FACULTAD DE MEDICINA
PONTIFICIA UNIVERSIDAD
CATÓLICA DE CHILE

XXXII CONGRESO DE LA SOCIEDAD CHILENA DE OSTEOLOGÍA Y METABOLISMO MINERAL - SCHOMM

"**Antirresortivos:** efecto en la mortalidad de mujeres postmenopáusicas "

Dr. Pablo Florenzano V.
Profesor Asociado
Depto. Endocrinología UC

Conflictos de Interés

Declaro que en los últimos 5 años he recibido de laboratorios, industrias o instituciones con fines comerciales:

- Fondos para investigacion:
    - Unrestricted research grant Ultragenyx pharmaceuticals:
        - Clinical And Molecular Characterization Of Patients With XLH And Other Forms Of FGF23-Mediated Hypophosphatemia In Chile.
        - Enthesopathy, osteoarthritis and muscular involvement and its correlation with biochemical abnormalities and quality of life in patients with X-Linked Hypophosphatemia (XLH)
- Consultorías: International Hypophosphataemia Network (IHN) Steering Committee (SC). Kyowa Kirin
- Invitación o apoyo para asistencia a cursos o congresos: No

Objetivos

- Revisar la evidencia sobre reducción de mortalidad de ácido zoledrónico.

- Entender mecanismos posibles del beneficio.

- Discutir implicancias clínicas.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 1, 2007 VOL. 357 NO. 18

Escuela de Medicina

Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture

Kenneth W. Lyles, M.D., Cathleen S. Colón-Emeric, M.D., M.H.Sc., Jay S. Magaziner, Ph.D., Jonathan D. Adachi, M.D.,

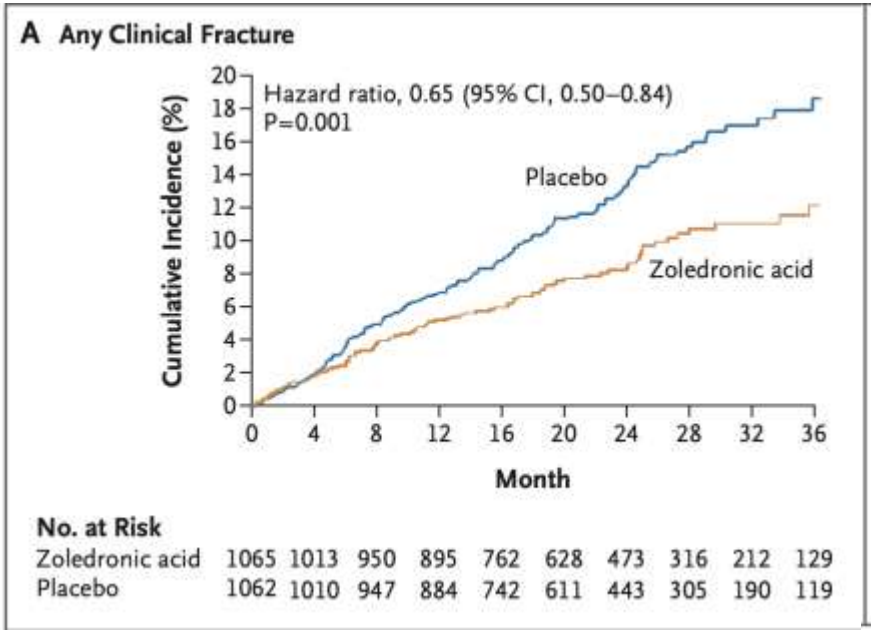
- Horizon Recurrent Fracture trial (HRFT)
- RCT de 2127 pacientes aleatorizados para recibir zoledronato 5 mg o placebo dentro de los 90 días posteriores a una fractura de cadera.
- Asociado a aporte de calcio y Vit D
- Edad $\bar{x}$ 70 a
- Seguimiento $\bar{x}$ 1,9 a
- 30% solo recibió una dosis de Zol

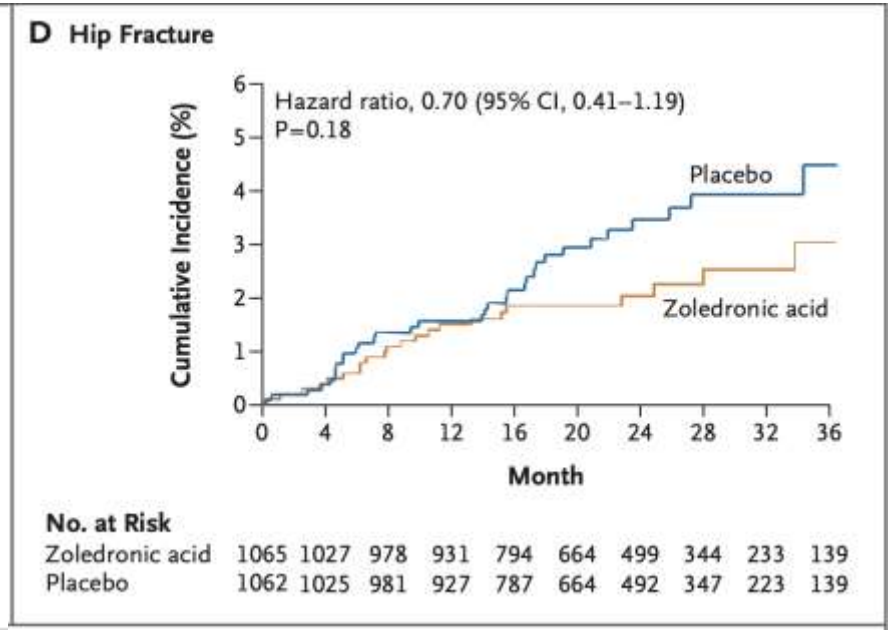
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 1, 2007 VOL. 357 NO. 18

Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture

Kenneth W. Lyles, M.D., Cathleen S. Colón-Emeric, M.D., M.H.Sc., Jay S. Magaziner, Ph.D., Jonathan D. Adachi, M.D.,



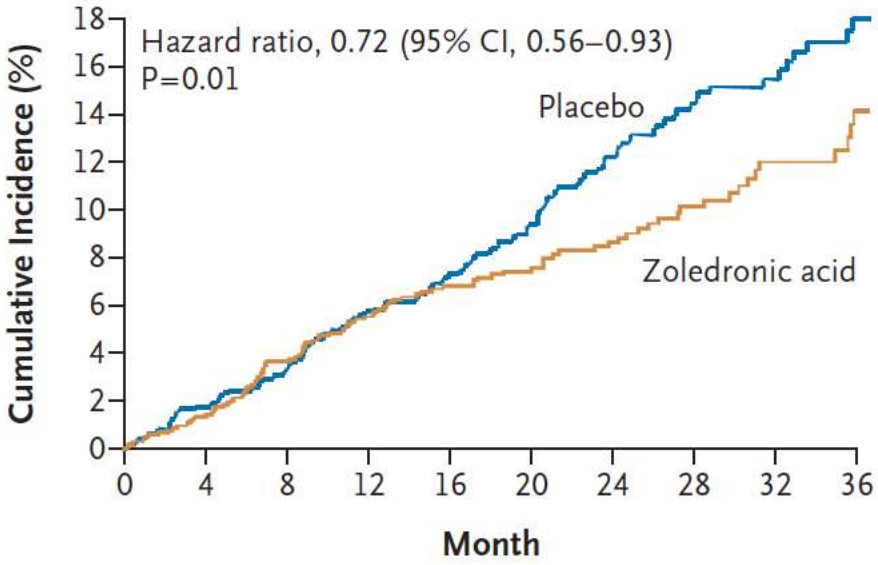


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 1, 2007 VOL. 357 NO. 18

Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture

Kenneth W. Lyles, M.D., Cathleen S. Colón-Emeric, M.D., M.H.Sc., Jay S. Magaziner, Ph.D., Jonathan D. Adachi, M.D.,



No. at Risk

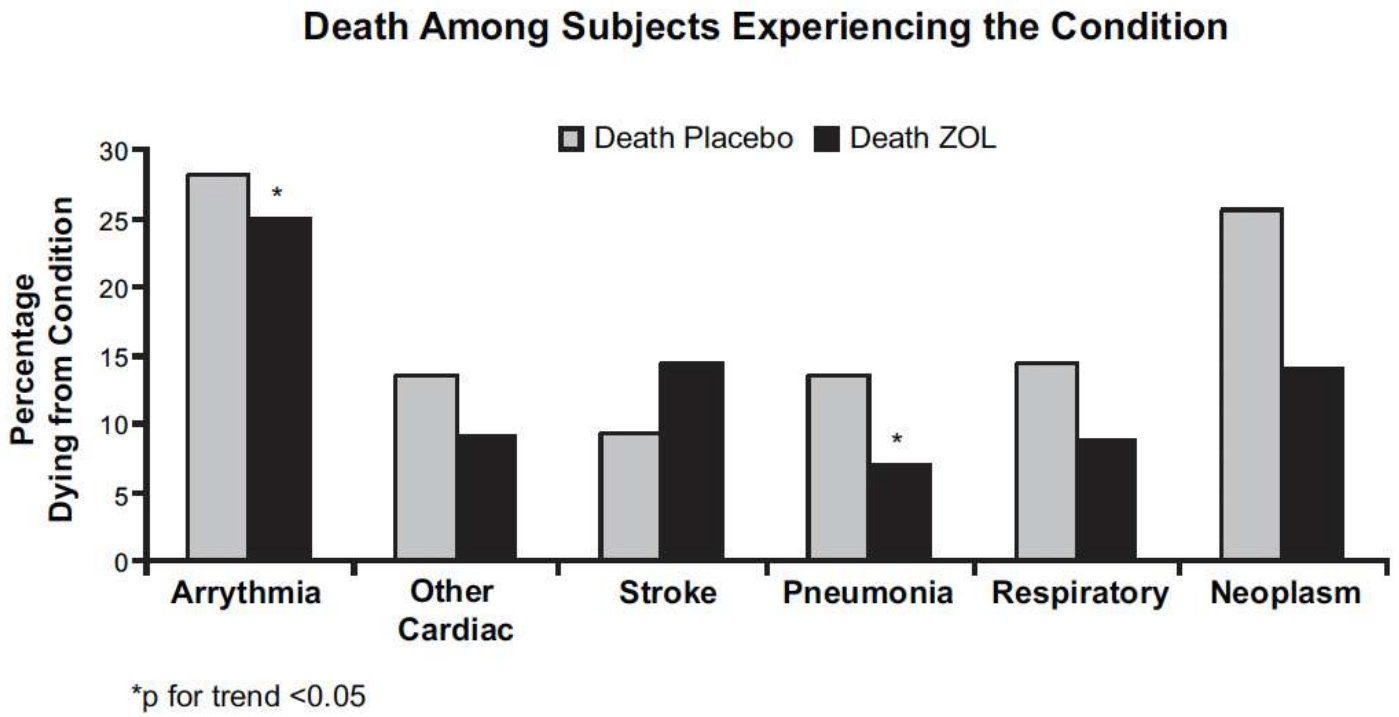
Zoledronic acid	1054	1029	987	943	806	674	507	348	237	144
Placebo	1057	1028	993	945	804	681	511	364	236	149

JBMR

Escuela de Medicina

Potential Mediators of the Mortality Reduction With Zoledronic Acid After Hip Fracture

Cathleen S Colón-Emeric,[1] Peter Mesenbrink,[2] Kenneth W Lyles,[1] Carl F Pieper,[1] Steven Boonen,[3] Pierre Delmas,[4] Erik F Eriksen,[5] and Jay Magaziner[6]



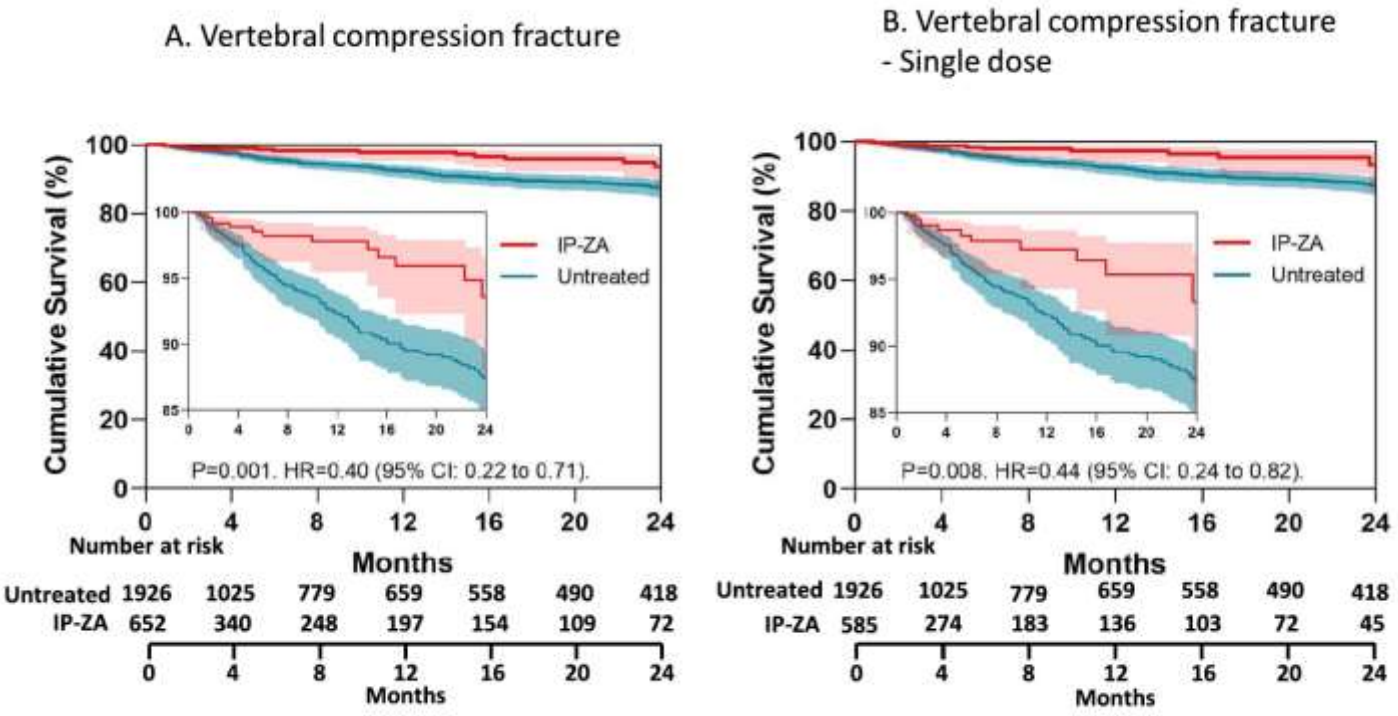
medicina.uc.cl

Zoledronic acid for hip fracture during initial hospitalization

WuQiang Fan[1,*], Xiaoxu Sun[1], Benjamin Z. Leder[1], Hang Lee[2], Thuan V. Ly[3], Charles T. Pu[4], Esteban Franco-Garcia[4], Marcy B. Bolster[5]

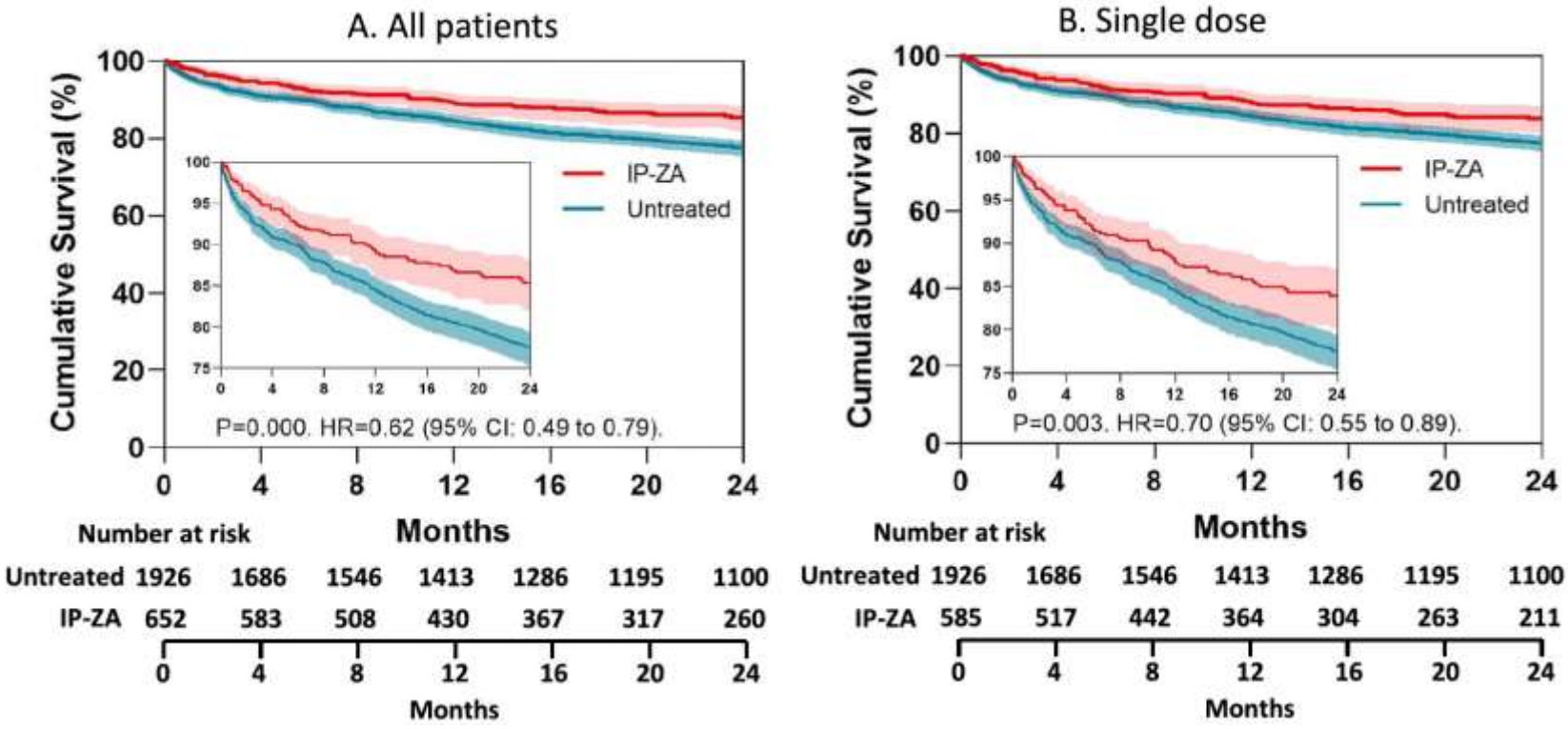
e Medicina

- Estudio observacional , con 650 sujetos y 2500 controles pareados (propensity score)
- Edad x̄ 80 a.
- Seguimiento a 2 años. 90% una sola dosis de Zol



Zoledronic acid for hip fracture during initial hospitalization

WuQiang Fan[1,*], Xiaoxu Sun[1], Benjamin Z. Leder[1], Hang Lee[2], Thuan V. Ly[3], Charles T. Pu[4], Esteban Franco-Garcia[4], Marcy B. Bolster[5]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fracture Prevention with Zoledronate in Older Women with Osteopenia

Ian R. Reid, M.D., Anne M. Horne, M.B., Ch.B., Borislav Mihov, B.Phty., Angela Stewart, R.N., Elizabeth Garratt, B.Nurs., Sumwai Wong, B.Sc., Katy R. Wiessing, B.Sc., Mark J. Bolland, Ph.D., Sonja Bastin, M.B., Ch.B., and Gregory D. Gamble, M.Sc.

- RCT de 6 años, monocéntrico, doble ciego
- 2000 mujeres (edad $\bar{x}$ 71 años) con "osteopenia" aleatorizadas a 5 mg IV cada 18 meses x 4 dosis Vs Placebo
- T score cadera $\bar{x}$ - 1,6.

- **Outcome primario:** Fracturas
- **Outcomes secundarios:** Eventos CV / incidencia total de cancer / mortalidad

N Engl J Med 2018;379:2407-16.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fracture Prevention with Zoledronate in Older Women with Osteopenia

Table 2. Overview of Fracture Data at 6 Years.

Fracture Category	Placebo (N=1000)			Zoledronate (N=1000)			Hazard Ratio with Zoledronate (95% CI)
	Fractures	Fractures per 1000 Woman-Yr (95% CI)	Women with Fracture	Fractures	Fractures per 1000 Woman-Yr (95% CI)	Women with Fracture	
	no.		*no.*	*no.*		*no.*	
Fragility*	227	38.5 (33.8–43.8)	190	131	22.1 (18.5–26.1)	122	0.63 (0.50–0.79)
Symptomatic†	276	46.9 (41.6–52.6)	214	185	31.2 (26.9–35.9)	163	0.73 (0.60–0.90)
Vertebral							
Total	64	10.9 (8.4–13.8)	49	25	4.2 (2.8–6.1)	23	0.45 (0.27–0.73)§
Symptomatic	39	6.6 (4.8–9.0)	34	14	2.4 (1.3–3.9)	14	0.41 (0.22–0.75)
Nonvertebral							
Fragility‡	178	30.2 (26.0–34.9)	148	108	18.2 (15.0–21.9)	101	0.66 (0.51–0.85)
Hip	12	2.0 (1.1–3.5)	12	8	1.3 (0.6–2.6)	8	0.66 (0.27–1.16)
Forearm or wrist	68	11.6 (9.0–14.6)	63	38	6.4 (4.6–8.7)	36	0.56 (0.37–0.85)

N Engl J Med 2018;379:2407-16.

ORIGINAL ARTICLE

JBMR®

Escuela de Medicina

Effects of Zoledronate on Cancer, Cardiac Events, and Mortality in Osteopenic Older Women

Ian R Reid,[1,2] Anne M Horne,[1] Borislav Mihov,[1] Angela Stewart,[1] Elizabeth Garratt,[1] Sonja Bastin,[2] and Gregory D Gamble[1]

Event	ZOL Group		Placebo Group		Hazard Ratio (95% CI)	Rate Ratio (95% CI)
	Events	Women	Events	Women		
Death (all)	27	27	41	41	0.65 (0.40-1.06)	-
Death (no fracture)	22	22	39	39	**0.51 (0.30-0.87)**	-
Myocardial Infarction	25	24	43	39	0.60 (0.36-1.00)	**0.58 (0.35-0.94)**
Stroke	20	17	22	20	-	0.90 (0.49-1.66)
Cardiovascular Composite	71	53	98	69	0.76 (0.53-1.08)	**0.72 (0.53-0.98)**
Total Cancers	87	84	121	121	-	**0.68 (0.52-0.89)**
Breast Cancer	23	23	39	39	0.60 (0.36-1.00)	**0.59 (0.35-0.98)**

Reid IR, et al. J Bone Miner Res. 2019; 35:20-27.

ORIGINAL ARTICLE

JBMR®

Effects of Zoledronate on Cancer, Cardiac Events, and Mortality in Osteopenic Older Women

Ian R Reid,[1,2] Anne M Horne,[1] Borislav Mihov,[1] Angela Stewart,[1] Elizabeth Garratt,[1] Sonja Bastin,[2] and Gregory D Gamble[1]

Por cada 1000 años-persona de tratamiento en mujeres mayores con baja densidad ósea, ZOL puede prevenir:

17 fracturas por fragilidad
2 muertes
5 Eventos vasculares
7 Cánceres

Reid IR, et al. J Bone Miner Res. 2019; 35:20-27.

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Association Between Drug Treatments for Patients With Osteoporosis and Overall Mortality Rates

A Meta-analysis

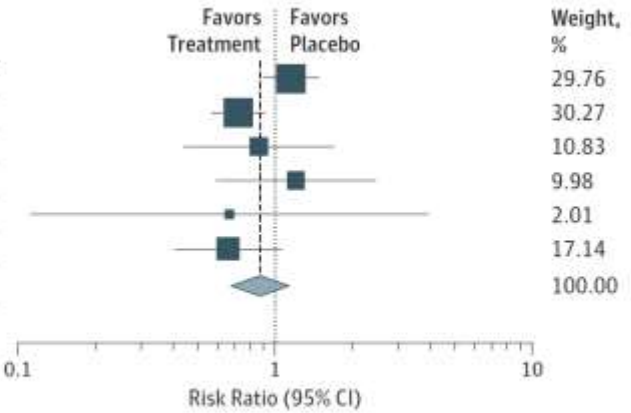
Steven R. Cummings, MD; Li-Yung Lui, MA, MS; Richard Eastell, MD, FRCP; Isabel E. Allen, PhD

- 38 RCT tratamiento farmacológico de osteoporosis (>100 000 participantes)
- No hay asociación significativa entre todos los tratamientos farmacológicos y mortalidad. RR 0,98 (IC 95%: 0,91-1,05)
- Sin efecto de bisfosfonatos en general o Ac. Zoledrónico

Figure 4. Forest Plot for Zoledronate Treatments and Overall Mortality

Source	Treatment No./Total No.	Placebo No./Total No.	Risk Ratio (95% CI)
Black et al,[31] 2007	130/3862	112/3852	1.16 (0.90-1.48)
Lyles et al,[29] 2007	101/1054	141/1057	0.72 (0.56-0.91)
Boonen et al,[50] 2012	15/588	18/611	0.87 (0.44-1.70)
Greenspan et al,[51] 2015	14/89	12/92	1.21 (0.59-2.46)
Nakamura et al,[52] 2017	2/333	3/332	0.66 (0.11-3.95)
Reid et al,[30] 2018	27/1000	41/1000	0.66 (0.41-1.06)
Total	289/6926	327/6944	0.88 (0.68-1.13)

I^2 for heterogeneity = 48.2%

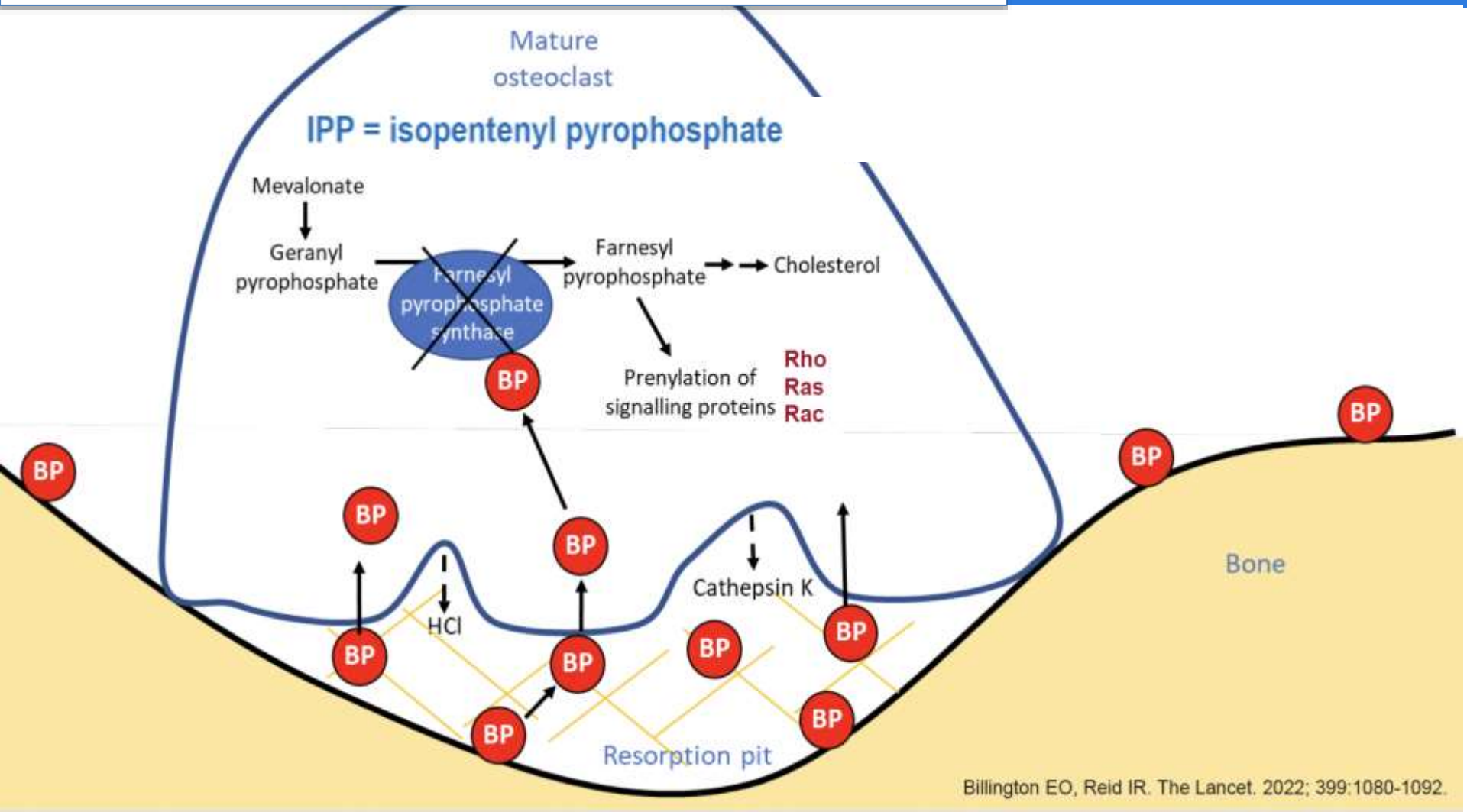


For each study, the solid circle indicates the effect size from the random effects model; whiskers, the 95% CI of the study; and gray block, the relative size of the study compared with other studies. The diamond indicates the overall effect size of all studies combined.

Objetivos

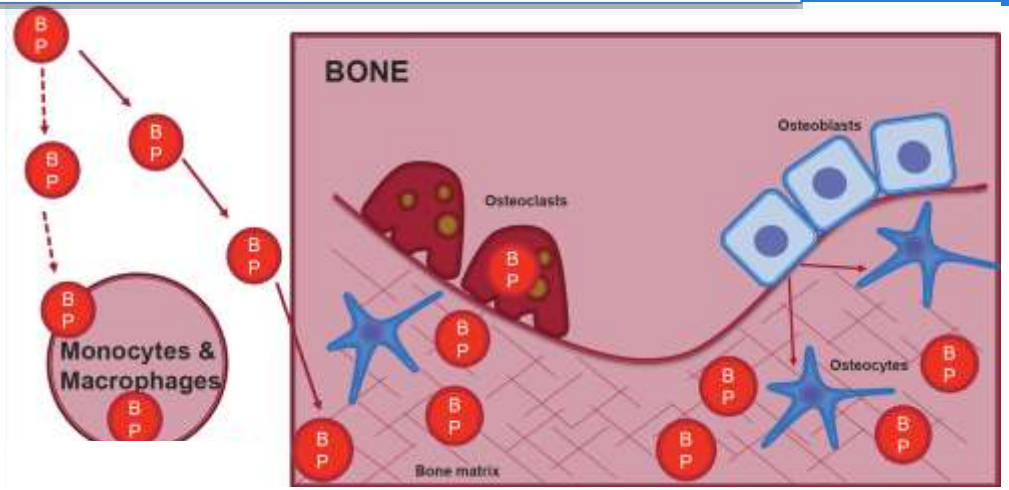
- Revisar la evidencia sobre reducción de mortalidad
- Entender mecanismos posibles
- Discutir implicancias clínicas

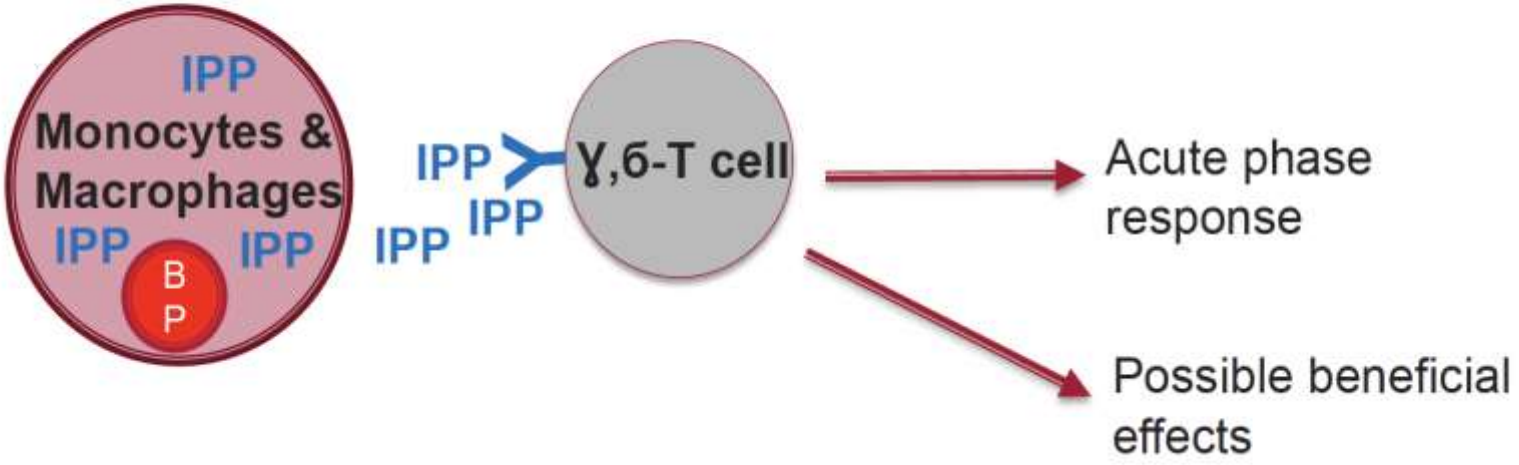
Mecanismo acción BF nitrogenados



Billington EO, Reid IR. The Lancet. 2022; 399:1080-1092.

Mecanismo acción BF nitrogenados





Mecanismo acción BF-CV

Inhibición vía mavelonato en macrófagos, músculo liso vascular o endotelio:

↓ Aterosclerosis , por unión a placas calcificadas y macrofagos lesionales

↓ Calcificación vascular x inhibición MPP

↑ Función endotelial

↑ Secreción óxido nítrico

Billington, Current Osteoporosis Reports. 2020

Mecanismo acción BF-cáncer

En tejido óseo :

↓ activación y proliferación de células pre-malignas durmientes en tejido oseo

En tumor:

↓ Prenilación, promueve apoptosis> Citotoxicidad

↓ Actividad de los macrófagos asociados a tumores

↓ Angiogénesis tumoral (VEFG)

Billington, Current Osteoporosis Reports. 2020

Objetivos

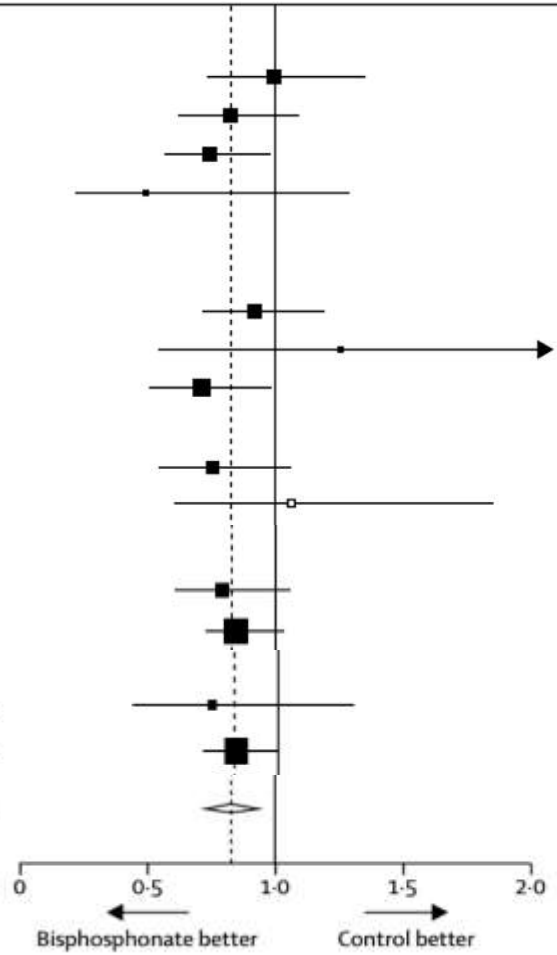
- Revisar la evidencia sobre reducción de mortalidad
- Entender mecanismos posibles
- Discutir implicancias clínicas

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

ASCO International

Category	Events/women		Bisphosphonate events		Ratio of annual event rates bisphosphonate : control	Rate ratio (CI)
	Allocated bisphosphonate	Allocated control	Log-rank O–E	Variance of O–E		
(a) Age, years (trend χ^2_1=4·9; 2p=0·03)						
<45	164/2475 (6·6%)	151/2141 (7·1%)	–0·3	71·3		1·00 (0·79–1·26)
45–54	152/3532 (4·3%)	173/3224 (5·4%)	–14·2	74·3		0·83 (0·61–1·11)
55–69	168/3314 (5·1%)	196/3022 (6·5%)	–25·1	84·4		0·74 (0·56–0·98)
≥70	13/531 (2·4%)	22/521 (4·2%)	–5·1	7·1		0·49 (0·19–1·29)
Age unknown	0/4 (0·0%)	0/2 (0·0%)				
(b) Menopausal status (trend χ^2_1=3·5; 2p=0·06)						
Premenopausal	217/3296 (6·6%)	212/2875 (7·4%)	–7·9	96·4		0·92 (0·71–1·20)
Perimenopausal	28/461 (6·1%)	19/367 (5·2%)	2·0	8·8		
Postmenopausal	252/6099 (4·1%)	311/5668 (5·5%)	–42·1	128·0		0·72 (0·57–0·90)
(c) ER status (χ^2_1=0·6; 2p=0·4)						
ER negative	107/1964 (5·4%)	135/1684 (8·0%)	–15·7	56·4		0·76 (0·54–1·07)
ER unknown	42/637 (6·6%)	47/690 (6·8%)	1·2	20·9		1·06 (0·60–1·86)
(f) Bisphosphonate type (χ^2_4=0·3; 2p=0·6)						
Clodronate	139/2514 (5·5%)	165/2539 (6·5%)	–16·7	67·5		0·78 (0·57–1·07)
Aminobisphosphonate	358/7342 (4·9%)	377/6371 (5·9%)	–27·9	169·7		0·85 (0·70–1·03)
(j) Chemotherapy (χ^2_1=0·3; 2p=0·6)						
Absence	39/1616 (2·4%)	53/1616 (3·3%)	–6·3	21·0		0·74 (0·48–1·14)
Presence	458/8240 (5·6%)	489/7294 (6·7%)	–38·3	216·2		0·84 (0·70–1·00)
Total	**497/9856 (5·0%)**	**542/8910 (6·1%)**	**–44·6**	**237·1**		**0·829 (0·730–0·941) 2p=0·004**



-Lancet. 2015 Oct 3;386(10001):1353-1361.

Summary of Updated Recommendations

Recommendation 1.1

- Adjuvant bisphosphonate therapy should be discussed with all postmenopausal patients (natural or therapy-induced) with primary breast cancer, irrespective of hormone receptor status and HER2 status, who are candidates to receive adjuvant systemic therapy. Adjuvant bisphosphonates, if used, are not substitutes for standard anticancer modalities.

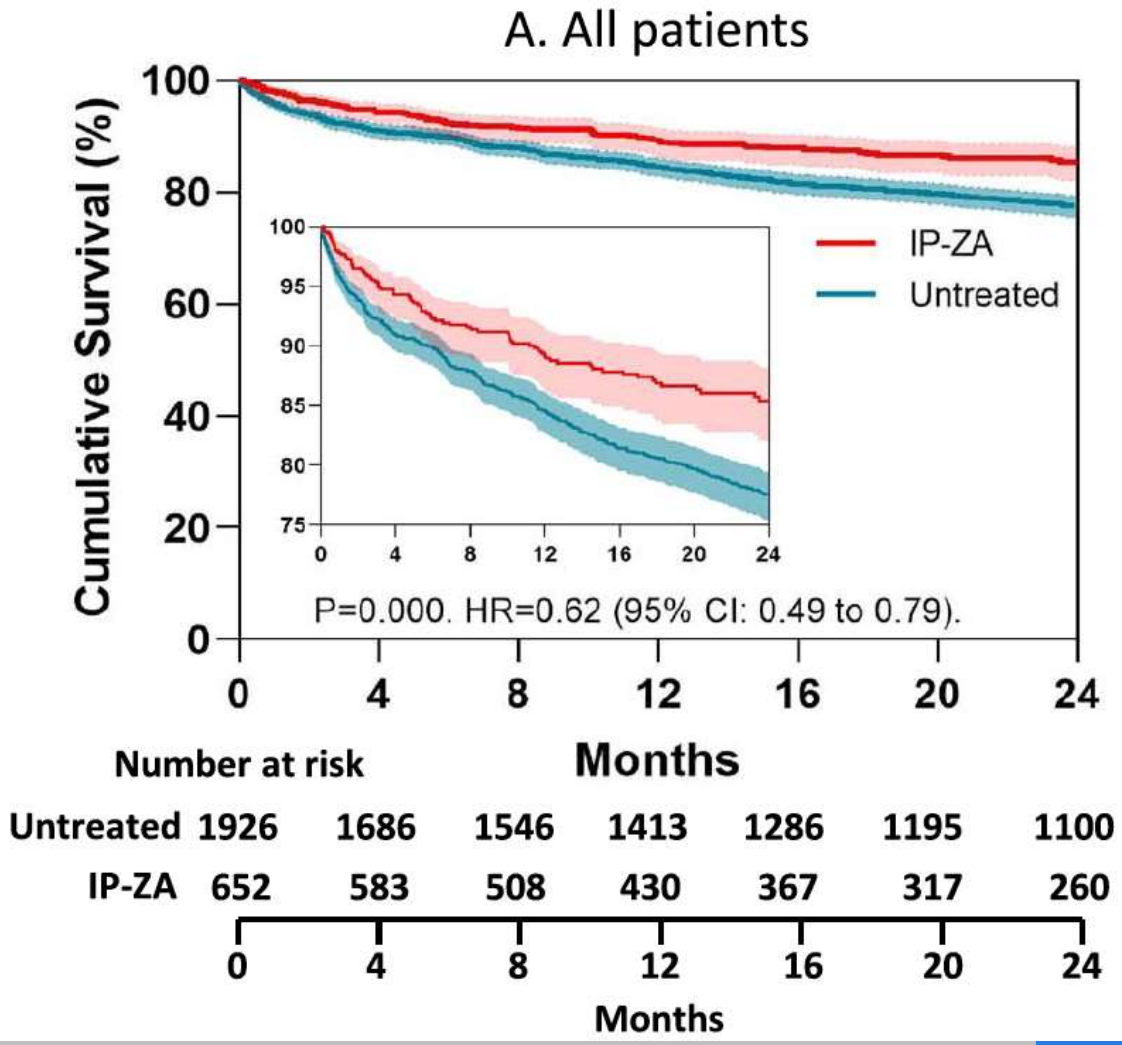
Informal consensus

Evidence Quality	Strength of Recommendation
Intermediate	Moderate

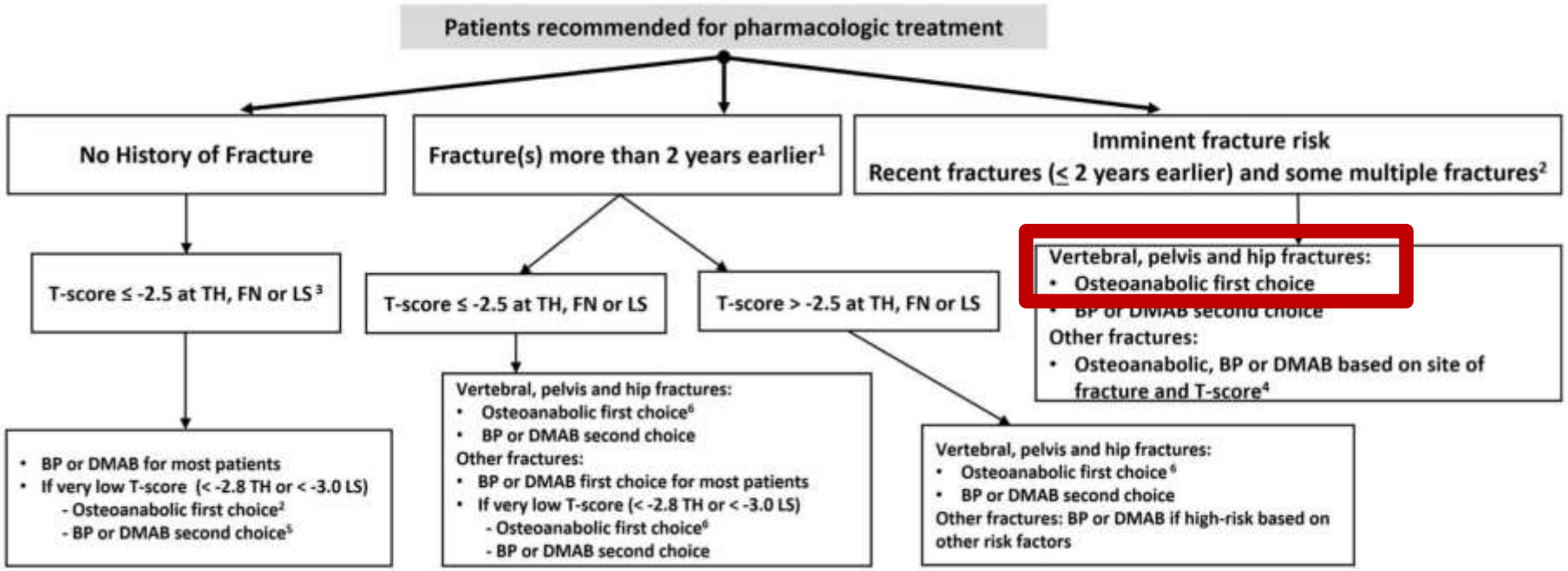
- The benefit of adjuvant bisphosphonate therapy will vary depending on the underlying risk of recurrence and is associated with a modest improvement in overall survival. The NHS PREDICT tool (https://breast.predict.nhs.uk/) provides estimates of benefit of adjuvant bisphosphonate therapy and may aid in shared decision-making.
- Factors influencing the decision to recommend adjuvant bisphosphonate use that should be weighed in the discussion with patients include the patient's risk of recurrence, the risk of side effects, financial toxicity, drug availability, patient preferences, comorbidities, and life expectancy

Beneficios mortalidad intervenciones comprobadas (RRR):

- AAS in IAM 25%
- Bloqueo RAA en falla cardíaca 20%
- Vacuna influenza en EPOC 37%
- Suspender tabaquismo 40%


A. All patients
Cumulative Survival (%)
100
80
60
40
20
0
0
4
8
12
16
20
24
Months
IP-ZA
Untreated
P=0.000. HR=0.62 (95% CI: 0.49 to 0.79).
Number at risk
Untreated 1926 1686 1546 1413 1286 1195 1100
IP-ZA 652 583 508 430 367 317 260

- Guías ASBMR/BHOF: tratamiento farmacológico en pacientes con OP



Cosman F, Lewiecki EM, Eastell R, *et al.* Goal-directed osteoporosis treatment: ASBMR/BHOF task force position statement 2024. *J Bone Miner Res.* 2024 Sep 26;39(10):1393–1405.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fracture Prevention with Infrequent Zoledronate in Women 50 to 60 Years of Age

Mark J. Bolland, M.B., Ch.B., Ph.D., Zaynah Nisa, B.Nurs., Anna Mellar, B.Sc., Chiara Gasteiger, Ph.D., Veronica Pinel, M.D., Borislav Mihov, B.Phty., Sonja Bastin, M.B., Ch.B., Andrew Grey, M.D., Ian R. Reid, M.D., Greg Gamble, M.Sc., and Anne Horne, M.B., Ch.B.

- 1056 mujeres , edad promedio 56 a
- RCT a 3 grupos:
  - Zol 5 mg x 1 v
  - Zol 5 mg cada 5 a x 2 v
  - Placebo
- Seguimiento 10 años
- RRR Fx fragilidad +/- 30%

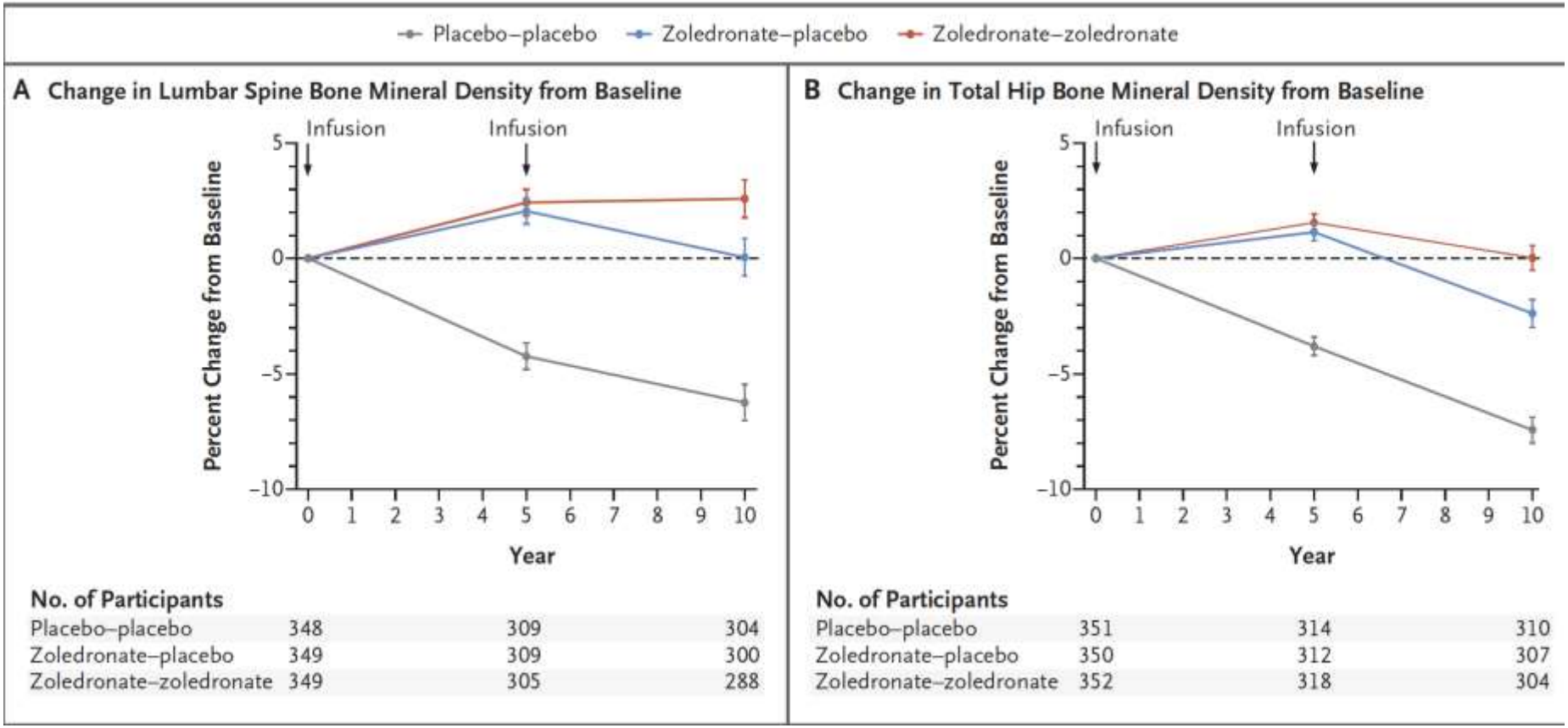
N Engl J Med 2025;392:239-48.

The NEW ENGLAND JOURNAL of MEDICINE

Escuela de Medicina

ORIGINAL ARTICLE

Fracture Prevention with Infrequent Zoledronate in Women 50 to 60 Years of Age



No. of Participants			
Placebo–placebo	348	309	304
Zoledronate–placebo	349	309	300
Zoledronate–zoledronate	349	305	288

No. of Participants			
Placebo–placebo	351	314	310
Zoledronate–placebo	350	312	307
Zoledronate–zoledronate	352	318	304

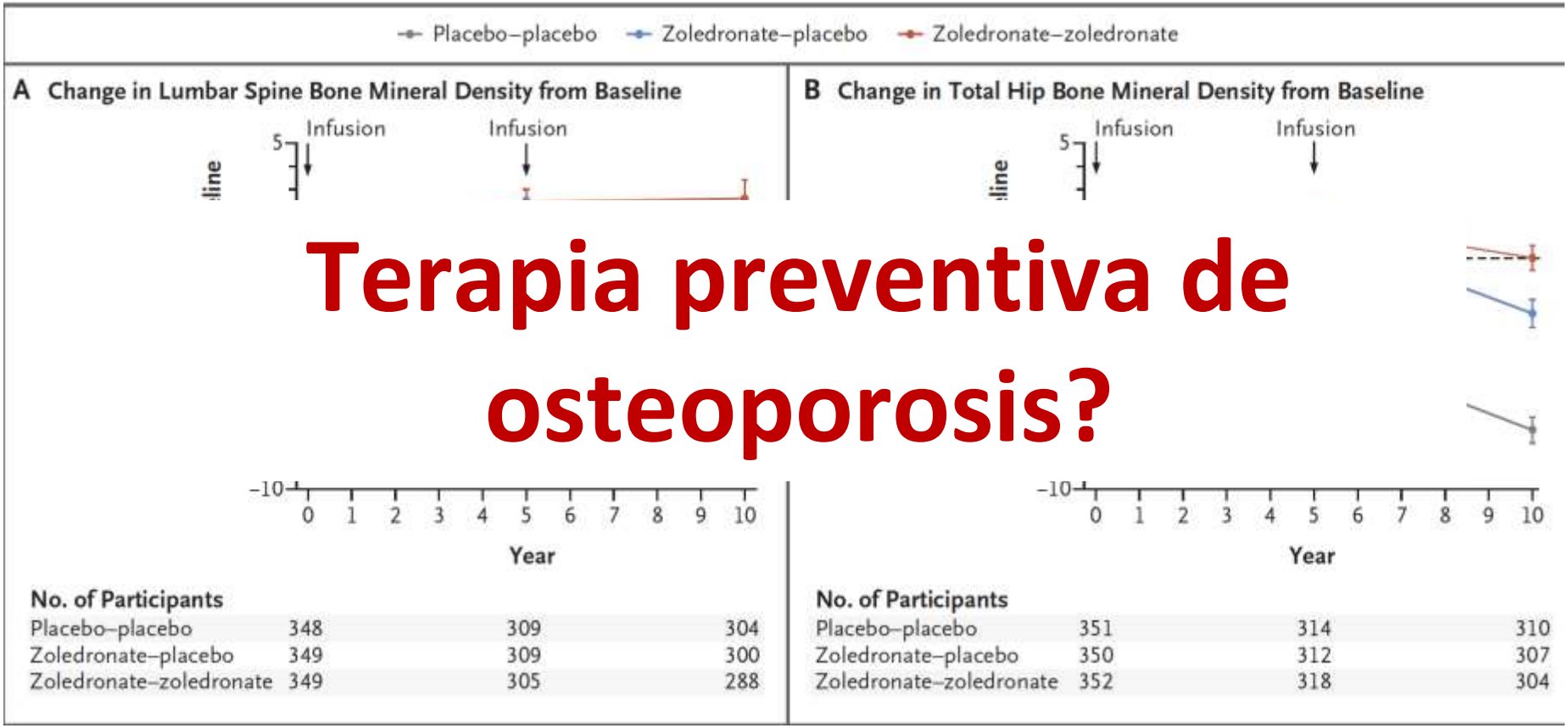
medicina.uc.cl

The NEW ENGLAND JOURNAL of MEDICINE

Escuela de Medicina

ORIGINAL ARTICLE

Fracture Prevention with Infrequent Zoledronate in Women 50 to 60 Years of Age



No. of Participants

Placebo–placebo	348	309	304
Zoledronate–placebo	349	309	300
Zoledronate–zoledronate	349	305	288

Placebo–placebo	351	314	310
Zoledronate–placebo	350	312	307
Zoledronate–zoledronate	352	318	304

Terapia preventiva de osteoporosis?

medicina.uc.cl

Mensajes a recordar:

- Estudios básicos muestran mecanismos plausibles de beneficio CV y antineoplásico de Acido Zoledrónico.
- No existe evidencia clínica aún para recomendar el uso de BF con estos objetivos.
- Evidencia clínica muestra beneficio de mortalidad en pacientes con fractura reciente de cadera y como terapia adyuvante en cáncer de mama de alto riesgo de recurrencia.
- Se requieren estudios diseñados con estos desenlaces como objetivos primarios.

FACULTAD DE MEDICINA
PONTIFICIA UNIVERSIDAD
CATÓLICA DE CHILE

Escuela de Medicina

"**Antirresortivos:** efecto en la mortalidad de mujeres postmenopáusicas "

Dr. Pablo Florenzano V.
Profesor Asociado
Depto. Endocrinología UC