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CONTROVERSIA

¿EDAD AVANZADA Y PLURIPATOLOGÍA SON UN CONDICIONANTE PARA EL TRATAMIENTO DE LA OSTEOPOROSIS?

Manuel Sosa Henríquez
Servicio de Medicina Interna
Unidad Metabólica Ósea


Transportes Olmos SA

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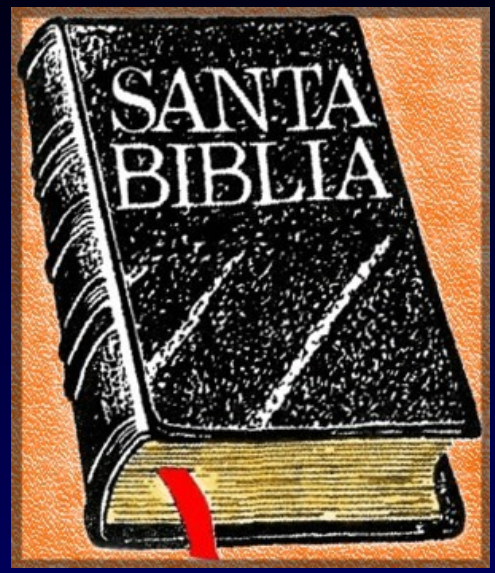


No solo de pan vive el hombre
Mateo 13, 4

No solo con fármacos se trata al paciente

Sosa 16, 8

1. Dejar de fumar

A Meta-Analysis of the Effects of Cigarette Smoking on Bone Mineral Density

Kenneth D. Ward, Robert C. Klesges

Osteoporos Int 2001;68:259-70

86 estudios 40753 pacientes.
FV: Mujeres 13% y varones 32%
Cadera: Mujeres: 31% Varones 40%

Tobacco smoking and risk of hip fracture in men and women

Susanne Høidrup,[a] Eva Prescott,[a] Thorkild IA Sørensen,[a] Adam Gottschau,[a] Jes Bruun Lauritzen,[b] Marianne Schroll[c] and Morten Grønbæk[a]

Int J Epidemiology 2000;29:253-9

3 estudios longitudinales daneses. Más de 30.000 personas examinadas.
A los 5 años, los varones que dejan de fumar reducen el RR de fractura de cadera al de los no fumadores

2. Moderar el consumo de alcohol

Alcohol intake as a risk factor for fracture

John A. Kanis · Helena Johansson · Olof Johnell
Anders Oden · Chris De Laet · John A. Eisman
Huibert Pols · Alan Tenenhouse

Osteoporos Int 2005:16:737-42

Studios CaMos, DOES y Rotterdam. 5939 varones y 11032 mujeres.
3 y más bebidas al día incrementa el riesgo de fractura:
- 23% cualquier fractura
- 38% cualquier fractura osteoporótica
- 48% fractura de cadera

El abandono del hábito alcohólico mejora la DMO

Peris P et al. Bone mass improves in alcoholics after 2 years of abstinence. J Bone Miner Research. 1994;9:1607-12

3. Realizar ejercicio físico de manera continua

Habitual physical activity and bone mineral density in postmenopausal women in England

Carol AC Coupland,[a] Susan J Cliffe,[a] E Joan Bassey,[b] Matthew J Grainge,[a] David J Hosking[c] and Clair ED Chilvers[a]

Int J Epidemiol 1999;28:241-6

Estudio EPIC 7784 mujeres. UK (Nottingham). Caminar y subir escaleras aumenta la DMO en cuello femoral y cadera total

Physical activity and hip fracture: a population-based case-control study

Bahman Y Farahmand,[a] Per-Gunnar Persson,[a] Karl Michaëlsson,[b] John A Baron,[c] Akke Alberts,[d] Tahere Moradi,[e] Sverker Ljunghall[f] for the Swedish Hip Fracture Study Group[g]

Int J Epidemiol 2000;29:308-14

Suecas. 4589 mujeres. 33% reducción RR fractura de cadera caminando 1-2 horas por semana y 52% caminando mas de 3 horas por semana

4. Tiazidas

Estudio Rotterdam

7.891 pacientes

Utilizándose al menos 1 año se reduce el RR de fractura de cadera 54%

Article

Thiazide Diuretics and the Risk for Hip Fracture

Mariette W.C.J. Schoofs, MD, MSc; Marjolein van der Klift, PhD; Albert Hofman, MD, PhD; Chris E.D.H. de Laet, MD, PhD; Ron M.C. Herings, PharmD, PhD; Theo Stijnen, PhD; Huibert A.P. Pols, MD, PhD; and Bruno H.Ch. Stricker, MB, PhD

Background: Since most hip fractures are related to osteoporosis, treating accelerated bone loss can be an important strategy to prevent hip fractures. Thiazides have been associated with reduced age-related bone loss by decreasing urinary calcium excretion.

Objective: To examine the association between dose and duration of thiazide diuretic use and the risk for hip fracture and to study the consequences of discontinuing use.

Design: Prospective population-based cohort study.

Setting: The Rotterdam Study.

Participants: 7891 individuals 55 years of age and older.

Measurements: Hip fractures were reported by the general practitioners and verified by trained research assistants. Details of all dispensed drugs were available on a day-to-day basis. Exposure to thiazides was divided into 7 mutually exclusive categories: never use, current use for 1 to 42 days, current use for 43 to 365 days, current use for more than 365 days, discontinuation of use since 1 to 60 days, discontinuation of use since 61 to 120 days, and discontinuation of use since more than 120 days.

Results: 281 hip fractures occurred. Relative to nonuse, current use of thiazides for more than 365 days was statistically significantly associated with a lower risk for hip fracture (hazard ratio, 0.46 [95% CI, 0.21 to 0.96]). There was no clear dose dependency. This lower risk disappeared approximately 4 months after thiazide use was discontinued.

Conclusions: Thiazide diuretics protect against hip fracture, but this protective effect disappears within 4 months after use is discontinued.

Ann Intern Med. 2003;139:476-482. www.annals.org

For author affiliations, see end of text.

Hip fractures are associated with substantial morbidity and mortality. The costs of surgery and rehabilitation are a burden on public health resources, especially because the incidence of hip fracture increases as the population ages (1, 2). Most hip fractures are related to osteoporosis, and treating accelerated bone loss may therefore be an important strategy to prevent hip fractures (3).

Thiazide diuretics are widely used as antihypertensive agents. They are inexpensive and effective and have few important adverse effects (4). Thiazides are thought to protect against age-related bone loss by reducing urinary calcium excretion (5). This bone-sparing effect could lead to reduced fracture incidence in patients treated for hypertension. Several epidemiologic studies have examined the effect of thiazides on bone mineral density and fracture incidence. Although bone mineral density was found to be increased in thiazide users, the difference was often small (6–12). Thiazides were found to have a protective effect on hip fracture in most studies (9, 12–17), but occasionally an increased risk was found (18). Most of the studies, however, had limitations. Some studies included detailed drug-dispensing data but limited information on potential confounders and effect modifiers (15, 18, 19). Other studies had small patient samples or used only baseline interview data on thiazide use (9, 12, 16, 20) without accounting for timing of thiazide use (14, 20, 21). Detailed information on thiazide dose and duration of use was often absent or unreliable because no data on day-to-day use were available. Because of these limitations, it is still unclear how long thiazides have to be taken to affect fracture incidence and how long this effect persists after thiazide use is discontinued.

We conducted a prospective, population-based cohort study using detailed drug-dispensing information, as well as extensive information on potential risk factors, to examine the association between current and past use of thiazides and the incidence of hip fractures in men and women 55 years of age and older. We also studied the effect of discontinuing thiazide use on fracture risk.

Methods

Study Sample

This study was conducted as part of the Rotterdam Study, a prospective, population-based cohort study on the occurrence and determinants of disease and disability in elderly persons (22). In 1990, all inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, who were 55 years of age or older and had lived in the district for at least 1 year were invited to participate in the study. Of the 10 275 eligible persons, 7983 (78%) participated. Participants gave informed consent and permission to retrieve information from medical records. At baseline, between 1990 and 1993, trained interviewers administered an extensive questionnaire covering socioeconomic background and medical history, among other topics, during a home interview. During subsequent visits to the study center, additional interviewing, laboratory assessments, and clinical examinations were performed. Information on vital status is obtained at regular time intervals from the municipal authorities in Rotterdam. The Medical Ethics Committee of the Erasmus MC, Rotterdam, the Netherlands, approved the study.

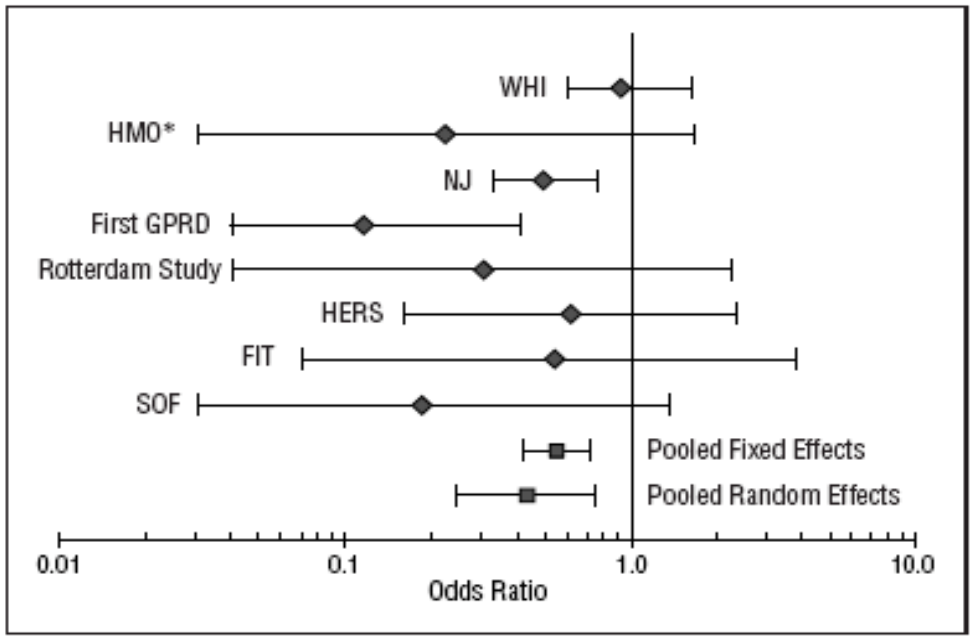
For the present study, all participants were followed from 1 June 1991 until they had an incident hip fracture,

MWCJ Schoofs et al Annals of Internal Medicine 2003;139:476-82

5. Estatinas

Reducción del RR de fractura de cadera 57%

Reducción RR FNV: 31%



ORIGINAL INVESTIGATION

Use of Statins and Fracture

Results of 4 Prospective Studies and Cumulative Meta-analysis of Observational Studies and Controlled Trials

Douglas C. Bauer, MD; Greg R. Mundy, MD; Sophie A. Jamal, MD; Dennis M. Black, PhD; Jane A. Cauley, DrPH; Kristine E. Ensrud, MD, MPH; Marjolein van der Klift, MSc; Huibert A. P. Pols, MD, PhD

Background: The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are widely used for the treatment of hyperlipidemia, and recent in vitro and animal data suggest that statins promote bone formation and increase bone strength.

Methods: To determine whether statin use is associated with a reduced risk for fracture, we analyzed statin use and fracture rates in 4 large prospective studies (the Study of Osteoporotic Fractures, the Fracture Intervention Trial, the Heart and Estrogen/Progestin Replacement Study, and the Rotterdam Study). We searched MEDLINE through January 2002 and abstracts from major scientific meetings and performed a cumulative meta-analysis of published and unpublished observational studies and clinical trials. The meta-analysis included 8 observational studies and 2 clinical trials that reported statin use and documented fracture outcomes.

Results: After adjustment for multiple factors, including age, body mass index, and estrogen use, we found a trend toward fewer hip fractures (relative hazards [RHs], 0.19-0.62) and, to a lesser extent, nonspine fractures (RHs, 0.49-0.95) among statin users in each of the 4 prospective studies. The meta-analysis of observational studies was consistent with these findings. The summary odds ratio (OR) for statin use and hip fracture was 0.43 (95% confidence interval [CI], 0.25-0.75), whereas that for nonspine fracture was 0.69 (95% CI, 0.55-0.88). The meta-analysis of clinical trial results did not support a protective effect with statin use for hip fracture (summary OR, 0.87; 95% CI, 0.48-1.58) or nonspine fracture (OR, 1.02; 95% CI, 0.83-1.26).

Conclusions: Observational studies suggest that the risk for hip and nonspine fractures is lower among older women taking statin medications for hyperlipidemia, but post hoc analyses of cardiovascular trials do not. Controlled trials specifically designed to test the effect of statins on skeletal metabolism and fracture are needed.

Arch Intern Med. 2004;164:146-152

Author affiliations are listed at the end of this article.

Dr Bauer has consulted for Pfizer and Astra Zeneca and has received research support from Merck. Dr Mundy has consulted for Astra Zeneca and Novartis, has a research contract with Biogen, and has stock in Osteoscreen, Inc. Dr Black has received research support from Merck and Novartis. Dr Cauley has received research funding from Merck, Pfizer, Eli Lilly, Roche, and Wyeth Ayerst and is on the speaker bureau for Eli Lilly and Proctor and Gamble. Dr Ensrud has received research grant support from Merck, Eli Lilly, Berlex, and Pfizer. Dr Pols has consulted for Merck, Eli Lilly, and Aventis/Procter and Gamble.

THE 3-HYDROXY-3-METHYLglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are widely used medications for the treatment of hyperlipidemia. Recent in vitro and in vivo animal studies have found that these agents promote bone formation, possibly by stimulating osteoblast transcription of bone morphogenetic protein 2 (BMP-2).[1] If such beneficial effects are also found in humans, statins might be clinically useful for the prevention and treatment of osteoporosis.

Although the lipid effects of statins have been widely studied, few human data are available about the skeletal effects of these agents. Several case-control studies have found that statin use is associated with a reduced risk for fracture,[2-4] and other studies have suggested that bone mass is higher among individuals prescribed statin medications.[5,6] However, a recent reanalysis of one of the previously published case-control studies[7] and another large prospective cohort study[8] failed to find any association between statin use and fracture. Furthermore, post hoc analyses from 2 clinical trials designed to assess the cardiovascular effects of statins found no protective effect.[9,10]

CME course available at www.archinternmed.com

We hypothesized that the bone anabolic effects observed in animal models might also be apparent with the clinical use of statins, particularly in postmenopausal women. Therefore, we examined the effect of statin use on bone mass and fracture rates among older women enrolled in 4 large prospective studies. To estimate the overall effect of statin use on hip and nonspine fracture rates, we com-

Bauer et al. **Use of statins and fracture: results of 4 prospective studies and cumulative meta-analysis of observational studies and controlled trials. Arch Intern Med 2004;164:146-52**

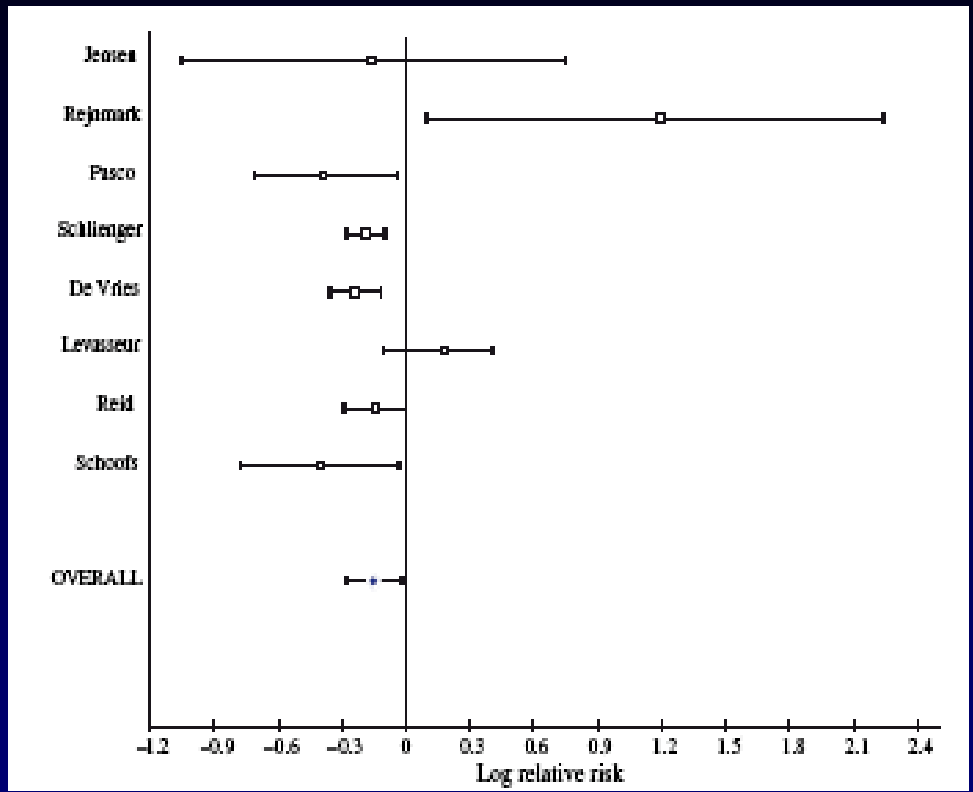
6. Beta-bloqueantes

Meta-análisis

Tiazidas: Reducción 14%

Beta-bloqueantes: 14%

IECA: 19%



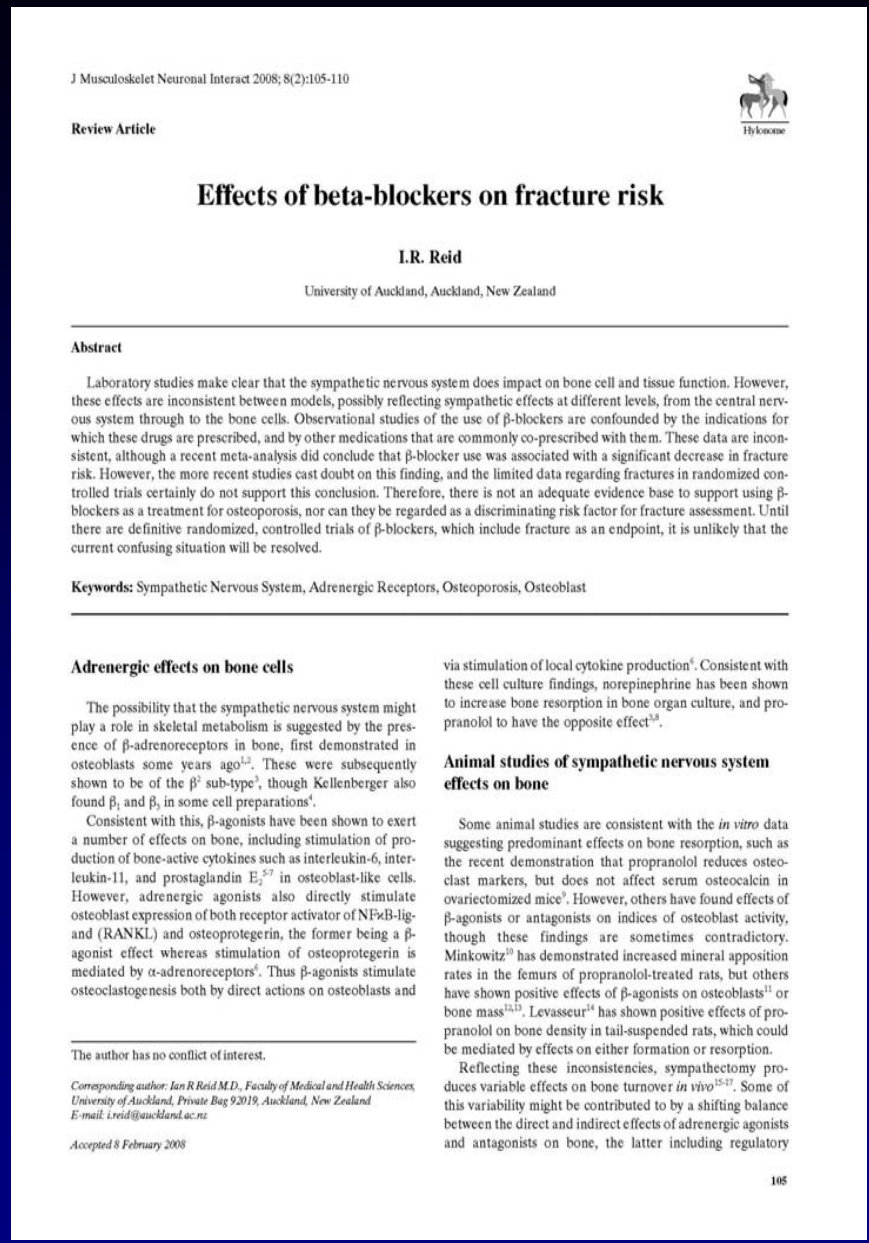
Wiens M et al: Effects of anti-hypertensive drug treatments on fracture outcomes: a meta-analysis of observational studies. J Intern Med 2006;260:350-62

6. Beta-bloqueantes

Revisión sistemática

Datos no concluyentes

Parece existir una tendencia a que los beta-bloqueantes reducen el RR de FX



J Musculoskelet Neuronal Interact 2008; 8(2):105-110

Review Article

Hylonome

Effects of beta-blockers on fracture risk

I.R. Reid

University of Auckland, Auckland, New Zealand

Abstract

Laboratory studies make clear that the sympathetic nervous system does impact on bone cell and tissue function. However, these effects are inconsistent between models, possibly reflecting sympathetic effects at different levels, from the central nervous system through to the bone cells. Observational studies of the use of β-blockers are confounded by the indications for which these drugs are prescribed, and by other medications that are commonly co-prescribed with them. These data are inconsistent, although a recent meta-analysis did conclude that β-blocker use was associated with a significant decrease in fracture risk. However, the more recent studies cast doubt on this finding, and the limited data regarding fractures in randomized controlled trials certainly do not support this conclusion. Therefore, there is not an adequate evidence base to support using β-blockers as a treatment for osteoporosis, nor can they be regarded as a discriminating risk factor for fracture assessment. Until there are definitive randomized, controlled trials of β-blockers, which include fracture as an endpoint, it is unlikely that the current confusing situation will be resolved.

Keywords: Sympathetic Nervous System, Adrenergic Receptors, Osteoporosis, Osteoblast

Adrenergic effects on bone cells

The possibility that the sympathetic nervous system might play a role in skeletal metabolism is suggested by the presence of β-adrenoreceptors in bone, first demonstrated in osteoblasts some years ago[1,2]. These were subsequently shown to be of the β^2 sub-type[3], though Kellenberger also found β_1 and β_3 in some cell preparations[4].

Consistent with this, β-agonists have been shown to exert a number of effects on bone, including stimulation of production of bone-active cytokines such as interleukin-6, interleukin-11, and prostaglandin E_2[5-7] in osteoblast-like cells. However, adrenergic agonists also directly stimulate osteoblast expression of both receptor activator of NFκB-ligand (RANKL) and osteoprotegerin, the former being a β-agonist effect whereas stimulation of osteoprotegerin is mediated by α-adrenoreceptors[6]. Thus β-agonists stimulate osteoclastogenesis both by direct actions on osteoblasts and via stimulation of local cytokine production[6]. Consistent with these cell culture findings, norepinephrine has been shown to increase bone resorption in bone organ culture, and propranolol to have the opposite effect[3,8].

Animal studies of sympathetic nervous system effects on bone

Some animal studies are consistent with the *in vitro* data suggesting predominant effects on bone resorption, such as the recent demonstration that propranolol reduces osteoclast markers, but does not affect serum osteocalcin in ovariectomized mice[9]. However, others have found effects of β-agonists or antagonists on indices of osteoblast activity, though these findings are sometimes contradictory. Minkowitz[10] has demonstrated increased mineral apposition rates in the femurs of propranolol-treated rats, but others have shown positive effects of β-agonists on osteoblasts[11] or bone mass[12,13]. Levasseur[14] has shown positive effects of propranolol on bone density in tail-suspended rats, which could be mediated by effects on either formation or resorption.

Reflecting these inconsistencies, sympathectomy produces variable effects on bone turnover *in vivo*[15-17]. Some of this variability might be contributed to by a shifting balance between the direct and indirect effects of adrenergic agonists and antagonists on bone, the latter including regulatory

The author has no conflict of interest.

Corresponding author: Ian R Reid M.D., Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand
E-mail: i.reid@auckland.ac.nz

Accepted 8 February 2008

Reid I. J Musculoeskelet Neuronal Interact 2008;8:105-10

7. Prevención de las caídas

- Los pacientes con fractura de cadera habían tenido un promedio de 1.9 caídas el año anterior
- El 24% se había caído repetidamente

Formiga F, et al: Characteristics of falls producing hip fractures in nonagenarians. J Nutr Health Aging. 2008;12:664-7

Formiga F et al: Factors associated with hip fracture-related falls among patients with a history of recurrent falling. Bone 2008;43:941-4

Formiga F et al: Características de las caídas que producen fractura de cadera en una población anciana. Rev Clin Esp 2006;206:314-8

EFECTO FORMIGA

1. Deja de fumar
2. Modera el consumo de alcohol
3. Comienza a realizar ejercicio
4. Le indicamos una tiazida*
5. Le indicamos una estatina*
6. Le indicamos un beta-bloqueante*
7. Le aplicamos el plan “Formiga”
8. Adecuamos el Calcio y la Vitamina D

¿Necesita realmente que le añadamos un fármaco más?

* Si lo precisa

¿Hay vida más allá de la medicación?

CONTROVERSIA

¿EDAD AVANZADA Y PLURIPATOLOGÍA SON UN CONDICIONANTE PARA EL TRATAMIENTO DE LA OSTEOPOROSIS?

¿Es preciso añadir más fármacos?

Primum non-nocere

Tienen efectos secundarios

Ninguno reduce el riesgo de fractura al 100%

Muy pocos reducen el riesgo de fractura de cadera

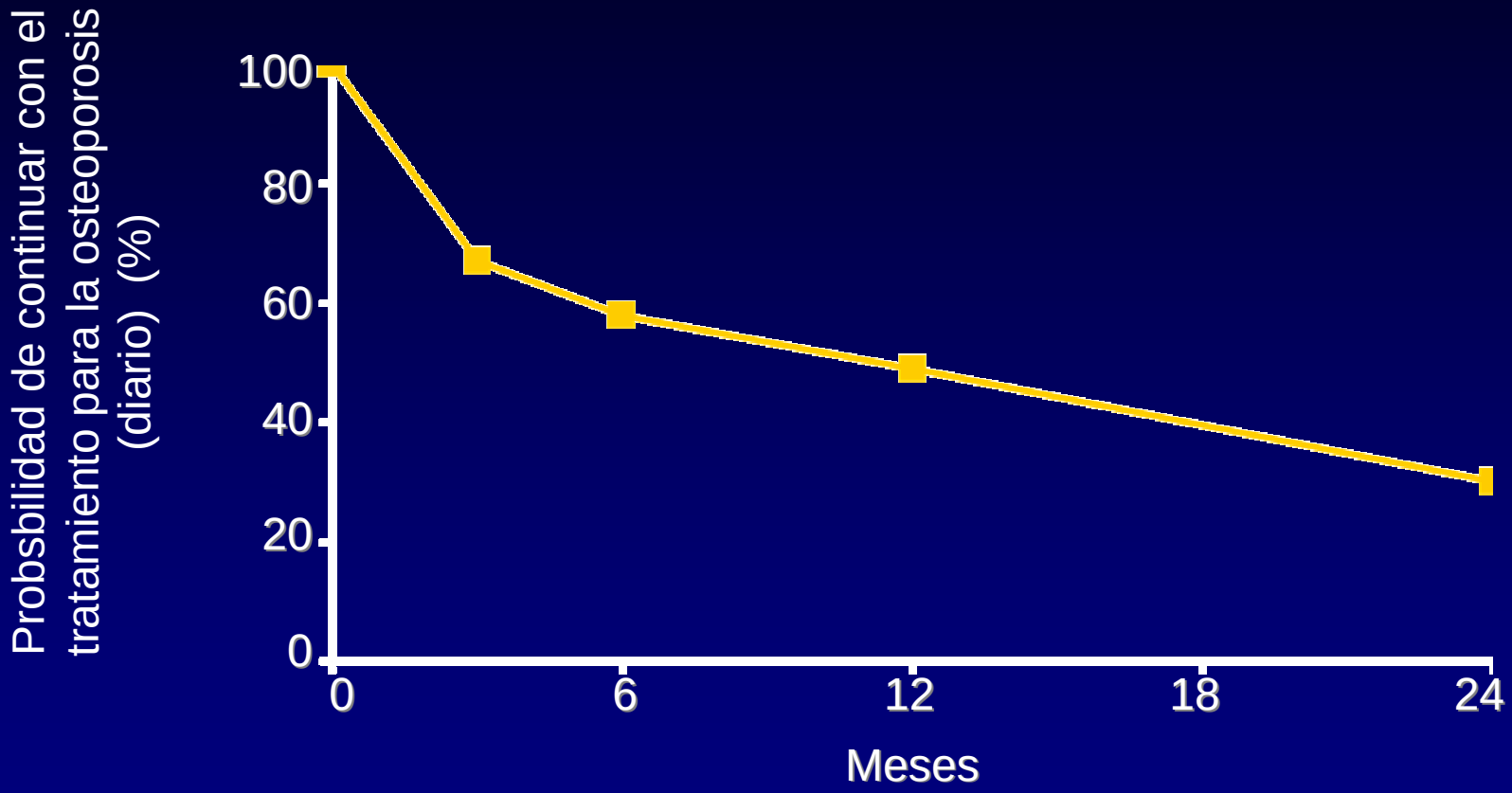
Fármacos en los que no se ha demostrado reducción del riesgo de fractura de cadera

1. Etidronato
2. Ibandronato
3. Pamidronato
4. Raloxifeno
5. Calcitonina
6. PTH 1-34
7. PTH intacta

1. Calcio y Vitamina D
2. Alendronato
3. Risedronato
4. Zoledronato

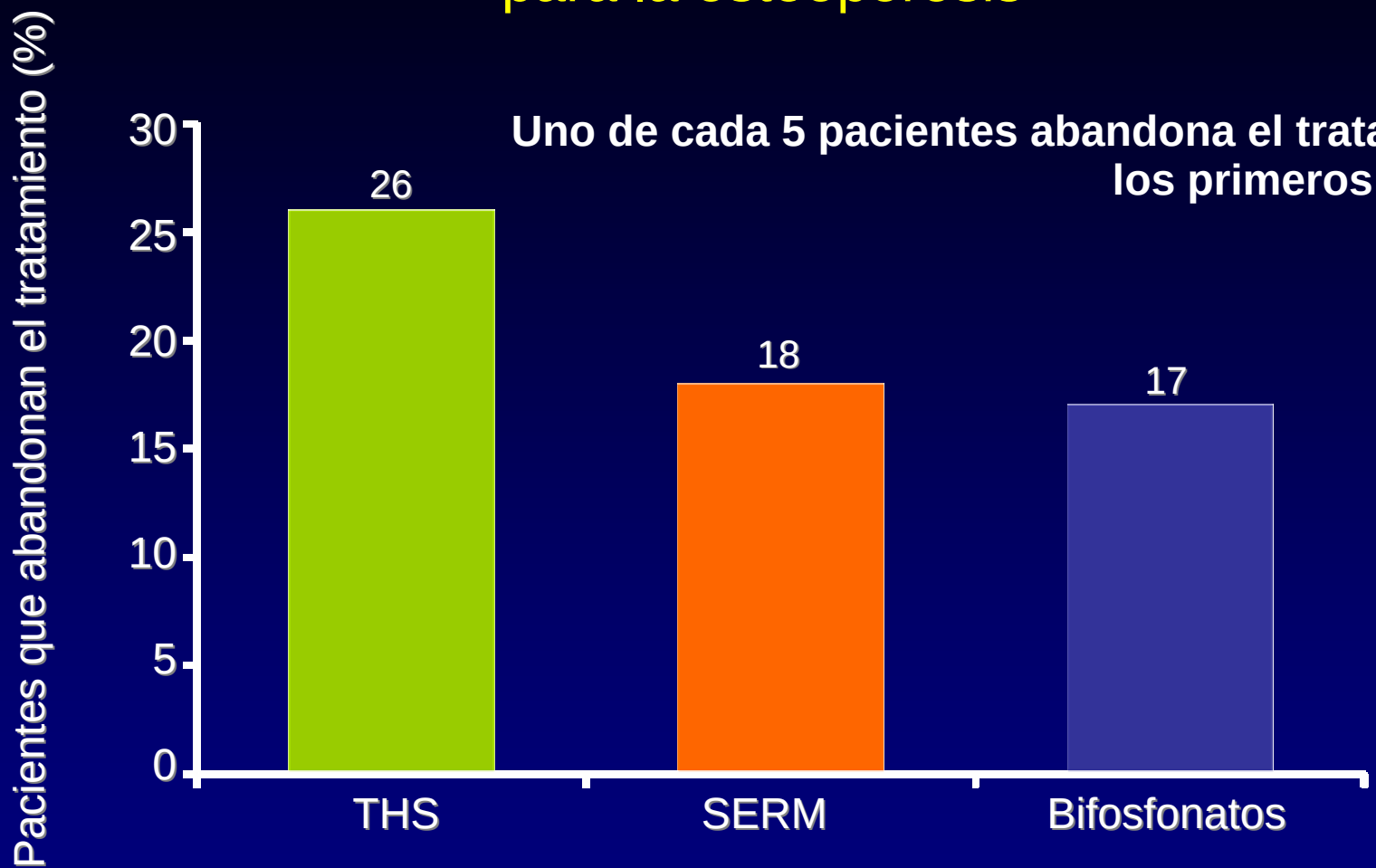
Estroncio

Los pacientes no toman correctamente el tratamiento para la osteoporosis



Lombas C, et al. J Bone Miner Res 2001;16(Suppl. 1):S529

Los pacientes no toman correctamente el tratamiento para la osteoporosis

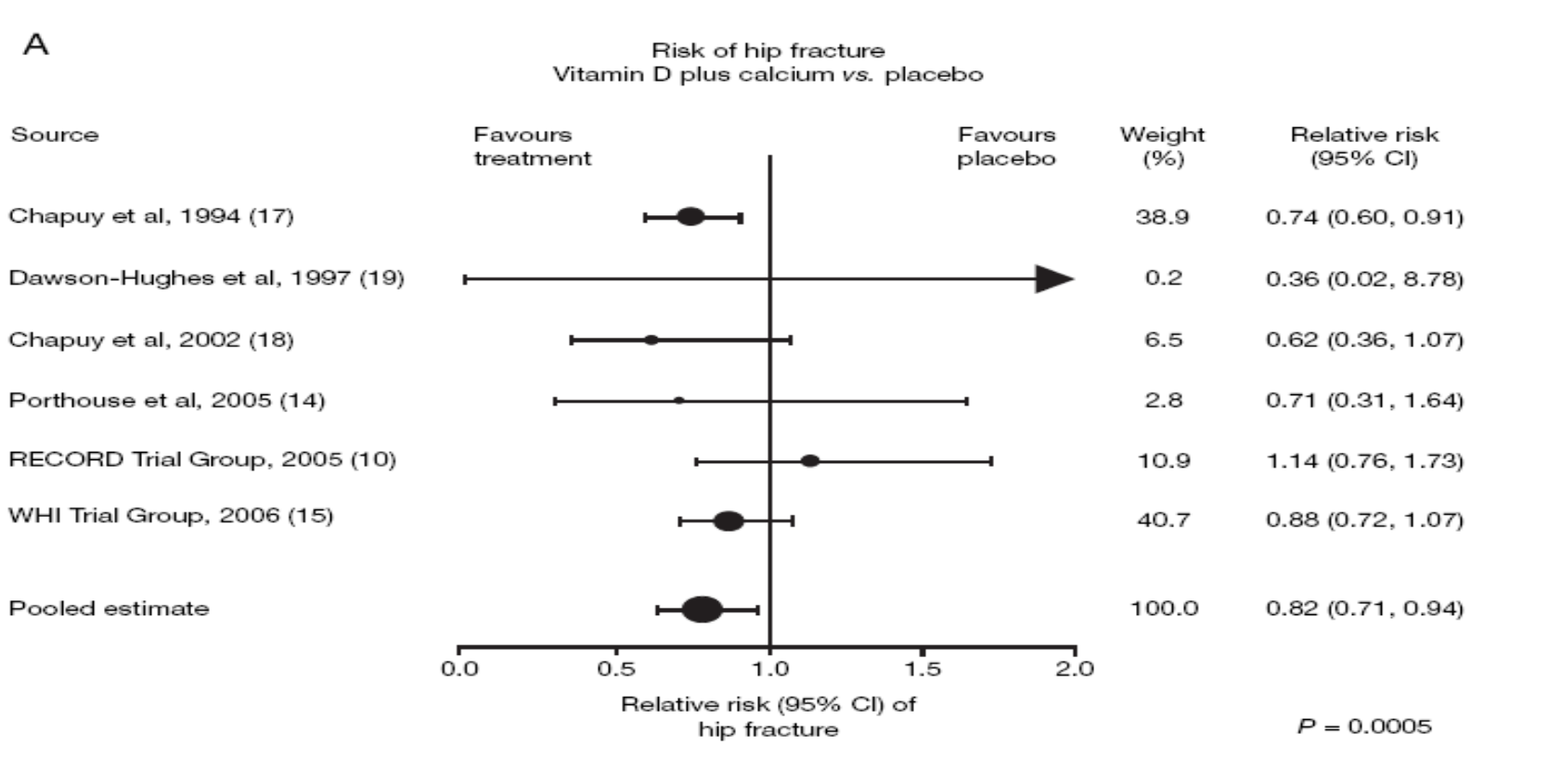


Uno de cada 5 pacientes abandona el tratamiento en los primeros 6-7 meses

***77% de los pacientes recibían tratamiento semanal**

Tosteson A, et al. Am J Med 2003;115:209–16
Bandeira F, et al. J Bone Miner Res 2003;18(Suppl. 2):S379

Reducción del RR de fractura de cadera con Calcio y Vitamina D. Meta-análisis



Boonen S et al. J Clin Endocrinol Metab 2007

Efectos extraóseos de la Vitamina D

Prevención de caídas (Efecto Formiga)

Reducción del riesgo en un 35% (1)
(En personas mayores de 70 años y particularmente en mujeres)

Muchas otras patologías

- HTA y riesgo cardiovascular
- Psoriasis
- Cáncer
- Esclerosis múltiple
- Diabetes
- Otras: AR, LES, enf. inflamatoria intestinal …(2)

(1) Bischoff-Ferrari et al. JAMA 2004;291:1999-2006.

(2) Holick M. Mayo Clin Proc 2006;81:353-73

Mortalidad. Ca y Vitamina D

- 5 estudios :

  Ca y Vitamina D (RECORDA, Porthouse, Larsen)
  Vitamina D sola (Smith, RECORDB, Meyer)

  Total de 28.710 participantes edad media 77a (48-103)

- **Ca y Vitamina D:** HR 0,88 (0,81-0,97) p = 0,01
- **Vit D sola:** HR 0,95 (0,85-1,05) p = 0,28

Abrahamsen B et al ASBMR 2009

La Salud no tiene precio

Pero la Sanidad tiene un presupuesto

Conclusiones

1. Disponemos de un buen número de medidas no-farmacológicas que son muy eficaces en la reducción del riesgo de fractura: ejercicio físico, dejar de fumar, moderar el alcohol que sistemáticamente se olvidan
2. Los pacientes con pluripatología y los de edad avanzada suelen estar polimedicados y algunos de estos fármacos pueden ser beneficiosos para el hueso
3. Los pacientes por lo general no toman como debieran la medicación para la osteoporosis. Hay una elevada tasa de incumplimiento

Conclusiones

4. El calcio y la vitamina D son eficaces en la reducción del riesgo de fractura e incluso reducen la mortalidad
5. La Vitamina D tiene además muchos efectos extraóseos beneficiosos. Estos pueden obtenerse por la dieta y por exposición solar
6. En la reducción del riesgo de fractura, la prevención de las caídas es una medida tan eficaz o más que cualquiera de los fármacos disponibles en el mercado para el tratamiento de la osteoporosis