

Title page

Title:

Cumulative network meta-analyses, practice guidelines, and actual prescriptions for post-menopausal osteoporosis: a meta-epidemiological study.

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Abstract

Purpose: To compare the results of cumulative network meta-analyses (NMAs) with the recommendations in post-menopausal osteoporosis practice guidelines and actual prescribing practices in the US.

Methods: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus were searched to retrieve randomized controlled trials (RCTs) on July 2017. The Agency for Healthcare Research and Quality's National Guideline Clearinghouse and associated society websites were searched to retrieve guidelines on June 2018. We used the Medical Expenditure Panel Survey (MEPS) to analyze prescription data from 1996 to 2015. Two independent investigators selected eligible RCTs. One investigator selected potential eligible guidelines, which were confirmed by another investigator. Two independent investigators extracted data from included RCTs. One investigator extracted recommendations from guidelines, which were confirmed by another investigator. (Registration: UMIN000031894)

Results: We analyzed data from 1995, 2000, 2005, 2010, and 2015. We chose hip fracture as the primary outcome of cumulative NMAs. We included 51 trials, 17 guidelines, and 5099 post-menopausal osteoporosis patients from the MEPS. Bisphosphonate, including alendronate, and combination of vitamin D and calcium (vDCA) were consistently recommendable from an efficacy viewpoint in NMAs and recommended in guidelines. Alendronate was the most prescribed drug (more than 30% over the observation period); however, vDCA was seldom prescribed. The maximum proportion was 5.3% from 2011 to 2015.

Conclusions: In postmenopausal osteoporosis, there was no apparent discrepancy between guideline recommendations and drug prescribing rankings, with the exception

68 of vDCa, when we used cumulative NMAs as references.

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Keywords: postmenopausal osteoporosis, cumulative network meta-analyses, clinical practice guidelines, meta-epidemiological study, hip fracture

Mini-abstract: We compared the cumulative network meta-analyses with the recommendations in post-menopausal osteoporosis practice guidelines and actual prescribing practices in the US. There was no apparent discrepancy between guideline recommendations and drug prescribing rankings, with the exception of vitamin D and calcium, when we used cumulative NMAs as references.

Background

Evidence practice gap, or the delay in incorporating research results into practices, is receiving increasing attention of clinicians and consumers alike [1–3].

One of its many possible causes is a time delay between the publication of individual study results and the recommendations provided in clinical practice guidelines (CPGs) [4]. There are empirical studies suggesting that cumulative network meta-analyses (NMAs) can lead to timely recommendations for guidelines. Because NMAs synthesize both direct and indirect evidence from clinical trials, they have more statistical power than conventional pairwise MAs [5, 6]. Only one study has compared cumulative NMAs and guideline recommendations from the view of timely recommendation [5]. The study focused on first-line medical therapies for primary open-angle glaucoma and found some gaps between recommendable drugs based on NMAs and recommended drugs in guidelines. Its primary outcome was intraocular pressure, which would not need long follow-ups.

Another cause may be a time delay between evidence, either as individual studies or as guideline recommendations, and the real-work prescriptions by the clinicians. The above-mentioned study did not investigate the differences between cumulative NMAs and actual practices, which is the true evidence practice gap.

We took post-menopausal osteoporosis as an example. Our study aims were first to compare the results of cumulative NMAs of a true outcome with the recommendations in relevant practice guidelines and then to examine the agreement between the results of cumulative NMAs and actual prescriptions in the real world.

METHODS

We developed the study protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [7] and its adaptation for meta-epidemiological studies [8]. We registered our protocol in UMIN-CTR as UMIN000031894. We have published our protocol elsewhere [9]. Supplemental Table 1 shows the PRISMA checklist.

Systematic review and cumulative NMAs of osteoporosis drugs

Study identification and data extraction

We retrieved eligible original article data from the postmenopausal osteoporosis CPG of the Endocrine Society [10]. The search date was 7 July 2017. The inclusion criteria were parallel-group randomized controlled trials (RCTs) on postmenopausal women with primary osteoporosis or osteopenia at risk of developing fragility fractures. We included commonly used medications as interventions including teriparatide, selective estrogen receptor modulators, denosumab, romosozumab, estrogen with or without progesterone, calcitonin, strontium ranelate, tibolone, or intact parathyroid hormone. We also included nutritional supplements commonly recommended for osteoporosis including calcium and vitamin D when they were used as monotherapies. When dietary supplements were allowed or provided in addition to study medications, so long as they were provided equally between the treatment arms, we considered the study as comparison between the medications. Control conditions were placebo, no treatment, or treatment as usual. The primary outcome was new hip fractures at the time of the latest follow-up in the included studies. This outcome was chosen from the viewpoint of its impact on patients' prognoses

[11]. We did not limit our search by language, region.

Pairs of reviewers independently screened the titles and abstracts then examined the full-text articles to decide upon their eligibility. When disagreements occurred, they were discussed and a third author acted as an arbiter whenever necessary. The authors used the Cochrane tool to assess the risk of bias [12].

Statistical analyses

We conducted random-effect cumulative NMAs of the identified network of trials at 5-year intervals (Table 1) [13]. Each drug or their combination was treated as a node in this network. We chose hip fractures during the study period as the primary outcome because of the magnitude of its impact on quality of life. We used a multi-level hierarchical model with components at the following levels: study, individual drug, and drug class. This model accounted for the within-study correlation of multigroup trials and also incorporated class effects [14–16]. Given the clinical and methodological heterogeneity of the populations and methods among the included trials, we used the random effects model in our primary analyses. We assessed the transitivity assumption of the entire data set in the final NMA. We examined the consistency of the total network through both local and global tests of inconsistency. We tested small study effects and publication biases using the comparison-adjusted funnel plot, taking placebo as the common comparator [17].

We pooled the relative odds ratios of all active medications in comparison with placebo in ranked forest plots. We also examined the hierarchy of treatment rankings by using the surface under the cumulative ranking curve (SUCRA) [17, 18]. A SUCRA value can indicate the ranking of the treatment while accounting both for the location and the

variance of all relative treatment effects. The larger the SUCRA value, the better the ranking of the treatment [17, 18]. SUCRA values themselves are not comparable for networks with different number of treatments. We conducted the cumulative NMA in a frequentist framework using Stata 15.1 (StataCorp, College Station, TX, USA) [19, 20].

The certainty of evidence

We evaluated the overall grading of the evidence of the main outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach using CINeMA (Confidence in Network Meta-Analysis Software) [21, 22]. In GRADE approach each outcome is appraised as to its certainty of evidence in four levels varying between high, moderate, low and very low [23]. We defined the “recommendable drug” as a drug that is more effective in preventing hip fractures than placebo with moderate or higher certainty of evidence.

Identification of practice guideline recommendations

We searched the websites of the Agency for Healthcare Research and Quality’s National Guideline Clearinghouse [24], American Association of Clinical Endocrinologists [25], American College of Physicians [26], Endocrine Society [27], and The North American Menopause Society [28] for the term “osteoporosis” on 15 June 2018. We did not search official journals of each organization. One author (YK) selected the guidelines for the treatment of postmenopausal osteoporosis from U.S.-based organizations since 2000. Two of five independent authors (YK, YL, AO, MK, and YT) extracted data from each guideline. We resolved disagreements through discussion.

Real-world prescriptions

The Medical Expenditure Panel Survey (MEPS) is based on nationally representative samples of the US non-institutionalized civilian population. MEPS uses sampling weights adjusting for survey non-response and population totals from the Current Population Survey [29], and can therefore be used to derive nationally representative estimates. We used the Household Component Files, which contain detailed information about demographic information and prescribed medicines for respondents [29]. We included all female respondents aged 50 years and older who were classified as “206 Osteoporosis”. The cut-off value of 50 was in accordance with previous reports [30, 31]. We excluded those who were classified as “202 Rheumatoid arthritis and related disease”, because they would have rheumatoid arthritis or steroid-induced osteoporosis [32]. We also excluded those who were classified as “158 Chronic renal failure”, because they may have mineral and bone disorders [33]. We also excluded those who were classified as “cancer” (the codes are from 11 to 44), because they may have bone metastases that need to be treated with bone modifying agents [34].

We determined the prescription proportions and rankings using the 5-year prescription proportion of each drug category. We made a dictionary by searching for the proprietary and nonproprietary names using the following terms from the “pharmacologic class” of the National Drug Code Directory [35]. Bisphosphonate [EPC], Parathyroid Hormone Analog [EPC], Selective Estrogen Receptor Modulators [MoA], RANK Ligand Inhibitor [EPC], Estrogen [EPC], Progestin [EPC], Calcitonin [EPC], Calcium [Chemical/Ingredient], Vitamin D2 Analog [EPC], and Vitamin D3 Analog [EPC]. One author (YK) classified nutritional supplement names that were unclassifiable by the above dictionary.

The numerator was the number of patients who were prescribed each specific drug within 5 years. The denominator was the number of included patients within the same 5 years. We used Python 3.6 (Python Software Foundation), and STATA 15.1 (StataCorp, College Station, TX, USA) to analyze data from the MEPS.

Comparison of NMA rankings, CPG recommendations, and real-world prescriptions

We compared the results of the cumulative NMAs with recommendations by CPGs and actual prescriptions at 5-year intervals. The MEPS started in 1996; therefore, we chose 1996 as the first year of prescription ranking.

Because there is bound to be some time lag as randomized evidence is generated, synthesized, integrated into recommendations and translated into practice, the time frame for the comparisons was set as shown in Table 1. First, because the median time from the last search to the publication of systematic reviews has been found to be 8.0 months (range: 0 to 47), we included trials published up to 1 year prior to conducting the cumulative NMA [36]. As there should be no time lag between the latest evidence synthesis and the CPG recommendations, we expected the NMA results to be reflected in the CPGs published in the ensuing five years. In 2000 a meta-epidemiological study showed a delay of 9.3 years between evidence review and its implementation [37]. This delay may have been shortened in recent years [4]. We, therefore, compared the results from the NMA and the CPG recommendations with actual prescriptions written at least 1 year later.

We first compared the rankings of NMAs, CPG, and actual prescriptions. We checked whether recommendable drugs based on cumulative NMAs were recommended in CPGs.

We also checked the ranking of the recommendable drugs in the prescription ranking.

RESULTS

cumulative NMA

We included 51 trials enrolling 183,161 patients. They compared 18 drugs in addition to placebo. Forty-three studies (84%) compared an active drug with a placebo. Supplemental Table 2 shows the individual characteristics of the included studies and their risk of bias. Both intervention and control patients received sufficient dose of vitamin D and calcium in most trials. Fig. 1 depicts the network diagrams of the included trials at each reference year. We found no statistically significant global or local inconsistency. We also found no small study effects using a comparison-adjusted funnel plot (Supplemental Fig. 2).

Fig. 2 shows the forest plot of individual drugs and its respective certainty of evidence in terms of the efficacy to prevent hip fractures at each reference year. In 1995, vitamin D and calcium supplements was significantly superior to placebo for the outcome of hip fractures. However, the certainty of evidence was rated low; this certainty of evidence improved to moderate after 2005. Since 2000, alendronate has shown statistically significant efficacy over placebo, with moderate or higher certainty of evidence. Risedronate has shown efficacy with moderate certainty of evidence since 2005, whereas zoledronate, denosumab, and hormone therapy started demonstrating efficacy only after 2010. Supplemental Table 3 presents the details of evaluations of certainty of evidence. Supplemental Fig. 1 shows the SUCRA rankings.

Practice guideline recommendations

From a total of 29 citations, we found 18 guidelines (Supplemental Fig. 3, Supplemental

Table 4). We have summarized the guidelines' recommendations in Table 2.

Real-world prescriptions

We included a total of 5,099 interviewed women with postmenopausal osteoporosis from the MEPS (Supplemental Fig. 4). Table 3 shows the estimated proportion of patients treated with each anti-osteoporotic drugs or supplements in the US. Alendronate was consistently the most frequently prescribed drug.

Comparisons of NMA rankings, CPG recommendations, and real-world prescriptions

Table 2 shows the comparison of the results from cNMAs and the guideline recommendations. Recommendable drugs based on cumulative NMAs were recommended in all CPGs during a certain period, except for the hormone therapy.

Table 4 shows the comparison of the results from cNMAs and the real world prescriptions. Bisphosphonate, including alendronate and risedronate, were highly used even before they became recommendable based on cumulative NMAs. VDCa were recommendable drugs since 2006 but underused.

DISCUSSION

To our knowledge, this is the first study to investigate the differences between the results of cumulative NMAs and the recommendations in post-menopausal osteoporosis practice guidelines and actual prescribing practices in the US. From an efficacy point of view, all recommendable drugs based on cumulative NMAs were recommended by guidelines in five-year time frame. US physicians prescribed recommendable drugs, but the patients

270 did not take vitamin D and calcium.

271 The importance of making timely recommendations to allow for updates to individual
272 recommendations as soon as new relevant evidence becomes available has been recently
273 receiving renewed interest as living systematic reviews [2, 38]. A previous case study
274 showed that it takes several years from research review and synthesis to the first policy
275 statement [4]. A previous case study on open angle glaucoma showed that cumulative
276 NMAs would enable guideline developers to make timely recommendations [5]. In our
277 study, the recommendable drugs based on the cumulative NMAs were recommended in
278 the guidelines in a timely fashion. Such a timely recommendation in the case of
279 osteoporosis may have been possible due to the correlation between surrogate outcomes
280 (i.e. bone mineral density) and true outcomes in osteoporosis (i.e. hip fractures) [39]. In
281 other words, in the case of postmenopausal osteoporosis, there was no problem in making
282 recommendations at an early stage based on the results of surrogate outcome studies.
283 Further study is warranted in the areas where surrogate outcomes are less useful.

284 In contrast to bisphosphonate, vDcA were less commonly taken by post-menopausal
285 osteoporosis patients. A cohort study conducted in Spain showed that approximately
286 30% of treated postmenopausal osteoporosis patients suffered from vitamin D
287 deficiency and nearly all patients did not take sufficient calcium [40]. In the US, 74% of
288 the general adult population did not take sufficient vitamin D and 39% did not take
289 sufficient calcium [41]. For nearly a decade, the recommendable and recommended
290 treatment has not been used sufficiently in practice. Further investigation to improve the
291 implementation of nutritional guidelines is warranted.

292 The increase in the number of untreated patients between 2011 and 2015 compared with
293 the previous 5 years would be due to the decrease in the use of bisphosphonates due to

concerns about side effects. The FDA announced a Drug Safety Communication in 2010 regarding the risk of atypical femur fractures associated with the long-term use of bisphosphonates. A previous pharmacy claim records study showed the downward trend of bisphosphonates after 2011 [42]. The results were consistent with the previous study. This study results suggests that physicians should pay attention not only to the results of individual studies but also to the cumulative NMAs to know the true efficacy. The interpretation of the results of individual studies often have bias that gives a good impression [43]. It will be important to follow guidelines that provide timely cumulative NMAs and transparent recommendations.

There are several limitations to this study. First, we could not obtain two guidelines published by the National Osteoporosis Foundation in 2005 and 2010, because copies were no longer available at the Osteoporosis Foundation. However, we were able to retrieve the guidelines published in 2003, 2008, and 2014, which may not be significantly different from 2005 and 2010 editions. Second, there were few RCTs comparing active drugs. Therefore, we often had to estimate their efficacy based on star-shaped networks around placebo. The ranking of active constituents may therefore change with the addition of future trials, but their efficacy compared to placebo would not. In addition, the observed lack of evidence for statistical inconsistency in the network may be due to the limited statistical power because the network included only a small number of RCTs comparing active drugs. Third, we made an arbitrary assumption that moderate or better certainty of evidence with efficacy were recommendable. As more evidence accumulates, more effective drugs may become recommendable. Fourth, we did not investigate the

influence of other pathways toward prescription, such as industry payments and advertisements [44]. Another study focusing on physicians as the unit of analysis is needed. Fifth, hormone therapy and raloxifene would be prescribed for post-menopausal symptoms including osteoporosis. This bias would increase the proportion of hormone therapy and raloxifene, but not have affected the downward trend. Sixth, MEPS Household Component data is based on self-reported diagnosis and prescription data [29]. A validation study showed that the sensitivity of diagnosis of osteoporosis was about 50 % [45]. The prescription data is cross-checked by the pharmacies survey. A validation study excluding over-the-counter drugs showed the number of drug fills were reasonably accurate compared with claims [46]. Seventh, because of the data availability, our study compared prescription and CPGs only in the US. Further study is warranted to compare prescription with CPGs in other countries.

Conclusion

In postmenopausal osteoporosis, when we used cumulative NMAs as reference, no apparent discrepancy between guideline recommendations and drug prescription rankings was observed, with the exception of vDCa. Further research is warranted to investigate other disease areas which may lack drugs of clear choices, as well as other processes influencing prescribing practices.

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collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Compliance with Ethical Standards:

Because all data were retrieved from public databases, institutional review board approval is not required.

Conflict of Interest

TAF reports personal fees from Meiji, Mitsubishi-Tanabe, MSD and Pfizer and a grant from Mitsubishi-Tanabe, outside the submitted work; TAF has a patent 2018-177688 pending.

Yuki Kataoka, Yan Luo, Anna Chaimani, Akira Onishi, Miho Kimachi, Yasushi Tsujimoto, Mohammad Hassan Murad, Tianjing Li, and Andrea Cipriani declare that they have no conflict of interest.

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493
494
495

496 Figure 1. Network graphs of drugs

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498 Legend:

499 Each node represents one drug. The size of the node is proportional to the number of participants randomized to that drug. The lines
500 represent direct comparisons. The width of the lines represents the number of trials.

501 Abal=abaloparatide; alen=alendronate; baze=bazedoxifene; Ca=calcium; calc=calcitonin; deno=denosumab; horm=hormone therapy;
502 iban=ibandronate; laso=lasofoxifene; plac=placebo; ralo=raloxifene; rise=risedronate; romo=romosozumab; stro=strontium ranelate;
503 teri=teriparatide; tibo=tibolone; vDCa=vitamin D and calcium; vitD= vitamin D; zole=zoledronate.

504

505 Figure 2. Forest plot and certainty of evidence for efficacy in preventing hip fractures

506

507 Legend:

508 GRADE working group certainty of evidence definitions

509 High quality (H): We are very confident that the true effect lies close to that of the estimate of the effect; Moderate quality (M): We are
510 moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but a substantial difference is
511 possible; Low quality (L): Our confidence in the effect estimate is limited: The true effect may be substantially different from the
512 estimate of the effect; Very low quality (VL): We have very little confidence in the effect estimate: The true effect is likely to be
513 substantially different from the estimate of effect.

514 Abal=abaloparatide; alen=alendronate; baze=bazedoxifene; Ca=calcium; calc=calcitonin; CoE=certainty of evidence; deno=denosumab;
515 horm=hormone therapy; iban=ibandronate; laso=lasofoxifene; OR = odds ratio; plac=placebo; ralo=raloxifene; rise=risedronate;
516 romo=romosozumab; stro=strontium ranelate; teri=teriparatide; tibo=tibolone; vDCa=vitamin D and calcium; vitD= vitamin D;
517 zole=zoledronate.

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