

## **Appendix A: Search Methodology**

# Appendix A: Search Methodology

## LOW BONE DENSITY – SEARCH METHODOLOGIES

**SEARCH #1A (Run 9/4/09):**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 2005-8/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh]  
OR bone density

AND

alendronate\* OR fosamax OR risedronate\* OR actonel OR etidronate\* OR didronel OR  
ibandronate\* OR boniva OR pamidronate\* OR aredia OR zoledronic acid OR zometa  
OR droloxifene\* OR denosumab

NOT

animal\* NOT (human OR humans\*)

**NUMBER OF ITEMS RETRIEVED: 1953**

=====

**SEARCH #1B (Run 9/4/09):**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 2005-8/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh]  
OR bone density

AND

bisphosphonate\*

NOT

animal\* NOT (human OR humans\*)

**NUMBER OF ITEMS RETRIEVED: 1018**

=====

**SEARCH #2A:**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

International Pharmaceutical Abstracts – 2005-6/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2n)mineral OR bone(2n)density

AND

alendronate? OR fosamax OR risedronate? OR actonel OR etidronate? OR didronel OR ibandronate? OR boniva OR pamidronate? OR aredia OR zoledronic()acid OR zometa OR droloxifene? OR denosumab

**NUMBER OF ITEMS RETRIEVED: 522**

=====

**SEARCH #2B:**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

International Pharmaceutical Abstracts – 2005-6/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2n)mineral OR bone(2n)density

AND

bisphosphonate?

**NUMBER OF ITEMS RETRIEVED: 263**

=====

**SEARCH #3A:**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

Embase – 2005-9/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2n)mineral OR bone(2n)density

AND

alendronate? OR fosamax OR risedronate? OR actonel OR etidronate? OR didronel OR ibandronate? OR boniva OR pamidronate? OR aredia OR zoledronic()acid OR zometa OR droloxifene? OR denosumab

**NUMBER OF ITEMS RETRIEVED: 2471**

=====

**SEARCH #3B:**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

Embase – 2005-6/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2n)mineral OR bone(2n)density

AND

bisphosphonate?

NOT

Results of Search 3A

**NUMBER OF ITEMS RETRIEVED: 558**

=====

**SEARCH #4A (Efficacy) :**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 2005-9/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh] OR bone density

AND

raloxifene\* OR evista OR tamoxifen\* OR nolvadex OR emblon OR fentamox OR soltamox OR tamofen OR bazedoxifene\* OR lasofoxifene\* OR selective estrogen receptor modulators OR serm OR serms

**NUMBER OF ITEMS RETRIEVED: 780**

=====

**SEARCH #4B (Efficacy) :**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 2005-9/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh] OR bone density

AND

strontium

**NUMBER OF ITEMS RETRIEVED: 222**

=====

**SEARCH #4C (Efficacy) :**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 2005-9/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh]  
OR bone density  
AND  
tibolone

**NUMBER OF ITEMS RETRIEVED: 69**

=====

**SEARCH #4D (Efficacy) :**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 2005-9/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh]  
OR bone density  
AND  
pth OR parathyroid hormone\*  
NOT  
animal\* NOT (human OR humans) OR rat OR rats OR mice  
NOT  
Results of previous searches

**NUMBER OF ITEMS RETRIEVED: 1486**

=====

**SEARCH #4E (Efficacy) :**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 2005-9/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh]  
OR bone density  
AND  
"Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen\*[tiab] OR  
estradiol\*  
NOT  
animal\* NOT (human OR humans) OR rat OR rats OR mice OR monkey\*  
NOT  
Results of previous searches

**NUMBER OF ITEMS RETRIEVED: 927**

=====

**SEARCH #4F (Efficacy) :**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 2005-9/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh]  
OR bone density

AND

calcium

NOT

animal\* NOT (human OR humans) OR rat OR rats OR mice

NOT

Results of previous searches

**NUMBER OF ITEMS RETRIEVED: 2874**

=====

**SEARCH #4G (Efficacy) :**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 2005-9/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh]  
OR bone density

AND

vitamin d

NOT

animal\* NOT (human OR humans) OR rat OR rats OR mice OR monkey\*

NOT

Results of previous searches

**NUMBER OF ITEMS RETRIEVED: 655**

=====

**SEARCH #4H (Efficacy) :**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 2005-9/2009

**SEARCH STRATEGY:**

teriparatide

NOT

pth OR parathyroid hormone\*

**NUMBER OF ITEMS RETRIEVED: 216**

=====

**SEARCH #4I (Efficacy) :**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

Embase– 2005-11/5/2009

**LANGUAGE: English**

**OTHER LIMITERS: Human**

**SEARCH STRATEGY:**

osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2w)mineral OR bone(2n)density/ in Title, Subject Heading fields

and

calcium or vitamin(d) ORr estrogen OR oestrogen OR estradiol? OR lasofoxifene? OR pth OR parathyroid()hormone? OR teriparatide OR forteo OR preos OR raloxifene? OR evista OR selective()estrogen()receptor()modulator? OR serm OR serms OR exercise OR physical()activity/ in Title, Subject Heading fields

NOT

editorial OR letter

**NUMBER OF ITEMS RETRIEVED: 8608**

=====

**SEARCH #4J (Efficacy) :**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

Embase– 2005-11/17/2009

**LANGUAGE: English**

**OTHER LIMITERS: Human**

**SEARCH STRATEGY:**

osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2w)mineral OR bone(2n)density in Title, Subject Heading fields

and

lasofoxifene? OR denosumab OR pth OR parathyroid()hormone? OR teriparatide? OR forteo OR preos

NOT

editorial OR letter

**NUMBER OF ITEMS RETRIEVED: 2793**

=====

**SEARCH #5 (Compliance):**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 2005-10/14/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**

osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh]  
OR bone density

AND

noncompliant\* OR non-compliant\* OR nonadher\* OR non-adher\* OR refuse OR refusal  
OR treatment refusal OR patient compliance OR compliant\* OR comply OR complies OR  
complying OR adher\* OR persistence

AND

alendronate\* OR fosamax OR risedronate\* OR actonel OR etidronate\* OR didronel OR  
ibandronate\* OR boniva OR pamidronate\* OR aredia OR zoledronic acid OR zometa  
OR droloxifene\* OR denosumab OR raloxifene\* OR evista OR tamoxifen\* OR nolvadex  
OR emblon OR fentamox OR soltamox OR tamofen OR bazedoxifene\* OR lasofoxifene\*  
OR selective estrogen receptor modulators OR serm OR serms OR calcium OR pth OR  
parathyroid hormone\* OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action]  
OR estrogen\*[tiab] OR estradiol\* OR vitamin d OR testosterone OR exercise\* OR  
exercising OR physical activity OR "Exercise Therapy"[Mesh] OR drug therapy OR  
drug[tiab] OR drugs[tiab] OR medication\* OR therapy[tiab] OR therapies[tiab] OR  
treatment[tiab]

**NUMBER OF ITEMS RETRIEVED: 953**

**NUMBER OF ITEMS RETRIEVED AFTER MANUALLY REMOVING DUPLICATES  
FROM SEARCH 4A AND REMOVING ANIMAL-ONLY STUDIES: 389**

=====

**SEARCH #6**

**WEB OF SCIENCE FORWARD CITATION SEARCHES ON THE FOLLOWING  
ARTICLES (SEARCH PERFORMED 10/19/09):**

**Bell, K.J.L. "Value of routine monitoring of bone mineral density after starting  
bisphosphonate treatment: secondary analysis of trial data." BMJ Online First,  
2009.**

**Chen, P.Q. "Change in lumbar spine BMD and vertebral fracture risk reduction in  
teriparatide-treated postmenopausal women with osteoporosis." Journal of Bone  
and Mineral Research, Vol 21, Number 11, 2006.**

**Cummings, S.R. "The effects of tibolone in older postmenopausal women," NEJM  
359;7. August 14, 2008**

**Reginster, J-Y. "Effects of long-term strontium ranelate treatment on the risk of  
nonvertebral and vertebral fractures..." Arthritis & Rheumatism, Vol. 58, No. 6,  
June 2008, pp. 1687-1695.**

**Sarkar, S. "Relationships between bone mineral density and incident vertebral  
fracture risk with raloxifene therapy." Journal of Bone and Mineral Research, Vol.  
17, No. 1, 2002.**

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**SEARCH #7A (Frax) :**  
**DATABASE SEARCHED & TIME PERIOD COVERED:**  
PubMed – 2005-11/11/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**  
frax

**NUMBER OF ITEMS RETRIEVED: 100**  
=====

**SEARCH #7B(Frax) :**  
**DATABASE SEARCHED & TIME PERIOD COVERED:**  
Embase – 2005-11/12/2009

**SEARCH STRATEGY:**  
osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2w)mineral OR  
bone(2n)density  
AND  
frax

**NUMBER OF ITEMS RETRIEVED: 31**  
=====

**SEARCH #8(Monitoring) :**  
**DATABASE SEARCHED & TIME PERIOD COVERED:**  
PubMed – 2005-11/11/2009

**LANGUAGE: English**

**SEARCH STRATEGY:**  
osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh]  
OR bone density  
AND  
monitor\*  
NOT  
animal\* NOT (human OR humans)

**NUMBER OF ITEMS RETRIEVED: 1369**  
=====

**SEARCH #9(Related Articles) :**  
**DATABASE SEARCHED & TIME PERIOD COVERED:**  
PubMed – 2005-11/11/2009

**SEARCH STRATEGY:**  
“Related Articles” search on:

Bell, K.J.L., "Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data." BMJ Online First, 2009.

BMJ. 2009 Jun 23;338:b2266.

**NUMBER OF ITEMS RETRIEVED: 100**

=====

**SEARCH #10(Adverse Effects) :**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 2005-12/3/2009

**LANGUAGE: English**

**OTHER LIMITERS: Human**

**SEARCH STRATEGY:**

osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh]  
OR bone density

AND

alendronate\* OR fosamax OR risedronate\* OR actonel OR etidronate\* OR didronel OR  
ibandronate\* OR boniva OR pamidronate\* OR aredia OR zoledronic acid OR zometa  
OR droloxifene\* OR denosumab OR bisphosphonate\* OR raloxifene OR lasofoxifene  
OR serm OR serms OR selective estrogen receptor modulator\* OR calcium OR "vitamin  
d" OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen\*[tiab]  
OR estradiol\* OR oestrogen OR pth OR parathyroid hormone\* OR teriparatide OR forteo  
OR preos

AND

"adverse effects "[Subheading] OR ("Drug Toxicity"[Mesh] OR "toxicity "[Subheading])  
OR adverse OR harm OR harmful OR safe[tiab] OR safety[tiab] OR toxic\*[tiab] OR risk  
OR risks OR risking

OR

osteoporosis or osteopenia or osteopaenia or fracture\* or bone mineral OR fractures[mh]  
OR bone density

AND

raloxifene OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR  
estrogen\*[tiab] OR estradiol\* OR oestrogen OR (hormone\* AND menopus\*)

AND

thrombosis OR thrombophlebitis OR phlebitis OR clot OR clots OR clotting

OR

alendronate\* OR fosamax OR risedronate\* OR actonel OR etidronate\* OR didronel OR  
ibandronate\* OR boniva OR pamidronate\* OR aredia OR zoledronic acid OR zometa  
OR droloxifene\* OR denosumab OR bisphosphonate\*

AND

esophageal OR esophagus OR fibrillat\*

OR

raloxifene

AND

flash\* OR flush\*

**NUMBER OF ITEMS RETRIEVED (AFTER REMOVAL OF DUPLICATES): 441**

## **Appendix B: Data Abstraction Forms**

# Appendix B: Data Abstraction Forms

## Short Form Screener for all studies

### RAND EPC LBD2 – Full-text Screener

Article ID: _____	Reviewer: _____
First Author: _____ (Last Name Only)	
Study Number: _____ of _____	Description: _____
(Enter '1 of 1' if only one) (if more than one study)	

1. Does this study include humans?
  - No ..... 1 **STOP**
  - Yes ..... 2
  
2. Study design: Check all that apply
  - Descriptive (historical, editorial, etc.) .....  **STOP**
  - Background .....  **GO TO 11**
  - Review/meta-analysis .....
  - Randomized clinical trial .....
  - Trial with open-label extension .....
  - Controlled clinical trial .....
  - Cohort/case control - 1000+ subjects .....
  - Cohort/case control - under 1,000 subjects ....
  - Case Report .....
  - Other: \_\_\_\_\_
  
3. Intervention(s) studied: Check all that apply

Alendronate (Fosamax)..... <input type="checkbox"/>	Pamidronate (Aredia) (APD) .... <input type="checkbox"/>
Bisphosphonates ..... <input type="checkbox"/>	PTH (Teriparatide) (Forteo)..... <input type="checkbox"/>
Calcium ..... <input type="checkbox"/>	PTH (1-84) (Preos) ..... <input type="checkbox"/>
Vitamin D ..... <input type="checkbox"/>	Raloxifene (Evista)..... <input type="checkbox"/>
Denosumab ..... <input type="checkbox"/>	Risedronate (Actonel)..... <input type="checkbox"/>
Estrogen ..... <input type="checkbox"/>	Strontium ranelate..... <input type="checkbox"/>
Etidronate (Didronel) ..... <input type="checkbox"/>	Zoledronic acid (Zometa) ..... <input type="checkbox"/>
Ibandronate (Boniva) ..... <input type="checkbox"/>	Physical activity..... <input type="checkbox"/>
Lasofloxifene ..... <input type="checkbox"/>	None of the above ..... <input type="checkbox"/>
  
4. Which outcomes are used? Check all that apply
  - Bone density .....
  - Bone formation or bone turnover .....
  - Fractures .....
  - Adverse events .....
  - Adherence .....
  - None of the above .....  **STOP**
  
5. Does the article contain data on any of the following? Check all that apply
  - Efficacy .....
  - Safety/adverse events .....
  - Adherence .....
  - Risk assessment .....
  - DXA (Bone density monitoring) .....
  - None of the above .....  **STOP**
  
6. Participant enrollment criteria: Check all that apply
  - Healthy .....
  - Osteopenia/low bone density .....
  - Osteoporosis .....
  - Fracture .....
  - Other: \_\_\_\_\_
  - None of the above .....  **STOP**

7. Does the population comprise only persons currently being treated for cancer, Paget's disease, or multiple myeloma?
  - No ..... 1
  - Yes ..... 2 **STOP**
  
8. Study population: Check all that apply
  - Men .....
  - Pre-menopausal women .....
  - Post-menopausal women .....
  - Women otherwise undefined .....
  - Other: \_\_\_\_\_
  - Unclear .....

Age

  - Adults 65 and over .....
  - Adults under 65 .....
  - Other: \_\_\_\_\_
  - Unclear .....

Race

  - Exclusively Caucasian .....
  - Non-Caucasian included .....
  - Other: \_\_\_\_\_
  - Unclear .....

Other

  - Steroid-induced osteoporosis .....
  - Kidney disease .....
  - Liver transplant .....
  - Other: \_\_\_\_\_
  - Other: \_\_\_\_\_
  
9. Is the study part of a named trial?
  - No ..... 1
  - Yes: ..... 2
  
10. Do you think this article might be a duplicate or include the same data as another study?
  - No ..... 1
  - Yes: ..... 2
  
11. Is there a reference that needs to be checked in order to complete this screener?
  - No ..... 1
  - Yes: ..... 2

### Notes

Check here if this study was from the original LBD report.



**RAND EPC – LBD Update  
Detailed Abstraction Form for Trials**

4. What were the study's exclusion criteria?

CHECK ALL THAT APPLY

- Ambulatory.....  00
- Age under \_\_\_\_ years.....  01
- Age over \_\_\_\_ years.....  02
- Pregnancy .....  03
- Carcinoma or suspected carcinoma .....  04
- Cardiovascular disease .....  05
- Diabetes .....  06
- Endocrine disease (not diabetes) NOS .....  07
  - Hypothyroidism .....  08
  - Hyperthyroidism .....  09
  - Hyperparathyroidism .....  10
  - Hypoparathyroidism .....  11
- Hypocalcemia .....  12
- Hypercalcemia.....  13
- Vitamin D deficiency .....  14
- Hepatic insufficiency .....  15
- Metabolic bone disorder other than osteoporosis  
(e.g. Paget's, renal osteodystrophy, osteomalacia,  
rheumatoid arthritis, SLE) .....  16
- LS spine abnormalities prohibiting DXA.....  17
- Organ transplantation .....  18
- Renal insufficiency .....  19
- Gastrointestinal disease .....  20
  - Sprue .....  21
  - Inflammatory bowel disease .....  22
  - Malabsorption syndrome .....  23
  - Upper GI .....  24

- Nephrolithiasis .....  25
- Urolithiasis .....  26
- Venous thromboembolic disease .....  27
  - Active.....  28
  - Ever .....  29
- Anticonvulsants .....  30
- Aluminum.....  31
- Bisphosphonates .....  32
- Calcitonin .....  33
- Calcium includes antacids .....  34
- Coumarins.....  35
- Fluoride.....  36
- H2-blockers .....  37
- Hormone use NOS.....  40
  - Androgen .....  41
  - Menopausal .....  42
  - hormonal therapy ....  42
  - Estrogen agonists .....  43
  - including estrogen ....  43
  - Progestin .....  44
  - SERMS .....  45
  - Estrogen agonists ....  46
  - Anabolic steroids ....  47
  - Testosterone.....  48
  - Contraception.....  49
  - Previous PTH use ...  50
- Lipid lowering agents .....  51
- Proton pump inhibitors .....  52
- Vitamin D use.....  53
- Corticoids/Glucocorticoids.....  54
- Gallium nitrate .....  55
- Mithramycin .....  56
- Medications known to affect skeleton .....  57
- Not Reported .....  99

Additional exclusion criteria:

**RAND EPC – LBD Update  
Detailed Abstraction Form for Trials**

5. Were patients class-naive? CIRCLE ONE
- Yes ..... 1
- No ..... 2
- Not reported..... 9

6. Randomization: Was the study described as randomized and was the sequence generation for the randomization appropriate? CIRCLE ONE
- Yes, method adequate ..... 1
- Yes, but method unclear or inadequate ..... 2
- No, not randomized ..... 3

7. Did the method of randomization provide for concealment of allocation?\* CIRCLE ONE
- Yes..... 1
- No ..... 2
- Concealment not described ..... 8

\*Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.

8. Is the study described as\*: CIRCLE ONE
- Double blind..... 1
- Single blind, patient..... 2
- Single blind, outcome assessment ..... 3
- Single blind, not described..... 4
- Blind, NOS ..... 5
- Open ..... 6
- Blinding not described..... 8
- Not applicable ..... 9

\*This item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.

9. If reported, was the method of double blinding appropriate? CIRCLE ONE
- Yes..... 1
- No ..... 2
- Double blinding method not described..... 8
- Not applicable..... 9

10. Were outcome assessors masked to the treatment allocation?\* CIRCLE ONE
- Yes ..... 1
- Yes, but not described ..... 2
- No ..... 3
- Not reported..... 9

\*Outcome Assessor blinding adequacy should be assessed for the primary outcomes. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or: for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability); the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes"

11. Was the care provider masked to the treatment allocation?\* CIRCLE ONE
- Yes..... 1
- Yes, but not described ..... 2
- No ..... 3
- Not reported..... 9

\*This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful

12. Was the patient masked to the treatment allocation? CIRCLE ONE
- Yes..... 1
- Yes, but not described ..... 2
- No ..... 3
- Not reported..... 9

**RAND EPC – LBD Update  
Detailed Abstraction Form for Trials**

13. Was the withdrawal/drop-out rate described and was the reason given?

- Yes described for all .....1
- Yes described for some .....2
- Not described .....3
- Unclear .....8
- Not applicable .....9

14. Was the withdrawal/drop-out rate acceptable (e.g., 20% short term, 30% long term)?

- Yes .....1
- No.....2
- Don't know .....9

15. Were cointerventions avoided or similar among index and control groups?\*

- Yes .....1
- No.....2
- Don't know .....9

\*This item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups.

16. Was an intention to treat (ITT) analysis described? Were all participants' data included in the analysis, according to the treatment group to which they were originally assigned, regardless of whether they completed the treatment/study?

- Yes .....1
- Possibly .....2
- No, unlikely.....3
- N/A (no controls/effectiveness analysis) ..9

17. Sample size: (Enter N or 999 for not reported)

Screened: \_\_\_\_\_ Eligible: \_\_\_\_\_

Enrolled: \_\_\_\_\_ Withdrawn: \_\_\_\_\_

Loss to follow-up: \_\_\_\_\_

18. Was there a run-in and/or wash-out period?

- Run-in only ..... 1
- Wash-out only ..... 2
- Both run-in and wash-out ..... 3
- Neither ..... 4
- Unclear..... 8
- Not applicable ..... 9

19. What was the study's setting? CHECK ALL

- Multi-center .....
- Single setting .....
- Ambulatory/community practice ....
- VA Health Care System .....
- Long term care facility .....
- Other: \_\_\_\_\_ ...
- Setting not reported .....

20. Where was the study conducted? CHECK ALL

- US .....
- Canada .....
- South/Central America .....
- UK.....
- Western Europe.....
- Eastern Europe .....
- Australia/New Zealand .....
- Japan .....
- Asia (not Japan) .....
- Other \_\_\_\_\_ ...
- Not reported .....

21. What was the study's funding source?

CHECK ALL

- Government .....
- Hospital.....
- Industry .....
- Private (non-industry).....
- Other .....
- Unclear .....
- Not reported SKIP TO Q23 .....

22. Did the article include a statement on the role of the funder?

- Yes ..... 1
- No ..... 2
- Not applicable ..... 9

23. What was the percent of female participants? ENTER NUMBER OR 999.9

\_\_\_\_\_ . \_\_\_\_\_ %

24. What racial/ethnic groups were studied? CHECK ALL

- Caucasian .....
- African Ancestry .....
- Hispanic.....
- Asian .....
- Native American .....
- Eskimo/Inuit .....
- Other \_\_\_\_\_ .....
- Not reported .....

**RAND EPC – LBD Update  
Detailed Abstraction Form for Trials**

25. What were the subjects' ages?  
Enter 999 for not reported

Mean | Median .....

Age Range ..... to .....

26. What were the comorbidities reported in the study? CHECK ALL THAT APPLY

- |                          |                          |                            |                          |
|--------------------------|--------------------------|----------------------------|--------------------------|
| Asthma .....             | <input type="checkbox"/> | Rheumatoid arthritis ..... | <input type="checkbox"/> |
| Breast cancer .....      | <input type="checkbox"/> | SLE .....                  | <input type="checkbox"/> |
| COPD .....               | <input type="checkbox"/> | PUD .....                  | <input type="checkbox"/> |
| Diabetes .....           | <input type="checkbox"/> | Pancreatitis .....         | <input type="checkbox"/> |
| ETOH use .....           | <input type="checkbox"/> | Bleeding .....             | <input type="checkbox"/> |
| Glucocorticoid use ..... | <input type="checkbox"/> | Renal calculi .....        | <input type="checkbox"/> |
| Hypertension .....       | <input type="checkbox"/> |                            |                          |

Other: .....  
Not reported .....

27. Were groups similar at baseline, in terms of age, BMI (or equivalent) and race/ethnicity (if US study)?

Yes ..... 1  
No ..... 2  
Not reported ..... 9

28. Did the placebo/control group receive standard care?

Yes ..... 1  
No ..... 2  
Not reported ..... 9

29. What was the method of adverse events assessment? CHECK ALL

- Monitored.....  
Elicited by investigator .....  
Reported spontaneously by patient .....  
Other: .....  
Not reported .....

**INTERVENTIONS**

30. Interventions given to EVERYONE in the study:

Interventions given to everyone	Dose	Units	Frequency	Duration of treatment	Units
None ..... 0					
Calcium ..... 1	---	---	---	---	---
Estrogen ..... 2	---	---	---	---	---
Testosterone ..... 3	---	---	---	---	---
Vitamin D ..... 4	---	---	---	---	---
Corticosteroids ..... 5	---	---	---	---	---
Other ..... 6	---	---	---	---	---
Other ..... 7	---	---	---	---	---
	Enter # or range 996 Unclear 997 Variable 998 Not applicable 999 Not reported	Enter a number 1 g 2 mg 3 µg 4 IU 97 Unclear 98 Not applicable 99 Not reported	Enter a number 1 Daily 2 Weekly 3 Monthly 4 Yearly 96 Unclear 97 Variable 98 Not applicable 99 Not reported	Enter a number 996 Unclear 997 Variable 998 Not applicable 999 Not reported	Enter a number 1 Day 2 Week 3 Month 4 Year 97 Unclear 98 Not applicable 99 Not reported

31. Total number of arms:

\_\_\_\_\_

32.

**RAND EPC – LBD Update  
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Arm/ Group	Sample size	Interventions <small>ENTER CODE</small>	Dose <small>ENTER # OR RANGE</small>	Units <small>ENTER CODE</small>	Frequency <small>ENTER CODE</small>	Tx Duration <small>ENTER #</small>	Units <small>ENTER CODE</small>
<b>1</b>	_____ N ENTERING	Usual care .....00 Placebo.....01 Control .....02	_____	_____	_____	_____	_____
	_____ N COMPLETING	Alendronate .....03 Etidronate .....07 Ibandronate .....08 Pamidronate .....09 Risedronate .....12	_____	_____	_____	_____	_____
	_____ N ANALYZED	Zoledronic acid .15 Calcitonin .....04 PTH (terparatide) .10 PTH (1-84).....301	_____	_____	_____	_____	_____
	_____ # OF EXCLUSIONS	Lasifoxifene ....302 Raloxifene .....11 Estrogen .....06 Estrogen patch 303 Est/progest. ....304 Progesterone ...100 Testosterone .....14	_____	_____	_____	_____	_____
		Denosumab .....05 Calcium .....16 Flouride .....73 Strontium .....305	_____	_____	_____	_____	_____
		Vitamin D .....17 Vitamin K .....71 Exercise .....18	_____	_____	_____	_____	_____
			_____	_____	_____	_____	_____
			_____	_____	_____	_____	_____
			_____	_____	_____	_____	_____
			_____	_____	_____	_____	_____
			_____	_____	_____	_____	_____
			_____	_____	_____	_____	_____
			_____	_____	_____	_____	_____
	Enter # 9997. Unclear 9998. Not applicable 9999. Not reported		Enter # or range 997. Unclear 998. N/A 999. Not reported	Enter a number 1. g 2. mg 3. µg 4. IU 97. Unclear 98. Not applicable 99. Not reported	Enter a number 1. Daily 2. Weekly 3. Monthly 4. Yearly 97. Unclear 99. Not applicable 99. Not reported	Enter a number 996. Unclear 997. Variable 998. Not applicable 999. Not reported	Enter a number 1. Day 2. Week 3. Month 4. Year 97. Unclear 98. Not applicable 99. Not reported

**RAND EPC – LBD Update  
Detailed Abstraction Form for Trials**

Arm/ Group	Sample size	Interventions <small>ENTER CODE</small>	Dose <small>ENTER # OR RANGE</small>	Units <small>ENTER CODE</small>	Frequency <small>ENTER CODE</small>	Tx Duration <small>ENTER #</small>	Units <small>ENTER CODE</small>	
<b>3</b>	<p>_____ N ENTERING</p> <p>_____ N COMPLETING</p> <p>_____ N ANALYZED</p> <p>_____ # OF EXCLUSIONS</p>	<p>Usual care .....00</p> <p>Placebo .....01</p> <p>Control .....02</p> <p>Alendronate .....03</p> <p>Etidronate .....07</p> <p>Ibandronate .....08</p> <p>Pamidronate .....09</p> <p>Risedronate .....12</p> <p>Zoledronic acid.15</p> <p>Calcitonin .....04</p> <p>PTH (teriparatide) ..10</p> <p>PTH (1-84).....301</p> <p>Lasifoxifene .....302</p> <p>Raloxifene .....11</p> <p>Estrogen .....06</p> <p>Estrogen patch 303</p> <p>Est/progest. ....304</p> <p>Progesterone ...100</p> <p>Testosterone .....14</p> <p>Denosumab .....05</p> <p>Calcium .....16</p> <p>Flouride .....73</p> <p>Strontium .....305</p>	_____	_____	_____	_____	_____	_____
<b>4</b>	<p>_____ N ENTERING</p> <p>_____ N COMPLETING</p> <p>_____ N ANALYZED</p> <p>_____ # OF EXCLUSIONS</p>	<p>Vitamin D .....17</p> <p>Vitamin K .....71</p> <p>Exercise .....18</p>	_____	_____	_____	_____	_____	
	<p>Enter #</p> <p>9996. Unclear</p> <p>9998. Not applicable</p> <p>9999. Not reported</p>		<p>Enter # or range</p> <p>997. Unclear</p> <p>998. N/A</p> <p>999. Not reported</p>	<p>Enter a number</p> <p>1. g</p> <p>2. mg</p> <p>3. µg</p> <p>4. IU</p> <p>97. Unclear</p> <p>98. Not applicable</p> <p>99. Not reported</p>	<p>Enter a number</p> <p>1. Daily</p> <p>2. Weekly</p> <p>3. Monthly</p> <p>4. Yearly</p> <p>97. Unclear</p> <p>99. Not applicable</p> <p>99. Not reported</p>	<p>Enter a number</p> <p>996. Unclear</p> <p>997. Variable</p> <p>998. Not applicable</p> <p>999. Not reported</p>	<p>Enter a number</p> <p>1. Day</p> <p>2. Week</p> <p>3. Month</p> <p>4. Year</p> <p>97. Unclear</p> <p>98. Not applicable</p> <p>99. Not reported</p>	

**RAND EPC – LBD Update  
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**OUTCOMES**

33. Did the article report the following? CHECK ALL
- Adherence .....
- Contamination .....

*Adherence:* The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (for ex: surgery), this item is irrelevant.

*Contamination:* refers to whether some portion of the placebo group actually received/used the active intervention.

34. Are fractures specified as the primary outcome?
- Yes ..... 1
- No ..... 2

35. Which outcomes were measured? CHECK ALL
- Bone mineral density by DXA – Hip.....  01
- Bone mineral density by DXA - Spine ...  02
- Hip fracture .....  03
- Proximal humerus fracture.....  04
- Radial fracture .....  05
- Vertebral fracture.....  06
- Non-vertebral fracture.....  07
- Total fractures .....  08
- Radiographic vertebral fractures.....  09
- Symptomatic vertebral fractures .....  10
- Other .....  11
- Other .....  12
- Other .....  13
- None of the above .....  99

36. When were fracture outcomes measured?

Baseline?	YES / NO	
Follow-up	Time from baseline	Unit 1: Day 2: Week 3: Month 4: Year 5: Unclear 8: Not reported 9: Variable
1 <sup>st</sup>		
2 <sup>nd</sup>		
3 <sup>rd</sup>		
4 <sup>th</sup>		
5 <sup>th</sup>		
6 <sup>th</sup>		
7 <sup>th</sup>		
8 <sup>th</sup>		
9 <sup>th</sup>		
10 <sup>th</sup>		
11 <sup>th</sup>		
12 <sup>th</sup>		
13 <sup>th</sup>		
14 <sup>th</sup>		
15 <sup>th</sup>		
Additional		



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**Answer only the questions that are highlighted**

**4. What were the study's exclusion criteria?**

CHECK ALL THAT APPLY

- Ambulatory .....  00
- Age under \_\_\_\_ years .....  01
- Age over \_\_\_\_ years .....  02
- Pregnancy .....  03
- Carcinoma or suspected carcinoma .....  04
- Cardiovascular disease .....  05
- Diabetes .....  06
- Endocrine disease (not diabetes) NOS .....  07
  - Hypothyroidism .....  08
  - Hyperthyroidism .....  09
  - Hyperparathyroidism .....  10
  - Hypoparathyroidism .....  11
- Hypocalcemia .....  12
- Hypercalcemia .....  13
- Vitamin D deficiency .....  14
- Hepatic insufficiency .....  15
- Metabolic bone disorder other than osteoporosis  
 (e.g. Paget's, renal osteodystrophy, osteomalacia,  
 rheumatoid arthritis, SLE) .....  16
- LS spine abnormalities prohibiting DXA .....  17
- Organ transplantation .....  18
- Renal insufficiency .....  19
- Gastrointestinal disease .....  20
  - Sprue .....  21
  - Inflammatory bowel disease .....  22
  - Malabsorption syndrome .....  23
  - Upper GI .....  24

- Nephrolithiasis .....  25
- Urolithiasis .....  26
- Venous thromboembolic disease .....  27
  - Active .....  28
  - Ever .....  29
- Anticonvulsants .....  30
- Aluminum .....  31
- Bisphosphonates .....  32
- Calcitonin .....  33
- Calcium includes antacids .....  34
- Coumarins .....  35
- Fluoride .....  36
- H2-blockers .....  37
- Hormone use NOS .....  40
  - Androgen .....  41
  - Menopausal .....  42
    - hormonal therapy .....  42
  - Estrogen agonists .....  43
    - including estrogen .....  43
  - Progestin .....  44
  - SERMS .....  45
  - Estrogen agonists .....  46
  - Anabolic steroids .....  47
  - Testosterone .....  48
  - Contraception .....  49
  - Previous PTH use .....  50
- Lipid lowering agents .....  51
- Proton pump inhibitors .....  52
- Vitamin D use .....  53
- Corticoids/Glucocorticoids .....  54
- Gallium nitrate .....  55
- Mithramycin .....  56
- Medications known to affect skeleton .....  57
- Not Reported .....  99

Additional exclusion criteria:

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**5. Were patients class-naive?**

CIRCLE ONE

- Yes ..... 1
- No ..... 2
- Not reported..... 9

**6. Randomization: Was the study described as randomized and was the sequence generation for the randomization appropriate?**

CIRCLE ONE

- Yes, method adequate ..... 1
- Yes, but method unclear or inadequate ..... 2
- No, not randomized ..... 3

**7. Did the method of randomization provide for concealment of allocation?\***

CIRCLE ONE

- Yes..... 1
- No ..... 2
- Concealment not described ..... 8

\*Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.

**8. Is the study described as\*:**

CIRCLE ONE

- Double blind ..... 1
- Single blind, patient ..... 2
- Single blind, outcome assessment ..... 3
- Single blind, not described ..... 4
- Blind, NOS ..... 5
- Open ..... 6
- Blinding not described..... 8
- Not applicable ..... 9

\*This item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.

**9. If reported, was the method of double blinding appropriate?**

CIRCLE ONE

- Yes ..... 1
- No ..... 2
- Double blinding method not described..... 8
- Not applicable..... 9

**10. Were outcome assessors masked to the treatment allocation?\***

CIRCLE ONE

- Yes ..... 1
- Yes, but not described ..... 2
- No ..... 3
- Not reported..... 9

\*Outcome Assessor blinding adequacy should be assessed for the primary outcomes. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or; for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes"

**11. Was the care provider masked to the treatment allocation?\***

CIRCLE ONE

- Yes ..... 1
- Yes, but not described ..... 2
- No ..... 3
- Not reported..... 9

\*This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful

**12. Was the patient masked to the treatment allocation?**

CIRCLE ONE

- Yes ..... 1
- Yes, but not described ..... 2
- No ..... 3
- Not reported..... 9

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**13. Was the withdrawal/drop-out rate described and was the reason given?**

- Yes described for all .....1
- Yes described for some .....2
- Not described .....3
- Unclear .....8
- Not applicable .....9

**14. Was the withdrawal/drop-out rate acceptable (e.g., 20% short term, 30% long term)?**

- Yes .....1
- No .....2
- Don't know .....9

**15. Were cointerventions avoided, similar, or controlled for among index and control groups?\***

- Yes .....1
- No .....2
- Don't know .....9

\*This item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups.

**16. Was an intention to treat (ITT) analysis described? Were all participants' data included in the analysis, according to the treatment group to which they were originally assigned, regardless of whether they completed the treatment/study?**

- Yes .....1
- Possibly .....2
- No, unlikely .....3
- N/A (no controls/effectiveness analysis) ..9

**17. Sample size: (Enter N or 999 for not reported)**

Screened: \_\_\_\_\_ Eligible: \_\_\_\_\_  
Enrolled: \_\_\_\_\_ Withdrawn: \_\_\_\_\_  
Loss to follow-up: \_\_\_\_\_

**18. Was there a run-in and/or wash-out period?**

- Run-in only ..... 1
- Wash-out only ..... 2
- Both run-in and wash-out ..... 3
- Neither ..... 4
- Unclear ..... 8
- Not applicable ..... 9

**19. What was the study's setting? CHECK ALL**

- Multi-center .....
- Single setting .....
- Ambulatory/community practice ....
- VA Health Care System .....
- Long term care facility .....
- Other: \_\_\_\_\_
- Setting not reported .....

**20. Where was the study conducted? CHECK ALL**

- US .....
- Canada .....
- South/Central America .....
- UK .....
- Western Europe .....
- Eastern Europe .....
- Australia/New Zealand .....
- Japan .....
- Asia (not Japan) .....
- Other .....
- Not reported .....

**21. What was the study's funding source? CHECK ALL**

- Government .....
- Hospital .....
- Industry .....
- Private (non-industry) .....
- Other .....
- Unclear .....
- Not reported SKIP TO Q23 .....

**22. Did the article include a statement on the role of the funder?**

- Yes ..... 1
- No ..... 2
- Not applicable ..... 9

**23. What was the percent of female participants? ENTER NUMBER OR 999.9**

\_\_\_\_\_ . \_\_\_\_\_ %

**24. What racial/ethnic groups were studied? CHECK ALL**

- Caucasian .....
- African Ancestry .....
- Hispanic .....
- Asian .....
- Native American .....
- Eskimo/Inuit .....
- Other .....
- Not reported .....

**X1. From where were patients identified? CIRCLE ONE**

- Single clinic or hospital ..... 1
- Single long-term care facility ..... 2
- Multiple clinic ..... 3
- Single community ..... 4
- Regional ..... 5
- Nat'l/Int'l ..... 6
- Other ..... 7
- Unclear ..... 9

**X2. How were patients selected? CIRCLE ONE**

- Population-based, systematic, or representative sample ..... 1
- Combination ..... 2
- Part of a trial ..... 3
- Other ..... 4
- Unclear ..... 9

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 Answer only the questions that are highlighted

**25. What were the subjects' ages?**

Enter 999 for not reported

Mean | Median .....

Age Range ..... to .....

**26. What were the comorbidities reported in the study?**

CHECK ALL THAT APPLY

- Asthma .....  Rheumatoid arthritis .....
- Breast cancer .....  SLE .....
- COPD .....  PUD .....
- Diabetes .....  Pancreatitis .....
- EtOH use .....  Bleeding .....
- Glucocorticoid use .....  Renal calculi .....
- Hypertension .....
- Other: .....
- Not reported .....

**27. Were groups similar at baseline, in terms of age, BMI (or equivalent) and race/ethnicity (if US study)?**

- Yes ..... 1
- No ..... 2
- Not reported ..... 9

**28. Did the placebo/control group receive standard care?**

- Yes ..... 1
- No ..... 2
- Not reported ..... 9

**29. What was the method of adverse events assessment?**

CHECK ALL

- Monitored .....
- Elicited by investigator .....
- Reported spontaneously by patient .....
- Other: .....
- Not reported .....

**INTERVENTIONS**

**30. Interventions given to EVERYONE in the study:**

Interventions given to everyone	Dose	Units	Frequency	Duration of treatment	Units
None ..... 0					
Calcium ..... 1	---	---	---	---	---
Estrogen ..... 2	---	---	---	---	---
Testosterone ..... 3	---	---	---	---	---
Vitamin D ..... 4	---	---	---	---	---
Corticosteroids ..... 5	---	---	---	---	---
Other ..... 6	---	---	---	---	---
Other ..... 7	---	---	---	---	---
	Enter # or range 996 Unclear 997 Variable 998 Not applicable 999 Not reported	Enter a number 1. g 2. mg 3. ug 4. IU 97. Unclear 98. Not applicable 99. Not reported	Enter a number 1. Daily 2. Weekly 3. Monthly 4. Yearly 96. Unclear 97. Variable 98. Not applicable 99. Not reported	Enter a number 996 Unclear 997 Variable 998 Not applicable 999 Not reported	Enter a number 1. Day 2. Week 3. Month 4. Year 97. Unclear 98. Not applicable 99. Not reported

**31. Total number of arms:**

\_\_\_\_\_

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**Answer only the questions that are highlighted**

32.

Arm/ Group	Sample size	Interventions <small>ENTER CODE</small>	Dose <small>ENTER # OR RANGE</small>	Units <small>ENTER CODE</small>	Frequency <small>ENTER CODE</small>	Tx Duration <small>ENTER #</small>	Units <small>ENTER CODE</small>
<b>1</b>	_____ N ENTERING	Usual care .....00 Placebo .....01 Control .....02	_____	_____	_____	_____	_____
	_____ N COMPLETING	Alendronate .....03 Etidronate .....07 Ibandronate .....08 Pamidronate .....09 Risedronate .....12	_____	_____	_____	_____	_____
<b>2</b>	_____ N ENTERING	Zoledronic acid .15 Calcitonin .....04 PTH (teriparatide) .10 PTH (1-84) .....301	_____	_____	_____	_____	_____
	_____ N COMPLETING	Lasifoxifene .....302 Raloxifene .....11 Estrogen .....06 Estrogen patch 303 Est/progest. ....304 Progesterone ...100 Testosterone .....14	_____	_____	_____	_____	_____
<b>2</b>	_____ N ENTERING	Denosumab .....05 Calcium .....16 Flouride .....73 Strontium .....305	_____	_____	_____	_____	_____
	_____ N COMPLETING	Vitamin D .....17 Vitamin K .....71 Exercise .....18	_____	_____	_____	_____	_____
	_____ N ANALYZED		_____	_____	_____	_____	_____
	_____ # OF EXCLUSIONS		_____	_____	_____	_____	_____
	Enter # 9997. Unclear 9998. Not applicable 9999. Not reported		Enter # or range 997. Unclear 998. N/A 999. Not reported	Enter a number 1. g 2. mg 3. µg 4. IU 97. Unclear 98. Not applicable 99. Not reported	Enter a number 1. Daily 2. Weekly 3. Monthly 4. Yearly 97. Unclear 99. Not applicable 99. Not reported	Enter a number 996. Unclear 997. Variable 998. Not applicable 999. Not reported	Enter a number 1. Day 2. Week 3. Month 4. Year 97. Unclear 98. Not applicable 99. Not reported

**RAND EPC – LBD Update**  
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**Answer only the questions that are highlighted**

Arm/ Group	Sample size	Interventions <small>ENTER CODE</small>	Dose <small>ENTER # OR RANGE</small>	Units <small>ENTER CODE</small>	Frequency <small>ENTER CODE</small>	Tx Duration <small>ENTER #</small>	Units <small>ENTER CODE</small>
<b>3</b>		Usual care .....00					
	_____ N ENTERING	Placebo.....01	_____	_____	_____	_____	_____
		Control .....02					
		Alendronate .....03	_____	_____	_____	_____	_____
	_____ N COMPLETING	Etidronate .....07	_____	_____	_____	_____	_____
		Ibandronate .....08	_____	_____	_____	_____	_____
		Pamidronate .....09	_____	_____	_____	_____	_____
		Risedronate .....12	_____	_____	_____	_____	_____
	_____ N ANALYZED	Zoledronic acid .15	_____	_____	_____	_____	_____
		Calcitonin .....04	_____	_____	_____	_____	_____
		PTH (teriparatide) .10	_____	_____	_____	_____	_____
		PTH (1-84).....301	_____	_____	_____	_____	_____
	_____ # OF EXCLUSIONS	Lasifoxifene ....302	_____	_____	_____	_____	_____
		Raloxifene .....11	_____	_____	_____	_____	_____
		Estrogen .....06	_____	_____	_____	_____	_____
		Estrogen patch 303	_____	_____	_____	_____	_____
		Est/progest. ....304	_____	_____	_____	_____	_____
		Progesterone ...100	_____	_____	_____	_____	_____
		Testosterone .....14	_____	_____	_____	_____	_____
		Denosumab .....05	_____	_____	_____	_____	_____
		Calcium.....16	_____	_____	_____	_____	_____

**RAND EPC – LBD Update**  
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**Answer only the questions that are highlighted**

<b>4</b>	<p>_____ N ENTERING</p> <p>_____ N COMPLETING</p> <p>_____ N ANALYZED</p> <p>_____ # OF EXCLUSIONS</p> <p>Enter #            9996 Unclear            9998 Not applicable            9999 Not reported</p>							
	<p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>
			<p>Enter # or range            997 Unclear            998 N/A            999 Not reported</p>	<p>Enter a number            1 g            2 mg            3 ug            4 IU            97 Unclear            98 Not applicable            99 Not reported</p>	<p>Enter a number            1 Daily            2 Weekly            3 Monthly            4 Yearly            97 Unclear            98 Not applicable            99 Not reported</p>	<p>Enter a number            996 Unclear            997 Variable            998 Not applicable            999 Not reported</p>	<p>Enter a number            1 Day            2 Week            3 Month            4 Year            97 Unclear            98 Not applicable            99 Not reported</p>	

RAND EPC – LBD Update  
Detailed Abstraction Form for Observational studies  
Answer only the questions that are highlighted

**OUTCOMES**

**33. Did the article report the following?** CHECK ALL

- Adherence .....   
Contamination .....

*Adherence:* The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (for ex: surgery), this item is irrelevant.

*Contamination:* refers to whether some portion of the placebo group actually received/used the active intervention.

**34. Are fractures specified as the primary outcome?**

- Yes ..... 1  
No ..... 2

**35. Which outcomes were measured?** CHECK ALL

- Bone mineral density by DXA – Hip.....  01  
Bone mineral density by DXA - Spine ...  02  
Hip fracture .....  03  
Proximal humerus fracture.....  04  
Radial fracture .....  05  
Vertebral fracture .....  06  
Non-vertebral fracture.....  07  
Total fractures .....  08  
Radiographic vertebral fractures .....  09  
Symptomatic vertebral fractures .....  10  
Other .....  11  
Other .....  12  
Other .....  13  
None of the above .....  99

**36. When were fracture outcomes measured?**

Baseline?	YES / NO	
Follow-up	Time from baseline	Unit 1: Day 2: Week 3: Month 4: Year 5: Unclear 8: Not reported 9: Variable
1 <sup>st</sup>		
2 <sup>nd</sup>		
3 <sup>rd</sup>		
4 <sup>th</sup>		
5 <sup>th</sup>		
6 <sup>th</sup>		
7 <sup>th</sup>		
8 <sup>th</sup>		
9 <sup>th</sup>		
10 <sup>th</sup>		
11 <sup>th</sup>		
12 <sup>th</sup>		
13 <sup>th</sup>		
14 <sup>th</sup>		
15 <sup>th</sup>		
Additional		

RAND EPC – LBD Update  
Detailed Abstraction Form for Observational studies  
Answer only the questions that are highlighted

**QUALITY OF COHORT STUDIES**

**37. Are primary outcomes assessed using valid and reliable measures?**

- CIRCLE ONE
- Yes ..... 1  
No ..... 2  
Unclear/Not reported ..... 9

**38. Are outcome measures implemented consistently across all study participants?**

- CIRCLE ONE
- Yes ..... 1  
No ..... 2  
Unclear/Not reported ..... 9

**39. Were the important confounding and modifying variables taken into account in the design and analysis?**

- CIRCLE ONE
- Yes ..... 1  
No ..... 2  
Unclear/Not reported ..... 9

**40. How was the non-exposed cohort selected?**

- CIRCLE ONE
- Drawn from the same community as the exposed cohort ..... 1  
Drawn from a different source..... 2  
No description of the derivation of the non-exposed cohort ..... 3

**41. How was exposure to LBD drugs/exercise ascertained?**

- CIRCLE ONE
- Secure record (e.g. medical records) ..... 1  
Structured interview ..... 2  
Written self report..... 3  
Claims data ..... 4  
No description ..... 9

**42. Was it demonstrated that the outcome of interest was not present at the start of the study?**

- CIRCLE ONE
- Yes..... 1  
No ..... 2  
Unclear/Not reported ..... 9

# Long Form for Adherence Studies

## LBD2 Medication Adherence Long Form

Article ID: _____	Reviewer: _____
First Author: _____	(Last Name Only)
Study Number: _____ of _____	Description: _____
(Enter '1 of 1' if only one)	(if more than one study)

1. Study design CIRCLE ONE
- Cross-sectional ..... 1
  - Observational cohort (two or more points) ..... 2
  - Case control ..... 3
  - RCT ..... 4
  - CCT ..... 5
  - Unclear ..... 9

2. Was the study conducted exclusively in the US?
- Yes ..... 1
  - No ..... 2
  - Unclear ..... 9

3. From where were the patients identified?
- CHECK ONE AND SPECIFY WHICH, BELOW
- |                        |                          |   |
|------------------------|--------------------------|---|
| National ..... 1       | Single clinic/hosp/      | 6 |
| Multiple sites ..... 2 | pharmacy ..... 6         |   |
| Multi-State ..... 3    | Multiple clinics ..... 7 |   |
| State ..... 4          | Other ..... 8            |   |
| Health plan ..... 5    | Unclear ..... 98         |   |
|                        | Not specified ..... 99   |   |
- Specify: \_\_\_\_\_

4. Recruitment method CIRCLE ONE
- Random sample ..... 1
  - All patients with disease from study site ..... 2
  - Participants in clinical trial ..... 3
  - Claims data from payers ..... 4
  - Consecutive patients ..... 5
  - Convenience sample ..... 6
  - Volunteers, response to ads ..... 7
  - Other method: \_\_\_\_\_ ..... 8
  - Unclear ..... 98
  - Not specified ..... 99

5. Participant numbers ENTER NUMBER
- Invited to participate ..... \_\_\_\_\_
  - Enrolled ..... \_\_\_\_\_
  - Responding at baseline ..... \_\_\_\_\_
  - Responding at final follow-up ..... \_\_\_\_\_

6. Participants PERCENT
- Male ..... \_\_\_\_\_
  - Seniors (65 and older) ..... \_\_\_\_\_
  - Black/African American ..... \_\_\_\_\_
  - Hispanic ..... \_\_\_\_\_
  - Non-hispanic White ..... \_\_\_\_\_
  - American Indian/Alaska Native ..... \_\_\_\_\_
  - Asian Pacific Islander ..... \_\_\_\_\_
  - Other racial group ( \_\_\_\_\_ ) ..... \_\_\_\_\_
  - Other racial group ( \_\_\_\_\_ ) ..... \_\_\_\_\_

7. Type of adherence CHECK ALL THAT APPLY
- Non-fulfillment .....
  - Non-persistence .....
  - Non-adherence .....
  - Overadherence .....
  - Discontinuation .....
  - Not Specified .....
  - Other ( \_\_\_\_\_ ) .....

8. How is adherence assessed? CHECK ALL THAT APPLY
- Self-report/diary .....
  - Questionnaire .....
  - Telephone interview .....
  - In-person interview .....
  - Pill count (by someone other than patient) .....
  - Electronic monitoring .....
  - Pharmacy records/claims data .....
  - Medical records .....
  - Biological evidence .....
  - Clinical response .....
  - Other ( \_\_\_\_\_ ) .....
  - Unclear .....
  - Not specified .....

### LBD2 Medication Adherence Long Form

9. What is the length of time over which adherence is being measured (in months)?

\_\_\_\_\_

10. Which key questions does this article answer?

CHECK ALL THAT APPLY

- Adherence and persistence to medications for the treatment and prevention of osteoporosis.....
- Factors that affect adherence and persistence.....
- Effects of adherence and persistence on the risk of fractures.....
- None of the above.....

11. Which barriers and/or predictors?

CHECK ALL THAT APPLY

- |                                    | DISCUSSED                | FOR                      |    |
|------------------------------------|--------------------------|--------------------------|----|
| Patient characteristics.....       | <input type="checkbox"/> | <input type="checkbox"/> | 01 |
| Age.....                           | <input type="checkbox"/> | <input type="checkbox"/> | 02 |
| Gender.....                        | <input type="checkbox"/> | <input type="checkbox"/> | 03 |
| Race/ethnicity.....                | <input type="checkbox"/> | <input type="checkbox"/> | 04 |
| Marital status.....                | <input type="checkbox"/> | <input type="checkbox"/> | 05 |
| Employment status.....             | <input type="checkbox"/> | <input type="checkbox"/> | 06 |
| Socioeconomics status.....         | <input type="checkbox"/> | <input type="checkbox"/> | 07 |
| Education.....                     | <input type="checkbox"/> | <input type="checkbox"/> | 08 |
| Prescription insurance status..... | <input type="checkbox"/> | <input type="checkbox"/> | 09 |
| Depression.....                    | <input type="checkbox"/> | <input type="checkbox"/> | 10 |
| Costs/insurance.....               | <input type="checkbox"/> | <input type="checkbox"/> | 11 |
| Other: _____..                     | <input type="checkbox"/> | <input type="checkbox"/> | 12 |
| Other: _____..                     | <input type="checkbox"/> | <input type="checkbox"/> | 13 |
| Other: _____..                     | <input type="checkbox"/> | <input type="checkbox"/> | 14 |
| Other: _____..                     | <input type="checkbox"/> | <input type="checkbox"/> | 15 |
| Other: _____..                     | <input type="checkbox"/> | <input type="checkbox"/> | 16 |
| Other: _____..                     | <input type="checkbox"/> | <input type="checkbox"/> | 17 |

12. How is adherence measured?

CHECK ALL THAT APPLY

- Never filled prescription.....
- Delayed filling prescription.....
- # Days: \_\_\_\_\_ # Weeks: \_\_\_\_\_
- Undefined.....
- Discontinuation.....
- a) After \_\_\_\_\_ months
- b) After \_\_\_\_\_ months
- Medication possession ratio.....
- # Days in reporting period: \_\_\_\_\_
- Dichotomous  Continuous
- Cutoff Point: \_\_\_\_\_
- Proportion of Days Covered.....
- # Days in reporting period: \_\_\_\_\_
- Dichotomous  Continuous
- Cutoff Point: \_\_\_\_\_
- Prescription refill ratio.....
- # Days in reporting period: \_\_\_\_\_
- Dichotomous  Continuous
- Cutoff Point: \_\_\_\_\_
- Prescribed doses taken with specified period..
- # Days in reporting period: \_\_\_\_\_
- Dichotomous  Continuous
- Cutoff Point: \_\_\_\_\_
- Validated scale.....
- Specify: \_\_\_\_\_
- Dichotomous  Continuous
- Cutoff Point: \_\_\_\_\_
- Other \_\_\_\_\_.....
- Other \_\_\_\_\_.....
- Unclear.....
- Not specified.....

**LBD2 Medication Adherence Long Form**

**RESULTS**

<b>Group</b>	<b>Rate</b>	
Overall:		<input type="checkbox"/> Adherence <input type="checkbox"/> Persistence
Arm 1:		<input type="checkbox"/> Adherence <input type="checkbox"/> Persistence
Arm 2:		<input type="checkbox"/> Adherence <input type="checkbox"/> Persistence
Arm 3:		<input type="checkbox"/> Adherence <input type="checkbox"/> Persistence
Arm 4:		<input type="checkbox"/> Adherence <input type="checkbox"/> Persistence
<b>Subgroups (specify):</b>		
		<input type="checkbox"/> Adherence <input type="checkbox"/> Persistence
		<input type="checkbox"/> Adherence <input type="checkbox"/> Persistence
		<input type="checkbox"/> Adherence <input type="checkbox"/> Persistence
		<input type="checkbox"/> Adherence <input type="checkbox"/> Persistence
		<input type="checkbox"/> Adherence <input type="checkbox"/> Persistence
		<input type="checkbox"/> Adherence <input type="checkbox"/> Persistence
		<input type="checkbox"/> Adherence <input type="checkbox"/> Persistence

**NOTES**

# **Appendix C- Evidence Tables**

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**Evidence Table C-7. Applicability Assessments**

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Papaioannou et al., 2008<sup>57</sup> Alendronate (Fosamax) Location: Canada Trial: CFOS Setting: Multicenter Jadad: 5 Age Mean/Range: 29/NR 39% Female Race: Not reported Screened: NR Eligible: 90 Enrolled: 56 Withdrawn: 9 Lost to follow-up: NR Analyzed: 56 Method of AE Assessment: Monitored, Elicited by investigator, Reported spontaneously by patient</p>	<p>Inclusion criteria: Age over 17 years, T-Score <math>\leq</math> -1.0 NOS, Confirmed cystic fibrosis  Exclusion criteria: Metabolic bone disorder other than osteoporosis, Organ transplantation, Renal insufficiency, Gastrointestinal disease, Corticoids/Glucocorticoids, Medications known to affect skeleton  Interventions: Placebo Weekly for 12 Month(s) vs. 70mg of Alendronate Weekly for 12 Month(s)  All received: Vitamin D, Calcium  No run-in or wash-out  Fracture outcomes assessed at baseline  Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures</p>	<p>Vertebral at 12 MOS: Alendronate vs Placebo: 0.0% vs 8.3% OR = 0.14 (95% CI 0.01, 2.23)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Fahrleitner-Pammer et al., 2009<sup>108</sup></p> <p>Ibandronate (Boniva)</p> <p>Location: Western Europe</p> <p>Setting: Single setting</p> <p>Jadad: 5</p> <p>Age Mean/Range: 44/NR</p> <p>100% Male</p> <p>Race: Caucasian</p> <p>Screened: 58 Eligible: 35 Enrolled: 35 Withdrawn: 3 Lost to follow-up: 0 Analyzed: 32</p> <p>Method of AE Assessment: Monitored</p>	<p>Inclusion criteria: Men, Cardiac transplant just prior to study entry</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Hyperthyroidism, Hyperparathyroidism, Hypocalcemia, Vitamin D deficiency, Renal insufficiency, Calcium includes antacids, Vitamin D use, Use of OP drugs; Liver enzymes more than 3x upper limit of normal; Prior transplant</p> <p>Interventions: Placebo every 3 Months for 1 Year(s) vs. 2mg of Ibandronate every 3 Months for 1 Year(s)</p> <p>All received: Calcium, Vitamin D, Triple immunosuppressive treatment</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline, 12 months</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Radiographic vertebral fractures</p>	<p>Vertebral - incident morphometric at 12 MOS: Ibandronate vs Placebo: 13.0% vs 53.0% OR = 0.15 (95% CI 0.04, 0.60) NNT=2.3 (95% CI 1.4-6.2)</p>

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Boonen et al., 2009<sup>76</sup> Risedronate (Actonel)  Location: US, Western Europe, Eastern Europe, Australia/New Zealand, Lebanon  Setting: Multicenter  Jadad: 3  Age Mean/Range: 61/36-84  100% Male  Race: Caucasian, Hispanic, Asian, Indian ?  Screened: 994 Eligible: NR Enrolled: 284 Withdrawn: NR Lost to follow-up: NR Analyzed: 284  Method of AE Assessment: Unclear</p>	<p>Inclusion criteria: Ambulatory, Men, Age over 29 years, T-score: Lumbar spine (LS) T-score &lt; or equal to -2.5 and Femoral neck t-score &lt; or equal to -1 or LS &lt; or equal to -1 and &lt; or equal to 2  Exclusion criteria: 20 OP (exc. Due to 10 hypogonadism with no Testosterone treatment); &gt; 1 OP fracture at screening or 1 within 6 months before screening; increased fracture risk  Interventions: Placebo Weekly for 24 Month(s) vs. 35mg of Risedronate Weekly for 24 Month(s)  All received: Calcium, Vitamin D  No run-in or wash-out  Fracture outcomes assessed at baseline, 24 months  Outcomes: Bone mineral density by DXA - Spine, Vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures, All cause mortality, BALP, BMD femoral trochanter, BMD proximal femur</p>	<p>Vertebral at 2 YRS: Risedronate 35mg/wk vs Placebo: 0.0% vs 0.0% OR = 4.45 (95% CI 0.23, 85.68)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Delmas et al., 2008<sup>87</sup> Risedronate (Actonel)</p> <p>Location: US, Canada, South America, UK, Western Europe, Eastern Europe</p> <p>Setting: Multicenter</p> <p>Jadad: 1</p> <p>Age Mean/Range: 65/NR</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: 3,027 Eligible: NR Enrolled: 1,231 Withdrawn: 183 Lost to follow-up: 2 Analyzed: 1,046</p> <p>Method of AE Assessment: Monitored, Elicited by investigator, Assessed and recorded</p>	<p>Inclusion criteria: Ambulatory, Post-menopausal women &gt;5 years, Age over 49 years, T-Score <math>\leq</math> -2.5 Spine &amp; T-score &lt; 2 (lumbar spine) + 1 prevalent fracture</p> <p>Exclusion criteria: Any bone-active drugs within 3 months of 1st dose of study drug; drug or alcohol abuse; BMI &gt; 32</p> <p>Interventions: 5mg of Risedronate Daily for 1 Year(s) vs. 75mg of Risedronate 2 consecutive days/mo for 1 Year(s)</p> <p>All received: Calcium, Vitamin D</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at 12 months</p> <p>Outcomes: Bone mineral density by DXA - Spine, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BMD proximal femur</p>	<p>Vertebral at 12 MOS: Risedronate 75mg 2CDM vs Risedronate 5mg/day: 1.1% vs 1.3% OR = 0.85 (95% CI 0.29, 2.54)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Delmas et al., 2008<sup>88</sup> Risedronate (Actonel)</p> <p>Location: US, Canada, South America, Western Europe, Eastern Europe, Australia/New Zealand, Lebanon</p> <p>Setting: Multicenter</p> <p>Jadad: 2</p> <p>Age Mean/Range: 65/NR</p> <p>100% Female</p> <p>Race: Caucasian, African Ancestry, Hispanic, Other</p> <p>Screened: 2,221 Eligible: NR Enrolled: 1,294 Withdrawn: 198 Lost to follow-up: NR Analyzed: 1,292</p> <p>Method of AE Assessment: Monitored, Reported spontaneously by patient</p>	<p>Inclusion criteria: Ambulatory, Post-menopausal women &gt;5 years, Age over 49 years, T-Score <math>\leq</math> -2.5 Spine, Good general health; at least 3 evaluable lumbar vertebral bodies</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Hyperthyroidism (uncorrected), Hyperparathyroidism, Hypocalcemia, Hypercalcemia, LS spine abnormalities prohibiting DXA, Renal insufficiency, Bisphosphonates, Calcitonin, Fluoride, Menopausal hormonal therapy, Estrogen agonists including estrogen, SERMS, Anabolic steroids, Previous PTH use, Corticoids/Glucocorticoids, Any condition that could prevent drug completion; Drug/alcohol abuse; Bilateral hip prostheses; BMI &gt; 32.5; Strontium use; Allergy to BPs; Abnormal clinical labs; Osteomalacia; lumbar spine T-score &lt; -5.0</p> <p>Interventions: 5mg of Risedronate Daily for 1 Year(s) vs. 150mg of Risedronate Monthly for 1 Year(s)</p> <p>All received: Calcium, Vitamin D</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes: Bone mineral density by DXA - Spine, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, BMD proximal femur, Bone Turnover</p>	<p>Vertebral at 12 MOS: Risedronate 150mg CMD vs Risedronate 5mg/day: 1.2% vs 1.2% OR = 0.99 (95% CI 0.37, 2.65)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Palomba et al., 2008<sup>77</sup> Risedronate (Actonel)</p> <p>Location: Western Europe Setting: Multicenter Jadad: 3 Age Mean/Range: 52/NR 100% Female Race: Not reported Screened: NR Eligible: NR Enrolled: 90 Withdrawn: NR Lost to follow-up: 9 Analyzed: 81 Method of AE Assessment: Monitored, Reported spontaneously by patient</p>	<p>Inclusion criteria: Post-menopausal women NOS, T-Score <math>\leq</math> -2.5 Spine, Inflammatory bowel disease in remission for = 6 mos.</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Endocrine disease (not diabetes) NOS, Hyperparathyroidism, Hypoparathyroidism, Hypocalcemia, Hypercalcemia, Vitamin D deficiency, Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Gastrointestinal disease, Bisphosphonates, Calcitonin, Fluoride, H2-blockers, Androgen, Menopausal hormonal therapy, Estrogen agonists including estrogen, Progestin, SERMS, Anabolic steroids, Testosterone, Proton pump inhibitors, Corticoids/Glucocorticoids, Medications known to affect skeleton, Metabolic disorders; treatment with Thiazide diuretics; Hyper- or hypophosphatemia; BMI &lt; 18 or &gt; 30; Smoking &gt; 10 cigarettes/d, drinking &gt; 3 alcoholic beverages/d, major med cond., vitamin D def.; needs that caused gastric irritation</p> <p>Interventions: Placebo vs. 35mg of Risedronate Weekly for 3 Year(s)</p> <p>All received: Calcium, Vitamin D</p> <p>Wash-out only</p> <p>Fracture outcomes assessed at baseline, 2 years, 3 years</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures, All cause mortality, Bone Turnover</p>	<p>Non-vertebral at 2 YRS: Risedronate vs Placebo: 2.5% vs 9.8% OR = 0.20 (95% CI 0.05, 0.85) NNT=6.9 (95% CI 4.8-48.1)</p> <p>Vertebral at 2 YRS: Risedronate vs Placebo: 10.0% vs 17.1% OR = 0.55 (95% CI 0.16, 1.95)</p> <p>Non-vertebral at 3 YRS: Risedronate vs Placebo: 2.5% vs 17.1% OR = 0.29 (95% CI 0.05, 1.75)</p> <p>Vertebral at 3 YRS: Risedronate vs Placebo: 7.5% vs 22.0% OR = 0.32 (95% CI 0.10, 1.09)</p>

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Ringe et al., 2009<sup>75</sup> Risedronate (Actonel)  Location: Western Europe Setting: Single setting  Jadad: 1  Age Mean/Range: 57/NR  100% Male  Race: Caucasian  Screened: 580 Eligible: NR Enrolled: 316 Withdrawn: 16 Lost to follow-up: 0 Analyzed: 300  Method of AE Assessment: Unclear</p>	<p>Inclusion criteria: Men, T-Score <math>\leq</math> -2.0 Hip, T-Score <math>\leq</math> -2.5 Spine, Osteoporosis score based on T-score and/or fractures and/or radiography  Exclusion criteria: Hypocalcemia, Bisphosphonates, Fluoride, Hypersensitivity to bisphosphonates  Interventions: Placebo Daily for 2 Year(s) + 500 or 800mg of Calcium Daily for 2 Year(s) + 1<math>\mu</math>g of Alfacalcidol Daily for 2 Year(s) or 1000I.U. of Vitamin D Daily for 2 Year(s) vs. 5mg of Risedronate Daily for 2 Year(s) + 1000mg of Calcium Daily for 2 Year(s) + 800I.U. of Vitamin D Daily for 2 Year(s) vs. 5mg of Risedronate Daily for 2 Year(s) + 1000mg of Calcium Daily for 2 Year(s) + 800I.U. of Vitamin D Daily for 2 Year(s)  No run-in or wash-out  Fracture outcomes assessed at baseline, 2 years  Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, BMD femoral trochanter, BMD femoral neck, Back pain, Change in height</p>	<p>Non-vertebral - in ref 12 at 12 MOS: Risedronate vs Placebo: 6.3% vs 10.8% OR = 0.57 (95% CI 0.26, 1.25)  Non-vertebral at 24 MOS: Risedronate vs Placebo: 11.8% vs 22.3% OR = 0.48 (95% CI 0.26, 0.87) NNT=9.6 (95% CI 5.3-49.8)</p>

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Chapman et al., 2009<sup>116</sup> Zoledronic acid (Zometa)</p> <p>Location: Australia/New Zealand</p> <p>Setting: Multicenter</p> <p>Jadad: 2</p> <p>Age Mean/Range: NR</p> <p>23% Female</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Enrolled: 22 Withdrawn: NR Lost to follow-up: NR Analyzed: 22</p> <p>Method of AE Assessment: Monitored, Elicited by investigator, Reported spontaneously by patient</p>	<p>Inclusion criteria: Men, Women otherwise undefined, Age over 17 years, T-Score <math>\leq</math> -2.0 Hip, T-Score <math>\leq</math> -2.0 Spine, Cystic fibrosis</p> <p>Exclusion criteria: Pregnancy, Hyperthyroidism, Hyperparathyroidism, Hypocalcemia, Hepatic insufficiency, Renal insufficiency, Bisphosphonates, Pre-existing fragility factors, on waiting list for lung transplant, hypogonadism, considered not being able to complete study</p> <p>Interventions: Placebo every 3 months for 21 Month(s) vs. 4-2mg of Zoledronic acid every 3 months for 21 Month(s)</p> <p>All received: Calcium, Vitamin D</p> <p>Run-in/wash-out unclear</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Radiographic vertebral fractures, All cause mortality, DXA distal forearm</p>	<p>Non-vertebral at 24 MOS: Zoledronic acid (IV) vs Placebo: 0.0% vs 0.0% OR = NC</p> <p>Vertebral at 24 MOS: Zoledronic acid (IV) vs Placebo: 0.0% vs 0.0% OR = NC</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Lyles et al., 2007<sup>115</sup></p> <p>Zoledronic acid (Zometa)</p> <p>Location: US, Canada, South America, Western Europe, Eastern Europe</p> <p>Setting: Multicenter</p> <p>Jadad: 5</p> <p>Age Mean/Range: 75/NR</p> <p>76% Female</p> <p>Race: Caucasian, African Ancestry, Hispanic, Other</p> <p>Screened: 2,664 Eligible: 2,127 Enrolled: 2,127 Withdrawn: 302 Lost to follow-up: 63 Analyzed: 2,127</p> <p>Method of AE Assessment: Unclear</p>	<p>Inclusion criteria: Ambulatory, Age over 50 years, Hip fracture repair within previous 90 days; Inability or unwillingness to take an Oral BP</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Metabolic bone disorder other than osteoporosis, Bisphosphonates without washout, Fluoride, Previous PTH use without washout, Strontium use; Sensitivity to BP; Potential to become pregnant; Creatinine clearance &lt; 30 ml/min; Serum Ca &gt; 11mg/dL or &lt; 8mg/dL; Life expectancy &lt; 6 months; Dementia without surrogate consent</p> <p>Interventions: Placebo Yearly for 1.9 Years (median) vs. 5mg of Zoledronic acid Yearly for 1.9 Years (median)</p> <p>All received: Calcium, Vitamin D</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes: Bone mineral density by DXA - Hip, Hip fracture, Non-vertebral fracture, Total fractures, Radiographic vertebral fractures</p>	<p>Any fracture at 24 MOS: Zoledronic acid 5 mg vs Placebo: 8.6% vs 13.9% OR = 0.63 (95% CI 0.48, 0.83) NNT=22.5 (95% CI 14.1-55.2)</p> <p>Hip fracture at 24 MOS: Zoledronic acid 5 mg vs Placebo: 2.0% vs 3.5% OR = 0.69 (95% CI 0.41, 1.17)</p> <p>Non-vertebral at 24 MOS: Zoledronic acid 5 mg vs Placebo: 7.6% vs 10.7% OR = 0.72 (95% CI 0.53, 0.97) NNT=37.6 (95% CI 19.8-386.6)</p> <p>Vertebral at 24 MOS: Zoledronic acid 5 mg vs Placebo: 1.7% vs 3.8% OR = 0.54 (95% CI 0.32, 0.90) NNT=58.8 (95% CI 32.2-339.6)</p>

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Saag et al., 2009<sup>223</sup></p> <p>Alendronate (Fosamax), PTH (Teriparatide) (Forteo)</p> <p>Location: Not reported</p> <p>Setting: Multicenter</p> <p>Jadad: 2</p> <p>Age Mean/Range: 57/NR</p> <p>81% Female</p> <p>Race: Caucasian</p> <p>Screened: 417 Eligible: 429 Enrolled: 428 Withdrawn: 170 Lost to follow-up: 17 Analyzed: 428</p> <p>Method of AE Assessment: Monitored, Reported spontaneously by patient</p>	<p><b>Inclusion criteria:</b> Ambulatory, Men, Women otherwise undefined, Age over 20 years, T-Score <math>\leq</math> -2.0 Hip, T-Score <math>\leq</math> -2.0 Spine, Corticosteroid use</p> <p><b>Exclusion criteria:</b> Carcinoma or suspected carcinoma, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Gastrointestinal disease, Bisphosphonates, Fewer than 3 lumbar vertebrae that could be evaluated, abnormal laboratory values</p> <p><b>Interventions:</b> 10mg of Alendronate Daily for 36 Month(s) + Placebo vs. 20<math>\mu</math>g of PTH (teriparatide) Daily for 36 Month(s) + Placebo</p> <p><b>All received:</b> Calcium, Vitamin D</p> <p><b>No run-in or wash-out</b></p> <p><b>Fracture outcomes assessed at baseline, 36 months</b></p> <p><b>Outcomes:</b> Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, CTX, PINP</p>	<p><b>Non-vertebral at 36 MOS:</b> Alendronate 10mg/day vs Teriparatide 20<math>\mu</math>g/day: 7.0% vs 7.5% OR = 0.93 (95% CI 0.45, 1.94)</p> <p><b>Vertebral at 36 MOS:</b> Alendronate 10mg/day vs Teriparatide 20<math>\mu</math>g/day: 7.7% vs 1.7% OR = 3.79 (95% CI 1.39, 10.32)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Okada et al., 2008<sup>224</sup>                      Alendronate (Fosamax),                      Vitamin D                      Location: Japan                      Setting: Single setting                      Jadad: 1                      Age                      Mean/Range: 34/17-47                      100% Female                      Race: Asian                      Screened: NR                      Eligible: 47                      Enrolled: 47                      Withdrawn: 14                      Lost to follow-up: NR                      Analyzed: 33                      Method of AE                      Assessment:                      Monitored</p>	<p>Inclusion criteria:                      Pre-menopausal women, Age under 48 years, Age over 16 years, Autoimmune disease</p> <p>Exclusion criteria:                      Metabolic bone disorder other than osteoporosis, Renal insufficiency,                      Corticoids/Glucocorticoids, Medications known to affect skeleton, Pregnancy,                      Lactation</p> <p>Interventions:                      1µg of Vitamin D Daily for 18 Month(s)                      vs.                      1µg of Vitamin D Daily for 18 Month(s) + 5mg of Alendronate Daily for 18 Month(s)</p> <p>All received:                      Prednisolone, Calcium</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline, 12 months, 18 months</p> <p>Outcomes:                      Bone mineral density by DXA - Spine, Vertebral fracture, Radiographic vertebral fractures</p>	<p>Vertebral at 18 MOS:                      Alfacalcidol + prednisolone + alendronate vs Alfacalcidol + prednisolone: 0.0% vs 25.0%                      OR = 0.10 (95% CI 0.01, 0.81) NNT=4.0 (95% CI 2.2-26.4)</p>

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Ringe et al., 2007<sup>58</sup></p> <p>Alendronate (Fosamax), Vitamin D</p> <p>Location: Not reported</p> <p>Trial: AAC TRIAE</p> <p>Setting: Single setting</p> <p>Jadad: 0</p> <p>Age Mean/Range: 66/NR</p> <p>63% Female</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Enrolled: 90</p> <p>Withdrawn: NR</p> <p>Lost to follow-up: NR</p> <p>Analyzed: 90</p> <p>Method of AE Assessment: Monitored, Reported spontaneously by patient</p>	<p>Inclusion criteria: Men, Post-menopausal women NOS, Osteoporosis NOS, T-Score <math>\leq</math> -2.5 Hip, Clinical fractures, radiographic conf. unclear, T-score spine <math>&lt;</math> -3.0</p> <p>Exclusion criteria: Bisphosphonates, Fluoride, Previous PTH use, Secondary osteoporosis</p> <p>Interventions: 1<math>\mu</math>g of Alfacalcidol Daily for 24 Month(s) + 500mg of Calcium Daily for 24 Month(s) vs. 70mg of Alendronate Weekly for 24 Month(s) + 1000mg of Calcium Weekly for 24 Month(s) + 1000I.U. of Alfacalcidol Daily for 24 Month(s) vs. 1<math>\mu</math>g of Alfacalcidol Daily for 24 Month(s) + 70mg of Alendronate Weekly for 24 Month(s) + 500mg of Calcium Weekly for 24 Month(s)</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline, 24 months</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Total fractures, Radiographic vertebral fractures, All cause mortality, Falls</p>	<p>Non-vertebral at 24 MOS: Alendronate + calcium + vitamin d vs Alfacalcidol + calcium: 20.0% vs 13.3% OR = 1.60 (95% CI 0.42, 6.16)</p> <p>Vertebral at 24 MOS: Alendronate + calcium + vitamin d vs Alfacalcidol + calcium: 13.3% vs 16.7% OR = 0.77 (95% CI 0.19, 3.15)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>de Nijs et al., 2006<sup>59</sup> Alendronate (Fosamax), Vitamin D Location: Western Europe Trial: STOP Setting: Multicenter Jadad: 5 Age Mean/Range: 61/NR 62% Female Race: Caucasian, African Ancestry, Other Screened: 210 Eligible: 201 Enrolled: 201 Withdrawn: 38 Lost to follow-up: NR Analyzed: 163 Method of AE Assessment: Monitored</p>	<p>Inclusion criteria: Men, Women otherwise undefined, Age under 91 years, Age over 17 years, Corticosteroid use, Rheumatic disease  Exclusion criteria: Hypothyroidism, Hyperthyroidism, Hyperparathyroidism, Hypocalcemia, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Nephrolithiasis, Bisphosphonates, Calcitonin, Fluoride, Hormone use NOS, Androgen, Testosterone, Vitamin D use, Corticoids/Glucocorticoids, Glucocorticoids &gt; 12 weeks; pregnant; breast feeding; hypercalciuria  Interventions: 10mg of Alendronate Daily for 18 Month(s) + Placebo Daily for 18 Month(s) vs. 1µg of Alfacalcidol Daily for 18 Month(s) + Placebo Daily for 18 Month(s)  All received: Calcium, Vitamin D  No run-in or wash-out  Fracture outcomes assessed at baseline  Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures</p>	<p>Non-vertebral at 18 MOS: Alendronate vs Alfacalcidol: 2.0% vs 3.0% OR = 0.68 (95% CI 0.12, 3.99)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Campbell et al., 2009<sup>230</sup></p> <p>Estrogen, Etidronate (Didronel)</p> <p>Location: UK</p> <p>Setting: Multicenter</p> <p>Jadad: 3</p> <p>Age Mean/Range: NR/NR</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: 47 Enrolled: 50 Withdrawn: 3 Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE Assessment: NR</p>	<p>Inclusion criteria: Ambulatory, Post-menopausal women NOS, Age under 60 years, Osteoporosis NOS, Corticosteroid use, Asthmatics</p> <p>Exclusion criteria: Not Reported</p> <p>Interventions: Control vs. 2mg of Estrogen Daily for 5 Year(s) + 0.625mg of Estrogen Daily for 5 Year(s) + 50µg of Estrogen patch for 5 Year(s) vs. 400mg of Etidronate Daily for 5 years for 2 weeks every 3 months Year(s) vs. 400mg of Etidronate Daily for 5 years for 2 weeks every 3 months Year(s) + 50µg of Estrogen patch for 5 Year(s) + 2mg of Estrogen Daily for 5 Year(s) + 0.625mg of Estrogen Daily for 5 Year(s)</p> <p>Run-in/wash-out unclear</p> <p>Fracture outcomes assessed at baseline, 2 years, 3 years, 4 years, 5 years</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures</p>	<p>Vertebral &amp; nonvertebral at 5 YRS: Etidronate vs No etidronate: 4.0% vs 8.0% OR = 0.48 (95% CI 0.05, 4.82)</p> <p>Vertebral &amp; nonvertebral- MHT at 5 YRS: Menopausal hormone therapy vs No menopausal hormone therapy: 0.0% vs 13.0% OR = 0.13 (95% CI 0.01, 1.31)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Sato et al., 2007<sup>74</sup></p> <p>Vitamin D, Risedronate (Actonel)</p> <p>Location: Japan</p> <p>Setting: Single setting</p> <p>Jadad: 5</p> <p>Age Mean/Range: 71/NR</p> <p>100% Male</p> <p>Race: Japanese</p> <p>Screened: NR Eligible: 279 Enrolled: 242 Withdrawn: 19 Lost to follow-up: NR Analyzed: 223</p> <p>Method of AE Assessment: Monitored, Elicited by investigator</p>	<p>Inclusion criteria: Men, Age over 64 years, Parkinson disease</p> <p>Exclusion criteria: Cardiovascular disease, Hypothyroidism, Hyperthyroidism, Hyperparathyroidism, Hepatic insufficiency, Renal insufficiency, Bisphosphonates, Calcitonin, Calcium includes antacids, Estrogen agonists including estrogen, Vitamin D use, Corticoids/Glucocorticoids, Parkinson disease at stage 5 of Hoehn and Yahr stage; Vitamin K intake; History of non-vertebral fracture, secondary osteoporosis.</p> <p>Interventions: Placebo Daily for 2 Year(s) vs. 2.5mg of Risedronate Daily for 2 Year(s)</p> <p>All received: Vitamin D</p> <p>Run-in/wash-out unclear</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes: Hip fracture, All cause mortality, BMD of metacarpal</p>	<p>Hip at 2 YRS: Risedronate vs Placebo: 2.5% vs 7.4% OR = 0.35 (95% CI 0.11, 1.12)</p>

Evidence Table C-1. Randomized Controlled Trials  
SERMs

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Cummings et al., 2010<sup>408</sup></p> <p>Lasofloxifene</p> <p>Location: 32 countries</p> <p>Trial: PEARL</p> <p>Setting: Multicenter</p> <p>Jadad: 1</p> <p>Age Mean/Range: 67/67-73</p> <p>100% Female</p> <p>Race: Caucasian, Asian, Other</p> <p>Screened: NR Eligible: NR Enrolled: 8,556 Withdrawn: 1,264 Lost to follow-up: NR Analyzed: 8,556</p> <p>Method of AE Assessment: Monitored</p>	<p>Inclusion criteria: Post-menopausal women NOS, Age under 81 years, Age over 59 years, T-Score <math>\leq</math> -2.5 Hip, T-Score <math>\leq</math> -2.5 Spine, Good or excellent health; mammogram within 6 month; no evidence of breast cancer</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Cardiovascular disease, Metabolic bone disorder other than osteoporosis, Venous thromboembolic disease, Active venous thromboembolic disease, Bisphosphonates, Fluoride, Estrogen agonists including estrogen, SERMs, Previous PTH use, Corticoids/Glucocorticoids, Stroke; <math>t &lt; -4.5</math>; Vertebral Fracture past 12 months; <math>&gt; 3</math> vertebral fracture on x-ray; raloxifene treatment; endometrial hyperplasia; tibolone treatment; unexplained bleeding (vaginal)</p> <p>Interventions: Placebo for 5 Year(s) vs. 0.25mg of Lasofloxifene Daily for 5 Year(s) vs. 0.5mg of Lasofloxifene Daily for 5 Year(s)</p> <p>All received: Calcium, Vitamin D</p> <p>Run-in only</p> <p>Fracture outcomes assessed at baseline, 24 months, 36 months, 60 months</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Hip fracture, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, BMD femoral trochanter, BMD femoral neck, BMD proximal femur, BMD-DXA Forearm, BMD-DXA Whole body, Breast Cancer, CVA, Cardiac events, Fatal CVA, PE, Venous thromembolic events</p>	<p>Hip fracture at 5 YRS: Lasofloxifene .25mg vs Placebo: 1.1% vs 1.2% OR = 0.88 (95% CI 0.54, 1.44) Lasofloxifene .5mg vs Placebo: 0.9% vs 1.2% OR = 0.77 (95% CI 0.47, 1.27)</p> <p>Non-vertebral at 5 YRS: Lasofloxifene .25mg vs Placebo: 9.4% vs 10.4% OR = 0.90 (95% CI 0.76, 1.07) Lasofloxifene .5mg vs Placebo: 8.1% vs 10.4% OR = 0.76 (95% CI 0.63, 0.91) NNT=43.2 (95% CI 26.2-122.9)</p> <p>Vertebral at 5 YRS: Lasofloxifene .25mg vs Placebo: 6.9% vs 9.5% OR = 0.71 (95% CI 0.58, 0.86) NNT=37.9 (95% CI 24.5-84.6) Lasofloxifene .5mg vs Placebo: 5.7% vs 9.5% OR = 0.58 (95% CI 0.47, 0.70) NNT=25.8 (95% CI 19.0-40.5)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
SERMs

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Ensrud et al., 2008<sup>122</sup> Raloxifene (Evista)</p> <p>Location: US, Canada, South America, UK, Western Europe, Eastern Europe, Asia, South Africa and Israel</p> <p>Setting: Multicenter</p> <p>Jadad: 4</p> <p>Age Mean/Range: 68/NR</p> <p>100% Female</p> <p>Race: Caucasian, African Ancestry, Hispanic, Asian</p> <p>Screened: 11,767 Eligible: 10,356 Enrolled: 10,101 Withdrawn: 2,062 Lost to follow-up: NR Analyzed: 10,101</p> <p>Method of AE Assessment: Monitored, Elicited by investigator, Reported spontaneously by patient</p>	<p>Inclusion criteria: Ambulatory, Post-menopausal women &gt;1 year, Age over 54 years, Coronary Heart Disease (CHD) or increase risk for CHD (based on list of criteria and score)</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Hepatic insufficiency, Renal insufficiency, Androgen, Menopausal hormonal therapy, Estrogen agonists including estrogen, Progestin, SERMS, Estrogen agonists, Anabolic steroids, Testosterone, MI within past 3 mos; NYHA class III or IV heart failure; Severe postmenopausal symptoms (reg. # RT); Current/recent participation in a clinical trial; CABG or perc. Graft within 3 mos.; Life expectancy &lt; 5 years; Unexplained uterine bleeding within past 6 mos.; History of DVT, pulmonary embolism; Jaundice; Poor med/psych risk for treatment with investigational drug</p> <p>Interventions: Placebo for 5.6 Year(s) vs. 60mg of Raloxifene Daily for 5.6 Year(s)</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessment time variable</p> <p>Outcomes: Hip fracture, Vertebral fracture, Non-vertebral fracture, Symptomatic vertebral fractures, All cause mortality, Wrist fracture</p>	<p>Hip/femur fracture at 5.6 YRS: Raloxifene 60mg/day vs Placebo: 1.8% vs 2.0% OR = 0.86 (95% CI 0.65, 1.15)</p> <p>Non-vertebral at 5.6 YRS: Raloxifene 60mg/day vs Placebo: 8.5% vs 8.7% OR = 0.99 (95% CI 0.86, 1.13)</p> <p>Vertebral at 5.6 YRS: Raloxifene 60mg/day vs Placebo: 1.3% vs 1.9% OR = 0.66 (95% CI 0.48, 0.90) NNT=154.0 (95% CI 87.9-620.7)</p> <p>Wrist at 5.6 YRS: Raloxifene 60mg/day vs Placebo: 2.1% vs 2.2% OR = 0.97 (95% CI 0.74, 1.26)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
SERMs

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Ishani et al., 2008<sup>252</sup></p> <p>Raloxifene (Evista)</p> <p>Location: US, Canada, South America, UK, Western Europe, Eastern Europe, Asia, Israel</p> <p>Setting: Multicenter</p> <p>Jadad: 2</p> <p>Age Mean/Range: 67/31-80</p> <p>100% Female</p> <p>Race: Caucasian</p> <p>Screened: 22,379 Eligible: NR Enrolled: 7,705 Withdrawn: 877 Lost to follow-up: 389 Analyzed: 7,705</p> <p>Method of AE Assessment: Monitored, Elicited by investigator, Reported spontaneously by patient, Reported in original report</p>	<p><b>Inclusion criteria:</b> Ambulatory, Post-menopausal women &gt;2 years, Osteoporosis score based on T-score and/or fractures and/or radiography, Femoral neck or lumbar spine BMD T-score = - 2.5 or low BMD and = 1 moderate or severe vertebral fracture or = 2 mild fracture or = 2 moderate fracture</p> <p><b>Exclusion criteria:</b> Carcinoma or suspected carcinoma, Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Malabsorption syndrome, Women were excluded if they had experienced bone disease other than osteoporosis, substantial postmenopausal symptoms or abnormal uterine bleeding, taken an androgen calcitonin, or bisphosphonate within the previous 2 months; been receiving fluoride therapy for more than 3 months during the previous 2 years; undergone systemic glucocorticoid therapy for more than 1 month within the past year; taken antiepileptic drugs or pharmacologic doses of cholecalciferol; had a history of thromboembolic disorders within the last 10 years (except in association with an injury); experienced endocrine disorders requiring therapy (except in association with an injury); experienced endocrine disorders requiring therapy (except for type 2 diabetes or hypothyroidism); had serum creatine levels above 225nmol/L (2.5 mg/dL); had active renal lithiasis, abnormal hepatic function, or untreated malabsorption; or consumed more than 4 alcoholic drinks per day. In addition, we excluded women with pathologic fractures, those from whom satisfactory thoracic and lumbar radiographs could not be obtained, and those with fewer than 2 lumbar and 4 thoracic vertebrae that were evaluable.</p> <p><b>Interventions:</b> Placebo Daily for 3 Year(s) vs. 60mg of Raloxifene Daily for 3 Year(s) vs. 120mg of Raloxifene Daily for 3 Year(s)</p> <p><b>All received:</b> Calcium, Vitamin D</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline, 24 months, 36</p> <p><b>Outcomes:</b> Bone mineral density by DXA - Spine, Hip fracture, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, BMD femoral neck, Bone Turnover</p>	<p>Number of people with fracture not reported for every arm</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
SERMs

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Silverman et al., 2008<sup>123</sup></p> <p>Raloxifene (Evista), Bazedoxifene</p> <p>Location: US, Canada, South America, Western Europe, Eastern Europe, Australia/New Zealand, Asia, South Africa</p> <p>Setting: Multicenter</p> <p>Jadad: 3</p> <p>Age Mean/Range: 66/NR</p> <p>100% Female</p> <p>Race: Caucasian, Other</p> <p>Screened: 26,749 Eligible: NR Enrolled: 7,492 Withdrawn: 2,501 Lost to follow-up: NR Analyzed: 7,492</p> <p>Method of AE Assessment: Monitored, Elicited by investigator, Reported spontaneously by patient</p>	<p>Inclusion criteria: Ambulatory, Post-menopausal women &gt;2 years, Age under 86 years, Age over 54 years, Osteoporosis score based on T-score and/or fractures and/or radiography, Healthy (Tscore -2.5 - -4); Low BMD or radiographically confirmed vertebral fracture and BMD = -4.0</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Metabolic bone disorder other than osteoporosis, Bisphosphonates, Calcitonin, Androgen, Estrogen agonists including estrogen, Progestin, SERMs, Previous PTH use, Vitamin D use, Conditions interfering w/DXA, pathological vertebral fracture; Vasomotor symptoms req. treatment; serious conditions e.g. endometrial hyperplasia; cancer within 10 years of study; endocrine disorders requiring treatment; untreated malabsorption disorders; DVT (active or History); pulmonary embolism; retinal vein thrombosis; elevated fasting cholesterol or triglycerides '</p> <p>Interventions: Placebo for 3 Year(s) vs. 60mg of Raloxifene Daily for 3 Year(s) vs. 20mg of Bazedoxifene Daily for 3 Year(s) vs. 40mg of Bazedoxifene Daily for 3 Year(s)</p> <p>All received: Calcium, Vitamin D</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline, 12 months, 24 months, 36 months</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, BMD femoral trochanter, BMD femoral neck, CTX, Osteocalcin</p>	<p>Non-vertebral at 3 YRS: Bazedoxifene 20mg vs Placebo: 5.7% vs 6.3% OR = 0.89 (95% CI 0.67, 1.20) Bazedoxifene 40mg vs Placebo: 5.6% vs 6.3% OR = 0.86 (95% CI 0.64, 1.15) Raloxifene 60mg/day vs Placebo: 5.9% vs 6.3% OR = 0.61 (95% CI 0.44, 0.84) NNT=49.8 (95% CI 30.3-139.6)</p> <p>Vertebral at 3 YRS: Bazedoxifene 20mg vs Placebo: 2.3% vs 4.1% OR = 0.56 (95% CI 0.39, 0.80) NNT=55.4 (95% CI 34.2-145.8) Bazedoxifene 40mg vs Placebo: 2.5% vs 4.1% OR = 0.61 (95% CI 0.43, 0.87) NNT=63.5 (95% CI 36.8-230.6) Raloxifene 60mg/day vs Placebo: 2.3% vs 4.1% OR = 0.57 (95% CI 0.39, 0.82) NNT=56.8 (95% CI 34.6-158.2)</p> <p>Vertebral - w/ prevalent fracture at 3 YRS: Bazedoxifene 20mg - w/ prevalent fracture vs Placebo - w/ prevalent fracture: 2.6% vs 4.8% OR = 0.54 (95% CI 0.39, 0.76) NNT=45.9 (95% CI 29.6-102.5) Bazedoxifene 40mg - w/ prevalent fracture vs Placebo - w/ prevalent fracture: 2.8% vs 4.8% OR = 0.58 (95% CI 0.41, 0.81) NNT=50.1 (95% CI 31.1-128.2) Raloxifene 60mg/day - w/ prevalent fracture vs Placebo - w/ prevalent fracture: 2.7% vs 4.8% OR = 0.56 (95% CI 0.40, 0.79) NNT=48.3 (95% CI 30.4-116.7)</p> <p>Vertebral - w/out prevalent fracture at 3 YRS: Bazedoxifene 20mg - w/out prevalent fracture vs Placebo - w/out prevalent fracture: 2.0% vs 3.1% OR = 0.65 (95% CI 0.43, 0.98) NNT=94.2 (95% CI 48.4-1750) Bazedoxifene 40mg - w/out prevalent fracture vs Placebo - w/out prevalent fracture: 2.1% vs 3.1% OR = 0.67 (95% CI 0.45, 1.01) Raloxifene 60mg/day - w/out prevalent fracture vs Placebo - w/out prevalent fracture: 1.8% vs 3.1% OR = 0.58 (95% CI 0.38, 0.88) NNT=77.4 (95% CI 43.9-326.5)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Parathyroid hormone

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Fogelman et al., 2008<sup>134</sup> PTH1-84 (Preos)</p> <p>Location: UK, Western Europe, Eastern Europe</p> <p>Trial: POWER</p> <p>Setting: Multicenter</p> <p>Jadad: 2</p> <p>Age Mean/Range: 59/NR</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: 532 Eligible: 187 Enrolled: 180 Withdrawn: 7 Lost to follow-up: 56 Analyzed: 180</p> <p>Method of AE Assessment: Monitored, Reported spontaneously by patient</p>	<p>Inclusion criteria: Age over 44 years, T-Score <math>\leq</math> -2.0 Hip, T-Score <math>\leq</math> -2.0 Spine, Menopausal hormone therapy, If 45-54 years of age, menopausal for at least 1 year, Able to administer PTH</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Hyperparathyroidism, Hypoparathyroidism, Hypercalcemia, Metabolic bone disorder other than osteoporosis, LS spine abnormalities prohibiting DXA, Renal insufficiency, Nephrolithiasis, Urolithiasis, weight &lt; 40kg</p> <p>Interventions: Placebo Daily for 18 Month(s) vs. 100<math>\mu</math>g of PTH (1-84) Daily for 18 Month(s)</p> <p>All received: Calcium, Vitamin D, Estrogen. Everyone continued their menopausal hormone therapy.</p> <p>Run-in only</p> <p>Fracture outcomes assessed at baseline, 24 months</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Total fractures, All cause mortality, DXA radius</p>	<p>Non-vertebral at 24 MOS: PTH 100mug vs Placebo: 3.3% vs 2.2% OR = 1.51 (95% CI 0.26, 8.86)</p> <p>Vertebral at 24 MOS: PTH 100mug vs Placebo: 0.0% vs 1.1% OR = 0.14 (95% CI 0.00, 6.82)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Parathyroid hormone

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Greenspan et al., 2007<sup>135</sup> PTH1-84 (Preos)</p> <p>Location: US, Canada, South America, Eastern Europe, Israel</p> <p>Trial: TOP</p> <p>Setting: Multicenter</p> <p>Jadad: 5</p> <p>Age Mean/Range: 65/57-73</p> <p>100% Female</p> <p>Race: Caucasian, African Ancestry, Hispanic, Asian, Native American, Hawaiian, Indian, Filipino, Greek</p> <p>Screened: 10,749 Eligible: 2,679 Enrolled: 2,532 Withdrawn: 831 Lost to follow-up: NR Analyzed: 2,532</p> <p>Method of AE Assessment: Elicited by investigator, Reported spontaneously by patient</p>	<p>Inclusion criteria: Postmenopausal women, age over 44, age under 55, T-score&lt;-3.0 with no prevalent fracture or T-score&lt;-2.5 with 1-4 vertebral fractures, OR postmenopausal women age &gt;55, T-score&lt;-2.5 and no vertebral fractures or T-score =-2.0 and 1-4 vertebral fractures</p> <p>Exclusion criteria: Hypercalcemia, Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Nephrolithiasis, Bisphosphonates, Fluoride, Previous PTH use, Medications known to affect skeleton, Estrogen therapy within 4 weeks; strontium use.</p> <p>Interventions: Placebo Daily for 18 Month(s) vs. 100µg of PTH (teriparatide) Daily for 18 Month(s)</p> <p>All received: Calcium, Vitamin D</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures, All cause mortality, BALP, BMD-DXA Forearm, BMD-DXA Whole body</p>	<p>Non-vertebral at 18 MOS: PTH vs Placebo: 5.6% vs 5.8% OR = 0.97 (95% CI 0.69, 1.35)</p> <p>Vertebral - w/ bl fracture at 18 MOS: PTH vs Placebo: 4.2% vs 8.9% OR = 0.47 (95% CI 0.23, 0.97) NNT=21.3 (95% CI 10.9-421.7)</p> <p>Vertebral - w/out bl fracture at 18 MOS: PTH vs Placebo: 0.7% vs 2.1% OR = 0.35 (95% CI 0.17, 0.74) NNT=70.9 (95% CI 41.4-248.2)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Denosumab

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Bone et al., 2008<sup>18</sup></p> <p>Denosumab</p> <p>Location: US, Canada</p> <p>Setting: Multicenter</p> <p>Jadad: 2</p> <p>Age Mean/Range: 59/NR</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: 695 Eligible: 332 Enrolled: 332 Withdrawn: 34 Lost to follow-up: 12 Analyzed: NR</p> <p>Method of AE Assessment: Monitored, Reported spontaneously by patient</p>	<p>Inclusion criteria: Ambulatory, Post-menopausal women NOS, Not receiving medications that affect bone metab; Free of conditions-other than OP-that affect bone metab.; No history of fracture after age 25; Lumbar BMD T-score between -1.0 and -2.5</p> <p>Exclusion criteria: Vitamin D deficiency, Metabolic bone disorder other than osteoporosis, Bisphosphonates, Calcitonin, Fluoride, Androgen, Menopausal hormonal therapy, Estrogen agonists including estrogen, SERMS, Anabolic steroids, Previous PTH use, Vitamin D use, Corticoids/Glucocorticoids, Strontium within 5 years of enrollment; Tibolone 6 weeks of enrollment; BP use of 3 mos-3 yrs with washout (12-months);</p> <p>Interventions: Placebo for 2 Year(s) vs. 60mg of Denosumab every 2 months for 2 Year(s)</p> <p>All received: Calcium, Vitamin D</p> <p>Wash-out only</p> <p>Fracture outcomes assessment time not reported</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, BMD Total body, Bone Turnover</p>	<p>Non-vertebral at 2 YRS: Denosumab vs Placebo: 1.0% vs 4.0% OR = 0.32 (95% CI 0.09, 1.20)</p> <p>Vertebral at 2 YRS: Denosumab vs Placebo: 0.0% vs 1.0% OR = 0.14 (95% CI 0.00, 6.82)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials

Denosumab

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Cummings et al., 2009<sup>119</sup></p> <p>Denosumab</p> <p>Location: US, Canada, South America, UK, Western Europe, Eastern Europe, Australia/New Zealand</p> <p>Trial: FREEDOM</p> <p>Setting: Multicenter</p> <p>Jadad: 0</p> <p>Age Mean/Range: 72/60-90</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Enrolled: 7,868 Withdrawn: 60 Lost to follow-up: NR Analyzed: 7,393</p> <p>Method of AE Assessment: Monitored</p>	<p>Inclusion criteria: Ambulatory, Post-menopausal women NOS, Age under 90 years, Age over 60 years, T-Score ≤ -2.5 Hip, T-Score ≤ -2.5 Spine</p> <p>Exclusion criteria: Vitamin D deficiency, Metabolic bone disorder other than osteoporosis, Bisphosphonates, Calcitonin, Fluoride, Menopausal hormonal therapy, SERMS, Previous PTH use, Vitamin D use, Corticoids/Glucocorticoids, T-score &lt; -4.0 @ hip or lumbar spine; Severe prevalent vertebral fracture</p> <p>Interventions: Placebo 2X per Year for 36 Month(s) vs. 60mg of Denosumab 2X per Year for 36 Month(s)</p> <p>All received: Calcium, Vitamin D</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline, 2 years, 3 years</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Hip fracture, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, BMD femoral trochanter, New vertebral fracture, Time to first hip fracture, Time to first non-vertebral fracture</p>	<p>Hip fracture at 36 MOS: Denosumab vs Placebo: 0.7% vs 1.2% OR = 0.59 (95% CI 0.36, 0.94) NNT=200.0 (95% CI 105.7-1854)</p> <p>Multiple new vertebral at 36 MOS: Denosumab vs Placebo: 0.6% vs 1.6% OR = 0.40 (95% CI 0.26, 0.61) NNT=100.0 (95% CI 67.9-189.9)</p> <p>New clinical vertebral at 36 MOS: Denosumab vs Placebo: 0.8% vs 2.6% OR = 0.34 (95% CI 0.24, 0.48) NNT=55.5 (95% CI 41.7-83.3)</p> <p>Non-vertebral at 36 MOS: Denosumab vs Placebo: 6.5% vs 8.0% OR = 0.80 (95% CI 0.67, 0.95) NNT=66.7 (95% CI 37.2-319.9)</p> <p>Vertebral at 36 MOS: Denosumab vs Placebo: 2.3% vs 7.2% OR = 0.34 (95% CI 0.27, 0.42) NNT=20.4 (95% CI 17.1-25.4)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-1. Randomized Controlled Trials  
Estrogen

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Boone et al., 2006<sup>139</sup> Estrogen Location: Canada Setting: Multicenter Jadad: 5 Age Mean/Range: 55/NR 100% Female Race: Not reported Screened: 355 Eligible: 91 Enrolled: 31 Withdrawn: 9 Lost to follow-up: NR Analyzed: 31 Method of AE Assessment: Monitored, Reported spontaneously by patient</p>	<p>Inclusion criteria: Ambulatory, Post-menopausal women NOS, Age under 66 years, Primary biliary cirrhosis; normal PAP, pelvic exam, breast exam; Hemoglobin &gt; 80mg/L</p> <p>Exclusion criteria: Vitamin D deficiency, Metabolic bone disorder other than osteoporosis, LS spine abnormalities prohibiting DXA, Organ transplantation, Estrogen agonists including estrogen, Progestin, Medications known to affect skeleton, Liver transplant; Serum bilirubin &gt;120 mmol/l; Contraindications to estrogen use; nonambulatory or immobile &gt; 3 mos in prev year; known sensitivity to patch</p> <p>Interventions: Placebo for 24 Month(s) vs. 0.05mg of Estrogen patch Daily for 24 Month(s) + 0.25mg of Est./progestin for 24 Month(s)</p> <p>All received: Calcium, Vitamin D</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline, 24 months</p> <p>Outcomes: Bone mineral density by DXA - Spine, Radiographic vertebral fractures, All cause mortality, BALP, NTX</p>	<p>Non-vertebral at 24 MOS: Estrogen/progestin vs Placebo: 0.0% vs 0.0% OR = NC</p> <p>Vertebral at 24 MOS: Estrogen/progestin vs Placebo: 0.0% vs 13.3% OR = 0.12 (95% CI 0.01, 1.98)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Frost et al., 2007<sup>158</sup></p> <p>Calcium</p> <p>Location: Western Europe</p> <p>Setting: Single setting</p> <p>Jadad: 1</p> <p>Age</p> <p>Mean/Range: 52/NR</p> <p>100% Male</p> <p>Race: German</p> <p>Screened: 40</p> <p>Eligible: 40</p> <p>Enrolled: 40</p> <p>Withdrawn: 7</p> <p>Lost to follow-up: NR</p> <p>Analyzed: 33</p> <p>Method of AE Assessment: NR</p>	<p>Inclusion criteria: Men, CHF Class 1, II or III Stable CHF for 3 months</p> <p>Exclusion criteria: Hyperthyroidism, Hyperparathyroidism, Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Inflammatory bowel disease, Medications known to affect skeleton</p> <p>Interventions: Placebo for 1 Year(s) vs. 1000mg of Calcium Daily for 1 Year(s)</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture</p>	<p>Vertebral at 12 MOS: Calcium 1000mg/day vs Placebo: 5.9% vs 6.3% OR = 0.94 (95% CI 0.06, 15.72)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Fujita et al., 2004<sup>159</sup></p> <p>Calcium</p> <p>Location: Japan</p> <p>Trial: KATSURAGI CALCIUM STUDY</p> <p>Setting: Single setting</p> <p>Jadad: 2</p> <p>Age Mean/Range: 80/NR</p> <p>100% Female</p> <p>Race: Asian</p> <p>Screened: NR Eligible: NR Enrolled: 58 Withdrawn: NR Lost to follow-up: NR Analyzed: 19</p> <p>Method of AE Assessment: NR</p>	<p>Inclusion criteria: Women otherwise undefined, Hospitalized</p> <p>Exclusion criteria: Not Reported</p> <p>Interventions: Placebo Daily for 2 Year(s) vs. 900mg of AAA- absorbable algal calcium Daily for 2 Year(s) vs. 900mg of Calcium carbonate Daily for 2 Year(s)</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Radiographic vertebral fractures, All cause mortality, DXA Whole body</p>	<p>Vertebral at 2 YRS: Active absorbable algal calcium vs Placebo: 0.0% vs 50.0% OR = 0.09 (95% CI 0.01, 1.06) Calcium carbonate vs Placebo: 28.6% vs 50.0% OR = 0.43 (95% CI 0.05, 3.73)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Law et al., 2006<sup>164</sup></p> <p>Vitamin D</p> <p>Location: UK</p> <p>Setting: Multicenter</p> <p>Jadad: 3</p> <p>Age Mean/Range: 85/NR</p> <p>76% Female</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: 3,717 Enrolled: 3,717 Withdrawn: NR Lost to follow-up: 669 Analyzed: 3,717</p> <p>Method of AE Assessment: Monitored</p>	<p>Inclusion criteria: Age over 59 years</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Bisphosphonates, Calcium includes antacids, Previous PTH use, Vitamin D use, Temporary residents-respite care</p> <p>Interventions: Control every 3 Months vs. 2.5mg of Vitamin D every 3 Months</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessment time unclear</p> <p>Outcomes: Non-vertebral fracture, All cause mortality, Falls</p>	<p>Hip at 10 MOS: Vitamin d vs Placebo: 1.3% vs 1.0% OR = 1.34 (95% CI 0.74, 2.42)</p> <p>Non-vertebral at 10 MOS: Vitamin d vs Placebo: 3.6% vs 2.6% OR = 1.41 (95% CI 0.97, 2.04)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Lyons et al., 2007<sup>203</sup></p> <p>Vitamin D</p> <p>Location: UK</p> <p>Setting: Multicenter, Longterm care, Shelters and other residential</p> <p>Jadad: 5</p> <p>Age Mean/Range: 84/NR</p> <p>76% Female</p> <p>Race: Not reported</p> <p>Screened: 5,745 Eligible: 4,443 Enrolled: 3,440 Withdrawn: 699 Lost to follow-up: 1,606 Analyzed: 3,440</p> <p>Method of AE Assessment: Monitored</p>	<p>Inclusion criteria: Men, Women otherwise undefined, Residence in nursing homes or sheltered housing</p> <p>Exclusion criteria: Vitamin D use, Contra-indication to vitamin D supplementation</p> <p>Interventions: Placebo vs. 2.5 or 100,000mg of Vitamin D(ergocalciferol) 3 X per year for 3 Year(s)</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessment time variable</p> <p>Outcomes: Hip fracture, Radial fracture, Vertebral fracture, Non-vertebral fracture, Symptomatic vertebral fractures, All cause mortality, BALP, Time to 1st fracture</p>	<p>All sites - All Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 14.1% vs 15.6% OR = 0.89 (95% CI 0.73, 1.07)</p> <p>All sites - First Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 11.9% vs 12.7% OR = 0.93 (95% CI 0.76, 1.14)</p> <p>Hip - All Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 7.4% vs 7.3% OR = 1.00 (95% CI 0.78, 1.29)</p> <p>Hip - First Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 6.5% vs 6.1% OR = 1.08 (95% CI 0.82, 1.42)</p> <p>Hip/wrist/forearm - All Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 9.3% vs 8.8% OR = 1.06 (95% CI 0.84, 1.34)</p> <p>Hip/wrist/forearm - First Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 8.1% vs 7.3% OR = 1.11 (95% CI 0.87, 1.43)</p> <p>Hip/wrist/forearm/vertebrae - All Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 9.5% vs 9.5% OR = 1.00 (95% CI 0.80, 1.26)</p> <p>Hip/wrist/forearm/vertebrae - First Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 8.3% vs 7.9% OR = 1.06 (95% CI 0.83, 1.35)</p> <p>Other Fracture - All Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 4.6% vs 6.1% OR = 0.74 (95% CI 0.55, 0.99) NNT=64.8 (95% CI 32.8-2550)</p> <p>Other Fracture - First Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 3.6% vs 4.8% OR = 0.73 (95% CI 0.53, 1.02)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Shiraki et al., 1996<sup>162</sup></p> <p>Vitamin D</p> <p>Location: Japan</p> <p>Setting: Multicenter</p> <p>Jadad: 4</p> <p>Age Mean/Range: 72/NR</p> <p>100% Female</p> <p>Race: Asian</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Enrolled: 113</p> <p>Withdrawn: 34</p> <p>Lost to follow-up: NR</p> <p>Analyzed: 113</p> <p>Method of AE Assessment: NR</p>	<p>Inclusion criteria: Ambulatory, Women otherwise undefined, Age over 59 years, Osteoporosis NOS</p> <p>Exclusion criteria: Hypothyroidism, Hyperthyroidism, Hyperparathyroidism, Hypoparathyroidism, Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, LS spine abnormalities prohibiting DXA, Renal insufficiency, No osteoporosis treatment within 6 months</p> <p>Interventions: Placebo Daily for 2 Year(s) vs. 0.75µg of Vitamin D Daily for 2 Year(s)</p> <p>All received: Calcium</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline, 12 months, 18 months, 24 months</p> <p>Outcomes: Bone mineral density by DXA - Spine, Radiographic vertebral fractures, All cause mortality, BMD-DXA Whole body</p>	<p>Non-vertebral at 2 YRS: 1a-hydroxy vitamin d vs Placebo: 0.0% vs 7.1% OR = 0.15 (95% CI 0.01, 1.44)</p> <p>Vertebral at 2 YRS: 1a-hydroxy vitamin d vs Placebo: 5.4% vs 7.1% OR = 0.75 (95% CI 0.12, 4.55)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Smith et al., 2007<sup>163</sup></p> <p>Vitamin D</p> <p>Location: UK</p> <p>Setting: Multicenter, Community</p> <p>Jadad: 5</p> <p>Age Mean/Range: 79/NR</p> <p>54% Female</p> <p>Race: Not reported</p> <p>Screened: 13,487 Eligible: 11,302 Enrolled: 9,440 Withdrawn: 4,570 Lost to follow-up: NR Analyzed: 9,440</p> <p>Method of AE Assessment: Monitored, Elicited by investigator</p>	<p>Inclusion criteria: Men, Women otherwise undefined, Age over 74 years</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Hypocalcemia, Renal insufficiency, Nephrolithiasis, Vitamin D use, Treated osteoporosis, bilateral total hip replacement, sarcoidosis</p> <p>Interventions: Placebo Yearly for 3 Year(s) vs. 300,000I.U. of Vitamin D Yearly for 3 Year(s)</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline, 12 months, 18 months, 24 months, 36 months</p> <p>Outcomes: Bone mineral density by DXA - Hip, Hip fracture, Radial fracture, Non-vertebral fracture, All cause mortality, Falls</p>	<p>Hip or femur at 36 MOS: Vitamin d vs Placebo: 1.4% vs 0.9% OR = 1.49 (95% CI 1.03, 2.18)</p> <p>Non-vertebral at 36 MOS: Vitamin d vs Placebo: 6.5% vs 5.9% OR = 1.10 (95% CI 0.93, 1.30)</p> <p>Wrist at 36 MOS: Vitamin d vs Placebo: 1.4% vs 1.1% OR = 1.23 (95% CI 0.85, 1.77)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Larsen et al., 2004<sup>152</sup>                      Calcium, Vitamin D                      Location: Western Europe                      Setting: Community practices                      Jadad: 0                      Age                      Mean/Range: 75/NR                      60% Female                      Race: Not reported                      Screened: NR                      Eligible: 9,605                      Enrolled: NR                      Withdrawn: NR                      Lost to follow-up: NR                      Analyzed: 9,605                      Method of AE Assessment: NR</p>	<p>Inclusion criteria:                      Ambulatory, Men, Women otherwise undefined, Age over 65 years</p> <p>Exclusion criteria:                      People living in nursing homes. Severely impaired persons living in sheltered homes for the elderly. Mental retardation and cannot give consent.</p> <p>Interventions:                      Control                      vs.                      1000mg of Calcium Daily + 400I.U. of Vitamin D Daily                      vs.                      Usual care                      vs.                      1000mg of Calcium Daily + 400I.U. of Vitamin D Daily</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes:                      Proximal humerus fracture, Radial fracture, Vertebral fracture, Non-vertebral fracture, All cause mortality, BALP, BMD femoral trochanter, Pelvic fractures, Hospital admission, For fracture</p>	<p>All fractures - men at 42 MOS:                      Both programs vs Placebo: 3.5% vs 3.1%                      OR = 1.13 (95% CI 0.67, 1.89)                      Calcium &amp; vitamin d vs Placebo: 3.0% vs 3.1%                      OR = 0.99 (95% CI 0.62, 1.57)                      Environment &amp; health program vs Placebo: 3.0% vs 3.1%                      OR = 0.99 (95% CI 0.62, 1.58)</p> <p>All fractures - women at 42 MOS:                      Both programs vs Placebo: 8.3% vs 11.1%                      OR = 0.73 (95% CI 0.56, 0.93) NNT=36.1 (95% CI 20.1-174.8)                      Calcium &amp; vitamin d vs Placebo: 8.6% vs 11.1%                      OR = 0.75 (95% CI 0.60, 0.94) NNT=41.2 (95% CI 22.6-232.7)                      Environment &amp; health program vs Placebo: 8.9% vs 11.1%                      OR = 0.78 (95% CI 0.62, 0.97) NNT=45.8 (95% CI 23.9-533.2)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Xia et al., 2009<sup>226</sup></p> <p>Calcium, Vitamin D</p> <p>Location: Asia</p> <p>Setting: Multicenter</p> <p>Jadad: 3</p> <p>Age Mean/Range: 70/67-74</p> <p>100% Female</p> <p>Race: Asian</p> <p>Screened: NR Eligible: NR Enrolled: 150 Withdrawn: 8 Lost to follow-up: NR Analyzed: 142</p> <p>Method of AE Assessment: Monitored, Reported spontaneously by patient</p>	<p>Inclusion criteria: Post-menopausal women NOS, Age over 65 years, T-Score <math>\leq</math> -1.0 Spine, BMI: 18-30</p> <p>Exclusion criteria: Hypothyroidism, Hyperthyroidism, Hyperparathyroidism, Hypoparathyroidism, Hypocalcemia, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Bisphosphonates, Calcitonin, Fluoride, Estrogen agonists including estrogen, SERMS, Anabolic steroids, Testosterone, Previous PTH use, Corticoids/Glucocorticoids, Tibolone use; calcitriol use within 3 months;</p> <p>Interventions: 600mg of Calcium Daily for 12 Month(s) + 125I.U. of Vitamin D Daily for 12 Month(s) vs. 0.25<math>\mu</math>g of Rocaltrol Daily for 12 Month(s) + 600mg of Calcium Daily for 12 Month(s) + 125I.U. of Vitamin D Daily for 12 Month(s)</p> <p>Run-in/wash-out unclear</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture</p>	<p>Vertebral at 12 MOS: Rocaltrol+Caltrate D vs Caltrate D: 1.4% vs 2.6% OR = 0.52 (95% CI 0.05, 5.10)</p>

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Author, Year, (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
Schwartz 2010 <sup>242</sup> (FIT/FLEX) <sup>409</sup> Alendronate	Randomized double-blind placebo-controlled trial among 1,099 postmenopausal women originally enrolled in the FIT trial and randomized to ALN 5 (30%) or 10 (30%) mg/d or placebo (40%) for an additional 5 years with mean ALN use of 5 years Women with vertebral frx at baseline (n=720)	A post-hoc analysis was performed to determine whether the effect of long-term ALN on fracture (clinical and morphometric vertebral, non-vertebral fracture) differs by vertebral fracture status and femoral neck (FN) T-score	Among women without vertebral fracture at FLEX baseline, continuation of ALN reduced non-vertebral fracture (NVF) in women with FLEX baseline FN T-score < -2.5 (RR 0.50; 95% CI 0.26-0.96) but not with T-score > -2.5 and < -2 (RR 0.79; 95% CI 0.37-1.66) or with T-score > -2 (RR 1.41; 95% CI 0.75-2.66) (p for interaction 0.019). Among women with a prevalent vertebral fracture at baseline, continued ALN reduced the risk of clinical vertebral fractures but not morphometric or non-vertebral fractures; Baseline FN T-score did not affect response to continued ALN	Continuing alendronate (for a total of 10 years) instead of stopping after 5 years reduces NVF risk in women without prevalent vertebral fracture whose FN T-score, achieved after 5 years of ALN, is < -2.5, but does not reduce risk of NVF in women whose T-score is > -2. Suggests that those who have already had substantial gains in BMD may not benefit further
Black 2006 <sup>239</sup> (FIT/FLEX) <sup>409</sup> Alendronate	1,099 postmenopausal women aged 55 to 81 years with low femoral neck BMD (0.68 g/cm <sup>2</sup> ) originally randomized to oral alendronate for 5 years (5 mg/d for 2 years, 10 mg thereafter). Women in active tx were then randomized to 5 mg/d (n=329) or 10mg/d (n=333) or placebo (n=437) for 5 additional years. All women also offered daily supplement containing 500 mg of calcium and 250 U of vitamin D. Assessed effect of continuing vs. stopping treatment after 5 years	1°: Hip BMD 2°: BMD at other sites Fracture incidence was exploratory outcome measure Lateral spine radiographs were obtained at FLEX baseline and at 36 and 60 months for morphometric vertebral fracture ascertainment.  Adverse events	(see <sup>239</sup> for results of the original FIT and FLEX trials) After 5 years, the cumulative risk of nonvertebral fractures (RR, 1.00; 95% CI, 0.76-1.32) was not significantly different between those continuing (19%) and discontinuing (18.9%) alendronate. Among those who continued, there was a significantly lower risk of clinically recognized vertebral fractures (5.3% for placebo and 2.4% for alendronate; RR, 0.45; 95% CI, 0.24-0.85) but no significant reduction in morphometric vertebral fractures (11.3% for placebo and 9.8% for alendronate; RR, 0.86; 95% CI, 0.60-1.22). Likewise, there was no difference in clinically recognized “any,” nonvertebral, hip, or forearm fractures.  The post hoc subgroup fracture analysis did not show significant trends with lower BMD or prevalent vertebral fractures at FLEX baseline for either nonvertebral or clinical vertebral fractures. However, the incidence of both types of fractures in the placebo group increased with lower baseline BMD or prevalent fracture. To compare nonvertebral fracture incidence in FIT and	Women who discontinued alendronate after 5 years showed a moderate decline in BMD and a gradual rise in biochemical markers but <i>no higher fracture risk</i> other than for clinical vertebral fractures compared with those who continued alendronate. These results suggest that for many women, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk. However, women at very high risk of clinical vertebral fractures may benefit by continuing beyond 5 years

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Author, Year, (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
			FLEX, they ran proportional hazards models among alendronate- treated participants with study and age as predictors and found that after adjustment for age, fracture incidence was similar in the 2 studies.	
Jamal 2007 <sup>410</sup> (FIT) <sup>409</sup> Alendronate	Postmenopausal women enrolled in fit (6,458); renal function estimated by creatinine clearance (eGFR) 581 women with severely reduced eGFR (9.9%)	Post hoc analysis of risk of spinal and clinical fractures with alendronate treatment in women with reduced vs. normal eGFR	Alendronate increased BMD regardless of eGFR, but women with reduced eGFR had a 5.6% (95% CI: 4.8–6.5) increase in total hip BMD compared with 4.8% (95% CI: 4.6–5.0) among women with normal to moderate renal dysfunction (interaction: <i>p</i> = 0.04). Compared with placebo, alendronate increased spine BMD by 6.6 ± 5.8%, but there was no significant interaction for the increase in spine BMD (interaction: <i>p</i> = 0.75). Treatment with alendronate reduced the risk of clinical fractures to a similar degree in those with (OR: 0.78; 95% CI: 0.51–1.21) and without reduced renal function (OR: 0.80; 95% CI: 0.70–0.93; <i>p</i> for interaction = 0.89). Treatment with alendronate reduced the risk of spine fractures to a similar degree in those with (OR: 0.72; 95% CI: 0.31–1.7) and without reduced renal function (OR: 0.50; 95% CI: 0.32–0.76; <i>p</i> for interaction = 0.44). There were no differences in adverse events by renal function	Alendronate is equally safe and effective in women with and without abnormal renal function (KQ2)
Watts 2005 <sup>403</sup> (VERT NA, <sup>93</sup> VERT MN, <sup>411</sup> and HIP) Risedronate	Postmenopausal osteoporotic women from three trials on 2.5 or 5 mg risedronate (n=2,561) or placebo (1,418)	Post-hoc analysis to assess association between change in BMD and fracture risk	3,979 patients had baseline and follow-up DXA measurements, either LS or FN Incident nonvertebral fractures: 138 (10.9% placebo) 169 (77% treated) Reduction in fracture risk 32% (HR 0.68(0.54, 0.85, <i>p</i> <0.001)) Among 123 patients with incident fractures for whom paired FN or LS DXA measures were available, LS BMD increased from baseline in 100 (6.4%) and decreased from baseline in 23 (7.8%), so there was no difference in frx response across changes in BMD(numbers represent cumulative change over 3 years). Similar results were found for FN BMD: of 162 patients with fractures, 100 (7.5%) had	In postmenopausal osteoporotic women taking risedronate, change in LS or FN BMD was not related to nonvertebral fracture incidence over 3 years

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Author, Year, (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
			increased BMD and 62 (7.6%) had decreased FN BMD.	
Siris 2008 <sup>240</sup> (VERT NA <sup>93</sup> and MN, <sup>411</sup> BMD NA and MN) <sup>92</sup> Risedronate	Post-hoc analysis of 620 postmenopausal women with osteopenia (femoral neck T-score between -1 and -2.5 SD and no prevalent fracture) from 4 trials who received 5 mg risedronate (n=311) or placebo (n=309) daily 1.5-3 yrs	Effect of risedronate on fragility fracture risk in subgroup of women with osteopenia, where outcome was defined as a composite of a patient's incident morphometric vertebral and osteoporosis-related nonvertebral fractures (i.e., six fracture types including clavicle, humerus, wrist, pelvis, hip or leg fractures), chosen to include all radiographically confirmed fractures	Cumulative 3-yr fragility fracture incidence 6.9% vs. 2.0% in placebo vs. active treatment (73% decrease p=0.023) Sensitivity analysis excluded women with LS BMD≤-2.5	Risedronate significantly reduced fracture risk in osteopenic women. Magnitude of effect same in sensitivity analysis subset (KQ2)
Watts 2008 <sup>412</sup> (VERT NA) <sup>93</sup> Risedronate	Analysis of effect of 1-year discontinuation Women who were at least 5 years postmenopausal, <85 years, and had either ≥2 vertebral fractures or one vertebral fracture and spinal T-score≤-2.0 at start of original study and completed original study (2.5/5 mg oral risedronate or placebo) N=799 enrolled in follow-up study; n=599 completed (79%)(290 original placebo, 309 original treated) All women received 1000 mg Ca/d and if baseline vitamin D levels were low, received vitamin D supplementation	BMD, markers Radiographic new vertebral fractures (assessors blinded); nonvertebral fractures (radiographic confirmation not required) at 48 months compared with 36 months  (AEs)	LS BMD: Original treated: decrease (-0.83%, -1.30%, -0.35%) although still significantly higher than at baseline and higher than the original placebo group: Original placebo: no significant change FN and trochanteric BMD also decreased significantly from the end of treatment but remained significantly higher than baseline  New vertebral fractures: 42/361 placebo patients (11.6%) 26/398 treated patients (6.5%) RR 0.54 (0.34, 0.86, p=0.009) (Decreased relative risk 46%)	In spite of loss of BMD, risk reduction for new vertebral fractures remained for patients from the original treatment group (KQ5?)
Boonen 2010 <sup>246</sup> (VERT NA <sup>93</sup> and MN, BMD NA and MN) Risedronate	Post-hoc analysis of relationship between age and effect of treatment on fracture risk Postmenopausal women with osteoporosis as defined by prevalent vertebral fractures, low BMD, or both treated with 5mg risedronate/d or placebo for 1-3yrs (1-2 yrs BMD; 3 yrs VERT) (n=3,229; 1,618 placebo and 1,611 risedronate) Average age 68, mean lumbar T-score -2.6, 72% had at least one prevalent vertebral fracture All women received 1000 mg Ca/d and if baseline vitamin D levels were low, received vitamin D supplementation	ITT analysis of incidence of OP-related fractures (any new morphometric vertebral or radiographically confirmed clinical fracture of the hip, pelvis, wrist, humerus, clavicle, or leg, or symptomatic vertebral fractures), clinical fractures, nonvertebral fractures, and morphometric fractures Age difference between placebo and treated group with same fracture risk and 3-year fracture risk	Irrespective of treatment, fracture risks were greater in older patients(p<0.001): RR (CI) Any: 1.04 (1.02, 1.05) Clinical: 1.04 (1.03, 1.06) Nonvertebral: 1.05 (1.03, 1.07) Morph vertebral: 1.03 (1.02, 1.05)  Irrespective of age, treatment reduced the risk of each type of fracture (p<0.001): Any: 0.58 (0.48, 0.70) Clinical: 0.54 (0.41, 0.69) Nonvertebral: 0.59 (0.44, 0.79)	Patients treated with risedronate have a significantly lower fracture risk, similar to that of untreated patients 10-20 years younger (KQ2?)

AE=Adverse Event, NR=Not Reported

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Author, Year, (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
			<p>Morph vertebral: 0.54 (0.43, 0.68)</p> <p>3-year fracture risks were markedly greater in the placebo group for each age group and each fracture type</p> <p>Comparing ages of pts who were at the same risk, patients in the placebo group were 10-20 years younger than treated patients with the same risk, depending on fracture type (any: 15.1 years; clinical: 14.4 yrs; nonvertebral: 10.3 yrs; morphometric vertebral: 19.8 yrs)</p>	
<p>Watts 2009 (2CDM trial)<sup>413</sup> Risedronate</p>	<p>Post-hoc (re-)analysis of Delmas et al., 2008<sup>87</sup> study that originally compared 2 consecutive days/month dosing strategy with daily treatment, head-to-head using a historical placebo control Inclusion criteria: Ambulatory, Post-menopausal women &gt;5 years, Age over 49 years, LS T-Score ≤ -2.5, or &lt; 2 with 1 prevalent frx</p> <p>Interventions: 5mg of Risedronate Daily vs. 75mg of Risedronate for 1 year vs. VERT placebo participants as historical control</p> <p>All received calcium, Vitamin D (n=1,229, 616 2CDM, 613 5mg/d)</p>	<p>BMD, semi-quantitative assessment of vertebral fractures</p>	<p>1-year fracture incidences: Placebo: 5.1% Historical risedronate 5mg/d: 1.0% Current risedronate 5mg/d: 1.5% Current 2CDM 75mg: 1.1%</p> <p>Vertebral fracture RR: Current risedronate 5mg/d: 0.28(0/08, 1.11)(p=0.016) Current 2CDM 75mg: 0.21(0.05, 0.88)(p=0.036) (79% risk reduction)</p>	<p>Use of historical control data may be viable alternative for comparing antifracture efficacy in trials that lacked a placebo control. Use of risedronate on 2 consecutive days a month reduced vertebral fracture risk at 1 year compared with placebo (KQ1)</p>
<p>Eastell 2009<sup>248</sup> (HORIZON-PFT)<sup>414</sup> Zoledronic Acid</p>	<p>Original study details and results in Black et al., 2007) Postmenopausal women ages 65-89, w/ FN T-scores ≤ -2.5 with or without evidence of prevalent vertebral fracture OR T-score ≤ -1.5 with radiological evidence of at least 2 mild or 1 moderate vertebral fracture. Prior oral BP use was allowed with washout duration dependent on previous use. Stratification by baseline BP</p>	<p>1°: New vertebral and hip fractures 2°: nonvertebral fractures, any clinical vertebral fracture, any clinical fracture, change in FN BMD</p>	<p>Zoledronic decreased vertebral fracture risk in all subgroups except those previously treated with BPs. Significant treatment-factor interactions were found for vertebral fracture and age (greater effects for younger women, &lt;70), BMI (greater effects for women who were overweight or obese), and Creatinine clearance (greater effect for</p>	<p>ZOL appears more effective in preventing vertebral fracture in younger women, overweight women, and women with normal renal function but was not affected by fracture risk factors or FN BMD. (KQ2)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Author, Year, (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
	medication use. 3-year study of IV zoledronic acid, once yearly Subgroup analysis Effect of age, BMI, and renal function		>60ml/min) No significant effects were found for hip fractures or nonvertebral fractures or across BMD changes	
Eriksen 2009 <sup>253</sup> (HORIZON- <b>Recurrent Fracture Trial [RFT]</b> ) <sup>414</sup> Zoledronic Acid (ZOL)	Men and women (n=2,127, 1,065 on active treatment and 1,062 on placebo), mean age 75, 76% women were administered ZOL within 90 days of surgical hip repair. Median follow-up time 1.9 yrs Post-hoc analysis Timing of first dose of zoledronic acid after hip fracture	1°: Time to first new clinical fracture of the axial or appendicular skeleton 2°: change in BMD of nonfractured hip, time to clinical vertebral, nonvertebral, hip fractures	Overall study showed 35% reduction in clinical fracture risk and 28% reduction in mortality with ZOL Timing of 1 <sup>st</sup> dose within (46% pts) or later than 6 weeks postop showed dosing later than 6 weeks was associated with greater increase in BMD at 12 mos, but BMD was similar at 24 mos. Clinical fracture reduction in pts dosed within 6 weeks was 33% (p<0.05) compared with 37% (p<0.05) in pts dosed later than 6 weeks. (so no difference with timing) Additional analysis looked at dosing at 2-week intervals from 0-12 weeks. Most patients received a first dose at 4-6 weeks, which was associated with significantly decreased antifracture efficacy; because of the small sample sizes in the other 2-week intervals, all CIs crossed 1. With the exception of the ≤2-week period, all intervals showed a consistent reduction in clinical fractures regardless of the timing of infusion. Mortality: All time periods except the ≤2-week period were associated with decreased all-cause mortality. Excluding the ≤2-week period, all other intervals showed larger RR reduction in time to next fracture and mortality. Clinical fractures reduced by 41% (p=0.0002), Nonvertebral fractures reduced by 44% (p=0.0077), Clinical vertebral fractures reduced by 53% (p=0.0084) Hip fractures reduced by 48% (p=0.0305) Mortality reduced by 30% (p=0.0095)	Administration of zoledronic acid to patients suffering low-trauma hip fracture 2 weeks or later after surgical repair increases hip BMD and indices significant reductions in risk of subsequent clinical vertebral, nonvertebral, and hip fractures and reduces mortality (KQ1?)
Boonen 2010 <sup>247</sup> (HORIZON PFT)	All (postmenopausal) female patients 75 years and over enrolled in one of the two trials (n=3,887) (compared with women <75, n=5,467)	Incidence of any clinical fracture, clinical vertebral, or nonvertebral fracture in women 75 and over with	Incidence of any clinical fracture (p<0.001), clinical vertebral fracture (p<0.001), or nonvertebral fracture (p<0.002) in	Post hoc analysis showed that once yearly ZOL is safe and effective in elderly postmenopausal women (≥75) with

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Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Author, Year, (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
and RFT) <sup>414</sup> Zoledronic Acid	Post-hoc analysis of post-menopausal women ≥75 with osteoporosis	osteoporosis	postmenopausal women ≥75 was significantly lower in the ZOL group compared with placebo over 3 years Benefit in relative risk reduction of clinical fractures, clinical vertebral fractures, and nonvertebral fractures was comparable in patients younger than 75 and those ≥75 1 and 3 years after treatment; treatment by age group interactions were not significant. However patients <75 showed a benefit in hip fracture reduction at 3 yrs that was not seen in those ≥75 (p=0.04 for treatment-by-age group interaction)	osteoporosis (KQ2)
Siris 2005 <sup>243</sup> (MORE) <sup>415</sup> (CORE) Raloxifene	CORE breast cancer trial open-label follow-up to MORE trial (8-year follow-up) n=4,011 women (2,725 received 60 mg/d raloxifene, 1286 placebo) Inclusion: ≤80 years, postmenopausal >2 years with hip or spinal T-score≤-2.5 or radiographically confirmed clinical fractures Exclusion: SERMS, hormone therapy, estrogen-dependent cancer, history of venous thromboembolism, treatment with cholestyramine, presence of severe postmenopausal symptoms requiring hormones, unblinding to MORE study assignment	2° outcome new nonvertebral fractures	Risk of at least one new nonvertebral fracture: Trx: 22.8% Placebo 22.9% HR 1.00, (0.82, 1.21) Risk of at least one new fracture at 6 major nonvertebral sites (clavicle, humerus, wrist, pelvis, hip, lower leg): 17.5% in both groups Posthoc Poisson analysis showed no overall effect on nonvertebral fracture risk, but a decreased risk at the 6 sites in women with prevalent vertebral fracture: HR 0.78 (0.63, 0.96) Lumbar spine and femoral neck BMD were significantly increased from baseline and significantly greater than untreated (lumbar spine: 4.3% from baseline and 2.2% from placebo; femoral neck: 1.9% from baseline, 3.0% from placebo)	After 8 years of treatment, raloxifene had no significant effect on nonvertebral fracture risk, except among women with prevalent vertebral fracture at baseline. However the study may not be powered to assess fractures
Nakamura 2006 <sup>250</sup> Raloxifene	Pooled analysis of two studies of Asian women (one Chinese, one Japanese) with postmenopausal osteoporosis being treated with raloxifene 60 mg/d or 120 mg/d vs. placebo Inclusion: ≥2 years postmenopausal ≤80 years 1° OP=L2-L4 T-score≤-2.5 Exclusion: 2° OP, pathologic fractures, severe postmenopausal symptoms requiring hormones, history of or suspected breast carcinoma, history	2° outcome: clinical vertebral and nonvertebral fractures, radiographically confirmed	In 1 <sup>st</sup> year of treatment, incidence of new clinical vertebral fractures were significantly decreased in both the 60 mg and pooled groups vs. placebo data not shown but p=0.01 for 60 mg and p=0.002 for pooled 60 and 120 mg  Incidence of new nonvertebral fractures was not significantly decreased from placebo: 60 mg: RR 0.41 (0.08, 2.09) Pooled 60, 120: RR 0.28 (0.05, 1.41)	Among Asian women, raloxifene (60, 120 mg) is effective in decreasing incident clinical vertebral frx but not new nonvertebral frx (KQ2)

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Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Author, Year, (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
	<p>of any other cancer within previous 5 years except excised superficial lesions, abnormal uterine bleeding, history of DVT or TE disorders, endocrine disorders requiring pharmacotherapy, acute or chronic hepatic disorder, impaired renal function; use of any bone active agents within 6 months prior to study</p> <p>Japanese women: N=97 placebo, 92 raloxifene 60 mg/d, 95 raloxifene 120 mg/d</p> <p>Chinese women: N=102 placebo, 102 raloxifene 60 mg/d</p> <p>Women did not differ in mean age, BMI, years post menopause; Japanese women may have had more prevalent vertebral fractures and lower T-scores</p>		<p>Incidence of any new clinical fractures decreased significantly in both groups from placebo: 60 mg: RR 0.17 (0.04, 0.75) (p=0.01) Pooled: RR 0.11 (0.03, 0.51)</p>	
<p>Sontag 2010<sup>244</sup> (MORE)<sup>415</sup> Raloxifene</p>	<p>Randomized double-blind placebo-controlled international trial enrolled two subgroups, one with BMD≤-2.5 and one with low BMD and prevalent vertebral fractures: treatment consisted of 60 or 120 mg/d raloxifene or placebo and Ca/vitamin D. Trial duration was 3 years plus one additional open year (n=7705)</p>	<p>Post-hoc analysis to compare effect on new fractures by prevalent fracture status and to compare effect on on risk for fractures and breast cancer vs. adverse events (venous thromboembolism [VTE])</p>	<p>Effect of raloxifene on absolute risk difference for fractures and for invasive breast cancer did not differ between those with and without prevalent fracture (-8.21%, -0.75% vs. -2.83%, -1.21%, respectively). IN those with, and without, prevalent fracture, risk for VTE was +0.91% and 0.28% respectively (trial not powered to test difference in these two numbers)</p>	<p>In women with and without prevalent fractures, the benefit of raloxifene for decreasing risk of fractures and invasive breast cancer outweigh the potential increases in VTE (include in Discussion?)</p>
<p>Kanis 2010<sup>241</sup> (MORE)<sup>415</sup> Raloxifene</p>	<p>See Sontag<sup>241</sup></p>	<p>Post-hoc analysis to assess the association between FRAX score and efficacy for clinical and vertebral fracture prevention</p>	<p>Raloxifene treatment was associated with an 18% decrease in the risk for all clinical fractures (HR 0.82, 95% CI 0.71, 0.95, p=0.0063) and 42% decrease in incident morphometric vertebral fractures (HR 0.58, 95% CI 0.48, 0.69, p&lt;0.001)</p> <p>No significant interaction was seen between fracture risk as assessed by FRAX and treatment efficacy. Efficacy was greater at lower ages. At the 90<sup>th</sup> percentile for age (75 years), risk reduction was 31% irrespective of FRAX. At younger ages, efficacy was higher and increased further with decreasing fracture probability.</p>	<p>Overall, the efficacy of raloxifene in reducing fracture risk was not associated with FRAX-determined fracture probability but at younger ages, efficacy was higher and increased with decreasing FRAX-determined probability (KQ 2)</p>
<p>Prince 2005</p>	<p>Follow-up to Fracture Prevention Trial (FPT) in</p>	<p>Follow-up to assess sustained effect</p>	<p>HR for nonvertebral fragility fractures in 20,</p>	<p>Results suggest sustained effect of treatment</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Author, Year, (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
<p><sup>416</sup> FPT<sup>130</sup> Teriparatide</p>	<p>which 1262 women were followed after discontinuation of the drug (20 or ug/d and placebo). Median length of time on active treatment 20 months (prior to early termination of trial due to possibility of increased risk of osteosarcoma, based on lab animal study). Median length of follow-up 30 months.</p>	<p>of drug on nonvertebral fragility fracture</p>	<p>40, and combined groups at 30-months were 0.62 (95% CI, 0.41, 0.93, p=0.022), 0.52 (95% CI, 0.40, 0.82, p=0.002), and 0.57 (95% CI, 0.40, 0.82, p=0.002) compared with placebo; HR adjusted for duration of drug use: 0.59 (95% CI, 0.39, 0.89, p=0.012), 0.52 (95% CI, 0.33, 0.81, p=0.004, and 0.55 (95% CI, 0.39, 0.79, p=0.001) compared with placebo From discontinuation to 30-month followup, HR for fracture were 0.73(95% CI, 0.45, 1.18, p=0.204), 0.54 (95% CI, 0.32, 0.92, p=0.022), and 0.64 (95% CI, 0.42, 0.97, p=0.035), respectively. At 6, 18, and 30 months follow-up, use of (other) osteoporosis therapy was 28%, 47%, and 60%. No difference among former treatment groups, however former placebo group was more likely to initiate than combined teriparatide group; therapy may have been initiated before or after a new fracture.</p>	<p>in reducing risk of nonvertebral fragility fracture up to 30 months after discontinuation of treatment, although majority of patients had initiated other treatment (KQ1?)</p>
<p>Chen 2006 <sup>407</sup> (FPT)<sup>130</sup> Teriparatide</p>	<p>Postmenopausal women randomized to 20 or 40 ug/d teriparatide or placebo (see <sup>416</sup> (n=1637)</p>	<p>Post-hoc analysis of association between change in BMD and fracture risk</p>	<p>In the teriparatide group, change in fracture risk was positively associated with change in spine BMD; in the placebo group, change in fracture risk was inversely related to change in spine BMD. In treated group, those with lowest BMD at baseline had largest % increases in BMD, confounding the relationship with fracture risk. In the placebo group, both baseline BMD and change in BMD affected change in fracture risk. In the treated group, neither baseline BMD nor change in BMD predicted change in fracture risk (although both contributed). Mean spine BMD increase in treated patients 0.09 g/cm<sup>2</sup> across tertiles of baseline spine BMD. Large changes and small changes resulted in similar fracture risk if endpoint BMD were similar. Teriparatide decreased fracture risk regardless of endpoint BMD. Depending on baseline BMD, teriparatide accounted for 30% to 41% of reduction in fracture risk.</p>	<p>Increases in BMD accounted for approximately 1/3 of the vertebral fracture risk reduction; the majority of risk reduction resulted from non-BMD determinants of bone strength</p>

Evidence Table C-2. Evidence Table for Post-hoc, Subgroup Analyses, and Followup Studies

Author, Year, (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
Boonen 2006 <sup>249</sup> FPT <sup>130</sup> Teriparatide	Postmenopausal women randomized to 20 ug/d teriparatide or placebo (see <sup>416</sup> (n=1085)+CA/vitamin D	Post-hoc analysis: of efficacy of teriparatide in women older $\geq 75$ (n=244) vs. $<75$ (n=841)	Teriparatide reduced the risk of new vertebral fractures similarly in the older and younger women: $<75$ : RR 0.35, Adjusted RR 9.2% (NNT=11, $p<0.01$ ) $\geq 75$ : RR 0.35, adjusted RR 9.9%, (NNT=11, $p<0.05$ ) Nonvertebral fragility fractures: $<75$ : RR 0.41, Adjusted RR 3.5% (NNT=29, $p<0.05$ ) $\geq 75$ : RR 0.75, adjusted RR 1.1%, (NNT=11, $p=0.661$ ) Treatment by age interactions were not significant	Age did not affect the treatment efficacy (or safety) of teriparatide in postmenopausal women with osteoporosis. (KQ2)
Prevrhal 2009 <sup>245</sup> FPT <sup>130</sup> Teriparatide	Postmenopausal women randomized to 20 or 40 ug/d teriparatide or placebo (see <sup>416</sup> (n=1637)	Reassessment of FPT data using combination of quantitative and qualitative radiology of spine	Using blinded quantitative radiographic (re-)assessment, vertebral fracture risk was reduced in the teriparatide (vs. placebo) groups by 84% (RR 0.16, $p<0.001$ ); risk of $\geq 2$ fractures was reduced by 94% (RR 0.06, $p<0.001$ ). Fractures in teriparatide group were of lesser severity. Absolute benefit of teriparatide was greatest in those with highest number and severity of prevalent vertebral fractures	Quantitative morphometry confirmed effects of teriparatide on vertebral fracture risk (KQ1?)
Watts 2009 <sup>406</sup> FPT <sup>130</sup> Teriparatide	Postmenopausal women randomized to 20 or 40 ug/d teriparatide or placebo (see <sup>416</sup> (n=1637) Analysis on a subset of participants who had FN BMD and spinal radiographs performed at baseline and 12 months	Post-hoc analysis by FN i.e., association between FN BMD and fracture efficacy	Treated women had a significantly reduced risk of new vertebral fractures (compared with placebo) regardless of change in FN BMD at 1 year. Women who lost FN BMD still had significant reductions in vertebral fracture risk relative to placebo (RR 0.11, 95% CI 0.03, 0.45). Risk reduction in treated group was similar across categories of FN BMD change (loss $>4\%$ to gain $>4\%$ ). Treatment resulted in significant increases in lumbar spine BMD over placebo regardless of FN BMD changes.	At 12 months after baseline, loss of FN BMD in postmenopausal women treated with teriparatide is nevertheless consistent with good treatment response in terms of reduction in risk of vertebral fracture

Evidence Table C-3. Large Randomized Controlled Trials from Original Report  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Cummings et al., 1998<sup>46</sup> Alendronate (Fosamax)</p> <p>Location: US Trial: FIT Setting: Multicenter Jadad: 5 Age Mean/Range: NR 100% Female Race: Not reported Screened: 26,137 Eligible: 10,668 Enrolled: 4,432 Withdrawn: 298 Lost to follow-up: NR Analyzed: 4,432 Method of AE Assessment: Monitored, Elicited by investigator</p>	<p>Inclusion criteria: Post-menopausal women &gt;2 years, Age under 80 years, Age over 54 years, Osteopenia NOS, Femoral neck BMD lesser than 0.68 g/cm<sup>2</sup>. No vertebral fracture</p> <p>Exclusion criteria: Cardiovascular disease, Hepatic insufficiency, Renal insufficiency, Malabsorption syndrome, Upper GI, Bisphosphonates, Calcitonin, Fluoride, Estrogen agonists including estrogen, Dysepsia requiring daily treatment; Hypertension; Medical problem for 3 years that prevent from participating in study</p> <p>Interventions: Placebo Daily for 2 Year(s) vs. 5mg of Alendronate Daily for 1 Year(s) followed by 10mg of Alendronate Daily for 1 Year(s)</p> <p>All received: Calcium, Vitamin D</p> <p>Run-in/wash-out unclear</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures</p>	<p>Any clinical fracture at 48 MOS: Alendronate vs Placebo: 12.3% vs 14.1% OR = 0.85 (95% CI 0.72, 1.02)</p> <p>Any nonvertebral fracture at 48 MOS: Alendronate vs Placebo: 11.8% vs 13.3% OR = 0.87 (95% CI 0.73, 1.04)</p> <p>Hip fracture at 48 MOS: Alendronate vs Placebo: 0.9% vs 1.1% OR = 0.82 (95% CI 0.45, 1.49)</p> <p>Other clinical fracture at 48 MOS: Alendronate vs Placebo: 8.2% vs 10.2% OR = 0.79 (95% CI 0.64, 0.96) NNT=49.9 (95% CI 27.0-327.0)</p> <p>Vertebral fracture, ≥1 at 48 MOS: Alendronate vs Placebo: 2.1% vs 3.8% OR = 0.55 (95% CI 0.38, 0.79) NNT=58.8 (95% CI 36.6-150.3)</p> <p>Vertebral fracture, ≥2 at 48 MOS: Alendronate vs Placebo: 0.2% vs 0.5% OR = 0.42 (95% CI 0.15, 1.21)</p> <p>Wrist at 48 MOS: Alendronate vs Placebo: 3.7% vs 3.2% OR = 1.16 (95% CI 0.84, 1.60)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-3. Large Randomized Controlled Trials from Original Report  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Fogelman et al., 2000<sup>92</sup></p> <p>Risedronate (Actonel)</p> <p>Location: UK, Western Europe</p> <p>Setting: Multicenter</p> <p>Jadad: 1</p> <p>Age</p> <p>Mean/Range: NR</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: NR</p> <p>Eligible: NR</p> <p>Enrolled: 543</p> <p>Withdrawn: 178</p> <p>Lost to follow-up: NR</p> <p>Analyzed: 541</p> <p>Method of AE Assessment:</p> <p>Elicited by investigator, Reported spontaneously by patient</p>	<p>Inclusion criteria:</p> <p>Post-menopausal women &gt;1 year, Age under 80 years, T-Score <math>\leq</math> -2.0 Spine</p> <p>Exclusion criteria:</p> <p>Carcinoma or suspected carcinoma, Hyperthyroidism, Hyperparathyroidism, Metabolic bone disorder other than osteoporosis, LS spine abnormalities prohibiting DXA, Vitamin D use, Medications known to affect skeleton</p> <p>Interventions:</p> <p>Placebo Daily for 24 Month(s)</p> <p>vs.</p> <p>2.5mg of Risedronate Daily for 24 Month(s)</p> <p>vs.</p> <p>5mg of Risedronate Daily for 24 Month(s)</p> <p>All received:</p> <p>Calcium</p> <p>No run-in or wash-out</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes:</p> <p>Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Radiographic vertebral fractures</p>	<p>Fracture counts reported at baseline only</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-3. Large Randomized Controlled Trials from Original Report  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Harris et al., 1999<sup>93</sup></p> <p>Risedronate (Actonel)</p> <p>Location: US</p> <p>Trial: VERT</p> <p>Setting: Multicenter</p> <p>Jadad: 5</p> <p>Age Mean/Range: NR</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: 9,400 Eligible: 2,458 Enrolled: 2,458 Withdrawn: 1,674 Lost to follow-up: 35 Analyzed: 2,246</p> <p>Method of AE Assessment: Monitored, Reported spontaneously by patient</p>	<p>Inclusion criteria: Ambulatory, Post-menopausal women &gt;5 years, Age under 85 years, T-Score ≤ -2.0 Spine, Radiographic fractures, clinically silent, Clinical fractures, radiographically confirmed</p> <p>Exclusion criteria: Bisphosphonates, Calcitonin, Fluoride, Estrogen agonists including estrogen, Progestin, Estrogen agonists, Anabolic steroids, Conditions that might interfere with the evaluation of bone loss; Use of calcitriol and cholecalciferol</p> <p>Interventions: Placebo Daily for 3 Year(s) vs. 2.5mg of Risedronate Daily for 1 Year(s) vs. 5mg of Risedronate Daily for 3 Year(s)</p> <p>All received: Calcium</p> <p>Run-in/wash-out unclear</p> <p>Fracture outcomes assessed at baseline, 2 years, 3 years</p> <p>Outcomes: Bone mineral density by DXA - Spine, Non-vertebral fracture, Radiographic vertebral fractures</p>	<p>New vertebral fracture at 36 MOS: Risedronate 5mg vs Placebo: 8.8% vs 13.7% OR = 0.61 (95% CI 0.44, 0.85) NNT=20.2 (95% CI 12.1-61.8)</p> <p>Non-vertebral fracture at 36 MOS: Risedronate 5mg vs Placebo: 4.1% vs 6.4% OR = 0.63 (95% CI 0.40, 0.97) NNT=43.2 (95% CI 22.3-634.4)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-3. Large Randomized Controlled Trials from Original Report  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Reginster et al., 2000<sup>417</sup></p> <p>Risedronate (Actonel)</p> <p>Location: Western Europe, Australia/New Zealand</p> <p>Trial: VERT</p> <p>Setting: Multicenter</p> <p>Jadad: 2</p> <p>Age Mean/Range: NR</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: 4,400 Eligible: NR Enrolled: 1,226 Withdrawn: 684 Lost to follow-up: NR Analyzed: 1,222</p> <p>Method of AE Assessment: Monitored, Reported spontaneously by patient</p>	<p>Inclusion criteria: Ambulatory, Post-menopausal women &gt;5 years, Age under 86 years, Radiographic fractures, clinically silent, Clinical fractures, radiographically confirmed</p> <p>Exclusion criteria: LS spine abnormalities prohibiting DXA, Bisphosphonates, Calcitonin, Fluoride, Estrogen agonists including estrogen, Progestin, Estrogen agonists, Anabolic steroids, Vitamin D use</p> <p>Interventions: Placebo Daily for 3 Year(s) vs. 2.5mg of Risedronate Daily for 3 Year(s) vs. 5.0mg of Risedronate Daily for 3 Year(s)</p> <p>All received: Calcium, Vitamin D</p> <p>Run-in/wash-out unclear</p> <p>Fracture outcomes assessed at baseline, 2 years, 3 years</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Non-vertebral fracture, Radiographic vertebral fractures</p>	<p>New vertebral fracture at 36 MOS: Risedronate 5mg vs Placebo: 15.4% vs 25.7% OR = 0.53 (95% CI 0.37, 0.77) NNT=9.7 (95% CI 6.1-23.1)</p> <p>Osteoporosis-related nonvertebral fracture at 36 MOS: Risedronate 5mg vs Placebo: 8.9% vs 12.6% OR = 0.68 (95% CI 0.44, 1.06)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-3. Large Randomized Controlled Trials from Original Report  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Black et al., 2007<sup>113</sup></p> <p>Zoledronic acid (Zometa)</p> <p>Location: US, Canada, South America, Western Europe, Eastern Europe, Asia</p> <p>Trial: Horizon</p> <p>Setting: Multicenter</p> <p>Jadad: 3</p> <p>Age Mean/Range: NR</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: 18,421 Eligible: NR Enrolled: 7,765 Withdrawn: NR Lost to follow-up: NR Analyzed: 7,736</p> <p>Method of AE Assessment: Monitored, Elicited by investigator</p>	<p>Inclusion criteria: Age under 90 years, Age over 64 years, T-Score <math>\leq</math> -2.5 Hip, Tscore -1.5 or less with radiologic evidence of at least 2 mild vertebral fractures or one moderate vertebral fracture</p> <p>Exclusion criteria: Hypocalcemia, Hypercalcemia, Renal insufficiency, Fluoride, Anabolic steroids, Previous PTH use, Corticoids/Glucocorticoids, Previous use of strontium</p> <p>Interventions: Placebo Yearly for 2 Year(s) vs. 5mg of Zoledronic acid Yearly for 2 Year(s) - 3 doses total</p> <p>All received: Calcium, Vitamin D</p> <p>Run-in/wash-out unclear</p> <p>Fracture outcomes assessed at baseline, 24 months, 36 months</p> <p>Outcomes: Bone mineral density by DXA - Hip, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures</p>	<p>Any clinical fracture at 36 MOS: Zoledronic acid 5mg vs Placebo: 10.9% vs 16.0% OR = 0.65 (95% CI 0.56, 0.75) NNT=19.7 (95% CI 14.6-30.3)</p> <p>Clinical vertebral fracture at 36 MOS: Zoledronic acid 5mg vs Placebo: 0.7% vs 2.9% OR = 0.28 (95% CI 0.19, 0.41) NNT=44.0 (95% CI 33.8-63.2)</p> <p>Hip fracture at 36 MOS: Zoledronic acid 5mg vs Placebo: 1.8% vs 3.1% OR = 0.60 (95% CI 0.43, 0.83) NNT=80.5 (95% CI 48.8-229.2)</p> <p>Morphometric vertebral fracture at 36 MOS: Zoledronic acid 5mg vs Placebo: 3.3% vs 10.9% OR = 0.31 (95% CI 0.26, 0.39) NNT=13.1 (95% CI 11.2-15.9)</p> <p>Multiple morphometric vertebral fractures at 36 MOS: Zoledronic acid 5mg vs Placebo: 0.2% vs 2.3% OR = 0.20 (95% CI 0.12, 0.31) NNT=48.4 (95% CI 37.8-67.4)</p> <p>Non-vertebral at 36 MOS: Zoledronic acid 5mg vs Placebo: 10.3% vs 13.6% OR = 0.73 (95% CI 0.63, 0.86) NNT=30.7 (95% CI 20.2-63.9)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-3. Large Randomized Controlled Trials from Original Report  
SERMs

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Ettinger et al., 1999<sup>415</sup></p> <p>Raloxifene (Evista)</p> <p>Location: US, Canada, Other countries not specified</p> <p>Trial: MORE</p> <p>Setting: Multicenter</p> <p>Jadad: 1</p> <p>Age Mean/Range: 31-80</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: 22,379 Eligible: NR Enrolled: 7,705 Withdrawn: 1,804 Lost to follow-up: NR Analyzed: 7,755</p> <p>Method of AE Assessment: Monitored, Elicited by investigator</p>	<p>Inclusion criteria: Post-menopausal women &gt;2 years, T-Score ≤ -2.5 Hip, T-Score ≤ -2.5 Spine, Radiographic fractures, clinically silent, Clinical fractures, radiographically confirmed</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Endocrine disease (not diabetes) NOS, Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, LS spine abnormalities prohibiting DXA, Renal insufficiency, Malabsorption syndrome, Nephrolithiasis, Urolithiasis, Ever venous thromboembolic disease, Bisphosphonates, Calcitonin, Fluoride, Androgen, Estrogen agonists including estrogen, Corticoids/Glucocorticoids, Substantial postmenopausal symptoms; Abnormal uterine bleeding; Anti-seizure medications; Pharmacologic doses of cholecalciferol; Consumed greater than 4 alcoholic drinks a day; Pathologic fractures</p> <p>Interventions: Placebo Daily for 3 Year(s) vs. 60 or 120mg of Raloxifene Daily for 3 Year(s)</p> <p>All received: Calcium</p> <p>Run-in/wash-out unclear</p> <p>Fracture outcomes assessed at baseline, 36 months</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures</p>	<p>Ankle at 36 MOS: Raloxifene (30&amp;60mg) vs Placebo: 0.7% vs 1.1% OR = 0.59 (95% CI 0.35, 1.00) NNT=235.8 (95% CI 113.4-2957)</p> <p>Hip fracture at 36 MOS: Raloxifene (30&amp;60mg) vs Placebo: 0.8% vs 0.7% OR = 1.11 (95% CI 0.64, 1.93)</p> <p>Non-vertebral fracture at 36 MOS: Raloxifene (30&amp;60mg) vs Placebo: 8.5% vs 9.3% OR = 0.91 (95% CI 0.77, 1.07)</p> <p>Vertebral fracture at 36 MOS: Raloxifene (30&amp;60mg) vs Placebo: 6.0% vs 10.1% OR = 0.55 (95% CI 0.45, 0.67) NNT=24.5 (95% CI 18.2-37.5)</p> <p>Wrist at 36 MOS: Raloxifene (30&amp;60mg) vs Placebo: 2.9% vs 3.3% OR = 0.88 (95% CI 0.67, 1.15)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-3. Large Randomized Controlled Trials from Original Report  
Parathyroid hormone

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
<p>Neer et al., 2001<sup>130</sup></p> <p>PTH (Teriparatide) (Forteo)</p> <p>Location: 17 countries not listed</p> <p>Setting: Multicenter</p> <p>Jadad: 0</p> <p>Age Mean/Range: NR</p> <p>100% Female</p> <p>Race: Caucasian, Other</p> <p>Screened: 9,347 Eligible: NR Enrolled: 1,637 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE Assessment: Monitored, Reported spontaneously by patient</p>	<p>Inclusion criteria: Ambulatory, Post-menopausal women &gt;5 years, T-Score ≤ -1.0 Hip, T-Score ≤ -1.0 Spine, Radiographic fractures, clinically silent</p> <p>Exclusion criteria: Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Urolithiasis, Medications known to affect skeleton, Alcohol and drug abuse; Taking drugs that affect metabolism</p> <p>Interventions: Placebo Daily for 24 Month(s) vs. 20µg of PTH (teriparatide) Daily for 24 Month(s) vs. 40µg of PTH (teriparatide) Daily for 24 Month(s)</p> <p>All received: Calcium, Vitamin D</p> <p>Run-in/wash-out unclear</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Non-vertebral fracture, Radiographic vertebral fractures</p>	<p>Non-vertebral fracture, ≥1 at 21 MOS: PTH, 20 mug vs Placebo: 6.3% vs 9.7% OR = 0.63 (95% CI 0.40, 0.97) NNT=28.9 (95% CI 15.0-426.6) PTH, 40 mug vs Placebo: 5.8% vs 9.7% OR = 0.58 (95% CI 0.37, 0.90) NNT=25.3 (95% CI 14.1-127.9)</p> <p>Vertebral fracture, ≥1 at 21 MOS: PTH, 20 mug vs Placebo: 5.0% vs 14.3% OR = 0.34 (95% CI 0.22, 0.54) NNT=10.7 (95% CI 7.6-18.1) PTH, 40 mug vs Placebo: 4.4% vs 14.3% OR = 0.31 (95% CI 0.20, 0.49) NNT=10.1 (95% CI 7.3-16.3)</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-4. Observational Studies  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Quality
<p>Mamdani et al., 2007<sup>418</sup></p> <p>Bisphosphonates</p> <p>Location: Canada</p> <p>Age Mean/Range: NR</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Enrolled: 20,587 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE Assessment: NR</p>	<p>Inclusion criteria: Women otherwise undefined, Age over 65 years, Include only new prescription for etidronate, alendronate, or risedronate.</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Hypercalcemia, Metabolic bone disorder other than osteoporosis, Bisphosphonates, Medications known to affect skeleton, past history of hip fracture within 5 years. In long term facility, epilepsy, trauma hospitalization, pathological fracture</p> <p>Interventions: Alendronate + Denosumab + Risedronate vs. Etidronate + Denosumab + Calcium</p> <p>Fracture outcomes assessment time not reported</p> <p>Outcomes: Hip fracture</p>	<p>From where were patients identified? Regional</p> <p>How were patients selected? Population-based, systematic, or representative sample</p> <p>Are primary outcomes assessed using valid and reliable measures? Yes</p> <p>Are outcome measures implemented consistently across all study participants? Yes</p> <p>Were the important confounding and modifying variables taken into account in the design and analysis? Yes</p> <p>How was the non-exposed cohort selected? Drawn from the same community as the exposed cohort</p> <p>How was exposure to LBD drugs/exercise ascertained? Claims data</p> <p>Was it demonstrated that the outcome of interest was not present at the start of the study? Yes</p>

Evidence Table C-4. Observational Studies  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Quality
<p>Curtis et al., 2009<sup>419</sup></p> <p>Alendronate (Fosamax), Risedronate (Actonel)</p> <p>Location: US</p> <p>Age Mean/Range: NR/NR</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Enrolled: 19,063 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE Assessment: NR</p>	<p>Inclusion criteria: Women otherwise undefined</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Metabolic bone disorder other than osteoporosis, Bisphosphonates, HIV disease</p> <p>Interventions: 70mg of Alendronate Weekly for 3 Year(s) vs. 35mg of Risedronate Weekly for 3 Year(s)</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes: Hip fracture, Proximal humerus fracture, Radial fracture, Vertebral fracture, Non-vertebral fracture, Symptomatic vertebral fractures</p>	<p>From where were patients identified? Regional</p> <p>How were patients selected? Population-based, systematic, or representative sample</p> <p>Are primary outcomes assessed using valid and reliable measures? Yes</p> <p>Are outcome measures implemented consistently across all study participants? Yes</p> <p>Were the important confounding and modifying variables taken into account in the design and analysis? Yes</p> <p>How was the non-exposed cohort selected? Drawn from the same community as the exposed cohort</p> <p>How was exposure to LBD drugs/exercise ascertained? Claims data</p> <p>Was it demonstrated that the outcome of interest was not present at the start of the study? Yes</p>

Evidence Table C-4. Observational Studies  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Quality
<p>Abelson et al., 2009<sup>420</sup></p> <p>Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel)</p> <p>Location: US</p> <p>Age</p> <p>Mean/Range: NR/NR</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Enrolled: 210114 Withdrawn: NR Lost to follow-up: NR Analyzed: NR</p> <p>Method of AE Assessment: NR</p>	<p>Inclusion criteria: Women otherwise undefined, 3 months or more in datasource</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Metabolic bone disorder other than osteoporosis</p> <p>Interventions: 70mg of Alendronate Weekly for 12 Month(s) vs. 35mg of Risedronate Weekly for 12 Month(s) vs. 150mg of Ibandronate Weekly for 12 Month(s)</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes: Hip fracture, Vertebral fracture, Non-vertebral fracture</p>	<p>From where were patients identified? National/International</p> <p>How were patients selected? Population-based, systematic, or representative sample</p> <p>Are primary outcomes assessed using valid and reliable measures? Yes</p> <p>Are outcome measures implemented consistently across all study participants? Yes</p> <p>Were the important confounding and modifying variables taken into account in the design and analysis? No</p> <p>How was the non-exposed cohort selected? Drawn from the same community as the exposed cohort</p> <p>How was exposure to LBD drugs/exercise ascertained? Claims data</p> <p>Was it demonstrated that the outcome of interest was not present at the start of the study? Yes</p>

Evidence Table C-4. Observational Studies  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Quality
<p>Langsetmo et al., 2009<sup>421</sup> Bisphosphonates, Estrogen Location: Canada Trial: CAMOS Age Mean/Range: NR 100% Female Race: Not reported Screened: NR Eligible: NR Enrolled: 1,757 Withdrawn: NR Lost to follow-up: NR Analyzed: NR Method of AE Assessment: NR</p>	<p>Inclusion criteria: Age over 49 years, non-institutionalized. For cases: self-reported incident, low-trauma non-vertebral fractures. Controls - age and diagnosis-matched, no fracture</p> <p>Exclusion criteria: Calcitonin, SERMS, Residence not within 50km of 9 metropolitan centers</p> <p>Interventions: Control vs. Estrogen or Bisphosphonate</p> <p>Fracture outcomes assessed at baseline, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years</p> <p>Outcomes: Non-vertebral fracture</p>	<p>From where were patients identified? National/International</p> <p>How were patients selected? Population-based, systematic, or representative sample</p> <p>Are primary outcomes assessed using valid and reliable measures? Yes</p> <p>Are outcome measures implemented consistently across all study participants? Yes</p> <p>Were the important confounding and modifying variables taken into account in the design and analysis? Yes</p> <p>How was the non-exposed cohort selected? Drawn from the same community as the exposed cohort</p> <p>How was exposure to LBD drugs/exercise ascertained? Written self report</p> <p>Was it demonstrated that the outcome of interest was not present at the start of the study? Yes</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-4. Observational Studies  
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Quality
<p>Adami et al., 2009<sup>422</sup>                      Alendronate (Fosamax),                      Raloxifene (Evista),                      Risedronate (Actonel)                      Location: Western Europe                      Age                      Mean/Range: NR                      100% Female                      Race: Not reported                      Screened: NR                      Eligible: NR                      Enrolled: 1,515                      Withdrawn: NR                      Lost to follow-up: NR                      Analyzed: NR                      Method of AE                      Assessment:                      NR</p>	<p>Inclusion criteria:                      Post-menopausal women NOS, T-Score <math>\leq</math> -2.5 Hip, T-Score <math>\leq</math> -2.5 Spine, Clinical fractures, radiographic conf. unclear, heel bone, bone density <math>\leq</math>2.5 - on raloxifene (60mg/day), alendronate (70mg/ once a week) risedronate (35mg/weekly) -11 to 18 month adherence &gt;75%</p> <p>Exclusion criteria:                      Carcinoma or suspected carcinoma, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Corticoids/Glucocorticoids, Medications known to affect skeleton, 2 degree osteoporosis</p> <p>Interventions:                      Usual care</p> <p>Fracture outcomes assessed at baseline</p> <p>Outcomes:                      Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine</p>	<p>From where were patients identified?                      Multiple clinics</p> <p>How were patients selected?                      Population-based, systematic, or representative sample</p> <p>Are primary outcomes assessed using valid and reliable measures?                      Unclear/Not reported</p> <p>Are outcome measures implemented consistently across all study participants?                      Unclear/Not reported</p> <p>Were the important confounding and modifying variables taken into account in the design and analysis?                      Unclear/Not reported</p> <p>How was the non-exposed cohort selected?                      Drawn from the same community as the exposed cohort</p> <p>How was exposure to LBD drugs/exercise ascertained?                      Secure record (e.g. medical records)</p> <p>Was it demonstrated that the outcome of interest was not present at the start of the study?                      Yes</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-4. Observational Studies  
Parathyroid hormone

Citation & Study info	Eligibility, Interventions, Outcomes	Quality
<p>Langdahl et al., 2009<sup>423</sup></p> <p>PTH (Teriparatide) (Forteo)</p> <p>Location: UK, Western Europe, Eastern Europe</p> <p>Trial: EFOS</p> <p>Age Mean/Range: 72/NR</p> <p>100% Female</p> <p>Race: Not reported</p> <p>Screened: NR Eligible: NR Enrolled: 1,648 Withdrawn: NR Lost to follow-up: NR Analyzed: 1,356</p> <p>Method of AE Assessment: Reported spontaneously by patient</p>	<p>Inclusion criteria: Post-menopausal women NOS, Osteoporosis NOS, Patients beginning Teriparatide: trx.</p> <p>Exclusion criteria: Concurrent treatment investigational drug, contra-indications to teriparatide use</p> <p>Interventions: PTH (teriparatide)</p> <p>Fracture outcomes assessed at baseline, 6 months, 12 months, 18 months</p> <p>Outcomes: Non-vertebral fracture, Symptomatic vertebral fractures, All cause mortality, BALP, Back pain, HRQOL</p>	<p>From where were patients identified? Multiple clinics</p> <p>How were patients selected? Population-based, systematic, or representative sample</p> <p>Are primary outcomes assessed using valid and reliable measures? Yes</p> <p>Are outcome measures implemented consistently across all study participants? Yes</p> <p>Were the important confounding and modifying variables taken into account in the design and analysis? No</p> <p>How was exposure to LBD drugs/exercise ascertained? Written self report</p> <p>Was it demonstrated that the outcome of interest was not present at the start of the study? Yes</p>

Evidence Table C-4. Observational Studies  
Estrogen

Citation & Study info	Eligibility, Interventions, Outcomes	Quality
<p>Vestergaard et al., 2006<sup>424</sup> Estrogen Location: Western Europe Age Mean/Range: 52/NR 100% Female Race: Not reported Screened: NR Eligible: NR Enrolled: 258189 Withdrawn: NR Lost to follow-up: NR Analyzed: NR Method of AE Assessment: NR</p>	<p>Inclusion criteria: Women otherwise undefined, Cases= all women who sustained a fracture in 2000 in Denmark. Controls= 3 age-matched women from general population per case.</p> <p>Exclusion criteria: Not Reported</p> <p>Interventions: Less than 0.3; 0.3-0.99; Greater than 1 Defined Daily Dose of Est./progestin Daily vs. Less than 0.3; 0.3-0.99; Greater than 1 Defined Daily Dose of Estrogen patch Daily</p> <p>Fracture outcomes assessment time not reported</p> <p>Outcomes: Hip fracture, Vertebral fracture, All cause mortality, BALP, Any fracture, Colles fracture</p>	<p>From where were patients identified? National/International</p> <p>How were patients selected? Population-based, systematic, or representative sample</p> <p>Are primary outcomes assessed using valid and reliable measures? Yes</p> <p>Are outcome measures implemented consistently across all study participants? Yes</p> <p>Were the important confounding and modifying variables taken into account in the design and analysis? Yes</p> <p>How was the non-exposed cohort selected? Drawn from the same community as the exposed cohort</p> <p>How was exposure to LBD drugs/exercise ascertained? Secure record (e.g. medical records)</p> <p>Was it demonstrated that the outcome of interest was not present at the start of the study? Unclear/Not reported</p>

AE=Adverse Event, NR=Not Reported

Evidence Table C-4. Observational Studies  
Calcium/Vitamin D

Citation & Study info	Eligibility, Interventions, Outcomes	Quality
<p>Nieves et al., 2008<sup>425</sup> Calcium, Vitamin D Trial: NORA Age Mean/Range: 65/50-** 100% Female Race: Caucasian Screened: NR Eligible: NR Enrolled: 76,507 Withdrawn: NR Lost to follow-up: 24,463 Analyzed: 52,144</p>	<p>Inclusion criteria: Ambulatory, Post-menopausal women NOS, Age over 49 years, Completion of dietary questionnaire; Caucasian; Completion of followup questionnaire</p> <p>Exclusion criteria: Bisphosphonates, Calcitonin, SERMS, 1. Participation in any OP clinical trial 2. Osteoporosis (OP) 3. No BMD measurement w/in previous year</p> <p>Interventions: Fracture risk by self-reported calcium intake (&lt;500, 500-800, and ≥ 800 mg/day) and Vitamin D intake (&lt;200, 200-600, and ≥ 600 IU/day)</p> <p>Fracture outcomes assessed at baseline, 39 months</p> <p>Outcomes: Hip fracture, All cause mortality, Any osteoporosis related fracture</p>	<p>From where were patients identified? Multiple clinics</p> <p>How were patients selected? Population-based, systematic, or representative sample</p> <p>Are primary outcomes assessed using valid and reliable measures? No</p> <p>Are outcome measures implemented consistently across all study participants? Yes</p> <p>Were the important confounding and modifying variables taken into account in the design and analysis? Yes</p> <p>How was the non-exposed cohort selected? Drawn from the same community as the exposed cohort</p> <p>How was exposure to LBD drugs/exercise ascertained? Structured interview</p> <p>Was it demonstrated that the outcome of interest was not present at the start of the study? Yes</p>

Evidence Table C-4. Observational Studies  
Physical Activity

Citation & Study info	Eligibility, Interventions, Outcomes	Quality
<p>Feskanich et al., 2002<sup>426</sup></p> <p>Physical activity</p> <p>Location: US</p> <p>Trial: NURSES' HEALTH STUDY</p> <p>Age Mean/Range: 61/40-77</p> <p>100% Female</p> <p>Race: Caucasian, unclear</p> <p>Screened: NR Eligible: NR Enrolled: 61,200 Withdrawn: NR Lost to follow-up: NR Analyzed: 61,200</p> <p>Method of AE Assessment: NR</p>	<p>Inclusion criteria: Post-menopausal women NOS, Age under 56 years, Age over 29 years, Residence in 1 of 11 US states, nurses; For sub-analysis: post-menopausal women 40-77 years</p> <p>Exclusion criteria: Carcinoma or suspected carcinoma, Heart disease, stroke, osteoporosis, Hip fracture (prevalent)</p> <p>Interventions: Exercise</p> <p>Fracture outcomes assessed at baseline, 6 years, 8 years, 10 years</p> <p>Outcomes: Hip fracture</p>	<p>From where were patients identified? 11 states</p> <p>How were patients selected? Nurses received mail survey</p> <p>Are primary outcomes assessed using valid and reliable measures? No</p> <p>Are outcome measures implemented consistently across all study participants? Yes</p> <p>Were the important confounding and modifying variables taken into account in the design and analysis? Yes</p> <p>How was the non-exposed cohort selected? Drawn from the same community as the exposed cohort</p> <p>How was exposure to LBD drugs/exercise ascertained? Structured interview</p> <p>Was it demonstrated that the outcome of interest was not present at the start of the study? Yes</p>

Evidence Table C-5. Adherence

Author, Year, Drug, Design	Exclusively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Abrahamsen et al., 2009 <sup>292</sup> Alendronate (Fosamax)	No	National: Registries-Denmark	10,613	99	Fulfillment, Persistence, Adherence	Pharmacy records/claims data	Prescription refill ratio	3C	Unclear	Overall, (Adherence rates not reported)
Berecki-Gisolf et al., 2008 <sup>307</sup> Bisphosphonates	No	National: Australia	793	0	Unclear	Pharmacy records/claims data	Time until first Gap in refill	3A, 3B	No	Overall, 170.0 days Adherence
Blouin et al., 2007 <sup>293</sup> Alendronate (Fosamax), Etidronate (Didronel)	No	State: Quebec, Canada	4,130	0	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 12 months  Medication possession ratio, 365 days in reporting period, Dichotomous, Cutoff Point: 80.0	3A, 3B	No	Overall, 60.8% Adherence, 47.8% Persistence  Once weekly alendronate, 54.7% Persistence  Once weekly risedronate, 45.2% Persistence  Once daily alendronate, 48.2% Persistence  Once daily risedronate, 47.1% Persistence  Raloxifene, 48.0% Persistence  Nasal Calcitonin, 25.2% Persistence
Blouin et al., 2008 <sup>267</sup> Alendronate (Fosamax), Risedronate (Actonel)	No	National: Claims Database	30,259	0	Adherence	Pharmacy records/claims data	Cutoff Point: 0.8  Prescription refill ratio, Dichotomous, Cutoff Point: < 80%	3C	No	Cases (Fracture), 54.3% Adherence  Controls (No Fracture), 59.3% Adherence

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

Evidence Table C-5. Adherence

Author, Year, Drug, Design	Exclusively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Briesacher et al., 2007 <sup>294</sup> Alendronate (Fosamax), Risedronate (Actonel)	Yes	National: Medstat Databases	17,988	6	Persistence, Adherence	Pharmacy records/claims data	Proportion of Days Covered	3A, 3C	Yes	Overall-1st year, 55.0% Adherence and Persistence  Overall-2nd year, 45.0% Adherence and Persistence  Overall-3rd year, 41.0% Adherence and Persistence
Briesacher et al., 2010 <sup>271</sup> Bisphosphonates	Yes	Market scan database	61,125	10	Adherence	Pharmacy records/claims data	Medication possession ratio, 365 days in reporting period, Dichotomous, Cutoff Point: 80.0	3A, 3B	Yes	Monthly ibandronate, 49.0% Adherence, (MPR>80)  Weekly bisphosphonate, 49.0% Adherence, (MPR>80)  Daily bisphosphonate, 23.0% Adherence, (MPR>80)
Castelo-Branco et al., 2009 <sup>304</sup> Calcium, Vitamin D	No	Multiple clinics: Spain	7,624	6	Persistence, Adherence	Questionnaire	Validated scale, Morisky	3A, 3B	Unclear	Overall, 72.3% Persistence, 31.2% Adherence, (Morisky among persistent patients only)

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

Evidence Table C-5. Adherence

Author, Year, Drug, Design	Exclusively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Cotte et al., 2009 <sup>295</sup>  Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel)	No	National: France	2,990	0	Persistence, Adherence	Pharmacy records/claims data	Discontinuation  Medication possession ratio, Dichotomous, Continuous	3A, 3B	Yes	Monthly ibandronate, 47.5% Persistence  Weekly bisphosphonate, 30.4% Persistence  Monthly ibandronate, 74.1% Adherence, (MPR>80)  Weekly bisphosphonate, 65.8% Adherence, (MPR>80)
Cramer et al., 2006 <sup>296</sup> Study 1 of 3  Alendronate (Fosamax), Bisphosphonates, Risedronate (Actonel)	Yes	Integrated Healthcare Information Services	2,741		Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 12 months  Proportion of Days Covered, 365 days in reporting period, Continuous  Time until discontinuation	3A, 3B	Yes	Overall, 61.0% Adherence, 196.0 days Persistence  Weekly bisphosphonate, 69.0% Adherence, 227.0 days Persistence, 44.0% Persistence, (Persistence at 12 months)  Daily bisphosphonate, 58.0% Adherence, 185.0 days Persistence, 32.0% Persistence, (Persistence at 12 months)

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

Evidence Table C-5. Adherence

Author, Year, Drug, Design	Exclusively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Curtis et al., 2008 <sup>272</sup> Bisphosphonates	Yes	Health plan	101,038	5	Adherence	Pharmacy records/claims data	Medication possession ratio, Dichotomous, Continuous	3A, 3C	Yes	Overall, 39.0% Two years Adherence, (MPR>80 %), 35.0% Three years Adherence, (MPR>80 %)  Overall-Daily, 38.0% One year Adherence, (MPR>80 %)  Overall-Weekly, 45.0% One year Adherence, (MPR>80 %)
Dugard et al., 2009 <sup>305</sup> Bisphosphonates	No	Multiple sites: England	254	0	Persistence, Adherence	Written prescriptions	Discontinuation, 12 months, 60 months  Observed # of RX's written divided by expected, annually	3A, 3B	No	Overall, 44.0% Adherence, (Adherence at 12 months), 74.0% Persistence, (Persistence at 12 months), 23.0% Adherence, (Adherence at 60 months), 50.0% Persistence, (Persistence at 60 months)
Ettinger et al., 2006 <sup>281</sup> Bisphosphonates	Yes	Multi-State: NDC Health Database	211,319	0	Persistence	Pharmacy records/claims data	Discontinuation, 12 months  Proportion with at least 1 day of medication each month	3A, 3B	Yes	Weekly bisphosphonate, 56.7% Persistence, (Persistence at 12 months)  Daily bisphosphonate, 40.0% Persistence, (Persistence at 12 months)
Feldstein et al., 2009 <sup>276</sup> Bisphosphonates	Yes	Health plan: HMO-Oregon and Washington	3,658	0	Adherence	Pharmacy records/claims data	Proportion of Days Covered	3A, 3C	Yes	Overall-MPR>80 %, 45.0% patients Adherence
Gallagher et al., 2008 <sup>290</sup> Alendronate (Fosamax), Risedronate (Actonel)	No	National: General Practice Research Database UK	44,531	19	Persistence, Adherence	Medical records, Prescriptions dispensed	Discontinuation  Medication possession ratio	3A, 3B, 3C	Yes	Overall, 58.0% At 12 months Persistence

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

Evidence Table C-5. Adherence

Author, Year, Drug, Design	Exclusively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Gold et al., 2006 <sup>297</sup>  Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel)	Yes	IMS longitudinal Database	240,001	0	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 6 months  Medication possession ratio, 180 days in reporting period, Continuous, Time until Gap > 90 days	3A, 3B	Yes	Weekly risedronate, 83.3% mean MPR, 144.3 days Mean Persistence, 56.0% Persistence, (Persistence at 6 months)  Monthly ibandronate, 78.5% mean MPR, 100.1 days Mean Persistence, 29.0% Persistence, (Persistence at 6 months)  New users-Monthly ibandronate, 78.0% Adherence, 92.1 days Mean Persistence  New users-Weekly risedronate, 79.6% Adherence, 103.5 days Mean Persistence
Gold et al., 2007 <sup>282</sup>  Alendronate (Fosamax)	Yes	Health plan	4,769	0	Persistence	Pharmacy records/claims data	Delayed filling prescription 30 days	3B, 3C	Yes	Overall, 42.6% Persistence
Gold et al., 2009 <sup>298</sup>  Ibandronate (Boniva), Risedronate (Actonel)	Yes	IMS Health	263,383	7	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 12 months  Medication possession ratio, Continuous  Gap > 90 days, Cumulative Drug Availability	3A, 3B	Yes	Weekly risedronate, 80.0% mean MPR, 64.5% mean CDA, 250.0 days Mean Persistence, 40.0% Persistence, (Persistence at 12 months)  Monthly ibandronate, 74.7% mean MPR, 43.4% mean CDA, 151.0 days Persistence, 18.0% Persistence, (Persistence at 12 months)

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

Evidence Table C-5. Adherence

Author, Year, Drug, Design	Exclusively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Grazio et al., 2008 <sup>275</sup> Alendronate (Fosamax)	No	Multiple clinics: Croatia	102	6	Adherence	Unclear	Proportion of Days Covered, 365 days in reporting period, Dichotomous, Cutoff Point: 80.0  Prescribed doses taken with specified period, 365 days in reporting period, Dichotomous, Cutoff Point: 100.0	3A, 3B	Unclear	Overall, 65.7% Adherence, (Percent with Perfect Adherence)
Hansen et al., 2008 <sup>268</sup> Alendronate (Fosamax)	Yes	Single clinic/ hosp/pharmacy: Wisconsin VA medical center	198	100	Adherence	Pharmacy records/claims data	Prescription refill ratio, 730 days in reporting period, Dichotomous	3A, 3B	Unclear	Overall, 54.0% Adherence, (At 2 years)
Harris et al., 2009 <sup>283</sup> Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel)	Yes	Health plan: i3 Research Database	91,630	0	Persistence	Pharmacy records/claims data	Delayed filling prescription 30 days for weekly meds and 45 days for monthly meds	3A	Yes	Overall, 70.1% 90 days Persistence  Monthly oral Ibandronate, 73.3% Adherence  Weekly Bisphosphonate, 69.7% Adherence
Hoer et al., 2009 <sup>302</sup> Bisphosphonates	No	Health plan: German Statutory Sickness Fund	4,451	26	Persistence, Adherence	Pharmacy records/claims data	Discontinuation  Medication possession ratio, 180/360/720 days in reporting period, Dichotomous, Cutoff Point: 0.8	3B, 3C	Yes	Overall, 43.7% 12 months Adherence  Patients with previous fractures, 47.3% 12 months Persistence
Ideguchi et al., 2007 <sup>284</sup> Alendronate (Fosamax), Bisphosphonates, Etidronate (Didronel), Risedronate (Actonel)	No	Single clinic/ hosp/pharmacy: Japan	1,307	15	Persistence	Pharmacy records/claims data	Discontinuation	3A, 3B	Unclear	Overall, 74.8% Persistence, (Persistence at 12 months), 60.6% Persistence, (Persistence at 36 months), 51.7% Persistence, (Persistence at 60 months)

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

Evidence Table C-5. Adherence

Author, Year, Drug, Design	Exclusively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Ideguchi et al., 2008 <sup>280</sup> Bisphosphonates	No	Single clinic/ hosp/pharmacy: Yokohanna, Japan	1,307	15	Persistence	Pharmacy records/claims data	Discontinuation	3A, 3B	Unclear	(Data not Interpretable)
Jones et al., 2008 <sup>285</sup> Alendronate (Fosamax), Risedronate (Actonel)	No	State: Ontario	62,897	0	Persistence	Pharmacy records/claims data	Discontinuation, 12 months	3A, 3B	Unclear	Weekly risedronate, 54.4% Persistence, (Persistence at 12 months)  Weekly alendronate, 56.3% Persistence, (Persistence at 12 months)
Kamatari et al., 2007 <sup>306</sup> Alendronate (Fosamax), Risedronate (Actonel)	No	Multiple clinics: Japan	208	3	Unclear	Pharmacy records/claims data	No refill 28 days after due	3B	Unclear	Overall, 78.0% Adherent
Kertes et al., 2008 <sup>299</sup> Bisphosphonates	No	Health plan: Maccabi, Israel	4,448	0	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 12 months  Medication possession ratio, 365 days in reporting period, Dichotomous, Continuous, Cutoff Point: 0.8  # of days until gap > 30 days	3A, 3B	Unclear	Overall, 66.0% mean MPR Adherence, 52.5% Adherence, (MPR>80), 216.0 days Mean Persistence, 46.0% Persistence, (Persistence at 12 months)
McHorney et al., 2007 <sup>288</sup> Bisphosphonates	Yes	National Retail Pharmacy Chain	1,092	0	Persistence	Telephone interview, Pharmacy records/claims data	Discontinuation, 7 months	3A, 3B	Yes	Overall, 55.0% Persistence, (Persistence at 7 months)
Palacios et al., 2009 <sup>274</sup> Bisphosphonates, Calcium, Vitamin D, Estrogen, PTH (Teriparatide) (Forteo), Raloxifene (Evista), Strontium ranelate	No	Multiple clinics: Spain	1,179	0	Adherence	Questionnaire	Haynes and Sackett and Morisky combination	3A, 3B	Unclear	Overall, 39.2% Adherence

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

Evidence Table C-5. Adherence

Author, Year, Drug, Design	Exclusively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Penning-van Beest et al., 2008 <sup>269</sup>  Alendronate (Fosamax), Bisphosphonates, Risedronate (Actonel)	No	Pharmo	8,822	0	Adherence	Pharmacy records/claims data	Medication possession ratio, 90 days in reporting period, Dichotomous, Cutoff Point: 0.8	3A, 3C	Yes	Overall, 58.0% At 1 year Adherence, 66.0% At 6 months Adherence
Penning-van Beest et al., 2008 <sup>270</sup>  Bisphosphonates	No	Pharmo Database	8,822	0	Adherence	Pharmacy records/claims data	Medication possession ratio, 365 days in reporting period, Dichotomous	3A, 3B	Yes	Overall, 58.0% Adherence, (MPR>80)  Weekly bisphosphonate, 64.3% Adherence, (MPR>80)  Daily bisphosphonate (after July 2000), 52.0% Adherence, (MPR>80)  Daily bisphosphonate (before July 2000), 47.5% Adherence, (MPR>80)
Rabenda et al., 2008 <sup>303</sup>  Alendronate (Fosamax), Raloxifene (Evista)	No	National	99,924	0	Persistence, Adherence	Pharmacy records/claims data, Medical records	Medication possession ratio, 365 days in reporting period, Dichotomous  Proportion of Days Covered	3A, 3B, 3C	Unclear	Overall, 64.7% mean MPR, 40.4% at 12 months Persistence, 35.7% weeks Median Persistence  Daily alendronate, 58.6% Adherence, (48.1 % had a 12 month MPR = 80 %; 40.4 % in daily therapy; 57 % in weekly therapy; y = 80 %)  Weekly alendronate, 70.5% Adherence

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

Evidence Table C-5. Adherence

Author, Year, Drug, Design	Exclusively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Rabenda et al., 2008 <sup>300</sup> Alendronate (Fosamax)	No	National: Belgium	1,376	0	Persistence, Adherence	Pharmacy records/claims data	Medication possession ratio, 365 days in reporting period, Dichotomous, Cutoff Point: 80.0  Gap > 35 days	3A, 3B	Unclear	Overall, 48.7% Adherence, (MPR>80), 67.0% mean MPR Adherence, 41.0% Persistence, (Persistence at 12 months)  Daily alendronate, 65.9% Adherence, (MPR>80)  Weekly alendronate, 67.7% Adherence, (MPR>80)
Ringe et al., 2007 <sup>289</sup> Alendronate (Fosamax), Raloxifene (Evista), Risedronate (Actonel)	No	Multiple sites: Europe, Lebanon, South Africa	5,198	0	Persistence, Adherence	In-person interview	Discontinuation, 12 months  Prescribed doses taken with specified period, 365 days in reporting period, Dichotomous	3A, 3B	Yes	Overall, 80.8% Persistence, (Persistence at 12 months)  Raloxifene, 80.0% Adherence, 82.0% Persistence, (Persistence at 12 months)  Daily alendronate, 79.0% Adherence, 83.0% Persistence, (Persistence at 12 months)  Weekly alendronate, 65.0% Adherence, 74.0% Persistence, (Persistence at 12 months)  Daily risedronate, 76.0% Adherence, 79.0% Persistence, (Persistence at 12 months)

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

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Author, Year, Drug, Design	Exclusively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Ringe et al., 2009 <sup>278</sup> Alendronate (Fosamax), Risedronate (Actonel)	No	Single clinic/ hosp/pharmacy: Germany	204	0	Persistence	In-person interview	Discontinuation, 12 months	3A	No	Generic alendronate, 68.0% Persistence, (Persistence at 12 months)  Brand fosamax, 84.0% Persistence, (Persistence at 12 months)  Brand actonel, 94.0% Persistence, (Persistence at 12 months)
Roughead et al., 2009 <sup>291</sup> Bisphosphonates	No	National: Australian Veterans	42,885	37	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 12 months  Medication possession ratio, Dichotomous, Continuous, Cutoff Point: 0.8  Gap > 105 days	3A	No	Overall, 81.0% Adherence, (MPR>80), 66.0% mean MPR Adherence, 53.0% Persistence, (Persistence at 12 months)
Sewerynek et al., 2009 <sup>279</sup> Alendronate (Fosamax)		Single clinic/ hosp/pharmacy: Poland	118	0	Persistence	Not specified	Unclear	3A	Unclear	(Data not Interpretable)
Sheehy et al., 2009 <sup>286</sup> Alendronate (Fosamax), Risedronate (Actonel)	No	Quebec	32,804	10	Persistence	Pharmacy records/claims data	Refill gap > 1.5 x length of Rx	3A, 3B	Unclear	(Data on adherence rates not available)

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

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Author, Year, Drug, Design	Exclusively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Van den Boogaard et al., 2006 <sup>301</sup>  Alendronate (Fosamax), Bisphosphonates, Etidronate (Didronel), Risedronate (Actonel)	No	National: Pharmo	14,760	0	Persistence, Adherence	Pharmacy records/claims data	Continuous use (refill gap less than 7 days)	3A, 3B, 3C	Yes	Overall, 43.6% At one year Adherence, (Percentage of persistent patients by 15 % decreased number of osteoporotic fractures by 4 %), 27.4% At two years Adherence  Daily alendronate, 33.2% At one year Adherence  Weekly alendronate, 47.9% At one year Adherence  Daily risedronate, 33.4% At one year Adherence  Weekly risedronate, 47.4% At One year Adherence
Vytrisalova et al., 2008 <sup>273</sup>  Alendronate (Fosamax), Vitamin D, Raloxifene (Evista), Risedronate (Actonel)	No	Multiple clinics: Czech Republic	200	0	Adherence	Questionnaire	Prescribed doses taken with specified period, 30 days in reporting period, Dichotomous, Cutoff Point: 0.8  Following dosing instructions	3A, 3B	Unclear	Overall, 89.0% Adherence, (MPR>80), 58.0% Adherence, (Following dosing instructions)  Bisphosphonates, 89.0% Adherence, (MPR>80)  Raloxifene, 94.0% Adherence, (MPR>80)  Calcitonin, 88.0% Adherence, (MPR>80)

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

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Author, Year, Drug, Design	Exclusively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Weiss et al., 2007 <sup>287</sup>  Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel)	Yes	IMS longitudinal database	165,955	0	Persistence	Pharmacy records/claims data	Discontinuation, 1 months  # of days until Gap > 30 days	3A, 3B	Yes	Weekly alendronate, 116.0 days Mean Persistence, 54.2% Persistence, (Failing to refill after 1st rx)  Weekly risedronate, 113.0 days Mean Persistence, 52.3% Persistence, (Failing to refill after 1st rx)  Monthly ibandronate, 98.0 days Mean Persistence, 45.5% Persistence, (Failing to refill after 1st rx)
Yood et al., 2003 <sup>277</sup>  Bisphosphonates, Estrogen, Raloxifene (Evista)	Yes	Group Practice	176	0	Fulfillment, Adherence	Pharmacy records/claims data	# of prescriptions filled	3A	Yes	Overall-Participants, 70.1% Compliance  Overall-Refusers, 66.5% Compliance  Alendronate and Etidronate-All, 70.7% Compliance  Alendronate and Etidronate- Bisphon participants, 74.5% Compliance  Estrogen- All, 69.3% Compliance  Estrogen- Participants, 69.7% Compliance

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Adachi et al., 2009 <sup>324</sup> Alendronate (Fosamax)	Alendronate monohydrate 10 mg/day vs Placebo: Any adverse event: 57.0%(166/291) vs 51.7%(76/147) Breast cancer: 0.7%(2/291) vs 0.0%(0/147) Death: 0.0%(0/291) vs 0.0%(0/147) Diverticulitis: 0.3%(1/291) vs 0.0%(0/147) Dyspepsia: 7.9%(23/291) vs 0.0%(0/147) Esophgaeal spasm: 0.3%(1/291) vs 0.0%(0/147) Nonserious upper GI bleed: 0.3%(1/291) vs 0.0%(0/147) Serious adverse event: 1.4%(4/291) vs 0.7%(1/147) Serious upper GI event: 20.3%(59/291) vs 12.9%(19/147) Upper GI event: 22.7%(66/291) vs 20.4%(30/147) Withdrawals: 18.6%(54/291) vs 11.6%(17/147)
Hagino et al., 2009 <sup>427</sup> Alendronate (Fosamax)	Alendronate 5 mg vs Minodronate 1 mg: Any adverse event: 84.4%(114/135) vs 88.8%(119/134) Abnormal lab data: 21.5%(29/135) vs 29.1%(39/134) Drug related GI AE: 9.6%(13/135) vs 14.2%(19/134) Gastrointestinal adverse event: 37.0%(50/135) vs 39.6%(53/134) Serious adverse event: 2.2%(3/135) vs 4.5%(6/134) Withdrawals: 10.4%(14/135) vs 8.2%(11/134)
Heckbert et al., 2008 <sup>428</sup> Alendronate (Fosamax)	Alendronate (current user) vs No alendronate: Atrial fibrillation: all: 47.4%(27/57) vs 42.1%(672/1,598)
Lems et al., 2006 <sup>429</sup> Alendronate (Fosamax)	Alendronate 5 mg/day + Calcium 1000 mg/day + Vitamin D 400 mg/day vs Placebo + Calcium 1000 mg/day + Vitamin D 400 mg/day: Any adverse event: 68.1%(64/94) vs 72.5%(50/69) Any serious adverse event: 12.8%(12/94) vs 17.4%(12/69) Cardiovascular disease: 4.3%(4/94) vs 8.7%(6/69) Dyspepsia: 18.1%(17/94) vs 14.5%(10/69) Gastroenteritis: 1.1%(1/94) vs 2.9%(2/69) Infection: 2.1%(2/94) vs 0.0%(0/69) Malignancy: 0.0%(0/94) vs 1.4%(1/69) New incident vertebral deformities: 9.6%(9/94) vs 2.9%(2/69) Other: 11.7%(11/94) vs 17.4%(12/69) Patients with upper GI effects: 17.0%(16/94) vs 17.4%(12/69) Stomatitis: 1.1%(1/94) vs 1.4%(1/69) Ulcer: 3.2%(3/94) vs 2.9%(2/69) Upper GI symptoms: 2.1%(2/94) vs 1.4%(1/69) Withdrawals: 16.0%(15/94) vs 24.6%(17/69) Withdrawals due to adverse events: 16.0%(15/94) vs 21.7%(15/69)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Papaioannou et al., 2008 <sup>57</sup> Alendronate (Fosamax) Trial: CFOS	Alendronate 70 mg/week + Calcium 1000 mg + Vitamin D 800 IU vs Placebo 70 mg/week + Calcium 1000 mg + Vitamin D 800 IU: Any adverse event: 55.6%(15/27) vs 65.5%(19/29) Any serious adverse event: 25.9%(7/27) vs 10.3%(3/29) Bronchial superinfection: 3.7%(1/27) vs 0.0%(0/29) Constipation: 3.7%(1/27) vs 3.4%(1/29) Difficulty swallowing: 3.7%(1/27) vs 0.0%(0/29) Esophagitis: 3.7%(1/27) vs 0.0%(0/29) Exacerbation of cystic fibrosis: 11.1%(3/27) vs 10.3%(3/29) GI upset: 3.7%(1/27) vs 0.0%(0/29) Hypoglycemic seizure: 3.7%(1/27) vs 0.0%(0/29) Intestinal obstruction: 3.7%(1/27) vs 3.4%(1/29) Nausea and/or vomiting: 11.1%(3/27) vs 13.8%(4/29) Reflux: 3.7%(1/27) vs 0.0%(0/29) Stomach pain/burn: 3.7%(1/27) vs 3.4%(1/29) Withdrawals: 14.8%(4/27) vs 17.2%(5/29)
Yan et al., 2009 <sup>430</sup> Alendronate (Fosamax)	Alendronate 70 mg/week + Calcium 500 mg/day + Vitamin D 200 IU/day vs Placebo week + Calcium 500 mg/day + Vitamin D 200 IU/day: Any adverse event: 43.2%(121/280) vs 36.8%(103/280) Abdominal distention: 2.5%(7/280) vs 0.7%(2/280) Abdominal pain: 6.8%(19/280) vs 4.6%(13/280) Acid regurgitation: 1.8%(5/280) vs 3.6%(10/280) Dyspepsia: 1.1%(3/280) vs 2.9%(8/280) Nausea: 4.3%(12/280) vs 2.9%(8/280) Upper GI event: 16.8%(47/280) vs 15.4%(43/280) Vomiting: 0.4%(1/280) vs 0.7%(2/280)
Bunch et al., 2009 <sup>431</sup> Bisphosphonates	Bisphosphonate (angiographic database) vs Bisphosphonate (health plan database) vs No bisphosphonate (angiographic database) vs No bisphosphonate (health plan database): Atrial Fibrillation: 10.2%(10/98) vs 2.9%(220/7,489) vs 10.1%(964/9,525) vs 2.6%(792/29,996) Death: 32.7%(32/98) vs 1.8%(134/7,489) vs 18.8%(1,791/9,525) vs 2.0%(606/29,996) Myocardial infarction: 10.2%(10/98) vs 0.9%(68/7,489) vs 7.8%(739/9,525) vs 1.1%(343/29,996)
Cardwell et al., 2010 <sup>326</sup> Bisphosphonates	Bisphosphonates vs Control: Esophageal cancer: 0.2%(79/41,826) vs 0.2%(72/41,826) Gastric cancer: 0.1%(37/41,826) vs 0.1%(43/41,826)
Cartsos et al., 2008 <sup>432</sup> Bisphosphonates	Intravenous bisphosphonate: Cancer Group vs Intravenous bisphosphonate: Osteoporosis group vs No bisphosphonate: Cancer Group vs No bisphosphonate: Osteoporosis group vs Oral bisphosphonate: Cancer Group vs Oral bisphosphonate: Osteoporosis group: Inflammatory necrosis of jaw: 0.5%(39/8,207) vs 0.5%(9/1,751) vs 0.1%(251/235,553) vs 0.1%(339/263,352) vs 0.1%(31/24,579) vs 0.1%(150/176,889) Surgery: Cancer Process: 0.1%(6/8,533) vs 0.0%(0/1,853) vs 0.1%(161/235,553) vs 0.0%(105/263,352) vs 0.0%(11/25,025) vs 0.0%(58/179,827) Surgery: Necrotic Process: 0.2%(20/8,533) vs 0.2%(4/1,853) vs 0.0%(81/235,553) vs 0.0%(73/263,352) vs 0.0%(7/25,025) vs 0.0%(43/179,827)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Green et al., 2010 <sup>325</sup> Bisphosphonates	Bisphosphonates vs Control: Colorectal cancer: 15.1%(276/1,831) vs 16.8%(10365/61,832) Esophageal cancer: 20.7%(90/435) vs 16.6%(2,864/17,240) Stomach cancer: 15.4%(49/319) vs 16.8%(1,969/11,706)
McHorney et al., 2007 <sup>288</sup> Bisphosphonates	Bisphosphonates: Non-adherence: 44.6%(453/1,015) Non-adherence due to adverse events: 6.6%(67/1,015)
Payer et al., 2009 <sup>433</sup> Bisphosphonates, None of the interventions	Bisphosphonates: GI and muscular AE: 33.0%(672/2,035) Gastrointestinal symptoms: 28.0%(570/2,035) Muscular side effects: 32.0%(651/2,035) Symptoms of Reflux: 37.0%(753/2,035) Withdrawals due to adverse events: 0.0%(0/2,035)
Eisman et al., 2008 <sup>434</sup> Ibandronate (Boniva) Trial: DIVA	Intravenous ibandronate 2 mg every 2mo plus oral placebo + Calcium 500 mg + Vitamin D 400 IU vs Intravenous ibandronate 3 mg every 3mo plus oral placebo + Calcium 500 mg + Vitamin D 400 IU vs Intravenous placebo plus 2.5 mg daily oral ibandronate + Calcium 500 mg + Vitamin D 400 IU: Any adverse event: 88.6%(397/448) vs 85.3%(400/469) vs 87.7%(408/465) Anemia: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) Any serious adverse event: 16.3%(73/448) vs 13.2%(62/469) vs 14.4%(67/465) Death due to acute pancreatitis: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) Death due to gallbladder cancer: 0.0%(0/448) vs 0.0%(0/469) vs 0.2%(1/465) Death due to myocardial infarction: 0.2%(1/448) vs 0.4%(2/469) vs 0.0%(0/465) Death due to pulmonary edema: 0.0%(0/448) vs 0.0%(0/469) vs 0.2%(1/465) Death due to pulmonary embolism: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) Death due to ventricular arrhythmia and aortic dissection: 0.0%(0/448) vs 0.0%(0/469) vs 0.2%(1/465) Drug hypersensitivity: 0.0%(0/448) vs 0.2%(1/469) vs 0.0%(0/465) Esophageal ulcer: 0.0%(0/448) vs 0.2%(1/469) vs 0.0%(0/465) Gastric ulcer: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) Gastritis: 0.0%(0/448) vs 0.4%(2/469) vs 0.0%(0/465) Gastrointestinal ulcer: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) General flu-like symptoms: 1.6%(7/448) vs 4.5%(21/469) vs 18.9%(88/465) Increased hepatic enzyme: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) Influenza-like illness / acute-phase reaction: 5.6%(25/448) vs 4.9%(23/469) vs 1.5%(7/465) Melena: 0.0%(0/448) vs 0.2%(1/469) vs 0.0%(0/465) Myocardial infarction: 0.0%(0/448) vs 0.4%(2/469) vs 0.0%(0/465) Osteonecrosis of jaw: 0.0%(0/448) vs 0.0%(0/469) vs 0.0%(0/465) Polymyalgia rheumatica: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) Renal adverse event: 4.5%(20/448) vs 3.2%(15/469) vs 3.9%(18/465) Temporal arteritis: 0.0%(0/448) vs 0.2%(1/469) vs 0.0%(0/465) Withdrawals: 19.4%(87/448) vs 20.7%(97/469) vs 17.4%(81/465)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Lewiecki et al., 2010 <sup>435</sup> Ibandronate (Boniva) Trial: BONE, MOBILE, DIVA	Ibandronate vs Placebo: Non-serious atrial fibrillation: 0.4%(29/6,830) vs 0.5%(10/1,924) Serious atrial fibrillation: 0.4%(28/6,830) vs 0.4%(8/1,924)
McClung et al., 2009 <sup>436</sup> Ibandronate (Boniva)	Ibandronate 150 mg monthly + Calcium 500 mg/day + Vitamin D 400 IU/day vs Placebo + 150 mg monthly + Calcium 500 mg/day + Vitamin D 400 IU/day: Any adverse event: 77.9%(60/77) vs 77.1%(64/83) Any serious adverse event: 3.9%(3/77) vs 1.2%(1/83) Arthralgia: 15.6%(12/77) vs 9.6%(8/83) Bacterial infection: 1.3%(1/77) vs 1.2%(1/83) Chest pain: 1.3%(1/77) vs 0.0%(0/83) Death: 0.0%(0/77) vs 0.0%(0/83) Dyspepsia: 5.2%(4/77) vs 4.8%(4/83) GI disorder: 31.2%(24/77) vs 24.1%(20/83) Gastroesophageal reflux disease: 5.2%(4/77) vs 3.6%(3/83) Influenza-like illness: 5.2%(4/77) vs 0.0%(0/83) Life-threatening adverse event: 0.0%(0/77) vs 0.0%(0/83) Myalgia: 6.5%(5/77) vs 2.4%(2/83) Nausea: 6.5%(5/77) vs 3.6%(3/83)
Orwoll et al., 2010 <sup>370</sup> Ibandronate (Boniva) Trial: STRONG	Ibandronate vs Placebo: Any AE: 52.9%(46/87) vs 41.7%(20/48) Acute phase reaction: 3.4%(3/87) vs 4.2%(2/48) Any serious AE not leading to death: 6.9%(6/87) vs 8.3%(4/48) Arthralgia: 5.7%(5/87) vs 10.4%(5/48) Back pain: 4.6%(4/87) vs 6.3%(3/48) Constipation: 2.3%(2/87) vs 4.2%(2/48) Deaths: 1.1%(1/87) vs 4.2%(2/48) Drug-related AE: abdominal pain: 3.4%(3/87) vs 0.0%(0/48) Nasopharyngitis: 8.0%(7/87) vs 0.0%(0/48) Nausea: 4.6%(4/87) vs 0.0%(0/48) New morphometric vertebral fractures: 1.1%(1/87) vs 4.2%(2/48) Pain in extremity: 2.3%(2/87) vs 4.2%(2/48) Upper respiratory tract infection: 3.4%(3/87) vs 2.1%(1/48) Withdrawals: due to AE: 4.6%(4/87) vs 6.3%(3/48)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Stakkestad et al., 2008 <sup>437</sup> Ibandronate (Boniva) Trial: MOBILE	Oral ibandronate 100 mg/month + Calcium 500-1500 mg/day + Vitamin D 400 IU vs Oral ibandronate 150 mg/month + Calcium 500-1500 mg/day + Vitamin D 400 IU: Any adverse event: 56.0%(201/359) vs 53.1%(191/360) Chest pain: 0.0%(0/359) vs 0.3%(1/360) Death from Pancreatic cancer: 0.0%(0/359) vs 0.3%(1/360) Serious AE: 7.8%(28/359) vs 7.5%(27/360) Serious upper GI event: 0.0%(0/359) vs 0.0%(0/360) Upper GI event: 4.5%(16/359) vs 6.9%(25/360)
Adami et al., 2005 <sup>438</sup> Risedronate (Actonel)	Risedronate 15 mg/day vs Risedronate 5 mg/day vs Placebo: Abdominal pain: 8.0%(49/609) vs 9.1%(57/628) vs 7.2%(45/622) Duodenal ulcer: 0.7%(4/609) vs 0.0%(0/628) vs 0.3%(2/622) Duodenitis: 0.5%(3/609) vs 0.6%(4/628) vs 0.2%(1/622) Dyspepsia: 5.1%(31/609) vs 6.2%(39/628) vs 5.8%(36/622) Dysphagia: 0.5%(3/609) vs 0.6%(4/628) vs 0.6%(4/622) Esophageal ulcer: 0.0%(0/609) vs 0.2%(1/628) vs 0.0%(0/622) Esophagitis: 0.8%(5/609) vs 0.5%(3/628) vs 0.6%(4/622) GI disorder: 2.8%(17/609) vs 3.8%(24/628) vs 3.5%(22/622) GI hemorrhage: 0.2%(1/609) vs 0.0%(0/628) vs 1.0%(6/622) Gastritis: 1.5%(9/609) vs 2.1%(13/628) vs 2.1%(13/622) Hematemesis: 0.0%(0/609) vs 0.6%(4/628) vs 0.0%(0/622) Melena: 0.2%(1/609) vs 0.0%(0/628) vs 0.2%(1/622) Peptic ulcer: 0.0%(0/609) vs 0.2%(1/628) vs 0.0%(0/622) Stomach ulcer: 0.7%(4/609) vs 0.3%(2/628) vs 0.3%(2/622) Substernal chest pain: 0.2%(1/609) vs 0.3%(2/628) vs 0.3%(2/622)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Barrera et al., 2005 <sup>439</sup> Risedronate (Actonel) Trial: PEM	Risedronate 5mg/d or 30 mg/d: AEs: all: 3.1%(405/13,180) Allergy: 0.0%(2/13,180) Anemia: 0.0%(1/13,180) Conjunctivitis: 0.0%(3/13,180) Constipation: 1.2%(153/13,180) Deaths: cerebral vascular accident: 0.2%(28/13,180) Deaths: chronic obstructive pulmonary disease: 0.2%(30/13,180) Deaths: myocardial infarction: 0.3%(34/13,180) Diarrhea: 2.3%(305/13,180) Diplopia: 0.0%(1/13,180) Dry eye: 0.0%(6/13,180) Dry skin: 0.0%(1/13,180) Duodenitis: 0.0%(1/13,180) Dyspepsia: 6.5%(858/13,180) Edema: 1.4%(183/13,180) Episcleritis: 0.0%(1/13,180) Esophageal reflux: 0.0%(1/13,180) Facial edema: 0.0%(6/13,180) Fluid retention: 0.0%(1/13,180) GI unspecified: 1.6%(210/13,180) Hair loss: 0.0%(1/13,180) Headache/migraine: 1.6%(208/13,180) Hematemesis: 0.0%(3/13,180) Intolerance: 2.4%(315/13,180) Irritation of the eye: 0.0%(1/13,180) Jaundice: 0.0%(1/13,180) Malaise/lassitude: 1.6%(214/13,180) Melena: 0.0%(1/13,180) Menorrhagia: 0.0%(1/13,180) Mouth ulcer: 0.0%(4/13,180) Myalgia: 1.1%(140/13,180) Nausea/vomiting: reported in 2-6 month of treatment: 3.9%(515/13,180) Pain abdomen: 2.2%(295/13,180) Pain joint: 1.7%(223/13,180) Painful eye: 0.0%(1/13,180)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Barrera et al., 2005 <sup>439</sup>  Continued	Risedronate 5mg/d or 30 mg/d: Palpitation: 0.0%(1/13,180) Paresthesia: 0.0%(1/13,180) Photosensitivity: 0.0%(2/13,180) Pruritus: 0.0%(4/13,180) Rash: 1.3%(166/13,180) Rectal hemorrhage: 0.0%(1/13,180) Respiratory tract infection higher: 1.8%(243/13,180) Respiratory tract infection lower: 3.1%(407/13,180) Skin irritation: 0.0%(1/13,180) Sore eye: 0.0%(5/13,180) Sore mouth: 0.0%(2/13,180) Stevens-Johnson syndrome: 0.0%(1/13,180) Swollen tongue: 0.0%(1/13,180) Ulceration of ileostomy site: 0.0%(1/13,180) Unspecified AE: 1.2%(155/13,180) Urticaria: 0.0%(3/13,180) Visual disturbance: 0.0%(1/13,180) Discontinued drug: all: 26.0%(3,423/13,180)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
<p>Boonen et al., 2009<sup>76</sup> Risedronate (Actonel)</p>	<p>Risedronate 35 mg/wk vs Placebo:                      AEs: any: 70.2%(134/191) vs 73.1%(68/93)                      AEs: serious: 15.2%(29/191) vs 16.1%(15/93)                      Arthralgia: 5.8%(11/191) vs 8.6%(8/93)                      Atrial fibrillation: 1.0%(2/191) vs 3.2%(3/93)                      Back pain: 6.8%(13/191) vs 2.2%(2/93)                      Benign prostatic hyperplasia: 4.7%(9/191) vs 3.2%(3/93)                      Chest pain: 0.0%(0/191) vs 2.2%(2/93)                      Constipation: 8.4%(16/191) vs 5.4%(5/93)                      Death due to lung neoplasm: 0.0%(0/191) vs 1.1%(1/93)                      Death due to pulmonary embolism: 0.0%(0/191) vs 1.1%(1/93)                      Death due to shock: 0.0%(0/191) vs 1.1%(1/93)                      Death due to small lung cancer: 0.5%(1/191) vs 0.0%(0/93)                      Death due to sudden cardiac event: 0.5%(1/191) vs 0.0%(0/93)                      Headache: mild: 4.7%(9/191) vs 0.0%(0/93)                      Headache: moderate: 0.5%(1/191) vs 0.0%(0/93)                      Influenza: 5.8%(11/191) vs 5.4%(5/93)                      Myocardial infarction: 1.0%(2/191) vs 3.2%(3/93)                      Nasopharyngitis: 5.8%(11/191) vs 5.4%(5/93)                      Pain in extremity: 4.7%(9/191) vs 3.2%(3/93)                      Pulmonary embolism: 1.0%(2/191) vs 1.1%(1/93)                      Sudden cardiac death: 0.5%(1/191) vs 0.0%(0/93)                      Upper GI AEs: dyspepsia: 3.1%(6/191) vs 4.3%(4/93)                      Withdrawals: due to AE: 3.7%(7/191) vs 9.7%(9/93)                      Withdrawals: total: 8.4%(16/191) vs 19.4%(18/93)</p>
<p>Delmas et al., 2007<sup>262</sup> Risedronate (Actonel) Trial: IMPACT</p>	<p>Risedronate No reinforcement vs Risedronate Reinforcement:                      Death: 0.3%(3/1,154) vs 0.1%(1/1,228)                      Withdrawals: Total: 13.2%(152/1,154) vs 12.1%(149/1,228)                      Withdrawals: due to AE: 8.9%(103/1,154) vs 7.4%(91/1,228)</p>
<p>Delmas et al., 2008<sup>87</sup> Risedronate (Actonel)</p>	<p>Risedronate 5mg vs Risedronate 75mg:                      Arthralgia: 9.5%(58/613) vs 10.4%(64/616)                      Back pain: 10.8%(66/613) vs 8.8%(54/616)                      Fever or influenza-like illness: 0.0%(0/613) vs 0.6%(4/616)                      Moderate to severe upper GI Treatment-emergent AE: 6.2%(38/613) vs 7.5%(46/616)                      Treatment-emergent AE: all: 81.2%(498/613) vs 84.7%(522/616)                      Treatment-emergent AE: possibly or probably related serious: 0.5%(3/613) vs 0.6%(4/616)                      Treatment-emergent AE: resulting in death: 0.5%(3/613) vs 0.3%(2/616)                      Treatment-emergent AE: serious: 4.7%(29/613) vs 7.5%(46/616)                      Upper GI Treatment-emergent AE: 21.2%(130/613) vs 22.2%(137/616)                      Withdrawals: total: 14.8%(91/613) vs 14.6%(90/616)</p>

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Delmas et al., 2008 <sup>88</sup> Risedronate (Actonel)	<p>Risedronate 150mg a month vs Risedronate 5mg/d:            AEs: all: 79.2%(515/650) vs 78.5%(504/642)            AE potentially associated with acute phase reaction: 1.4%(9/650) vs 0.2%(1/642)            AEs: serious AE: 6.2%(40/650) vs 4.2%(27/642)            Arthralgia: 5.5%(36/650) vs 7.3%(47/642)            Atrial fibrillation: 0.6%(4/650) vs 0.5%(3/642)            Constipation: 5.8%(38/650) vs 7.3%(47/642)            Deaths: 0.0%(0/650) vs 0.5%(3/642)            Diarrhea: 8.2%(53/650) vs 4.7%(30/642)            Influenza: 8.9%(58/650) vs 4.2%(27/642)            Osteonecrosis of the jaw: 0.0%(0/650) vs 0.0%(0/642)            Selected musculoskeletal AE: 15.5%(101/650) vs 17.1%(110/642)            Upper GI tract AE: 19.8%(129/650) vs 17.1%(110/642)            Upper abdominal pain: 8.2%(53/650) vs 6.1%(39/642)            Withdrawals: due to AE: 8.6%(56/650) vs 9.5%(61/642)</p>
Li et al., 2005 <sup>440</sup> Risedronate (Actonel)	<p>Placebo + CaltrateD 600 mg vs Risedronate Sodium 5 mg + Caltrate D 600 mg:            Withdrawals: 13.3%(4/30) vs 6.7%(2/30)            Withdrawals due to adverse events: 3.3%(1/30) vs 6.7%(2/30)</p>
Mok et al., 2008 <sup>441</sup> Risedronate (Actonel)	<p>Placebo + Elemental calcium 1000 mg/day vs Risedronate 5 mg/day + Elemental calcium 1000 mg/day:            Allergic skin rash: 0.0%(0/60) vs 1.7%(1/60)            Confirmed esophagitis: 0.0%(0/60) vs 0.0%(0/60)            Death: 5.0%(3/60) vs 3.3%(2/60)            Diarrhea: 0.0%(0/60) vs 5.0%(3/60)            Dizziness: 1.7%(1/60) vs 0.0%(0/60)            Dyspepsia/epigastric pain: 5.0%(3/60) vs 16.7%(10/60)            Endoscopic gastritis: 5.0%(3/60) vs 5.0%(3/60)            Heartburn: 0.0%(0/60) vs 1.7%(1/60)            Nausea: 1.7%(1/60) vs 0.0%(0/60)            Skin itching: 1.7%(1/60) vs 1.7%(1/60)            Transient urticaria: 1.7%(1/60) vs 0.0%(0/60)            Withdrawals: 13.3%(8/60) vs 15.0%(9/60)            Withdrawals due to adverse events: 0.0%(0/60) vs 3.3%(2/60)</p>

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Palomba et al., 2008 <sup>77</sup> Risedronate (Actonel)	Placebo + 1,500 mg/d 1,25 dihydroxyvitamin 800 UI/d vs Risedronate 35 mg/week + 1,500 mg/d 1,25 dihydroxyvitamin 800 UI/d: Abdominal pain: 8.9%(4/45) vs 6.7%(3/45) Constipation: 2.2%(1/45) vs 2.2%(1/45) Death from MI: 2.2%(1/45) vs 0.0%(0/45) Dyspepsia: 4.4%(2/45) vs 4.4%(2/45) Dysphagia: 0.0%(0/45) vs 2.2%(1/45) Flatulence: 6.7%(3/45) vs 4.4%(2/45) Headache: 0.0%(0/45) vs 2.2%(1/45) Heartburn: 2.2%(1/45) vs 6.7%(3/45) Leg cramps: 2.2%(1/45) vs 0.0%(0/45) Withdrawals: 8.9%(4/45) vs 11.1%(5/45)
Ringe et al., 2009 <sup>75</sup> Risedronate (Actonel)	Placebo + Calcium + Vitamin D 800 IU/day vs Risedronate 5 mg/day + Calcium + Vitamin D 800 IU/day: Withdrawals: 6.3%(10/158) vs 3.8%(6/158) Withdrawals due to adverse events: 0.0%(0/158) vs 0.0%(0/158)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Ste-Marie et al., 2009 <sup>442</sup>	Risedronate 100 mg/mo + Elemental Calcium 1000 mg/day + Vitamin D 400 IU/day vs Risedronate 150 mg/mo + Elemental Calcium 1000 mg/day + Vitamin D 400 IU/day vs Risedronate 200 mg/mo + Elemental Calcium 1000 mg/day + Vitamin D 400 IU/day vs Risedronate 5 mg/day + Elemental Calcium 1000 mg/day + Vitamin D 400 IU/day:
Risedronate (Actonel)	Any adverse event: 52.7%(48/91) vs 61.4%(54/88) vs 56.8%(50/88) vs 51.5%(53/103) Abdominal pain: 2.2%(2/91) vs 6.8%(6/88) vs 9.1%(8/88) vs 3.9%(4/103) Abdominal pain upper: 4.4%(4/91) vs 11.4%(10/88) vs 8.0%(7/88) vs 6.8%(7/103) Any serious adverse event: 1.1%(1/91) vs 5.7%(5/88) vs 3.4%(3/88) vs 2.9%(3/103) Arthralgia: 4.4%(4/91) vs 9.1%(8/88) vs 5.7%(5/88) vs 5.8%(6/103) Back pain: 3.3%(3/91) vs 6.8%(6/88) vs 3.4%(3/88) vs 1.9%(2/103) Cervical spine stenosis: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Chest pain: 0.0%(0/91) vs 0.0%(0/88) vs 0.0%(0/88) vs 1.0%(1/103) Chronic bronchitis: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Coronary artery atherosclerosis: 0.0%(0/91) vs 0.0%(0/88) vs 0.0%(0/88) vs 1.0%(1/103) Coronary artery disease: 0.0%(0/91) vs 0.0%(0/88) vs 1.1%(1/88) vs 0.0%(0/103) Death: 0.0%(0/91) vs 0.0%(0/88) vs 0.0%(0/88) vs 0.0%(0/103) Diarrhea: 7.7%(7/91) vs 4.5%(4/88) vs 10.2%(9/88) vs 2.9%(3/103) Dyspepsia: 7.7%(7/91) vs 5.7%(5/88) vs 5.7%(5/88) vs 2.9%(3/103) Erosive esophagitis: 0.0%(0/91) vs 0.0%(0/88) vs 0.0%(0/88) vs 1.0%(1/103) Headache: 2.2%(2/91) vs 6.8%(6/88) vs 5.7%(5/88) vs 4.9%(5/103) Hypertension: 0.0%(0/91) vs 0.0%(0/88) vs 1.1%(1/88) vs 0.0%(0/103) Malignant lung neoplasm: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Moderate or severe upper GI event: 2.2%(2/91) vs 9.1%(8/88) vs 6.8%(6/88) vs 3.9%(4/103) Myalgia: 4.4%(4/91) vs 3.4%(3/88) vs 4.5%(4/88) vs 0.0%(0/103) Nasopharyngitis: 2.2%(2/91) vs 5.7%(5/88) vs 5.7%(5/88) vs 3.9%(4/103) Nausea: 3.3%(3/91) vs 3.4%(3/88) vs 8.0%(7/88) vs 1.9%(2/103) Ovarian cyst: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Paraparesis: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Pheochromocytoma: 1.1%(1/91) vs 0.0%(0/88) vs 0.0%(0/88) vs 0.0%(0/103) Pneumonia: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Supraventricular tachycardia: 0.0%(0/91) vs 0.0%(0/88) vs 1.1%(1/88) vs 0.0%(0/103) Tendon rupture: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Upper GI event: 13.2%(12/91) vs 22.7%(20/88) vs 19.3%(17/88) vs 18.4%(19/103) Upper respiratory tract infection: 5.5%(5/91) vs 9.1%(8/88) vs 9.1%(8/88) vs 3.9%(4/103) Urinary tract infection: 3.3%(3/91) vs 1.1%(1/88) vs 2.3%(2/88) vs 5.8%(6/103)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Boonen et al., 2008 <sup>443</sup> Zoledronic acid (Zometa)	Placebo + Calcium + Vitamin D vs Zoledronic Acid 5 mg + Calcium + Vitamin D: AEs: all: 93.9%(3,618/3,852) vs 95.5%(3,687/3,862) AEs: deaths: 2.9%(112/3,852) vs 3.4%(131/3,862) AEs: serious AE: 30.1%(1,160/3,852) vs 29.2%(1,127/3,862) Apical granuloma: 0.0%(1/3,852) vs 0.0%(0/3,862) Bone fistula: 0.0%(1/3,852) vs 0.0%(0/3,862) Bone infarction: 0.0%(0/3,852) vs 0.0%(1/3,862) Bone lesion: 0.0%(0/3,852) vs 0.0%(1/3,862) Bone lesion excision: 0.0%(1/3,852) vs 0.0%(0/3,862) Dental Caries: 0.6%(23/3,852) vs 0.5%(18/3,862) Dental alveolar anomaly: 0.0%(1/3,852) vs 0.0%(0/3,862) Dental necrosis: 0.1%(3/3,852) vs 0.0%(0/3,862) Dry socket: 0.1%(3/3,852) vs 0.0%(0/3,862) Estimated creatinine clearance < 30 ml/min: overall: 4.2%(152/3,658) vs 4.4%(160/3,621) Estimated creatinine clearance decreased by ≥ 30%: ml/min: overall: 4.8%(177/3,658) vs 5.0%(182/3,621) Exostosis: 0.5%(19/3,852) vs 0.4%(17/3,862) Increase in serum creatinine > 0.5 mg/100ml: overall: 2.0%(77/3,767) vs 2.8%(104/3,752) Mouth ulceration: 0.3%(10/3,852) vs 0.3%(11/3,862) Osteitis: 0.2%(7/3,852) vs 0.2%(7/3,862) Osteltis deformans: 0.0%(1/3,852) vs 0.0%(1/3,862) Osteolysis: 0.0%(0/3,852) vs 0.0%(1/3,862) Osteomyelitis: 0.0%(0/3,852) vs 0.1%(2/3,862) Osteomyelitis chronic: 0.0%(0/3,852) vs 0.0%(1/3,862) Osteonecrosis of jaw: 0.0%(1/3,852) vs 0.0%(1/3,862) Osteonecrosis of the hip: 0.1%(2/3,852) vs 0.1%(5/3,862) Periodontitis: 0.3%(12/3,852) vs 0.2%(7/3,862) Periostitis: 0.1%(2/3,852) vs 0.0%(0/3,862) Sinusitis: 2.7%(103/3,852) vs 2.2%(86/3,862) Sinusitis bacterial: 0.0%(1/3,852) vs 0.0%(1/3,862) Sinusitis fungal: 0.0%(0/3,852) vs 0.0%(1/3,862) Soft tissue inflammation: 0.0%(0/3,852) vs 0.0%(1/3,862) Soft tissue injury: 0.3%(12/3,852) vs 0.3%(11/3,862) Soft-tissue disorder: 0.0%(1/3,852) vs 0.0%(0/3,862) Soft-tissue infection: 0.0%(1/3,852) vs 0.0%(0/3,862) Tooth abscess: 0.5%(18/3,852) vs 0.6%(23/3,862) Urinary protein level > 2+: overall: 0.5%(19/3,758) vs 0.5%(19/3,749) Discontinuation: due to AE: 1.8%(69/3,852) vs 2.1%(81/3,862) Discontinuation: total: 15.3%(590/3,852) vs 16.2%(625/3,862)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Chapman et al., 2009 <sup>116</sup> Zoledronic acid (Zometa)	Zoledronate IV 2mg vs Placebo: Fever, rigor, bone pain in legs and chest: 10.0%(1/10) vs 0.0%(0/12) Flu-like illness: 80.0%(8/10) vs 8.3%(1/12) Musculoskeletal pain: 40.0%(4/10) vs 16.7%(2/12) Severe pain restricting movement requiring hospitalization: 10.0%(1/10) vs 0.0%(0/12)
Lyles et al., 2007 <sup>115</sup> Zoledronic acid (Zometa)	Zoledronic acid vs Placebo: Any AE: 82.3%(867/1,054) vs 80.6%(852/1,057) Adjudicated hypocalcemia: 0.3%(3/1,054) vs 0.0%(0/1,057) Any serious AE: 38.3%(404/1,054) vs 41.2%(436/1,057) Arrhythmia: 2.3%(24/1,054) vs 3.7%(39/1,057) Arthralgia: 3.1%(33/1,054) vs 2.2%(23/1,057) Atrial fibrillation: any event: 2.8%(29/1,054) vs 2.6%(27/1,057) Bone pain: 3.2%(34/1,054) vs 1.0%(11/1,057) Death: 9.6%(101/1,054) vs 13.3%(141/1,057) Death from cardiovascular causes: 3.4%(36/1,054) vs 4.9%(52/1,057) Death from cardiovascular disease: 1.0%(11/1,054) vs 1.7%(18/1,057) Death from cerebrovascular disease: 0.7%(7/1,054) vs 0.7%(7/1,057) Falls: 9.7%(102/1,054) vs 11.4%(120/1,057) Headache: 1.5%(16/1,054) vs 0.9%(9/1,057) Influenza-like symptoms: 0.6%(6/1,054) vs 0.3%(3/1,057) Musculoskeletal pain: 3.1%(33/1,054) vs 1.2%(13/1,057) Myalgia: 4.9%(52/1,054) vs 2.7%(29/1,057) Myocardial infarction: 1.2%(13/1,054) vs 1.6%(17/1,057) Ocular events possibly related to a study drug: 0.4%(4/1,054) vs 0.1%(1/1,057) Pyrexia: 8.7%(92/1,054) vs 3.1%(33/1,057) Renal event: increase in serum creatinine>0.5 mg/dl: 6.2%(55/886) vs 5.6%(50/900) Stroke: fatal event: 0.9%(9/1,054) vs 0.6%(6/1,057) Stroke: serious adverse event: 4.4%(46/1,054) vs 3.6%(38/1,057) Withdrawals: due to AE: 2.0%(21/1,054) vs 1.7%(18/1,057) Withdrawals: total: 18.3%(193/1,054) vs 29.9%(316/1,057)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
McClung et al., 2007 <sup>444</sup>  Zoledronic acid (Zometa)	Alendronate 70 mg/wk vs Zoledronic acid 5mg/wk: AEs: any: 95.5%(107/112) vs 114.2%(129/113) AEs: serious AE: 9.8%(11/112) vs 10.6%(12/113) Arthralgia: 10.7%(12/112) vs 17.7%(20/113) Back pain: 11.6%(13/112) vs 7.1%(8/113) Bronchitis: 1.8%(2/112) vs 5.3%(6/113) Cough: 5.4%(6/112) vs 2.7%(3/113) Death: 0.0%(0/112) vs 0.0%(0/113) Diarrhea: 1.8%(2/112) vs 5.3%(6/113) Fatigue: 1.8%(2/112) vs 9.7%(11/113) Headache: 13.4%(15/112) vs 16.8%(19/113) Hypocalcemia: 0.0%(0/112) vs 0.0%(0/113) Lab renal abnormality: 0.0%(0/112) vs 1.8%(2/113) Pain: 2.7%(3/112) vs 6.2%(7/113) Pain in extremity: 5.4%(6/112) vs 7.1%(8/113) Sinusitis: 4.5%(5/112) vs 6.2%(7/113) Upper respiratory tract infection: 12.5%(14/112) vs 8.0%(9/113) Urinary tract infection: 6.3%(7/112) vs 8.0%(9/113) Withdrawals: due to AE: 0.9%(1/112) vs 3.5%(4/113)
Etminan et al., 2008 <sup>445</sup>  Alendronate (Fosamax), Etidronate (Didronel)	Oral Bisphosphonate: Aseptic osteonecrosis: 28.3%(58/205)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Emkey et al., 2009 <sup>446</sup> Alendronate (Fosamax), Ibandronate (Boniva) Trial: MOTION	Alendronate 70 mg weekly + Calcium 500 mg + Vitamin D 400 IU vs Ibandronate 150 mg monthly + Calcium 500 mg + Vitamin D 400 IU: Any adverse event: 73.6%(632/859) vs 75.4%(659/874) All GI adverse events: 28.9%(248/859) vs 30.3%(265/874) Arthralgia: 5.7%(49/859) vs 5.4%(47/874) Back pain: 5.2%(45/859) vs 6.9%(60/874) Death: 0.5%(4/859) vs 0.2%(2/874) Duodenal ulcer: 0.1%(1/859) vs 0.0%(0/874) Dyspepsia: 5.6%(48/859) vs 6.9%(60/874) Erosive duodenitis: 0.1%(1/859) vs 0.0%(0/874) Esophagitis ulcerative: 0.1%(1/859) vs 0.0%(0/874) GI hemorrhagic: 0.1%(1/859) vs 0.0%(0/874) Gastric ulcer: 0.2%(2/859) vs 0.1%(1/874) Gastritis erosive: 0.2%(2/859) vs 0.1%(1/874) Gastritis hemorrhagic: 0.1%(1/859) vs 0.0%(0/874) Hypertension: 5.9%(51/859) vs 7.8%(68/874) Influenza: 4.2%(36/859) vs 5.6%(49/874) Intestinal hemorrhagic: 0.1%(1/859) vs 0.0%(0/874) Musculoskeletal and general disorders: 3.0%(26/859) vs 6.8%(59/874) Nasopharyngitis: 4.8%(41/859) vs 5.8%(51/874) Perforations, ulcers and bleeding: 0.9%(8/859) vs 0.5%(4/874) Rectal hemorrhage: 0.1%(1/859) vs 0.2%(2/874) Serious adverse event: 6.4%(55/859) vs 4.5%(39/874) Upper-GI adverse event: 17.2%(148/859) vs 17.5%(153/874) Upper-GI hemorrhage: 0.1%(1/859) vs 0.0%(0/874)
Hadji et al., 2008 <sup>447</sup> Alendronate (Fosamax), Ibandronate (Boniva) Trial: BALTTO II	Alendronate 70 mg weekly + Calcium + Vitamin D vs Ibandronate 150 mg monthly + Calcium + Vitamin D: Any adverse event: 34.6%(117/338) vs 37.5%(126/336) Constipation: 1.2%(4/338) vs 3.0%(10/336) Death: 0.0%(0/338) vs 0.0%(0/336) Diarrhea: 3.3%(11/338) vs 1.5%(5/336) Dyspepsia: 1.8%(6/338) vs 0.9%(3/336) GI disorder: 8.6%(29/338) vs 8.3%(28/336) Gastro-esophageal reflux disease: 0.6%(2/338) vs 1.2%(4/336) General disorders: 2.1%(7/338) vs 1.5%(5/336) Infections and infestations: 1.2%(4/338) vs 2.1%(7/336) Musculoskeletal and connective tissue disorder: 4.7%(16/338) vs 3.3%(11/336) Nervous system disorders: 1.2%(4/338) vs 2.1%(7/336) Serious AE: 1.8%(6/338) vs 2.4%(8/336) Severe GI events: 2.7%(9/338) vs 0.3%(1/336) Upper GI event: 7.1%(24/338) vs 5.7%(19/336) Withdrawals due to AE: 0.9%(3/338) vs 0.3%(1/336)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Li et al., 2009 <sup>448</sup> Alendronate (Fosamax), Ibandronate (Boniva)	Alendronate 70 mg/week + Calcium 500 mg/day + Vitamin D 200 IU/day vs Intravenous ibandronate 2 mg every 3mo + Calcium 500 mg/day + Vitamin D 200 IU/day: Acute renal failure: 0.0%(0/79) vs 0.0%(0/79) Bone pain after 1 month: 3.8%(3/79) vs 2.5%(2/79) Bone pain after 2-12 months: 0.0%(0/79) vs 0.0%(0/79) Fever after 1 month: 1.3%(1/79) vs 3.8%(3/79) Fever after 2-12 months: 0.0%(0/79) vs 0.0%(0/79) Influenza-like symptoms after 1 month: 7.6%(6/79) vs 12.7%(10/79) Influenza-like symptoms after 2-12 months: 3.8%(3/79) vs 0.0%(0/79) Muscle pain after 1 month: 5.1%(4/79) vs 29.1%(23/79) Muscle pain after 2-12 months: 3.8%(3/79) vs 0.0%(0/79) Osteonecrosis of jaw after 1 month: 0.0%(0/79) vs 0.0%(0/79) Osteonecrosis of jaw after 2-12 months: 0.0%(0/79) vs 0.0%(0/79) Other after 1 month: 0.0%(0/79) vs 3.8%(3/79) Other after 2-12 months: 0.0%(0/79) vs 0.0%(0/79) Peptic side effects after 1 month: 3.8%(3/79) vs 1.3%(1/79) Peptic side effects after 2-12 months: 2.5%(2/79) vs 0.0%(0/79) Withdrawals: 3.8%(3/79) vs 5.1%(4/79) Withdrawals due to adverse events: 1.3%(1/79) vs 2.5%(2/79)
Cadarette et al., 2009 <sup>449</sup> Alendronate (Fosamax), Risedronate (Actonel)	Alendronate vs Risedronate: Any upper GI diagnosis or procedure: 18.2%(1,058/5,818) vs 18.8%(867/4,602) Gastroprotective treatment: 31.7%(1,843/5,818) vs 34.5%(1,588/4,602) Hospitalization for upper GI bleed: 0.3%(16/5,818) vs 0.3%(15/4,602) Switched between therapies: 1.9%(111/5,818) vs 1.3%(60/4,602) Upper GI disease: 10.5%(612/5,818) vs 11.0%(508/4,602) Upper GI endoscopy: 2.3%(134/5,818) vs 2.0%(90/4,602) Upper GI symptom: 11.4%(662/5,818) vs 11.2%(516/4,602)
Reid et al., 2006 <sup>450</sup> Alendronate (Fosamax), Risedronate (Actonel) Trial: FACTS-INT'L	Alendronic acid 10 mg/day + Elemental calcium 1000 mg + Vitamin D 400 IU vs Risedronic acid 5mg/day + Elemental calcium 1000 mg + Vitamin D 400 IU: Any adverse event: 65.4%(306/468) vs 67.1%(314/468) Any serious adverse event: 5.1%(24/468) vs 10.0%(47/468) Death: 0.4%(2/468) vs 0.9%(4/468) Serious upper GI event: 0.4%(2/468) vs 0.9%(4/468) Upper GI event: 20.3%(95/468) vs 20.1%(94/468) Withdrawals: 8.1%(38/468) vs 9.4%(44/468)
Breart et al., 2009 <sup>451</sup> Alendronate (Fosamax), Strontium ranelate	Alendronate sodium vs Control: Venous thromboembolism: 0.7%(140/20,084) vs 0.5%(61/11,546)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Saag et al., 2007 <sup>452</sup> Alendronate (Fosamax), Zoledronic acid (Zometa)	<p>Alendronate vs Zoledronate:</p> <p>Any AE: 78.0%(46/59) vs 79.7%(55/69)</p> <p>Abdominal distension: 6.8%(4/59) vs 2.9%(2/69)</p> <p>Abdominal pain: 5.1%(3/59) vs 1.4%(1/69)</p> <p>Arthralgia: 10.2%(6/59) vs 5.8%(4/69)</p> <p>Back pain: 0.0%(0/59) vs 5.8%(4/69)</p> <p>Chest pain: 1.7%(1/59) vs 1.4%(1/69)</p> <p>Chills: 1.7%(1/59) vs 1.4%(1/69)</p> <p>Clinical remarkable changes in vital signs: 0.0%(0/59) vs 0.0%(0/69)</p> <p>Constipation: 5.1%(3/59) vs 1.4%(1/69)</p> <p>Death: 0.0%(0/59) vs 0.0%(0/69)</p> <p>Diarrhea: 0.0%(0/59) vs 2.9%(2/69)</p> <p>Dizziness: 5.1%(3/59) vs 0.0%(0/69)</p> <p>Dyspepsia: 5.1%(3/59) vs 10.1%(7/69)</p> <p>Elevation in alanine aminotransferase (ALT): 3.4%(2/59) vs 18.8%(13/69)</p> <p>Eructation: 5.1%(3/59) vs 1.4%(1/69)</p> <p>Fatigue: 5.1%(3/59) vs 2.9%(2/69)</p> <p>Flatulence: 3.4%(2/59) vs 1.4%(1/69)</p> <p>Headache: 15.3%(9/59) vs 8.7%(6/69)</p> <p>Hypocalcemia: 0.0%(0/59) vs 0.0%(0/69)</p> <p>Influenza-like illness: 1.7%(1/59) vs 1.4%(1/69)</p> <p>Low calcium levels: 0.0%(0/59) vs 0.0%(0/69)</p> <p>Muscle spasms: 6.8%(4/59) vs 4.3%(3/69)</p> <p>Myalgia: 3.4%(2/59) vs 7.2%(5/69)</p> <p>Nasopharyngitis: 3.4%(2/59) vs 10.1%(7/69)</p> <p>Nausea: 6.8%(4/59) vs 1.4%(1/69)</p> <p>Osteoarthritis: 5.1%(3/59) vs 5.8%(4/69)</p> <p>Pain: 0.0%(0/59) vs 0.0%(0/69)</p> <p>Pain in extremity: 6.8%(4/59) vs 2.9%(2/69)</p> <p>Pyrexia: 1.7%(1/59) vs 0.0%(0/69)</p> <p>Rash: 1.7%(1/59) vs 1.4%(1/69)</p> <p>Serious AE: 5.1%(3/59) vs 2.9%(2/69)</p> <p>Shoulder pain: 5.1%(3/59) vs 0.0%(0/69)</p> <p>Sinusitis: 5.1%(3/59) vs 4.3%(3/69)</p> <p>Upper respiratory tract infection: 11.9%(7/59) vs 7.2%(5/69)</p> <p>Withdrawals: 8.5%(5/59) vs 8.7%(6/69)</p>

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Reid et al., 2009 <sup>453</sup> Risedronate (Actonel), Zoledronic acid (Zometa)	Intravenous Zoledronic acid 5 mg + 1 g Calcium + Vitamin D 400-1200 IU/day + oral placebo vs Oral risedronate 5 mg/day + 1 g Calcium + Vitamin D 400-1200 IU/day + Intravenous placebo: Any adverse event: 77.4%(322/416) vs 66.9%(279/417) Abdominal pain: 2.4%(10/416) vs 1.9%(8/417) Acute renal failure: 0.2%(1/416) vs 0.5%(2/417) Allergic dermatitis: 0.5%(2/416) vs 1.9%(8/417) Anaemia: 2.4%(10/416) vs 2.9%(12/417) Anxiety: 1.0%(4/416) vs 1.2%(5/417) Any serious adverse event: 18.3%(76/416) vs 18.5%(77/417) Arthralgia: 9.9%(41/416) vs 7.4%(31/417) Asthenia: 3.8%(16/416) vs 3.6%(15/417) Asymptomatic hypocalcaemia: 0.2%(1/416) vs 0.0%(0/417) Atrial fibrillation: 0.7%(3/416) vs 0.0%(0/417) Back pain: 4.3%(18/416) vs 6.2%(26/417) Baseline creatinine clearance $\leq$ 30% after given drug: 0.2%(1/416) vs 0.5%(2/417) Baseline creatinine clearance $\leq$ 60ml/min and $\geq$ 30% after given drug: 0.2%(1/416) vs 0.5%(2/417) Blepharitis: 0.2%(1/416) vs 0.0%(0/417) Blurred vision: 0.0%(0/416) vs 0.5%(2/417) Bone pain: 3.1%(13/416) vs 2.2%(9/417) Bronchitis: 1.2%(5/416) vs 1.4%(6/417) Cataract: 1.7%(7/416) vs 1.7%(7/417) Chest pain: 0.5%(2/416) vs 0.7%(3/417) Chills: 3.4%(14/416) vs 0.7%(3/417) Conjunctivitis: 1.2%(5/416) vs 0.2%(1/417) Constipation: 2.2%(9/416) vs 2.4%(10/417) Contusion: 1.9%(8/416) vs 0.5%(2/417) Creatinine clearance $<$ 30 mL/min after given drug: 1.0%(4/416) vs 1.0%(4/417) Death: 1.0%(4/416) vs 0.7%(3/417) Depression: 1.7%(7/416) vs 1.7%(7/417) Diarrhea: 3.6%(15/416) vs 2.4%(10/417) Diplopia: 0.0%(0/416) vs 0.2%(1/417) Dizziness: 2.4%(10/416) vs 1.0%(4/417) Dyspepsia: 5.5%(23/416) vs 4.3%(18/417) Episcleritis: 0.0%(0/416) vs 0.2%(1/417) Fall: 1.7%(7/416) vs 1.0%(4/417) Fatigue: 3.1%(13/416) vs 1.4%(6/417) Gastritis: 1.2%(5/416) vs 1.4%(6/417)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Reid et al., 2009 <sup>453</sup>  Continued	Intravenous Zoledronic acid 5 mg + 1 g Calcium + Vitamin D 400-1200 IU/day + oral placebo vs Oral risedronate 5 mg/day + 1 g Calcium + Vitamin D 400-1200 IU/day + Intravenous placebo: Gastro-oesophageal reflux: 1.2%(5/416) vs 1.4%(6/417) Headache: 5.3%(22/416) vs 2.4%(10/417) Hypertension: 4.3%(18/416) vs 4.1%(17/417) Increase of lacrimation: 0.0%(0/416) vs 0.2%(1/417) Influenza: 3.4%(14/416) vs 1.9%(8/417) Influenza-like illness: 6.0%(25/416) vs 1.0%(4/417) Insomnia: 1.9%(8/416) vs 1.4%(6/417) Joint swelling: 1.0%(4/416) vs 0.5%(2/417) Keratoconjunctivitis sicca: 0.7%(3/416) vs 0.0%(0/417) Musculoskeletal chest pain: 1.9%(8/416) vs 0.0%(0/417) Musculoskeletal pain: 1.4%(6/416) vs 1.7%(7/417) Musculoskeletal stiffness: 1.2%(5/416) vs 0.2%(1/417) Myalgia: 9.1%(38/416) vs 3.4%(14/417) Nasopharyngitis: 2.9%(12/416) vs 2.6%(11/417) Nausea: 9.6%(40/416) vs 8.4%(35/417) Oedema peripheral: 2.9%(12/416) vs 2.2%(9/417) Osteonecrosis of long bones: 0.2%(1/416) vs 0.0%(0/417) Osteonecrosis of the jaw: 0.0%(0/416) vs 0.0%(0/417) Pain in limbs: 3.1%(13/416) vs 1.2%(5/417) Palpitations: 1.0%(4/416) vs 0.7%(3/417) Paraesthesia: 1.4%(6/416) vs 0.5%(2/417) Pneumonia: 1.4%(6/416) vs 1.9%(8/417) Proteinuria: 1.0%(4/416) vs 0.7%(3/417) Pyrexia: 12.7%(53/416) vs 3.6%(15/417) Rash: 0.7%(3/416) vs 1.9%(8/417) Rectal Haemorrhage: 1.0%(4/416) vs 0.0%(0/417) Sciatica: 2.4%(10/416) vs 0.2%(1/417) Serum creatinine increase by >44 umol/L: 1.9%(8/416) vs 1.4%(6/417) Sinusitis: 1.2%(5/416) vs 2.2%(9/417) Supraventricular tachycardia: 0.2%(1/416) vs 0.0%(0/417) Upper abdominal pain: 5.0%(21/416) vs 3.1%(13/417) Upper respiratory tract infection: 2.4%(10/416) vs 1.9%(8/417) Urinary tract infection: 5.0%(21/416) vs 4.1%(17/417) Vertigo: 1.9%(8/416) vs 1.2%(5/417) Vomiting: 4.8%(20/416) vs 2.4%(10/417)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Grosso et al., 2009 <sup>454</sup> Alendronate (Fosamax), Bisphosphonates, Risedronate (Actonel)	Bisphosphonates (either Alendronate 10mg daily or 70mg weekly OR Risedronate 5mg daily or 35mg weekly): Artrial fibrillation or atrial flutter: 8.3%(3,335/40,253)
Hong et al., 2009 <sup>455</sup> Alendronate (Fosamax), Bisphosphonates, Risedronate (Actonel)	Bisphosphonates: Osteonecrosis of the jaw (BRONJ): 0.1%(7/9,882)
Blumentals et al., 2009 <sup>456</sup> Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel)	Alendronate/Risedronate weekly vs Ibandronate 150 mg/mo: Severe GI events: during the follow-up period: 0.8%(70/8,608) vs 0.5%(45/8,608) Use of healthcare services: GI drugs: 24.6%(2,115/8,608) vs 25.7%(2,209/8,608) Use of healthcare services: GI endoscopy: 1.6%(139/8,608) vs 1.8%(158/8,608) Use of healthcare services: GI specialist visits: 5.7%(487/8,608) vs 6.2%(535/8,608) Use of healthcare services: X-ray use: 0.4%(34/8,608) vs 0.3%(23/8,608) Use of healthcare services: emergency care: 7.1%(611/8,608) vs 6.5%(562/8,608) Use of healthcare services: hospitalization: 4.2%(365/8,608) vs 3.8%(325/8,608) Use of healthcare services: outpatient visits: 69.2%(5,959/8,608) vs 71.5%(6,155/8,608) Use of healthcare services: outpatient visits related to GI diagnoses: 2.3%(201/8,608) vs 2.7%(233/8,608) Use of healthcare services: outpatient visits related to musculoskeletal diagnoses: 25.9%(2,230/8,608) vs 26.1%(2,246/8,608)
Ideguchi et al., 2007 <sup>284</sup> Alendronate (Fosamax), Bisphosphonates, Etidronate (Didronel), Risedronate (Actonel)	Bisphosphonates: Any adverse event: 9.5%(124/1,307) Diarrhea and/or constipation: 0.9%(12/1,307) Elevated liver function: 0.2%(3/1,307) Gastric pain: 4.6%(60/1,307) Heartburn: 0.5%(6/1,307) Increase of creatine kinase: 0.1%(1/1,307) Increase of creatinine: 0.3%(4/1,307) Laboratory abnormalities: 0.6%(8/1,307) Stomatitis: 0.6%(8/1,307)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Bonnick et al., 2007 <sup>225</sup> Alendronate (Fosamax), Calcium	Alendronate 10 mg/d vs Alendronate 10mg/d +Ca 1000 mg/d vs Calcium 100 mg/d: Clinical AEs: any: 93.2%(262/281) vs 87.9%(248/282) vs 91.3%(126/138) Clinical AEs: deaths: 0.4%(1/281) vs 0.7%(2/282) vs 0.0%(0/138) Clinical AEs: drug-related: 39.1%(110/281) vs 34.8%(98/282) vs 35.5%(49/138) Clinical AEs: serious: 10.7%(30/281) vs 14.2%(40/282) vs 19.6%(27/138) Upper GI AEs: any: 34.9%(98/281) vs 34.8%(98/282) vs 38.4%(53/138) Upper GI AEs: drug-related: 21.0%(59/281) vs 20.6%(58/282) vs 21.0%(29/138) Upper GI AEs: serious: 0.7%(2/281) vs 0.0%(0/282) vs 1.4%(2/138) Withdrawals: total: 29.5%(83/281) vs 32.6%(92/282) vs 30.4%(42/138)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Brown et al., 2009 <sup>367</sup>  Alendronate (Fosamax), Denosumab  Trial: DECIDE	Alendronate 70 mg/wk vs Denosumab 60 mg/6 mos: AEs: all AEs: 82.3%(482/586) vs 80.9%(480/593) AEs: serious AE: 6.3%(37/586) vs 5.7%(34/593) Arthralgia: 9.6%(56/586) vs 12.6%(75/593) Asymptomatic grade 2 decrease in albumin-adjusted serum calcium concentrations: 0.0%(0/586) vs 0.2%(1/593) Benign neoplasms of the breast: 0.0%(0/586) vs 0.3%(2/593) Benign neoplasms of the kidney: 0.0%(0/586) vs 0.3%(2/593) Benign neoplasms of the thyroid gland: 0.3%(2/586) vs 0.2%(1/593) Deaths: 0.2%(1/586) vs 0.2%(1/593) GI disorders: 28.7%(168/586) vs 27.7%(164/593) Infections - bronchitis: 3.6%(21/586) vs 3.2%(19/593) Infections - influenza: 7.2%(42/586) vs 6.9%(41/593) Infections - nasopharyngitis: 7.3%(43/586) vs 7.6%(45/593) Infections - serious: 1.0%(6/586) vs 1.5%(9/593) Infections - serious abscessed limb: 0.2%(1/586) vs 0.0%(0/593) Infections - serious diverticulitis: 0.0%(0/586) vs 0.5%(3/593) Infections - serious ear infection: 0.0%(0/586) vs 0.2%(1/593) Infections - serious infected cyst: 0.2%(1/586) vs 0.0%(0/593) Infections - serious localized infection (finger): 0.0%(0/586) vs 0.2%(1/593) Infections - serious pneumonia: 0.5%(3/586) vs 0.2%(1/593) Infections - serious pseudomembranous colitis: 0.0%(0/586) vs 0.2%(1/593) Infections - serious pyelonephritis: 0.0%(0/586) vs 0.2%(1/593) Infections - serious sepsis: 0.0%(0/586) vs 0.2%(1/593) Infections - serious upper respiratory tract infection: 0.2%(1/586) vs 0.0%(0/593) Infections - serious urosepsis: 0.0%(0/586) vs 0.2%(1/593) Infections - upper respiratory tract infection: 4.4%(26/586) vs 6.1%(36/593) Infections - urinary tract infection: 2.9%(17/586) vs 3.0%(18/593) Malignant neoplasm - serious breast cancer: 0.2%(1/586) vs 0.3%(2/593) Malignant neoplasm - serious gastric cancer: 0.0%(0/586) vs 0.2%(1/593) Malignant neoplasm - serious metastases to liver: 0.0%(0/586) vs 0.2%(1/593) Malignant neoplasm - serious metastatic neoplasm: 0.2%(1/586) vs 0.0%(0/593) Malignant neoplasm - serious mycosis fungoides: 0.0%(0/586) vs 0.2%(1/593) Malignant neoplasm - serious ovarian cancer recurrent: 0.2%(1/586) vs 0.0%(0/593) Malignant neoplasm - serious renal cell carcinoma stage unspecified: 0.0%(0/586) vs 0.2%(1/593) Malignant neoplasm - serious small cell lung cancer metastatic: 0.2%(1/586) vs 0.0%(0/593) Malignant neoplasm - serious squamous cell carcinoma: 0.0%(0/586) vs 0.2%(1/593) Malignant neoplasm - serious vaginal cancer: 0.2%(1/586) vs 0.0%(0/593) Neoplasms (benign or malignant): 2.6%(15/586) vs 3.5%(21/593) Withdrawals: due to all AE: 1.7%(10/586) vs 1.3%(8/593) Withdrawals: total: 9.2%(54/586) vs 6.1%(36/593)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Kendler et al., 2009 <sup>457</sup>  Alendronate (Fosamax), Denosumab  Trial: STAND	Alendronate 70 mg weekly + Calcium 1000 mg + Vitamin D 400 IU vs Subcutaneous denosumab 60 mg/6 months + Calcium 1000 mg + Vitamin D 400 IU: Any adverse event: 78.7%(196/249) vs 77.9%(197/253) Arthralgia: 10.4%(26/249) vs 5.9%(15/253) Back pain: 11.6%(29/249) vs 10.7%(27/253) Bronchitis: 5.6%(14/249) vs 6.3%(16/253) Clinical fractures: 1.6%(4/249) vs 3.2%(8/253) Constipation: 4.8%(12/249) vs 5.1%(13/253) Death: 0.0%(0/249) vs 0.4%(1/253) GI disorder: 24.1%(60/249) vs 22.9%(58/253) Infections: 37.3%(93/249) vs 43.9%(111/253) Nasopharyngitis: 10.8%(27/249) vs 13.4%(34/253) Neoplasms (benign or malignant): 3.6%(9/249) vs 3.6%(9/253) Pain in an extremity: 8.4%(21/249) vs 4.7%(12/253) Serious adverse event: 6.4%(16/249) vs 5.9%(15/253) Serious infection: 1.2%(3/249) vs 0.4%(1/253) Serious neoplasms (benign or malignant): 1.2%(3/249) vs 1.2%(3/253) Withdrawals: total: 4.4%(11/249) vs 4.0%(10/253)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Miller et al., 2008 <sup>458</sup> Alendronate (Fosamax), Denosumab	<p>Alendronate + Calcium 1000mg/day + Vitamin D 400 IU/day vs Denosumab + Calcium 1000mg/day + Vitamin D 400 IU/day vs Placebo + Calcium 1000mg/day + Vitamin D 400 IU/day:</p> <p>Any adverse event: 95.7%(44/46) vs 93.3%(293/314) vs 93.5%(43/46)            Adverse event requiring hospitalization: 0.0%(0/46) vs 3.2%(10/314) vs 0.0%(0/46)            Anemia: 13.0%(6/46) vs 1.6%(5/314) vs 2.2%(1/46)            Arthralgia: 17.4%(8/46) vs 23.6%(74/314) vs 30.4%(14/46)            Back pain: 15.2%(7/46) vs 20.1%(63/314) vs 13.0%(6/46)            Bronchitis: 8.7%(4/46) vs 8.3%(26/314) vs 10.9%(5/46)            Constipation: 13.0%(6/46) vs 6.4%(20/314) vs 2.2%(1/46)            Death due to Adenocarcinoma: 0.0%(0/46) vs 0.3%(1/314) vs 0.0%(0/46)            Death due to Brain neoplasm: 0.0%(0/46) vs 0.3%(1/314) vs 0.0%(0/46)            Death due to Cerebral vascular accident: 0.0%(0/46) vs 0.3%(1/314) vs 0.0%(0/46)            Death due to gastric cancer: 0.0%(0/46) vs 0.3%(1/314) vs 0.0%(0/46)            Development of neutralizing antibodies to denosumab: 0.0%(0/46) vs 0.0%(0/314) vs 0.0%(0/46)            Diarrhea: 8.7%(4/46) vs 8.9%(28/314) vs 13.0%(6/46)            Dyspepsia: 26.1%(12/46) vs 12.4%(39/314) vs 6.5%(3/46)            Gastroesophageal reflux disease: 15.2%(7/46) vs 12.7%(40/314) vs 4.3%(2/46)            Headache: 10.9%(5/46) vs 12.1%(38/314) vs 17.4%(8/46)            Hypertension: 10.9%(5/46) vs 15.3%(48/314) vs 4.3%(2/46)            Infections: 69.6%(32/46) vs 66.2%(208/314) vs 67.4%(31/46)            Influenza-like illness: 15.2%(7/46) vs 13.1%(41/314) vs 10.9%(5/46)            Muscle spasms: 10.9%(5/46) vs 10.2%(32/314) vs 15.2%(7/46)            Nasopharyngitis: 13.0%(6/46) vs 19.1%(60/314) vs 15.2%(7/46)            Nausea: 21.7%(10/46) vs 12.1%(38/314) vs 4.3%(2/46)            Osteoarthritis: 13.0%(6/46) vs 4.1%(13/314) vs 8.7%(4/46)            Pain in extremity: 15.2%(7/46) vs 17.5%(55/314) vs 17.4%(8/46)            Peripheral edema: 6.5%(3/46) vs 4.8%(15/314) vs 10.9%(5/46)            Serious Infections: 0.0%(0/46) vs 3.2%(10/314) vs 0.0%(0/46)            Serious adverse events: 17.4%(8/46) vs 17.8%(56/314) vs 10.9%(5/46)            Shoulder pain: 8.7%(4/46) vs 9.6%(30/314) vs 15.2%(7/46)            Sinusitis: 13.0%(6/46) vs 11.8%(37/314) vs 19.6%(9/46)            Symptomatic hypocalcemia: 0.0%(0/46) vs 0.0%(0/314) vs 0.0%(0/46)            Upper respiratory tract infection: 30.4%(14/46) vs 28.0%(88/314) vs 23.9%(11/46)            Urinary tract infection: 13.0%(6/46) vs 13.1%(41/314) vs 4.3%(2/46)            Withdrawals: 37.0%(17/46) vs 36.9%(116/314) vs 37.0%(17/46)</p>

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
<p>Tseng et al., 2006<sup>260</sup></p> <p>Alendronate (Fosamax), Estrogen</p>	<p>Alendronate 10 mg + Equine estrogen .625 mg + Medroxyprogesterone 5 mg + Calcium carbonate 500 mg/d vs Placebo + Equine estrogen .625 mg + Medroxyprogesterone 5 mg + Calcium carbonate 500 mg/d:</p> <p>Back pain: 1.3%(1/79) vs 1.4%(1/72)</p> <p>Epigastralgia: 1.3%(1/79) vs 0.0%(0/72)</p> <p>Epigastric discomfort: 0.0%(0/79) vs 2.8%(2/72)</p> <p>Esophageal irritation: 2.5%(2/79) vs 0.0%(0/72)</p> <p>General discomfort: 0.0%(0/79) vs 1.4%(1/72)</p> <p>Hemoptysis: 0.0%(0/79) vs 1.4%(1/72)</p> <p>Intolerance to menopausal hormone therapy: 2.5%(2/79) vs 1.4%(1/72)</p> <p>Light stroke: 0.0%(0/79) vs 1.4%(1/72)</p> <p>Withdrawals: 36.7%(29/79) vs 38.9%(28/72)</p> <p>Withdrawals due to adverse events: 7.6%(6/79) vs 9.7%(7/72)</p>
<p>Saag et al., 2009<sup>223</sup></p> <p>Alendronate (Fosamax), PTH (Teriparatide) (Forteo)</p>	<p>Alendronate 10 mg/day + Calcium + Vitamin D vs Teriparatide 20 ug/day + Calcium + Vitamin D:</p> <p>Any adverse event: 86.0%(184/214) vs 90.7%(194/214)</p> <p>Anemia: 7.9%(17/214) vs 5.1%(11/214)</p> <p>Any serious adverse event: 29.9%(64/214) vs 32.7%(70/214)</p> <p>Death: 7.0%(15/214) vs 4.2%(9/214)</p> <p>Dyspepsia: 7.0%(15/214) vs 4.2%(9/214)</p> <p>Dyspnea: 2.8%(6/214) vs 7.5%(16/214)</p> <p>Fatigue: 1.9%(4/214) vs 4.2%(9/214)</p> <p>Gastritis: 3.7%(8/214) vs 7.9%(17/214)</p> <p>Headache: 6.5%(14/214) vs 8.9%(19/214)</p> <p>Influenza: 11.2%(24/214) vs 8.4%(18/214)</p> <p>Insomnia: 1.4%(3/214) vs 5.6%(12/214)</p> <p>Joint injury: 2.8%(6/214) vs 0.5%(1/214)</p> <p>Nasopharyngitis: 6.1%(13/214) vs 3.3%(7/214)</p> <p>Nausea: 8.4%(18/214) vs 16.8%(36/214)</p> <p>Rash: 4.7%(10/214) vs 1.9%(4/214)</p> <p>Urinary tract infection: 13.6%(29/214) vs 10.3%(22/214)</p> <p>Viral infection: 0.0%(0/214) vs 2.3%(5/214)</p> <p>Weight loss: 4.2%(9/214) vs 0.0%(0/214)</p> <p>Withdrawals: 44.9%(96/214) vs 42.5%(91/214)</p>
<p>Antoniucci et al., 2007<sup>459</sup></p> <p>Alendronate (Fosamax), PTH184 (Preos)</p> <p>Trial: PATH</p>	<p>PTH 100 ug/d alone vs PTH 100 ug/d +alendronate 10 mg/d:</p> <p>AE other than hypercalciuria: 1.7%(2/119) vs 3.4%(2/59)</p> <p>Concurrent serum and urinary calcium elevations: 1.7%(2/119) vs 0.0%(0/59)</p> <p>Hypercalcemia: 13.4%(16/119) vs 15.3%(9/59)</p> <p>Hypercalciuria: 8.4%(10/119) vs 11.9%(7/59)</p>

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Huang et al., 2009 <sup>460</sup> Alendronate (Fosamax), Raloxifene (Evista)	Alendronate 10 mg/day OR 70 mg/weekly vs Raloxifene 60 mg: Acute myocardial infarction: 5.8%(1,216/21,037) vs 4.7%(294/6,220) Atrial fibrillation: 3.2%(663/21,037) vs 2.5%(158/6,220)
Binkley et al., 2009 <sup>259</sup> Alendronate (Fosamax), Vitamin D	Alendronate 70 mg +Vitamin D 2800 IU vs Alendronate 70 mg +Vitamin D 5600 IU: Clinical AE: with ≥1 AE: 51.5%(168/326) vs 47.2%(154/326) Clinical AE: with drug related AE: 4.0%(13/326) vs 5.2%(17/326) Clinical AE: with serious AE: 4.0%(13/326) vs 4.9%(16/326) Clinical AE: with serious drug related AE: 0.3%(1/326) vs 0.0%(0/326) Death (due to cerebellar hemorrhage): 0.3%(1/326) vs 0.0%(0/326) Lab AE: with ≥1 AE: 8.3%(27/326) vs 7.7%(25/326) Lab AE: with drug related AE: 0.3%(1/326) vs 2.8%(9/326) Lab AE: with serious AE: 0.0%(0/326) vs 0.0%(0/326) Lab AE: with serious drug related AE: 0.0%(0/326) vs 0.0%(0/326) Withdrawals: 2.8%(9/326) vs 4.6%(15/326)
Ringe et al., 2007 <sup>58</sup> Alendronate (Fosamax), Vitamin D Trial: AAC TRIAE	Alendronate 70 mg/week + Calcium 1000 mg/day + Vitamin D 1,000 IU/day vs Alfacalcidol 1 ug/day + Alendronate 70 mg/week + Calcium 500 mg/day vs Alfacalcidol 1 ug/day + Vitamin D 1,000 IU/day: Arthralgia: 3.3%(1/30) vs 0.0%(0/30) vs 0.0%(0/30) Back pain: 70.0%(21/30) vs 20.0%(6/30) vs 56.7%(17/30) Bone pain: 0.0%(0/30) vs 0.0%(0/30) vs 3.3%(1/30) Epigastric pain: 6.7%(2/30) vs 3.3%(1/30) vs 0.0%(0/30) Headache: 0.0%(0/30) vs 0.0%(0/30) vs 6.7%(2/30) Heartburn: 3.3%(1/30) vs 0.0%(0/30) vs 0.0%(0/30) Hypercalcemia: 0.0%(0/30) vs 0.0%(0/30) vs 0.0%(0/30) Hypercalcuria: 0.0%(0/30) vs 3.3%(1/30) vs 13.3%(4/30) Meteorism: 0.0%(0/30) vs 0.0%(0/30) vs 3.3%(1/30) Nausea: 0.0%(0/30) vs 3.3%(1/30) vs 0.0%(0/30) Obstipation: 6.7%(2/30) vs 6.7%(2/30) vs 6.7%(2/30) Soft bowels: 3.3%(1/30) vs 0.0%(0/30) vs 0.0%(0/30) Withdrawals due to adverse events: 0.0%(0/30) vs 0.0%(0/30) vs 0.0%(0/30)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
de Nijs et al., 2006 <sup>59</sup> Alendronate (Fosamax), Vitamin D Trial: STOP	Alendronate 10 mg + Elemental Calcium 500 mg + Vitamin D 400 IU vs Placebo (alfacalcidol) + Elemental Calcium 500 mg + Vitamin D 400 IU: Abdominal pain: 5.0%(5/100) vs 4.0%(4/101) Adverse events: 68.0%(68/100) vs 66.3%(67/101) Adverse events related to the study: 21.0%(21/100) vs 13.9%(14/101) Death: 2.0%(2/100) vs 1.0%(1/101) Death: Perforated sigmoid colon due to diverticulitis: 1.0%(1/100) vs 0.0%(0/101) Death: cerebrovascular accident: 0.0%(0/100) vs 1.0%(1/101) Death: non-Hodgkin's lymphoma: 1.0%(1/100) vs 0.0%(0/101) Death: stroke: 0.0%(0/100) vs 1.0%(1/101) Diarrhea: 3.0%(3/100) vs 6.9%(7/101) Dyspepsia: 7.0%(7/100) vs 7.9%(8/101) Gastrointestinal adverse event: 35.0%(35/100) vs 51.5%(52/101) Headache: 7.0%(7/100) vs 7.9%(8/101) Hypercalcemia ( calcium > 10.8 mg/dl): 3.0%(3/100) vs 6.9%(7/101) Hypocalcemia (calcium <8.8 mg/dl): 36.0%(36/100) vs 20.8%(21/101) Increase in creatinine (>.2 mg/dl): 8.0%(8/100) vs 15.8%(16/101) Laboratory Adverse events: 47.0%(47/100) vs 43.6%(44/101) Nausea: 2.0%(2/100) vs 7.9%(8/101) Other adverse events: 18.0%(18/100) vs 16.8%(17/101) Other symptoms: 18.0%(18/100) vs 24.8%(25/101) Skin disorder: 11.0%(11/100) vs 8.9%(9/101) Withdrawals: 21.0%(21/100) vs 16.8%(17/101) Withdrawals due to adverse events: 6.0%(6/100) vs 6.9%(7/101)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
<p>Obermayer-Pietsch et al., 2008<sup>461</sup></p> <p>Bisphosphonates, PTH (Teriparatide) (Forteo)</p> <p>Trial: EUROFORS</p>	<p>Teriparatide 20 ug/day + Calcium 500 mg/day + Vitamin D 400-800 IU/day:</p> <p>Any adverse event: 78.2%(394/504)</p> <p>Abdominal pain upper: 3.8%(19/504)</p> <p>Any serious adverse event: 17.5%(88/504)</p> <p>Arthralgia: 11.7%(59/504)</p> <p>Back pain: 5.2%(26/504)</p> <p>Bronchitis: 4.6%(23/504)</p> <p>Constipation: 4.2%(21/504)</p> <p>Contusion: 3.0%(15/504)</p> <p>Depression: 3.0%(15/504)</p> <p>Diarrhea: 6.2%(31/504)</p> <p>Dizziness: 5.0%(25/504)</p> <p>Dyspepsia: 3.0%(15/504)</p> <p>Edema peripheral: 3.0%(15/504)</p> <p>Headache: 6.9%(35/504)</p> <p>Hypercalcemia: 5.0%(25/504)</p> <p>Hypertension: 8.9%(45/504)</p> <p>Influenza: 4.0%(20/504)</p> <p>Muscle cramp: 6.2%(31/504)</p> <p>Nasopharyngitis: 6.3%(32/504)</p> <p>Nausea: 12.5%(63/504)</p> <p>Pain in extremity: 7.3%(37/504)</p> <p>Urinary tract infection: 3.4%(17/504)</p> <p>Withdrawals: 5.6%(28/504)</p> <p>Withdrawals due to adverse events: 1.2%(6/504)</p>
<p>Sato et al., 2007<sup>74</sup></p> <p>Vitamin D, Risedronate (Actonel)</p>	<p>Placebo + Vitamin D2 vs Risedronate 2.5mg + Vitamin D2:</p> <p>Abdominal pain: 2.5%(3/121) vs 3.3%(4/121)</p> <p>Death or intercurrent illness: 3.3%(4/121) vs 3.3%(4/121)</p> <p>Esophagitis: 0.0%(0/121) vs 2.5%(3/121)</p> <p>Withdrawals: 7.4%(9/121) vs 8.3%(10/121)</p>

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
McComsey et al., 2007 <sup>462</sup> Alendronate (Fosamax), Calcium, Vitamin D	Alendronate 70 mg weekly + Calcium carbonate 500 mg/2x day + Vitamin D 200 IU/2x day vs Placebo + Calcium carbonate 500 mg/2x day + Vitamin D 200 IU/2x day: Any adverse event: 69.0%(29/42) vs 57.5%(23/40) Abdominal pain: 0.0%(0/42) vs 2.5%(1/40) Cardiovascular system event: 2.4%(1/42) vs 10.0%(4/40) Chemistry abnormalities: 14.3%(6/42) vs 17.5%(7/40) Dyspepsia: 2.4%(1/42) vs 0.0%(0/40) Dysphagia: 2.4%(1/42) vs 0.0%(0/40) Endocrinology system event: 7.1%(3/42) vs 5.0%(2/40) GI event: 4.8%(2/42) vs 10.0%(4/40) General body event: 14.3%(6/42) vs 17.5%(7/40) Grade 3+ lab toxicities: 16.7%(7/42) vs 15.0%(6/40) Grade 3+ signs/symptoms: 0.0%(0/42) vs 15.0%(6/40) Hematological system event: 2.4%(1/42) vs 2.5%(1/40) Hepatic system event: 35.7%(15/42) vs 30.0%(12/40) Metabolic event: 11.9%(5/42) vs 10.0%(4/40) Neurological system event: 4.8%(2/42) vs 10.0%(4/40) Pain and burning in mouth: 2.4%(1/42) vs 0.0%(0/40) Pancreatic event: 7.1%(3/42) vs 7.5%(3/40) Renal event: 2.4%(1/42) vs 2.5%(1/40) Respiratory system event: 4.8%(2/42) vs 7.5%(3/40) Retrosternal pain: 0.0%(0/42) vs 2.5%(1/40) Serious adverse event: 19.0%(8/42) vs 35.0%(14/40) Skin event: 2.4%(1/42) vs 5.0%(2/40) Stomatitis: 2.4%(1/42) vs 0.0%(0/40) Swelling and pain in tongue: 2.4%(1/42) vs 0.0%(0/40) Urogenital system event: 0.0%(0/42) vs 5.0%(2/40) Withdrawals: 7.1%(3/42) vs 7.5%(3/40)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Vestergaard et al., 2010 <sup>463</sup> Alendronate (Fosamax), Etidronate (Didronel), Ibandronate (Boniva), Pamidronate (Aredia) (APD), PTH (Teriparatide) (Forteo), Raloxifene (Evista), Risedronate (Acto)	Alendronate vs Clodronate vs Ibandronate vs Raloxifene vs Risedronate vs Teriparatide vs Zolendronate: Atrial fibrillation: 1.3%(729/55,090) vs 2.1%(12/566) vs 0.0%(0/612) vs 1.1%(55/4,831) vs 0.0%(0/1,452) vs 0.0%(0/303) vs 0.0%(0/22)
Vestergaard et al., 2009 <sup>464</sup> Alendronate (Fosamax), Etidronate (Didronel), Ibandronate (Boniva), Pamidronate (Aredia) (APD), PTH184 (Preos), Raloxifene (Evista), Risedronate (Actonel), Stronti	Alendronate vs Clodronate vs Ibandronate vs Raloxifene vs Risedronate vs Zolendronate vs Control: Deep venous thromboembolism or pulmonary embolism: 0.4%(200/55,090) vs 1.6%(9/566) vs 0.0%(0/612) vs 0.5%(24/4,831) vs 0.0%(0/1,452) vs 0.0%(0/22) vs 0.5%(1,528/310,683)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone  
 AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
SERMs

Author, Year, Drug, Trial name	Adverse events reported
Cummings et al., 2010 <sup>408</sup>  Lasofloxifene  Trial: PEARL	Lasofloxifene 0.25mg vs Lasofloxifene 0.5mg vs Placebo: AEs: all: 95.5%(2,725/2,852) vs 95.9%(2,736/2,852) vs 95.0%(2,709/2,852) AEs: serious AE: 29.2%(834/2,852) vs 27.5%(784/2,852) vs 27.5%(783/2,852) All-cause mortality: 3.2%(90/2,852) vs 2.6%(73/2,852) vs 2.3%(65/2,852) Arthralgia: 25.9%(738/2,852) vs 26.5%(755/2,852) vs 30.4%(867/2,852) Deaths due to cancer: 1.2%(34/2,852) vs 0.9%(25/2,852) vs 0.7%(20/2,852) ER-positive breast cancer: 0.4%(11/2,729) vs 0.1%(4/2,745) vs 0.8%(21/2,740) Endometrial cancer: 0.1%(2/2,852) vs 0.1%(2/2,852) vs 0.1%(3/2,852) Endometrial hyperplasia: 0.1%(3/2,852) vs 0.1%(2/2,852) vs 0.0%(0/2,852) Endometrial hypertrophy: 7.4%(210/2,852) vs 5.9%(167/2,852) vs 1.2%(35/2,852) Fatal stroke: 0.4%(12/2,852) vs 0.2%(7/2,852) vs 0.2%(5/2,852) Hot flushes: 13.0%(372/2,852) vs 12.8%(365/2,852) vs 5.5%(158/2,852) Invasive breast cancer: 0.6%(16/2,729) vs 0.1%(3/2,745) vs 0.7%(20/2,740) Leg cramps: 22.2%(632/2,852) vs 25.2%(720/2,852) vs 13.3%(379/2,852) Major coronary heart disease event: 2.6%(73/2,852) vs 2.3%(65/2,852) vs 3.3%(95/2,852) Primary lung cancer: 0.5%(15/2,852) vs 0.5%(13/2,852) vs 0.1%(4/2,852) Pulmonary embolism: 0.4%(12/2,852) vs 0.3%(9/2,852) vs 0.1%(2/2,852) Stroke: 1.1%(31/2,852) vs 1.1%(32/2,852) vs 1.8%(50/2,852) Surgery for prolapse or incontinence: 1.9%(55/2,852) vs 1.6%(46/2,852) vs 1.2%(35/2,852) Uterine polyp: 6.2%(176/2,852) vs 7.2%(205/2,852) vs 0.8%(23/2,852) Vaginal candidiasis: 7.7%(220/2,852) vs 7.4%(211/2,852) vs 3.3%(93/2,852) Venous thromboembolic event: 1.7%(48/2,852) vs 1.3%(37/2,852) vs 0.6%(18/2,852) AE leading to study drug discontinuation: all: 13.9%(396/2,852) vs 12.9%(367/2,852) vs 12.3%(350/2,852)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

SERMs

Author, Year, Drug, Trial name	Adverse events reported
Gorai et al., 2009 <sup>265</sup>  Raloxifene (Evista)	Alfacalcidol 1 ug/d vs Alfacalcidol 1 ug/d +Raloxifene 60 mg/d vs Raloxifene 60 mg/d: Alopecia areata: 0.0%(0/44) vs 0.0%(0/48) vs 2.2%(1/45) Angina attack: 0.0%(0/44) vs 2.1%(1/48) vs 0.0%(0/45) Calcaneodynia: 2.3%(1/44) vs 0.0%(0/48) vs 0.0%(0/45) Cramp of limb: 0.0%(0/44) vs 0.0%(0/48) vs 4.4%(2/45) Diaphoresis: 0.0%(0/44) vs 2.1%(1/48) vs 0.0%(0/45) Digestive symptom (nausea, gastralgia): 0.0%(0/44) vs 6.3%(3/48) vs 2.2%(1/45) Diverticula of the colon (abdominal pain lower): 2.3%(1/44) vs 0.0%(0/48) vs 0.0%(0/45) Dizziness: 2.3%(1/44) vs 0.0%(0/48) vs 2.2%(1/45) Gallstones: 0.0%(0/44) vs 2.1%(1/48) vs 0.0%(0/45) Headache: 2.3%(1/44) vs 0.0%(0/48) vs 2.2%(1/45) Hepatic function disorder: 0.0%(0/44) vs 2.1%(1/48) vs 2.2%(1/45) Hot flash: 2.3%(1/44) vs 0.0%(0/48) vs 2.2%(1/45) Hypercalciuria: 9.1%(4/44) vs 0.0%(0/48) vs 0.0%(0/45) Itching paraesthesia: 0.0%(0/44) vs 0.0%(0/48) vs 6.7%(3/45) Knee pain: 2.3%(1/44) vs 0.0%(0/48) vs 0.0%(0/45) Leg cramp: 0.0%(0/44) vs 4.2%(2/48) vs 4.4%(2/45) Leg edema: 0.0%(0/44) vs 0.0%(0/48) vs 2.2%(1/45) Myalgia: 2.3%(1/44) vs 0.0%(0/48) vs 2.2%(1/45) Numbness of lower extremities: 0.0%(0/44) vs 2.1%(1/48) vs 0.0%(0/45) Sweaty: 0.0%(0/44) vs 0.0%(0/48) vs 2.2%(1/45) Symptoms of menopause: 0.0%(0/44) vs 4.2%(2/48) vs 0.0%(0/45) Thoracic pain: 0.0%(0/44) vs 2.1%(1/48) vs 0.0%(0/45) Weigh increased: 0.0%(0/44) vs 0.0%(0/48) vs 2.2%(1/45) Withdrawals: due to AE: 11.4%(5/44) vs 12.5%(6/48) vs 15.6%(7/45)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
SERMs

Author, Year, Drug, Trial name	Adverse events reported
Miller et al., 2008 <sup>384</sup> Raloxifene (Evista)	<p>Bazedoxifene 10mg vs Bazedoxifene 20mg vs Bazedoxifene 40mg vs Raloxifene 60 mg/d vs Placebo:            AEs: any: 95.3%(306/321) vs 96.0%(309/322) vs 94.4%(301/319) vs 92.3%(287/311) vs 95.8%(297/310)            AEs: any serious AE: 9.0%(29/321) vs 11.5%(37/322) vs 10.3%(33/319) vs 9.3%(29/311) vs 9.0%(28/310)            AEs: any treatment emergent AE: 93.1%(299/321) vs 94.4%(304/322) vs 91.5%(292/319) vs 89.7%(279/311) vs 93.2%(289/310)            Breast cancer: 0.3%(1/321) vs 0.6%(2/322) vs 0.0%(0/319) vs 0.3%(1/311) vs 0.6%(2/310)            Cerebral hemorrhage: 0.3%(1/321) vs 0.0%(0/322) vs 0.0%(0/319) vs 0.0%(0/311) vs 0.0%(0/310)            Cerebral ischemia: 0.0%(0/321) vs 0.0%(0/322) vs 0.0%(0/319) vs 0.3%(1/311) vs 0.0%(0/310)            Cerebrovascular accident: 0.0%(0/321) vs 0.0%(0/322) vs 0.3%(1/319) vs 0.0%(0/311) vs 0.0%(0/310)            Deaths: 0.6%(2/321) vs 0.0%(0/322) vs 0.9%(3/319) vs 0.0%(0/311) vs 0.3%(1/310)            Deep venous thrombosis: 0.0%(0/321) vs 0.6%(2/322) vs 0.0%(0/319) vs 0.0%(0/311) vs 0.3%(1/310)            Endometrial cancer: 0.0%(0/321) vs 0.0%(0/322) vs 0.0%(0/319) vs 0.0%(0/311) vs 0.3%(1/310)            Endometrial hyperplasia: 0.0%(0/321) vs 0.0%(0/322) vs 0.0%(0/319) vs 0.0%(0/311) vs 0.0%(0/310)            Hot flushes: 19.6%(63/321) vs 20.8%(67/322) vs 24.1%(77/319) vs 18.6%(58/311) vs 14.2%(44/310)            Leg cramps: 9.3%(30/321) vs 12.1%(39/322) vs 11.9%(38/319) vs 11.9%(37/311) vs 11.6%(36/310)            Myocardial infarction: 0.0%(0/321) vs 0.6%(2/322) vs 0.3%(1/319) vs 0.0%(0/311) vs 0.3%(1/310)            Phlebitis (superficial): 0.3%(1/321) vs 0.3%(1/322) vs 0.9%(3/319) vs 0.0%(0/311) vs 0.3%(1/310)            Pulmonary embolus: 0.0%(0/321) vs 0.0%(0/322) vs 0.3%(1/319) vs 0.0%(0/311) vs 0.0%(0/310)            Retinal vein thrombosis: 0.0%(0/321) vs 0.0%(0/322) vs 0.0%(0/319) vs 0.3%(1/311) vs 0.0%(0/310)            Withdrawals: due to AE: 16.2%(52/321) vs 17.1%(55/322) vs 17.9%(57/319) vs 13.8%(43/311) vs 15.2%(47/310)            Withdrawals: total: 32.1%(103/321) vs 30.4%(98/322) vs 30.4%(97/319) vs 28.0%(87/311) vs 27.4%(85/310)</p>
Mosca et al., 2009 <sup>383</sup> Raloxifene (Evista)	<p>Raloxifene 60 mg/d vs Placebo:            Atrial fibrillation: 6.4%(323/5,044) vs 6.6%(334/5,057)            Deaths: VTE: 0.2%(10/5,044) vs 0.1%(5/5,057)            Deaths: all cardiovascular deaths: 7.2%(362/5,044) vs 7.0%(355/5,057)            Deaths: cerebrovascular (stroke): 1.2%(59/5,044) vs 0.8%(39/5,057)            Deaths: hemorrhagic: 0.2%(10/5,044) vs 0.2%(12/5,057)            Deaths: ischemic: 0.6%(29/5,044) vs 0.3%(16/5,057)            Deaths: noncoronary deaths: 2.1%(107/5,044) vs 1.6%(81/5,057)            Deaths: stroke undetermined: 0.4%(19/5,044) vs 0.2%(11/5,057)            Stroke: Hemorrhagic: 0.4%(18/5,044) vs 0.6%(30/5,057)            Stroke: Ischemic: 3.9%(198/5,044) vs 3.4%(171/5,057)            Stroke: Undetermined: 0.8%(39/5,044) vs 0.6%(30/5,057)            Stroke: all: 4.9%(249/5,044) vs 4.4%(224/5,057)            Transient ischemic attacks: 1.7%(86/5,044) vs 1.8%(91/5,057)            VTE event: all: 2.0%(103/5,044) vs 1.4%(71/5,057)            VTE event: deep vein thrombosis: 1.3%(65/5,044) vs 0.9%(47/5,057)            VTE event: intracranial (retinal vein) thrombosis: 0.2%(8/5,044) vs 0.1%(6/5,057)            VTE event: other: 0.0%(2/5,044) vs 0.0%(1/5,057)            VTE event: pulmonary embolism: 0.7%(36/5,044) vs 0.5%(24/5,057)</p>

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

SERMs

Author, Year, Drug, Trial name	Adverse events reported
Silverman et al., 2008 <sup>123</sup>  Raloxifene (Evista), Bazedoxifene	<p>Bazedoxifene 20mg vs Bazedoxifene 40mg vs Raloxifene 60mg vs Placebo:                      AEs: any AE: 95.8%(1,806/1,886) vs 95.7%(1,792/1,872) vs 96.0%(1,775/1,849) vs 96.2%(1,813/1,885)                      AEs: any serious AE: 20.3%(382/1,886) vs 19.7%(368/1,872) vs 18.6%(344/1,849) vs 18.7%(353/1,885)                      Breast carcinoma: 0.3%(5/1,886) vs 0.2%(4/1,872) vs 0.4%(7/1,849) vs 0.4%(8/1,885)                      Breast cyst/fibrocystic breast disease: 0.7%(13/1,886) vs 0.6%(12/1,872) vs 1.7%(31/1,849) vs 1.0%(18/1,885)                      Deaths: 0.9%(17/1,886) vs 0.7%(13/1,872) vs 1.0%(19/1,849) vs 0.6%(11/1,885)                      Deep vein thrombosis: 0.4%(8/1,886) vs 0.5%(10/1,872) vs 0.4%(8/1,849) vs 0.1%(1/1,885)                      Endometrial carcinoma: 0.0%(0/1,886) vs 0.1%(2/1,872) vs 0.1%(2/1,849) vs 0.2%(3/1,885)                      Endometrial hyperplasia: 0.1%(1/1,886) vs 0.1%(1/1,872) vs 0.1%(1/1,849) vs 0.1%(1/1,885)                      Hemorrhagic stroke: 0.1%(1/1,886) vs 0.1%(1/1,872) vs 0.1%(2/1,849) vs 0.3%(5/1,885)                      Indeterminate: 0.4%(7/1,886) vs 0.2%(3/1,872) vs 0.2%(4/1,849) vs 0.2%(4/1,885)                      Ischemic stroke: 0.6%(11/1,886) vs 0.8%(15/1,872) vs 0.5%(9/1,849) vs 0.6%(11/1,885)                      Leg cramps: 10.9%(205/1,886) vs 10.9%(204/1,872) vs 11.7%(216/1,849) vs 8.2%(155/1,885)                      Myocardial infarction: 0.4%(8/1,886) vs 0.4%(8/1,872) vs 0.3%(6/1,849) vs 0.4%(8/1,885)                      Pulmonary embolus: 0.3%(5/1,886) vs 0.2%(3/1,872) vs 0.2%(4/1,849) vs 0.2%(4/1,885)                      Retinal vein thrombosis: 0.1%(2/1,886) vs 0.1%(1/1,872) vs 0.0%(0/1,849) vs 0.2%(3/1,885)                      Strokes: total: 1.0%(19/1,886) vs 1.0%(19/1,872) vs 0.8%(15/1,849) vs 1.1%(20/1,885)                      Vasodilatation: 12.6%(238/1,886) vs 13.0%(243/1,872) vs 12.0%(222/1,849) vs 6.3%(118/1,885)                      Venous thromboembolic events: 0.7%(13/1,886) vs 0.6%(12/1,872) vs 0.5%(10/1,849) vs 0.3%(5/1,885)                      Withdrawals: due to AE: 14.3%(269/1,886) vs 14.4%(270/1,872) vs 14.2%(262/1,849) vs 12.7%(240/1,885)                      Withdrawals: total: 33.5%(632/1,886) vs 34.3%(643/1,872) vs 32.3%(597/1,849) vs 33.4%(629/1,885)</p>
McClung et al., 2006 <sup>389</sup>  Lasofloxifene, Raloxifene (Evista)	<p>Lasofloxifene 0.25mg/d vs Lasofloxifene 1.0mg/d vs Raloxifene 60mg/d vs Placebo:                      AEs: any: 98.8%(81/82) vs 96.3%(79/82) vs 95.7%(156/163) vs 92.8%(77/83)                      AEs: serious: 6.1%(5/82) vs 9.8%(8/82) vs 8.6%(14/163) vs 4.8%(4/83)                      Atypia: 0.0%(0/82) vs 0.0%(0/82) vs 0.0%(0/163) vs 0.0%(0/83)                      Breast pain: 4.9%(4/82) vs 0.0%(0/82) vs 4.9%(8/163) vs 7.2%(6/83)                      Cancer: 0.0%(0/82) vs 0.0%(0/82) vs 0.0%(0/163) vs 0.0%(0/83)                      Hot flushes: 29.3%(24/82) vs 22.0%(18/82) vs 23.9%(39/163) vs 20.5%(17/83)                      Hyperplasia: 0.0%(0/82) vs 0.0%(0/82) vs 0.0%(0/163) vs 0.0%(0/83)                      Increase in pelvic organ prolapse: 0.0%(0/82) vs 0.0%(0/82) vs 0.0%(0/163) vs 0.0%(0/83)                      Leg cramps: 24.4%(20/82) vs 18.3%(15/82) vs 17.2%(28/163) vs 13.3%(11/83)                      Leukorrhoea: 14.6%(12/82) vs 8.5%(7/82) vs 1.8%(3/163) vs 3.6%(3/83)                      Thromboembolic event: 0.0%(0/82) vs 2.4%(2/82) vs 0.0%(0/163) vs 1.2%(1/83)                      Vaginal bleeding: 3.7%(3/82) vs 2.4%(2/82) vs 1.8%(3/163) vs 3.6%(3/83)                      Withdrawals: due to AE: 24.4%(20/82) vs 17.1%(14/82) vs 13.5%(22/163) vs 14.5%(12/83)                      Withdrawals: total: 37.8%(31/82) vs 30.5%(25/82) vs 28.8%(47/163) vs 31.3%(26/83)</p>

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

SERMs

Author, Year, Drug, Trial name	Adverse events reported
Pelayo et al., 2008 <sup>465</sup> Calcium, Raloxifene (Evista)	Raloxifene (60 mg/d) +CC (600 mg/d) vs Raloxifene (60 mg/d) +OHC (712 mg/d): Constipation: 0.0%(0/42) vs 4.2%(2/48) Hot flashes: 7.1%(3/42) vs 8.3%(4/48) Mild leg swelling: 2.4%(1/42) vs 4.2%(2/48) Nephrolithiasis: 0.0%(0/42) vs 2.1%(1/48) Nonspecific GI problems: 7.1%(3/42) vs 6.3%(3/48) Withdrawals due to adverse events: 9.5%(4/42) vs 14.6%(7/48) Withdrawals: total: 11.9%(5/42) vs 16.7%(8/48)
Anastasilakis et al., 2008 <sup>261</sup> PTH (Teriparatide) (Forteo), Raloxifene (Evista)	Risedronate 35 mg/wk vs Teriparatide 20 ug/d: Total number of any AE: 31.8%(7/22) vs 50.0%(11/22) Bone pain: 4.5%(1/22) vs 13.6%(3/22) Dizziness: 0.0%(0/22) vs 9.1%(2/22) Epigastric pain: 9.1%(2/22) vs 0.0%(0/22) Flushes: 0.0%(0/22) vs 4.5%(1/22) Hypercalcaemia: 4.5%(1/22) vs 9.1%(2/22) Nausea: 0.0%(0/22) vs 9.1%(2/22) Renal colic: 0.0%(0/22) vs 4.5%(1/22) Substernal burn: 13.6%(3/22) vs 0.0%(0/22)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Parathyroid hormone

Author, Year, Drug, Trial name	Adverse events reported
Miller et al., 2007 <sup>395</sup> PTH (Teriparatide) (Forteo) Trial: TPTD	Teriparatide 20ug/d vs Teriparatide 40ug/d vs Placebo: Hematuria: 0.8%(4/527) vs 0.7%(4/541) vs 1.1%(6/536) Hypercalcemia at 4-h after a dose: 2.1%(11/527) vs 5.2%(28/541) vs 0.4%(2/536) Hypercalciuria: 12.0%(63/527) vs 7.0%(38/541) vs 10.1%(54/536) Kidney calculus: 0.4%(2/527) vs 0.0%(0/541) vs 0.4%(2/536) Kidney pain: 0.6%(3/527) vs 0.2%(1/541) vs 0.0%(0/536) Normal urinary calcium excretion and hypercalcemia: 0.9%(5/527) Predose (>16 h after injection) hypercalcemia: 0.2%(1/527) vs 0.0%(0/541) vs 0.2%(1/536) Urinary tract calcifications: 0.2%(1/527) vs 0.2%(1/541) vs 0.0%(0/536) Urolithiasis: 1.1%(6/527) vs 0.4%(2/541) vs 0.4%(2/536)
Miller et al., 2007 <sup>395</sup> PTH (Teriparatide) (Forteo) Trial: TPTD	Teriparatide 20ug/d vs Teriparatide 40ug/d vs Placebo: Hypercalciuria at 1 month: 18.6%(27/145) vs 19.7%(26/132) vs 15.6%(22/141) Kidney calculus: 1.4%(2/145) vs 0.8%(1/132) vs 0.7%(1/141) Kidney pain: 0.0%(0/145) vs 0.8%(1/132) vs 0.0%(0/141) Urolithiasis: 3.4%(5/145) vs 3.8%(5/132) vs 3.5%(5/141)
Fogelman et al., 2008 <sup>134</sup> PTH184 (Preos) Trial: POWER	HT alone vs HT+PTH(1-84) 100 ug/d: AEs: > 1 serious AEs: 3.3%(3/90) vs 0.0%(0/90) AEs: serious: 8.9%(8/90) vs 4.4%(4/90) Dizziness: 5.6%(5/90) vs 10.0%(9/90) Hypercalcemia: 0.0%(0/90) vs 14.4%(13/90) Hypercalciuria: 16.7%(15/90) vs 43.3%(39/90) Nausea: 3.3%(3/90) vs 25.6%(23/90) Vomiting: 4.4%(4/90) vs 11.1%(10/90) Withdrawals: due to AE: 11.1%(10/90) vs 21.1%(19/90)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Parathyroid hormone

Author, Year, Drug, Trial name	Adverse events reported
<p>Greenspan et al., 2007<sup>135</sup> PTH184 (Preos) Trial: TOP</p>	<p>PTH 100 ug/d vs Placebo:            AEs: any: 94.0%(1,209/1,286) vs 92.9%(1,158/1,246)            AEs: serious AE: 6.6%(85/1,286) vs 7.8%(97/1,246)            Arthralgia: 21.9%(282/1,286) vs 22.2%(276/1,246)            Death due to MI: 0.1%(1/1,286) vs 0.1%(1/1,246)            Death due to cerebrovascular accident: 0.0%(0/1,286) vs 0.1%(1/1,246)            Dizziness: 11.5%(148/1,286) vs 8.3%(103/1,246)            Fatigue: 6.9%(89/1,286) vs 5.9%(73/1,246)            GI disorders: abdominal pain: 5.8%(74/1,286) vs 5.9%(74/1,246)            GI disorders: abdominal pain (upper): 6.5%(84/1,286) vs 6.3%(79/1,246)            GI disorders: constipation: 6.8%(87/1,286) vs 7.1%(89/1,246)            GI disorders: diarrhea: 7.5%(96/1,286) vs 7.5%(94/1,246)            GI disorders: dyspepsia: 7.7%(99/1,286) vs 6.7%(83/1,246)            GI disorders: nausea: 22.6%(291/1,286) vs 9.1%(114/1,246)            GI disorders: vomiting: 7.7%(99/1,286) vs 4.3%(54/1,246)            General disorder &amp; admin site conditions: asthenia: 5.7%(73/1,286) vs 5.2%(65/1,246)            General disorder &amp; admin site conditions: edema peripheral: 3.7%(47/1,286) vs 5.2%(65/1,246)            General disorder &amp; admin site conditions: fatigue: 6.9%(89/1,286) vs 5.9%(73/1,246)            Gout: 0.0%(0/1,286) vs 0.5%(6/1,246)            Headache: 28.5%(367/1,286) vs 23.0%(286/1,246)            Hypercalcemia: 28.0%(360/1,286) vs 4.5%(56/1,246)            Hypercalciuria: 46.0%(592/1,286) vs 22.3%(278/1,246)            Infections: 50.5%(649/1,286) vs 53.9%(671/1,246)            Metabolism and nutrition disorders: all: 34.4%(443/1,286) vs 14.4%(180/1,246)            Metabolism and nutrition disorders: hypercalcemia: 27.8%(358/1,286) vs 4.5%(56/1,246)            Muscle cramp: 5.3%(68/1,286) vs 3.9%(49/1,246)            Musculoskeletal, connective tissue, &amp; bone disorders: arthralgia: 21.9%(282/1,286) vs 22.2%(276/1,246)            Musculoskeletal, connective tissue, &amp; bone disorders: back pain: 18.7%(241/1,286) vs 20.0%(249/1,246)            Musculoskeletal, connective tissue, &amp; bone disorders: confirmed bone loss: 1.6%(21/1,286) vs 5.1%(64/1,246)            Musculoskeletal, connective tissue, &amp; bone disorders: muscle cramp: 5.3%(68/1,286) vs 3.9%(49/1,246)            Musculoskeletal, connective tissue, &amp; bone disorders: myalgia: 5.0%(64/1,286) vs 5.0%(62/1,246)            Musculoskeletal, connective tissue, &amp; bone disorders: neck pain: 4.0%(51/1,286) vs 5.1%(63/1,246)            Musculoskeletal, connective tissue, &amp; bone disorders: pain in extremity: 13.1%(168/1,286) vs 15.4%(192/1,246)            Myalgia: 5.0%(64/1,286) vs 5.0%(62/1,246)            Nausea: 22.6%(291/1,286) vs 9.1%(114/1,246)            Nervous system disorders: all: 42.0%(540/1,286) vs 38.5%(480/1,246)</p>

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Parathyroid hormone

Author, Year, Drug, Trial name	Adverse events reported
Greenspan et al., 2007 <sup>135</sup>  Continued	PTH 100 ug/d vs Placebo: Nervous system disorders: dizziness: 11.5%(148/1,286) vs 8.3%(103/1,246) Nervous system disorders: headache: 28.5%(367/1,286) vs 23.0%(286/1,246) Positive PTH antibody titers: 2.8%(36/1,286) vs 0.2%(2/1,246) Psychiatric disorders: all: 16.6%(214/1,286) vs 15.2%(190/1,246) Psychiatric disorders: insomnia: 7.1%(91/1,286) vs 6.2%(77/1,246) Renal and urinary disorders: all: 50.4%(648/1,286) vs 28.3%(352/1,246) Renal and urinary disorders: decreased creatinine renal clearance: 4.5%(58/1,286) vs 5.2%(65/1,246) Renal and urinary disorders: hypercalciuria: 46.0%(592/1,286) vs 22.3%(278/1,246) Renal calculi: 0.6%(8/1,286) vs 0.5%(6/1,246) Respiratory, thoracic, and mediastinal disorders: 18.3%(235/1,286) vs 20.3%(253/1,246) Vascular disorders: all: 14.9%(192/1,286) vs 14.7%(183/1,246) Vascular disorders: hypertension: 7.5%(97/1,286) vs 6.3%(78/1,246) Withdrawals: 13.6%(175/1,286) vs 9.4%(117/1,246) Withdrawals: due to AE: 30.2%(389/1,286) vs 24.6%(306/1,246)
Recker et al., 2009 <sup>466</sup>  PTH (Teriparatide) (Forteo), Strontium ranelate	Teriparatide: ≥1 predose serum calcium level>2.75mM: 7.7%(3/39) AEs: ≥1 AE: 41.0%(16/39) AEs: serious AE: 2.6%(1/39) Above ULN in total alkaline phosphatase: 28.2%(11/39) Above ULN in uric acid: 30.8%(12/39) Cerebrovascular accident: 0.0%(0/39) Lymphoma: 0.0%(0/39) Parathyroid adenoma: 0.0%(0/39) Withdrawals: due to AE: 5.1%(2/39) Withdrawals: total: 15.4%(6/39)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

## Evidence Table C-6. Adverse Events

## Denosumab

Author, Year, Drug, Trial name	Adverse events reported
Bone et al., 2008 <sup>118</sup>  Denosumab	Denosumab 60 mg/6 mos vs Placebo: Any AE: 94.0%(156/166) vs 94.6%(157/166) AE in >10% subjects: arthralgia: 24.7%(41/166) vs 25.3%(42/166) AE in >10% subjects: back pain: 19.9%(33/166) vs 19.9%(33/166) AE in >10% subjects: constipation: 10.8%(18/166) vs 4.8%(8/166) AE in >10% subjects: headache: 15.7%(26/166) vs 11.4%(19/166) AE in >10% subjects: influenza: 9.0%(15/166) vs 10.8%(18/166) AE in >10% subjects: nasopharyngitis: 21.7%(36/166) vs 18.7%(31/166) AE in >10% subjects: pain in extremity: 14.5%(24/166) vs 12.0%(20/166) AE in >10% subjects: pharyngolaryngeal pain (sore throat): 9.0%(15/166) vs 3.0%(5/166) AE in >10% subjects: rash: 8.4%(14/166) vs 3.0%(5/166) AE in >10% subjects: shoulder pain: 10.2%(17/166) vs 6.0%(10/166) AE in >10% subjects: sinusitis: 6.0%(10/166) vs 10.2%(17/166) AE in >10% subjects: upper respiratory tract infection: 11.4%(19/166) vs 13.3%(22/166) AE in >10% subjects: urinary tract infection: 10.8%(18/166) vs 10.2%(17/166) Deaths: 0.0%(0/166) vs 0.0%(0/166) Serious AE: gastrointestinal disorder: 1.2%(2/166) vs 0.0%(0/166) Serious AE: hepatobiliary disorder: 0.0%(0/166) vs 0.6%(1/166) Serious AE: infection: 4.8%(8/166) vs 0.6%(1/166) Serious AE: injury, poisoning, or procedural complication: 1.2%(2/166) vs 0.6%(1/166) Serious AE: musculoskeletal or connective tissue disorder: 1.8%(3/166) vs 1.2%(2/166) Serious AE: neoplasm - B cell lymphoma: 0.0%(0/166) vs 0.6%(1/166) Serious AE: neoplasm - breast cancer in situ: 0.6%(1/166) vs 0.0%(0/166) Serious AE: neoplasm - mycosis fungoides: 0.6%(1/166) vs 0.0%(0/166) Serious AE: neoplasm - ovarian cancer: 0.6%(1/166) vs 0.0%(0/166) Serious AE: neoplasm - uterine cancer: 0.6%(1/166) vs 0.0%(0/166) Serious AE: nervous system disorder: 0.0%(0/166) vs 0.6%(1/166) Serious AE: psychiatric disorder: 0.0%(0/166) vs 0.6%(1/166) Serious AE: reproductive system or breast disorder: 0.6%(1/166) vs 0.6%(1/166) Withdrawals: 6.0%(10/166) vs 9.0%(15/166) Withdrawals due to AE: 0.6%(1/166) vs 1.2%(2/166)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Denosumab

Author, Year, Drug, Trial name	Adverse events reported
Cohen et al., 2008 <sup>467</sup> Denosumab Trial: DENOSUMAB RA STUDY CORP	Denosumab 180 mg injections + Elemental Calcium 500-1000 mg + Vitamin D 400-800 IU vs Denosumab 60 mg injections + Elemental Calcium 500-1000 mg + Vitamin D 400-800 IU vs Subcutaneous placebo + Elemental Calcium 500-1000 mg + Vitamin D 400-800 IU: Any adverse event: 77.8%(56/72) vs 84.5%(60/71) vs 89.3%(67/75) Arthralgia: 5.6%(4/72) vs 8.5%(6/71) vs 2.7%(2/75) Bronchitis: 5.6%(4/72) vs 4.2%(3/71) vs 4.0%(3/75) Cough: 1.4%(1/72) vs 8.5%(6/71) vs 6.7%(5/75) Death: 0.0%(0/72) vs 0.0%(0/71) vs 0.0%(0/75) Infection requiring hospitalization: 2.8%(2/72) vs 1.4%(1/71) vs 1.3%(1/75) Influenza: 9.7%(7/72) vs 2.8%(2/71) vs 0.0%(0/75) Nasopharyngitis: 6.9%(5/72) vs 7.0%(5/71) vs 12.0%(9/75) Neoplasm: 1.4%(1/72) vs 1.4%(1/71) vs 2.7%(2/75) Rheumatoid arthritis flare: 29.2%(21/72) vs 29.6%(21/71) vs 33.3%(25/75) Serious adverse event: 8.3%(6/72) vs 4.2%(3/71) vs 9.3%(7/75) Sinusitis: 11.1%(8/72) vs 5.6%(4/71) vs 10.7%(8/75) Upper respiratory tract infection: 12.5%(9/72) vs 15.5%(11/71) vs 8.0%(6/75) Urinary tract infection: 4.2%(3/72) vs 5.6%(4/71) vs 1.3%(1/75) Withdrawals due to adverse events: 1.4%(1/72) vs 0.0%(0/71) vs 1.3%(1/75)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Denosumab

Author, Year, Drug, Trial name	Adverse events reported
Cummings et al., 2009 <sup>119</sup> Denosumab Trial: FREEDOM	Denosumab 60 mg/6 mos vs Placebo: AEs: all: 92.8%(3,605/3,886) vs 93.1%(3,607/3,876) AEs: serious: 25.8%(1,004/3,886) vs 25.1%(972/3,876) Atrial fibrillation: 0.7%(29/3,886) vs 0.7%(29/3,876) Cancer: overall: 4.8%(187/3,886) vs 4.3%(166/3,876) Cancer: serious: 3.7%(144/3,886) vs 3.2%(125/3,876) Cardiovascular event: 4.8%(186/3,886) vs 4.6%(178/3,876) Cellulitis (including erysipelas): overall: 1.2%(47/3,886) vs 0.9%(36/3,876) Cellulitis (including erysipelas): serious: 0.3%(12/3,886) vs 0.0%(1/3,876) Concussion: 0.0%(1/3,886) vs 0.3%(11/3,876) Coronary heart disease: 1.2%(47/3,886) vs 1.0%(39/3,876) Deaths: 1.8%(70/3,886) vs 2.3%(90/3,876) Decrease in serum calcium to levels below 8mg: 0.1%(4/3,886) vs 0.1%(5/3,876) Delayed fracture healing: 0.1%(2/3,886) vs 0.1%(4/3,876) Development of neutralizing antibodies to denosumab: 0.0%(0/3,886) vs 0.0%(0/3,876) Eczema: 3.0%(118/3,886) vs 1.7%(65/3,876) Falling: 4.5%(175/3,886) vs 5.7%(219/3,876) Flatulence: 2.2%(84/3,886) vs 1.4%(53/3,876) Hypocalcemia: 0.0%(0/3,886) vs 0.1%(3/3,876) Infection: overall: 52.9%(2,055/3,886) vs 54.4%(2,108/3,876) Infection: serious: 4.1%(159/3,886) vs 3.4%(133/3,876) Local reactions: 0.8%(33/3,886) vs 0.7%(26/3,876) Opportunistic infections: 0.1%(4/3,886) vs 0.1%(3/3,876) Osteonecrosis of the jaw: 0.0%(0/3,886) vs 0.0%(0/3,876) Peripheral vascular disease: 0.8%(31/3,886) vs 0.8%(30/3,876) Stroke: 1.4%(56/3,886) vs 1.4%(54/3,876) Withdrawals: due to AE: 2.4%(93/3,886) vs 2.1%(81/3,876)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Denosumab

Author, Year, Drug, Trial name	Adverse events reported
<p>McClung et al., 2006<sup>63</sup></p> <p>Denosumab</p> <p>Trial: DENOSUMAB BONE LOSS STUDY</p>	<p>Alendronate vs Denosumab (all doses) vs Placebo:</p> <p>Any AE: 91.3%(42/46) vs 87.3%(274/314) vs 89.1%(41/46)</p> <p>Arthralgia: 6.5%(3/46) vs 15.0%(47/314) vs 23.9%(11/46)</p> <p>Back pain: 8.7%(4/46) vs 11.5%(36/314) vs 8.7%(4/46)</p> <p>Contusion: 2.2%(1/46) vs 5.1%(16/314) vs 4.3%(2/46)</p> <p>Death: 0.0%(0/46) vs 0.0%(0/314) vs 0.0%(0/46)</p> <p>Detectable denosumab-binding antibodies: 0.0%(0/46) vs 0.6%(2/314) vs 0.0%(0/46)</p> <p>Diarrhea: 4.3%(2/46) vs 6.7%(21/314) vs 6.5%(3/46)</p> <p>Dyspepsia: 26.1%(12/46) vs 8.6%(27/314) vs 6.5%(3/46)</p> <p>Gastroesophageal reflux: 8.7%(4/46) vs 7.0%(22/314) vs 2.2%(1/46)</p> <p>Headache: 10.9%(5/46) vs 8.9%(28/314) vs 13.0%(6/46)</p> <p>Hypertension: 8.7%(4/46) vs 6.4%(20/314) vs 0.0%(0/46)</p> <p>Influenza: 6.5%(3/46) vs 8.0%(25/314) vs 2.2%(1/46)</p> <p>Nasopharyngitis: 10.9%(5/46) vs 14.6%(46/314) vs 13.0%(6/46)</p> <p>Nausea: 17.4%(8/46) vs 8.6%(27/314) vs 4.3%(2/46)</p> <p>Pain in extremity: 10.9%(5/46) vs 8.0%(25/314) vs 8.7%(4/46)</p> <p>Rash: 4.3%(2/46) vs 5.1%(16/314) vs 0.0%(0/46)</p> <p>Serious AE: 2.2%(1/46) vs 5.7%(18/314) vs 4.3%(2/46)</p> <p>Serious AE: abnormal clinical lab investigation: 0.0%(0/46) vs 0.3%(1/314) vs 0.0%(0/46)</p> <p>Serious AE: cardiac disorder: 0.0%(0/46) vs 0.6%(2/314) vs 4.3%(2/46)</p> <p>Serious AE: general disorder: 0.0%(0/46) vs 0.6%(2/314) vs 0.0%(0/46)</p> <p>Serious AE: infection: 0.0%(0/46) vs 1.0%(3/314) vs 0.0%(0/46)</p> <p>Serious AE: injury, poisoning, or procedural complication: 0.0%(0/46) vs 0.3%(1/314) vs 2.2%(1/46)</p> <p>Serious AE: metabolic and nutritional disorder: 2.2%(1/46) vs 0.0%(0/314) vs 0.0%(0/46)</p> <p>Serious AE: musculoskeletal or connective-tissue disorder: 0.0%(0/46) vs 0.6%(2/314) vs 2.2%(1/46)</p> <p>Serious AE: neoplasm: 0.0%(0/46) vs 1.9%(6/314) vs 0.0%(0/46)</p> <p>Serious AE: nervous system disorder: 0.0%(0/46) vs 0.3%(1/314) vs 0.0%(0/46)</p> <p>Serious AE: vascular disorder: 0.0%(0/46) vs 0.3%(1/314) vs 0.0%(0/46)</p> <p>Sinusitis: 6.5%(3/46) vs 6.1%(19/314) vs 6.5%(3/46)</p> <p>Upper respiratory tract infection: 17.4%(8/46) vs 19.4%(61/314) vs 13.0%(6/46)</p> <p>Urinary tract infection: 6.5%(3/46) vs 8.0%(25/314) vs 0.0%(0/46)</p> <p>Withdrawals: due to AE: 0.0%(0/46) vs 2.2%(7/314) vs 2.2%(1/46)</p>

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events

Estrogen

Author, Year, Drug, Trial name	Adverse events reported
Boone et al., 2006 <sup>139</sup> Estrogen	17β-estradiol (0.05 mg/d) then norethisterone acetate (0.24 mg/d) + 17β-estradiol (0.05 mg/d)® vs Placebo: Withdrawals: total: 50.0%(8/16) vs 6.7%(1/15)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Adverse Events  
Estrogen

Author, Year, Drug, Trial name	Adverse events reported
Bolland et al., 2008 <sup>398</sup>  Calcium	Calcium vs Placebo: Angina: 6.8%(50/732) vs 9.6%(71/739) Death: 4.6%(34/732) vs 3.9%(29/739) Myocardial infarction: 4.2%(31/732) vs 1.9%(14/739) Other chest pain: 2.2%(16/732) vs 2.0%(15/739) Stroke: 5.5%(40/732) vs 3.8%(28/739) Sudden death: 0.5%(4/732) vs 0.1%(1/739) Transient ischaemic attack: 4.5%(33/732) vs 2.8%(21/739)
Matsumoto et al., 2005 <sup>399</sup>  Vitamin D	ED-71 0.5ug/d vs ED-71 0.75ug/d vs ED-71 1.0ug/d vs Placebo: ≥1 episode of hypercalcemia over 2.6mmol/liter: 7.3%(4/55) vs 5.5%(3/55) vs 23.2%(13/56) vs 0.0%(0/53) ≥1 episode of hypercalciuria over 0.1mmol/liter GF: 7.3%(4/55) vs 9.1%(5/55) vs 25.0%(14/56) vs 0.0%(0/53) AEs: any serious AE: 10.9%(6/55) vs 12.7%(7/55) vs 5.4%(3/56) vs 7.5%(4/53) Blood calcium increased: 7.3%(4/55) vs 5.5%(3/55) vs 23.2%(13/56) vs 0.0%(0/53) Conjunctivitis: 3.6%(2/55) vs 5.5%(3/55) vs 0.0%(0/56) vs 0.0%(0/53) Cystitis NOS: 7.3%(4/55) vs 10.9%(6/55) vs 1.8%(1/56) vs 1.9%(1/53) Headache: 1.8%(1/55) vs 5.5%(3/55) vs 5.4%(3/56) vs 0.0%(0/53) Stomachache NOS: 7.3%(4/55) vs 0.0%(0/55) vs 1.8%(1/56) vs 0.0%(0/53) Urine calcium increased: 7.3%(4/55) vs 9.1%(5/55) vs 25.0%(14/56) vs 1.9%(1/53)
Xia et al., 2009 <sup>226</sup>  Calcium, Vitamin D	Caltrate D (600 mg calcium and 125 iu vitamin D) vs Rocaltrol (0.25 ug/d) +Caltrate D (600 mg calcium and 125 iu vitamin D): Calcification: 0.0%(0/76) vs 0.0%(0/74) Renal lithiasis: 0.0%(0/76) vs 0.0%(0/74) Withdrawals: total: 5.3%(4/76) vs 5.4%(4/74)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone

AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

## Evidence Table C-7. Applicability Assessments

Citations	Drugs	Primary Care	Inclusion/exclusion minimal*	Outcome= fx	Duration>6mos/Adherence	Adverse events	Sample size*	ITT	Total
Bone, 2008 <sup>118</sup>	Denosumab	y	y	y	y/n	y	332	n	5.5 out of 7
Bonnick, 2007 <sup>225</sup>	alendronate vs. alendronate+calcium	y	y (many exclusion criteria) n (PM women with primary biliary cirrhosis)	n (fx reported as AEs)	y/y	y	484	y (modified)	6 out of 7
Boone, 2006 <sup>139</sup>	estrogen	n	n (CF)	y	y/y	y	31	n	3 out of 7
Boonen, 2009 <sup>76</sup>	risedronate	y	y (male)	y	y/n	y	284	y	6.5 out of 7
Campbell, 2009 <sup>230</sup>	estrogen (and etidronate)	y	n (GC users w/asthma)	y	y/n	n	47	n	but men 2.5 out of 7
Chapman, 2009 <sup>116</sup>	zoledronic acid	n	n(CF)	y	y/y	y	22	y	4 out of 7
Cummings, 2009 <sup>119</sup>	Denosumab	y	y (many exclusion criteria)	y	y/y	y	7,868	y	7 out of 7
Cummings, 2010 <sup>408</sup>	lasofoxifene	y	y	y	y/n	y	8,556	y	6.5 out of 7
de Nijs, 2006 <sup>59</sup>	alendronate and vitamin D	n	n (GC-users w/autoimmune diseases) p (excl users of other osteoporosis meds and obese women)	y	y/n	y	163	n	3.5 out of 7
Delmas, 2008 <sup>87</sup>	risedronate	y	p (excl users of other osteoporosis meds and many comorbidities) n (women w/CHD; many exclusion criteria)	y	y/y	y	1,231	n	5 out of 7
Delmas, 2008 <sup>88</sup>	risedronate	y	n (women w/CHD; many exclusion criteria)	y	y/y	y	1,294	n	5 out of 7
Ensrud, 2008 <sup>122</sup>	raloxifene	y	n (male heart transplant)	y	y/y	y	10,101	y	6 out of 7
Fahrleitner-Pammer, 2009 <sup>108</sup>	ibandronate	n	n (male heart transplant)	y	y/n	y	35	n	2.5 out of 7
Fogelman, 2008 <sup>134</sup>	PTH 1-84	y	y	y	y/y	y	180	y	7 out of 7
Frost, 2007 <sup>158</sup>	calcium	n	n (men with CHF)	y	y/n	y	33	n	2.5 out of 7
Fujita, 2004 <sup>159</sup>	calcium	n	n(hosp women)	y	y/n	n	19	n	1.5 out of 7
Greenspan, 2007 <sup>135</sup>	PTH 1-84	y	y	y	y/y	y	2,532	y	7 out of 7

## Evidence Table C-7. Applicability Assessments

Citations	Drugs	Primary Care	Inclusion/exclusion minimal*	Outcome= fx	Duration>6mos/Adherence	Adverse events	Sample size*	ITT	Total
Ishani, 2008 <sup>252</sup>	raloxifene	y	y (stratification by renal failure status)	y	y/n	y	7,492	y	6.5 out of 7
Larsen, 2004 <sup>152</sup>	Calcium and Vitamin D	y	y	y	y/n	n	9,605	y	5.5 out of 7
Law, 2006 <sup>164</sup>	Vitamin D	y	y	y	y/n	n	3,717	y	5.5 out of 7
Lyles, 2007 <sup>115</sup>	zoledronic acid	y	y (prior hip fx)	y	y/nr (not relevant, once-yearly)	y	2,127	y	7 out of 7
Lyons, 2007 <sup>203</sup>	Vitamin D	y	y n (GC-users w/autoimmune diseases)	y	y/y	y(mort only)	3,440	y	7 out of 7
Okada, 2008 <sup>224</sup>	alendronate and vitamin D	y	n (IBD pts)	y	y/n	y	47	n	4.5 out of 7
Palomba, 2008 <sup>77</sup>	risedronate	n	n (CF)	y	y/y	y	90	y	4 out of 7
Papaioannou, 2008 <sup>57</sup>	alendronate and vitamin D	n	y	y	y/y	y	56	y	4 out of 7
Ringe, 2007 <sup>58</sup>	alendronate and vitamin D	y	n (male, small German clinic)	y	y/n	y	90	y	5.5 out of 7
Ringe, 2009 <sup>75</sup>	risedronate	y	n (GC-users)	y	y/n	y	316	y	5.5 out of 7 but men
Saag, 2009 <sup>223</sup>	alendronate and PTH	y	n (males with Parkinsons)	y	y/n	y	428	y	5.5 out of 7
Sato, 2007 <sup>74</sup>	Risedronate and vitamin D	n	y	y	y/n	y	223	n	3.5 out of 7
Shiraki, 1996 <sup>162</sup>	Vitamin D	y	y n (many exclusion criteria, incl vitamin D use)	y	y/n	n	113	y	5.5 out of 7
Silverman, 2008 <sup>123</sup>	raloxifene	y	y	y	y/n	y	7,492	y	5.5 out of 7
Smith, 2007 <sup>163</sup>	Vitamin D Calcium and Vitamin D	y	y	y	y/y	y	9,440	y	7 out of 7
Xia, 2009 <sup>226</sup>	D	y	y (Chinese women)	y	y/n	y	150	y	6.5 out of 7

p= possible; ITT= Intention to Treat; fx= Fracture; NR= Not Reported; \* If sample size is greater than a 100 then it is a yes

## **Appendix D: List of Excluded Studies**

## Appendix D. Excluded Studies:

### Reject Descriptive:

1. Al-Azzawi F. Prevention of postmenopausal osteoporosis and associated fractures: Clinical evaluation of the choice between estrogen and bisphosphonates. *Gynecol Endocrinol.* 2008 Nov;24(11):601-9.
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17. Stefanick ML. Risk-benefit profiles of raloxifene for women. *N Engl J Med.* 2006 Jul 13;355(2):190-2.

18. Vasikaran SD. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case-control study. *Osteoporos Int.* 2009 Aug;20(8):1457-8.
19. Wass JA. Bisphosphonate-induced osteonecrosis of the jaws: CT and MRI spectrum of findings in 32 patients. *Clin Radiol.* 2008 Jan;63(1):78-9.

### Reject Irrelevant Design:

1. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. *BMJ.* 2010;340:b5463.
2. Adachi J, Lynch N, Middelhoven H, Hunjan M, Cowell W. The association between compliance and persistence with bisphosphonate therapy and fracture risk: a review. *BMC Musculoskelet Disord.* 2007;8:97.
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### Reject No Enrollment Criteria

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### Reject No Relevant Interventions

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