggressive” because the subject has the metabolic syndrome?

*Haffner S, et al. Circulation 2003*



## A Call for Aggressive Treatment

Our experts agree that early and aggressive therapy directed at dyslipidemia and insulin resistance, although at present unproven, is an attractive treatment strategy for the metabolic syndrome. In addition to behavioral intervention (weight loss, diet, and exercise), therapy with fibrates, metformin thiazolidinediones, and possibly dual peroxisome proliferator-activated receptor ( $\alpha$  and  $\gamma$ ) agents may be useful in addressing the central physiological disturbances. Treatment of clinical risk factors (dyslipidemia, hyperglycemia, and hypertension) should be even more intensive than called for by current guidelines based on the additive “global” risk posed for the syndrome itself. At present, no consensus optimal “targets” for LDL, blood pressure, etc, in the treatment of metabolic syndrome have been determined.

*Kereiakes, DJ, et al. Circulation 2003*

## MINI-REVIEW: EXPERT OPINIONS



- We have little direct evidence on the treatment of non-diabetic subjects with the metabolic syndrome.
- No evidence-based guidelines address this issue at present

*Haffner S, et al. Circulation 2003*

## MINI-REVIEW: EXPERT OPINIONS



- Some evidence suggests the metabolic syndrome is indeed “more than the sum of its parts,” but we have only just begun to explore its pathogenic basis and therapeutic implications.

*Reilly MP, et al. Circulation 2003*

# LDL 143 mg/dL

**Table 3.** Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals\*

- Cigarette smoking
  - Hypertension (blood pressure  $\geq 140/90$  mm Hg or on antihypertensive medication)
  - Low HDL cholesterol ( $<40$  mg/dL)<sup>†</sup>
- Family history of premature CHD (CHD in male first-degree relative  $<55$  years; CHD in female first-degree relative  $<65$  years)
- Age (men  $\geq 45$  years; women  $\geq 55$  years)

*NHBLI. ATP III. JAMA 2001*

# LDL 143 mg/dL

**Table 5.** LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories\*

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)†
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor‡	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

NHBLI. ATP III. JAMA 2001

## LDL 143 mg/dL

### TABLE 5. Clinical Approach to the Treatment of Dyslipidemia in the Metabolic Syndrome: Calculate Global Risk Even if Fewer Than 2 or More Major Risk Factors

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Target therapy on the basis of global risk

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If global risk is 15–20% and +metabolic syndrome, consider treating as if global risk is >20%\*

If global risk is 5–10% and +metabolic syndrome, consider treating as if is high-risk primary prevention† ●

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\*CHD risk equivalent with LDL cholesterol goal <100 mg/dL.

†Global risk of 10–20% LDL cholesterol goal <130 mg/dL.



*Chobanian AV, Bakris GL, Black HR, et al.*

**The Seventh Report of the Joint  
National Committee on Prevention,  
Detection, Evaluation, and Treatment  
of High Blood Pressure  
The JNC 7 report**

*JAMA 2003;289:2560-72*

# PAO 135/90 mmHg

**Table 1.** Classification and Management of Blood Pressure for Adults Aged 18 Years or Older

BP Classification	Systolic BP, mm Hg*		Diastolic BP, mm Hg*	Lifestyle Modification	Management*	
					Initial Drug Therapy	
					Without Compelling Indication	With Compelling Indications†
Normal	<120	and	<80	Encourage		
Prehypertension	120-139	or	80-89	Yes	No antihypertensive drug indicated	Drug(s) for the compelling indications‡
Stage 1 hypertension	140-159	or	90-99	Yes	Thiazide-type diuretics for most; may consider ACE inhibitor, ARB, $\beta$ -blocker, CCB, or combination	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, $\beta$ -blocker, CCB) as needed
Stage 2 hypertension	$\geq$ 160	or	$\geq$ 100	Yes	2-Drug combination for most (usually thiazide-type diuretic and ACE inhibitor or ARB or $\beta$ -blocker or CCB)§	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, $\beta$ -blocker, CCB) as needed

JNC 7. JAMA, 2003

# Sindrome metabolica: quali obiettivi terapeutici

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## 3. Treat insulin resistance in nondiabetic subjects

Drug treatment to directly reduce insulin resistance is promising, but clinical trials to prove reduction of CVD are lacking.

*NHLBI/AHA. Circulation 2004*

Except for metformin, no clinical trial data support the use of drugs to improve insulin sensitivity in non-diabetic subjects, although this is an area of active interest

*Haffner S, et al. Circulation 2003*

There are no evidence-based guidelines to provide therapeutic targets for treatment of the central manifestations of the insulin resistance

*ACE/AACE, 2003*

## Scenario Clinico (3)

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- La paziente torna all'osservazione circa 8 anni dopo, all'età di 52 anni.
- Ha sospeso i progestinici dopo circa un anno di terapia e non ha più mestruato.
- A 47 anni comparsa di sintomi menopausali: il climaterio viene confermato dal ginecologo, che non prescrive terapia sostitutiva ormonale a causa dei problemi metabolici e del fumo.

## Scenario Clinico (3)

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- Negli ultimi tempi il peso è leggermente aumentato e i valori pressori risultano spesso elevati (fino a 160/100 mmHg).
- Recentemente, comparsa di malessere, astenia, dispnea da sforzo, cardiopalmo, occasionale senso di peso epigastrico, senza chiara relazione con i pasti e con l'attività fisica.
- Per l'incremento dei valori glicemici, ha iniziato terapia con glibenclamide 2.5 mg due volte al dì e dieta 1200 Cal. con limitato apporto di carboidrati.

## Dati di laboratorio (3)

	<b>Baseline</b>	<b>1 anno</b>	<b>9 anni</b>
<b>BMI</b>	29.7	30.9	<b>33.6</b>
<b>Glicemia</b>	112	120	<b>243</b>
<b>HbA1c</b>	-	6.1	<b>8.9</b>
<b>Colesterolo tot.</b>	221	225	<b>251</b>
<b>Colesterolo HDL</b>	42	41	<b>38</b>
<b>Colesterolo LDL</b>	141	143	<b>148</b>
<b>Trigliceridi</b>	187	205	<b>284</b>
<b>Uricemia</b>	6.0	6.7	<b>7.0</b>
<b>PAO</b>	135/88	135/90	<b>140/100</b>

## Indagini strumentali (3)

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- ECG: Ritmo sinusale 84 bpm, alterazioni aspecifiche della ripolarizzazione.
- Holter-ECG: occasionali extrasistoli ventricolari monomorfe, breve episodio compatibile con ischemia (asintomatico).
- Eco-colordoppler TSA: placche hard bilaterali al bulbo estese al tratto iniziale delle carotidi interne, con stenosi non emodinamicamente significative (25% a dx, 30% a sin).
- EGDS negativa.

## Indagini strumentali (3)

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- Ecocardiogramma: discinesia ventricolare sin, con riduzione di grado moderato della frazione di eiezione.
- Coronarografia: stenosi coronariche multiple



## Decisione clinica (4)

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- La paziente è stata sottoposta a rivascolarizzazione coronarica ed ha iniziato trattamento con isosorbide mononitrato 50 mg/die, acido acetilsalicilico 100 mg/die, enalapril 10 mg/die, simvastatina 20 mg/die.

## Esami di laboratorio (4)

	Baseline	1 anno	9 anni	Dopo 3 mesi
<b>BMI</b>	29.7	30.9	33.6	<b>30.5</b>
<b>Glicemia</b>	112	120	243	<b>167</b>
<b>HbA1c</b>	-	6.1	8.9	<b>7.1</b>
<b>Colesterolo tot.</b>	221	225	251	<b>190</b>
<b>Colesterolo HDL</b>	42	41	38	<b>45</b>
<b>Colesterolo LDL</b>	141	143	148	<b>110</b>
<b>Trigliceridi</b>	187	205	284	<b>176</b>
<b>Uricemia</b>	6.0	<b>6.7</b>	7.0	<b>7.4</b>
<b>PAO</b>	135/88	135/90	140/100	<b>120/75</b>