Calcium Channel Blockers with and without Nitrates for the Prognosis of Patients with Coronary Vasospastic Angina: A Meta-Analysis

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Abstract:

**Background:** A systematic review and meta-analysis was conducted to assess the most effective treatment (long-term administration of calcium channel blockers [CCBs] with and without any form of long-acting nitrates [nitrates]) for reducing the incidence of major adverse cardiac events (MACEs) in patients with vasospastic angina (VSA).

**Methods:** We comprehensively searched MEDLINE (PubMed) and Japan Medical Abstracts Society (ICHUSHI) databases in August 2020 for eligible studies examining the impact of any CCBs with and without nitrates on MACEs in patients with VSA angiographically diagnosed using intracoronary provocation tests. MACE was defined as a composite of cardiac death, nonfatal myocardial infarction, unstable angina, admission due to medically resistant chest pain, and operation of an implantable cardioverter-defibrillator.

**Results:** Among the 10,278 studies, five studies (four from Japan and one from South Korea) reporting hazard ratios by adjusting the baseline factors using the Cox proportional hazard model and propensity-score matched analysis were selected. In total, 3,640 patients treated with CCBs (any CCBs without nitrates group; n = 2,104) and CCBs plus nitrates (CCBs plus nitrates group, n = 1,536) for a mean follow-up duration of 32-70.5 months were enrolled. MACEs occurred in 323 (8.9%) patients. The CCBs plus nitrates group had a higher risk of MACEs than the any CCBs without nitrates group (risk ratio, 1.51; 95% confidence interval, 1.13-2.01; heterogeneity $I^2$ = 42.9%; p = 0.13) in the random-effects model.

**Conclusions:** Long-term use of CCBs with nitrates did not improve the prognosis in Japanese and South Korean patients with VSA compared to that with long-term use of any CCBs without nitrates.

**Key words:** Cardiovascular diseases, Pharmacology, Secondary prevention

Introduction

Coronary vasospastic angina (VSA) is caused by coronary artery spasm, which is associated with various myocardial ischemic diseases, such as unstable angina (UA), myocardial infarction (MI), malignant ventricular arrhythmia, heart failure, and sudden death. Calcium channel blockers (CCBs) are the first-line treatment for the long-term management of patients with VSA according to the serial guidelines of the Japanese Circulation Society (JCS) 2008 and 2013. However, there are limitations to the long-term treatment with CCBs only for controlling VSA because of unstable coronary vasoconstrictions during a long-term clinical follow-up period. Therefore, second-line medications with primary CCBs are important to maintain coronary spasm activity in patients with VSA.

According to the diagnostic criteria of the Coronary Vasomotion Disorders International Study (COVADIS) Group, VSA is a short-acting nitrate-responsive angina. Therefore, any forms of long-acting nitrates (nitrates) have been widely used concomitantly with CCBs in the treatment of VSA due to its rapid and potent vasodilatory effect. However, nitrates have a level IIa evidence for the treatment of VSA following CCBs. The recent guidelines by the European Society of...
Cardiology for the diagnosis and management of chronic coronary syndromes and MI with nonobstructive coronary arteries have stated that CCBs and nitrates constitute the primary treatment of choice for VSA. However, the impact of the long-term additional administration of nitrates with first-line CCBs on the adverse events in patients with VSA compared to that of any CCBs without nitrates has been controversial. In addition, regardless of the vasomotion type of VSA according to the acetylcholine provocation test, both long-term CCBs and nitrates have been shown to be independent predictors of recurrent angina.

Therefore, we conducted a systematic review and meta-analysis to assess the most effective treatment (long-term administration of CCBs with and without any form of nitrates) for reducing the incidence of adverse outcomes in patients with VSA. For this purpose, studies with unified diagnosis of intracoronary provocation tests and evidence-based treatment for VSA published posterior to the publication of the JCS 2008 guidelines were selected. In addition, studies with a mean observational interval of >1 year administration of CCBs with and without nitrates were selected to examine the long-term prognosis of patients with VSA. Furthermore, to exclude the bias of nitrate administration in non-randomized studies, studies individually estimating the hazard ratio (HR) of nitrates by adjusting the baseline factors, including multivessel spasm, a risk factor of VSA prognosis, using the Cox proportional hazard model or propensity score-matched analysis were statistically integrated.

Methods

Search strategy and selection process

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Ethics approval was not required for this meta-analysis because none of the patients at our institute were included. We searched for published studies indexed in MEDLINE (PubMed) and Japan Medical Abstracts Society (IChUSHI) databases in August 2020 using the terms “coronary spastic angina,” “coronary vasospasm,” “vasospastic angina,” and “coronary artery spasm.” As defined by the COVADIS group, the term “VSA” was used for coronary vasospastic angina.

Figure 1 shows a flow diagram of the selection process. A total of 7,544 potentially relevant articles in PubMed and 2,734 articles in IChUSHI were identified by Y. M. and T. I., respectively. The selection process included the following: identification, screening, eligibility, and inclusion of full-text articles published after the publication of the JCS guideline for VSA (after 2008); publication in English; examination of patients diagnosed by the intracoronary provocation tests to angiographically define VSA; and comparisons of the long-term prognosis between patients with VSA treated with nitrates concomitant with the first-line CCBs (CCBs plus nitrates group) and those treated with first-line CCBs alone or plus secondary-line CCBs without nitrates (any CCBs without nitrates group) for a mean observational interval of >1 year. Among the 10 studies, when several studies were published from the same institute or group, the most relevant study was selected. There were six studies estimating the effect size (HR of nitrates with 95% confidence intervals [CIs]) by adjusting the baseline factors using the Cox proportional hazard model. However, we could not obtain the raw number of cardiac events from a study. Thus, five studies (study numbers 1st, 2nd, 3rd, 4th, and 5th) involving 3,640 patients with VSA-1,536 in the CCBs plus nitrates group and 2,104 in the any CCBs without nitrates group were included.

Assessment of the included studies and meta-analysis

Data on the following VSA-related factors were collected from the five studies: duration of patient enrollment, number of institution, and inclusion and exclusion criteria (Table 1); number of patients, mean age, number of males and females, percentage of diabetes, number of current smokers and patients with multivessel spasm, and mean left ventricular ejection fraction (Table 2); and number and percentage of patients prescribed CCBs (CCB prescription), agent and percentage of any CCBs (types of CCBs), administration of first-line CCBs after diagnosis of VSA (dose of CCBs), number and percentage of patients prescribed nitrates (nitrate prescription), kinds and doses of nitrates, protocol about CCBs and nitrates after diagnosis of VSA (administration of CCBs and nitrates after diagnosis of VSA), and percentage and number of nicorandil, angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs), hydroxymethylglutaryl-coenzyme A reductase inhibitor (statin), and beta-blockers (Table 3).

In all the five retrospective non-randomized studies, all individual HRs and 95% CIs were derived from the Cox proportional hazard models for time-to-first event endpoints. Thus, the baseline factors in each study, including additional administration of CCBs and/or nitrates at doctors’ discretion (Table 3 and 4), were statistically adjusted.

The common primary endpoint was the occurrence of major adverse cardiac events (MACEs), including cardiac death, nonfatal MI, UA, rehospitalization due to medically resistant chest pain, and proper operation of implantable cardioverter-defibrillator (Table 4 and 5). The clinical events mentioned were trouble with VSA during the follow-up period. The frequency of MACEs in the entire CCBs plus nitrates group (11.5%) was not compared with that in the entire any CCBs without nitrates group (7.0%, Table 5) because we could not adjust all the baseline factors across all studies.

Pooled HR and 95% CI were used to summarize the estimates. Data were extracted from study numbers 2nd, 3rd, and 5th and were directly informed by the corresponding authors of study numbers 1st and 4th. The random effects model was used to calculate risk ratios (RRs) and 95% CIs, and hetero-
Among the 10,278 studies, five are selected. VSA, coronary vasospastic angina; CCB, calcium channel blocker; nitrates, any form of long-acting nitrates

Heterogeneity ($I^2$) analysis was performed using STATA version 16 “meta esize,” “meta sum,” and “meta forestplot, eform.” (Lightstone corp., Tokyo, Japan), using the commands of. Publication bias was assessed by the heterogeneity of effect
Table 1. Enrollment of the five studies

| Study no. | 1      | 2       | 3      | 4      | 5      |
|-----------|--------|---------|--------|--------|--------|
| Author    | Ogawa  | Kosugi  | Takahashi | Ishii | Park   |
| journal   | Circ J 2009 | Circ J 2011 | Eur Heart J 2015 | JACC 2015 | YMJ 2018 |
| Enrollment| 1997–2005 | January 1998 to December 2003 | September 2007 to December 2008 | January 1991 to December 2010 | November 2004 to May 2014 |
| Number of institution | 1 | 2 | 47 | 1 | 1 |
| Inclusion criteria | Positive cases of the acetylcholine provocation test with normal coronary angiogram | Positive cases of the acetylcholine provocation test with normal coronary angiogram | Positive cases of the acetylcholine provocation test according the guideline of the JCS 2013 | Positive cases of the acetylcholine provocation test according the guideline of the JCS 2013 | Positive cases of the acetylcholine provocation test without significant coronary artery disease |
| Exclusion criteria | CAG with organic stenosis, recent myocardial infarction within 30 days, acute coronary syndrome, heart failure, liver disease, creatinine level > 1.5 mg/dL, apparent acute inflammation, malignant disease | Hypotension due to drugs, liver function disturbance, clinical signs of acute infection, autoimmune disorders, serum creatinine level > 2.0 mg/dL, hepatic disease, suspected malignancy | N/A | N/A | Prior coronary artery bypass graft, prior percutaneous coronary intervention, advanced heart failure, serum creatinine ≥ 2 mg/dL |

Table 2. Patient characteristics in the five studies

| Study No | 1       | 2       | 3       | 4       | 5       |
|----------|---------|---------|---------|---------|---------|
| Author   | Ogawa   | Kosugi  | Takahashi | Ishii   | Park    |
| Journal  | Circ J 2009 | Circ J 2011 | Eur Heart J 2015 | JACC 2015 | Yonsei 2018 |
| Number of patients | 88 | 231 | 826 | 873 | 1622 |
| Age (years) | 59 ± 9.3 | 60 ± 10 | 66 (58-73) | 63.4-65.0 | 56.7-57.0 |
| Male/Female | 76/12 | 154/77 | 618/208 | 487/386 | 756/866 |
| Diabetes (%) | 22.2 | 25.1 | 17.2 | 20.5 | 16.5 |
| Hypertension (%) | 38.9 | 55.0 | 47.0 | 41.5 | 45.8 |
| Current smoker (%) | 61.1 | 14.3 | 59.2 | 52.7 | 20.9 |
| Multi-vessel spasm (%) | 50.0 | 86.1 | 36.1 | 42.4 | 29.5 |
| Left ventricular ejection fraction (%) | N/A | 66.0-68.3 | N/A | 70.4-71.3 | 59.3-59.4 |

Results

Enrollment

Table 1 shows the enrollment, number of institutes, and inclusion and exclusion criteria in the five studies. The enrollment period ranged from 1991 to 2014. Three studies (study numbers 1, 4, and 5) were single-center studies, one study (study number 2) was a two-center study, and the other study (study number 3) was a multicenter study involving 47 institutions. All patients were diagnosed with VSA according to the acetylcholine provocation test. In three studies, several exclusion criteria were described.

Patient characteristics

Table 2 shows the baseline patient characteristics of 3,640 patients with VSA. The mean age ranged from 56.7 to 66 years. The percentages of males, diabetes, hypertension, current smokers, and multi-vessel spasm were 57.4%, 18.3%, 45.5%, 37.8%, and 38.2%, respectively.

Medications

Table 3 shows the medications used. CCBs were administered to 98.2% of the entire cohort. In three studies, CCB details were described. Any form of nitrate was administered to 42.2% of the entire cohort. In two studies, nitrate details were described.

In three studies, when refractory angina developed, other CCBs or any form of nitrates or nicorandil was added to
Nitrate Administration for VSA

Table 3. Medications used in the five studies

| Study No | 1 | 2 | 3 | 4 | 5 |
|----------|---|---|---|---|---|
| Author   | Ogawa | Kosugi | Takahashi | Ishii | Park |
| Journal  | Circ J 2009 | Circ J 2011 | Eur Heart J 2015 | JACC 2015 | YMJ 2018 |
| CCBs prescription (n, %) | 86, 97.8 | 231, 100 | 817, 98.9 | 819, 93.8 | 1622, 100 |
| Types of CCBs (agent, %) | Diltiazem 61.4/Nifedipine 30.7/Amodioline 6.8/ | Diltiazem 50.7/Nifedipine 35.2/Amodioline 16.9/others 3.5, combination of CCBs 10.0 | N/A | N/A | Diltiazem, 100 |
| Dose of CCBs | Diltiazem 100-200 mg/day or nifedipine 20-40 mg/day | Amodioline 5–10 mg/day, diltiazem 100–200 mg/day, nifedipine 20–40 mg/day | N/A | N/A | Diltiazem 30-180 mg/day |
| Nitrates prescription (n, %) | 53, 60.2 | 86, 37.2 | 413, 50.0 | 173, 19.8 | 811, 50.0 |
| Dose and types of nitrates | Oral 38.9 ± 9.2 mg | Of 68 patients, 27 with continuous long-acting oral ISDN-R, 41 with continuous ISMN 40 mg without a dose-free interval, 18 patients with transdermal NTG with intermittent use. | N/A | N/A | N/A |
| Administration of CCBs and nitrate after diagnosis of VSA | When angina was refractory or adverse effects of VSA were developed, other CCBs, or any types of nitrates, or nicorandil were added. | The choice of CCBs and use of nitrates were determined by the patients’ individual physician; the use of nitrates was not assigned in a randomized manner. When angina was refractory or adverse effects developed, other CCBs or medications including nitrates or nicorandil were prescribed. | CCBs as the first-line therapy for VSA, and nitrates are currently used mainly as a concomitant therapy | CCBs as the first-line therapy for VSA, and nitrates are currently used mainly as a concomitant therapy | Dosctors discretion |
| Nicorandil (n, %) | 17, 18.9 | 71, 30.7 | 177, 21.4 | 57, 6.5 | N/A |
| ACE-I/ARB (n, %) | N/A | 59, 25.5 | 177, 21.4 | 177, 20.3 | 253, 15.5 |
| Statin (n, %) | N/A | 87, 37.7 | 272, 32.9 | 255, 29.2 | 610, 37.6 |
| Aspirin (n, %) | N/A | N/A | 374, 45.0 | 308, 35.3 | 227, 14.0 |
| B-blocker (n, %) | N/A | N/A | 24, 2.9 | 54, 6.2 | 136, 8.4 |

CCB, calcium channel blocker; VSA, vasospastic angina; ISDN-R, isosorbide dinitrate-retard; ISMN, isosorbide mononitrate; NTG, nitroglycerin; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; statin, hydroxymethylglutaryl-coenzyme A reductase inhibitor

first-line CCBs.

The prescribed percentages of nicorandil, ACE-I/ARB, statin, and β-blocker in three to four studies were 6.5%-30.7%, 15.5%-25.5%, 29.2%-37.6%, and 2.9%-8.4%, respectively.

Statistics, estimated endpoints, and incidences of MACE

Table 4 shows the statistics, estimated endpoints, and incidence of MACEs. Individual HRs were derived from the Cox proportional hazard models for time-to-first event endpoints by adjusting the baseline factors. The mean follow-up duration ranged from 32 to 70.5 months. The frequencies of all-cause death and cardiac death were 0.55% and 0.33%, respectively. The frequency of patients with nonfatal MI and UA in the entire cohort was 2.9%. The frequency of patients rehospitalized due to medically resistant chest pain and MACEs was 6.1% and 9.3%, respectively.

Raw data and HRs of MACEs

Table 5 shows the raw data and outcomes of the Cox proportional hazard model of MACEs. The HRs of nitrate administration ranged from 0.505 to 5.18, and the p-values ranged from 0.004 to 0.257.

Meta-analysis results

After integrating the five studies, the CCBs plus nitrates group had a higher risk of MACE than the any CCBs without nitrates group (RR, 1.51; 95% CI, 1.13-2.01; heterogeneity $I^2 = 42.9%$; $p = 0.13$) in the random effects model (Figure 2).
Table 4. Statistics, estimated endpoints, and incidence of MACEs in the five studies

| Study no. | 1    | 2    | 3    | 4    | 5    |
|-----------|------|------|------|------|------|
| Author    | Ogawa| Kosugi| Takahashi| Ishii| Park |
| journal   | Circ J 2009 | Circ J 2011 | Eur Heart J 2015 | JACC 2015 | YMJ 2018 |
| Baseline adjustment (statistics) | Cox proportional hazard model | Cox proportional hazard model | Propensity score matching and multi-variable Cox proportional hazard model | Cox proportional hazard model | Cox proportional hazard model after propensity score matching |
| Primary endpoint (cardiac events) | Rehospitalization by angina attack, chest symptom | Sudden cardiac death, readmission for ACS (AMI and UA) | Cardiac death, non-fatal MI, hospitalization due to UA, HF, appropriate ICD shocks | Cardiac death, hospitalization for acute myocardial infarction, and unstable angina pectoris | Mortality (cardiac and non-cardiac death), PCI, MI, cerebrovascular accident, repeat CAG |
| Definition and symptom of repeat chest symptom | Chest pain, chest oppression, zonesthesias, back pain, sore throat, thirst sensation, and cold sweats with chest pain | ST segment depression (≥1.0 mm) or elevation (≥1.0 mm) with or without chest pain during the 24-h Holter recording under the use of CCBs | N/A | N/A | N/A |
| Re-evaluation of ischemia during follow-up interval (%) | 17.0 | 9.1 | N/A | N/A | N/A |
| Mean observational interval (month) | 59.9 ± 39.0 | 70.5 (ranging from 4.8 to 140) | 32 (17-46) | 49 ± 19 | 60.8 (up to 5 years) |
| All-cause death (n, %) | 0 | 7.3 | 1.2 | 3.034 | 9.056 |
| Cardiac death (n, %) | 0 | 7.3 | 1.2 | 3.034 | 1.005 |
| AMI/UA (n, %) | N/A | 22.95 | 45.54 | 40.46 | N/A |
| MI (n, %) | 1, 1.3 | 2, 0.87 | 3, 0.36 | 6, 0.69 | 10, 0.62 |
| Rehospitalization for angina attack (n, %) | 2, 2.5 | N/A | N/A | 34, 3.9 | N/A |
| Any re-vascularization (n, %) | N/A | N/A | N/A | N/A | N/A |
| Chest symptoms (n, %) | 48, 54.5 | N/A | N/A | N/A | 134, 8.3 |
| Heart failure (n, %) | N/A | N/A | 0 | N/A | N/A |
| Appropriate ICD shock (n, %) | N/A | 1, 0.43 | 2, 0.24 | N/A | N/A |

MACE, major adverse cardiac event; AMI, acute myocardial infarction; UA, unstable angina; MI, myocardial infarction; ICD, implantable cardioverter-defibrillator; ACS, acute coronary syndrome; HF, heart failure; PCI, percutaneous coronary intervention

Interpretations of the long-term management of patients with VSA by CCBs and nitrates

Table 6 summarizes the interpretations of the long-term management of patients with VSA by CCBs and nitrates in each study. In three studies (study numbers 1, 2, and 4), nitrate use was the predictor of MACEs. In study number 3, a sub-analysis showed the significance of nitrates for MACEs.

The first-line use of CCBs for patients with VSA was consistent in all studies, as shown in Table 2. However, the limitation of VSA control by long-term CCBs alone and the necessity of secondary agents were stated in three studies.

Three studies discussed the ineffectiveness and/or deleterious impact of long-term nitrate administration on the basic mechanisms of MACEs in patients with VSA.

Discussion

The meta-analysis integrating the five studies showed that the long-term continuous administration of nitrates as a second-line medication concomitantly with first-line CCBs did not improve the long-term prognosis of Japanese and South Korean patients with VSA, which was indicated by the increase in the RR of MACE by 51% compared to that with any CCBs without nitrates (Figure 2).

The present meta-analysis was conducted according to the inconsistency of the long-term administration of first-line CCBs with second-line nitrates for patients with VSA, as mentioned by the COVADIS Group5 and previous studies from Japan and South Korea3,4,8-14. Since the serial JCS guidelines for VSA1,2 were cited in all studies, the diagnosis of VSA by intracoronary spasm provocation tests and evidence-based treatments for VSA were unified. All five studies individually calculated the HRs of nitrate administra-
Figure 2. Pooled estimates and risk ratios (RR) of the incidence of major adverse cardiac events (MACEs) in patients with vasospastic angina treated long term with calcium channel blocker (CCB) with nitrates (CCBs plus nitrates) versus CCBs without nitrates (any CCBs without nitrates).

Black circles represent RRs, and the attached horizontal lines represent 95% confidence intervals (CIs). The size of the circles reflects the statistical weight of the study using the random effects model. A diamond data marker represents the overall adjusted RR and 95% CI for the outcome. The horizontal axis represents the value of the RR.

Hazard ratio of nitrate administration

| Study No | Author | Journal | CCBs plus nitrates group | any CCBs without nitrates group |
|----------|--------|---------|--------------------------|--------------------------------|
| 1        | Ogawa  | Circ J 2009 | Total: 53 | Total: 35 |
|          |        |          | MACE: 33 | MACE: 15 |
| 2        | Kosugi | Circ J 2011 | Total: 86 | Total: 145 |
|          |        |          | MACE: 17 | MACE: 12 |
| 3        | Takahashi | Eur Heart J 2015 | Total: 413 | Total: 413 |
|          |        |          | MACE: 26 | MACE: 21 |
| 4        | Ishii  | JACC 2015 | Total: 173 | Total: 700 |
|          |        |          | MACE: 16 | MACE: 27 |
| 5        | Park   | YMJ 2018  | Total: 811 | Total: 811 |
|          |        |          | MACE: 84 | MACE: 72 |

95% CI of nitrate administration

| Study No | Author | Journal | CCBs plus nitrates group | any CCBs without nitrates group |
|----------|--------|---------|--------------------------|--------------------------------|
| 1        | Ogawa  | Circ J 2009 | Total: 53 | Total: 35 |
|          |        |          | MACE: 33 | MACE: 15 |
| 2        | Kosugi | Circ J 2011 | Total: 86 | Total: 145 |
|          |        |          | MACE: 17 | MACE: 12 |
| 3        | Takahashi | Eur Heart J 2015 | Total: 413 | Total: 413 |
|          |        |          | MACE: 26 | MACE: 21 |
| 4        | Ishii  | JACC 2015 | Total: 173 | Total: 700 |
|          |        |          | MACE: 16 | MACE: 27 |
| 5        | Park   | YMJ 2018  | Total: 811 | Total: 811 |
|          |        |          | MACE: 84 | MACE: 72 |

P-values

| Study No | Author | Journal | CCBs plus nitrates group | any CCBs without nitrates group |
|----------|--------|---------|--------------------------|--------------------------------|
| 1        | Ogawa  | Circ J 2009 | Total: 53 | Total: 35 |
|          |        |          | MACE: 33 | MACE: 15 |
| 2        | Kosugi | Circ J 2011 | Total: 86 | Total: 145 |
|          |        |          | MACE: 17 | MACE: 12 |
| 3        | Takahashi | Eur Heart J 2015 | Total: 413 | Total: 413 |
|          |        |          | MACE: 26 | MACE: 21 |
| 4        | Ishii  | JACC 2015 | Total: 173 | Total: 700 |
|          |        |          | MACE: 16 | MACE: 27 |
| 5        | Park   | YMJ 2018  | Total: 811 | Total: 811 |
|          |        |          | MACE: 84 | MACE: 72 |

HR, hazard ratio; CCB, calcium channel blockers; CI, confidence interval; MACE, major adverse cardiac event; MI, myocardial infarction; PCI, percutaneous coronary intervention.

The unimproved effect of chronic nitrate use in patients with VSA was driven by increased coronary spasm activity and medical therapy tolerance during the follow-up period, as three reports stated (Table 6). The known basic mechanisms of the adverse effects of chronic nitrate use are endothelial dysfunction, tachyphylaxis, neurohormonal activation, inflammation for MACEs by adjusting the baseline factors using Cox proportional hazard models (Table 4). Two studies applied propensity-score matched analysis to adjust the baseline factors. Thus, in these retrospective studies, different baseline factors and doctors’ discretion to prescribe CCBs and/or nitrates on the HRs of nitrates were statistically adjusted (Table 6). The grade of heterogeneity was <50%, which was not significant (Figure 2). Therefore, this meta-analysis is the first to examine the impact of the long-term continuous administration of nitrates as a second-line treatment concomitantly with the first-line CCBs compared to that of long-term continuous administration of any CCBs without nitrates in Japanese and South Korean patients with VSA. Approximately one-third of MACEs were cardiac death, nonfatal MI, and UA during medical therapy (Table 4). Therefore, we insisted on serious concerns regarding the widespread long-term nitrate administration with CCBs for patients with VSA in daily practice.
and nitrate tolerance. However, the underlying mechanisms of these effects need to be elucidated\(^\text{10}\). The associations between mitochondrial aldehyde dehydrogenase 2\(^\text{19}\) and nitrate tolerance have been examined.

In the clinical setting, the impact of chronic long-acting nitrates in patients with cardiovascular diseases has been debated. The deleterious effects of nitrates on various major cardiovascular diseases, such as chronic coronary artery disease\(^\text{20,21}\), acute MI\(^\text{22}\), old MI\(^\text{23}\), acute decompensated heart failure\(^\text{24}\), and heart failure with reduced\(^\text{25}\) and preserved\(^\text{26}\) ejection fraction, have been reported. Since VSA is closely related to these five major cardiovascular diseases as the underlying causes\(^\text{27}\), the unimproved effect of nitrates on VSA could be profoundly attributable to these results and statements. Therefore, further prospective studies are necessary to clarify the underlying mechanism of the unimproved effects of long-term nitrates administration on major cardiovascular diseases. Recently, empagliflozin, a sodium glucose transporter 2 inhibitor, significantly reduced the frequency of major cardiovascular events (EMPA-REG OUTCOME trial)\(^\text{28}\) by ameliorating the endothelial dysfunction in patients with diabetes\(^\text{29}\). Therefore, the protective impact of sodium glucose transporter 2 inhibitors on the long-term clinical outcomes in patients with VSA should be clarified.

Refractory VSA, defined as VSA resistant to at least two antianginal agents, CCBs and nitrates or several CCBs, has been highlighted\(^\text{30}\). Refractory VSA occurs in approximately 14% patients with VSA\(^\text{31}\). In the present study, approximately 40% MACEs were defined as refractory angina during the mean observational interval (Table 4). Re-evaluation of ischemia was essential during the long-term observational interval in patients with refractory VSA because stenosis is a predictor of MACEs\(^\text{32}\). Lee et al.\(^\text{33}\) reported that recurrent chest pain in patients with VSA was due to transient and functional causes such as an increased vascular tone or the post-stenotic reduction of perfusion pressure related to autonomic dysregulation rather than atherothrombotic progression since the frequency of revascularization was merely 0.9%. Therefore, additional nitrate administration increases patient susceptibility to refractory angina compared to any CCBs without nitrates (Table 6). However, management decisions were made according to the doctor’s discretion, and when we consider routine clinical practice, combination therapy is more frequently used and is associated with more severe symptoms. In the present statistical review, we were unable to check whether the use of CCB plus nitrates was

| Study no. | Predictors of MACE | Discussion about the long-term management of VSA by CCBs | Discussion about the long-term management of VSA by CCBs plus nitrates |
|-----------|-------------------|----------------------------------------------------------|---------------------------------------------------------------------|
| 1         | Nitrates          | CCBs are unable to completely suppress the chest symptoms in many cases, needing multiple CCBs or combining other drugs. | VSA was difficult to control even by additional nitrate administration concomitant with CCB, by inducing a tolerance that makes the patient more susceptible to VSA. |
| 2         | Long-term nitrate treatment, a refractory response to CCBs, pre-angina (UA on admission), patient age ≥ 60 years, CRP ≥ 0.25 mg/dL on admission, active smoking status, LVEF ≤ 50%, eGFR ≤ 60 at discharge | CCBs are highly effective in suppressing coronary spasms in patients with VSA. However, it remains unclear whether CCBs can reduce oxidative stress. The present study showed that there were no significant differences in cardiac events among the patients treated with amlopidine, nifedipine, diltiazem, or other CCBs. | Long-term nitrate treatment, even in the CCBs treatment, might be a contributory factor in the poor outcomes of patients with VSA, by associating with nitrate tolerance and endothelial dysfunction. Long-term nitrate treatment in addition to CCBs did not reduce the incidence of cardiac events in patients with VSA. |
| 3         | Conventional nitrate plus nicorandil, nitrates (skin patch and/or oral administration), dual or more nitrates, GTN, and nicorandil | To control angina symptom, 60% of patients with VSA require medications in addition to initial treatment. Nifedipine reduced the frequency of angina attack in patients with VSA who were refractory to ISDN with a good tolerability. Subsequently, several randomized trials with a large number of patients confirmed the superiority of CCBs (nifedipine and diltiazem) over ISDN. | Since the patients were sufficiently treated with CCBs, this result may indicate no additive beneficial effects of nitrates on the top of CCBs therapy in patients with VSA. Rather, the patients with nitrates tended to have a higher risk of MACE. The possible aggravating mechanisms include the rapid development of tolerance, generation of reactive oxygen species with resultant endothelial dysfunction, sympathetic nerve activation, and increase in sensitivity to vasoconstrictors. |
| 4         | Stenosis at the site of spasm, nitrates | Calcium channel blockers are essential for the treatment of patients with spasm. | It needs to be confirmed in large randomized prospective studies before one can establish a true cause–effect relationship between the use of nitrates and prognosis. |
| 5         | Male, statins, B-blockers | CCB affecting vasoconstriction by reaction of VSA. | Long-term nitrate therapy added to diltiazem in these patients produced no long-term additional beneficial effect over diltiazem alone. Vascular smooth muscle cell is more directly related to the pathophysiology of VSA compared with endothelial dysfunction of deficient bioactivity of NO. |

CCB, calcium channel blocker; UA, unstable angina; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; GTN, glyceryl trinitrate; VSA, vasospastic angina; ISDN, isosorbide dinitrate; NO, nitric oxide
related to more severe angina symptoms or signs. In addition, the impact of dose dependency of CCBs and nitrates on the prognosis of VSA could not be fully examined (Table 3). This is because the doses of CCBs and nitrates were dependent on blood pressure. Furthermore, the present study could not fully estimate the impacts of supportive therapies such as coronary revascularization, nicaloril, Rho-A/ROCK pathway, statins, ACE-Is and/or ARBs, classified as having level Ia and Ib evidence in the current guidelines. Therefore, precise mechanism, optimal treatment, and clinical outcomes of patients with refractory VSA needed to be further researched.

The optimal timing of the use of nitrates for circadian variation in chest pain attacks is classified as having level Ia evidence. In addition, the use of short-acting nitrate at chest pain attacks is classified as having level I evidence. The current guidelines state the importance of the intermittent or eccentric dose use by implementing a nitrate-free period to reduce tolerance. In the present meta-analysis, 18 patients in study number 2 received long-acting transdermal nitrates with a dose-free interval (intermittent transdermal treatment) (Table 3); however, the effects of the intermittent use of long-acting nitrates or timely use of short-acting nitrate on MACE could not be fully evaluated. In addition, the impacts of higher dose and combination of nitrates on MACEs in patients with VSA could not be estimated. However, study number 4 reported that a combination of nitrates has significant deleterious effects on MACEs. Further, as mentioned above, doctors altered the dose by maintaining the blood pressure. Therefore, further evidence is necessary to determine the long-term beneficial effects of nitrates with CCB in the prevention of MACEs.

The present study has the following limitations. First, the present meta-analysis was conducted by integrating only five studies. As described above, the CCBs plus nitrates group may have included patients who were administrated nitrates because of CCB-resistant VSA and these patients may have contributed to worse outcomes, despite the systematic review’s strict selection process without heterogeneity in Japanese and Korean patients with VSA (Figure 2). Second, studies focusing on the impact of long-term administration of CCBs on the prognosis of patients with VSA also showed the unimproved effect of the long-term additional administration of nitrates. The impacts of medication doses, forms, and combination of CCBs on MACEs could not be fully estimated. Third, the clinical symptoms immediately before the events, such as discontinuation of medications or forgetting to take medicines or the rebound phenomenon, could not be thoroughly evaluated.

In conclusion, the present meta-analysis showed that long-term use of long-acting nitrates concomitantly with the first-line CCBs did not improve the prognosis in Japanese and South Korean patients with angiographically defined VSA compared to that with long-term use of any CCB without nitrates.

Conflicts of Interest
None

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