

# INPLASY PROTOCOL

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All other authors have no  
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## The effect of long-term nitrate therapy in patients with vasospastic angina: A systematic review and meta-analysis

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**Review question / Objective:** To assess the effect of chronic nitrate therapy in patients with vasospastic angina (VSA). **P:** the patients is diagnosed with vasospastic angina **I:** chronic nitrate therapy with or without channel blockers (CCBs) therapy **C:** calcium channel blockers (CCBs) therapy or no therapy **O:** all-cause mortality, cardiac death, myocardial infarction, revascularization, and recurrent angina for re-hospitalization.

**Condition being studied:** Vasospastic angina (VSA) is characterized chest pain at rest arising from myocardial ischemia due to abrupt and rigorous coronary artery spasm. The prognosis of patients with VSA is generally favorable when taken calcium channel blockers (CCBs) therapy. Currently, CCBs is the cornerstone for the treatment of VSA not only in controlling of severe angina symptoms but also play an irreplaceable role in improving long-term prognosis. Nitrate as a vasodilators has been widely used in vasospastic angina for reduce the severe angina. However, the efficacy of chronic nitrate therapy in patients with VSA remains uncertain. The Guidelines for Diagnosis and Treatment of Patients With Vasospastic Angina (Coronary Spastic Angina) (JCS 2013) have regarded long-acting nitrates for prevention of coronary spasm (Class IIa). Indeed, a recent study suggested that long-term nitrates therapy may present a worsen prognosis in VSA, while another study shows neutral outcome. There is currently a lack of consensus regarding chronic nitrate treatment. Therefore, We performed a systematic review and meta analysis to investigate the long-term efficacy of chronic nitrate therapy for VSA patients.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 April 2020 and was last updated on 22 April 2020 (registration number INPLASY202040133).

### INTRODUCTION

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## METHODS

**Search strategy:** We searched the PubMed, Embase, and Cochrane databases with the data to December 31, 2019. Search keywords: “nitrate,” “isosorbide mononitrate,” “nicorandil,” “nitroglycerin,” “isosorbide dinitrate,” “angina pectoris, variant,” “Prinzmetal angina,” “vasospastic angina,” “Coronary spastic angina,” “coronary spasm,” “coronary vasospasm,” and “variant Angina.” Pubmed: #1: (((((((("angina pectoris, variant"[MeSH Terms] OR Prinzmetal angina[Title/Abstract]) OR vasospastic angina[Title/Abstract]) OR Coronary spastic angina[Title/Abstract]) OR coronary spasm[Title/Abstract]) OR coronary

vasospasm[Title/Abstract]) OR Variant Angina[Title/Abstract]) #2: (((("nitrates"[MeSH Terms] OR isosorbide mononitrate[Title/Abstract]) OR nitroglycerin[Title/Abstract]) OR isosorbide dinitrate[Title/Abstract]) OR nicorandil[Title/Abstract])) #3: #1 AND #2. Embase: #1: ('variant angina pectoris'/exp OR 'prinzmetal angina':ti,ab,kw OR 'vasospastic angina':ti,ab,kw OR 'coronary spastic angina':ti,ab,kw OR 'coronary spasm':ti,ab,kw OR 'coronary vasospasm':ti,ab,kw OR 'variant angina':ti,ab,kw) #2: ('nitric acid derivative'/exp OR 'isosorbide mononitrate':ti,ab,kw OR 'glyceryl trinitrate':ti,ab,kw OR nicorandil:ti,ab,kw OR 'isosorbide dinitrate':ti,ab,kw) #3: #1 AND #2. Cochrane Library: #1: MeSH descriptor: [Angina Pectoris, Variant] all tree(s) exploded. #2: (Prinzmetal angina):ti,ab,kw OR ("vasospastic angina pectoris"):ti,ab,kw OR (Coronary spastic angina):ti,ab,kw OR (coronary spasm):ti,ab,kw OR (coronary vasospasm):ti,ab,kw. #3: MeSH descriptor: [Nitrates] all tree(s) exploded. #4: (isosorbide mononitrate):ti,ab,kw OR ("nitroglycerine"):ti,ab,kw OR ("isosorbide-dinitrate"):ti,ab,kw OR (nicorandil):ti,ab,kw. #5: #1 OR #2. #6: #3 OR #4. #7: #5 AND #6.

**Participant or population:** Patients with variant angina need to met the following criteria which included: (1) patients who had variant angina, which was defined by spontaneous coronary spasm at rest and/or effort, accompanied by a transient ST-segment elevation or depression of more than 0.1 mV; (2) documented coronary spasm on the coronary angiogram or ergonovine provocation coronary angiogram; (3) documented coronary spasm on the coronary angiogram or ergonovine provocation coronary angiogram.

**Intervention:** Patients with vasospastic angina who have taken long-term nitrate therapy whether they taken calcium channel blockers or not, nitrate including isosorbide mononitrate, nitroglycerin, isosorbide dinitrate, nicorandil.

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**Comparator:** Patients with vasospastic angina who have not taken long-term nitrate therapy whether they taken calcium channel blockers or not.

**Study designs to be included:** All studies identified as potentially relevant on the basis of title or abstract will be selected for full review with no pre-specified restrictions.

**Eligibility criteria:** Studies were included a reference to the following criteria: 1) diagnosed of VSA on the basis of the (JCS 2013) criteria; 2) used at least two comparison groups, one received chronic nitrate therapy and another without; 3) a follow-up duration must more than 12 months and documented clinical outcomes (e.g., all-cause mortality, cardiac mortality, myocardial infarction, re-hospitalization due to unstable or recurrent angina and revascularization). Exclusion criteria included duplicate data published, in which case the article reported the largest sample of VSA was included. To avoid potential data overlap, single-center studies were excluded which could be found in the multicenter international registries study.

**Information sources:** We searched the PubMed, Embase, and Cochrane databases with the data to December 31, 2019.

**Main outcome(s):** Main Outcomes including all-cause mortality, major adverse cardiac events (MACE), defined as cardiac death, myocardial infarction, hospitalization due to unstable angina pectoris, heart failure, revascularization.

**Additional outcome(s):** Cardiac death, myocardial infarction, revascularization, and recurrent angina for re-hospitalization.

**Quality assessment / Risk of bias analysis:** The Newcastle–Ottawa quality assessment scale (NOS) (18) was used to evaluate the quality of these studies. The factors included the selection of the study groups, comparability of groups, and ascertainment of the exposure and outcomes. Studies that

get more than 7 scores were regarded as high quality.

**Strategy of data synthesis:** Baseline information of categorical variables and continuous variables were reported as proportions or mean differences with 95% confidence intervals (CI). Q statistics and I<sup>2</sup> statistics were used to test the heterogeneity of included studies and a P values 50% was considered as significant heterogeneity. The effect size for the outcomes (Odds Ratio, OR) and 95% confidence intervals (CI) was calculated by using random-effects models. Sensitivity analysis was performed by sequentially deleting each qualifying study.

**Subgroup analysis:** None.

**Sensibility analysis:** Sensitivity analysis was performed by sequentially deleting each qualifying study.

**Country(ies) involved:** China.

**Keywords:** Vasospastic angina, nitrate therapy, meta -analysis.

**Contributions of each author:**

Author 1 - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy, collected the data, drafted the manuscript.

Author 2 - The author revised the paper.

Author 3 - The author provided statistical expertise.

Author 4 - The author read, provided feedback and approved the final manuscript.

Author 5 - The author conceived and designed research.