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**Complete List of Authors:**
- Kataoka, Yuki
- Luo, Yan; School of Public Health in the Graduate School of Medicine, Kyoto University
- Chaimani, Anna
- Onishi, Akira; Kobe University Graduate School of Medicine School of Medicine, Department of Rheumatology and Clinical Immunology
- Kimachi, Miho; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology
- Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Healthcare Epidemiology; Kyoritsu Hospital, Nephrology and Dialysis
- Murad, M. Hassan; Mayo Clinic
- Li, Tianjing; Johns Hopkins University,
- Cipriani, Andrea; University of Oxford, Department of Psychiatry
- Furukawa, Toshi; Kyoto University, Graduate School of Medicine and School of Public Health

**Keywords:**
- practice guideline, Network Meta-Analysis, Process Assessment (Health Care)
Title page

Title

Cumulative network-metanlyses, practice guidelines and actual prescriptions of drug treatments for post-menopausal osteoporosis: A study protocol

Authors:

Yuki Kataoka, youkiti@gmail.com

Yan Luo, lilacuo@gmail.com

Anna Chaimani, anna.chaimani@parisdescartes.fr

Akira Onishi, telonishi@gmail.com

Miho Kimachi, cuisse.de.nymph@gmail.com

Yasushi Tsujimoto, yssh0108@yahoo.co.jp

Mohammad Hassan Murad, Murad.Mohammad@mayo.edu

Tianjing Li, tli19@jhu.edu

Andrea Cipriani, andrea.cipriani@psych.ox.ac.uk

Toshi A Furukawa, furukawa@kuhp.kyoto-u.ac.jp

Affiliations:

1. Hospital Care Research Unit, Hyogo Prefectural Amagasaki General Medical
20 Center, 2-17-77 Higashi-Naniwa-Cho, Amagasaki, Hyogo 660-8550, Japan
21 2. Department of Health Promotion and Human Behavior, School of Public Health in
22 the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyoku,
23 Kyoto 606-8501, Japan
24 3. Epidemiology and Statistics, Sorbonne Paris Cité Research Center (CRESS), Paris
25 Descartes University, 1 place du Parvis Notre-Dame, Paris 75004, France
26 4. Department of Rheumatology and Clinical Immunology, Kobe University Graduate
27 School of Medicine, 7 Chome-5-2 Kusunokicho, Chuo, Kobe, Hyōgo Prefecture
28 650-0017, Japan.
29 5. Department of Healthcare Epidemiology, School of Public Health in the Graduate
30 School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyoku, Kyoto
31 606-8501, Japan
32 6. Department of Nephrology and Dialysis, Kyoritsu Hospital, 16-5 Chuo-cho,
33 Kawanishi, Hyogo 666-0016, Japan
34 7. Mayo Clinic–Preventive Medicine, Rochester, MN, Minnesota 55905, USA.
35 8. Johns Hopkins Bloomberg School of Public Health–Epidemiology, 615 N. Wolfe
36 Street, Baltimore, MD, Maryland 21205, USA
37 9. Department of Psychiatry, University of Oxford, Warneford Ln, Oxford OX3 7JX,
38 Oxford, UK
39
40 **Corresponding author:**
41 Toshi A Furukawa
42 Department of Health Promotion and Human Behavior, School of Public Health in the
43 Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyoku, Kyoto
Abstract

Introduction

Cumulative network-meta-analysis (cumulative NMA) is a method to provide a global comparison of multiple treatments with real-time update to evidence users. Several studies investigated the ranking of cumulative NMA and the recommendations of practice guidelines. However, to the best of our knowledge, no study has evaluated the cumulative NMA ranking and prescription patterns. Here, we present a protocol for a meta-epidemiological investigation to compare the results of cumulative NMA with the recommendations in post-menopausal osteoporosis practice guidelines, and with the actual prescriptions.

Method and analysis

We will use the data of primary trials from the upcoming postmenopausal osteoporosis clinical practice guideline of the Endocrine Society. We will conduct cumulative NMA using all eligible trials and generate hierarchy of treatment rankings by using the surface under the cumulative ranking curve. We will search practice guidelines in relevant society websites. Two review authors will extract the practice recommendations. We will utilize data from the Medical Expenditures Panel Survey, a U.S representative sample of the noninstitutionalized population, to determine the prescription patterns.

Ethics and dissemination

Because all data will be retrieved from public databases, Institutional review board approval is not required. We will publish our findings in a peer-reviewed journal and present key findings at conferences.
Trial registration number: UMIN000031894

Strengths and limitations of this study

- This study is novel because it will compare rankings of drugs based on cumulative NMA with both clinical practice guideline recommendations and actual prescriptions.

- This study will describe the time-lag between the body of evidence and actual practice.

- We anticipate that prescription patterns are also influenced by insurance and payment policies.
Recommendations in clinical practice guidelines (CPGs) must be “informed by a systematic review (SR) of evidence and an assessment of the benefits and harms of alternative care options”. Incorporating SR and meta-analysis (MA) into CPGs has greatly improved the credibility of CPGs in the past decades. However, conventional pairwise MAs have one major drawback in presenting a summary of continuously growing evidence with an increasing number of treatment options, as so often happens in modern medicine, because we often have few if any direct comparison trials among important treatment alternatives. Network meta-analysis (NMA) combines direct and indirect comparisons and can summarize the relative efficacy between three or more treatment alternatives, and cumulative NMA can provide global comparisons of multiple treatment options with repeated updates. Moreover, because NMAs use all the available direct and indirect evidence, they can provide strong evidence earlier than conventional pairwise meta-analyses.

Whether successive revisions of CPGs in various fields of medicine have been able to incorporate such rigorous evidence updates remains an open question. One recent study compared the rankings by cumulative NMAs and recommendations of CPGs for open-angle glaucoma and found that cumulative NMAs can contribute to more timely recommendations than had traditionally been possible. This study, however, did not examine the influence of the updated evidence and the CPGs on the actual prescriptions by physicians for the disease. The translation of clinical knowledge from randomized controlled trials (RCTs) through cumulative NMAs and CPGs to actual prescription patterns by physicians is at the heart of evidence-based practices and therefore deserves greater scrutiny.
Postmenopausal osteoporosis is a common disease worldwide and in the United States; its prevalence is increasing with the aging of the populations. The U.S. Food and Drug Administration (FDA) has approved twelve classes of drugs for this condition. Several American and international societies and organizations have developed clinical practice guidelines for the use of these drugs, but there is much diversity in the real-world prescription patterns. This study aims to compare the results of cumulative NMAs with the recommendations in post-menopausal osteoporosis practice guidelines, and with the actual prescription practices.

METHODS AND ANALYSIS

Systematic review and cumulative network-meta-analyses of osteoporosis drugs

Study identification and data extraction

We will retrieve eligible original articles and data from the upcoming postmenopausal osteoporosis clinical practice guideline of the Endocrine Society. The inclusion criteria are:

i) Parallel-group randomized controlled trials

ii) Trials studied post-menopausal women with primary osteoporosis or osteopenia at risk of developing fragility fractures

iii) Trials evaluated commonly used medications approved by FDA for osteoporosis including bisphosphonates, teriparatide, selective estrogen receptor modulators, denosumab, estrogen with or without progesterone, calcitonin, lasofoxifene, strontium ranelate, tibolone, intact parathyroid hormone (PTH 1-84), calcium, vitamin D or placebo. Combination therapy will be included.

iv) Trials must have evaluated the primary outcome of interest in this study, namely,
new hip fractures at the time of the longest follow-up in the included studies. Hip fracture was designated as primary because of its clinical impact of patients' prognosis.  

Two independent researchers assessed the risk of bias of the included studies following the Cochrane Collaboration risk of bias tool. We resolved any disagreement through discussion of the two assessors or, where necessary, in consultation with a third assessor.  

Statistical analyses  
We will conduct random-effects cumulative NMAs of the identified network of trials at 5-year intervals (see below for Comparisons of NMA rankings, CPG recommendations and actual prescriptions). Each drug as well as each combination of drugs will be treated as a node in this network. We will assess the transitivity assumption of the whole data set in the final NMA; if confirmed, we will not validate it at every time point re-analysis. We will use a multi-level hierarchical model with components at the following levels: study, individual drug, and drug class. This model accounts for the within-study correlation of multigroup trials and also incorporates class effect. We will examine the consistency of the total network through both local and global tests of inconsistency. We will test small study effects and publication bias using the comparison-adjusted funnel plot taking placebo as the common comparator. We will examine the hierarchy of treatment rankings by using the surface under the cumulative ranking curve (SUCRA). A SUCRA value can indicate a 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.\textsuperscript{21,22} We will also show the relative treatment effects of all active medications in comparison with placebo in ranked forest plots. We will not adjust for multiple comparisons in successive NMAs as we are not interested in establishing superiority or inferiority of particular comparisons.

We will use Stata 15.1 (StataCorp, College Station, TX, USA) to conduct NMAs.\textsuperscript{23,24}

**Identification of practice guideline recommendations**

We will search the website of AHRQ's National Guideline Clearinghouse,\textsuperscript{25} American Association of Clinical Endocrinologists,\textsuperscript{26} American College of Physicians,\textsuperscript{27} Endocrine Society,\textsuperscript{28} and The North American Menopause Society\textsuperscript{29} using the following term: "osteoporosis". One author (YK) will select guidelines for the treatment of postmenopausal osteoporosis from U.S.-based organizations because we will evaluate the U.S. prescriptions. Two independent authors (YK and YL) will extract recommendation from guidelines. We will resolve disagreements through discussion and, if necessary, though arbitration by a third author (AO).

**Real-world prescriptions**

Medical Expenditure Panel Survey (MEPS) is a survey from nationally representative samples of the US non-institutionalized civilian population. MEPS uses sampling weights reflecting adjustments for survey non-response and population totals from the Current Population Survey\textsuperscript{30} and can therefore be used to derive nationally representative estimates. We will use the Household Component Files which contain
detailed information about demographic information and prescribed medicines for respondents. We will include all female respondents aged 50 years and older who have been classified as “206 Osteoporosis”. The cut-off value of 50 is in accordance with previous reports. We will exclude those who have been classified as “202 Rheumatoid arthritis and related disease”, because they may have steroid-induced osteoporosis. We will also exclude those who have been classified as “158 Chronic renal failure”, because they would have mineral and bone disorders. We will also exclude those who have been classified as “cancer” (the codes are from 11 to 44), because they sometimes have bone metastasis which need to be treated with bone modifying agents.

The prescription proportions and rankings will be determined by the annual prescription proportion of each drug category. The proprietary and nonproprietary names will be searched using the following terms from pharmacologic class of National Drug Code Directory: 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].

The numerator will be the number of patients who were prescribed each specific drug within five years. The denominator will be the number of patients who were female, over 50-years, and diagnosed as osteoporosis within the same five years. The greater proportion will mean the higher ranking.

We will use Python 3.6 (Python Software Foundation), STATA 15.1 (StataCorp, College Station, TX, USA) and R 3.3.2 (R foundation for Statistical Computing) to handle data from MEPS.
Comparisons of NMA rankings, CPG recommendations and real-world prescriptions

We will compare results from cumulative NMAs with recommendations by CPGs and with actual prescriptions every five years. Because there is bound to be some time lag as randomized evidence is generated, synthesized, integrated into recommendations and transferred to practice, the time frame for the comparisons will be set as shown in Table 1. First, because the median time from last search to publication of systematic reviews has been found to be 8.0 months (range: 0 to 47), we will include trials published up to 1 year prior to conducting the cumulative NMA. As there should be no time lag between the latest evidence synthesis and the CPG recommendations, we expect the NMA results to be reflected in the CPGs published in the ensuing five years. In 2000 a meta-epidemiological study showed a delay by 9.3 years between evidence review and its implementation. This delay may have been shortened in recent years. We will therefore compare the results from NMA and the CPG recommendations with actual prescriptions one or more years later than them. We will graphically present the changes in the rankings based on cumulative NMAs and on actual prescriptions between 1995 through 2015.

In comparing cumulative NMA rankings based on best-available evidence in the world literature and the CPG recommendations and the prescriptions in USA, we will take into consideration the drug approval dates by FDA as well as the dates when each drug became off-patent. To examine the influence of drug costs, we will tabulate the drug prices while on patent and also conduct a sensitivity analysis by limiting the analyses to patients with insurance.
ETHICS AND DISSEMINATION

Because all data will be retrieved from public databases, this study does not require institutional review board approval. We have registered this protocol in the University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR). The registration number is UMIN000031894. We will publish our findings in a peer-reviewed journal and also may present them at conferences.

DISCUSSION

We have presented the study protocol to compare the results of cumulative NMA with the recommendations in CPGs, and with the actual prescriptions.

To our knowledge, this is the first effort to evaluate the influence of cumulative evidence to CPGs and physicians’ attitude simultaneously. By using cumulative NMA the real-time trend of cumulative evidence and comprehensive network of available treatments will be presented. By using the MEPS, it is possible to estimate the representative prescription trends in the U.S. There are several limitations for this study. First, physicians’ choice would be affected by reasons other than evidence, such as the policy of insurance companies or the marketing efforts of pharmaceutical company. These factors are difficult to quantify and will warrant a separate study. Second, we should not prescribe teriparatide and bisphosphonate for long term because of their harm. In this study we plan to compare the proportion of prescriptions in MEPS, which will therefore likely underestimate the rankings of the teriparatide and bisphosphonate in comparison with its incident
In conclusion, this study will provide useful empirical evidence to compare the results of cumulative NMA with the recommendations in CPGs, and with the actual prescriptions. The expected findings will show the magnitude of the impact of comprehensive evidence in CPGs and real-world prescriptions.

Acknowledgement

We would like to thank the valuable comments from the members of Research Group on Meta-epidemiology at The Kyoto University School of Public Health (Tomoko Fujii, Yusuke Tsutsumi, Aran Tajika, and Kenji Omae)

Contributions

YK and TAF contributed to the conception and design of the research. YK and TAF are fully responsible for writing the protocol. TAF supervised the research, and all the co-authors contributed important intellectual contents to the revised protocol and gave final approval of the protocol before submission.

After the publication of the protocol, we plan the following contributions of each author:

YK and AC will conduct statistical analyses. YK will write the draft manuscript. TAF and all the other co-authors will revise the manuscript critically for important intellectual content. TAF will supervise the research, and all authors will give final approval of the protocol before submission.

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Research) Grant Number 17K19808 to TAF. The funder plays no role in developing the protocol.

281 Competing interests

TAF has received lecture fees from Janssen, Meiji, Mitsubishi-Tanabe, MSD and Pfizer.

He has received royalties from Igaku-Shoin and Nihon Bunka Kagaku-sha publishers.

He has received research support from Mitsubishi-Tanabe and Mochida. All the other authors report no competing interests to declare.

REFERENCES


DOI:10.5489/cuaj.4796.


Rouse B, Cipriani A, Shi Q, Coleman AL, Dickersin K, Li T. Network


Camacho PM, Petak SM, Binkley N, *et al.* American Association of Clinical
Endocrinologists and American College of Endocrinology Clinical Practice


Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment


27 American College of Physicians. https://www.acponline.org (accessed Jan 19,
360  2018).


363  19, 2018).

364  30  Medical Expenditure Panel Survey Home.


366  31  Farley JF, Blalock SJ. Trends and determinants of prescription medication use


368  32  Wright NC, Looker AC, Saag KG, *et al.* The recent prevalence of osteoporosis

369  and low bone mass in the United States based on bone mineral density at the


371  33  Combe B, Landewe R, Daien CI, *et al.* 2016 update of the EULAR

372  recommendations for the management of early arthritis. *Ann Rheum Dis* 2017;

373  76: 948–59.

374  34  Moe SM, Drueke TB, Group  for the KW. KDIGO clinical practice guideline

375  for the diagnosis, evaluation, prevention and treatment of chronic kidney disease


Table 1. Timeframe for comparisons

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RCTs, randomized controlled trials; NMA, network-meta-analysis; CPGs, clinical practice guidelines.

What does “RCTs to pool” mean? Is lagging of 1 year reasonable?
Table 1
Timeframe for comparisons

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| Complete List of Authors: | Kataoka, Yuki  
Luo, Yan; School of Public Health in the Graduate School of Medicine, Kyoto University  
Chaimani, Anna  
Onishi, Akira; Kobe University Graduate School of Medicine School of Medicine, Department of Rheumatology and Clinical Immunology  
Kimachi, Miho; School of Public Health in the Graduate School of Medicine, Kyoto University, Department of Healthcare Epidemiology  
Tsujimoto, Yasushi ; School of Public Health in the Graduate School of Medicine, Kyoto University, Healthcare Epidemiology; Kyoritsu Hospital, Nephrology and Dialysis  
Murad, M. Hassan; Mayo Clinic  
Li, Tianjing; Johns Hopkins University,  
Cipriani, Andrea; University of Oxford, Department of Psychiatry  
Furukawa, Toshi; Kyoto University, Graduate School of Medicine and School of Public Health |
| Primary Subject Heading: | Evidence based practice |
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Title page

Title

Cumulative network-meta-analyses, practice guidelines and actual prescriptions of drug treatments for post-menopausal osteoporosis: A study protocol for Cumulative Network Meta-analyses and Meta-epidemiological Study

Authors:

Yuki Kataoka¹, youkiti@gmail.com

Yan Luo², lilacluo@gmail.com

Anna Chaimani³, anna.chaimani@parisdescartes.fr

Akira Onishi⁴, telonishi@gmail.com

Miho Kimachi⁵, cuisse.de.nymph@gmail.com

Yasushi Tsujimoto⁵,⁶, yssh0108@yahoo.co.jp

Mohammad Hassan Murad⁷, Murad.Mohammad@mayo.edu

Tianjing Li⁸, tli19@jhu.edu

Andrea Cipriani⁹, andrea.cipriani@psych.ox.ac.uk

Toshi A Furukawa², furukawa@kuhp.kyoto-u.ac.jp

Affiliations:
20 1. Hospital Care Research Unit, Hyogo Prefectural Amagasaki General Medical
21 Center, 2-17-77 Higashi-Naniwa-Cho, Amagasaki, Hyogo 660-8550, Japan
22 2. Department of Health Promotion and Human Behavior, School of Public Health in
23 the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku,
24 Kyoto 606-8501, Japan
25 3. Epidemiology and Statistics, Sorbonne Paris Cité Research Center (CRESS), Paris
26 Descartes University, 1 place du Parvis Notre-Dame, Paris 75004, France
27 4. Department of Rheumatology and Clinical Immunology, Kobe University Graduate
28 School of Medicine, 7-Chome-5-2 Kusunokicho, Chuo, Kobe, Hyōgo Prefecture
29 650-0017, Japan.
30 5. Department of Healthcare Epidemiology, School of Public Health in the Graduate
31 School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto
32 606-8501, Japan
33 6. Department of Nephrology and Dialysis, Kyoritsu Hospital, 16-5 Chuo-cho,
34 Kawanishi, Hyogo 666-0016, Japan
35 7. Mayo Clinic–Preventive Medicine, Rochester, MN, Minnesota 55905, USA.
36 8. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health,
37 615 N. Wolfe Street, Baltimore, MD, Maryland 21205, USA
38 9. Department of Psychiatry, University of Oxford, Warneford Ln, Oxford OX3 7JX,
39 Oxford, UK
40
41 **Corresponding author:**
42 Toshi A Furukawa
43 Department of Health Promotion and Human Behavior, School of Public Health in the
Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyō-ku, Kyoto 606-8501, Japan
Phone: +81-75-753-9491
Fax: +81-75-753-4641
Email: furukawa@kuhp.kyoto-u.ac.jp

Word count: 2485

Keywords: Practice Guideline, Network Meta-Analysis, Process Assessment (Health Care)
Abstract

Introduction

Cumulative network-meta-analysis (cumulative NMA) is a method to provide a global comparison of multiple treatments with real-time update to evidence users. Several studies investigated the ranking of cumulative NMA and the recommendations of practice guidelines. However, to the best of our knowledge, no study has evaluated the cumulative NMA ranking and prescription patterns. Here, we present a protocol for a meta-epidemiological investigation to compare the results of cumulative NMA with the recommendations in post-menopausal osteoporosis practice guidelines, and with the actual prescriptions.

Method and analysis

We will use the data of primary trials from the upcoming postmenopausal osteoporosis clinical practice guideline of the Endocrine Society. We will conduct cumulative NMA using all eligible trials and generate hierarchy of treatment rankings by using the surface under the cumulative ranking curve. We will search practice guidelines in relevant society websites. Two review authors will extract the practice recommendations. We will utilize data from the Medical Expenditures Panel Survey, a U.S representative sample of the noninstitutionalized population, to determine the prescription patterns.

Ethics and dissemination

Because all data will be retrieved from public databases, Institutional review board approval is not required. We will publish our findings in a peer-reviewed journal and present key findings at conferences.
Strengths and limitations of this study

- This study is novel because it will compare rankings of drugs based on cumulative NMA with both clinical practice guideline recommendations and actual prescriptions.

- This study will delineate the time-lag between the body of evidence and guideline recommendations, and actual practice.

- Physicians’ choice would be affected by reasons other than evidence about efficacy, which cannot be considered in this study.
INTRODUCTION

Recommendations in clinical practice guidelines (CPGs) should be “informed by a systematic review (SR) of evidence and an assessment of the benefits and harms of alternative care options”\(^1\). Incorporating SR and meta-analysis (MA) into CPGs has greatly improved the credibility of CPGs in the past decades.\(^2\)\(^-\)\(^4\) However, conventional pairwise MAs that compare two interventions at a time is insufficient for analyzing the increasing number of treatment options in a coherent manner because not all treatment alternatives have been compared directly in randomized trials.\(^5\)\(^-\)\(^7\) Network meta-analysis (NMA) combines direct and indirect evidence and generates the relative effects of three or more treatment alternatives in a single analysis. Cumulative NMA can provide global comparisons of multiple treatment options with repeated updates.\(^7\)\(^,\)^\(^8\) Moreover, because NMAs use both direct and indirect evidence, they can provide answers earlier than conventional pairwise MAs.\(^8\)

Whether successive revisions of CPGs in various fields of medicine have been able to incorporate such rigorous evidence updates remains an open question. One recent study compared the rankings by cumulative NMAs and recommendations of CPGs for open-angle glaucoma and found that cumulative NMAs can contribute to more timely recommendations than had traditionally been possible.\(^9\) This study did not intend to examine the influence of the updated evidence and the CPGs on the actual prescriptions by physicians for the disease. The translation of clinical knowledge from randomized controlled trials (RCTs) through cumulative NMAs and CPGs to actual prescription patterns by physicians is at the heart of evidence-based practices and therefore deserves greater scrutiny.

Postmenopausal osteoporosis is a common disease worldwide and in the United States;
its prevalence is increasing with the aging of the populations.\textsuperscript{10,11} The U.S. Food and Drug Administration (FDA) has approved twelve classes of drugs for this condition.\textsuperscript{12} Several US and international societies and organizations have developed clinical practice guidelines for the use of these drugs,\textsuperscript{12-14} but the real-world prescription patterns vary widely.\textsuperscript{15} This study aims to compare the results of cumulative NMAs with the recommendations in post-menopausal osteoporosis practice guidelines, and with the actual prescription practices.

\section*{METHODS AND ANALYSIS}

\subsection*{Systematic review and cumulative NMAs of osteoporosis drugs}

\subsubsection*{Study identification and data extraction}

We will retrieve eligible original articles and data from the upcoming postmenopausal osteoporosis clinical practice guideline of the Endocrine Society. We will use a recently completed search for relevant studies (last search date: July 7th 2017) that we have conducted for the guideline. The inclusion criteria are:

\begin{enumerate}
\item Parallel-group RCTs
\item Trials studied post-menopausal women with primary osteoporosis or osteopenia at risk of developing fragility fractures
\item Trials evaluated commonly used medications including bisphosphonates, teriparatide, selective estrogen receptor modulators, denosumab, estrogen with or without progesterone, calcitonin, lasofoxifene, strontium ranelate, tibolone, or intact parathyroid hormone (PTH 1-84). We will also include nutritional supplements commonly recommended for osteoporosis including calcium and vitamin D. Control conditions may include placebo, no treatment or treatment as
Trials must have evaluated the primary outcome of interest in this study, namely, new hip fractures at the time of the longest follow-up in the included studies. Hip fracture was designated as primary because of its clinical impact of patients' prognosis.\(^1\)\\n
We did not limit language, geographical location or publication date.

Two of ten review authors independently examined each title and abstract identified in the search to exclude obviously irrelevant reports, then independently examine full-text articles to determine eligibility. If there were any disagreements, the same authors discussed disagreements; a third author helped reach consensus if necessary. The same independent pairs of reviewers also evaluated the risk of bias following the Cochrane risk of bias tool\(^1\)\(^7\). They resolved any disagreement through discussion of the two assessors or, where necessary, in consultation with a third assessor.

**Statistical analyses**

We will conduct random-effects cumulative NMAs of the identified network of trials at 5-year intervals (see below for Comparisons of NMA rankings, CPG recommendations and actual prescriptions).\(^1\)\(^8\) Each drug as well as each combination of drugs will be treated as a node in this network. We will assess the transitivity assumption of the whole data set in the final NMA; if confirmed, we will not validate it at every time point re-analysis. We will use a multi-level hierarchical model with components at the following levels: study, individual drug, and drug class. This model accounts for the within-study correlation of multigroup trials and also incorporates class effect.\(^1\)\(^9\)\(^-\)\(^2\)\(^1\)
Given the clinical and methodological heterogeneity of the populations and methods
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Identification of practice guideline recommendations

We will search the website of AHRQ's National Guideline Clearinghouse,\textsuperscript{26} American
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postmenopausal osteoporosis from U.S.-based organizations because we will evaluate
the U.S. prescriptions. Two of five independent authors (YK, YL, AO, MK, and YT)
will extract data from each guideline. We will extract publication year, developers, drug
treatment recommendations and their strength, and whether the recommendations were
based on systematic reviews or not. We will resolve disagreements through discussion
and, if necessary, though arbitration by another author (YK, YL, AO, MK, or YT).

Real-world prescriptions
Medical Expenditure Panel Survey (MEPS) is a survey from nationally representative
samples of the US non-institutionalized civilian population. MEPS uses sampling
weights reflecting adjustments for survey non-response and population totals from the
Current Population Survey and can therefore be used to derive nationally
representative estimates. We will use the Household Component Files which contain
detailed information about demographic information and prescribed medicines for
respondents. We will include all female respondents aged 50 years and older who have
been classified as “206 Osteoporosis”. The cut-off value of 50 is in accordance with
previous reports. We will exclude those who have been classified as “202 Rheumatoid arthritis and related disease”, because they may have steroid-induced
osteoporosis. We will also exclude those who have been classified as “158 Chronic renal failure”, because they would have mineral and bone disorders. We will also
exclude those who have been classified as “cancer” (the codes are from 11 to 44),
because they sometimes have bone metastasis which need to be treated with bone
modifying agents.
The prescription proportions and rankings will be determined by the 5-year prescription proportion of each drug category. The proprietary and nonproprietary names will be searched using the following terms from pharmacologic class of National Drug Code Directory: 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].

The numerator will be the number of patients who were prescribed each specific drug within five years. The denominator will be the number of patients who were female, over 50 years, and diagnosed as osteoporosis within the same five years. The greater proportion will mean the higher ranking.

We anticipate that we can start retrieving data in December 2018.

We will use Python 3.6 (Python Software Foundation), and STATA 15.1 (StataCorp, College Station, TX, USA) to handle data from MEPS.

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

We will compare results from cumulative NMAs with recommendations by CPGs and with actual prescriptions at 5-year intervals. MEPS started in 1996. We therefore 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 will be set as shown in Table 1. First, because the median time from last search to publication of systematic reviews has been found to be 8.0
months (range: 0 to 47), we will include trials published up to 1 year prior to conducting
the cumulative NMA.\(^{38}\) As there should be no time lag between the latest evidence
synthesis and the CPG recommendations, we expect the NMA results to be reflected in
the CPGs published in the ensuing five years. In 2000 a meta-epidemiological study
showed a delay by 9.3 years between evidence review and its implementation.\(^{39}\) This
delay may have been shortened in recent years.\(^{40}\) We will therefore compare the results
from NMA and the CPG recommendations with actual prescriptions one or more years
later than them.

This is a descriptive study. We will visually explore the differences between evidences
from NMA, CPG and actual prescriptions. We will not conduct statistical tests for
comparison.

In comparing cumulative NMA rankings based on best-available evidence in the world
literature and the CPG recommendations and the prescriptions in US, we will take into
consideration the drug approval dates for osteoporosis by FDA as well as the dates
when each drug became off-patent. To examine the influence of drug costs, we will
tabulate the approval and off-patent date of each drug while on patent and also conduct
a sensitivity analysis by limiting the analyses to patients with insurance.

**Patient and Public Involvement**

The study group developed this study protocol without patient involvement. This study
will use only anonymized public data without new patient recruitment. We will
disseminate the results via web sites and social network services to patients with
osteoporosis.
ETHICS AND DISSEMINATION

Because all data will be retrieved from public databases, this study does not require institutional review board approval. We have registered this protocol in the University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR). The registration number is UMIN000031894. We will prepare the publication in accordance with PRISMA guideline\textsuperscript{41} and its adaptation for meta-epidemiological studies.\textsuperscript{42} We will publish our findings in a peer-reviewed journal and also may present them at conferences.

DISCUSSION

We have presented the study protocol to compare the results of cumulative NMA with the recommendations in CPGs, and with the actual prescriptions. To our knowledge, this is the first effort to evaluate the influence of cumulative evidence to CPGs and physicians’ attitude simultaneously. By using cumulative NMA the real-time trend of cumulative evidence and comprehensive network of available treatments will be presented.\textsuperscript{6,7} By using the MEPS, it is possible to estimate the representative prescription trends in the U.S.\textsuperscript{31}

There are several limitations for this study. First, physicians’ choice would be affected by reasons other than evidence, such as the policy of insurance companies or the marketing efforts of pharmaceutical company.\textsuperscript{43,44} These factors are difficult to quantify and will warrant a separate study. Second, we should not prescribe teriparatide and bisphosphonate for long term because of their harm.\textsuperscript{45} In this study we plan to compare the proportion of prescriptions in MEPS, which will therefore likely underestimate the rankings of the teriparatide and bisphosphonate in comparison with its incident prescriptions.
In conclusion, this study will provide useful empirical evidence to compare the results of cumulative NMA with the recommendations in CPGs, and with the actual prescriptions. The expected findings will show the magnitude of the impact of comprehensive evidence in CPGs and real-world prescriptions.

Acknowledgement

We would like to thank the valuable comments from the members of Research Group on Meta-epidemiology at The Kyoto University School of Public Health (Tomoko Fujii, Yusuke Tsutsumi, Aran Tajika, and Kenji Omae).

Contributions

YK and TAF contributed to the conception and design of the research. YK and TAF are fully responsible for writing the protocol. TAF supervised the research, and TL, AO, MK, YT, MHM, TL, and AC contributed important intellectual contents to the revised protocol and gave final approval of the protocol before submission.

After the publication of the protocol, we plan the following contributions of each author: YK and AC will conduct statistical analyses. YK, YL, AO, MK, YT will retrieve data from guidelines. YK will write the draft manuscript. TAF, YL, AO, MK, YT, MHM, TL, and AC will revise the manuscript critically for important intellectual content. TAF will supervise the research, and YL, AO, MK, YT, MHM, TL, AC, TAF will give final approval of the manuscript before submission.

Funding

This study is supported in part by JSPS KAKENHI (Grant-in-Aid for Scientific
Research) Grant Number 17K19808 to TAF. The funder plays no role in developing the protocol.

Competing interests

TAF has received lecture fees from Janssen, Meiji, Mitsubishi-Tanabe, MSD and Pfizer. He has received royalties from Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mitsubishi-Tanabe and Mochida. All the other authors report no competing interests to declare.

REFERENCES


319 DOI:10.5489/cuaj.4796.


Rouse B, Cipriani A, Shi Q, Coleman AL, Dickersin K, Li T. Network


19 Owen RK, Tincello DG, Keith RA. Network meta-analysis: development of a
three-level hierarchical modeling approach incorporating dose-related constraints.


Combe B, Landewe R, Daien CI, et al. 2016 update of the EULAR


Hanney SR, Castle-Clarke S, Grant J, *et al.* How long does biomedical research take? Studying the time taken between biomedical and health research and its


418 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for


420 6: e1000097.

421 Murad MH, Wang Z. Guidelines for reporting meta-epidemiological


423 Clemens J, Gottlieb JD. Do Physicians’ Financial Incentives Affect Medical


425 Yeh JS, Franklin JM, Avorn J, Landon J, Kesselheim AS. Association of

426 Industry Payments to Physicians With the Prescribing of Brand-name Statins in


428 Ro C, Cooper O. Bisphosphonate drug holiday: Choosing appropriate candidates.

### Table 1. Timeframe for comparisons

<table>
<thead>
<tr>
<th>Publication year of RCTs</th>
<th>cumulative NMA</th>
<th>CPGs</th>
<th>Prescription ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2014</td>
<td>2015</td>
<td>2015-2017</td>
<td>-</td>
</tr>
</tbody>
</table>

RCTs, randomized controlled trials; NMA, network-meta-analysis; CPGs, clinical practice guidelines.
# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

**Instructions to authors**

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:


<table>
<thead>
<tr>
<th>Reporting Item</th>
<th>Page Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Identification</strong></td>
<td>1</td>
</tr>
<tr>
<td>#1a Identify the report as a protocol of a systematic review</td>
<td>1</td>
</tr>
<tr>
<td><strong>Update</strong></td>
<td>NA</td>
</tr>
<tr>
<td>#1b If the protocol is for an update of a previous systematic review, identify as such</td>
<td>NA</td>
</tr>
<tr>
<td>#2 If registered, provide the name of the registry (such as PROSPERO) and registration number</td>
<td>5</td>
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<tr>
<td><strong>Contact</strong></td>
<td>1-3</td>
</tr>
<tr>
<td>#3a Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
<td>1-3</td>
</tr>
<tr>
<td><strong>Contribution</strong></td>
<td>14</td>
</tr>
<tr>
<td>#3b Describe contributions of protocol authors and identify the guarantor of the review</td>
<td>14</td>
</tr>
<tr>
<td>#4 If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important changes</td>
<td>NA</td>
</tr>
</tbody>
</table>
Sources #5a Indicate sources of financial or other support for the review 14

Sponsor #5b Provide name for the review funder and / or sponsor 14

Role of sponsor or funder #5c Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol 14

Rationale #6 Describe the rationale for the review in the context of what is already known 6-7

Objectives #7 Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) 7

Eligibility criteria #8 Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review 7-8

Information sources #9 Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage 10

Search strategy #10 Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated 7

Study records - data management #11a Describe the mechanism(s) that will be used to manage records and data throughout the review 8-10

Study records - selection process #11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) 8-10

Study records - data collection process #11c Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators 8-10

Data items #12 List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications 8-10
<table>
<thead>
<tr>
<th>Outcomes and prioritization</th>
<th>#13 List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias in individual studies</td>
<td>#14 Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis</td>
</tr>
<tr>
<td>Data synthesis</td>
<td>#15a Describe criteria under which study data will be quantitatively synthesised</td>
</tr>
<tr>
<td></td>
<td>#15b If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ)</td>
</tr>
<tr>
<td></td>
<td>#15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)</td>
</tr>
<tr>
<td></td>
<td>#15d If quantitative synthesis is not appropriate, describe the type of summary planned</td>
</tr>
<tr>
<td>Meta-bias(es)</td>
<td>#16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)</td>
</tr>
<tr>
<td>Confidence in cumulative evidence</td>
<td>#17 Describe how the strength of the body of evidence will be assessed (such as GRADE)</td>
</tr>
</tbody>
</table>

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