**Supplementary Materials to**

**Bisphosphonates and Risk of Cardiovascular Events: A Meta-Analysis**

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|  |  |
| --- | --- |
| **Text 1.** | Systematic Search Strategy |
| **Table 1.** | Characteristics of Eligible Randomized Controlled Trials by Availability of Cardiovascular Event Data |
| **Table 2.** | Randomized Controlled Trials of Bisphosphonates with Available Data on Cardiovascular Events |
| **Table 3.** | Quality of Included Randomized Controlled Trials of Bisphosphonates |
| **Table 4.** | Number of Adverse Cardiovascular Events by Bisphosphonate Dose |
| **Table 5.** | Stratified Analysis of Bisphosphonates and Adverse Cardiovascular Events by Study Quality |
| **Figure 1.** | Assessment of Study Quality |
| **Figure 2.** | Subgroup Meta-Analysis of Total Cardiovascular Events Associated with Use of Bisphosphonates |
| **Figure 3.** | Subgroup Meta-Analysis of Atrial Fibrillation Associated with Use of Bisphosphonates |
| **Figure 4.** | Subgroup Meta-Analysis of Myocardial Infarction Associated with Use of Bisphosphonates |
| **Figure 5.** | Subgroup Meta-Analysis of Stroke Associated with Use of Bisphosphonates |
| **Figure 6.** | Subgroup Meta-Analysis of Cardiovascular Death Associated with Use of Bisphosphonates |
| **References for Supplementary Materials** | |

**Text S1. Systematic Search Strategy**

We used the following search terms to identify randomized controlled trials of bisphosphonates. The search was initially performed on August 4, 2013, and updated on July 28, 2014.

1) MEDLINE:

Search #1: (diphosphonates[mh] OR etidron\*[tiab] OR clodron\*[tiab] OR tiludron\*[tiab] OR pamidron\*[tiab] OR neridron\*[tiab] OR olpadron\*[tiab] OR alendron\*[tiab] OR ibandron\*[tiab] OR risedron\*[tiab] OR zoledron\*[tiab])

Search #2: ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh])) AND adult [mh]

Search #3: (Comment[ptyp] OR Editorial[ptyp] OR Guideline[ptyp] OR Letter[ptyp] OR Meta-Analysis[ptyp] OR Review[ptyp] OR systematic[sb])

Search #4: (#1 AND #2) NOT #3

2) EMBASE:

Search #1: (‘bisphosphonic acid derivative’:cl OR etidrona\*:ab,ti OR clodron\*:ab,ti OR tiludron\*:ab,ti OR pamidron\*:ab,ti OR neridron\*:ab,ti OR olpadron\*:ab,ti OR alendron\*:ab,ti OR ibandron\*:ab,ti OR risedron\*:ab,ti OR zoledron\*:ab,ti)

Search #2: ((random$:ab,ti OR factorial$:ab,ti OR crossover$:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR placebo$:ab,ti OR 'double blind':ab,ti OR 'single blind':ab,ti OR assign$:ab,ti OR allocat$:ab,ti OR volunteer$:ab,ti OR 'crossover procedure':cl OR 'double blind procedure':cl OR 'randomized controlled trial':cl OR 'single blind procedure':cl) NOT ([animals]/lim NOT [humans]/lim)) AND ([adult]/lim OR [aged]/lim)

Search #3: ([editorial]/lim OR [letter]/lim OR [meta analysis]/lim OR [systematic review]/lim OR [review]/lim)

Search #4: ((#1 AND #2) NOT #3) AND [embase]/lim

**Table S1. Characteristics of Eligible Randomized Controlled Trials by Availability of Cardiovascular Event Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **RCTs with CV Event Data** | **RCTs without CV Event Data** | ***P\**** |
| Number of eligible RCTs | 58 | 112 |  |
| Type of bisphosphonate, *n (%)* |  |  | 0.01 |
| Alendronate | 29 (50.0) | 33 (29.5) |  |
| Ibandronate | 7 (12.1) | 10 (8.9) |  |
| Risedronate | 8 (13.8) | 25 (22.3) |  |
| Zoledronic acid | 9 (15.5) | 13 (11.6) |  |
| Others† | 5 (8.6) | 31 (27.7) |  |
| Sample size |  |  |  |
| Bisphosphonate group, *median (IQR)* | 158 (86, 563) | 37 (21, 87) | <0.001 |
| No bisphosphonate group, *median (IQR)* | 92 (48, 286) | 35 (20, 79) | <0.001 |
| Participant characteristics‡ |  |  |  |
| Mean age, *years, mean (SD)* | 63.0 (7.6) | 58.8 (11.6) | 0.005 |
| Proportion of female, *%, mean (SD)* | 84.4 (29.2) | 75.1 (30.8) | 0.06 |
| Mean weight, *kg, mean (SD)* | 64.8 (5.5) | 66.2 (8.3) | 0.48 |
| Mean body mass index, *kg/m2, mean (SD)* | 25.4 (1.4) | 25.0 (3.2) | 0.51 |
| Follow-up duration, *months, median (IQR)* | 24 (12, 36) | 12 (12, 24) | 0.003 |

Abbreviations: CV, cardiovascular; IQR, interquartile range; RCT, randomized controlled trial; SD, standard deviation.

\* P-values were computed from two-sample t tests or Wilcoxon Ranksum tests for continuous variables and chi-square test for categorical variables.

† Other bisphosphonates include clodronate, etidronate, minodronate, pamidronate, and tiludronate.

‡ The number of trials that reported relevant characteristics was 163 for the mean age, 164 for proportion of female, 62 for the mean weight, and 88 for the mean body mass index.

**Table S2. Randomized Controlled Trials of Bisphosphonates with Available Data on Cardiovascular Events**

| **Trial Name or Author (Year)** | **Bisphosphonate** | **Route** | **Sample Size** | | **Mean**  **Age**  *y* | **Women**  % | **Wt**  *kg* | **BMI**  *kg/m2* | **Sm**  % | **Study Population Characteristics** | **FU**\*  *m* | **Reported Events** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *BIS* | *CTR* |
| Adami (1993)[1]† | Alendronate 10-20mg/d | PO | 140 | 71 | 59 | 100 | 60 | NR | 18 | Post-menopause  Osteoporosis | 24 | AF |
| Chesnut (1995)[2]† | Alendronate 5-20mg/d | PO | 94 | 31 | 63 | 100 | 63 | NR | NR | Post-menopause  Osteoporosis | 24 | AF |
| Devogelaer (1996)[3]† | Alendronate 5-20mg/d | PO | 311 | 205 | 63 | 100 | 61 | 25 | 10 | Post-menopause  Osteoporosis | 36 | AF |
| Tucci (1996)[4]† | Alendronate 5-20mg/d | PO | 286 | 192 | 65 | 100 | NR | 24 | NR | Post-menopause  Osteoporosis | 36 | AF |
| FIT I (1996)[5]† | Alendronate 5-10mg/d | PO | 1022 | 1005 | 71 | 100 | NR | NR | 11 | Post-menopause  Osteoporosis | 36 | AF |
| Bone (1997)[6]† | Alendronate 5mg/d | PO | 93 | 91 | 71 | 100 | 61 | NR | NR | Post-menopause  Osteoporosis | 24 | AF |
| EPIC (1998)[7,8]† | Alendronate 2.5-5mg/d | PO | 997 | 502 | 55 | 100 | NR | 25 | 20 | Post-menopause  No osteoporosis | 24,  48 | AF, Total CV events |
| FIT II (1998)[9]† | Alendronate 5-10mg/d | PO | 2214 | 2218 | 68 | 100 | NR | NR | 10 | Post-menopause  Osteoporosis | 48 | AF |
| Greenspan (1998)[10]† | Alendronate 5-10mg/d | PO | 60 | 60 | 70 | 100 | 65 | 26 | NR | Post-menopause | 36 | AF |
| McClung (1998)[11]† | Alendronate 5-20mg/d | PO | 265 | 90 | 52 | 100 | 64 | 24 | 37 | Post-menopause  No osteoporosis | 36 | AF |
| Saag (1998)[12]† | Alendronate 5-10mg/d | PO | 318 | 159 | 55 | 70 | NR | NR | NR | Long-term steroid use | 12 | AF |
| Lindsay (1999)[13]† | Alendronate 10mg/d | PO | 214 | 214 | 62 | 100 | NR | 24 | NR | Post-menopause  Osteoporosis, on HRT | 12 | AF |
| FOSIT (1999)[14]† | Alendronate 10mg/d | PO | 950 | 958 | 63 | 100 | 64 | NR | NR | Post-menopause  Osteopenia/osteoporosis | 12 | AF |
| Downs (2000)[15]† | Alendronate 10mg/d | PO | 118 | 58 | 65 | 100 | NR | 26 | NR | Post-menopause  Osteoporosis | 12 | AF |
| Orwoll (2000)[16]† | Alendronate 10mg/d | PO | 146 | 95 | 63 | 0 | NR | 25 | 26 | Osteoporosis | 24 | AF, Total CV events |
| Bell (2002)[17]† | Alendronate 10mg/d | PO | 33 | 32 | 66 | 100 | 70 | NR | NR | Post-menopause  Osteoporosis | 24 | AF |
| Greenspan (2002)[18]† | Alendronate 10mg/d | PO | 164 | 163 | 79 | 100 | NR | NR | NR | Post-menopause  Osteoporosis | 24 | AF |
| Palomba (2002)[19] | Alendronate 5-10mg/d | PO | 86 | 43 | 61 | 100 | NR | 25 | NR | Surgical menopause  Osteoporosis, on ERT | 24 | MI, CV death |
| van der Poest Clement (2002)[20]† | Alendronate 10mg/d | PO | 21 | 20 | 46 | 44 | NR | 25 | NR | Fracture | 12 | AF |
| Ascott-Evans (2003)[21]† | Alendronate 10mg/d | PO | 95 | 49 | 57 | 100 | NR | 25 | NR | Post-menopause  Osteopenia/osteoporosis | 12 | AF |
| Greenspan (2003)[22] | Alendronate 10mg/d | PO | 93 | 93 | 72 | 100 | 70 | 28 | 6 | Post-menopause  Osteoporosis | 36 | MI |
| Hosking (2003)[23]† | Alendronate 70mg/w | PO | 219 | 108 | 69 | 100 | NR | 25 | NR | Post-menopause  Osteoporosis | 12 | AF |
| Milller (2004)[24]† | Alendronate 70mg/w | PO | 97 | 46 | 66 | 0 | 79 | 26 | 11 | Osteoporosis | 12 | AF |
| Chevrel (2006)[25] | Alendronate 10mg/d | PO | 31 | 33 | 37 | 39 | NR | NR | NR | Osteogenesis Imperfecta | 36 | Total CV events |
| Lems (2006)[26] | Alendronate 5-10mg/d | PO | 94 | 69 | 62 | 56 | NR | NR | NR | Rheumatoid arthritis  Low-dose prednisone | 12 | Total CV events |
| McClung (2006)[27]  Lewiecki (2007)[28] | Alendronate 70mg/w | PO | 47 | 46 | 63 | 100 | NR | 26 | NR | Post-menopause  Osteopenia/osteoporosis | 12,  24 | Total CV events |
| Bonnick (2007)[29]† | Alendronate 10mg/d | PO | 563 | 138 | 66 | 100 | NR | NR | 0 | Post-menopause  Osteoporosis | 24 | AF |
| Stoch (2009)[30]† | Alendronate 70mg/w | PO | 114 | 59 | 53 | 58 | NR | NR | NR | Rheumatic disorders  Long-term prednisone | 12 | AF, CV death |
| Eastell (2011)[31] | Alendronate 70mg/w | PO | 57 | 57 | 65 | 100 | NR | 25 | NR | Post-menopause  Osteoporosis | 12 | Total CV events |
| Roux (1998)[32] | Etidronate 400mg/d for 14d cycled every 3m | PO | 59 | 58 | 59 | 64 | NR | NR | NR | High-dose steroid | 12 | MI, CV death |
| Wimalawansa (1998)[33] | Etidronate 400mg/d for 14d cycled every 3m | PO | 17 | 18 | 65 | 100 | NR | 25 | NR | Post-menopause  Osteoporosis | 48 | MI, CV death |
| Ravn (1996)[34] | Ibandronate 0.25-5mg/d | PO | 150 | 30 | 64 | 100 | 67 | NR | NR | Post-menopause  Osteopenia/osteoporosis | 12 | MI, ST, CV death |
| Adami (2004)[35] | Ibandronate 1-2mg once | IV | 392 | 128 | 66 | 100 | 64 | NR | NR | Post-menopause  Osteoporosis | 12 | Total CV events |
| BONE (2004)[36]‡ | Ibandronate 2.5mg/d or 20mg/2d for 12 doses/3m | PO | 1954 | 975 | 69 | 100 | 67 | NR | NR | Post-menopause  Osteoporosis | 36 | AF |
| IVF (2004)[37]‡ | Ibandronate 0.5-1mg/3m | IV | 1911 | 949 | 67 | 100 | NR | NR | NR | Post-menopause  Osteoporosis | 36 | AF, Total CV events |
| MOBILE (2006)[38]‡ | Ibandronate 2.5mg/d or 100-150mg/m | PO | 1583 | - | 66 | 100 | 64 | 26 | NR | Post-menopause  Osteoporosis | 24 | AF |
| DIVA (2008)[39]‡ | Ibandronate PO 2.5mg/d or IV 2mg/2m or IV 3mg/3m | PO  IV | 1382 | - | 66 | 100 | 64 | 26 | NR | Post-menopause  Osteoporosis | 24 | AF |
| Hakala (2012)[40] | Ibandronate 150mg/m | PO | 68 | 72 | 64 | 100 | NR | 30 | NR | Post-menopause  No osteoporosis | 12 | ST |
| Matsumoto (2009)[41] | Minodronate 1mg/d | PO | 343 | 331 | 72 | 100 | NR | 23 | NR | Post-menopause  Osteoporosis | 24 | AF, CHD, HF |
| Eggelmeijer (1996)[42] | Pamidronate 300mg/d | PO | 54 | 51 | 50 | 68 | NR | NR | NR | Rheumatoid arthritis  Not treated with steroid | 36 | MI, CV death |
| Shetty (2006)[43] | Pamidronate 90mg once | IV | 18 | 19 | 58 | 41 | NR | 28 | NR | Total hip replacement for osteoarthritis | 60 | CHD |
| Mortensen (1998)[44]§ | Risedronate 5mg/d or cyclically | PO | 75 | 36 | 51 | 100 | NR | NR | NR | Post-menopause  No osteoporosis | 24 | AF, ST, CV death |
| Cohen (1999)[45]§ | Risedronate 2.5-5mg/d | PO | 151 | 77 | 60 | 66 | NR | NR | NR | High-dose steroid | 12 | AF, ST, CV death |
| VERT-NA (1999)[46]§ | Risedronate 2.5-5mg/d | PO | 1638 | 820 | 69 | 100 | 67 | NR | NR | Post-menopause  Osteoporosis | 36 | AF, ST, CV death |
| Reid (2000)[47]§ | Risedronate 2.5-5mg/d | PO | 194 | 96 | 59 | 62 | NR | NR | NR | High-dose steroid | 12 | AF, ST, CV death |
| VERT-MN (2000)[48]§ | Risedronate 2.5-5mg/d | PO | 815 | 407 | 71 | 100 | NR | NR | NR | Post-menopause  Osteoporosis | 36 | AF, ST, CV death, total CV events |
| HIP (2001)[49]§ | Risedronate 2.5-5mg/d | PO | 6197 | 3134 | 78 | 100 | 61 | NR | NR | Post-menopause  Osteoporosis | 36 | AF, ST, CV death |
| Shiraki (2003)[50] | Risedronate 1-5mg/d | PO | 125 | 43 | 61 | 99 | 50 | NR | NR | Post-menopause  Osteoporosis | 9 | Total CV events |
| Boonen (2009)[51] | Risedronate 35mg/w | PO | 191 | 93 | 61 | 0 | NR | 25 | NR | Osteoporosis | 24 | AF, MI |
| HORIZON-  PFT (2007)[52,53] | Zoledronic acid 5mg/y | IV | 3862 | 3852 | 73 | 100 | NR | 25 | NR | Post-menopause  Osteoporosis | 36 | AF, MI, ST, CV death |
| HORIZON-  RFT (2007)[53-55] | Zoledronic acid 5mg/y | IV | 1054 | 1057 | 75 | 76 | NR | 25 | NR | Recent surgical repair of low-trauma hip fracture | 23 | AF, MI, ST, CV death |
| Grey (2009)[56-58] | Zoledronic acid 5mg once | IV | 25 | 25 | 64 | 100 | 68 | NR | 6 | Post-menopause  Osteopenia | 24,  36,  60 | AF |
| McClung (2009)[59] | Zoledronic acid 5mg once or 5mg/y | IV | 379 | 202 | 60 | 100 | NR | 27 | NR | Post-menopause  Osteopenia | 24 | AF |
| Boonen (2012)[60] | Zoledronic acid 5mg/y | IV | 588 | 611 | 66 | 0 | NR | NR | NR | Osteoporosis | 24 | AF, CHD, MI, total CV events |
| Grey (2012)[61] | Zoledronic acid 1-5mg once | IV | 135 | 45 | 65 | 100 | 66 | NR | 1 | Post-menopause  Osteopenia | 12 | AF |
| Bai (2013)[62] | Zoledronic acid 5mg/y | IV | 242 | 241 | 57 | 100 | NR | 24 | NR | Post-menopause  Osteoporosis | 24 | Total CV events |
| Chao (2013)[63] | Zoledronic acid 5mg/y | IV | 327 | 333 | 55 | 100 | NR | 24 | NR | Post-menopause  Osteoporosis | 36 | Total CV events |
| Dalbeth (2014)[64] | Zoledronic acid 5mg/y | IV | 50 | 50 | 56 | 53 | NR | NR | NR | Tophaceous gout | 24 | Total CV events |

Abbreviations: AF, atrial fibrillation; BIS, bisphosphonate; BMI, body mass index; CHD, coronary heart disease; CTR, control; CV, cardiovascular; d, day; DIVA, Dosing IntraVenous Administration; EPIC, Early Postmenopausal Intervention Cohort study; ERT, estrogen replacement therapy; FIT, Fracture Intervention Trial; FOSIT, Fosamax International Trial; FU, follow-up; HF, heart failure; HIP, Hip Intervention Program Study; HORIZON-PFT, the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial; HORIZON-RFT, the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Recurrent Fracture Trial; HRT, hormone replacement therapy; IV, intravenous; IVF, IntraVenous Fracture study; m, month; MI, myocardial infarction; MOBILE, Monthly Oral iBandronate in LadiEs; NR, not reported; PO, per os; Sm, smoking; ST, stroke; VERT-MN, Vertebral Efficacy with Risedronate Therapy Multinational Study; VERT-NA, Vertebral Efficacy with Risedronate Therapy North America Study; w, week; Wt, weight; y, year.

\* Some trials reported data on cardiovascular events at different follow-up time.

† Data on atrial fibrillation were available in the meta-analysis by Barrett-Connor et al.[65]

‡ Data on atrial fibrillation were available in the pooled analysis of 4 trials by Lewiecki et al.[66]

§ Data on atrial fibrillation, stroke, and cardiovascular death were available in the pooled analysis of 6 trials by Karam et al.[67] The sample size of bisphosphonate group and placebo group in the pooled analysis (NBIS=10018 and NPLC=5048, respectively) was larger than the sum of sample size that was originally reported in individual trials (NBIS=9070 and NPLC=4570, respectively).

**Table S3. Quality of Included Randomized Controlled Trials of Bisphosphonates\***

| **Trial Name or Author (Year)** | **Generation of Random Sequence** | **Concealment of Allocation** | **Blinding of Participants and Personnel** | **Blinding of**  **CV Outcome Assessors** | **Adequacy of Follow-Up in**  **Safety Analysis** | **CV Event Reporting** | **Ascertainment of CV Events** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Adami (1993)[1]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Chesnut (1995)[2]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Devogelaer (1996)[3]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Tucci (1996)[4]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| FIT I (1996)[5]† | Inadequate | Adequate | Adequate | Adequate | Adequate | Incomplete | Adequate |
| Bone (1997)[6]† | Inadequate | Inadequate | Adequate | Adequate | Inadequate | Incomplete | Inadequate |
| EPIC (1998)[7,8]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| FIT II (1998)[9]† | Inadequate | Adequate | Adequate | Adequate | Adequate | Incomplete | Adequate |
| Greenspan (1998)[10]† | Inadequate | Inadequate | Adequate | Adequate | Inadequate | Incomplete | Inadequate |
| McClung (1998)[11]† | Inadequate | Inadequate | Adequate | Adequate | Inadequate | Incomplete | Inadequate |
| Saag (1998)[12]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Lindsay (1999)[13]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| FOSIT (1999)[14]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Downs (2000)[15]† | Inadequate | Inadequate | Adequate | Adequate | Inadequate | Incomplete | Inadequate |
| Orwoll (2000)[16]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Bell (2002)[17]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Greenspan (2002)[18]† | Adequate | Inadequate | Adequate | Adequate | Inadequate | Incomplete | Inadequate |
| Palomba (2002)[19] | Adequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| van der Poest (2002)[20]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Ascott-Evans (2003)[21]† | Adequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Greenspan (2003)[22] | Adequate | Adequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Hosking (2003)[23]† | Adequate | Inadequate | Adequate | Adequate | Inadequate | Incomplete | Inadequate |
| Milller (2004)[24]† | Adequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Chevrel (2006)[25] | Adequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Lems (2006)[26] | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| McClung (2006)[27]  Lewiecki (2007)[28] | Inadequate | Inadequate | Inadequate | Inadequate | Adequate | Incomplete | Inadequate |
| Bonnick (2007)[29]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Stoch (2009)[30]† | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Eastell (2011)[31] | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Roux (1998)[32] | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Wimalawansa (1998)[33] | Adequate | Inadequate | Inadequate | Inadequate | Inadequate | Complete | Inadequate |
| Ravn (1996)[34] | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Adami (2004)[35] | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| BONE (2004)[36]‡ | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| IVF (2004)[37]‡ | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| MOBILE (2006)[38]‡ | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| DIVA (2008)[39]‡ | Inadequate | Adequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Hakala (2012)[40] | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Matsumoto (2009)[41] | Adequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Eggelmeijer (1996)[42] | Inadequate | Inadequate | Adequate | Adequate | Inadequate | Incomplete | Inadequate |
| Shetty (2006)[43] | Adequate | Inadequate | Adequate | Adequate | Inadequate | Incomplete | Inadequate |
| Mortensen (1998)[44]§ | Inadequate | Inadequate | Adequate | Adequate | Inadequate | Incomplete | Inadequate |
| Cohen (1999)[45]§ | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| VERT-NA (1999)[46]§ | Adequate | Adequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Reid (2000)[47]§ | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| VERT-MN (2000)[48]§ | Inadequate | Inadequate | Adequate | Adequate | Inadequate | Incomplete | Inadequate |
| HIP (2001)[49]§ | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Shiraki (2003)[50] | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Boonen (2009)[51] | Inadequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| HORIZON-  PFT (2007)[52,53] | Inadequate | Inadequate | Adequate | Adequate | Adequate | Complete | Adequate |
| HORIZON-  RFT (2007)[53-55] | Inadequate | Adequate | Adequate | Adequate | Adequate | Complete | Inadequate |
| Grey (2009)[56-58] | Adequate | Adequate | Adequate | Adequate | Inadequate | Incomplete | Inadequate |
| McClung (2009)[59] | Adequate | Adequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Boonen (2012)[60] | Adequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Grey (2012)[61] | Adequate | Inadequate | Adequate | Adequate | Adequate | Incomplete | Inadequate |
| Bai (2013)[62] | Inadequate | Inadequate | Inadequate | Inadequate | Inadequate | Incomplete | Inadequate |
| Chao (2013)[63] | Inadequate | Inadequate | Inadequate | Inadequate | Inadequate | Incomplete | Inadequate |
| Dalbeth (2014)[64] | Adequate | Adequate | Adequate | Adequate | Inadequate | Incomplete | Inadequate |

Abbreviations: CV, cardiovascular; DIVA, Dosing IntraVenous Administration; EPIC, Early Postmenopausal Intervention Cohort study; FIT, Fracture Intervention Trial; FOSIT, Fosamax International Trial; HIP, Hip Intervention Program Study; HORIZON-PFT, the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial; HORIZON-RFT, the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Recurrent Fracture Trial; IVF, IntraVenous Fracture study; MOBILE, Monthly Oral iBandronate in LadiEs; VERT-MN, Vertebral Efficacy with Risedronate Therapy Multinational Study; VERT-NA, Vertebral Efficacy with Risedronate Therapy North America Study.

\* Study quality was evaluated in the following 7 quality standards: 1) generation of random sequence, 2) concealment of allocation, 3) blinding of patients and personnel, 4) blinding of cardiovascular outcome assessors, 5) follow-up loss (>20%) in the safety analysis, 6) completeness of cardiovascular outcome reporting, and 7) ascertainment of cardiovascular outcomes.

**Table S4. Number of Adverse Cardiovascular Events by Bisphosphonate Dose\***

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Total CV Events** | | **Atrial Fibrillation** | | **MI** | | **Stroke** | | **CV Death** | |
| **Dose**† | **N** | **Nevents / Ntotal (%)** | **N** | **Nevents / Ntotal (%)** | **N** | **Nevents / Ntotal (%)** | **N** | **Nevents / Ntotal (%)** | **N** | **Nevents / Ntotal (%)** |
| **Alendronate** | | | | | | | | | | |
| Placebo | 5 | 111 / 733 (15.1) | 15 | 13 / 2173 (0.6) | 2 | 1 / 136 (0.7) | 0 | - | 2 | 0 / 102 (0) |
| PO 2.5mg/d | 1 | 64 / 330 (19.4) | 0 | - | 0 | - | 0 | - | 0 | - |
| PO 5mg/d | 1 | 59 / 333 (17.7) | 1 | 0 / 93 (0) | 1 | 1/ 44 (2.3) | 0 | - | 1 | 1 / 44 (2.3) |
| PO 10mg/d | 4 | 33 / 281 (11.7) | 13 | 15 / 2802 (0.5) | 1 | 2 / 135 (1.5) | 0 | - | 2 | 2 / 156 (1.3) |
| PO 20mg/d | 0 | - | 1 | 0 / 72 (0) | 0 | - | 0 | - | 0 | - |
| **Ibandronate** | | | | | | | | | | |
| Placebo | 2 | 73 / 1077 (6.8) | 2 | 18 / 1924 (0.9) | 1 | 0 / 30 (0) | 2 | 1 / 102 (1.0) | 1 | 1 / 30 (3.3) |
| PO 0.25-1mg/d or  IV 0.5-1mg/3m | 2 | 152 / 2303 (6.6) | 1 | 18 / 1911 (0.9) | 1 | 0 / 90 (0) | 1 | 0 / 90 (0) | 1 | 0 / 90 (0) |
| PO 2.5-3mg/d | 0 | - | 3 | 29 / 3606 (0.8) | 1 | 1 / 30 (3.3) | 1 | 0 / 30 (0) | 1 | 0 / 30 (0) |
| PO 5mg/d or  IV 1mg/m | 0 | - | 2 | 10 / 1313 (0.8) | 1 | 0 / 30 (0) | 2 | 1 / 98 (1.0) | 1 | 0 / 30 (0) |
| **Risedronate** | | | | | | | | | | |
| Placebo | 2 | 40 / 450 (8.8) | 7 | 97 / 10189 (1.0) | 1 | 3 / 93 (3.2) | 6 | 77 / 5048 (1.5) | 6 | 96 / 5048 (1.9) |
| PO 1mg/d | 1 | 0 / 39 (0) | 0 | - | 0 | - | 0 | - | 0 | - |
| PO 2.5mg/d | 2 | 30 / 447 (6.7) | 5 | 66 / 4998 (1.3) | 0 | - | 5 | 71 / 4998 (1.4) | 5 | 83 / 4998 (1.7) |
| PO 5mg/d | 2 | 38 / 454 (8.4) | 7 | 72 / 5211 (1.4) | 1 | 2 / 191 (1.0) | 6 | 70 / 5020 (1.4) | 6 | 80 / 5020 (1.6) |
| **Zoledronic acid** | | | | | | | | | | |
| Placebo | 4 | 48 / 1235 (3.9) | 5 | 105 / 5767 (1.8) | 3 | 64 / 5520 (1.2) | 2 | 126 / 4909 (2.6) | 2 | 89 / 4909 (1.8) |
| IV 1mg/y | 0 | - | 1 | 0 / 45 (0) | 0 | - | 0 | - | 0 | - |
| IV 2.5mg/y | 0 | - | 1 | 0 / 45 (0) | 0 | - | 0 | - | 0 | - |
| IV 5mg/y | 4 | 49 / 1207 (4.1) | 5 | 130 / 5928 (2.2) | 3 | 60 / 5504 (1.1) | 2 | 133 / 4916 (2.7) | 2 | 75 / 4916 (1.5) |

Abbreviations: CV, cardiovascular; d, day; IV, intravenous; m, month; MI, myocardial infarction; PO, per os; y, year.

\* Trials that did not report outcome data for specific doses were excluded.

† Average daily dose was calculated for oral bisphosphonate regimen.

**Table S5. Stratified Analysis of Bisphosphonates and Adverse Cardiovascular Events by Study Quality\***

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Total CV Events** | | **Atrial Fibrillation** | | **MI** | | **Stroke** | | **CV Death** | |
| **Quality Standard** | **N**† | **M-H OR (95% CI)** | **N**† | **M-H OR (95% CI)** | **N**† | **M-H OR (95% CI)** | **N**† | **M-H OR (95% CI)** | **N**† | **M-H OR (95% CI)** |
| **Generation of Random Sequence** | | | | | | | | | | |
| Adequate | 3 | 1.09 (0.69, 1.71) | 3 | 1.22 (0.55, 2.71) | 4 | 3.34 (1.09, 10.2) | 0 | - | 2 | 2.20 (0.22, 21.7) |
| Inadequate | 11 | 0.97 (0.82, 1.14) | 18 | 1.07 (0.92, 1.25) | 6 | 0.82 (0.58, 1.17) | 5 | 0.99 (0.82, 1.19) | 7 | 0.87 (0.72, 1.06) |
| *P for interaction* |  | 0.66 |  | 0.76 |  | 0.05 |  | - |  | 0.46 |
| **Concealment of Allocation** | | | | | | | | | | |
| Adequate | 1 | 1.00 (0.37, 2.73) | 3 | 1.13 (0.86, 1.48) | 2 | 0.84 (0.42, 1.67) | 1 | 1.21 (0.78, 1.88) | 1 | 0.69 (0.45, 1.07) |
| Inadequate | 13 | 0.98 (0.84, 1.15) | 18 | 1.05 (0.88, 1.27) | 7 | 1.01 (0.69, 1.47) | 4 | 0.95 (0.77, 1.16) | 8 | 0.94 (0.75, 1.17) |
| *P for interaction* |  | 0.97 |  | 0.70 |  | 0.70 |  | 0.40 |  | 0.30 |
| **Blinding of Participants and Personnel** | | | | | | | | | | |
| Adequate | 11 | 0.98 (0.83, 1.15) | 21 | 1.08 (0.92, 1.25) | 9 | 0.95 (0.68, 1.33) | 5 | 0.99 (0.82, 1.19) | 8 | 0.88 (0.72, 1.06) |
| Inadequate | 3 | 1.00 (0.43, 2.33) | 0 | - | 1 | 3.17 (0.12, 83.2) | 0 | - | 1 | 3.17 (0.12, 83.2) |
| *P for interaction* |  | 0.98 |  | - |  | 0.48 |  | - |  | 0.47 |
| **Blinding of CV Outcome Assessor** | | | | | | | | | | |
| Adequate | 11 | 0.98 (0.83, 1.15) | 21 | 1.08 (0.92, 1.25) | 9 | 0.95 (0.68, 1.33) | 5 | 0.99 (0.82, 1.19) | 8 | 0.88 (0.72, 1.06) |
| Inadequate | 3 | 1.00 (0.43, 2.33) | 0 | - | 1 | 3.17 (0.12, 83.2) | 0 | - | 1 | 3.17 (0.12, 83.2) |
| *P for interaction* |  | 0.98 |  | - |  | 0.48 |  | - |  | 0.47 |
| **Loss to Follow-Up in Safety Analysis** | | | | | | | | | | |
| Adequate | 10 | 0.99 (0.83, 1.18) | 15 | 1.12 (0.94, 1.35) | 8 | 0.94 (0.67, 1.31) | 4 | 1.04 (0.82, 1.33) | 6 | 0.89 (0.66, 1.21) |
| Inadequate | 4 | 0.92 (0.65, 1.32) | 6 | 0.98 (0.74, 1.29) | 2 | 3.00 (0.30, 29.7) | 1 | 0.92 (0.70, 1.22) | 3 | 0.87 (0.68, 1.12) |
| *P for interaction* |  | 0.69 |  | 0.43 |  | 0.34 |  | 0.61 |  | 0.96 |
| **CV Event Reporting** | | | | | | | | | | |
| Complete | 0 | - | 2 | 1.23 (0.94, 1.61) | 3 | 0.84 (0.58, 1.21) | 2 | 1.05 (0.82, 1.35) | 3 | 0.90 (0.66, 1.23) |
| Incomplete | 14 | 0.98 (0.84, 1.14) | 19 | 1.01 (0.84, 1.22) | 7 | 1.79 (0.79, 4.03) | 3 | 0.91 (0.69, 1.20) | 6 | 0.87 (0.68, 1.11) |
| *P for interaction* |  | - |  | 0.26 |  | 0.21 |  | 0.55 |  | 0.94 |
| **Ascertainment of CV Events** | | | | | | | | | | |
| Adequate | 0 | - | 3 | 1.22 (0.97, 1.52) | 1 | 0.82 (0.55, 1.30) | 1 | 0.99 (0.73, 1.33) | 1 | 1.18 (0.74, 1.88) |
| Inadequate | 14 | 0.98 (0.84, 1.14) | 18 | 0.97 (0.78, 1.19) | 9 | 1.17 (0.70, 1.96) | 4 | 0.99 (0.78, 1.25) | 8 | 0.83 (0.67, 1.02) |
| *P for interaction* |  | - |  | 0.16 |  | 0.58 |  | 0.98 |  | 0.21 |

Abbreviations: CI, confidence interval; CV, cardiovascular; M-H, Mantel Haenszel; MI, myocardial infarction; OR, odds ratio

\* Heterogeneity by study quality standards (*P* value for interaction) was assessed using meta-regression.

† Trials with no events were excluded.

**Figure S1. Assessment of Study Quality\***



Abbreviation: CV, cardiovascular.

\* Study quality was evaluated in the following 7 quality standards: 1) generation of random sequence, 2) concealment of allocation, 3) blinding of patients and personnel, 4) blinding of cardiovascular outcome assessors, 5) follow-up loss (>20%) in the safety analysis, 6) completeness of cardiovascular outcome reporting, and 7) ascertainment of cardiovascular outcomes.

**Figure S2. Subgroup Meta-Analysis of Total Cardiovascular Events Associated with Use of Bisphosphonates\***



Abbreviations: CI, confidence interval; CV, cardiovascular; IV, intravenous; M-H, Mantel Haenszel; OR, odds ratio; PO, per os.

\* Heterogeneity by subgroup (*P* value for interaction) was assessed using meta-regression.

**Figure S3. Subgroup Meta-Analysis of Atrial Fibrillation Associated with Use of Bisphosphonates\***



Abbreviations: CI, confidence interval; IV, intravenous; M-H, Mantel Haenszel; OR, odds ratio; PO, per os.

\* Heterogeneity by subgroup (*P* value for interaction) was assessed using meta-regression.

**Figure S4. Subgroup Meta-Analysis of Myocardial Infarction Associated with Use of Bisphosphonates\***



Abbreviations: CI, confidence interval; IV, intravenous; M-H, Mantel Haenszel; OR, odds ratio; PO, per os.

\* Heterogeneity by subgroup (*P* value for interaction) was assessed using meta-regression.

**Figure S5. Subgroup Meta-Analysis of Stroke Associated with Use of Bisphosphonates\***



Abbreviations: CI, confidence interval; IV, intravenous; M-H, Mantel Haenszel; OR, odds ratio; PO, per os.

\* Heterogeneity by subgroup (*P* value for interaction) was assessed using meta-regression.

**Figure S6. Subgroup Meta-Analysis of Cardiovascular Death Associated with Use of Bisphosphonates\***



Abbreviations: CI, confidence interval; CV, cardiovascular; IV, intravenous; M-H, Mantel Haenszel; OR, odds ratio; PO, per os.

\* Heterogeneity by subgroup (*P* value for interaction) was assessed using meta-regression.

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