INPLASY

Therapeutic Strategies for Post-Menopausal Atherosclerosis: A Systematic Review of Drug Interventions in Animal Models

INPLASY202560033
doi: 10.37766/inplasy2025.6.0033
Received: 7 June 2025
Published: 7 June 2025

Zulkefli, SB; Mohamad, F; Abdul Nasir, NA; Shuid, AN; Azme, N.

Corresponding author:
Nasibah Azme

nasibah@uitm.edu.my

Author Affiliation:
Universiti Teknologi MARA.

ADMINISTRATIVE INFORMATION

Support - Universiti Teknologi MARA.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202560033

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 June 2025 and was last updated on 7 June 2025.

INTRODUCTION

Review question / Objective Review Question: What drug-based therapeutic strategies have been evaluated for the treatment or prevention of atherosclerosis in post-menopausal animal models, and what are their effects on atherosclerosis-related outcomes?
Objectives:To systematically identify and review preclinical studies that investigate pharmacological interventions aimed at reducing atherosclerosis in post-menopausal animal models.
To compare the effectiveness of various drug interventions in reducing atherosclerosis as assessed by morphological, biochemical, or molecular outcomes.
To summarize the types of animal models used to simulate post-menopausal atherosclerosis and the experimental designs applied.
To identify research gaps and inform future translational studies targeting atherosclerosis in post-menopausal women.

Condition being studied Atherosclerosis is a chronic, progressive inflammatory disease characterized by the accumulation of lipids, inflammatory cells, and fibrous elements in the arterial walls, leading to plaque formation, vascular stiffening, and reduced blood flow. It is a major underlying cause of cardiovascular diseases such as coronary artery disease, stroke, and peripheral arterial disease.
In post-menopausal women, the risk of developing atherosclerosis significantly increases due to the decline in estrogen levels, which are known to exert protective effects on the cardiovascular system. Estrogen deficiency contributes to endothelial dysfunction, lipid profile alterations, increased oxidative stress, and inflammation, all of which accelerate atherogenesis.
To understand the pathophysiology and test therapeutic strategies, animal models mimicking post-menopausal atherosclerosis, typically involving ovariectomy combined with high-fat diets or genetic modifications, are commonly used in preclinical research.

METHODS

Search strategy A comprehensive literature search on PubMed, Scopus, and Web of Science that included articles published until March 2025 were carried out using the keywords:
1) atherosclerosis AND
2) therapeutic* OR “drug therapy” OR “early intervention*” OR therap* OR intervention* OR treatment* OR “investigational drug*” OR “investigational treatment*” OR “investigational therap*” AND
3) menopause OR “post menopaus*” OR gonadotropins OR menopausal OR "postmenopausal" OR period AND
4) animal*.

Participant or population This review will focus on animal models that simulate post-menopausal atherosclerosis.
Eligible models include female animals subjected to ovariectomy (surgical removal of ovaries) to mimic estrogen deficiency, with or without additional modifications such as high-fat diet feeding, genetic predispositions (e.g., ApoE-knockout), or other methods used to induce atherosclerosis. All animal models used in preclinical research (e.g., mice, rats, rabbits) will be considered, regardless of strain, age, or housing condition, as long as they are used to model both post-menopausal and atherosclerotic conditions.

Intervention This review will evaluate pharmacological interventions that aim to treat or prevent atherosclerosis in post-menopausal animal models. Interventions may include synthetic drugs, natural compounds, hormones (e.g., estrogen or its analogs), anti-inflammatory agents, lipid-lowering therapies (e.g., statins, fibrates), antioxidants, or any other experimental or clinically relevant drug treatments.
The review will include monotherapies and combination therapies, regardless of the dose, duration, or route of administration, as long as the intervention targets atherosclerosis in the context of post-menopausal animal models.

Comparator The comparators will include untreated control groups, placebo groups, or vehicle-treated groups in post-menopausal animal models of atherosclerosis. In some studies, comparisons between different pharmacological agents or different doses of the same intervention may also be included. All comparators must be within the context of a post-menopausal atherosclerosis model to allow meaningful evaluation of intervention effects.

Study designs to be included This review will include original preclinical studies involving in vivo animal experiments that investigate drug interventions for atherosclerosis in post-menopausal models.

Eligibility criteria
Inclusion Criteria:
1-Original research articles reporting in vivo animal studies involving post-menopausal models (e.g., ovariectomized animals) with induced atherosclerosis.
2-Studies that evaluate the effect of pharmacological interventions aimed at preventing or reducing atherosclerosis.
3-Articles published in English.
4-Studies reporting quantitative outcomes related to atherosclerosis, such as plaque area, lipid accumulation, inflammatory markers, or vascular histology.

Exclusion Criteria:
1-In vitro or ex vivo studies.
2-Studies not involving both menopause and atherosclerosis as central components.
3-Review articles, conference abstracts, case reports, editorials, or letters to the editor.
4-Non-English publications.
5-Studies lacking a control or comparator group.

Information sources Electronic databases: PubMed, Scopus and Web of Science (WOS).

Main outcome(s) The main outcomes of this review will focus on the effectiveness of drug interventions in reducing atherosclerosis in post-menopausal animal models. Outcomes will include quantitative or qualitative assessments of atherosclerotic burden, such as:

1-Plaque size or area (e.g., en face analysis, cross-sectional plaque area)
2-Lipid profile changes (e.g., serum cholesterol, LDL, HDL, triglycerides)
3-Histological evaluations (e.g., H&E staining of arterial tissue)
4-Immunohistochemistry (IHC) for atherosclerosis-related markers (e.g., VCAM-1, α-SMA)
5-Inflammatory markers or oxidative stress indicators if related to atherosclerosis outcomes

Effect measures will include mean differences, percent change, or qualitative improvement in atherosclerosis markers between intervention and control groups. The timing of outcome assessment will vary depending on each study’s experimental duration but must be reported post-intervention.

Quality assessment / Risk of bias analysis The quality assessment of included primary studies will be conducted using the McMaster Critical Review Form for Quantitative Studies, which is suitable for evaluating methodological rigor in animal experimental research. This tool assesses aspects such as study purpose, design, sample size, allocation method, outcome measures, intervention integrity, and data analysis.
To ensure inter-rater reliability, two independent reviewers will perform the quality assessment. Any discrepancies will be discussed and resolved through consensus. Cohen's Kappa coefficient will be calculated to evaluate the level of agreement between reviewers.

Strategy of data synthesis The data will be synthesized narratively and descriptively, summarizing the characteristics of each study, including the animal model used, type and dosage of drug intervention, route and duration of administration, control group, and method of atherosclerosis assessment.
A structured summary table will be developed to compare interventions and outcomes across studies.

Subgroup analysis No formal statistical subgroup analysis is planned. However, studies will be organized and presented according to the type of animal model used, eg: mice, rats, rabbits, monkeys, etc.

Sensitivity analysis No formal sensitivity analysis is planned, as this review will not involve a meta-analysis.

Country(ies) involved Malaysia.

Keywords therapeutic; drug; animal model; menopause; atherosclerosis.

Contributions of each author
Author 1 - Siti Bazilah Zulkefli.
Email: 2024863812@student.uitm.edu.my
Author 2 - Fathimah Mohamad.
Email: drfathimah@uitm.edu.my
Author 3 - Nurul Alimah Abdul Nasir.
Email: nurulalimah@uitm.edu.my
Author 4 - Ahmad Nazrun Shuid.
Email: anazrun@uitm.edu.my
Author 5 - Nasibah Azme.
Email: nasibah@uitm.edu.my