Associazione Medici Endocrinologi

AME 2003 - 3° Congresso Nazionale

Palermo, 7-9 novembre 2003

Workshop Clinici Interattivi

2. Sindrome Metabolica

Discussant

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Scenario Clinico (1)

• La signora Letizia è un'impiegata comunale di 42 anni, vedova, in buone condizioni generali, in sovrappeso dall'adolescenza e con recente riscontro di lieve iperglicemia a digiuno.

• Pregressa diagnosi di sindrome dell'ovaio policistico.

• 5 anni prima lieve diabete gestazionale (trattato con sola dieta), in corso di gravidanza gemellare ottenuta dopo stimolo farmacologico.

Scenario Clinico (1)

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)

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)

Obiettivamente

- BMI 29.7 kg/m2, circonferenza vita 89 cm (WHR 0.93)
- Irsutismo di grado lieve-moderato, lieve acanthosis nigricans al collo e alle ascelle, lieve epatomegalia.
- PAO 135/88 mmHg.

Dati di laboratorio (1)

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
- Uricemia 6.0 mg/dl

Dati di laboratorio (1)

OGTT

- Glicemia 120 min. 176 mg/dl
- Insulinemia 120 min. 189 mU/l

Profilo endocrino basale

- LH 12.8 U/l
- FSH 5.6 U/l
- Testosterone totale 3.2 nmol/l
- PRL e TSH Nella norma

Indagini strumentali (1)

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

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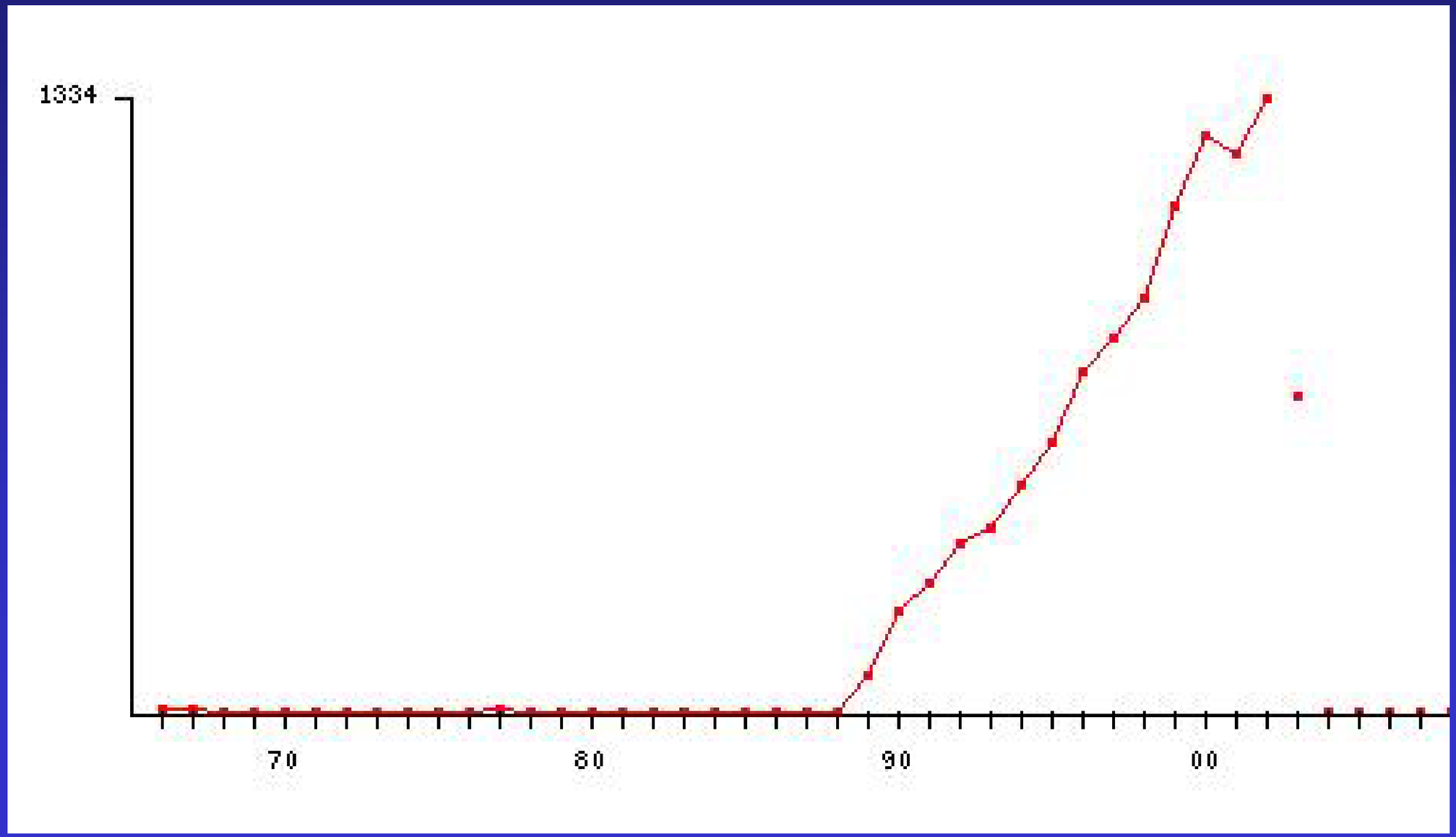
1. Quale tra i seguenti, non rientra tra i criteri diagnostici della sindrome metabolica?

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]: 990 articoli



Metabolic Syndrome

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]: **990 articoli**

- 369 Review, Editoriali, Lettere
- 34 Clinical trial
- 20 Randomized controlled trials

Sindrome metabolica

- **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).

Scott CL. Am J Cardiol 2003

Sindrome metabolica

- **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?)

Scott CL. Am J Cardiol 2003

American College of Endocrinology (ACE)
American Association of Clinical Endocrinologists (AACE)

Position Statement on the Insulin Resistance Syndrome

Endocr Pract 2003;9:240-52

Sindrome Metabolica

…we will use the term Insulin Resistance Syndrome to describe the consequences of insulin resistance and compensatory hyperinsulinemia, thereby focusing on the underlying pathophysiology that unites the cluster of related abnormalities.

ACE-AACE, 2003

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

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

- 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

ATP III definition is easier to use in clinical practice because does not required:

- glucose tolerance testing
- insulin concentration measurements
- microalbuminuria testing.

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

NHBLI. ATP III. JAMA 2001

Laaksonen DE, Lakka HM, Niskanen LK, et al.

Metabolic syndrome and development of diabetes mellitus

Application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study

Am J Epidemiol 2002;156:1070-1077

Lorenzo C, Okoloise M, Williams K, et al.

The Metabolic Syndrome as Predictor of Type 2 Diabetes The San Antonio Heart Study

Diabetes Care 2003;26:3153-3159

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 >or=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.

Ford ES, et al. Diabetes Care 2003

Metabolic Syndrome

Risk Factor	Defining Level	Sig.ra Letizia
• Abdominal obesity* (waist circumference)†		
Men	>102 cm (>40 in)	89 cm
Women	>88 cm (>35 in)	
• Triglycerides	≥150 mg/dL	187 mg/dL
• High-density lipoprotein cholesterol		
Men	<40 mg/dL	42 mg/dL
Women	<50 mg/dL	
• Blood pressure	≥130/≥85 mm Hg	135/88 mmHg
• Fasting glucose	≥110 mg/dL	112 mg/dL

NHBLI. ATP III. JAMA 2001

Diagnosi

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

CLINICAL QUESTIONS

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2. 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%

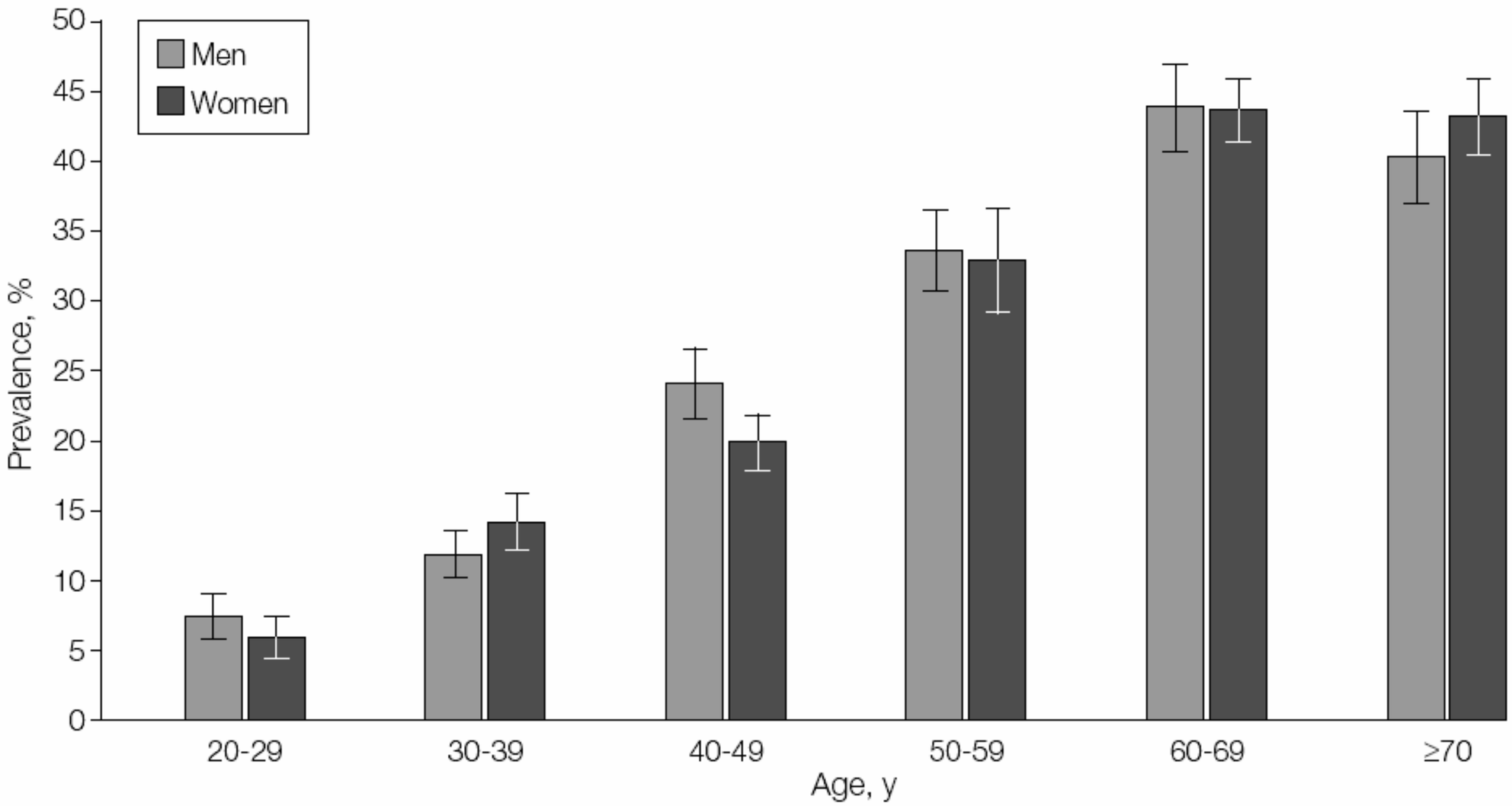
Ford ES, Giles WH, Dietz WH.

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



Ford ES, et al. JAMA 2002

Park Y-W, Zhu S, Palaniappan L, et al.

The metabolic syndrome. Prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994

Arch Intern Med 2003;163:427-436.

CLINICAL QUESTIONS

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3. Qual è il trattamento di prima scelta per la sig.ra Letizia?

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

Sindrome metabolica: quali obiettivi terapeutici

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

- 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

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

Sindrome metabolica
Riduzione del peso e attività fisica

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*

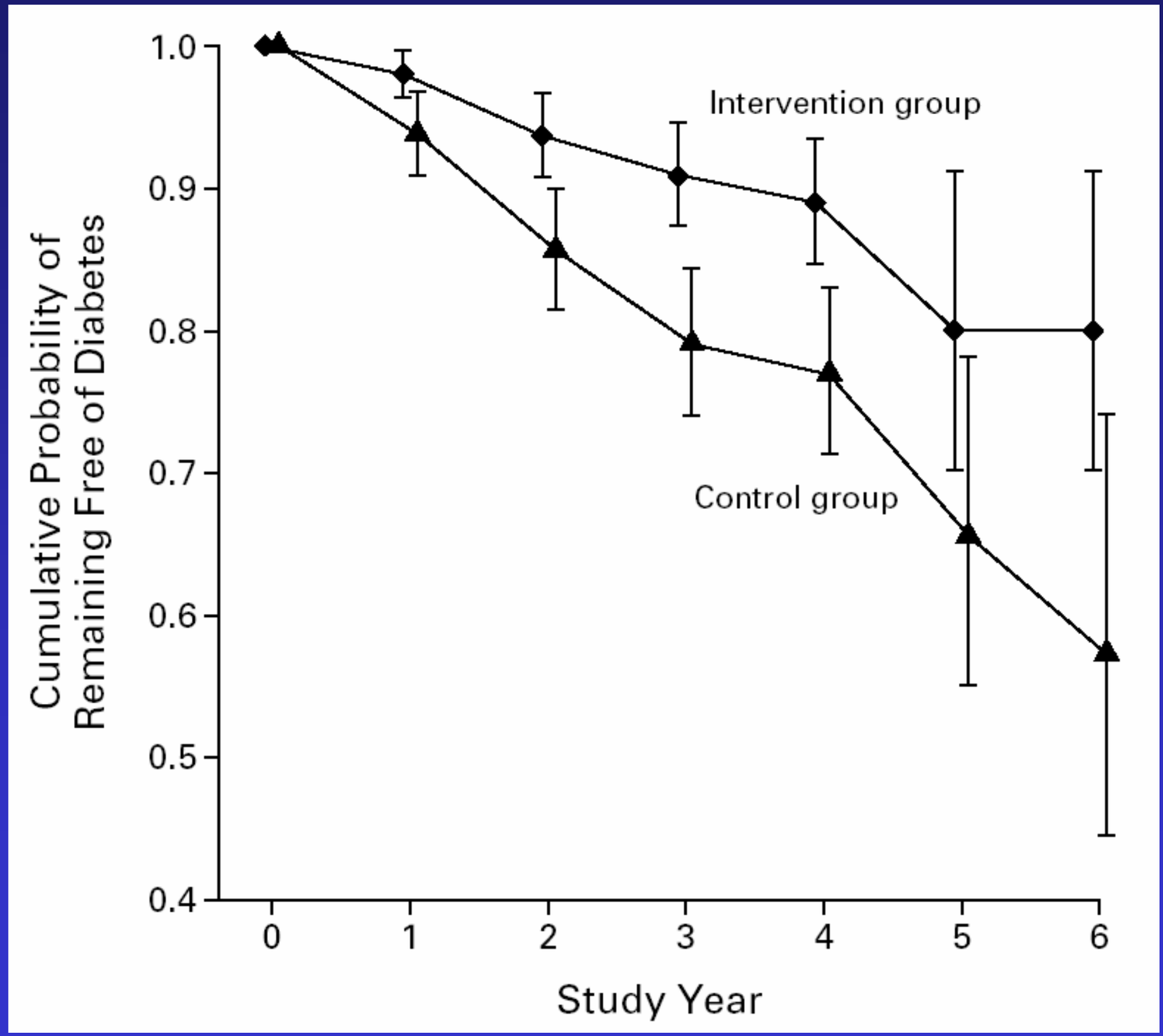
ACE-AACE, 2003

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

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 preventire un evento (diabete)

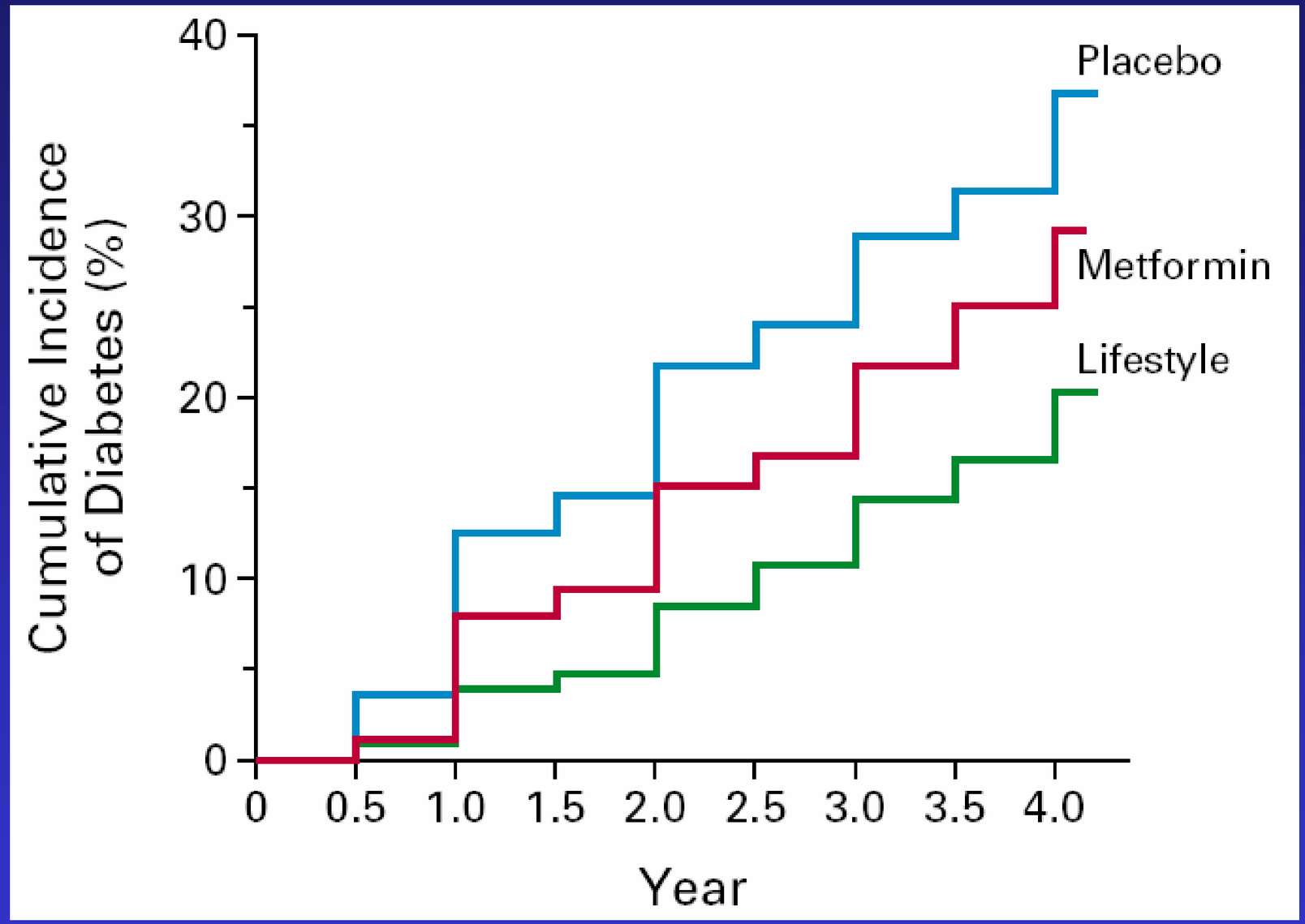
Tuomilehto J, et al. N Engl J Med 2001

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

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 preventire un evento (diabete)

Knowler WC, et al. N Engl J Med 2002

ACP JOURNAL CLUB

Evidence-Based Medicine for Better Patient Care

- Sorveglianza *core* di riviste (40-50)

- Selezione articoli in base a
  - Rilevanza clinica
  - Adeguatezza metodologica

- Abstract strutturato e commentato

- 1 articolo = 1 pagina

The Finnish Diabetes Prevention Study

- The intervention may not be as effective in usual practice because of differences that may exist between the volunteer participants and usual patients and because of the inability of usual-practice systems to provide intensive and individualized dietary and exercise interventions.

- Clinicians should not be overly skeptical about their ability to modify a patient's lifestyle, because the goals may not need to be ambitious to be effective.

Montori V. ACP J Club 2001

The Diabetes Prevention Program Group

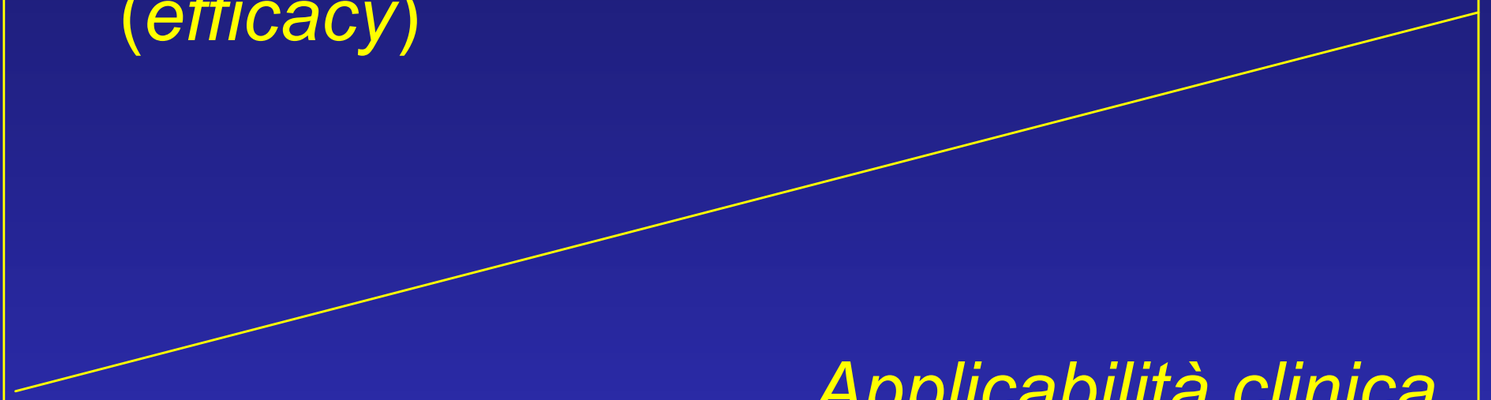
- Although lifestyle modification may be more effective and perhaps less expensive, metformin treatment may be easier to implement and sustain.
- Lifestyle modification requires expertise in behavior modification and the effective mobilization of community resources to support the patient.
- Financial and logistical barriers may limit the implementation of an intensive lifestyle-modification intervention in clinical practice.

Montori V. ACP J Club 2001

Explanatory
RCTs

Condizioni sperimentali ideali

Validità interna
(*efficacy*)



Applicabilità clinica
(*effectiveness*)

Pragmatic
RCTs

Setting assistenziali reali

Cartabellotta A. Occhio Clinico 2002

The Diabetes Prevention Program Group

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

Decisione clinica (1)

- 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)

• 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 Letizia rimane amenorroica

Dati di laboratorio (2)

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

CLINICAL QUESTIONS

?

4. 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)

- 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.

Knowler WC, et al. N Engl J Med 2002

CLINICAL QUESTIONS

?

5. Ritenete che il rischio cardiovascolare della sig.ra Letizia avrebbe giustificato un trattamento farmacologico:

1. Anti-ipertensivi
2. Ipolipemizzanti
3. 1 + 2
4. No*

*mantenere solo le modificazioni dello stile di vita

Sindrome metabolica: quali obiettivi terapeutici

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

1. Behavioral

- Weight loss
- Increased physical activity

2. Pharmacological (treat underlying conditions)

- Lipid disorders
- Hypertension
- Diabetes

3. Treat insulin resistance in non-diabetic subjects

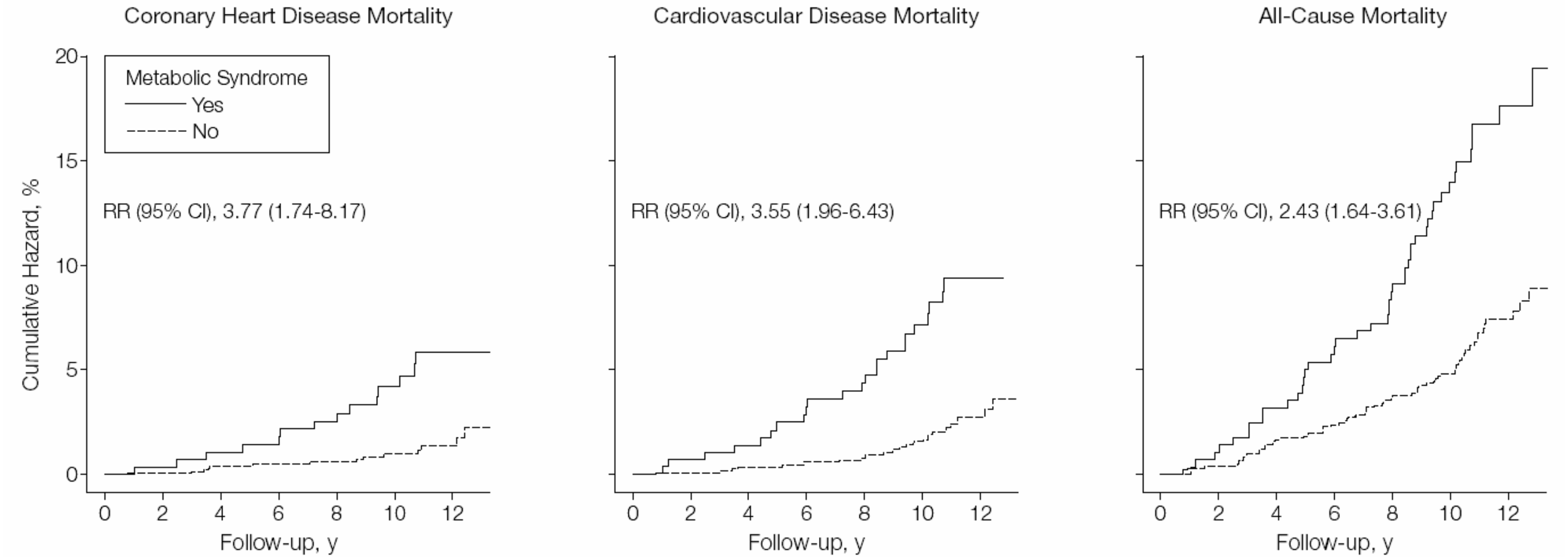
Haffner S, et al. Circulation 2003

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



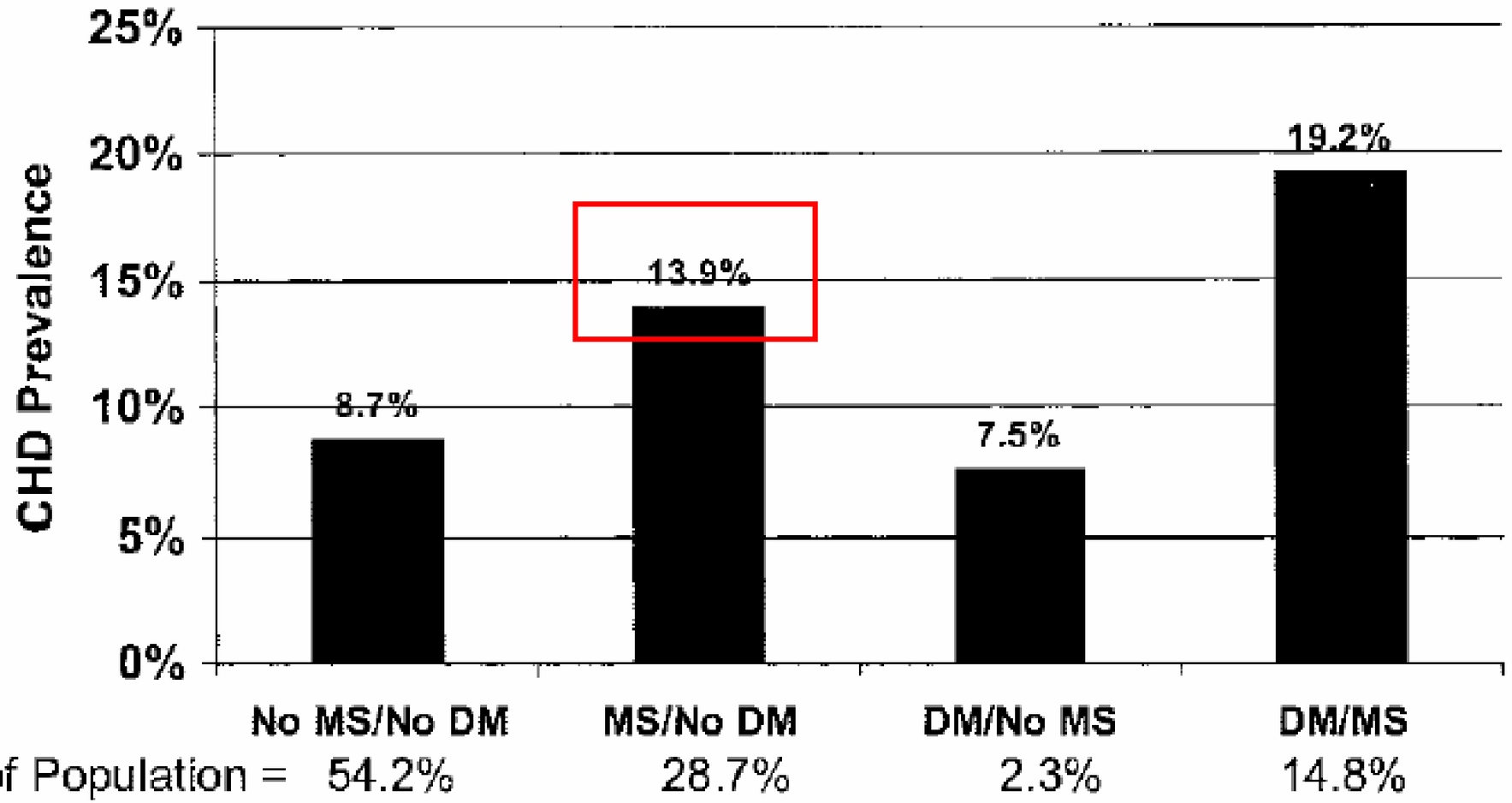
Cardiovascular disease and all-cause mortality are increased in men with the metabolic syndrome, even in the absence of baseline CVD and diabetes.

Lakka HM, et al. JAMA 2002

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.[15]

Alexander CM, et al. Diabetes 2003

Sindrome metabolica: il rischio cardiovascolare

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

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 (α and γ) 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 ≥140/90 mm Hg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)†
- Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
- Age (men ≥45 years; women ≥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

Target therapy on the basis of global risk
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†

*CHD risk equivalent with LDL cholesterol goal <100 mg/dL.
†Global risk of 10–20% LDL cholesterol goal <130 mg/dL.

Haffner S, et al. Circulation 2003

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*	Management*		
				Lifestyle Modification	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, β-blocker, CCB, or combination	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed
Stage 2 hypertension	≥160	or	≥100	Yes	2-Drug combination for most (usually thiazide-type diuretic and ACE inhibitor or ARB or β-blocker or CCB)§	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed

JNC 7. JAMA, 2003

Sindrome metabolica: quali obiettivi terapeutici

3. Treat insulin resistance in nondiabetic subjects

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)

- 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)

- 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, il medico curante ha prescritto glibenclamide 2.5 mg due volte al dì e dieta 1200 Cal. con limitato apporto di carboidrati.

Dati di laboratorio (3)

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

Indagini strumentali (3)

- 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)

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

Decisione clinica (4)

• 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
BMI	29.7	30.9	33.6	**30.5**
Glicemia	112	120	243	**167**
HbA1c	-	6.1	8.9	**7.1**
Colesterolo tot.	221	225	251	**190**
Colesterolo HDL	42	41	38	**45**
Colesterolo LDL	141	143	148	**110**
Trigliceridi	187	205	284	**176**
Uricemia	6.0	**6.7**	7.0	**7.4**
PAO	135/88	135/90	140/100	**120/75**