

Misuse of Bisphosphonates

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Introduction

- Bisphosphonates are chemically stable analogues of pyrophosphate compounds.
- First introduced in 1962.
- Reduce both vertebral and nonvertebral fractures.

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- Mechanism of action
 - affinity for binding to bone mineral
 - inhibition of osteoclastic resorption
- Half life: 10 years

Indications

- Prevention & treatment of osteoporosis in men and postmenopausal women.
- Patients at increased risk of osteoporotic fracture including those with long-term use of steroids, proton pump inhibitors and hormone replacement therapy.

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- Hypercalcemia of malignancy
- Paget's disease of bone
- Multiple myeloma
- Metastatic bone disease in breast, prostate, lung and other cancers

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- Generally safe and well tolerated.
- Misuses may cause several morbidities leading to reduced quality of life and also increasing mortality.

Materials and Methods

- A comprehensive literature search for relevant studies was done.
- Total 60 publications were retrieved from the electronic and manual searches. Among them 35 papers were selected and sorted by area of focus.

Results

- Without proper indications
- Extended duration of therapy

No Proper Indications

- No risk or low risk of fracture
- Osteopenia with less than 10-year fracture risk as determined by the WHO FRAX (Fracture Risk Assessment tool) regimen

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- Randomized trials of bisphosphonates in women without osteoporosis have shown an improvement in bone mineral density (BMD) but not fracture risk, the only relevant clinical endpoint.

Ref: McClung MR, Wasnich RD, Hosking DJ, et al. Early Postmenopausal Intervention Cohort Study. Prevention of postmenopausal bone loss: six-year results from the Early Postmenopausal Intervention Cohort Study. J Clin Endocrinol Metab. 2004 Oct;89(10):4879-85..

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- The National Osteoporosis Foundation (USA) recommends bisphosphonate use only in osteopenic patients with a 10-year risk of >3% for hip fracture or >20% for major osteoporotic fracture.

Ref: Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. [FDA Briefing Document]. Page 8.

Duration of Therapy

Atypical Fractures of Femur (AFF)



In 2009, among 310 case reports of AFF examined by the ASBMR task force, 291 of the published reports (94%) identified bisphosphonate use as a comorbidity, with a mean treatment duration of 7 years.

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- Risk for AFF was associated with bisphosphonate treatment for >5 years in a case control study of a large population-based cohort of elderly women (aged ≥ 68 years at initiation of bisphosphonates).

Ref: Park-Wyllie LY, Mamdani MM, Juurlink DN et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. JAMA. 2011;305:783–789.

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.

^aThe full list of covariates for the adjusted model are given in eAppendix 2 (available at <http://www.jama.com>).

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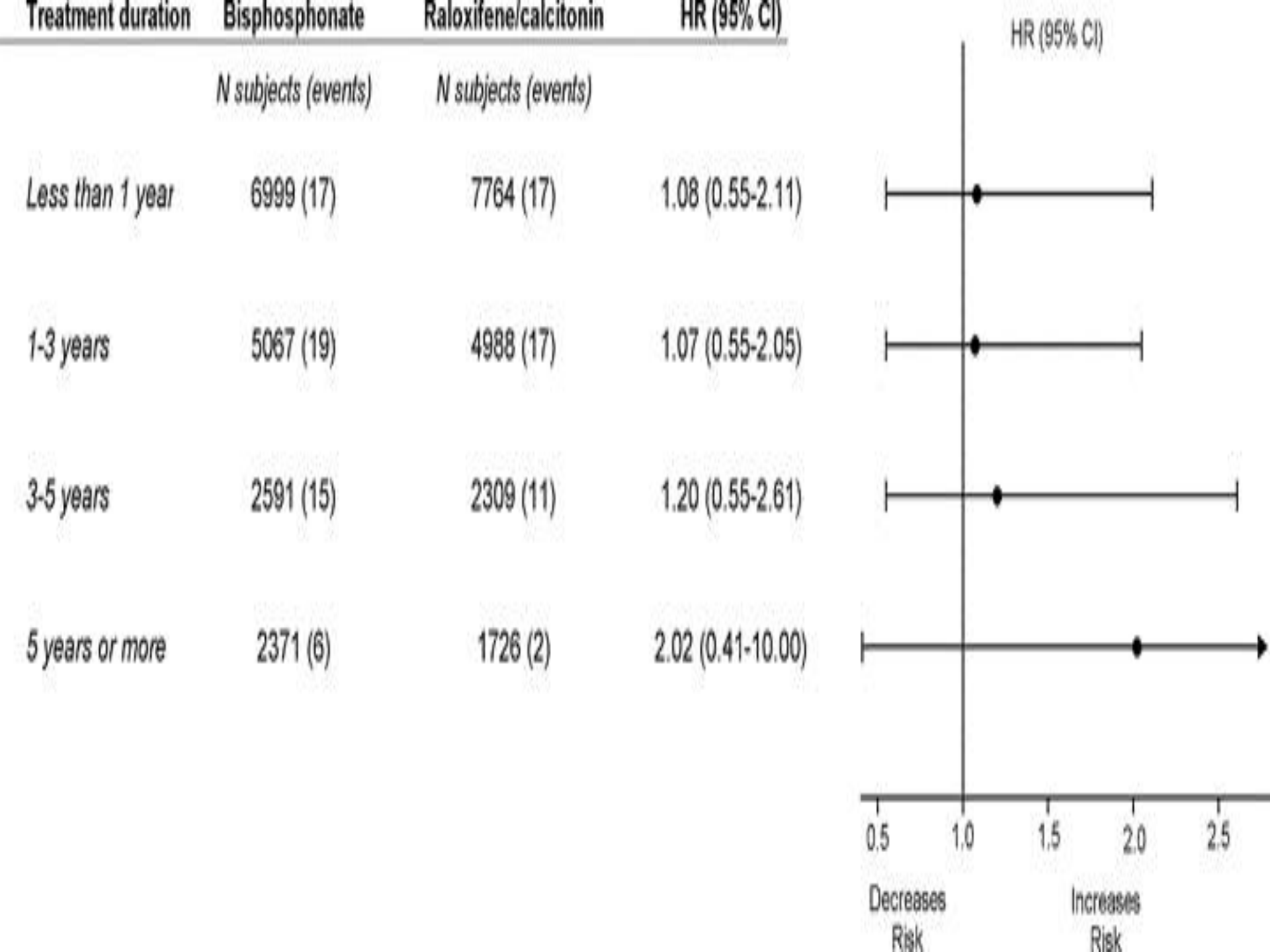
- Fracture Intervention Trial Long-term Extension (FLEX) study also showed no benefit of bisphosphonates in almost all patients beyond 5 years of use, even in high-risk women with osteoporosis and a history of vertebral fracture.

Ref: Ott SM. What is the optimal duration of bisphosphonate therapy? Cleve Clin J Med. 2011 Sep;78(9):619-30

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- In a large propensity score–matched cohort study no significant differences were noted between two groups for the risk of AFF stratified by treatment duration, although the HR was 2.02 with a wide confidence interval (95% CI 0.41–10.00) among those treated for longer than 5 years.

*Ref: Watts N, Diab D. Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab. 2010;95:1555–1565.
D'Agostino RJ. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998;17:2265–2281.*



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- These results suggest no significant advantage of continuing drug therapy beyond 5 years.
- Evidences are mixed.
- Further investigation into the origin of AFFs is required.

Osteonecrosis of Jaw

- The incidence of this complication is around 0.03% to 6.2%.
- Prolonged use greater than 5 years exposes patients to serious risks like osteonecrosis of the jaw which may increase 3–4 fold.

Ref: Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. [FDA Briefing Document]. Pages 19, 23.

- Study revealed that bisphosphonate (BP)-related osteonecrosis of the jaw (BRONJ) is increased with duration of therapy.

Ref: Sedghizadeh PP, Jones AC, LaVallee C. Population pharmacokinetic and pharmacodynamic modeling for assessing risk of bisphosphonate-related osteonecrosis of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 February; 115(2): 224–232

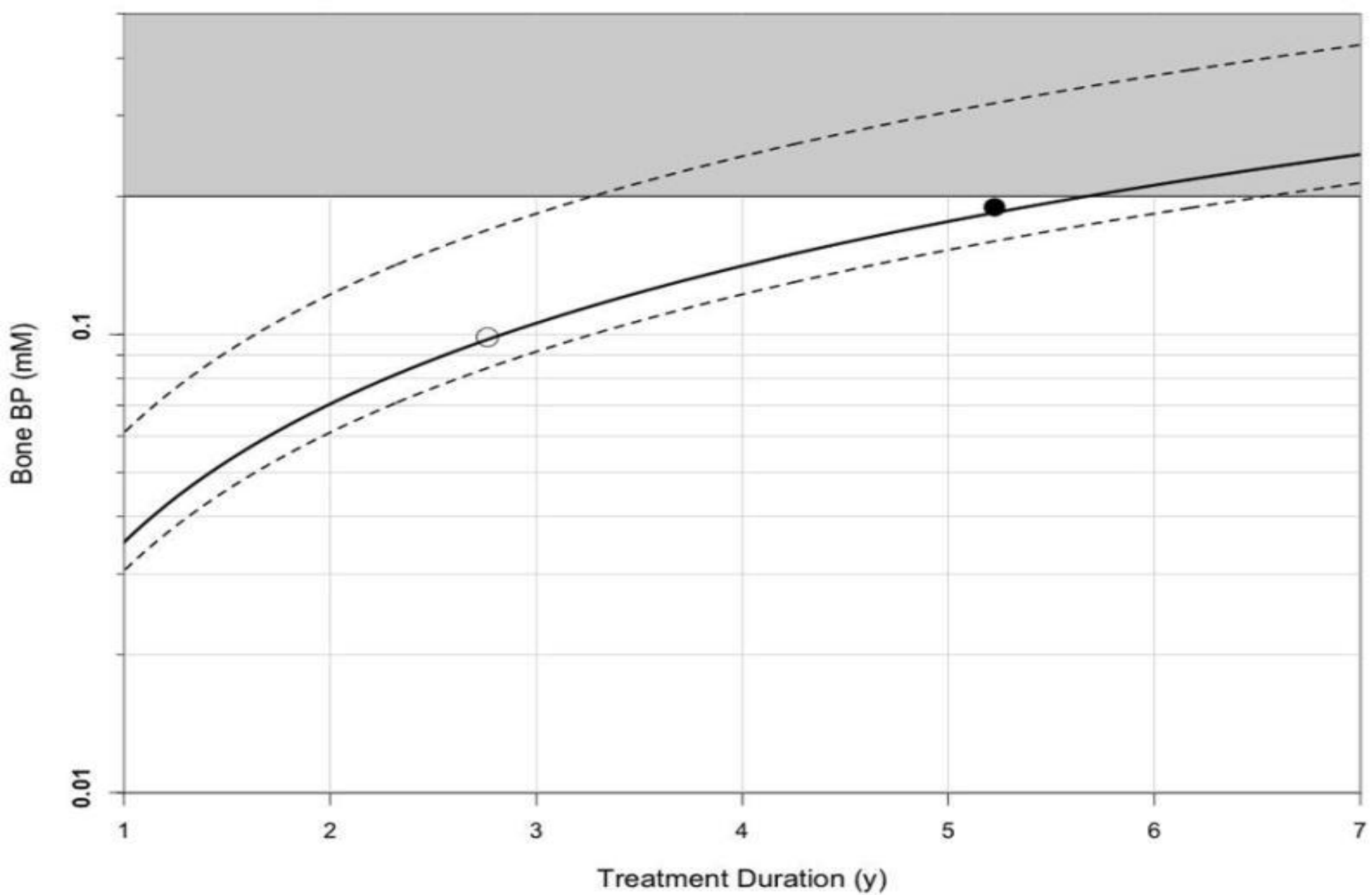


Figure: Region of potential BRONJ bone toxicity above a threshold bone BP concentration of 0.2 mM

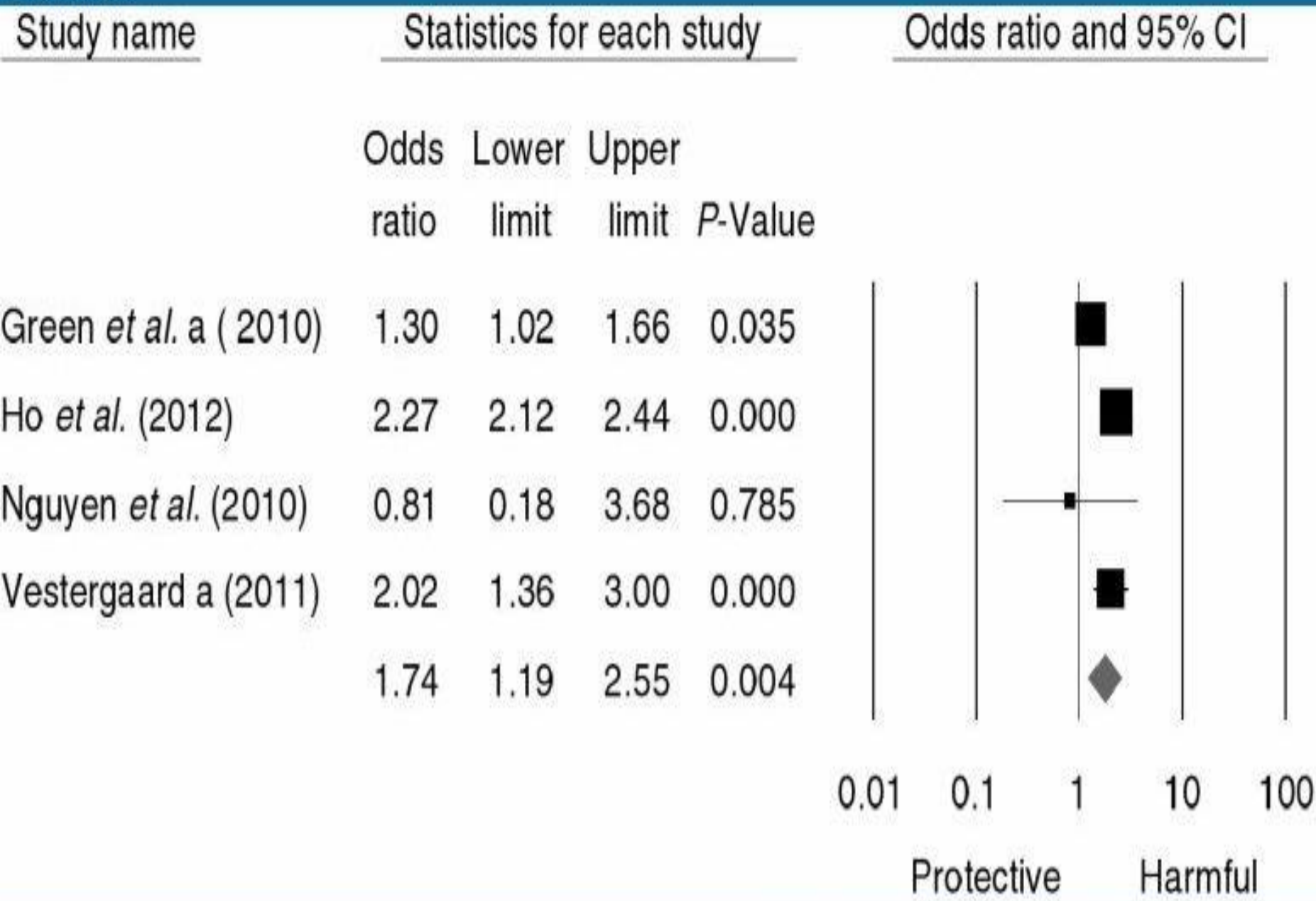
Esophageal cancer

- Epidemiological evidence suggests that bisphosphonate treatment can increase the risk of esophageal cancer.

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- One meta-analysis showed that there was a positive relationship between exposure to bisphosphonates and esophageal cancer, with an odds ratio (OR) of 1.74 with a 95% CI of 1.19–2.55 ($P < 0.001$).

Ref: Andrici J, Tio M, Eslick GD. Meta-analysis: Oral bisphosphonate and the risk of esophageal cancer. Aliment pharmacol ther 2012; 36(8): 708-716

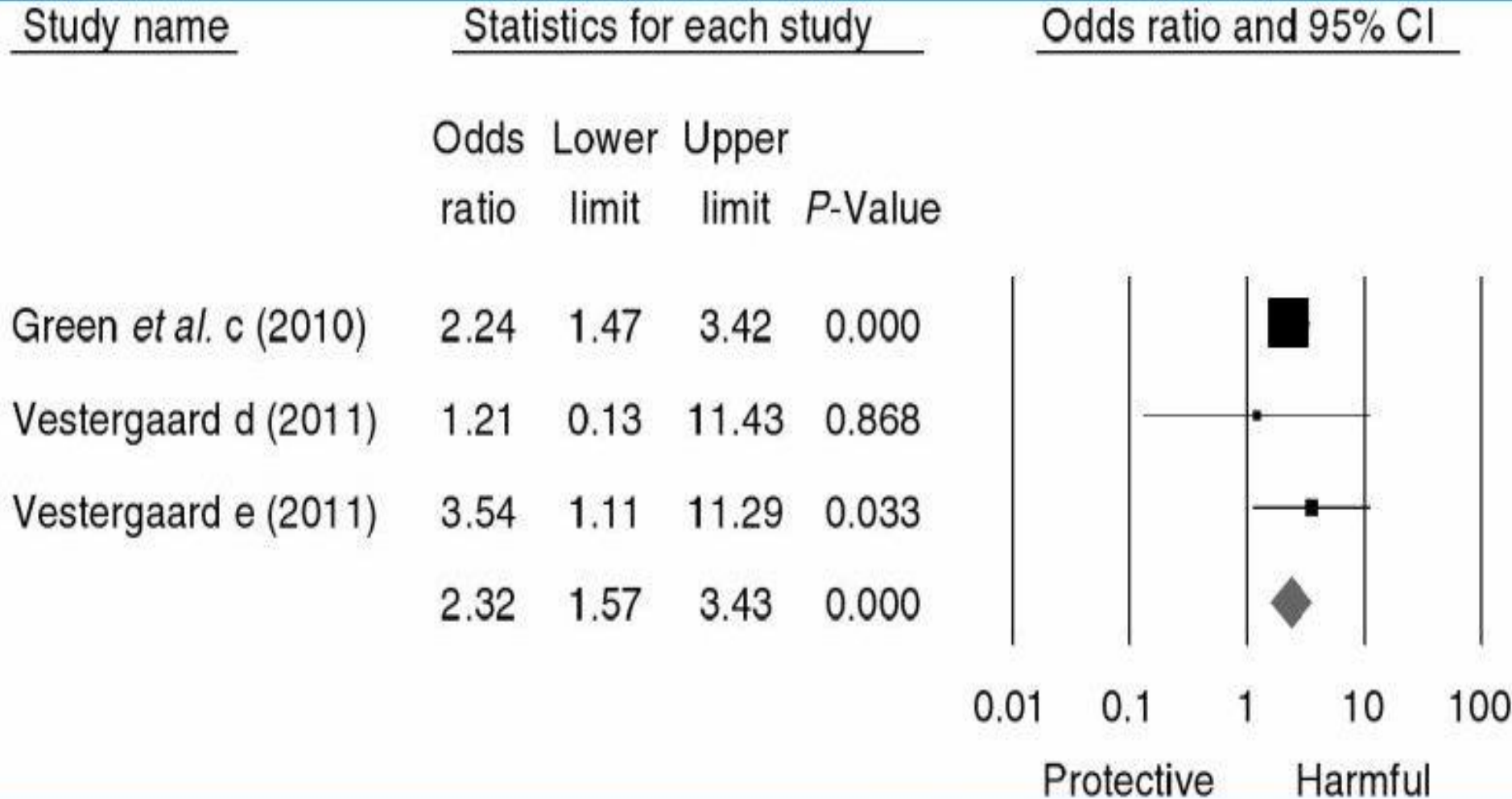


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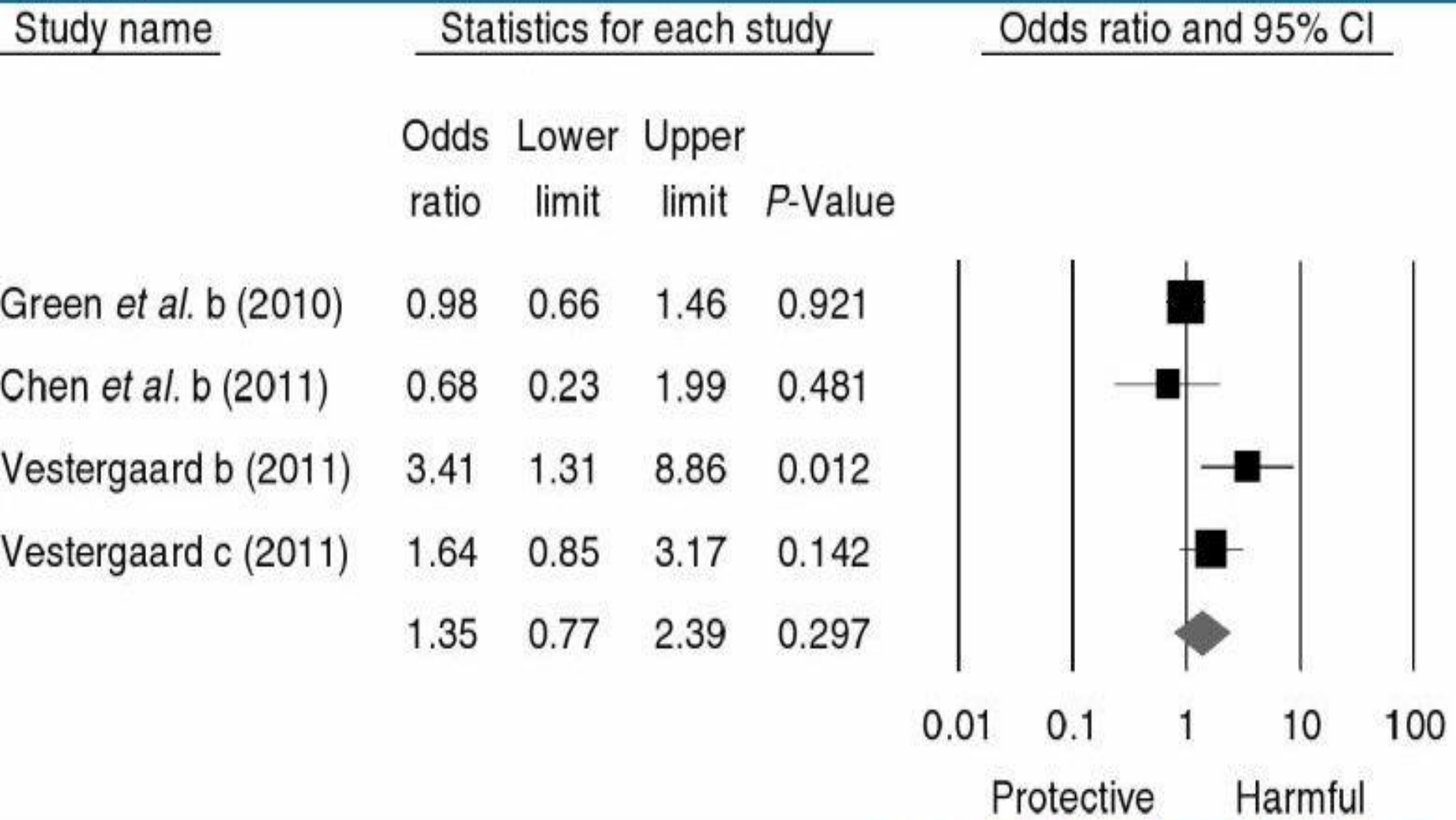
- An increased risk of esophageal cancer was also found in the group exposed to bisphosphonates for a longer period of time, compared with the group who experienced a shorter period of exposure (OR 2.32; 95% CI 1.57–3.43 vs. OR 1.35; 95% CI 0.77–2.39).

Longer exposure

Medscape



Shorter Exposure



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- In Europe and North America, the incidence of esophageal cancer at age 60–79 is typically 1 per 1000 population over five years, and this is estimated to increase to about 2 per 1000 with five years' use of oral bisphosphonates.

Ref: Jane Green, Gabriela Czanner, Gillian Reeves et al. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ. 2010; 341: c4444.

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- More studies are needed to confirm the relationship between exposure to bisphosphonates and risk of esophageal cancer.

Recommendation

- Long-term use of bisphosphonates for the prevention of osteoporotic fractures must be limited to 5 years.
- The indication for bisphosphonate treatment for osteopenic women must be removed, unless the patient has a significant 10-year fracture risk as determined by the World Health Organization's (WHO) FRAX algorithm.

Conclusion

- Patients should be selected carefully before prescribing these drugs.
- Clinicians should rely upon their judgment and re-evaluate the patients timely to reduce the risks.
- Further studies are needed to establish the causal relationship between misuses of bisphosphonates and the harmful effects.

**Thank
you**

