INPLASY PROTOCOL

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Corresponding author:
Mahshad Sabri

mahshadsabri97@gmail.com

Author Affiliation:
Iran university of medical sciences.

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None declared.

The Additive Prognostic Value of Coronary Artery Calcium Scoring and Single-Photon Emission Computed Tomography (SPECT) on Major Adverse Cardiac Events (MACE): A Systematic Review and Meta-analysis PROTOCOL

Sabri, M[1]; Hosseini, Y[2]; Sani, R[3].

Review question / Objective: **Is coronary artery calcium scoring (CAC) able to add prognostic value to single-photon emission computed tomographic (SPECT) or not?**
Condition being studied: **More and more often, major advanced cardiac events (MACE) are contemplated as leading causes of death. The growing proportion of aging population, the pervasive influence of sedentary lifestyle and alteration of dietary habits has made coronary artery diseases more frequent.**
Information sources: **We searched PUBMED, MEDLINE, EMBASE, SCOPUS and The Web of Science databases for published material earlier than December 2022.The reviews, editorials, animal studies, conference presentations, case reports, case series, book chapters, letters, and proceeding abstracts were excluded. Studies without any English translation were likewise omitted. In case of multiple publications of the same article or identical studies on same series of participants, the most recent study or the longest follow-up were included in our meta-analysis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 January 2023 and was last updated on 22 January 2023 (registration number INPLASY202310073).

INTRODUCTION

Review question / Objective: **Is coronary artery calcium scoring (CAC) able to add prognostic value to single-photon emission computed tomographic (SPECT) or not?**

Rationale: **Myocardial perfusion imaging (MPI) through single-photon emission computed tomography (SPECT) is a well-established, non-invasive and widespread procedure for prognostic evaluation of patients suspected to CAD. Such a nevertheless functional modality cannot be**

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employed for detecting non-flow-limiting defects. Coronary artery calcification (CAC), on the other hand, is an earlier marker of atherosclerosis and usually precedes the development of CAD many years. Quantifying the coronary artery calcium scoring (CACS) with non-enhanced CT has made this advancement possible since its results have been reported to be closely correlated with atherosclerotic plaque burden. According to current guidelines, patients are usually evaluated by MPI for diagnosis of significant ischemia and calcified coronary plaques and their subsequent prognosis are usually computed via CACS not as a part of routine evaluation guidelines, but more typically for research purposes. Each modality has its own limitations; calcium scoring helps the anatomical assessment of coronary arteries and their plaque burdens while myocardial perfusion imaging focuses predominantly on functional imaging of heart muscle. Assessing patients solely by one imaging might lead physicians to miss and management. We decided to determine whether coronary artery calcium scoring (CACS) manages to add prognostic value to single-photon emission computed tomographic (SPECT) or not. Patients with normal SPECT results come to our specific attention as we are going to find out if CACS can act as a predictor for MACE in them and widen the diagnostic scope of CAD.

Condition being studied: More and more often, major advanced cardiac events (MACE) are contemplated as leading causes of death. The growing proportion of aging population, the pervasive influence of sedentary lifestyle and alteration of dietary habits has made coronary artery diseases more frequent.

METHODS

Search strategy: Our search strategy encompassed wide variety of keywords about coronary syndromes and "coronary calcification score" equivalents such as: "calcium deposit", "calcium score", Agatston, CAC, "coronary CT calcium", "coronary computed tomographic calcium scan", CACS, "coronary calcification" and CACT, as well as interchangeable for SPECT including: "single photon emission computed tomography", SPET, GSPECT, "multi-gated acquisition scan", MUGA, "gamma camera", scintigraphy, "cardiac gated acquisition", "scintillation camera", "radionuclide ventriculography", "cardiac functional imaging". From the reference list of review articles, we also carried out manual search to identify missed yet-important articles.

Participant or population: Suspected asymptomatic patients or symptomatic ones with coronary artery disease.

Intervention: Coronary calcium score quantified by Agatston method (through EBCT, MSCT, CACT with or without attenuation correction) and computed via automatic or manual techniques.

Comparator: One-day or two-day MPI protocol using any of radionuclide agents of Thallium, Technetium, Teboroxime after stress testing with pharmacological stress or exercise stress.

Study designs to be included: Follow-up for MACE (Major Adverse Cardiovascular Events), prospectively or retrospectively, were done in all studies. These events were defined as death due to cardiovascular disease or one of the following: myocardial infarction, acute coronary syndrome, admission to hospital for unstable angina or coronary catheterization that resulted in angioplasty or coronary artery bypass surgery further than 90 days from SPECT date.

Eligibility criteria: Studies containing patients who had been suspected or symptomatic CAD and asymptomatic patients without any previous history of CAD but with cardiovascular risk factors were included. 2) The study populations must have been evaluated by CAC scoring (by CT, MSCT and EBCT) and MPI (by SPECT, SPET or gated SPECT) 3) Calcium score results must have been reported in Agatson units 4) Patient population had to be followed up during a period and major

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adverse cardiac event including late revascularizations, cardiac deaths and non-fatal MIs must have been reported meanwhile. We excluded the articles based on the following criteria: 1) CACS must not have been computed via visual technique (VECAS); 2) Studies which had not provided any definite abnormal SPECT rates among at least two different CAC categories.

Information sources: We searched PUBMED, MEDLINE, EMBASE, SCOPUS and The Web of Science databases for published material earlier than December 2022.The reviews, editorials, animal studies, conference presentations, case reports, case series, book chapters, letters, and proceeding abstracts were excluded. Studies without any English translation were likewise omitted. In case of multiple publications of the same article or identical studies on same series of participants, the most recent study or the longest follow-up were included in our meta-analysis.

Main outcome(s): The primary outcome was the occurrence of MACEs, including cardiac death, non-fatal MI, UA, and late revascularization. Cardiac death, non-fatal MI, and UA were defined according to the Third Universal Definition of MI, American College of Cardiology Foundation, and the American Heart Association. Late revascularization was defined as either percutaneous coronary intervention or coronary artery bypass graft, after 90 days from the SPECT or cardiac CT examination.

Data management: Data was handled using EndNote application software in merging the results from the resources and finding duplications. Afterwards, the Rayyan system (http://rayyan.ai/) was employed to screen the data according to the title and abstracts and irrelevant articles was excluded. If the abstract of an article was considered vague or ambiguous, the full text was reviewed to define usefulness. All remained full texts were assessed for eligibility by three separate reviewers independently and any divergence was resolved through consensus. Opted studies then were evaluated for data extraction by three independent reviewers in consensus to derive the information including the name of first author, year of publication, clinical characteristics of patients (e.g. age, gender, symptoms,...), CAC score brackets to define patient subgroups, negative or positive SPECT result and statistics about each CAC score subgroup, myocardial ischemia rate and MACE.

Quality assessment / Risk of bias analysis: Quality assessment of articles was completed using JBI critical appraisal tool for observational cohort studies. This checklist includes 10 questions with multiple choice answers (yes, no, not applicable and unclear).

Strategy of data synthesis: The meta-analysis was performed by STATA vs.16.0 . The heterogeneity assumption was checked by I2 statistics and if less than 50% fixed effect model was used, if not random effects models was used. Pooled odds ratios and 95% confidence intervals (CI) for dichotomous outcomes were calculated using a random effects model considering the probable heterogeneity and methodological differences and a P-value of less than 0.05 was considered significant. Continuous variables were reported asmean±SD.

Subgroup analysis: If the included studies have high heterogeneity a subgroup analysis will be performed. The subgroup analysis will be performed according to age, gender, specific medical condition, pre-evaluation risk and condition and duration of follow-up.

Sensitivity analysis: Not applicable in this study.

Language restriction: Non-English studies were not included.

Country(ies) involved: Iran.

Keywords: coronary calcium score(CAC), myocardial perfusion imaging, single photon emission computer tomography (SPECT), major adverse cardiac outcomes (MACE).

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Contributions of each author:

Author 1 - Mahshad Sabri - Author one contributed to preliminary reserach, electronic data base search, screening of articles, data extraction, data analysis and writting of the article.
Email: mahshadsabri97@gmail.com
Author 2 - Yasaman Hosseini - Author two contributed to preliminary reserach, electronic data base search, screening of articles, data extraction and data analysis.
Email: hosseiniyhh@gmail.com
Author 3 - Roya Sani - Author three contributed to preliminary reserach, electronic data base search, screening of articles, and data extraction.
Email: dr.royasani@yahoo.com

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