Efficacy and safety of statins and ezetimibe in primary prevention of cardiovascular disease in the elderly: A systematic review protocol.

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ABSTRACT

Cardiovascular diseases (CVD) are the leading cause of death globally (1). The risk increases with age. Statins and ezetimibe are indicated for the prevention of CVD and its efficacy in secondary prevention (patients who have had an adverse CVD event) has been demonstrated in all age groups (2). However, there is controversy about its use in primary prevention (people without established CVD) in the elderly (3, 4), since the patients older than 75 years are a group of underrepresented population in clinical trials. This age threshold has been used in meta-analysis of randomized controlled trials that did not shown evidence of an effect in cardiovascular events in people older than 75 years without vascular disease (5–7) . The latest clinical guidelines published in the United States and Europe differ notably in their recommendations (8–10).
As other medicines, statins and ezetimibe are not exempt from adverse events. These are more frequent in geriatric patients, since comorbidities and polypharmacy frequently coexist. These factors can increase the risk of drug interactions and contribute to the impairment of renal and hepatic function (11).
We describe a protocol for a systematic review that will evaluate the effectiveness and safety of statins and ezetimibe in people over 75 years of age.

Title

1 Efficacy and safety of statins and ezetimibe in primary prevention of cardiovascular disease in the elderly: A systematic review protocol.

Author Contributions

2 JFG: conceptualization, methodology, developing the search strategy and literature search, data selection, extraction, statistical analysis, and writing the protocol and original draft. IIR: Support in the search strategy and bibliographic search, data selection and extraction, review and edit the protocol. NAI: Support in the search strategy and bibliographic search, review and edit the protocol. AEG: Support in the search strategy and bibliographic search, review and edit the protocol. JGP: conceptualization, methodology, develop the search strategy and search, review and edit the protocol and the manuscript. CL: Assist, edit and review protocol and manuscript.

Support

3 The protocol and systematic review are part of the main author's doctoral thesis. It will also include the results of a study on health outcomes of statin and ezetimibe deprescription strategy in the elderly, funded by the Institute of Health Carlos III (ISCIII) through the project PI21/01931 and co-financed by the European Union in the Call for Action Strategy in Health (AES) 2021.

Rationale

4 Cardiovascular diseases (CVD) are the leading cause of death globally (1). The risk increases with age. Statins and ezetimibe are indicated for the prevention of CVD and its efficacy in secondary prevention (patients who have had an adverse CVD event) has been demonstrated in all age groups (2). However, there is controversy about its use in primary prevention (people without established CVD) in the elderly (3, 4), since the patients older than 75 years are a group of underrepresented population in clinical trials. This age threshold has been used in meta-analysis of randomized controlled trials that did not shown evidence of an effect in cardiovascular events in people older than 75 years without vascular disease (5–7) . The latest clinical guidelines published in the United States and Europe differ notably in their recommendations (8–10).
As other medicines, statins and ezetimibe are not exempt from adverse events. These are more frequent in geriatric patients, since comorbidities and polypharmacy frequently coexist. These factors can increase the risk of drug interactions and contribute to the impairment of renal and hepatic function (11).
We describe a protocol for a systematic review that will evaluate the effectiveness and safety of statins and ezetimibe in people over 75 years of age.

Objective

5 To assess effectiveness and safety of statins and ezetimibe in people over 75 years of age in primary prevention of CVD.
Population: patients older than 75 years who do not have a history of CVD defined as ischemic heart disease, ischemic cerebrovascular disease, or peripheral arterial disease.
Intervention: Treatment with statins and/or ezetimibe for the primary prevention of CVD.
Comparator: placebo or no intervention.
Outcomes: Death from any cause. Hospitalization. Major cardiovascular event: non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. For adverse effects: selfreported muscle symptoms, clinically confirmed muscle disorders, liver dysfunction, kidney failure, diabetes mellitus and eye diseases.

Methods

6 Eligibility criteria
The studies that we will include in the review will be those carried out on the general population (primary care setting), over 75 years of age and who are undergoing lipid-lowering treatment with a statin or ezetimibe indicated for the prevention of CVD Inclusion Criteria:
Clinical trials and analytical observational studies published since 2010 or systematic reviews and meta-analyses published in the last 5 years (2018-2023) (12) that report data on the population over the age of 75.
Studies carried out in primary care setting, in the general population and in primary prevention of CVD.
Studies whose data of outcomes of interest have been obtained or can be calculated.
Studies with at least 1,000 patients.
Clinical practice guidelines that issue recommendations on the use of statins or ezetimibe in people over 75 and in primary prevention of CVD; that are evidence-based.
Exclusion Criteria:
Studies in a specific subset of the population (eg, hospital outpatients, institutionalized, studies based on disease or diagnosis).
Studies published exclusively as abstracts.
Studies published in a language other than English or Spanish.
Observational studies that select active principles.

7 Information sources
A systematic search of the literature will be conducted through the following sources: Cochrane Library, Pubmed, CENTRAL, Epistemonikos and EMBASE, with the date of consultation from January 2010 until January 2022.
Primary studies will be identified through the ClinicalTrials.gov database, the Spanish Clinical Trials Registry (REEC), the EU Clinical Trials Registry, the EU post-authorization study registry (ENCePP), and the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization. A search in PROSPERO will be carried out to identify completed and/or ongoing reviews.

8 Search Strategy

Based on the PICO elements, a preliminary search conducted on December 27th of 2022 is described on the Appendix 1.

The strategy will be built with the following keywords and boolean operators for the initial question:

("Ezetimibe" AND" primary prevention [Mesh]); ("statins" AND "primary prevention" [Mesh])

9 Data management

Database search results will be imported into an Access® database. We will collate multiple reports of the same study.

10 Selection process

Title and abstract will be screened by two independent reviewers using the following questions:

1) Does the title or abstract describe a study involving statins or ezetimibe?

2) Does the title or abstract describe a study in general population or primary care (not in a specific subset of the population)?

If both reviewers answer "no" for one of the questions the study will be excluded. Conflicts between the two reviewers will be discussed, if necessary a third reviewer will participate until an agreement is reached. A full manuscript screening will be performed by two reviewers. This screening will include following questions:

3) Does the title or abstract describe a study involving elderly people (over 75)?

4) Is the study conducted in primary prevention or primary and secondary prevention of CVD?

5) Is the study an observational study (cohorts), Clinical Trials (randomized or not), systematic reviews or meta-analyses?

6) Is the study written in English or Spanish?

7) Is the study published after 2010?

8) Is the study master size at least 1,000?

9) Can the study provide effectiveness or safety outcomes versus placebo o no intervention in primary prevention of CVD?

Studies will be excluded if answered "no" for one or more of the questions. The exclusion reason will be recorded at this screening level.

We will include clinical practice guidelines that issue recommendations on the use of statins or ezetimibe in people over 75 and in primary prevention of CVD; that are evidence-based. For assessing this we will use items 7-11 in the domain 3. Rigor of Development of AGREE II Instrument. (13)

11 Data collection process

Data from studies will be extracted with a data extraction form into an electronic spreadsheet and it will be reviewed. Data extraction form will be tested on 5 studies randomly selected. Data extracted will include:

1. General information: journal name, language, country, author's name and affiliation, year of publication, funding information.

2. Type of study: Observational studies (cohorts), Clinical Trials (randomized or not), systematic

reviews or meta-analyses.
3. Duration of the study and/or follow-up time.
4. Limitations of the study.
5. Population characteristics: sex and age.
6. Intervention and comparator: Lipid-lowering agent studied: statin, ezetimibe, or both.
7. Outcomes: type, mean differences from control, unit of results, lower/upper 95% CI, standard error, standard deviation, P-value, and time point of each measurement.
For dichotomous outcomes information: number of each one, proportion, total number of each one, unit of results, odd ratio, relative risk, lower/ upper 95% CI, P-value, and time point of each measurement.

12 Data items

Outcomes and priorization
Effectiveness and efficacy data: mortality, hospital admission, or major cardiovascular event (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death).
Adverse effects: self-reported muscle symptoms, clinically confirmed muscle disorders, liver dysfunction, renal insufficiency, diabetes, and eye diseases.

Risk of bias in individual studies
The risk of bias assessment will be performed using the RoB 2 tool for randomized trials and the ROBINS-I tool for non-randomised studies (14). Two reviewers will independently assess the risk of bias of the studies. Disagreements will be resolved by consensus, if necessary a third reviewer will participate until an agreement is reached.
Studies will be classified as low risk of bias or moderate to high risk of bias.

Data synthesis
If the results are sufficiently homogeneous, we will do a meta-analysis.
Heterogeneity between estimates will be tested using the I^2 statistic. An I^2 value greater than 75% will be considered as highly heterogeneous. The meta-analysis would be performed using a random effects model. Pooled prevalence would be calculated with a 95% confidence interval. Those variables identified a priori as possible sources of variation in the estimate of the effect will be evaluated: risk of bias and method of data collection.
The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology will be applied to evaluate the quality of the evidence for the main outcomes (15).