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Original Article

# Impact of Total Risk Management on Coronary Plaque Regression in Diabetic Patients with Acute Coronary Syndrome

## - Sub Analysis of JAPAN-ACS Study -

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***Aim*: Diabetic patients with coronary artery disease have a high incidence of cardiovascular events, which was associated with increased coronary plaque volume. Low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) play pivotal roles in the progression of coronary plaque. Several trials have shown that intervention for a single risk factor reduced the development of coronary plaque progression. However, it remained uncertain whether total risk management for LDL-C, BP, and glycosylated Hb (HbA1c) has a beneficial effect on coronary plaque volume in diabetic patients.**

***Methods*: This study was a sub-study of the JAPAN-ACS that was a prospective, randomized, open-label trial that evaluated the impact of intensive lipid-lowering therapy on coronary plaque volume in patients with acute coronary syndrome (ACS). Among a total of 252 patients, 73 diabetic patients were analyzed. We examined the impact of total risk management (LDL-C <80 mg/dL, systolic BP <130 mmHg, and HbA1c <6.5%) on changes in coronary plaque volume. The patients were divided into four groups according to the number of risk factors that achieved the target value.**

***Results*: Baseline characteristics were similar among the groups. The degree of coronary plaque regression was greater in patients who achieved total risk management. The number of risk factors that achieved the target level was associated with the extent of the coronary plaque volume reduction in a dose-dependent manner.**

***Conclusion*: Total risk management that focused on LDL-C, BP, and HbA1c had a beneficial impact on the coronary plaque regression in diabetic patients with ACS.**

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**Key words:** Diabetes mellitus, Total risk management, Intravascular ultrasound, Coronary plaque, Statin



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## Introduction

Diabetes mellitus is associated with increased adverse cardiovascular events in patients with coronary artery disease (CAD)[1-4]. Large clinical trials failed to show the efficacy of intensive glucose control in reducing cardiovascular deaths in diabetic patients[5-7]. How-

ever, STENO II trial demonstrated that total risk management decreased cardiac events in diabetes[8].

Diabetic patients with CAD have a markedly high incidence of adverse cardiovascular events, which was associated with increased coronary plaque volume. Furthermore, low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) play pivotal roles in the progression of coronary plaque[9]. Trials of intervention for a single risk factor have shown the impact on reducing the development of coronary plaque progression[10-12]. For example, intensive LDL-C lowering and lowering blood pressure is associated with additional benefit in terms of clinical events and plaque progression[13]. However, it remained uncertain that a total management of LDL-C, blood glucose, and BP has a beneficial impact on plaque regression in diabetic patients with CAD. We already reported a randomized study "JAPAN-ACS," which demonstrated aggressive lipid-lowering therapy with statin that resulted in a significant regression of coronary atherosclerotic plaques in patients with acute coronary syndrome (ACS)[14]. In addition, patients with diabetes were less likely to have regression of plaque volume in the study[15]. The aim in this study was to evaluate the impact of intensive and total risk factor management on coronary plaque regression in diabetic patients with ACS as post hoc analysis from JAPAN-ACS.

## Methods

The study design of the JAPAN-ACS study has been published elsewhere[14, 16]. In brief, JAPAN-ACS was a prospective, randomized open-label study conducted with multi-centers to examine the effect of intensive lipid-lowering therapy with a statin on coronary plaque regression at the non-culprit site in patients with ACS. The patients were randomized to the pitavastatin or atorvastatin group. The intravascular ultrasound (IVUS) examination was performed at baseline and 10 months after the treatment. Intensive LDL-C lowering therapy with statin resulted in remarkable regression of coronary plaque volume by 17% in both groups. There was no significant difference in the percent change in plaque volume between the two statin groups.

The aim of this study was to examine an association between total risk management and change in coronary plaque volume in diabetic patients with ACS. This study was conducted in accordance with the Declaration of Helsinki, with the approval of the institutional review boards of all 33 participating institutions. Written informed consent for participation in the study was obtained from each of the patients enrolled in the study.

The study populations were divided into four groups according to the number of risk factors that achieved the target level at 10 months after ACS, including LDL-C, systolic BP, and HbA1c. The target level of each risk factor was as follows: LDL-C of less than 80 mg/dL, HbA1c of less than 6.5%, and a systolic blood pressure (SBP) of less than 130 mmHg. According to the number of risk factors that achieved the target level, the study population was classified into four groups (Group A: 0 risk factor achieved, Group B: 1 factor, Group C: 2 risk factors, and Group D: all three risk factors achieved). Intra-group comparisons were performed regarding clinical characteristics, medication, and coronary plaque volume at baseline and follow-up.

**Intravascular Ultrasound Procedure and Examination**

Details of the IVUS procedure and examination have been documented elsewhere[14]. In brief, following IVUS-guided percutaneous coronary intervention (PCI) for the culprit lesion in the patients with ACS, a final IVUS examination for analysis was performed in the culprit vessel. The IVUS catheter Atlantis SR Pro2 (Boston Scientific, Natik, USA) was used and a motorized pullback device withdrew the transducer at the speed of 0.5 mm/s. The consoles used were the ClearView or Galaxy 2 system (Boston Scientific, Natik, USA). The same imaging system and IVUS catheter were used for both the baseline and the follow-up examination.

Two independent experienced investigators performed the quantitative IVUS analysis at the central core laboratory. The target segment for analysis was identified at a non-PCI site of the culprit vessel (>5 mm proximal or distal to the PCI site) based on some reproducible indices. Manual tracing was performed in every 0.1 mm cross-sectional image using a software for IVUS measurement (echoPlaque2, INDEC systems Inc., Santa Clara, California). The software automatically interpolated the tracings of five cross sections between the two manually traced images. Therefore, the volume was calculated from each of the 0.017-mm spaced segments. IVUS measurements were performed according to the standards of the American College of Cardiology and the European Society of Cardiology[17]. The percent change in coronary PV was calculated as follows:

PV (follow up) – (baseline) / PV (baseline) × 100

Coronary PV was calculated as the sum of the differences between the EEM cross-sectional area and the lumen cross-sectional area across all evaluated frames as follows: $PV = \Sigma(EEM_{CSA} - LUMEN_{CSA})$, where $EEM_{CSA}$ = external elastic membrane cross-sectional area and $LUMEN_{CSA}$ = luminal cross-sectional

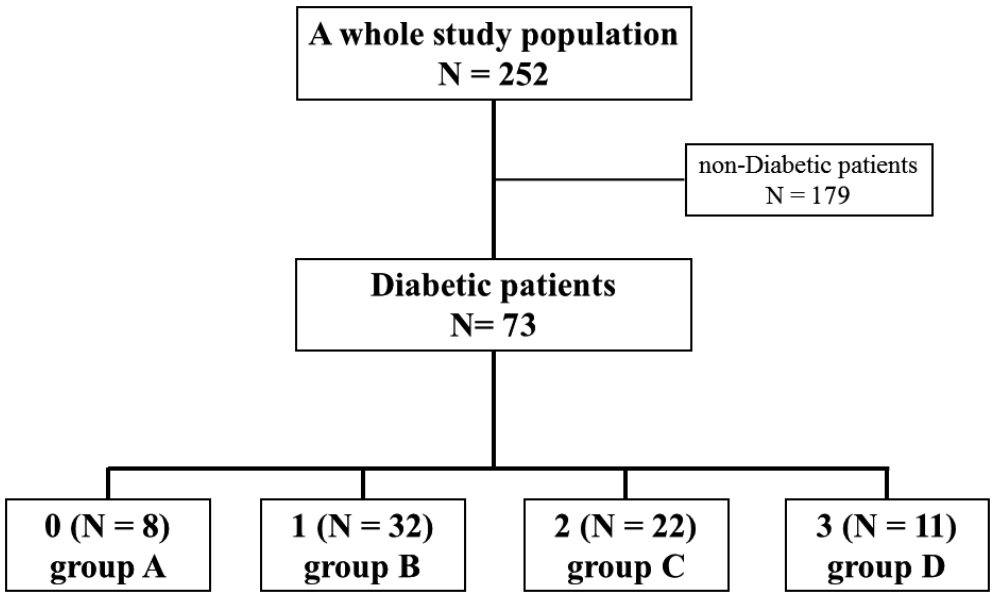


**Fig. 1.** A flow chart of the study population

Among a whole study population of 252, 73 diabetic patients were classified into four groups according to the number of risk factors that achieved the target level at follow-up.

area.

The percent plaque volume (% PV) was calculated using the following formula: % PV = Σ (EEM$_{CSA}$ − LUMEN$_{CSA}$) / Σ(EEM$_{CSA}$) × 100

**Statistical Analysis**

We used the full analysis set (FAS) of the JAPAN-ACS study for this sub-analysis. Patients with measurable IVUS data both at enrollment and at the follow-up were analyzed. Following descriptive statistics, comparisons of continuous variables between groups were performed using analysis of variance (ANOVA) or Kruskal–Wallis test according to the distributions. Comparisons of categorical variables between groups were performed using the chi-square test. Relationships between LDL-C, HbA1c, and SBP at follow-up and the percent change in coronary plaque volume were assessed by Pearson's correlation coefficient test. In addition, we examined the relationship between major cardiac events (myocardial infarction and revascularizations) across the groups. The significance level was set at 5% for the two-sided test (and 2.5% for one-sided test). All analyses were performed using JMP ver.9.0.1 and SAS software ver. 9.2 (SAS Institute Inc, Cary, NC) by an independent statistician. The authors had full access to and took full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

## Results

A total of 73 diabetic patients were classified into four groups according to the numbers of risk factors that achieved the target level at follow-up (**Fig. 1**). None of the risk factors achieved the target levels in 8 (11.0%) patients (group A), one factor achieved the target levels in 32 (43.8%) patients (group B), two factors achieved the target levels in 22 (30.1%) patients (group C), and all the factors achieved the target levels in 11 (15.1%) patients (group D).

**Baseline Patients Characteristics**

Baseline characteristics of the four groups are shown in **Table 1**. Body mass index and smoking habit were significantly different among the groups ($p = 0.02$ and $p = 0.03$, respectively). Although there was no significant difference across the four groups in other baseline demographics and characteristics, patients in group D were relatively younger, more frequent of the male gender, and less frequent of hypertension. With respect to concomitant medications, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), diuretic, sulfonylurea and α-GI were administered in a higher rate in group A. Administration of antiplatelet agents, including aspirin and thienopyridine, is similar across the groups. In terms of lipid profiles, blood glucose and BP at baseline and follow-up were similar at baseline but differed significantly at follow-up across the

**Table 1.** Baseline characteristics and concomitant medications

| Characteristic | The number of risk factors managed | | | | |
|---|---|---|---|---|---|
| | 0 ($n$ = 8) | 1 ($n$ = 32) | 2 ($n$ = 22) | 3 ($n$ = 11) | $p$ value |
| Age(years) | 62.6 ± 12.4 | 62.1 ± 10.5 | 66.1 ± 10.0 | 58.0 ± 9.8 | 0.2 |
| Male gender, $n$ (%) | 6 (75.0) | 26 (81.3) | 18 (81.8) | 10 (90.9) | 0.8 |
| BMI, kg/m$^2$ | 25.8 ± 4.7 | 24.3 ± 3.4 | 24.0 ± 2.8 | 27.8 ± 4.4 | 0.02 |
| Hypertension, $n$ (%) | 5 (62.5) | 24 (75.0) | 17 (77.3) | 6 (54.6) | 0.5 |
| Smoking, $n$ (%) | 5 (62.5) | 20 (62.5) | 8 (36.4) | 2 (18.2) | 0.03 |
| Type of ACS, $n$ (%) | | | | | 0.7 |
| STEMI | 6 (75.0) | 17 (53.1) | 12 (54.6) | 9 (81.8) | |
| NSTEMI | 1 (12.5) | 7 (21.9) | 5 (22.7) | 1 (9.1) | |
| UAP | 1 (12.5) | 8 (25.0) | 5 (22.7) | 1 (9.1) | |
| Culprit vessel, $n$ (%) | | | | | 0.08 |
| RCA | 3 (37.5) | 14 (43.8) | 7 (31.8) | 2 (18.2) | |
| LAD | 5 (62.5) | 9 (28.1) | 10 (45.5) | 8 (72.7) | |
| LCX | 0 | 9 (28.1) | 5 (22.7) | 1 (9.1) | |
| Analysis segment, $n$ (%) | | | | | 0.9 |
| Proximal to the treated site | 6 (75.0) | 25 (78.1) | 19 (83.4) | 9 (81.8) | |
| Disital to the treated site | 2 (25.0) | 7 (21.9) | 3 (13.6) | 2 (18.2) | |
| Type of stent, $n$ (%) | | | | | 0.8 |
| BMS | 7 (87.5) | 20 (62.5) | 14 (63.6) | 7 (63.6) | |
| DES | 1 (12.5) | 11 (34.4) | 7 (31.8) | 4 (36.4) | |
| POBA | 0 | 1 (3.1) | 0 | 1 (9.1) | |
| Concomitant Medications, $n$ (%) | | | | | |
| Aspirin | 8 (100) | 32 (100) | 22 (100) | 11 (100) | - |
| Ticlopidine | 8 (100) | 26 (81.3) | 18 (81.8) | 10 (90.9) | 0.3 |
| Clopidogrel | 0 | 3 (9.4) | 0 | 1 (9.1) | 0.2 |
| Beta-blocker | 5 (62.5) | 12 (37.5) | 14 (63.6) | 5 (45.5) | 0.2 |
| ACEI | 4 (50.0) | 8 (25.0) | 7 (31.8) | 2 (18.2) | 0.5 |
| ARB | 6 (75.0) | 18 (56.3) | 12 (54.6) | 4 (36.4) | 0.4 |
| Calcium channel blocker | 0 | 7 (21.9) | 7 (31.8) | 2 (27.3) | 0.2 |
| Diuretic | 2 (25.0) | 2 (6.3) | 4 (18.2) | 1 (9.1) | 0.4 |
| PPAR-γ agonist | 0 | 6 (18.8) | 2 (9.1) | 2 (18.2) | 0.3 |
| Sulfonylurea | 5 (62.5) | 8 (25.0) | 5 (22.7) | 2 (18.2) | 0.2 |
| α-Gl | 4 (50.0) | 11 (34.4) | 3 (13.6) | 3 (27.3) | 0.2 |

Abbreviations: BMI, body mass index; ACS, acute coronary syndrome; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; UAP, unstable angina pectoris; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex; BMS, bare metal stent; DES, drug-eluting stent; POBA, plain old balloon angioplasty; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; PPAR-γ, peroxisome proliferator-activated receptor-γ; α-Gl, α-glucosidase inhibitor

groups (**Table 2**).

**Results of the IVUS Study**

There were no significant differences across the groups in the coronary plaque volume, vessel volume, lumen volume, and % plaque volume at baseline (**Table 3**). A significant positive correlation was observed between the percent change in plaque volume and LDL-C or HbA1c at follow-up, while no statistical significance was found in the correlation of blood pressure and the plaque volume (**Fig. 2a**, **b**, **c**). The percent changes in plaque volume were −1.3 ± 12.1%, −10.5 ± 13.7%, −14.8 ± 13.7%, and −23.0 ± 13.6% in groups A, B, C, and D, respectively. The number of risk factor that achieved the target level was significantly associated with an extent of the coronary plaque volume reduction in a dose-dependent manner ($p$ for trend = 0.00024) (**Fig. 3**).

**Major Adverse Cardiac Events (MACE)**

There were no differences in the incidence of MACE, including all-cause mortality, non-fatal myocardial infarction, and repeat revascularization, across the groups (**Table 4**).

**Table 2.** Laboratory results

| | The number of risk factors managed | | | | |
|---|---|---|---|---|---|
| Laboratory results | 0 ($n=8$) | 1 ($n=32$) | 2 ($n=22$) | 3 ($n=11$) | $p$ value |
| Baseline | | | | | |
| LDL-C (mg/dL) | 133.8 ± 39.0 | 136.5 ± 29.7 | 128.2 ± 35.8 | 124.5 ± 26.9 | 0.7 |
| HDL-C (mg/dL) | 40.1 ± 7.3 | 43.4 ± 11.6 | 47.7 ± 12.1 | 44.7 ± 7.2 | 0.3 |
| Triglyceride (mg/dL) | 113.4 ± 37.9 | 140.1 ± 54.6 | 113.3 ± 64.2 | 123.7 ± 50.0 | 0.3 |
| hs-CRP (mg/L, IQR) | 26.4 (7.4-66.4) | 14.4 (4.8-38.1) | 17.4 (4.8-80.3) | 17.1 (6.0-31.0) | 0.8 |
| HbA1c (%) | 7.3 ± 0.9 | 7.5 ± 1.6 | 6.9 ± 1.3 | 7.3 ± 1.7 | 0.5 |
| SBP (mmHg) | 127.0 ± 26.7 | 147.0 ± 28.8 | 140.7 ± 26.7 | 137.3 ± 17.4 | 0.3 |
| DBP (mmHg) | 77.3 ± 15.9 | 82.2 ± 14.1 | 78.7 ± 17.8 | 78.0 ± 10.7 | 0.7 |
| Follow up | | | | | |
| LDL-C (mg/dL) | 106.3 ± 14.8 | 93.1 ± 28.9 | 67.0 ± 20.3 | 58.9 ± 11.0 | $<.001$ |
| HDL-C (mg/dL) | 45.8 ± 10.1 | 47.5 ± 16.1 | 50.2 ± 12.4 | 53.5 ± 7.6 | 0.5 |
| Triglyceride (mg/dL) | 137.9 ± 67.3 | 146.7 ± 62.0 | 100.7 ± 56.8 | 95.3 ± 39.6 | 0.013 |
| hs-CRP (mg/L, IQR) | 0.41 (0.29-1.00) | 1.00 (0.36-2.6) | 0.37 (0.20-0.91) | 0.54 (0.23-11.9) | 0.2 |
| HbA1c (%) | 7.8 ± 1.7 | 7.4 ± 1.4 | 6.3 ± 0.79 | 5.6 ± 0.41 | $<.001$ |
| SBP (mmHg) | 140.6 ± 12.0 | 136.1 ± 18.1 | 130.5 ± 17.8 | 115.1 ± 10.6 | 0.003 |
| DBP (mmHg) | 80.5 ± 10.6 | 76.6 ± 13.0 | 76.9 ± 14.8 | 67.2 ± 7.6 | 0.1 |

Abbreviations: LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; CRP, C-reactive protein; HbA1c, glycosylated hemoglobin; SBP, systolic blood pressure; DBP, dyastolic blood pressure.

**Table 3.** Baseline IVUS parameters

| | The number of risk factors managed | | | | |
|---|---|---|---|---|---|
| IVUS parameters | 0 ($n=8$) | 1 ($n=32$) | 2 ($n=22$) | 3 ($n=11$) | $p$ value |
| plaque volume ($mm^3$) | 57.9 ± 27.4 | 59.0 ± 25.2 | 52.5 ± 28.8 | 59.4 ± 29.1 | 0.8 |
| plaque volume ($mm^3$) | 109.9 ± 47.8 | 124.5 ± 56.6 | 103.9 ± 51.1 | 119.0 ± 57.2 | 0.6 |
| plaque volume ($mm^3$) | 51.9 ± 22.4 | 65.5 ± 35.8 | 51.4 ± 24.8 | 59.7 ± 34.5 | 0.4 |
| % plaque volume | 52.0 ± 6.4 | 48.6 ± 10.5 | 49.8 ± 7.5 | 50.4 ± 9.2 | 0.8 |

Abbreviation: IVUS, intravascular ultrasound

## Discussion

The present study of the sub-analysis of the JAPAN-ACS trial demonstrated that intensive and total risk management for LDL-C, HbA1c, and SBP had a beneficial effect on reducing coronary plaque volume in diabetic patients with ACS.

Diabetes is associated with worse clinical outcomes in CAD patients. One major reason is that CAD of diabetic patients tends to be a more complex disease characterized by small, diffuse, calcified, and multivessel involvement than that of non-diabetes[18, 19]. Despite the recent advances in the techniques and devices used during PCI, the morbidity and mortality of CAD in diabetic patients continues to be high, even in the current DES era[20]. In addition, diabetic patients are more likely to have comorbid diseases such as hypertension and dyslipidemia. Although the evidence of secondary prevention for CAD through treatment for the comorbid diseases has been established, THE cardiovascular event rate remains high in diabetic patients. That is partly explained by the fact that the risk factor control to achieve the target level of each factor is insufficient. Farkouh *et al*. examined whether risk factor control was achieved appropriately in the following three large-scale clinical trials: the clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE)[21], the bypass angioplasty revascularization investigation in type 2 diabetes (BARI-2D)[22], and the future revascularization evaluation in patients with diabetes mellitus (FREEDOM)[23]. The results showed unexpectedly low achievement rates[24]. One-year achievement rates of risk factors [LDL-C < 100 mg/dL, (70 mg/dL in

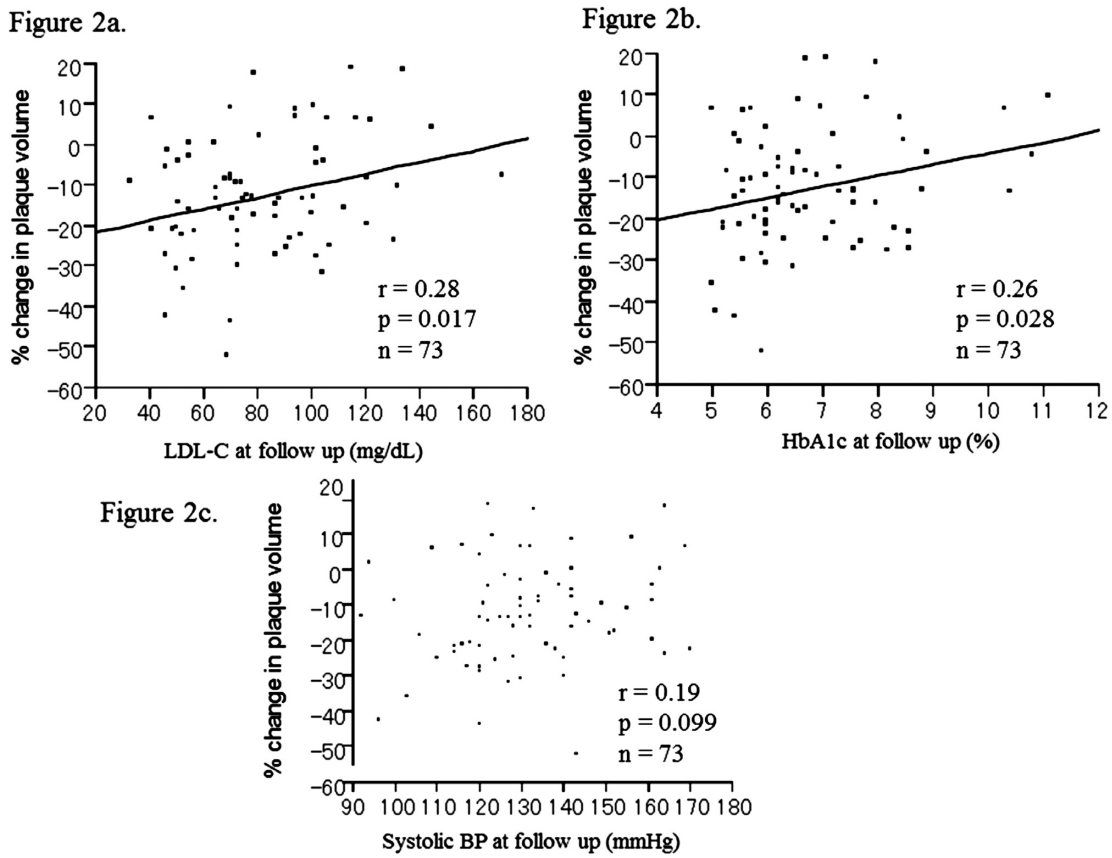


**Fig. 2.** Correlation between percent change in plaque volume and variables, including LDL-C, HbA1c, and systolic BP

A significant positive correlation was observed between the percent change in plaque volume and LDL-C or HbA1c at follow-up, while no significant correlation was found between the plaque volume and systolic BP.

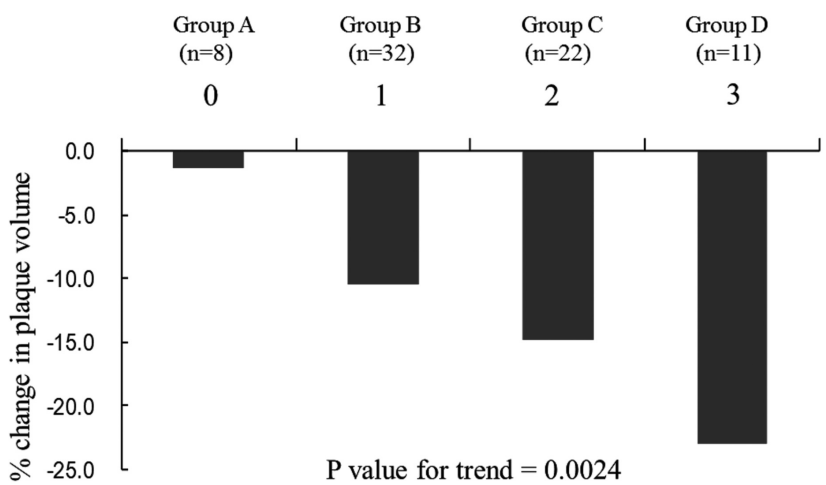


**Fig. 3.** The relationship between plaque volume reduction and the number of risk factors that achieved the target level

The number of risk factors that achieved the target level was significantly associated with an extent of the coronary plaque volume reduction in a dose-dependent manner

**Table 4.** Major adverse cardiac events

| | The number of risk factors managed | | | | |
|---|---|---|---|---|---|
| Adverse cardiac events | 0 ($n=8$) | 1 ($n=32$) | 2 ($n=22$) | 3 ($n=11$) | $p$ value |
| MACE, all | 3 (37.5) | 8 (25.0) | 9 (40.9) | 2 (18.2) | 0.5 |
| MI | 0 | 0 | 0 | 0 | - |
| TLR | 1 (12.5) | 3 (9.4) | 7 (31.8) | 1 (9.1) | 0.2 |
| TVR (non-TLR) | 2 (25.0) | 1 (3.1) | 2 (9.1) | 1 (9.1) | 0.3 |
| non-TVR | 0 | 5 (15.6) | 1 (4.6) | 0 | 0.1 |

Abbreviations: MACE, major adverse cardiovascular event; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization

the FREEDOM trial), HbA1c<7.0%, systolic blood pressure<130 mmHg, and smoking cessation] were 18%, 23%, and 8% in the COURAGE, BARI-2D, and FREEDOM trials, respectively. Although the achievement rate was not originally included in the clinical trial endpoints, these results prompted us to review our clinical practices regarding not only adherence to evidence-based medical therapy but also whether risk management is being properly achieved.

The importance of the total risk management has been demonstrated in the STENO II trial[8]. The trial has shown that intensive intervention to hypertension, hyperglycemia, dyslipidemia, and microalbuminuria with pharmacologic therapy including aspirin and ACEI and implementation of behavior modification could reduce blood pressure, HbA1c, lipid profiles, as well as urinary albumin excretion rate in diabetic patients with albuminuria. Furthermore, the intensive intervention to multiple risk factors also reduced the future risk of cardiovascular events during the mean follow-up period of 7.8 years compared with conventional therapy. Although our study differs from the STENO II trial in terms of the study design, therapeutic intervention, and target goal for each risk factor, our result has its novelty in that we demonstrated the relationship in a dose-dependent manner between the number of risk factors (LDL-C, HbA1c, and BP) that achieved the target level and reduction in coronary artery plaque volume, which is an established surrogate marker of future cardiovascular events[25, 26]. Our previous study showed that plaque regression assessed by volumetric IVUS was associated with a low incidence of cardiovascular events among patients with ACS[25]. Nichols *et al.* also proved the relationship between the burden of coronary atherosclerosis and adverse cardiovascular events in eight clinical trials that used serial IVUS[26]. Regarding the effect of intensive glucose lowering on cardiovascular events, previous large clinical trials failed to show the efficacy of intensive glucose lowering in reducing cardiovascular deaths in diabetic patients[5-7]. However, a meta-analysis including four large clinical trials reported that intensive glucose lowering compared with less-intensive glucose lowering was associated with 15% relative risk reduction for myocardial infarction during an average follow-up of 4.4 years[27]. Although the mechanisms of the beneficial effect of intensive glucose lowering on reduction in myocardial infarction were not revealed, intensive glucose lowering might have affected coronary plaque to some extent. Based on these data along with a fact that no evidence of an effect of blood pressure lowering therapy alone on coronary plaque regression has been established as shown in the present study as well, it would be conceivable that LDL-C lowering and glucose lowering rather than BP control are more important in terms of coronary plaque regression.

In our study, no difference was observed in MACE among the four groups, which might be attributable to the short-term follow-up period. Previous reports showed that the effect of BP lowering on cardiovascular events occurs within months[28, 29] while that of lipid lowering is observed after 1 to 2 years[8, 30, 31]. In addition, the effect of glucose lowering on diabetes-related clinical outcomes occur even later[32]. Besides, the benefit of total risk management on reduction in cardiovascular events was observed during a relatively long-term period of around 8 years in the STENO II trial. Taken together, an extended follow-up period is desirable to examine the effect of total risk management on cardiovascular events in the present study.

## Limitation

The current study has some limitations that are inherent to the study design. First, because our results were derived from the subgroup analysis, the number of the patients in each group was relatively small and not equally distributed to the four groups. Second, the association between total risk management and coro-

nary plaque volume reduction was not examined by regression analysis. Thus, a causal relationship could not demonstrate in this study. Third, the effect of total risk management on coronary plaque volume was examined as a sub-analysis and was not a pre-specified endpoint of the original study. Therefore, undetermined factors might affect the results of this study. In addition, as we did not take consistent measures for the each risk factor in our study, it is beyond the scope of our study that to what extent pharmacological or non-pharmacological therapy had effects on improvement of the risk factors. Future research is desirable to consider consistent measures, including dietary intervention, exercise, and smoking cessation, to manage risk factor control.

## Conclusion

Total risk management for blood pressure, LDL-C, and HbA1c had a beneficial effect on reduction in coronary plaque volume in diabetic patients with ACS.

## Acknowledgement

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## Trial Registrations

ClinicalTrials.gov Identifier: NCT01223586
http://clinicaltrials.gov/ct2/show/NCT01223586
UMIN Unique trial Number: UMIN000003166
https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000003375&language=E

## Conflicts of Interest

Dr. Naito has no conflict of interest. Dr. Daida has received honoraria for the lectures and research grants from Kowa pharmaceutical, Pfizer and Astellas Pharma. Dr. Morimoto has received honoraria for the lectures from Kowa pharmaceutical and Pfizer, and served as consultant of data safety monitoring board for Pfizer. Dr. Miyauchi has received honoraria for the lectures from Kowa pharmaceutical, Pfizer and Astellas Pharma. Dr. Hiro has received honoraria for the lectures from Kowa pharmaceutical, Pfizer and Astellas Pharma. Dr. Kimura has received honoraria for the lectures from Kowa pharmaceutical, Pfizer and Astellas Pharma, and research grant from Kowa pharmaceutical. Dr. Nakagawa has received honoraria for the lectures from Kowa pharmaceutica, Pfizer and Astellas Pharma. Dr. Yamagishi has received honoraria for the lectures from Kowa pharmaceutical, Pfizer and Astellas Pharma and has received research grant from Kowa pharmaceutical and Astellas Pharma. Dr. Ozaki has received honoraria for the lectures from Pfizer and Kowa pharmaceutical, and research grant from Kowa pharmaceutical. Dr. Matsuzaki has received honoraria for the lectures from Kowa pharmaceutical, Pfizer and Astellas Pharma, and research grant from Pfizer and Astellas Pharma.

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