INPLASY

PHARMACOLOGICAL INTERVENTIONS FOR INTRAPLAQUE NEOVASCULARIZATION IN ATHEROSCLEROSIS

INPLASY202430005

doi: 10.37766/inplasy2024.3.0005

Received: 01 March 2024

Published: 01 March 2024

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ADMINISTRATIVE INFORMATION

Support - Faculty of Medicine, Universiti Kebangsaan Malaysia (Grant Number: FF-2023-077).

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202430005

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 March 2024 and was last updated on 01 March 2024.

INTRODUCTION

Review question / Objective This literature aims to comprehensively assess the pharmacological interventions for inhibiting intraplaque neovascularization in the preclinical setting.

Condition being studied Advanced atherosclerosis is linked to plaque instability, which can result in rupture and the onset of a heart attack. Evidence gathered from human atheroma plaques indicates that intraplaque neovascularization poses a risk to plaque stability and may lead to plaque haemorrhage. While neovascularization has been extensively explored in the context of cancer, research on pharmacological inhibition of this phenomenon in atherosclerosis remains limited. Hence, targeting the neovascularization within the atheroma plaque has the potential to mitigate the plaque's vulnerability.

METHODS

Search strategy Three bibliographic databases including PubMed, Web of Science, OVID and Scopus will be utilized for literature searching by using relevant key terms to address the research question. Original articles published in English between January 2013 – January 2024 will be identified and screened for eligibility. The outcome parameters for plaque stability will be determined to serve as guidelines for inclusion articles. Two independent reviewers will carry out literature selection and characterization. The evidence will be extracted using ad-hoc tables and qualitatively synthesized.

Participant or population Preclinical models of atherosclerosis, regardless of animal species and type of cells.

Intervention Any novel or conventional drugs or compounds that aim to inhibit intraplaque neovascularization will be included in this review, regardless of the mechanism, route of

administration, drug dosage and duration of intervention.

Comparator The comparator groups did not receive any intervention or treated with a conventional drug.

Study designs to be included Preclinical (in-vitro, in-vivo, ex-vivo) studies will be included. Clinical studies, observational studies, retrospective studies, editorials, reviews, book chapters, abstracts, and conference proceedings will be excluded.

Eligibility criteria Any preclinical studies that predominantly target intraplaque neovascularization or hemorrhage will be included.

Information sources A computerized database search will be conducted on PubMed, Web of Science, OVID and Scopus with the following set of search terms: ((treatment) OR (therapy) OR (therapeutic strategy) OR (drug)) AND ((atherosclerosis) OR (intraplaque neovascularization) OR (intraplaque angiogenesis) OR (intraplaque vasculature) OR (intraplaque neovessel) OR (intraplaque microvessel)) AND ((stable plaque) OR (stable coronary artery plaque) OR (plaque stabilization) OR (stabilize plaque) OR (unstable plaque)).

Main outcome(s) Primary outcomes include: i. Changes in intraplaque neovessel number, density, or maturity; ii. Erythrocyte expression to indicate intraplaque hemorrhage.

Additional outcome(s) Additional parameters such as: i. Changes in the plaque vulnerability index (determined through collagen deposition, smooth muscle cells or macrophage expression); ii. Changes in plaque size or ratio of plaque to lumen area.

Data management Two reviewers (N.S.N.H and A.U.) will independently screen and extract the information from the included studies based on a standardized form of data collection. The third reviewer (N.N.M.A) will resolve any disagreement through discussion. The relevant data and evidence will be collected and documented in Microsoft Excel. The following data will be recorded: author, publication time, literature title, study design, intervention characteristics, findings, and outcome measures.

Quality assessment / Risk of bias analysis The risk of bias (ROB) will be evaluated independently by two reviewers (N.S.N.H and A.U). Any disagreement will be discussed and clarified with the third reviewer (N.N.M.A). The Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) risk of bias tool will be utilized for animal studies. The instrument comprises 10 elements encompassing six dimensions of bias, namely, selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Responses of 'yes,' 'no,' and 'unsure' individually signify 'low,' 'high,' and 'unclear' RoB, and these outcomes will be shown on the Cochrane RoB tool. In the case of in vitro studies, a personalized RoB assessment tool, derived from the Joanna Briggs Institute checklist for non-randomized experimental studies will be applied. The customized RoB tool encompasses three domains: 1) Reporting quality: information on the pharmacological intervention and sample utilized; 2) Performance bias: the use of reliable tools and/or reagents for outcome measurement; and 3) Detection bias: the use of standard/appropriate controls and the conduct of multiple outcome measurements. Each domain will be categorized as having a high, moderate, low, or unclear RoB.

Strategy of data synthesis Both study characteristics and findings will be documented and qualitatively synthesized. The evidence will be elucidated narratively. A meta-analysis will be performed if the data allows. The risk of bias will be defined and discussed narratively.

Subgroup analysis Where possible, we intend to evaluate the effect of the pharmacological interventions with their associated signalling pathway on intraplaque neovascularization and hemorrhage.

Sensitivity analysis A sensitivity analysis will be carried out if a meta-analysis is performed.

Language restriction English.

Country(ies) involved Malaysia.

Keywords angiogenesis inhibitors; atherosclerosis; coronary artery disease; intraplaque hemorrhage; intraplaque neovascularization.

Contributions of each author

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