

INPLASY PROTOCOL

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None declared.

Bisphosphonates and the risk of stroke: A systematic review and meta-analysis

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Review question / Objective: To determine the association between bisphosphonate use and risk of stroke based on up-to-date evidence. **P:** Adult patients eligible for bisphosphonate use **I:** Bisphosphonate use **C:** Without bisphosphonate use **O:** Stroke risk **S:** Clinical trials, cohort studies, or case-control studies.

Condition being studied: Some studies have suggested that bisphosphonates may reduce the risk of stroke, while the relevant evidence is inconsistent and inconclusive.

Eligibility criteria: Studies will be included in the systematic review if: (1) the studies presented outcome measurements for stroke in patients with and without bisphosphonate use; (2) they reported the relative risk (RR) of stroke between bisphosphonate users and non-users (including those without treatment or taking other antiosteoporotic agents rather than bisphosphonates), or the RR could be derived from the study's data; (3) the study designs were clinical trials, cohort studies or case-control studies; (4) they were published as original articles or with original data.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 March 2022 and was last updated on 18 March 2022 (registration number INPLASY202230085).

INTRODUCTION

Review question / Objective: To determine the association between bisphosphonate use and risk of stroke based on up-to-date evidence. **P:** Adult patients eligible for bisphosphonate use **I:** Bisphosphonate use

C: Without bisphosphonate use **O:** Stroke risk **S:** Clinical trials, cohort studies, or case-control studies.

Rationale: Owing to the shared common risk factors for osteoporosis and stroke, many osteoporosis patients are also at

high risk of stroke; thus, stroke prevention in these populations is a crucial clinical issue. The growing evidence has indicated that bone mineralization and vascular calcification are regulated by shared biological mechanisms, and the relationship between osteoporosis and atherosclerosis is also found because of their potentially shared pathophysiologic mechanisms. Bisphosphonates are effective bone resorption inhibitors. Previous studies also suggested that bisphosphonates could interfere vascular calcification process and may have an inhibitory effect on the atherosclerosis process.

Condition being studied: Some studies have suggested that bisphosphonates may reduce the risk of stroke, while the relevant evidence is inconsistent and inconclusive.

METHODS

Search strategy: We search for studies evaluating the effects of bisphosphonate on the risk of stroke in PubMed, Embase, Scopus, and Cochrane library databases. In brief, we search for articles using a combination of the terms: “bisphosphonates” and “Stroke”; each bisphosphonate drug name and both the ischemic and hemorrhagic stroke are used for searching.

Participant or population: Adult patients eligible for bisphosphonate use.

Intervention: Bisphosphonate use.

Comparator: Placebo, other antiosteoporotic drugs, or no bisphosphonate use.

Study designs to be included: Clinical trials, cohort studies, or case-control studies.

Eligibility criteria: Studies will be included in the systematic review if: (1) the studies presented outcome measurements for stroke in patients with and without bisphosphonate use; (2) they reported the relative risk (RR) of stroke between bisphosphonate users and non-users

(including those without treatment or taking other antiosteoporotic agents rather than bisphosphonates), or the RR could be derived from the study’s data; (3) the study designs were clinical trials, cohort studies or case-control studies; (4) they were published as original articles or with original data.

Information sources: PubMed, Embase, Scopus, and Cochrane library.

Main outcome(s): Stroke (regardless of subtypes such as ischemic stroke, hemorrhagic stroke, or transient ischemic attack).

Additional outcome(s): Ischemic stroke, hemorrhagic stroke, and stroke death.

Quality assessment / Risk of bias analysis: At least two reviewers will independently evaluate the quality of included studies using the Newcastle–Ottawa Scale for cohort/case-control studies and Cochrane Risk of Bias Tool for randomized controlled trials.

Strategy of data synthesis: We will synthesize the relative risks (RRs) and odds ratios (ORs) obtained from both the RCTs and observational studies to calculate the pooled RRs in our meta-analysis. The ORs will probably be pooled together with RRs since the values of ORs would be close to those of RRs if the endpoint occurs relatively infrequently.

Subgroup analysis: Several subgroup analyses will be performed to assess the effects of study-level factors on the outcome estimates and the possible sources of heterogeneity; the factors included bisphosphonate type, comparison type, study design, follow-up time, geographic location, and study population (restriction on female population or cancer population).

Sensitivity analysis: Leave-one-out sensitivity analyses will be performed by omitting each study individually to evaluate the influence of each study on the overall pooled estimates.

Country(ies) involved: Taiwan and the U.S.

Keywords: Bisphosphonates; stroke; meta-analysis.

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