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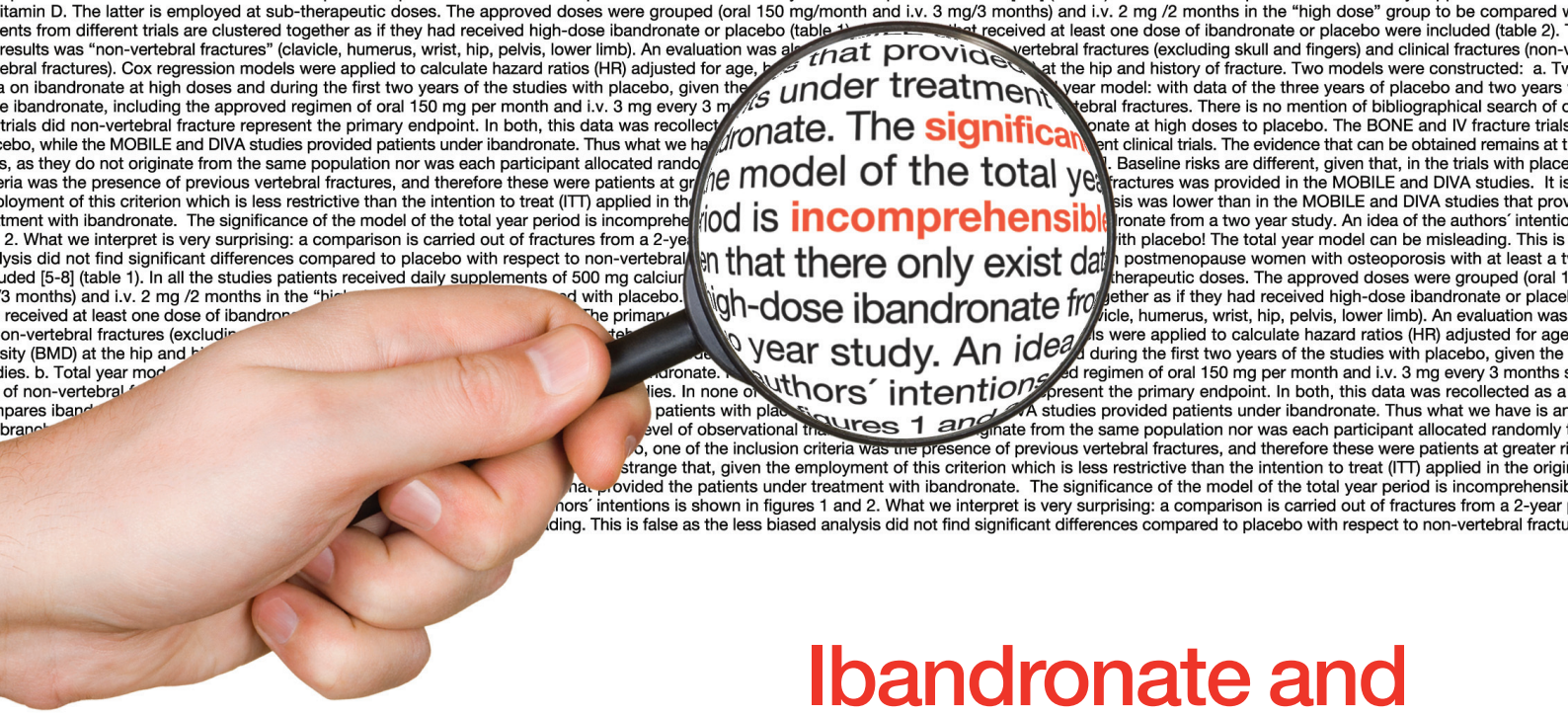

Summary

Objetive: an evaluation of two meta-analyses published on the efficacy of ibandronate in the prevention of non-vertebral fractures and the possible application of their results in clinical practice. **Material and methods:** a critical appraisal of the two meta-analyses is performed and a comparison of the results of the meta-analyses with a NICE meta-analysis of the same trials is carried out. In addition, the implementation of the results of the two meta-analyses in a Spanish Clinical Guideline is critically appraised. **Results:** Both meta-analyses employ individual patient data but they lose patients with respect to the original trial. High-dose regimens are clustered and include the commercialized oral presentation of 150 mg/month and intravenous 3 mg every 3 months. Financing was provided by pharmaceutical companies. Harris´meta-analysis makes an indirect comparison between the branches of placebo and ibandronate in different clinical trials. One of these analyses is incorrect for comparing results from different treatment periods. In the other analysis, no significant differences with placebo were found. Craney´s meta-analysis found differences in favour of ibandronate at high doses against 2.5 mg per day, but it has not been shown that this regimen does not increase risks when compared to placebo. The conclusions of the meta-analysis do not accord with the results. A NICE review did not find any evidence of the efficacy of ibandronate. The manner in which a practical guideline available has incorporated the results of the meta-analysis is absolutely false. **Conclusions:** the meta-analyses that have attempted to evaluate the efficacy of ibandronate in the prevention of non-vertebral fractures present conflicts of interest and problems of grouping different doses, indirect comparisons, incorrect analysis and modifications in populations. It has not been demonstrated that ibandronate at habitual doses is effective. The conclusions of the authors are excessively favourable, and consequently this has been magnified in the practical guidelines.

Ibandronate and the prevention of non-vertebral fractures. A critical appraisal of two meta-analyses on individual patient data

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Introduction

Ibandronate is a bisphosphonate available in 150 mg oral monthly and 3 mg quarterly intravenous presentations. It is indicated in the treatment of osteoporosis in postmenopausal women with a high risk of fracture.

The Product Information leaflet indicates that it has shown reductions in the risk of vertebral fracture, although the efficacy in femoral neck fractures has not been established[1].

Two meta-analyses have been published with the aim of evaluating the efficacy of ibadronate in non-vertebral fractures in postmenopausal women with osteoporosis. Both coincide in the application of individual patient data extracted from the original studies[2,3].

Meta-analyses that apply individual patient data present advantages when compared to those that aggregate results of studies, as they allow for more precise evaluations like time-to-event analyses and the application of multivariate models. Problems encountered include accessibility to the data which most commonly is property of pharmaceutical companies and there is no assurance that all the information is made available[4].

We will determine the validity and applicability of both studies making a critical appraisal.

Ibandronate and the risk of non-vertebral and clinical fractures in women with postmenopausal osteoporosis: results of a meta-analysis of phase III studies. Harris TS, et al[2]

This consists of an analysis of the individual patient data in four clinical trials involving ibandronate. An evaluation was carried out of the risk of non-vertebral fractures and clinical fractures. The conclusion found was that high dose ibandronate, which includes marketed regimens, is significantly effective with regard to clinical fractures and non-vertebral fractures.

SUMMARY OF THE ORIGINAL ARTICLE	CRITICAL APPRAISAL
Financing The study was financed by Roche and GlaxoSmith-Kline. One of the authors is employed by Roche.	
Investigation question It is desirable to know whether ibandronate at doses 150 mg oral monthly and 3 mg IV quarterly reduces the risk of non-vertebral and clinical fractures with respect to placebo.	
Methods Four phase III clinical trials with ibandronate in postmenopausal women with osteoporosis with at least a two-year follow-up were included[5-8] (table 1). In all the studies patients received daily supplements of 500 mg calcium and 400 IU of vitamin D. The latter is employed at sub-therapeutic doses. The approved doses were grouped (oral 150 mg monthly and i.v. 3 mg/3 months) and i.v. 2 mg /2 months in the “high dose” group to be compared with placebo. Groups of patients from different trials are clustered together as if they had received high-dose ibandronate or placebo (table 1).	There is no mention of bibliographical search of other studies. In none of the trials did non-vertebral fracture represent the primary endpoint. This data was recollected either as a safety variable or a secondary efficacy endpoint. Very different dose regimens are grouped. No trial compares ibandronate at high doses to placebo. The BONE and IV fracture trials provided patients with placebo, while the MOBILE and DIVA studies provided patients under ibandronate. Thus what we have is an indirect comparison of the branches of different clinical trials. The evidence that can be obtained remains at the level of observational trials, as they do not originate from the same population nor was each participant allocated randomly to take either high-dose ibandronate or placebo[4]. Baseline risks are different, given that, in the trials with placebo, one of the inclusion criteria was the presence of previous vertebral fractures, and therefore these were patients at greater risk.

Table 1. Studies included.

TRIAL	INCLUSION CRITERIA	PRIMARY ENDPOINT	NON-VERTEBRAL FRACTURES COMMUNICATED AS A RESULT OF	TREATMENT GROUPS	DURATION
BONE[5]	Lumbar BMD T-score (-2.0 to -5.0) and 1-4 vertebral fractures	Vertebral fracture	Secondary efficacy	Intermittent 20 oral mg doses 2.5 mg oral daily **Placebo**	**3 years**
IV Fracture[6]	Lumbar BMD T-score (-2.0 to -5.0) and 1-4 vertebral fractures	Vertebral fracture	Secondary efficacy	1 mg IV / 3 months 0.5 mg IV/ 3 months **Placebo**	**3 years**
MOBILE[7]	Lumbar BMD T-score (-2.5 to -5.0)	Change in lumbar BMD	Safety	2.5 mg oral daily 50+50 mg oral / month 100 mg oral / month **150 mg oral / month**	**2 years**
DIVA[8]	Lumbar BMD T-score (-2.5 to -5.0)	Change in lumbar BMD	Safety	Oral 2.5 mg oral daily **2 mg IV / 2 months** **3 mg IV/ 3 months**	**2 years**

Treatment groups included in Harris´ meta-analysis and the duration of the trials are highlighted.
BMD: Bone mineral density

SUMMARY OF THE ORIGINAL ARTICLE

All patients that received at least one dose of ibandronate or placebo were included (table 2).

The primary endpoint of the results was "non-vertebral fractures" (clavicle, humerus, wrist, hip, pelvis, leg). An evaluation was also made of the group of non-vertebral fractures (excluding skull, fingers and toes) and clinical fractures (non-vertebral + symptomatic vertebral fractures).

Cox regression models were applied to calculate *hazard ratios* (HR) adjusted for age, baseline bone mineral density (BMD) at the hip and history of fracture.

Two models were constructed:
a. Two-year model: includes data on ibandronate at high doses and during the first two years of the studies with placebo, given the different duration of the studies.
b. All-year model: with data of the three years of placebo and two years with ibandronate.

CRITICAL APPRAISAL

No data on baseline prevalence of vertebral fractures was provided in the MOBILE and DIVA studies.

It is strange that, given the employment of this criterion which is less restrictive than the intention to treat (ITT) applied in the original trials, the number of patients in the meta-analysis was lower than in the MOBILE and DIVA studies that provided the patients under treatment with ibandronate (table 2).

The significance of the all-year model is incomprehensible given that there only exist data on high-dose ibandronate from two year studies. An idea of the authors intentions is shown in figures 1 and 2.
What we interpret is very surprising: a comparison is carried out of fractures from a 2-year period with ibandronate with those of a 3-year study with placebo!

(*) The Hazard ratio (HR) is a measure of association, employed in the analysis of survival applying Cox regression. It is similar to relative risk with the difference that it incorporates time in which the events occur. A complete review on HR can be read at: Martínez-González MA et al. ¿Qué es el hazard ratio? Nociones de análisis de supervivencia. Med Clin (Barc). 2008;131(2):65-72.

Table 2. Populations (ITT) of the trials included in the meta-analyses.

TRIAL	TREATMENT GROUPS	HARRIS META-ANALYSIS[2]	CRANNEY META-ANALYSIS[3]	PUBLISHED IN TRIAL*
BONE[5]	Intermittent 20 mg oral dose	976	1,954	977
	2.5 mg oral daily	977		977
	Placebo	975	975	975
	Total	**2,928**	**2,929**	**2,929**
IV Fracture[6]	1 mg IV / 3 months	961	1,911	961
	0.5 mg IV / 3 months	950		950
	Placebo	949	949	949
	Total	**2,860**	**2,860**	**2,860**
MOBILE[7]	2.5 mg oral daily	392	393	395
	50+50 mg oral monthly	391		396
	100 mg oral monthly	392	1,179	396
	150 mg oral monthly	391		396
	Total	**1,566**	**1,572**	**1,583**
DIVA[8]	2.5 mg oral daily	457	457	465
	2 mg IV / 2 months	440	902	448
	3 mg IV / 3 months	459		469
	Total	**1,356**	**1,359**	**1,382**
MOBILE+DIVA	**Total**	**2,922**	**2,931**	**2,965**

(*) In the trials published, the population with ITT was defined as those patients that received at least one dose and attended one follow-up appointment.

SUMMARY OF THE ORIGINAL ARTICLE

Results
Table 3. Figures 1 and 2.

Conclusion
High-dose ibandronate, including the approved regimens 150 mg oral monthly and 3 mg IV quarterly significantly reduces the risk of non-vertebral fractures.

CRITICAL APPRAISAL

The all-year model can be misleading

This is false as the less biased analysis did not find significant differences compared to placebo with respect to non-vertebral fractures.

Table 3. Comparison of high-dose ibandronate with placebo with regard to the rate of fractures.

	TWO-YEAR MODEL		ALL-YEAR MODEL	
FRACTURE	**HR**	**95%CI**	**HR**	**95%CI**
Key non-vertebral	0.717	0.48 to 1.08	0.656	0.45 to 0.96
Non-vertebral	0.729	0.51 to 1.04	0.701	0.50 to 0.99
Clinical	0.706	0.54 to 0.93	0.730	0.56 to 0.95

Figure 1. Percentages of fractures in the 2-year model and the all-year model (adapted from reference 2).

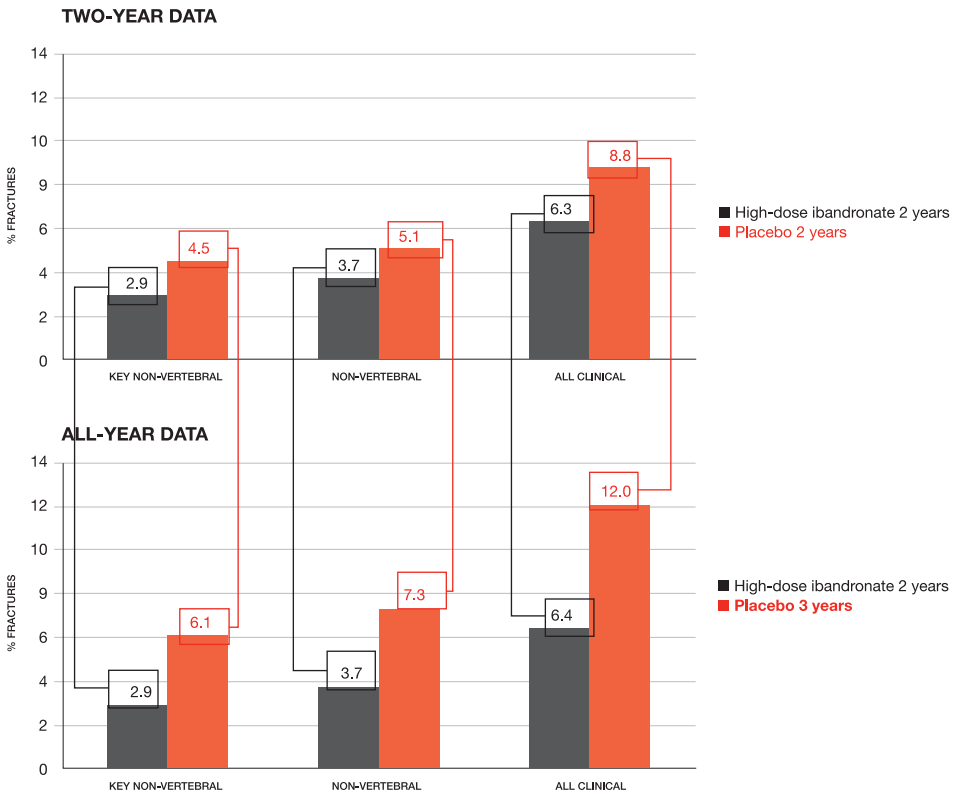
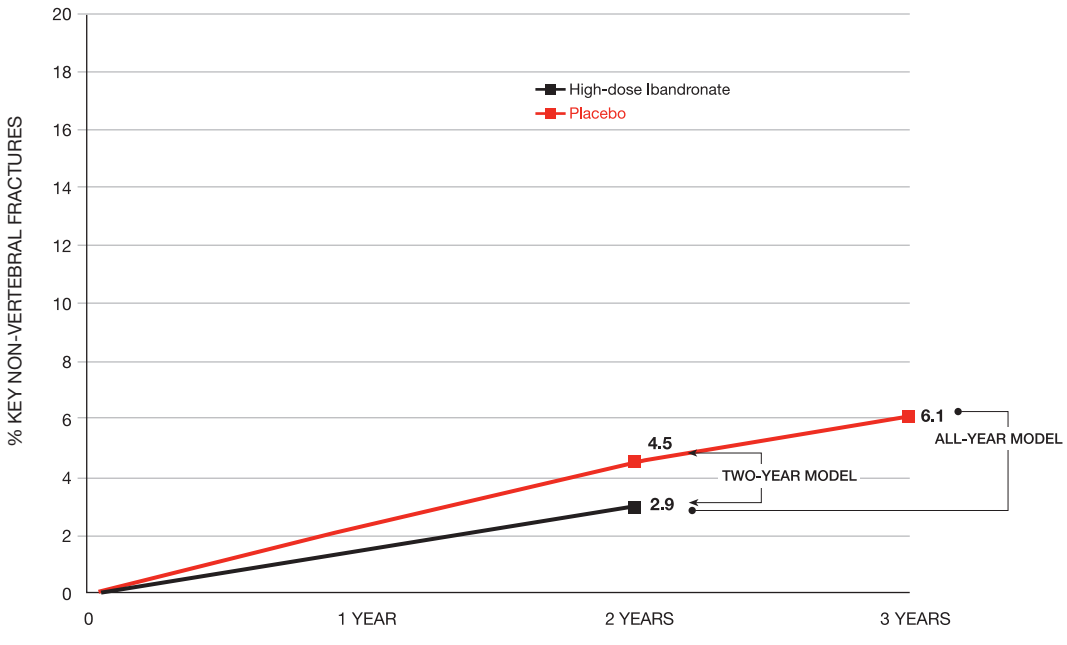


Figure 2. Percentage of non-vertebral fractures over the years. As there is only data on ibandronate for two years, it makes no sense to make a comparison with a 3-year period on placebo.



In summary, there is a comparison between one arm of active treatment from a group of trials and the placebo arm of another group of trials. Non-vertebral fractures were declared as secondary efficacy endpoints in the first group, and as adverse effects in the latter group of trials. The level of evidence that can be obtained from this procedure does not go beyond that of an observational trial and the strength of the recommendations based on the data available is scarce. Given these limitations, we find that no sufficient evidence exists to affirm that ibandronate at commercial doses is better than placebo in the prevention of non-vertebral fractures.

Ibandronate for the prevention of nonvertebral fractures: a pooled analysis of individual patient data. Cranney A, et al[3]

This is a meta-analysis of individual patient data of clinical trials that compare high dose (commercialized) with low dose ibandronate. Their efficacy in preventing non-vertebral fractures was evaluated. It was concluded that high doses of ibandronate offer a reduction in the incidence of non-vertebral fractures when compared to low doses.

SUMMARY OF THE ORIGINAL ARTICLE	CRITICAL APPRAISAL
Financing The study received aid from Hoffman-Roche. Hoffman, Roche and GlaxoSmithKline provided the individual data of the patients. It was affirmed that the analysis was carried out with no influence by these companies.	
Investigation question The aim was to estimate the efficacy of high-dose ibandronate with respect to low doses in the prevention of non-vertebral fractures in postmenopausal women with osteoporosis.	
Selection of trials A systematic search for clinical trials of at least one year duration was performed. The trials were considered therapeutic when the baseline lumbar BMD was T-score ≤ -2.5 or the baseline prevalence of vertebral fractures was > 20% or the average age was > 60 years. Eight trials were evaluated. All these studies were performed by the pharmaceutical companies that provided the individual data to the investigators. With regard to the main analysis, data was provided only from the MOBILE and DIVA studies.	In none of the trials was non-vertebral fracture the primary endpoint.
Methods A comparison of groups of high-dose ibandronate (150 mg oral monthly, 3 mg IV quarterly and 2 mg IV every 2 months) with the rest of the doses (2.5 mg oral daily, 50+50 mg monthly and 100 mg monthly) and with low doses (2.5 mg oral daily). For each comparison only the studies that provided data from both groups of doses were employed in order to maintain randomization. The primary endpoint was “key non-vertebral” fractures (clavicle, humerus, hip, wrist, pelvis, leg).	Very different dose regimens are grouped.

SUMMARY OF THE ORIGINAL ARTICLE	CRITICAL APPRAISAL
An ITT analysis of survival for a two-year period was performed. Cox regression models were employed to calculate HR adjusted for age, baseline lumbar BMD and history of clinical fractures.	It is not clear what the ITT analysis means given that the populations studied in the meta-analysis were lower than those in the published trials MOBILE and DIVA (table 2).
Results (Table 4) Data on the comparison between 25 mg daily and placebo were also provided: n = 3,212; HR before adjustment = 1.073 (95%CI 0.79 – 1.46)	Information given on the populations in the results table was not the same as that communicated in the other part of the same article (compare tables 2 and 4 of this article, which correspond to pages 294 and 295 of the original article respectively). The populations are different from the published trials and practically coincide with the meta-analysis by Harris (table 2).
Conclusions The data suggest that high-dose ibandronate, that includes 150 mg oral monthly, 3 mg IV quarterly for 2 years, produces a significant reduction in non-vertebral fractures in comparison to low-dose 2.5 mg daily. The summary simply concludes that high-dose ibandronate (oral 150 mg a month, i.v. 3 mg/3 months) significantly reduces the risk of non-vertebral fractures in postmenopausal women.	High doses are compared to low doses. It has not yet even been established that treatment with ibandronate does not increase the incidence of non-vertebral fractures when compared to placebo. The conclusion in the summary of the article dose not coincide with that of the article.

Table 4. Comparison of high and low doses of ibandronate with regard to the rate of non-vertebral fractures.

TRIALS	POPULATION	HIGH-DOSE REGIMENS	LOW-DOSE REGIMENS	HR	95%CI
DIVA[8]	**1,356**	2 mg IV / 2 months 3 mg IV / 3 months	2.5 mg oral daily	0.569	0.324 to 0.997
MOBILE[7] **DIVA**[8]	**2,139**	150 mg oral monthly IV 2 mg / 2 months IV 3 mg / 3 months	2.5 mg oral daily	0.620	0.395 to 0.973
MOBILE[7] **DIVA**[8]	**2,924**	150 mg oral monthly 2 mg IV / 2 months 3 mg IV / 3 months	2.5 mg oral daily 50+50 mg oral monthly 100 mg oral monthly	0.634	0.427 to 0.943

Adapted from table 2 of Cranney et al[3].

Application of the results from both meta-analysis

The question to be answered to a clinician is: does ibadronate, at the high doses employed (normally 150 mg monthly), really reduces the risk of non-vertebral fractures and especially hip fractures in postmenopausal women with osteoporosis?

To attempt to answer this question, we first encounter a problem that there is no clinical trial designed to respond to it. The primary endpoint of the trials with high dose ibandronate was the variation in BMD.

After the submission of the MOBILE and DIVA studies, the European Medicines Agency (EMEA) proposed an indication for the "treatment of osteoporosis to reduce the risk of vertebral fractures", with the clarification that "the efficacy in femur neck fractures was not established"[9, 10].

The National Institute for Clinical Excellence (NICE) carried out a meta-analysis with the authorized doses with respect to 2.5 mg daily dose using as the primary endpoint the results published from trials available: "clinical osteoporotic fractures," a criteria less restrictive than those of the meta-analyses we have evaluated. This analysis was not as precise as when individual patient data are employed but, at least it is focussed on the authorized doses, there was no shuffle of populations from the trials and the incidences of fractures in each group were provided (table 5).

Given the evidence, the conclusion is that ibandronate at the authorized doses has not shown differences when compared to 2.5 mg daily. Moreover, in the BONE trial, ibandronate at 2.5 mg daily did not show differences when compared to placebo with regard to clinical non-vertebral fractures (Relative Risk = 1.11 95%CI 0.83 to 1.49). The level of evidence available is very low as it is indirect and includes different variables[11].

One examining the data on the prevention of fractures presented in the original trials, we discovered a very different interpretation of the results than that offered by the meta-analyses commented. The data in the original trials is coherent with the approved indications by the regulating agencies.

Let us look at the information available up to now:

· **In one trial** evaluating vertebral fractures **(BONE)** no differences were found when comparing 2.5 mg daily ibandronate (doses not commercialised) with placebo in the prevention of non-vertebral fractures.

· **Two trials (MOBILE and DIVA)** designed to evaluate changes in BMD with high-dose ibandronate compared to 2.5 mg daily, did not find significant differences in clinical osteoporosis-related fractures.

· **The Harris meta-analysis.** Employing indirect comparisons, and therefore with a lower level of evidence, no significant differences were found between high dose ibandronate compared to placebo with regard to the prevention of non-vertebral fractures after two years.

· **The Cranney meta-analysis.** Although this study found significant differences in favour of high dose ibandronate when compared to a 2.5 mg daily dose in the reduction of the risk of fracture, it has not yet been shown that there is no increase in the risk of fracture with the 2.5 mg dose when compared to placebo.

· **The NICE review and the EMEA evaluation.** No evidence of efficacy is found with respect to the prevention of non-vertebral fractures.

Table 5. Comparison of high and low dose ibandronate with regard to clinical fractures.

TRIAL	HIGH DOSE	FRACTURES/N	LOW DOSE	FRACTURES/N	RR	95%CI
MOBILE[7]	150 mg oral monthly	27/396	2.5 mg oral daily	24/395	1.12	0.66 to 1,91
DIVA[8]	IV 3 mg / 3 months	23/469	2.5 mg oral daily	29/465	0.79	0.46 to 1.34
Group					0.94	0.65 to 1.36

The foundations of a systematic review include transparency and reproducibility, which is impossible to obtain when the data lies in the power of companies and no one else has access to the information. In this sense, the meta-analyses we have commented on lack absolute numbers of the main non-vertebral fractures in each group of treatment in the different studies.

How much influence have these meta-analysis had in clinical practice?

In the Guidelines for Good Clinical Practice in Osteoporosis (2nd edition) the logotypes of the Ministry of Health of Spain (Ministerio de Sanidad y Consumo) and the General College of Physicians of Spain (Organización Médica Colegial) appear alongside those of GlaxoSmithKline and Roche. Both of the meta-analyses evaluated are cited. The following table appears in this document.

This table contains a large degree of falsehood within just a few lines:

The meta-analyses by Harris and Cranney never evaluated the 150 mg monthly dose separately. If anything can be obtained from the Harris analysis, it is that the high-dose ibandronate did not show a reduction in non-vertebral fractures with respect to placebo. The greatest level of evidence that can be obtained is “B”.

Level of evidence A in hip fractures cannot be derived from these meta-analyses. The argument given is that key non-vertebral fractures include the hip. But, hip fracture was never evaluated separately in these meta-analyses, and given all the data available, the EMEA concluded that the efficacy in preventing femoral neck fractures has not been established.

Acknowledgements

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Table 6. Original table critically appraised in this article.

Levels of evidence against fracture

Drug	Route of administration and dose	Vertebral fractures	Non-vertebral fractures	Hip fractures
Ibandronate	150 mg oral monthly	A	A	A*

* Key non-vertebral fractures include the hip. New data from the Harris-Cranney meta-analysis. The meta-analyses on ibandronate are the only existing ones, besides that carried out on zoledronic acid, showing the efficacy in the prevention of non-vertebral fractures with non-daily doses

See reference No 12.

Conclusions

No study exists whose objective is the evaluation of fractures at the doses of ibandronate employed in clinical practice.

The meta-analyses that have attempted to evaluate tha efficacy of ibandronate in the prevention of non-vertebral fractures contain evident conflicts of interest and present various problems such as clustering of different doses, indirect comparisons, incorrect analysis and suspicious changes in populations.

It has not been demonstrated that ibandronate at the doses employed in clinical practice is effective in the prevention of non-vertebral fractures.

The conclusions made by the authors of the studies evaluated are distortedly favourable for the drug, a problem that has been magnified by their inclusion in practical guidelines. Perhaps it is not that surprising, given that the study was financed by the same pharmaceutical companies that manufacture the drug.

References

1. Bonviva. Resumen de las características del producto. Roche Farma S.A. Julio 2009.

2. Harris ST, Blumentals WA, Miller PD. Ibandronate and the risk of non-vertebral and clinical fractures in women with postmenopausal osteoporosis: results of a meta-analysis of phase III studies. Curr Med Res Opin. 2008;24(1):237-45.

3. Cranney A, Wells GA, Yetisir E, Adami S, Cooper C, Delmas PD, et al. Ibandronate for the prevention of non-vertebral fractures: a pooled analysis of individual patient data. Osteoporos Int. 2009;20(2):291-7.

4. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2008. Disponible en www.cochrane-handbook.org.

5. Chesnut IC, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004;19(8):1241-9.

6. Recker R, Stakkestad JA, Chesnut CH, 3rd, Christiansen C, Skag A, Hoiseth A, et al. Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. Bone. 2004;34(5):890-9.

7. Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis. 2006;65(5):654-61.

8. Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Prince R, et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. J Rheumatol. 2008;35(3):488-97.

9. European Public Assessment Report (EPAR). Bonviva (ibandronic acid). Scientific discussion. London (UK):European Medicines Agency; Sep 2005. Procedure N.º: EMEA/H/C/501/X/01. Disponible en http://www.emea.eu.int.

10. European Public Assessment Report (EPAR). Bonviva (ibandronic acid). Scientific discussion. London (UK):European Medicines Agency; 2007. Procedure N.º: EMEA/H/C/501/X/03. Disponible en http://www.emea.eu.int.

11. National Institute for Health and Clinical Excellence. Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk . (Systematic reviews of clinical effectiveness prepared for the guideline) London: NICE, Sep 2008. http://www.nice.org.uk/guidance/index.jsp?action=folder&o=42361.

12. Carbonell Abella C, Valdés y Llorca C. Tratamiento. In: IM&C SA, ed. *Guía de Buena Práctica Clínica en Osteoporosis (2ª edición)*. Madrid 2008:59-93.

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