AACE

Orlando
2016

Drug Holidays

Disclosures

- Advisory boards: Alexion, Amgen, Lilly, Merck, Radius Health
- Scientific grants: Alexion, Amgen, Immunodiagnostics, Lilly, Merck, Regeneron, Radius Health, Roche Diagnostics, Ultrageneics
- Speakers Bureaus: None
- Equity : None

HOW LONG TO TREAT?

- Usually not a question for other chronic diseases
  - Hypertension
  - Dyslipidemia
  - Diabetes
  - CHF

- For Osteoporosis : "Is not, is probably not, perhaps is not, maybe not yet; it'll be over….."

Miller PD Exp Opinion Pharmacotherapy 2003
Bonnick SL JCD 2011
Khosla S et al JCEM 2012
McClung MR et al Am J Med 2012
Strim O et al OI 2015
McClung MR OI 2015
Adler R et al JBMR 2016

I Started My Holiday One Year Ago, and I don't know how to judge whether it's over !

Moses and God 1313 BC

Bisphosphonate "Drug Holiday"

- 1. Not a topic of discussion when BP 1st launched (1995)
- 2. Became a consideration after July 9,2002 (WHI JAMA publication) when BP Rx increased in younger post-menopausal women.
- 3. Became more widely discussed after FLEX (Black D et al JAMA 2006), and the better science defining BP Pharmacology became available (Russell G OI, 1970 and Bone 2010).
- 4. FRAX™ also drove the drug holiday discussion in women who, by the FRAX™ calculation had been at low risk before bisphosphonates were started.
- 5. Still, not a standard of care in the USA, though the FDA, and most other "bone" professional societies suggest considering a holiday in lower risk patients after 3-5 years of use.

Miller PD In: Best Practice and Research Clinical Endocrinology and Metabolism 2008; 22 (5): 849-868.

September 9, 2011
FDA Advisory Committee Hearing on Bisphosphonate Duration of Use

1. Little evidence of continual efficacy beyond 5 years

2. Safety concerns re atypical sub trochanteric femur fractures with longer term use

http://www.fda.gov/downloads/dvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugs

Is The Question:

"Is There Evidence for Efficacy Beyond 5 years ?"

A Fair Question ?

No study can maintain a placebo group for long periods to have robust long term fracture data between the original randomized placebo vs treatment groups

Bisphosphonate Pharmacology

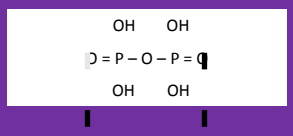
Is Unique

The Pioneers of Bisphosphonates (P–C–P) Pharmacology

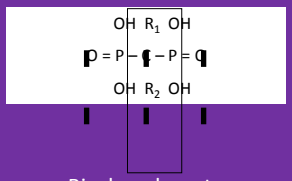
Herbert Fleisch, MD
Switzerland

Gideon Rodan, MD
USA

Graham Russell,MD
Oxford, UK



Pyrophosphate



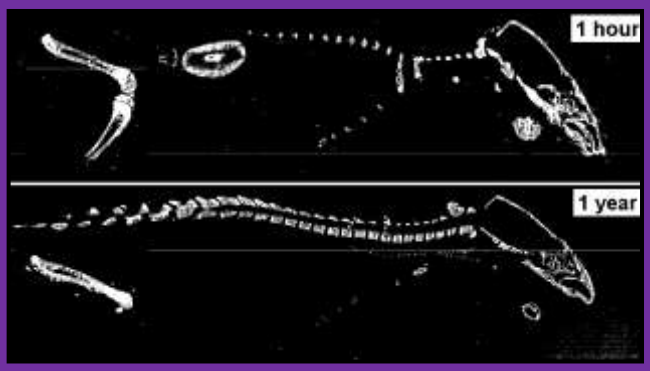
Bisphosphonate

Bisphosphonates

- 1. Not metabolized
- 2. Retained in bone
- 3. Re-cycled
- 4. Maintain some biological activity after discontinuation

Russell G et al BONE 2011

Rat Skeleton after Single dose ^{14}C-labeled IV Zoledronic Acid

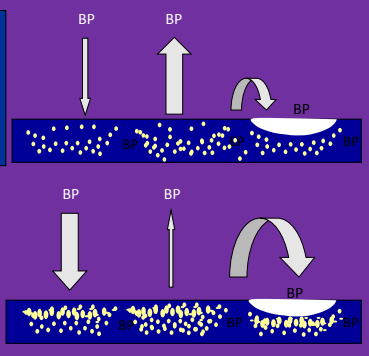


From Green JR Personal Communication

BISPHOSPHONATE UPTAKE AND DETACHMENT FROM BONE SURFACES

Lower Affinity BP
- Less uptake
- More diffusion in bone
- High desorption
- Low reattachment

Higher Affinity BP
- More uptake
- Less diffusion in bone
- Low desorption
- High reattachment



Graham Russell et al. Osteo Int 2008; 19: 733-759

Despite the Pharmacology of Bisphosphonates

Perhaps they may not have a prolonged effect
on
fracture reduction in osteoporosis patients when
stopped ?

Miller PD JCEM 2016 (in press)

Clinical Trial Data

On which bisphosphonate “holidays” are based
is
based on very small patient numbers

FLEX Trial
Fosamax Long-Term Extension

A re-randomization of the original

FIT 1 and FIT 2 alendronate registration trials

6,459 from the FIT trials

1,099 of the treated groups entered FLEX

FN BMD < 0.68 gm/cm²

376 from FIT 1 (VCF)

723 from FIT 2 (No VCF)

Black D et al JAMA 2008

An Example of How Change in the Reference Database Affected FIT-FLEX

The number of patients with "osteoporosis" was cut in half

T-score Range	Original Hologic Reference Values	NHANES III Reference Values
0 to -1.0	0 (0%)	2 (0.1%)
-1.0 to -2.0	36 (0.8%)	1362 (30.7%)
-2.0 to -2.5	934 (21.1%)	1435 (32.4%)
Less than -2.5	3460 (78.1%)	1631 (36.8%)

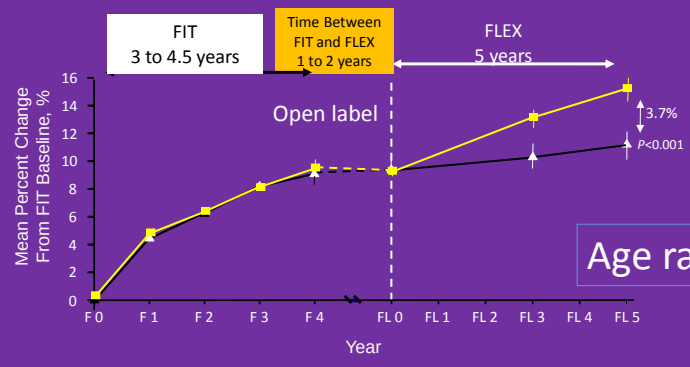
Database: Hologic 10/25/91 | NHA 02/01/97

FIT 2: Lowest FN -1.6 by Hologic

FIT 2: NHA Lowest FN -2.0

Cummings SR, et al. JAMA. 1998; 280:2077

Lumbar Spine BMD Change in FLEX Population: From Beginning of FIT to Completion of FLEX



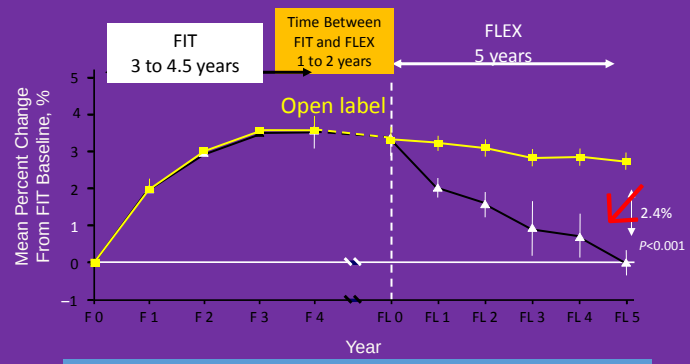
Age range: 69-91 yo

▲ = ALN/placebo (n = 437)

▮ = ALN/ALN (pooled 5-mg and 10-mg groups: n = 662)

Black DM et al. *JAMA*. 2006.

Total Hip BMD Change in FLEX Population: From Beginning of FIT to Completion of FLEX



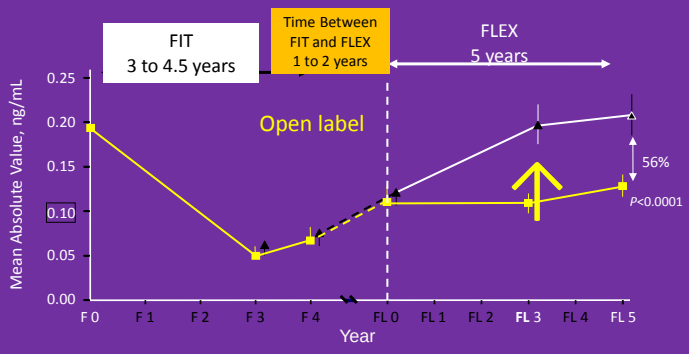
▲ = ALN/placebo (n = 437)

▮ = ALN/ALN (pooled 5-mg and 10-mg groups: n = 662)

F = FIT; FL = FLEX .

Black DM et al. *JAMA*. 2006;296:2927–2938.

Serum CTx: Mean Absolute Value Change From FIT and FLEX Baselines

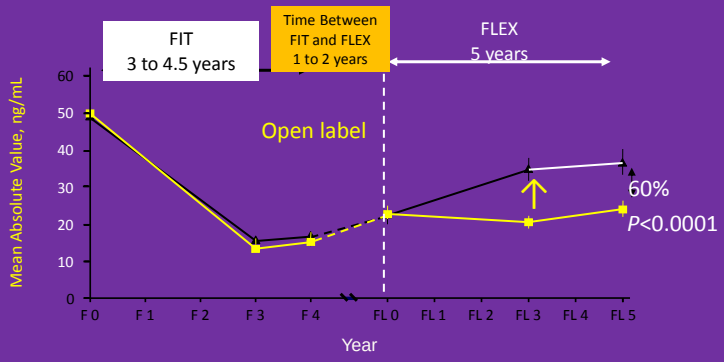


▲ = ALN/placebo N= 97

■ = ALN/ALN pooled doses N= 139

Black D et al JAMA 2006

Serum P1NP: Mean Absolute Value Change From FIT and FLEX Baselines



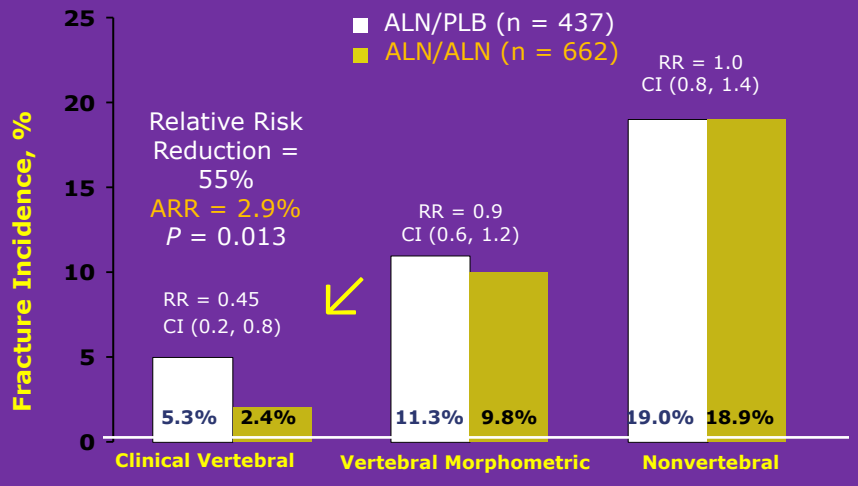
▲ = ALN/placebo (n = 97)

■ = ALN/ALN (pooled 5-mg and 10-mg groups: n = 139)

P1NP = N-propeptide of type 1 collagen.

Black DM et al. *JAMA*. 2006

FLEX: Incidence of Fractures (prospective)

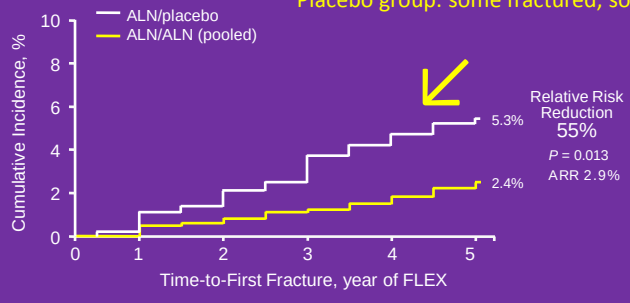


N = 23/16

Black DM, et al. *JAMA.* 2006;296:2927-38.

More Clinical (Painful) VCF During Drug Holiday

Placebo group: some fractured; some did not



ALN = alendronate; ARR = absolute risk reduction.

Modified from Black DM et al. JAMA. 2006;296:2927-2938.

The Truth In FLEX

- 1. The primary analyses was a change in BMD and fracture assessment was an exploratory end-point.

- 2. The increase in the clinical vertebral fracture or non-vertebral risk with discontinuation of alendronate prospectively was NOT related to the level of baseline BMD nor baseline prevalent VCF in FLEX. (Table 4 in Black D et al JAMA 2006).

Interaction Between Baseline T-score or VCF and Risk Reduction

Table 4. Effect of Alendronate on Fracture Risk Among Subgroups of Baseline Femoral Neck BMD and Prevalent Vertebral Fracture*

Or alendronate discontinuation

Subgroup	No.	Nonvertebral Fractures: Placebo, No. (%)	Nonvertebral Fractures: Alendronate, No. (%)	Nonvertebral Fractures: RR (95% CI)	Clinical Vertebral Fractures: Placebo, No. (%)	Clinical Vertebral Fractures: Alendronate, No. (%)	Clinical Vertebral Fractures: RR (95% CI)
Baseline BMD T score at femoral neck							
>-2.0	461	18 (10.1)	42 (14.9)	1.5 (0.86-2.6)	3 (1.7)	4 (1.4)	0.84 (0.18-4.2)
>-2.5 to ≤-2.0	311	26 (20.6)	38 (20.5)	1.0 (0.63-1.7)	9 (7.1)	3 (1.6)	0.22 (0.05-0.74)
≤-2.5	322	39 (29.5)	43 (22.6)	0.77 (0.50-1.2)	11 (8.3)	9 (4.7)	0.57 (0.23-1.40)
P value for interaction†				.40			.72
Prevalent vertebral fracture							
No	723	48 (16.7)	61 (14.1)	0.86 (0.59-1.3)	11 (3.8)	7 (1.6)	0.42 (0.16-1.1)
Yes	376	35 (23.3)	62 (27.7)	1.20 (0.80-1.8)	12 (8.0)	9 (4.0)	0.47 (0.19-1.1)
P value for interaction‡				.23			.85

Abbreviations: BMD, bone mineral density; CI, confidence interval; RR, relative risk.
*Analyses of RR and assessment of interaction were done with unadjusted proportional hazards models. Parallel analyses of morphometric vertebral fracture did not show any significant trends for alendronate efficacy among subgroups.
†Interaction between BMD as a continuous variable and treatment.
‡Interaction between prevalent vertebral fracture status and treatment.

Black D et al JAMA 2006

Editorial NEJM

Acknowledged that in FLEX there was NO INTERACTION between either baseline BMD or prevalent VCF and the change in risk for new clinical vertebral fracture or non-vertebral fracture (prospective)

Cummings SR , Black D et al NEJM 2012

Data from FLEX and Horizon

- 1. Neither provide definitive information on fracture risk in patients who continue or discontinue treatment.
- 2. In both the effect of continued treatment was an exploratory aim, did not include the entire randomized populations, limited power to detect modest differences in fracture rates reflected in wide confidence intervals in fracture outcomes. Neither T-score or prior VCF could predict who would/would not fracture off therapy.
- 3. Fractures were only clinical vertebral (FLEX) or morphometric vertebral (HORIZON).
-
- 4. Non-vertebral fracture reduction in FLEX was a post-hoc analysis

Boonen S et al JBMR 2012

Think, Don't Just Accept Dogma/Status Quo

"Only doubt is certain and disbelief worth believing. Without this courage there can be no learning. Believe nothing."

Anonymous

Osteoporosis Drug Holidays

A Re-Thinking of the Data

Perhaps we should not stop anyone with "low" BMD, prior fractures or older (69+)

And…..

BMD changes or BTM may (or may not) be useful in deciding when a holiday is over

Summary Minutes of the Joint Meeting of the Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee
September 9, 2011

- "…no data to truly support that restricting the duration of use was beneficial for patients requiring long-term bisphosphonate treatment for osteoporosis"
- ". . .the committee was not confident that implementing a drug holiday or discontinuing bisphosphonate use after a period time would be beneficial"
- ". . . the committee recommended that the label should further clarify the duration of use for bisphosphonates"
- The committee members who voted "No" (17-6) noted that the labeling does not need further clarification at this time and that it should only include information that is known since there is a lack of data on the benefit versus risk of limiting the duration of use of bisphosphonates.

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM278481.pdf

- Decisions to continue treatment must be based on individual assessment of risks and benefits and on patient preference
- Patients at low risk for fracture (e.g., younger patients without a fracture history and with BMD approaching normal) may prove to be good candidates for discontinuation of bisphosphonate therapy after 3 to 5 years
- Patients at increased risk for fracture (e.g., older patients with a history of fracture and BMD remaining in the osteoporotic range) may benefit further from continued bisphosphonate therapy

FDA Perspective

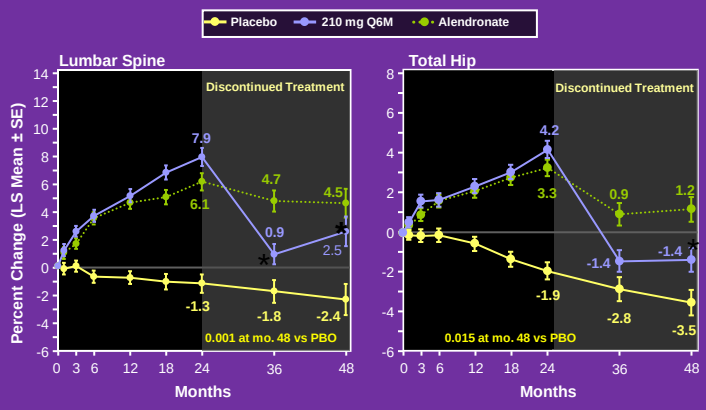
Whitaker M et al. N Engl J Med. 2012;366:2048-2051.

Is The Trend to Stop a BP

An uncertain trend ?

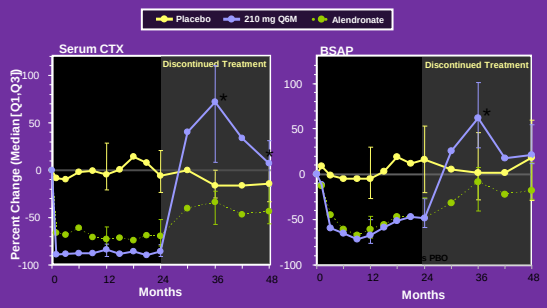
Why Not a Holiday for Other Osteoporosis Drugs ?

Effect of Discontinuation of Denosumab on LS and TH BMD



Miller PD et al. Bone. 2008;43:222-229.

Effect of Discontinuation of Denosumab on sCTX and BSAP Levels



*$P < 0.001$ at mo. 36 and = 0.025 at mo. 48 vs PBO

Miller PD et al. Bone. 2008;43:222-229.

Where Are We in 2016 ?

Should Drug Holidays Be Considered? (or Revaluated) ?

- YES (to which question) ?

- But consider ONLY in lower risk patients:
- no prior fracture, T-scores > -2.0, and younger age (<65 years)
- and……..
- Because we have no data on patients with steroid use, stage 3-5 CKD, diabetes mellitus and other diseases that increase fall risk (Parkinsons, MS, etc) one must use caution and clinical judgement in any patient not "fitting" the strict randomization criteria of FIT/FLEX

Treat the Person, Not Just Their Bones

"The good physician treats the disease; the great physician treats the patient who has the disease."

Sir William Osler

Why Are Osteoporosis Pharmacological Treatments Declining ? Confusion and……

FEAR

Australian Broadcasting Company. ONJ with bisphosphonates. Dec 11, 2007.

Diane Sawyer. Atypical femur fractures with bisphosphonates. March 8, 2010.

ASBMR Reports on Atypical Femoral Fractures


JBMR

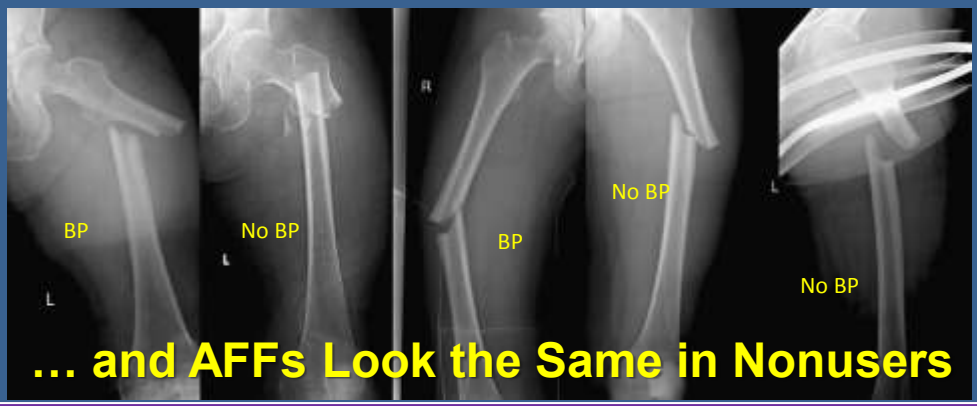
Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the american society for bone and mineral Research

No Causality Established

- Shane E et al JBMR 2010
- Shane E et al JBMR 2014

AFFs Occur in Nonusers …

- ASBMR, 2010: **"It is also important to note that atypical fractures have been reported in patients who have not been exposed to BPs."**
- ASBMR 2014: **"Every study included AFF patients unexposed to BPs."**



2010 Shane JBMR; 2014 Shane JBMR; 2011 Tan OI 43

How Uncontrolled Case Series

May Lead to Beliefs

The epidemiological data (retrospective) associating bisphosphonates with ASFF are mostly uncontrolled and NONE have controlled for baseline BMD

Confounded by Indication

The very patients who are more likely to receive bisphosphonates (low bone mass) are the ones that have a higher risk for all forms of femur fractures, including sub-trochanteric

Authors Acknowledge Confounding


Bisphosphonate Use and Atypical Fractures of the Femoral Shaft

"The increased risks of femur fracture, irrespective of fracture location, that were associated with bisphosphonate use are probably the consequence of osteoporosis."

Variable	Bisphosphonate Users (N=83,311)		Nonusers of Bisphosphonates (N=1,437,820)		Age-Adjusted Relative Risk (95% CI)
	No. of Fracture Cases	Crude Incidence no./10,000 patient-yr	No. of Fracture Cases	Crude Incidence no./10,000 patient-yr	
Diagnosis from registry data					
Any hip fracture, ICD-10 code S720, S721, or S722	1255	151	10,585	74	1.32 (1.25–1.40)
Femoral-neck fracture, ICD-10 code S720	599	72	5,655	39	1.19 (1.09–1.29)
Trochanteric fracture, ICD-10 code S721	528	63	4,136	29	1.41 (1.29–1.54)
Subtrochanteric fracture, ICD-10 code S722	128	15	794	5.5	1.80 (1.50–2.17)
Femoral-shaft fracture, ICD-10 code S723	105	13	324	2.3	3.83 (3.08–4.78)
Subtrochanteric or femoral-shaft fracture	233	28	1,118	7.8	2.34 (2.03–2.70)

2011 Schilcher NEJM

Different Results With Different Definitions

Criteria	2011 Schilcher	2013 Schilcher
Total # of AFFs	59	80
AFFs w/ BP Use	46 (78%)	49 (61%)
AFFs w/ No BP Use	13 (22%)	31 (39%)
Total # of Subtroch/Shaft	322	277
Subtroch/Shaft w/ BP Use	72 (22%)	69 (25%)
Subtroch/Shaft w/ No BP Use	250 (78%)	208 (75%)

2011 Schilcher NEJM; 2013 Schilcher Bone

FDA "Duration of Use" Hearing

Based on the assumption that risk of ASFF IS related to duration of use

Bisphosphonate-Associated Atypical Femur Fractures Are Associated with Duration of Use

Incidence of atypical femur fractures according to duration of bisphonate exposure (unadjusted and age-adjusted, showing incidence and 95% confidence intervals)

True incident rate should have, as the denominator,
the number of patient year exposure (total cohort, total exposure)
rather than duration of BP exposure
Dell's paper is NOT a true incident rate

Dell R et al JBMR 2012

Incidence Rate Calculation

- The Dell et al description of how they calculated the incidence rate is not quite right. The paper says that the denominator was the person-time contributed by persons in the cohort over the 5-year study period.
- This limitation is important b/c the failure or inability to use patient-years of BP use for the denominator inhibits Dell's data from being a true incidence rate calculation, and then of course the duration of use analysis included gaps in BP prescriptions, so those numbers may well be off as well.

Frost C et al Stat Med 2008

Holidays

- 1. Limitation of use predicated on the unique pharmacology of BP's and the assumption that any "persistent" effect on BMD or turnover translates into persistent effect on fractures.
- 2. The limitation of duration of use is predicated on the belief that ASFF risk increased with the increase duration of BP use.
- 3. FLEX actually dismisses the 1st theory-BMD change and BTM change in FLEX in those off therapy did not predict more or less fractures in those on holidays; nor did the baseline BMD or prevalent VCF predict who might vs who might not develop a fracture on holiday.
- 4. All epidemiological reports on BP-associated ASFF are confounded by indication.

So, What's The Take-home Message ?

Holidays from osteoporosis therapies have poor evidence for justifying a "drug break".

Treat the patient and continuously treat the high risk patient

(older, osteopenic without prevalent VCF)