Il profilo di rischio dei farmaci per l'osteoporosi: dai dati del progetto BEST alle nuove evidenze della letteratura

Giampiero Mazzaglia
Società Italiana di Medicina Generale & Agenzia Regionale di Sanità della Toscana

Bisphosphonates
Efficacy
Safety
Trade-off

OSTEOPOROSI: OPZIONI TERAPEUTICHE

- **Anabolic Agents**
  - Parathyroid hormone
  - Sodium flouride
  - Growth hormone
  - Insulin-like growth factor-1
  - Statins
  - RANK-L, Denosumab

- **Antiresorptives**
  - Estrogens
  - Selective estrogen receptor modulators
  - Bisphosphonates
  - Calcitonin

Others: Calcium, Vitamin D

Bisphosphonates for Osteoporosis — Where Do We Go from Here?

Marcea Whitaker, M.D., Jia Guo, Ph.D., Theresa Kehoe, M.D., and George Benson, M.D.

Long-Term Efficacy against Fracture for Three Bisphosphonates in Core Registration and Extension Studies.*

Study Phase	Alendronate (Fosamax)		Risedronate (Actonel)		Zoledronic Acid (Reclast)	
	Yr	Patients with Osteoporotic Fracture	Yr	Patients with Osteoporotic Fracture	Yr	Patients with Osteoporotic Fracture
Core registration study†	0–4	Placebo, 21.0%; alendronate, 10.6%	0–3	Placebo, 32.1%; risedronate, 20.5%	0–3	Placebo, 20.0%; zoledronic acid, 9.8%
Extension study	5–10	Alendronate/alendronate, 17.7%; alendronate/ placebo, 16.9%	4–5	Placebo, 32.1%; risedronate/ risedronate, 19.3%;	4–6	Zoledronic acid/zoledronic acid, 8.6%; zoledronic acid/placebo, 12.0%
			6–7	Risedronate/ risedronate/ risedronate, 13.3%		

10.1056/nejmp1202619

FDA: CONCLUSIONI

"In light of the potential risks that may be associated with long-term use of bisphosphonates for the treatment and/or prevention of osteoporosis, the sum of available long-term efficacy data appears to suggest that bisphosphonate therapy could be safely discontinued for some period of time."

BIFOSFONATI: PROFILO DI SICUREZZA

ASSOCIATO ALL'USO A LUNGO TERMINE

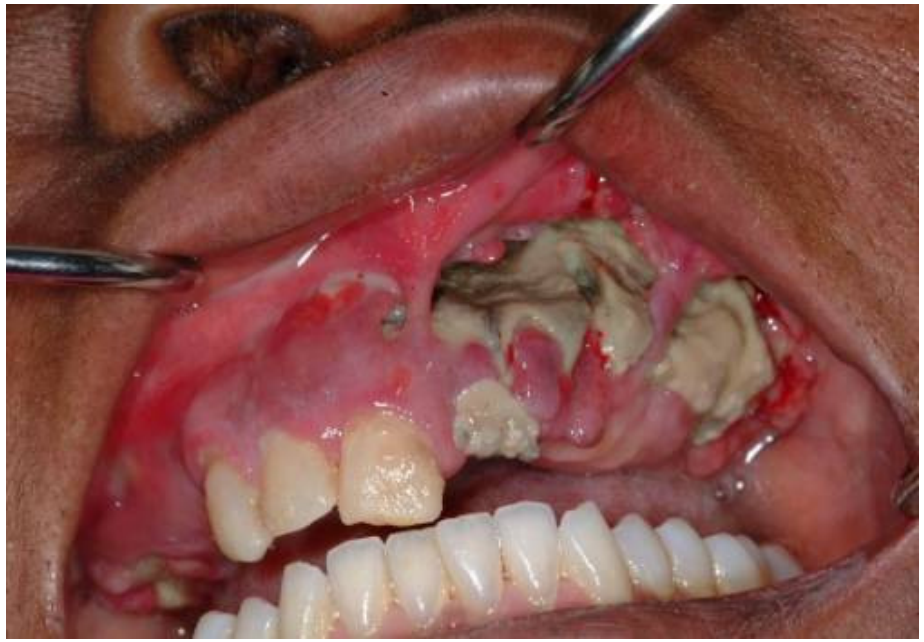
- **Osteonecrosi della Mandibola**
- **Fratture atipiche**
- **Carcinoma esofageo**
- Insufficienza valvolare

ALTRE POTENZIALI REAZIONI AVVERSE

- Fibrillazione atriale
- **Disturbi gastrointestinali** **(associati alla modalità di somministrazione)**
- Ipocalcemia
- Tossicità renale

OSTEONECROSI DELLA MANDIBOLA (ONJ)

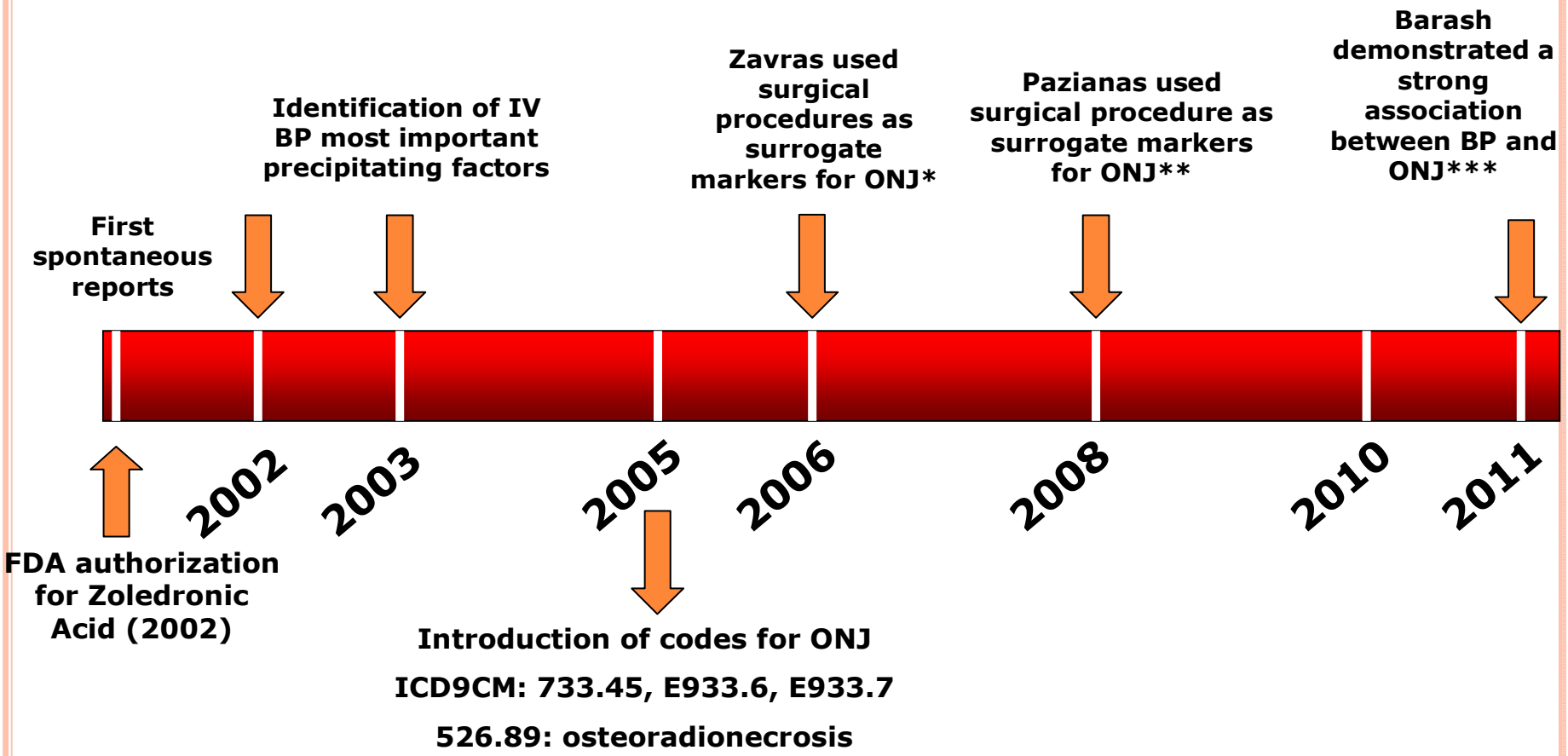
- The ONJ clinical picture mainly consists of non-healing ulcerated oral lesions and visible necrotic bone, which are sometimes associated with a diffuse jaw or facial pain.
- The exact etiologic mechanisms remain unclear but it might relate, in part, to altered bone remodeling or local tissue effects in susceptible patients.



ONJ: DATI DI SORVEGLIANZA

- **Bifosfonati iniettivi:**
  - incidenza stimata intorno al 4-10%
  - oltre il 95% delle segnalazioni spontanee
- **Bifosfonati orali:**
  - Jung TI (2007) J Bone Miner Res. S298: 0.00038%
  - Lo JC (2010) J Oral Maxillofac Surg 68:243-253: 0.05-0.21%
  - Mavrokokki T (2007) J Oral Maxillofac Surg 65:415-423: 0.01-0.04%. A seguito di un estrazione dentale: incidenza intorno a 0.09-0.35%.

ADVERSE EVENTS, ICD9CM & ONJ



*Zavras er al., *J Oral Mxillofac Surg 2006; 64: 917-23*
**Pazianas et al. *Osteoporos Int, 2008; 19:773-79*
****Barasch, et al. J Dent Res 90(4) 2011*

ONJ: STUDI EPIDEMIOLOGICI -1-

DEFINIZIONE EVENTO: ICD9CM CPT: 21015-25-26-34-40-45-46-47

"Chirurgia della mascella e della mandibola"

	Cases N=697	Controls N=2808	Crude RR (CI 95%)	Adjusted RR (CI 95%)
At least 1 prescription of Bisphosphonates, %	**13.8**	**12.3**	**1.14 (0.89-1.45)**	**0.91 (0.70-1.19)**
Days' supply, %				
1-228	**5.0**	**3.9**	**1.30 (0.88-1.92)**	**1.20 (0.80-1.79)**
229-631	**4.9**	**3.9**	**1.27 (0.86-1.88)**	**1.03 (0.68-1.55)**
>=632	**3.9**	**4.5**	**0.85 (0.56-1.30)**	**0.62 (0.40-0.98)**

Pazianas et al. *Osteoporos Int, 2008; 19:773-79*

ONJ: STUDI EPIDEMIOLOGICI -2-

Table 3. Multivariate Model Results for All Participants

Factor	Comparison Group	Reference Group	Odds Ratio (95%CI)	P-value	Overall P-value
Biophosphonate use defined as None/Oral/Intravenous (Case = 137/Control = 367)					
Suppuration	Yes	No	7.8 (1.8, 34.1)	-	0.006
Extraction (matched to quadrant)	Matched extraction	No/mismatched extraction	7.6 (2.4, 24.7)	-	< 0.001
Radiation to head or neck	Yes	No	24.1 (4.9, 118.4)	-	< 0.0001
Bisphosphonate use	Oral	None	12.2 (4.3, 35.0)	< 0.0001 < 0.0001	< 0.0001

Table 4. Multivariate Model Results for Participants without Cancer (Case = 30, Control = 81)

Factor	ONJ Cases	Controls	Odds Ratio (95%CI)	P-value
Suppuration	Yes	No	11.9 (2.0, 69.5)	0.006
Extraction (matched to quadrant)	Matched extraction	Any extraction	6.6 (1.6, 26.6)	0.008
Bisphosphonate use	Yes	No	7.2 (2.1, 24.7)	0.002

Barasch, et al. *J Dent Res 90(4) 2011*

BISPHOSPHONATES EFFICACY-SAFETY TRADEOFF (BEST) STUDY:
BANDO AIFA 2006

- *10 Unità coinvolte*
- *Informazioni provenienti da 4 Regioni e 10 ASL (18 milioni)*

- *115.772 pazienti con frattura osteoporotica identificati*

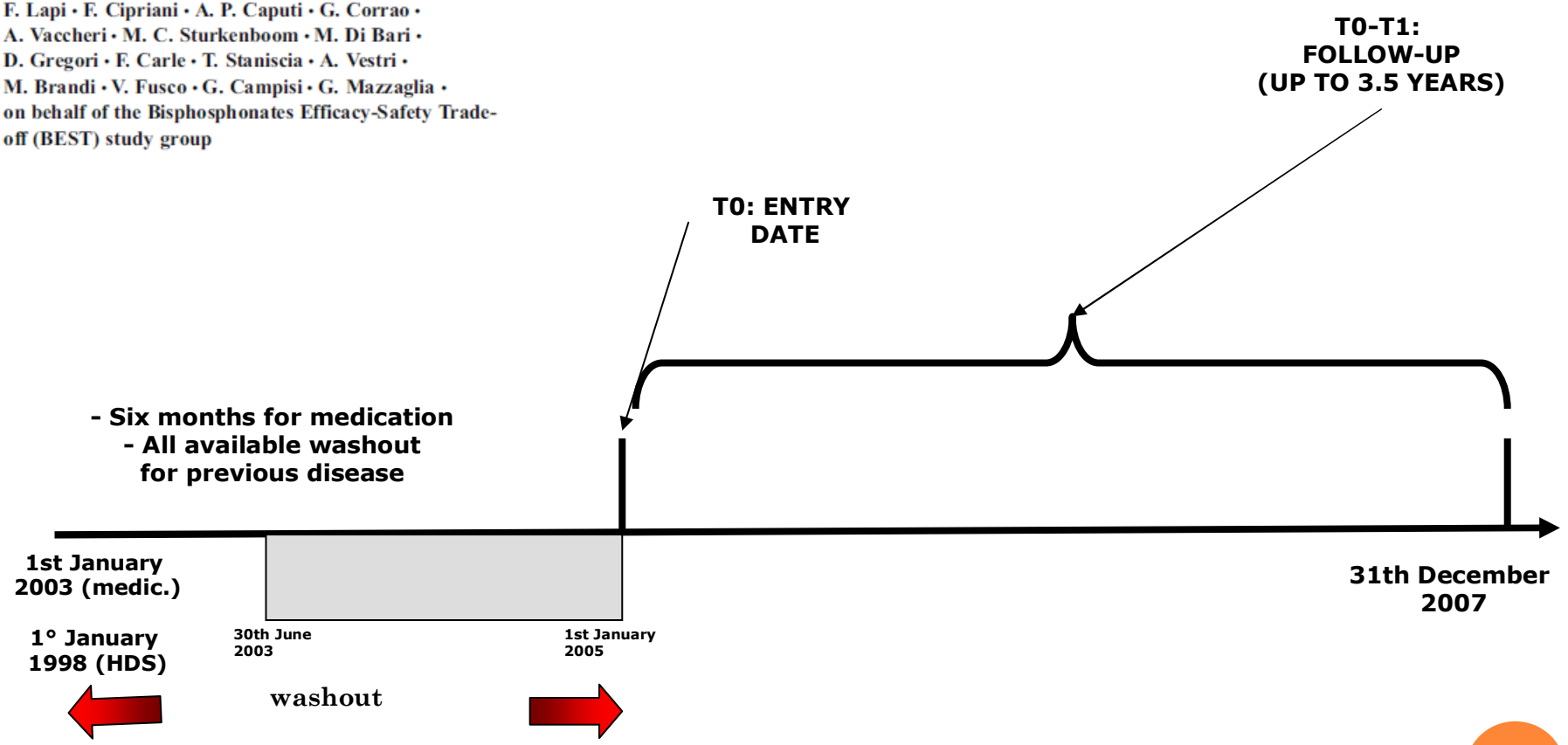
- *5 obiettivi specifici: rischio di ONJ e sanguinamento GI; epidemiologia delle fratture; uso dei BP; relazione tra aderenza al trattamento e le fratture secondarie*

Osteoporos Int
DOI 10.1007/s00198-012-2013-y

ORIGINAL ARTICLE

Assessing the risk of osteonecrosis of the jaw due to bisphosphonate therapy in the secondary prevention of osteoporotic fractures

F. Lapi · F. Cipriani · A. P. Caputi · G. Corrao · A. Vaccheri · M. C. Sturkenboom · M. Di Bari · D. Gregori · F. Carle · T. Staniscia · A. Vestri · M. Brandi · V. Fusco · G. Campisi · G. Mazzaglia · on behalf of the Bisphosphonates Efficacy-Safety Trade-off (BEST) study group

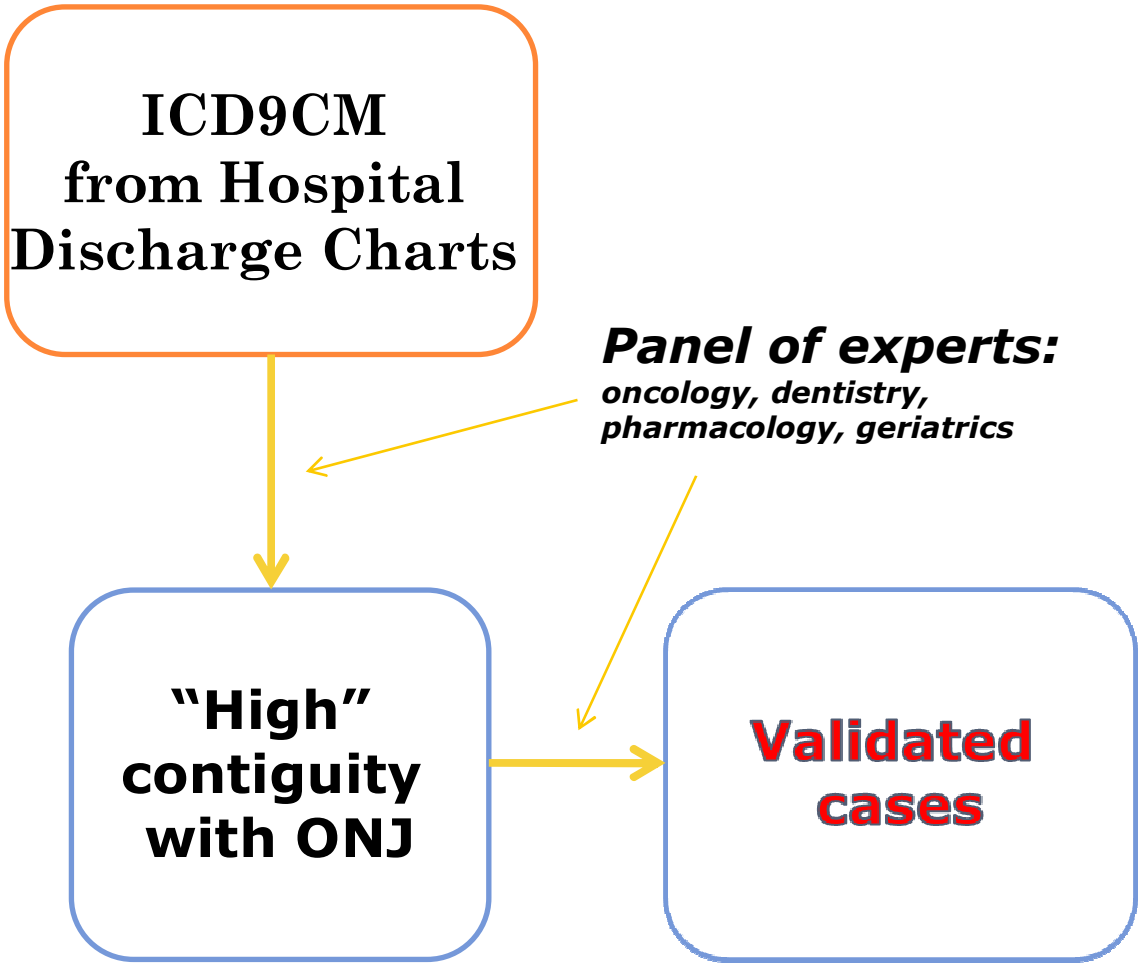


Washout (exclusion criteria): age <55 yrs, ICD9CM of tumour, Paget disease, (all available washout), previous use of BP (6 months)

T0 (ENTRY DATE): ICD9CM of INCIDENT osteoporotic fracture

T1 (EXIT DATE): ICD9CM related to ONJ, tumour diagnosis, Paget disease, death, data availability (31th Dec 2007)

BEST: VALIDAZIONE ONJ



Possible (39 cases):
Absence of exclusion criteria

Probable (22 cases):
Absence of exclusion criteria; (i) sign or symptoms suggesting necrotic bone lesions, inflammatory jaw condition not related to strict dental causes, and open lesions/ulcers of the jaw were recorded. (ii) the ONJ was specifically mentioned in the medical chart; (iii) pain was not directly referred to dental extraction or other surgical procedures.

Lapi et al. *Osteoporos Int* (DOI 10.1007/s00198-012-2013-y)

BEST: INCIDENZA * ONJ NEI SOGGETTI ESPOSTI AI BP ORALI

BP use	Possible ID (95% CI)	Probable ID (95% CI)
yes	40.0 (20.8-76.9)	13.3 (4.3-41.3)
>=80%	**109.2 (27.3-436.3)**	-
79-40%	**73.1 (27.5-194.9)**	18.3 (2.5-41.3)
<40%	**19.7 (6.4-61.2)**	13.2 (3.3-52.6)
no	36.5 (28.2-47.2)	13.8 (9.1-21.0)

*ID (Incidence Density) 100000 persons-year; *% of days covered; no exclusion criteria have been applied*

Lapi et al. *Osteoporos Int (*DOI 10.1007/s00198-012-2013-y*)*

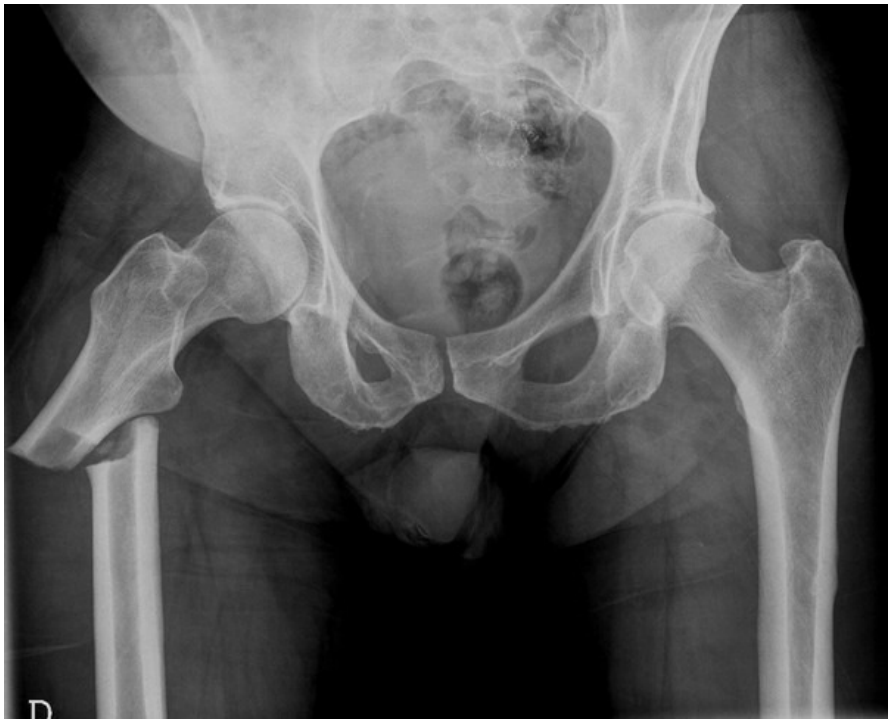
BEST: STUDIO CASO-CONTROLLO SUL RISCHIO ONJ NEI SOGGETTI ESPOSTI AI BP ORALI

	Cases N=61	Controls N=1220	unadjusted OR (CI 95%)	adjusted OR (CI 95%)
BP use (yes vs. no)	10 (16.4)	118 (9.7)	1.9 (0.9-3.8)	1.7 (0.8-3.6)
BP use				
Never users	51 (83.6)	1102 (90.3)	Reference	Reference
Past users	0	40 (3.3)	-	-
Current users				
Main analysis	**10 (16.4)**	**78 (6.4)**	**2.9 (1.3-6.0)**	**2.8 (1.3-5.9)**
Only probable cases				**2.5 (0.7-9.5)**
Propensity matched controls				**2.3 (1.1-5.1)**

Lapi et al. *Osteoporos Int (*DOI 10.1007/s00198-012-2013-y*)*

FRATTURE ATIPICHE

- Nel Marzo 2005 viene pubblicato un articolo su *The Journal of Clinical Endocrinology & Metabolism* che descrive nove casi con fratture non traumatiche, esposti ad alendronato da 3-8 anni.
- La biopsia delle creste iliache rivela una soppressione del turnover osseo in tutti i pazienti.
- Gli autori suggeriscono un possibile effetto causale dell'alendronato, in virtù del ruolo di inibizione del turnover osseo.



FRATTURE ATIPICHE:
DEFINIZIONE

Table 6: Major and Minor Features of Atypical Fractures

Major Features

- Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
- Associated with no trauma or minimal trauma, as in a fall from a standing height or less
- Transverse or short oblique configuration
- Non-comminuted
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex

Minor Features

- Localized periosteal reaction of the lateral cortex (beaking or flaring)
- Generalized increase in cortical thickness of the diaphysis
- Prodromal symptoms such as dull or aching pain in the groin or thigh
- Bilateral fractures and symptoms
- Delayed healing
- Comorbid conditions (e.g., vitamin D deficiency, RA, hypophosphatasia)
- Use of pharmaceutical agents (e.g., bisphosphonates, glucocorticoids, proton pump inhibitors)

American Society for Bone and Mineral Research. J Bone Miner Res. 2010;25:2267-94.

EVIDENZE DA UNA REVISIONE FDA

- **Selezionati 9 studi osservazionali ed un RCT**
- **Eterogeneità nella definizione di frattura atipica con maggiore aderenza ai criteri standard negli studi pubblicati dopo il 2010**
- **Complessivamente gli studi indicano un aumento del rischio associato all'uso di BP, mentre l'evidenza sulla relazione durata-risposta fornisce risultati inconsistenti.**
- **L'incidenza risulta piuttosto bassa ed estremamente variabile in relazione allo studio; di conseguenza anche il rischio assoluto**

Problemi metodologici potrebbero sovrastimare il rischio (confounding by indication, residual confounding)

BISPHOSPHONATE USE AND ATYPICAL FRACTURES OF THE FEMORAL SHAFT

Table 1. Risk of Atypical Femoral Fracture Associated with Bisphosphonate Use during the 3 Years (2005–2008) Preceding the Fracture.*

Variable	No. of Women	Cases of Atypical Fracture		Age-Adjusted Relative Risk (95% CI)	Age-Adjusted Absolute Risk (95% CI)
		No. of Atypical Fracture Cases	Crude Incidence *no./10,000 patient-yr*		
Bisphosphonate use					
Never	1, 437,820	13	0.09	1.0 (reference)	
Ever	83,311	46	5.5	47.3 (25.6–87.3)	0.0005 (0.0004–0.0007)
Duration of use					
<1.0 yr	15,672	3	1.9	18.4 (5.3–64.3)	0.0002 (0.0000–0.0004)
1.0–1.9 yr	21,406	4	1.9	17.0 (5.7–50.7)	0.0002 (0.0000–0.0004)
≥2.0 yr	46,233	39	8.4	67.0 (35.8–125.8)	0.0008 (0.0006–0.0011)
Time since last use					
<1.0 yr	83,311	42	5.0	42.9 (22.9–80.4)	0.0005 (0.0004–0.0007)
1.0–1.9 yr	70,036	1	0.1	3.5 (1.0–11.9)	<0.0001 (0.0000–0.0000)
≥2.0 yr	75,583	3	0.4	3.2 (1.0–10.1)	<0.0001 (0.0000–0.0001)

N Engl J Med 2011;364:1728-37.

BISPHOSPHONATE USE AND THE RISK OF SUBTROCHANTERIC OR FEMORAL SHAFT FRACTURES IN OLDER WOMEN

Table 2. Risk of Subtrochanteric or Femoral Shaft Fractures Among Women Taking Bisphosphonate Therapy

	Duration of Bisphosphonate Therapy			
	Transient, <100 days	Short-term Use, 100 days to 3 years	Intermediate Use, 3 to 5 Years	Long-Term Use, ≥5 Years
No. (%) of patients				
Case (n = 716)	42 (5.9)	349 (48.7)	204 (28.5)	121 (16.9)
Control (n = 3580)	218 (6.1)	1832 (51.2)	1070 (29.9)	460 (12.9)
Odds Ratio (95% CI)				
Crude	1.0 [Reference]	1.00 (0.70-1.43)	1.08 (0.73-1.59)	1.74 (1.11-2.73)
Adjusted[a]	1.0 [Reference]	0.90 (0.48-1.68)	1.59 (0.80-3.15)	2.74 (1.25-6.02)

Abbreviation: CI, confidence interval.
[a]The full list of covariates for the adjusted model are given in eAppendix 2 (available at http://www.jama.com).

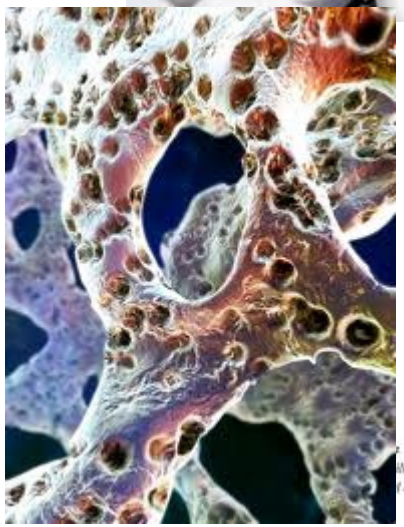
JAMA. 2011;305(8):783-789.

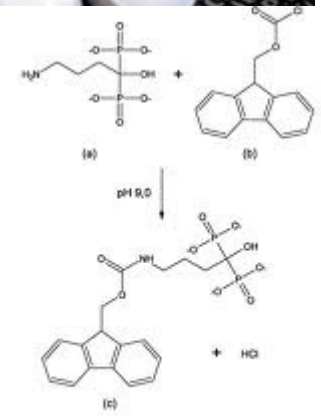
EVENTI GASTROINTESTINALI

1. Sin dall'introduzione dell'alendronato nel 1995 i BP sono stati associati ad eventi gastrointestinali, da una semplice irritazione della mucosa gastrica fino a complicanze più severe, come il sanguinamento gastrointestinale.

2. Recentemente, è stata ipotizzata un associazione tra BP e carcinoma dell'esofago

3. Tutte le schede tecniche riportano sia nelle avvertenze sia come eventi avversi le reazioni di tipo gastrointestinale





3. Reação de derivatização do alendronato (a) com 9-fluorenilmetilcloroformato (FMOC) (b), originando produto cromóforo (c) de detecção no UV. Adaptada da ref. 17

EVENTI GASTROINTESTINALI: STUDI EPIDEMIOLOGICI -1-

1. L'evidenza proveniente dalla segnalazione spontanea potrebbe nascere da errori nella dose e nella modalità di somministrazione
2. Alto rischio all'atto della somministrazione di BP (maggiore probabilità di uso di FANS, corticosteroidi)
3. Detection bias
4. Studi epidemiologici necessari anche per chiarire una possibile base biologica rispetto al potenziale rischio di carcinoma dell'esofago

	Cases	Controls	Unadjusted ORs	Adjusted ORs and 95% CIs
Number of subjects	3253	65 060		
No use of bisphosphonates	2364	50 212	1	REFERENCE
Current use	36	716	1.01	1.01 (0.72–1.43)
Past use	46	889	1.04	0.96 (0.71–1.31)
NSAIDS				
Current use	283	3258	1.84	1.75 (1.53–1.99)
Past use	464	9093	1.08	0.97 (0.88–1.08)
COX-2 inhibitors				
Current use	173	1901	1.93	1.83 (1.55–2.16)
Past Use	365	6960	1.11	0.98 (0.87–1.10)
NSAIDs +bisphosphonates	13	134	2.11	2.00 (1.12–3.57)
COX-2 inhibitors +bisphosphonates	11	94	2.52	2.38 (1.26–4.50)

Odds ratios were adjusted for age, gender, number of physician visits and use of the following prescription drugs: selective serotonin reuptake inhibitors, warfarin, heparin, antiplatelets and antacids.

Aliment Pharmacol Ther. 2009;29:1188–1192

EVENTI GASTROINTESTINALI: STUDI EPIDEMIOLOGICI -2-

Table 5 Adjusted risk of gastroduodenal ulcers before and after administration of a wide range of drugs against osteoporosis[a]

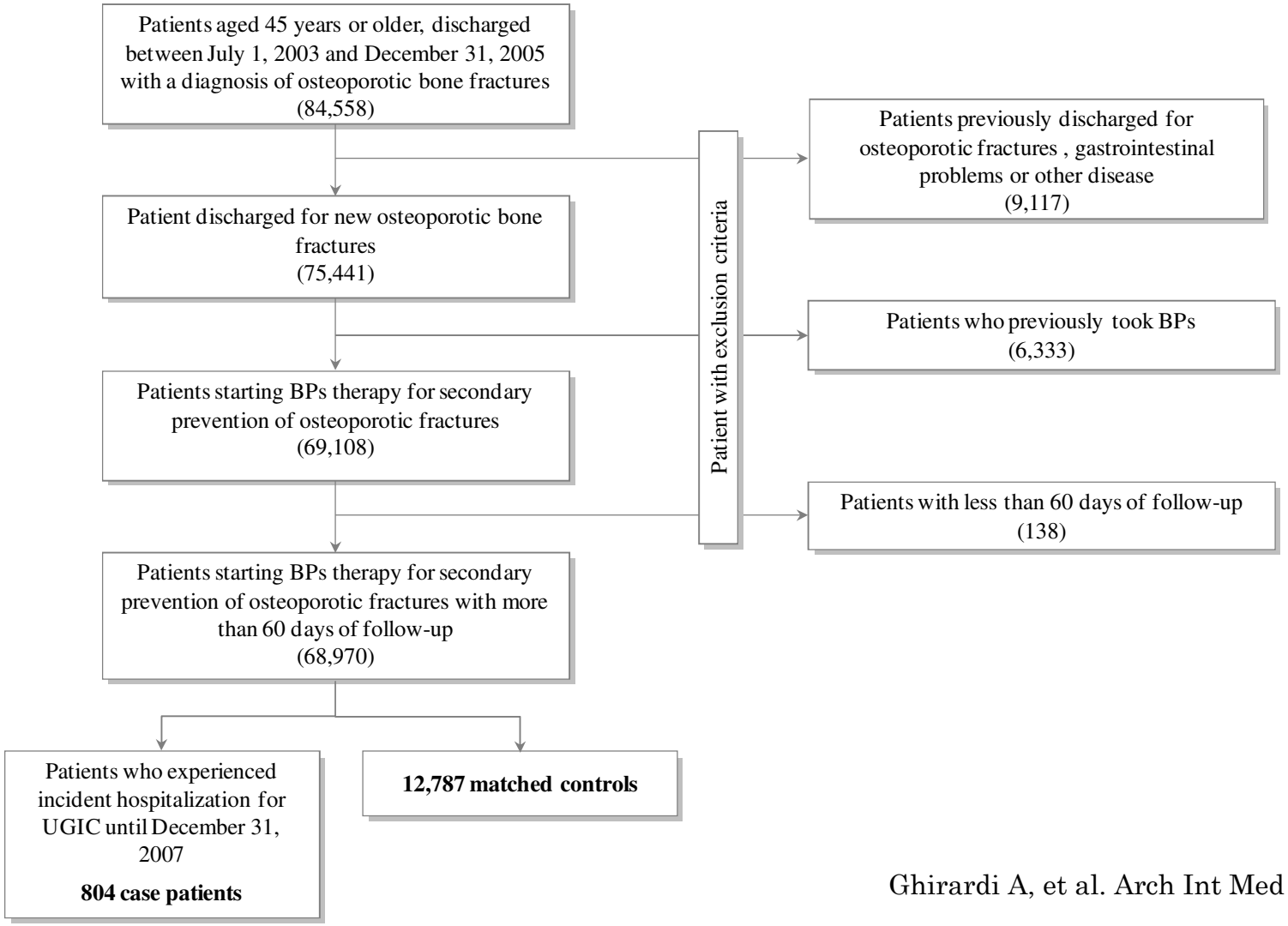
Drug	OR (95% CI) before initiation	HR (95% CI) after initiation
Raloxifene	1.23 (1.07–1.42)*	1.11 (0.83–1.49)
Parathyroid hormone	1.30 (0.76–2.21)	–
Etidronate	1.39 (1.32–1.45)*	1.40 (1.31–1.49)*
Clodronate	1.01 (0.63–1.62)	2.01 (1.08–3.73)*
Pamidronate	0.14 (0.02–0.93)*	–
Alendronate	1.12 (1.08–1.16)*	1.45 (1.31–1.61)*
Ibandronate	0.88 (0.60–1.29)	–
Risedronate	1.00 (0.78–1.28)	–
Zoledronate	–	–
Strontium ranelate	1.21 (0.93–1.58)	–

OR odds ratio, *95% CI* 95% confidence interval, *HR* hazard ratio, *NSAID* nonsteroidal anti-inflammatory drug

[a] OR of gastroduodenal ulcers before initiation of drugs against osteoporosis and HR of gastroduodenal ulcers after initiation of drugs against osteoporosis compared to nonusers. The OR before initiation is adjusted for alcoholism, NSAID use, use of potassium supplements, and use of drugs against gastroduodenal ulcers by logistic regression. The HR after initiation is adjusted for gastroduodenal event before initiation, alcoholism, use of NSAIDs or aspirin, use of potassium supplements, and use of drugs against gastroduodenal acid secretion by Cox proportional hazard regression

Calcif Tissue Int (2010) 86:110–115

GASTROINTESTINALI:
DATI BEST-1-



Ghirardi A, et al. Arch Int Med (submitted)

EVENTI GASTROINTESTINALI:
DATI BEST-2-

	Unadjusted OR *	Adjusted OR *
BPs exposure (Unexposed)		
Anytime †	1.12 (0.89 to 1.40)	0.98 (0.77 to 1.24)
Current †	1.04 (0.74 to 1.47)	0.86 (0.60 to 1.22)
Past †	1.17 (0.88 to 1.57)	1.07 (0.80 to 1.44)
Use of other medicaments ‡		
Antidepressants	-	1.19 (0.98 to 1.46)
Antithrombotic	-	1.12 (0.94 to 1.33)
Gastroprotective agents	-	1.61 (1.34 to 1.93)
Corticosteroids	-	1.38 (1.04 to 1.84)
Statins	-	0.73 (0.52 to 1.02)
Calcium channel blockers	-	0.97 (0.78 to 1.22)
Other antihypertensive drugs	-	1.04 (0.88 to 1.22)
Nonsteroidal antiinflammatory drugs	-	1.95 (1.61 to 2.36)
Co-morbidity # (0)		
≥1	-	2.63 (2.16 to 3.20)

Ghirardi A, et al. Arch Int Med (submitted)

CARCINOMA ESOFAGEO

Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

JAMA. 2010;304(6):657-663

Fonte dati: GPRD

BMJ 2010;341:c4444

Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort

Table 2. Esophageal and Gastric Cancer Incidence in the Bisphosphonate and Matched Control Cohorts

	Bisphosphonate		Control		Risk			
					Unadjusted		Adjusted[a]	
Bisphosphonate Category	Cases	Person-Years	Cases	Person-Years	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Any bisphosphonate Prescribed	116	165 400	115	163 479	1.00 (0.77-1.29)	.98	0.96 (0.74-1.25)	.77
Incidence after cumulative prescriptions greater than (in DDDs)[b]								
183	75	104 678	75	104 104	1.00 (0.72-1.37)	.98	1.01 (0.73-1.40)	.96
365	50	73 364	53	73 171	0.94 (0.64-1.39)	.76	0.98 (0.66-1.45)	.90
730	28	40 326	29	40 491	0.97 (0.58-1.63)	.91	0.96 (0.56-1.63)	.87
1095	16	22 813	17	22 891	0.95 (0.48-1.87)	.88	0.90 (0.44-1.81)	.76
Total bisphosphonate intake during follow-up (in DDDs/d)[c]								
Low (0-<0.24)	48	62 922	45	63 648	1.08 (0.72-1.62)	.71	0.95 (0.63-1.45)	.83
Medium (≥0.24-<0.89)	35	58 161	36	55 334	0.93 (0.58-1.48)	.74	0.96 (0.59-1.54)	.86
High (≥0.89)	33	44 316	34	44 497	0.98 (0.60-1.58)	.92	0.96 (0.59-1.58)	.89

	Oesophagus		
Oral bisphosphonates	Prescriptions*	Cases/ controls	RR† (95% CI)
Not prescribed	NA	2864/14 376	1.00
Prescribed	13.6/2.4	90/345	1.30 (1.02 to 1.66)
No of prescriptions:			
1-9	3.6/1.0	40/214	0.93 (0.66 to 1.31)
≥10	21.6/3.5	50/131	1.93 (1.37 to 2.70)
Estimated duration of use‡:			
≤1 year	4.9/0.3	31/155	0.98 (0.66 to 1.46)
1-3 years	13.0/2.0	26/114	1.12 (0.73 to 1.73)
≥3 years	22.2/4.6	33/76	2.24 (1.47 to 3.43)

CARCINOMA ESOFAGEO

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies

28 October 2010
EMA/CHMP/PhVWP/652824/2010
Patient Health Protection

Monthly report **Issue number: 1010**

Pharmacovigilance Working Party (PhVWP)
October 2010 plenary meeting

Bisphosphonates for oral use – Risk of oesophageal irritation but insufficient evidence to conclude a causal relationship with oesophageal cancer

There is insufficient evidence to suggest a definite causal relationship between oral bisphosphonates and oesophageal cancer. However, bisphosphonate tablets can cause irritation to the oesophagus and therefore patients should follow the instructions in the package leaflet on how to take the medicine and report signs of oesophageal irritation to their physician, such as difficulties or pain on swallowing, chest pain or heartburn. In individual patients with known Barrett's oesphoagus, physicians should carefully consider the benefits and potential risks of treatment with alendronic acid or ibandronic acid.

CONCLUSIONI

- **Profilo di beneficio-rischio positivo:**
  - nelle condizioni di un adeguata aderenza e di una durata non superiore a 4-5 anni
  - Per i pazienti ad alto rischio e nella prevenzione delle fratture vertebrali il profilo di beneficio-rischio appare positivo anche per durata superiore
- Rischio di ONJ e fratture atipiche per un periodo di trattamento superiore a 3 anni consistente ma piuttosto basso in termini assoluti (necessità di strategie di minimizzazione del rischio)
- Necessari ulteriori studi per la conferma relativa a Fibrillazione Atriale, Insufficienza valvolare, carcinoma esofageo
- Non emergono dati relativi agli altri eventi GI severi (ulcera, sanguinamento)