Associazione Medici Endocrinologi

AME 2001 - 1° Congresso Nazionale

Udine, 25-26 maggio 2001

Workshop Clinici Interattivi

1. Osteoporosi

Discussant

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Scenario Clinico (1)

- La signora Maria è una casalinga di 60 anni sposata con due figli, moderata fumatrice (10 sigarette/die), senza episodi rilevanti all'anamnesi familiare e fisiologica.

- All'età di 43 anni, in seguito a diagnosi di carcinoma della mammella, viene sottoposta ed intervento chirurgico, preceduto da chemioterapia e seguito da radioterapia.

- Alcuni mesi dopo la chemioterapia compare amenorrea, seguita da intensa sintomatologia climaterica, durata alcuni anni e poi gradualmente scomparsa.

- I periodici controlli hanno sempre dato esito negativo

Scenario Clinico (2)

- Circa due anni fa, in seguito alla comparsa di epigastralgia, esegue gastroscopia che documenta un'esofagite severa con gastrite atrofica HP positiva.

- La paziente esegue terapia eradicante e terapia di mantenimento per l'esofagite con inibitori della pompa protonica e H_2-antagonisti.

Scenario Clinico (3)

• Nel giugno 1998 (a 58 anni) - su suggerimento del marito, medico oculista - esegue una densitometria ossea.

	T-score	Z-score
L1-L4	-2.8 (=72%)	-1.9 (=81%)
Femore totale	-1.4 (=86%)	-0.9 (=91%)

• Altre indagini eseguite (calcemia, fosforemia, fosfatasi alcalina, PTH, TSH, vitamina D, osteocalcina, cortisolemia, ACTH) non rilevano cause di osteoporosi secondaria.

CLINICAL QUESTIONS

1. Esistono dei criteri *evidence-based* per definire l'appropriatezza della densitometria ossea?

2. Gli inibitori della pompa protonica e/o gli H_2-antagonisti hanno un ruolo documentato nell'eziologia dell' osteoporosi?

3. Quali tra i seguenti trattamenti sono supportati da consistenti prove di efficacia che dimostrino la prevenzione primaria delle fratture nelle donne con osteoporosi menopausale?

- Terapia sostitutiva ormonale
- Raloxifene
- Alendronato
- Risedronato
- Calcio + vitamina D
- Calcitonina
- PTH

4. Lo studio MORE ha dimostrato che, nelle donne con osteoporosi in età in post-menopausale, il trattamento con raloxifene per tre anni aumenta la densità ossea e riduce l'incidenza di fratture vertebrali.

Quest'evidenza è applicabile alla signora Maria ?

Espallargues M, Dolors Estrada M, Sola M, et al

Technology assessment Guidelines for the indication of bone densitometry in the assessment of fracture risk

Catalan Agency for Health Technology Assessment,1999

From the results of the qualitative and quantitative analysis, fracture RFs (related to a decrease in BM) were classified in the following categories, according to the magnitude of the associated fracture risk:

1. **High risk**: RFs considered to have a twice as high associated relative risk (RR) of fracture, or more
2. **Moderate risk**: RFs considered to have an associated fracture RR between once and twice as high (1<RR<2)
3. **No risk**: RFs considered to have risk values close to 1 (null value or 1), and RFs with protective effect (RR<1)
4. **Not classifiable**: RFs where the relationship with the fracture could not be determined, either due to insufficient information available, or to contradictory information, were included here

High risk	Moderate risk	No risk
Advanced age (> 70-80 years)	Gender (female)	Caffeine intake
Low body mass[1] (BMI < 20-25 Kg/m^2)	Smoking (active smoker)	Taking tea
Weight loss[2]	Low sun ligth exposure (none or low)	Menopause[9]
Physical inactivity[3]	Familiar background of osteoporotic fracture[6]	Nulliparity
Corticoids (except inhaled or dermic)	Iatrogenic menopause[7]	Drinking fluoridated water
Anticonvulsivants	Early menopause (< 45 years)	Thiazide diuretics
Primary hyperparathyroidism[4]	Short fertile period (< 30 years)	
Diabetes mellitus tipe I[4]	Late menarche (> 15 years)	
Anorexia nervosa[4]	No breastfeeding	
Gastrectomy[4]	Low calcium intake[8] (< 500-850 mg/day)	
Pernicious anemia[4]	Hyperparathyroidism (N/E)	
Prior osteoporotic fracture[5]	Hyperthyroidism	
	Diabetes mellitus (tipe II o N/S)	
	Rheumatoid arthritis	

Bone densitometry is indicated if the patient presents with:

2 or more ***high risk*** risk factors (RFs)

or

4 or more ***moderate risk*** RFs

or

1 or more ***high risk*** RFs

+

2 or more ***moderate risk*** RFs

CAHTA 1999

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2. Farmaci antisecretori e rischio di osteoporosi

MEDLINE

osteoporosis[MESH] AND
("Histamine H2 Antagonists"[MESH] OR omeprazole[MESH])

Adachi Y, Shiota E, Matsumata T, et al

Bone mineral density in patients taking H2-receptor antagonist

Calcif Tissue Int 1998;62:283-5

• Thirty-three patients taking cimetidine, ranitidine, or famotidine for more than 2 years were analyzed.

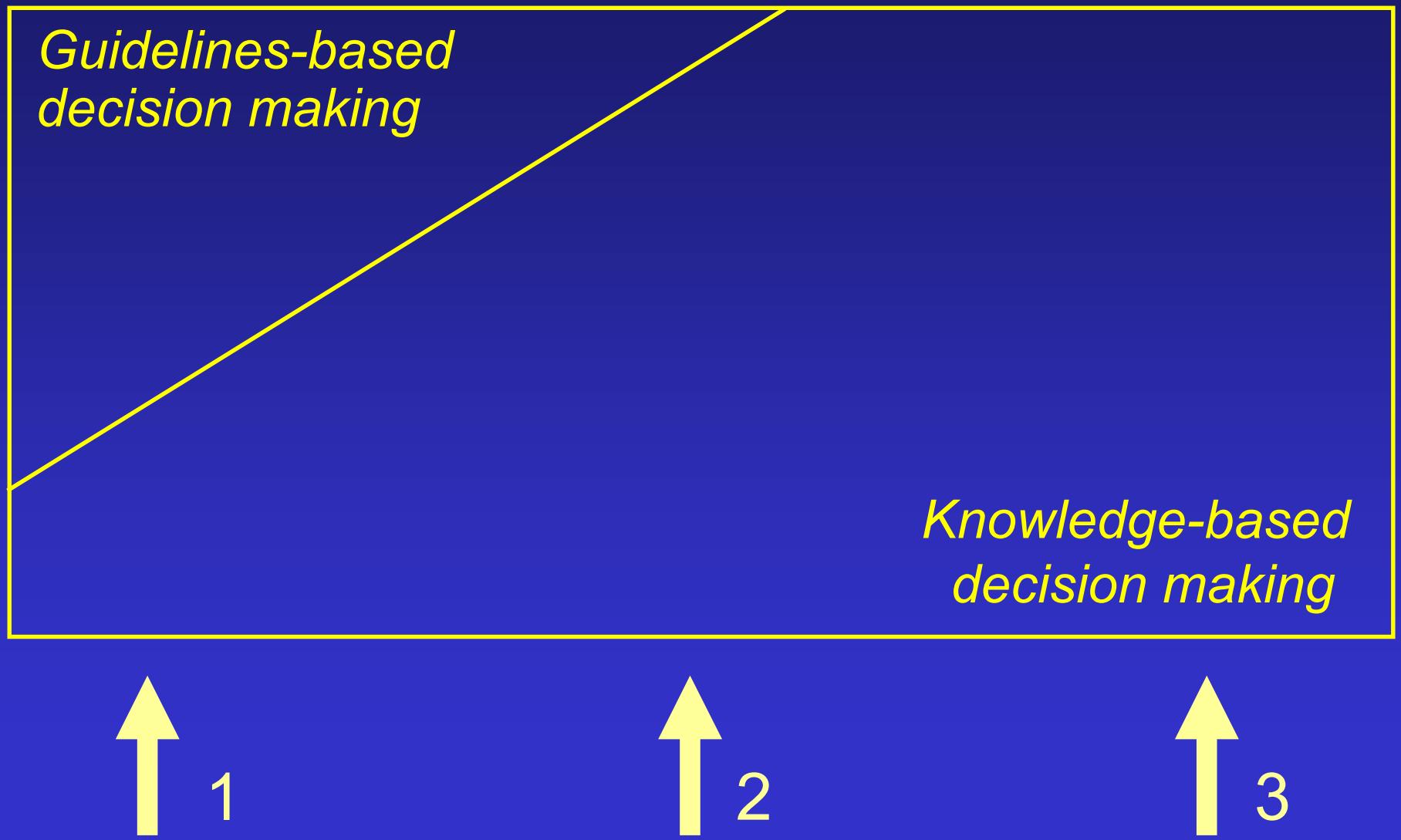
• We measured BMD of L2-L4 using dual energy X-ray absorptiometry. Osteoporosis (BMD less than 0.70 g/cm2) was found only in three patients (9%).

• As compared with healthy controls, age- and sex-matched BMD ranged from 74.4% to 132.9%, with a mean of 97.0%, and was not influenced by the period of HRA use (<5 years versus >5 years or more).

• Chronic use of HRA has little influence on the degree of BMD, and suggest that decreased gastric acidity is not always associated with osteoporosis after gastrectomy.

Adachi Y, et al. Calcif Tissue Int 1998

3. Osteoporosi: prove di efficacia dei trattamenti



Linee Guida Osteoporosi

Ricercando il termine “osteoporosis” nelle principali banche dati di linee guida - oltre che in MEDLINE - sono state identificate 9 linee guida (LG) pubblicate negli ultimi 5 anni da Istituzioni differenti

Linee Guida Osteoporosi (1)

- 1996 American Association of Clinical Endocrinologists
  American College of Endocrinology
- 1996 Osteoporosis Society of Canada
- 1998 American Health Care Association
  American Medical Directors Association
- 1998 Society of Obstetricians and Gynaecologists of Canada
- 1999 Brigham and Women's Hospital (Boston)

Linee Guida Osteoporosi (2)

- 1999 American Academy of Orthopaedic Surgeons
  American College of Obstetricians and Gynecologists
  American Geriatrics Society
  American College of Radiology
  American College of Rheumatology
  American Academy of Physical Medicine and Rehabilitation
  American Association of Clinical Endocrinologists
  National Osteoporosis Foundation
  The Endocrine Society
  American Society for Bone and Mineral Research
- 2000 Office of Medical Applications of Research
- 2000 Royal College of Physicians
- 2001 NIH Consensus Development Panel on Osteoporosis

Johnston BL, Conly BL

Guidelinitis: A new syndrome?

Can J Infect Dis 2000

The quality of clinical practice guidelines

What's news ?

Shaneyfelt MT, Mayo-Smith MF, Rothwangl J

Are Guidelines Following Guidelines?

The Methodological Quality of Clinical Practice Guidelines in the Peer-Reviewed Medical Literature

JAMA 1999;281:1900-5

Valutazione metodologica di 279 LG (score a 25 item)

Figure 1. Distribution of the Mean Number of Methodological Standards Satisfied by Guidelines

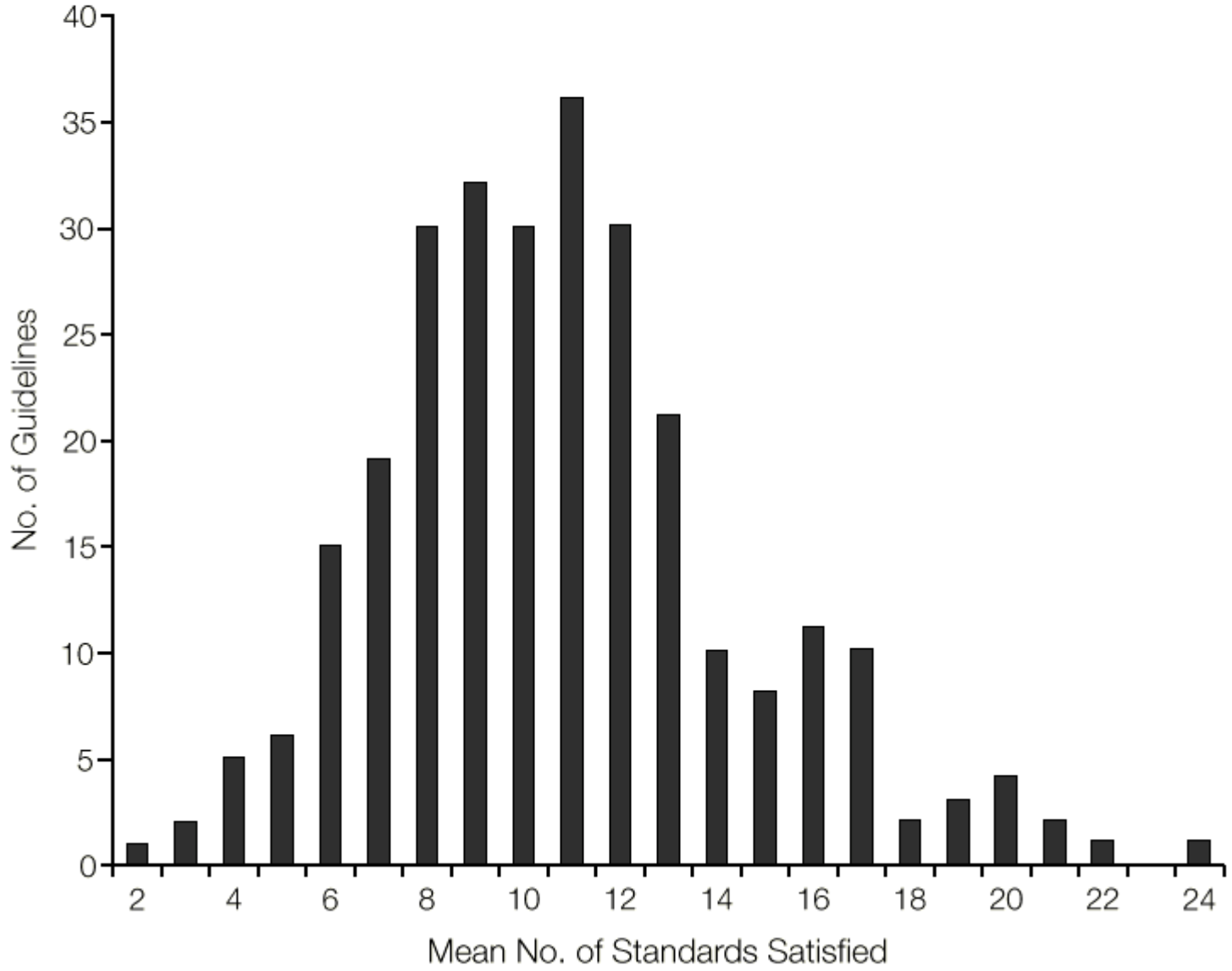
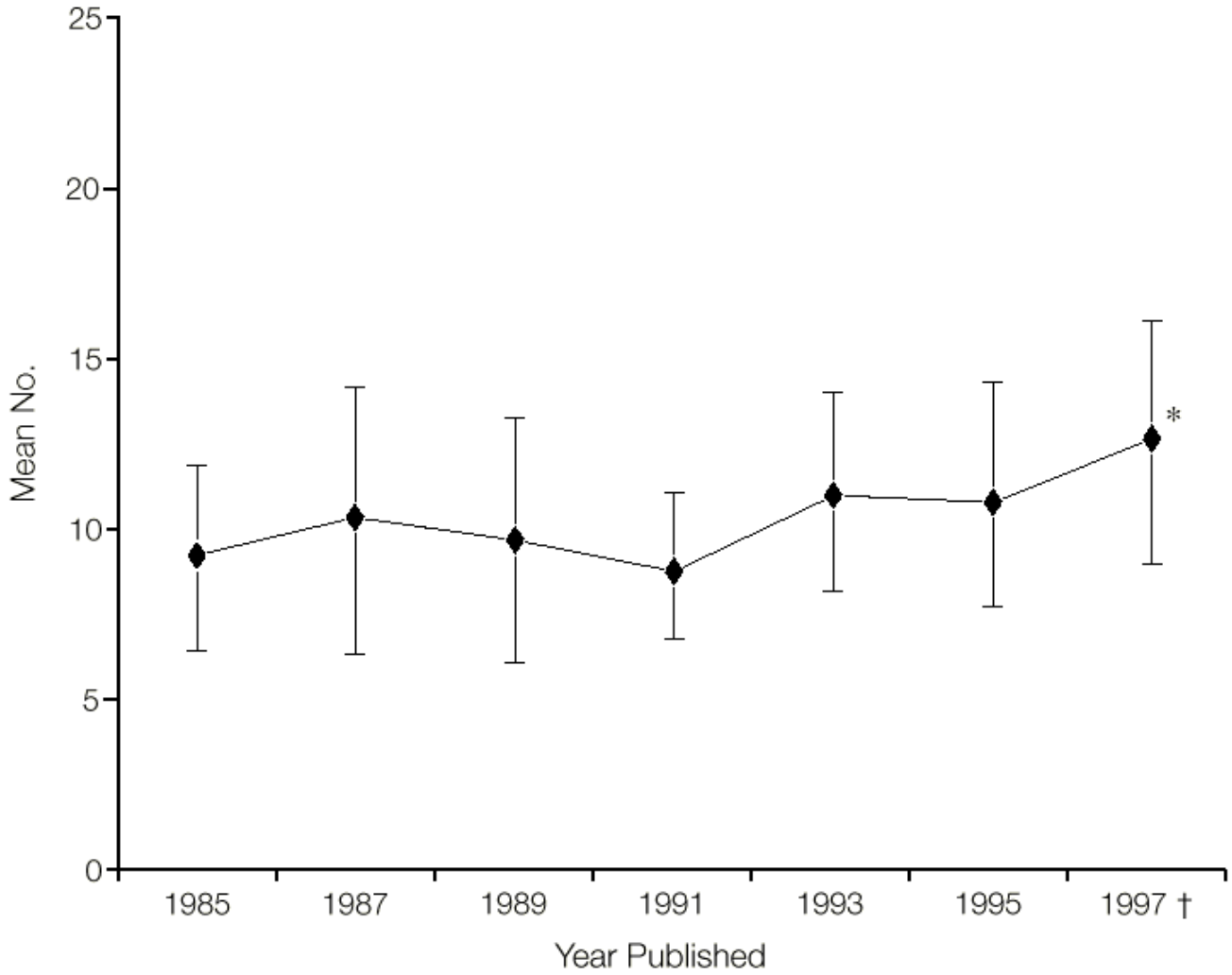


Figure 2. Mean Number of Methodological Standards Satisfied by Guidelines



Asterisk indicates $P<.01$ for trend across all years; dagger indicates that only guidelines published through June 1997 are included. Error bars indicate SDs.

Grilli R, Magrini N, Penna A, Mura G, Liberati A

Practice guidelines developed by specialty societies The need for a critical appraisal

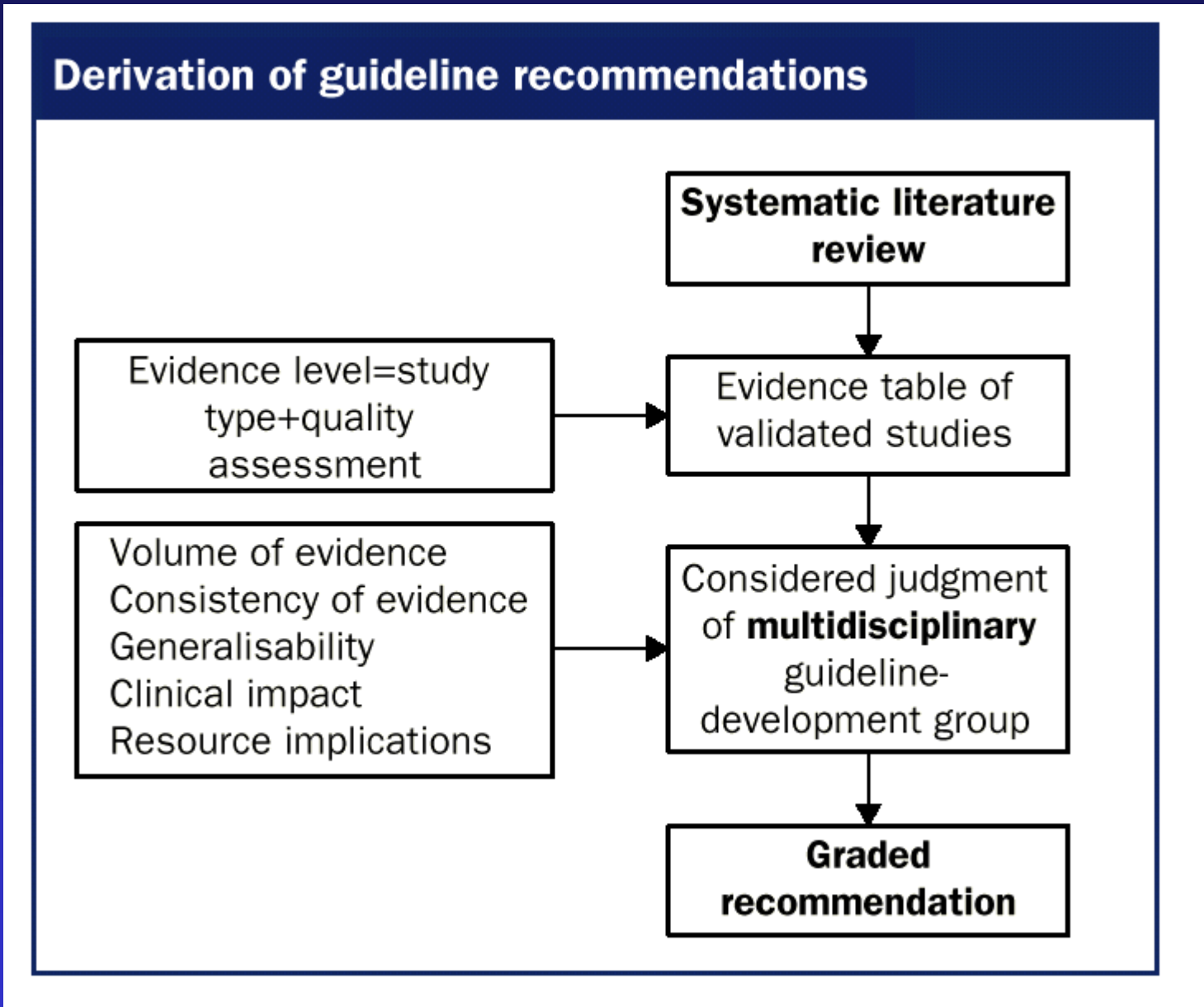
Lancet 2000;355:103-6

Valutazione metodologica di 431 LG (score a 3 item)

	1988–91 (n=48)	1992–93 (n=81)	1994–95 (n=125)	1996–98 (n=177)	p for trend
Full description of professionals	6 (12%)	9 (11%)	11 (9%)	27 (15%)	0·99
Search undertaken	1 (2%)	4 (5%)	14 (11%)	32 (18%)	<0·001
Grading of recommendation	3 (6%)	5 (6%)	21 (17%)	48 (27%)	<0·001

Table 2: **Number of guidelines that met the three quality criteria according to year of publication**

Grilli R, et al. Lancet 2000



Miller J, et al. Lancet 2000

AGREE

Appraisal of Guidelines for Research & Evaluation

www.agreecollaboration.org

- Strumento per la valutazione di qualità delle LG
- Elaborata da un gruppo internazionale
- Finanziamento della Comunità Europea

- 23 item
  - obiettivi della LG
  - coinvolgimento delle parti in causa
  - rigore metodologico
  - chiarezza espositiva
  - applicabilità ed indipendenza editoriale

Royal College of Physicians
Bone and Tooth Society of Great Britain

Osteoporosis
Clinical guidelines for Prevention and Treatment

London: Royal College of Physicians, 2000

Updated on January 5, 2001

Grading of recommendations and evidence levels

Levels of evidence are defined as follows:

Ia	from meta-analysis of randomised controlled trials (RCTs)
Ib	from at least one RCT
IIa	from at least one well designed controlled study without randomisation
IIb	from at least one other type of well designed quasi-experimental study
III	from well designed non-experimental descriptive studies, eg comparative studies, correlation studies, case-control studies
IV	from expert committee reports or opinions and/or clinical experience of authorities
I	from meta-analysis of observational studies (see following text)

The quality of the guideline recommendations is similarly graded to indicate the levels of evidence on which they are based:

grade A	evidence levels Ia and Ib
grade B	evidence levels IIa, IIb and III
grade C	evidence level IV

Royal College of Physicians, 2000

Recommendations concerning interventions for the prevention of osteoporosis

Intervention	Bone mineral density	Vertebral fracture	Hip fracture
Exercise	A	B	B
Pharmacological calcium (± vitamin D)	A	B	B
Dietary calcium	B	B	B
Smoking cessation	B	B	B
Reduced alcohol consumption	C	C	B
Oestrogen	A	B	B
Raloxifene	A	A	–
Etidronate	A	–	–
Alendronate	A	–	–

Royal College of Physicians, 2000

Recommendations concerning interventions for the treatment of osteoporosis

Intervention	Bone mineral density	Vertebral fracture	Hip fracture
Calcium (± vitamin D)	A	A	B
Oestrogen	A	A	B
Alendronate	A	A	A
Etidronate	A	A	B
Calcitonin	A	A	B
Fluoride*	A	A†	–
Anabolic steroids	A	–	B
Calcitriol	A	A†	C

* These agents are not at present licensed in the UK for use in osteoporosis but are used in specialist centres.
† Inconsistent data.

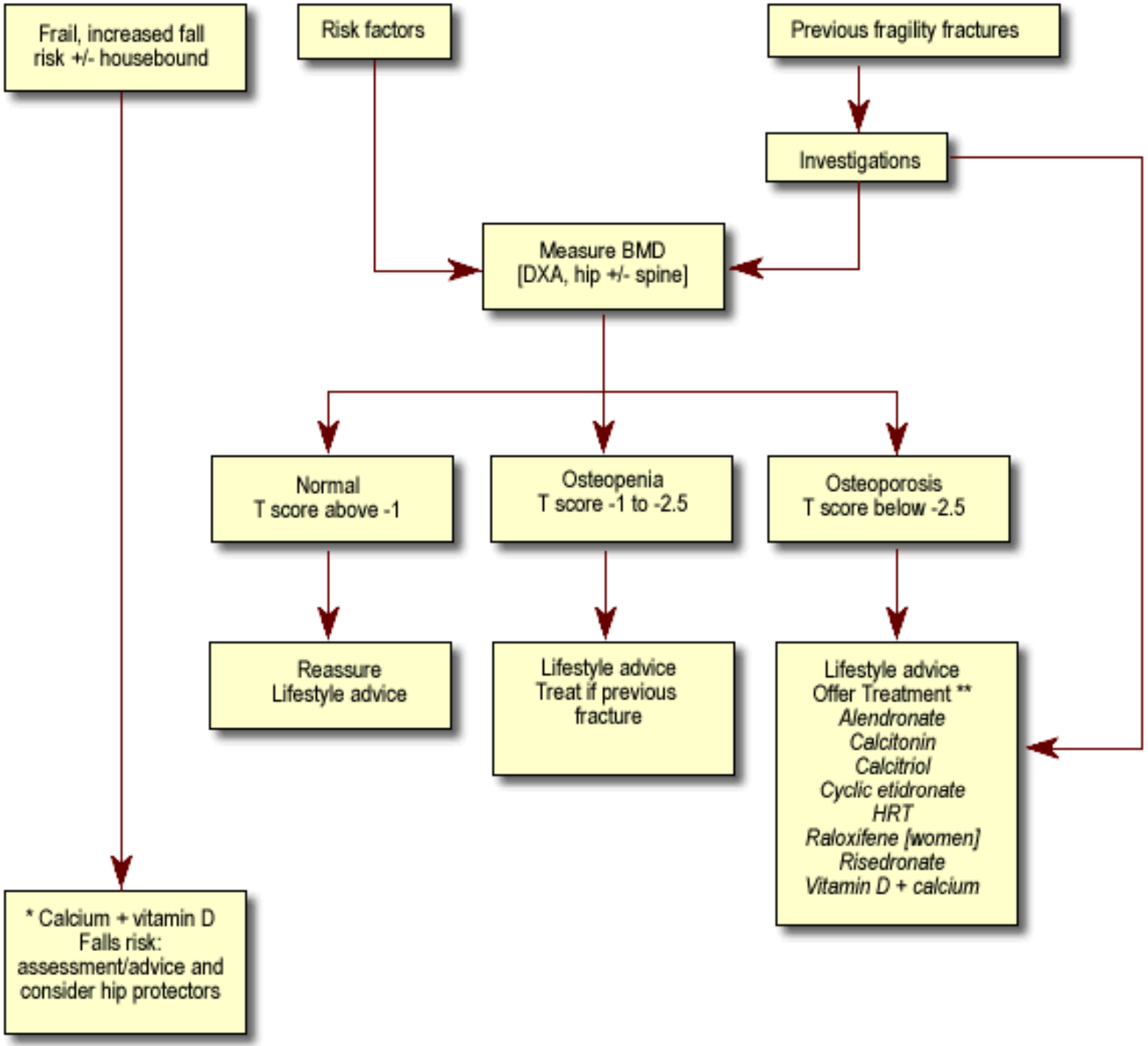
Royal College of Physicians, 2000

Effect of interventions on the prevention/reduction of postmenopausal bone loss

• Alendronate	A
• Calcitonin	A
• Calcitriol	A
• Calcium	A
• Cessation of smoking	B
• Cyclic etidronate	A
• HRT	A
• Physical exercise	A
• Raloxifene	A
• ↓ Alcohol intake	C
• Risedronate	A
• Tibolone	A
• Vitamin D + calcium	A

Antifracture efficacy of interventions in postmenopausal osteoporotic woman

	Spine	Non-vertebral	Hip
• Alendronate	A	A	A
• Calcitonin	A	B	B
• Calcitriol	A	A	nd
• Calcium	A	B	B
• Calcium + vit D	nd	A	A
• Cyclic etidronate	A	B	B
• Hip protectors	-	-	A
• HRT	A	A	B
• Physical exercise	nd	B	B
• Raloxifene	A	nd	nd
• Risedronate	A	A	A
• Tibolone	nd	nd	nd
• Vitamin D	nd	B	B


Frail, increased fall risk +/- housebound
Risk factors
Previous fragility fractures
Investigations
Measure BMD [DXA, hip +/- spine]
Normal T score above -1
Osteopenia T score -1 to -2.5
Osteoporosis T score below -2.5
Reassure Lifestyle advice
Lifestyle advice Treat if previous fracture
Lifestyle advice Offer Treatment ** Alendronate Calcitonin Calcitriol Cyclic etidronate HRT Raloxifene [women] Risedronate Vitamin D + calcium
* Calcium + vitamin D Falls risk: assessment/advice and consider hip protectors

Neer RM, Arnaud CD, Zanchetta JR, et al

Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis

N Engl J Med May, 10 2001

Zarnke KB,Campbell NRC,McAlister FA,Levine M

A novel process for annually updating clinical practice guidelines for hypertension. Background and methodological approach

Can J Cardiol 2000;16:1094-102

4. Applicabilità dello studio MORE

Rothwell PM

Can overall results of clinical trials be applied to all patients?

Lancet 1995;345:1616-19

Users'guides to the medical literature

XIV. How to decide on the applicability of clinical trial results to your patient. JAMA 1998;279:545-9

XX. Integrating reasearch evidence with care of the individual patient JAMA 2000; 283:2829-36

- Are there differences in demographic or clinical characteristics of my patient that can alter response to the treatment? (eg: higher or lower baseline risk of an event as compared to the patients in the trial)

- Has my patient comorbid conditions, or is he receiving concurrent treatments tha can alter his response to the treatment, or bring about risk of harm?

- Are there important differences in local health resources that may diminish the safety and efficacy of the treatment ? (eg: distance from a laboratory to perform the tests necessary for titration of warfarin).

- Treatments requiring technical skill (eg: surgery, endoscopic treatments) or sophisticated equipment: is my setting sufficient to reproduce the results obtained in the trial?

4. Studio MORE: i criteri di esclusione

- Altre malattie ossee
- Sintomi post-menopausali sostanziali
- Sanguinamento uterino anormale
- **Storia di cancro al seno** o endometriale o di disturbi tromboembolici
- Altre forme neoplastiche
- Disordini endocrini intrattamento, ad eccezione di diabete di tipo 2 o ipotiroidismo
- Litiasi renale, funzionalità epatica o renale anormale, malassorbimento non trattato
- Consumo di più di quattro bevande alcooliche al giorno
- Assunzione di farmaci:
  - androgeni, calcitonina, bifosfonati nei precedenti 6 mesi;
  - estrogeni orali nei precedenti 2 mesi
  - fluoruri per più di 3 mesi nei precedenti 2 anni
  - glucocorticoidi sistemici per più di un mese nell'ultimo anno
  - antiepilettici o colecalciferolo.

Il metodo di presentazione dei risultati

Medici, amministratori sanitari e pazienti sono più entusiasti nei confronti degli interventi terapeutici presentati con misure di efficacia relativa, che hanno la capacità di enfatizzarne l'efficacia.

Naylor CD, et al. Ann Intern Med 1992
Forrow L, et al. Am J Med 1992
Bobbio M, et al. Lancet 1994
Bucher HC, et al. BMJ 1994
Fahey T, et al. BMJ 1995
Hux JE, et al. Med Decis Making 1995

BENEFIT
Evento= Fratture vertebrali

	Evento		Rischio di sviluppare l'evento
	Presente	Assente	
Trattati	35	1455	EER= 0.023
Controlli	68	1454	CER= 0.045

- Riduzione del Rischio Relativo — RRR= 47% (19% to 76%)
- Riduzione del Rischio Assoluto — RRA= 0.021 (0.008 to 0.034)
- **Numero Necessario da Trattare — NNT= 47 (29 to 120)**

PEP trial. Lancet 2000

NNT nello studio MORE

Tutte

• 60 mg	29 (20 to 52)
• 120 mg	22 (17 to 33)

Con precedenti fratture

• 60 mg	16 (10 to 38)
• 120 mg	10 (7 to 15)

Senza precedenti fratture

• 60 mg	47 (29 to 120)
• 120 mg	59 (33 to 274)

≥ 1 vertebral fracture with raloxifene vs placebo in postmenopausal osteoporosis at 3 years†

Women	Raloxifene dose	Raloxifene	Placebo	RRR (95%)	NNT
All	60 mg/d	6.6%	10.1%	35% (21 to 47)	29 (20 to 52)
	120 mg/d	5.4%	10.1%	46% (33 to 56)	22 (17 to 33)
With previous fractures	60 mg/d	14.7%	21.2%	35% (19 to 48)	16 (10 to 38)
	120 mg/d	10.7%	21.2%	53% (40 to 63)	10 (7 to 15)
With no previous fractures	60 mg/d	2.3%	4.5%	47% (22 to 65)	47 (29 to 120)
	120 mg/d	2.8%	4.5%	38% (9 to 57)	59 (33 to 274)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

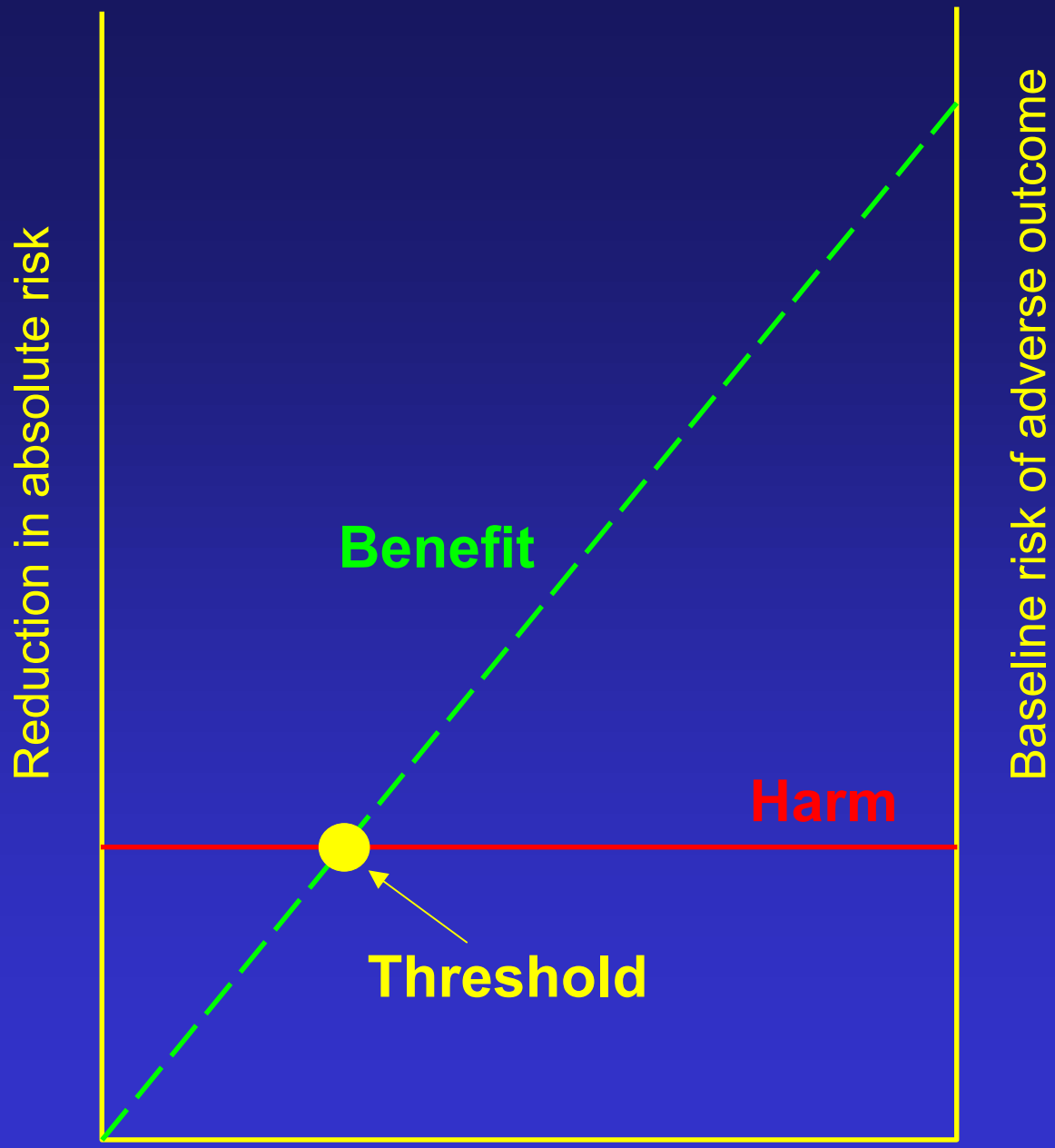
ACP Journal Club, March/April 2000

Il rischio basale

- Il beneficio che il paziente individuale può ottenere da un intervento terapeutico cresce proporzionalmente al suo rischio basale di sviluppare l'evento sfavorevole.

- Il rischio di effetti avversi conseguenti al trattamento é indipendente da tale rischio basale.

Glasziou P et al. BMJ 1995



Glasziou P, et al.
BMJ 1995

HARM

Evento= Trombosi venosa profonda o embolia polmonare

	Evento		Rischio di sviluppare l'evento
	Presente	Assente	
Trattati	49	5080	EER= 0.010
Controlli	8	2568	CER= 0.003

Number Needed to Harm

NNH= 155 (101 to 330)

PEP trial. Lancet 2000