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ing cardiovascular deaths in diabetic patients[5-7]. However, 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

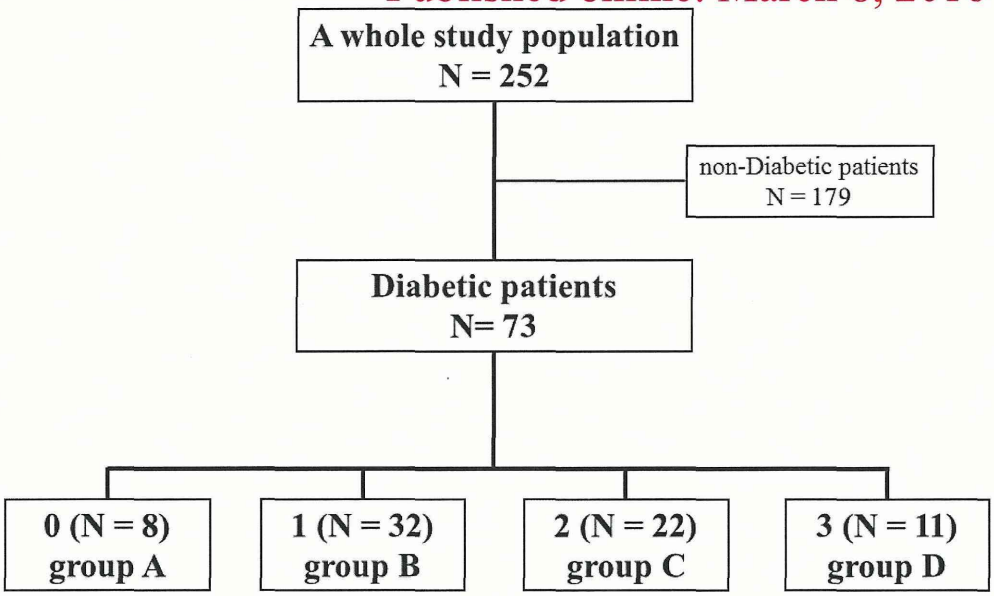

Fig. 1. A flow chart of the study population

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.

frames as follows: $PV = \Sigma(EEM_{CSA} - LUMEN_{CSA})$, where EEM_{CSA} = external elastic membrane cross-sectional area and $LUMEN_{CSA}$ = luminal cross-sectional area.

The percent plaque volume (% PV) was calculated using the following formula: $\%\ PV = \Sigma(EEM_{CSA} - LUMEN_{CSA}) / \Sigma(EEM_{CSA}) \times 100$

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,

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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

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 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**).

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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

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**).

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

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Figure 2a.

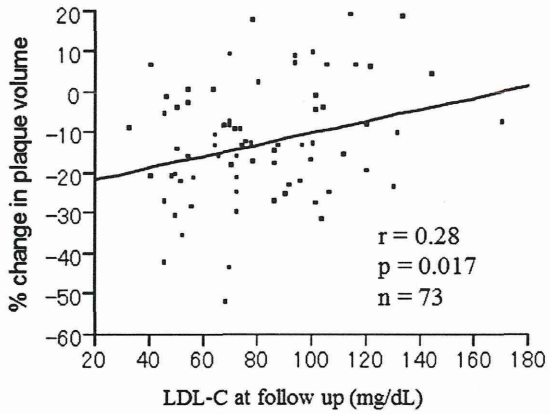

Figure 2b.

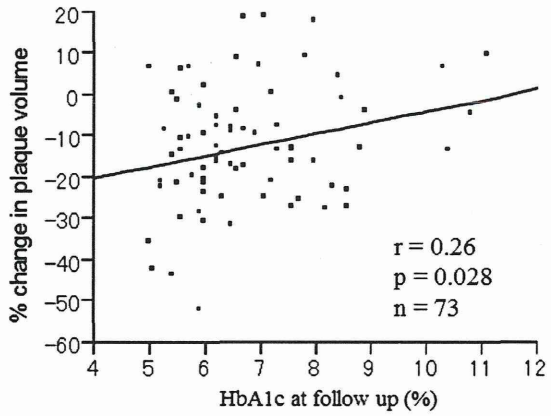

Figure 2c.

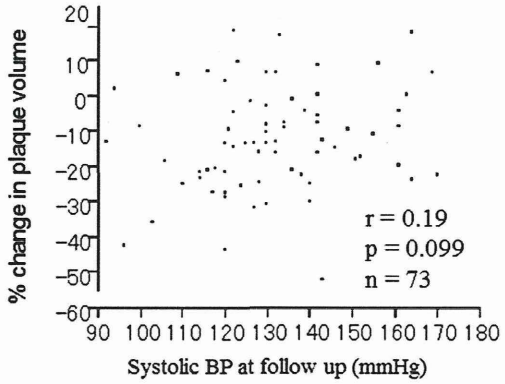

Fig. 2. Correlation between percent change in plaque volume and variables, including LDL-C, HbA1c, and systolic BP

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.

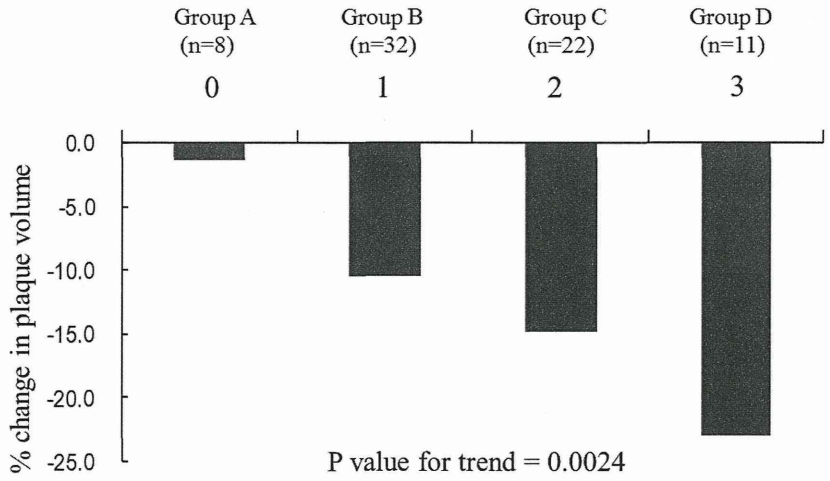

Fig. 3. The relationship between plaque volume reduction and the number of risk factors that achieved the target level

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

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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

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 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 coronary 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.

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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.

References

1) Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham study. JAMA, 1979; 241: 2035-2038
2) Bartnik M, Malmberg K, NorhammarA, Tenerz A, Ohrvik J, Rydén L: Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. Eur Heart J, 2004; 25: 1990-1997
3) Coutinho M, Gerstein HC, Wang Y, Yusuf S: The relationship between glucose and incident cardiovascular events: a meta-regression analysis of published data from 20 studies of 95783 individuals followed for 12.4 years. Diabetes Care, 1999; 22: 233-240
4) Miettinen H, Lehto S, Salomaa V, Mähönen M, Niemelä M, Haffner SM, Pyörälä K, Tuomilehto J: Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. Diabetes Care, 1998; 21: 69-75
5) ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M,

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Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med, 2008; 358: 2560-2572
6) Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators: Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med, 2009; 360: 129-139
7) ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F: Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med, 2010; 362: 1575-1585
8) Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med, 2003; 348: 383-393
9) Boyle PJ: Diabetes mellitus and macrovascular disease: mechanisms and mediators. Am J Med, 2007; 120: S12-S17
10) Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN; REVERSAL Investigators: Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA, 2004; 291: 1071-1080
11) Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E, Topol EJ; CAMELOT Investigators: Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA, 2004; 292: 2217-2225
12) Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, Jure H, De Larochellière R, Staniloae CS, Mavromatis K, Saw J, Hu B, Lincoff AM, Tuzcu EM; PERISCOPE Investigators: Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA, 2008; 299: 1561-1573
13) Chhatriwalla AK1, Nicholls SJ, Wang TH, Wolski K, Sipahi I, Crowe T, Schoenhagen P, Kapadia S, Tuzcu EM, Nissen SE: Low levels of low-density lipoprotein cholesterol and blood pressure and progression of coronary atherosclerosis. J Am Coll Cardiol, 2009; 53: 1110-1115
14) Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S, Yamaguchi T, Daida H, Matsuzaki M; JAPAN-ACS Investigators: Effect of Intensive Statin Therapy on Regression of Coronary Atherosclerosis in Patients with Acute Coronary Syndrome: A Multicenter Randomized Trial Evaluated by Volumetric Intravascular Ultrasound Using Pitavastatin Versus Atorvastatin (JAPAN-ACS Study). J Am Coll Cardiol, 2009; 54: 293-302
15) Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S, Yamaguchi T, Daida H, Matsuzaki M; JAPAN-ACS Investigators: Diabetes Mellitus is a major negative determinant of coronary plaque regression during statin therapy in patients with acute coronary syndrome. Circ J, 2010; 74: 1165-1174
16) Miyauchi K, Kimura T, Morimoto T, Nakagawa Y, Yamagishi M, Ozaki Y, Hiro T, Daida H, Matsuzaki M: Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS) -Rationale and Design-. Circ J, 2006; 70: 1624-1628
17) Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG: American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS). J Am Coll Cardiol, 2001; 37: 1478-1492
18) Norhammar A, Malmberg K, Diderholm E, Lagerqvist B, Lindahl B, Rydén L, Wallentin L: Diabetes mellitus: the major risk factor in unstable coronary artery disease even after consideration of the extent of coronary artery disease and benefits of revascularization. J Am Coll Cardiol, 2004; 43: 585-591
19) Creager MA, Lüscher TF, Cosentino F, Beckman JA: Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part I. Circulation, 2003; 108: 1527-1532
20) Bangalore S, Kumar S, Fusaro M, Amoroso N, Kirtane AJ, Byrne RA, Williams DO, Slater J, Cutlip DE, Feit F: Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient years of follow-up from randomized trials. BMJ, 2012; 345: e5170
21) Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS; COURAGE Trial Research Group: Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med, 2007; 356: 1503-1516
22) BARI 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE: A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med, 2009; 360: 2503-2515
23) Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S 3rd, Bertrand M, Fuster V; FREEDOM Trial Investigators: Strategies for multivessel revascularization in patients with diabetes. N Engl J Med, 2012; 367: 2375-2384
24) Farkouh ME, Boden WE, Bittner V, Muratov V, Hartigan P, Ogdie M, Bertolet M, Mathewkutty S, Teo K, Maron

DJ, Sethi SS, Domanski M, Frye RL, Fuster V: Risk factor control for coronary artery disease secondary prevention in large randomized trials. J Am Coll Cardiol, 2013; 61: 1607-1615
25) Dohi T, Miyauchi K, Okazaki S, Yokoyama T, Yanagisawa N, Tamura H, Kojima T, Yokoyama K, Kurata T, Daida H: Plaque regression determined by intravascular ultrasound predicts long-term outcomes of patients with acute coronary syndrome. J Atheroscler Thromb, 2011; 18: 231-239
26) Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, Uno K, Tuzcu EM, Nissen SE: Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol, 2010; 55: 2399-2407
27) Control Group, Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, Evans GW, Gerstein HC, Holman RR, Moritz TE, Neal BC, Ninomiya T, Patel AA, Paul SK, Travert F, Woodward M: Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia, 2009; 52: 2288-2298
28) Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH: Blood pressure, stroke, and coronary heart disease. 2. Short-term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. Lancet, 1990; 335: 827-838
29) Weber MA, Julius S, Kjeldsen SE, Brunner HR, Ekman S, Hansson L, Hua T, Laragh JH, McInnes GT, Mitchell L, Plat F, Schork MA, Smith B, Zanchetti A: Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE trial. Lancet, 2004; 363: 2049-2051
30) LIPID Study Group (Long-term Intervention with Pravastatin in Ischaemic Disease): Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. Lancet, 2002; 359: 1379-1387
31) Ford I, Murray H, Packard CJ, Shepherd J, MacFarlane PW, Cobbe SM: Long-term follow-up of the West of Scotland Coronary Prevention Study. N Engl J Med, 2007; 357: 1477-1486
32) UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet, 1998; 352: 837-853

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EDITORIAL

Investigating the Quality of Care in Cardiovascular Medicine

Takeshi Morimoto, MD, PhD

Quality of care should be a core value within modern healthcare systems. Cardiovascular medicine is the one of the most advanced medical subspecialties in providing evidence-based, state-of-the-art practices in developed countries. In spite of this, in the USA, medical interventions, not diseases themselves, resulted in approximately 44,000–98,000 fatalities per year and roughly 1 in 100 patients admitted to hospitals died because of a medical intervention.[1] The risk of undergoing medical care is considered the worst compared to many industries and other human activities (**Figure 1**).[2] We are aware that medicine has saved many more lives in history; therefore, we have conducted much research in both basic and clinical sciences to maximize saved lives and minimize injuries from medical interventions. Much clinical research has attempted to explore the association between disease management and patient outcomes, whereas basic science research has investigated the principles of such association, even before the association has been identified.

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Clinical researchers investigate the association between disease management, such as drugs, devices, diagnostic tools, severity classification, and symptom gradients, and patient outcomes, including some surrogate measures. Well-conducted research has provided data relevant to clinical practice, and many more patients who were not investigated under the researches also receive the benefit of such proven disease management. However, who would not enjoy the state-of-the-art practice? Of course, there are other factors that become obstacles to the dissemination of state-of-the-art practice, such as lack of funds or a lower educational level of patients and the general public. Japan is a unique country among the developed countries in that, within its healthcare system, all patients can receive ideal standard practice under universal healthcare insurance with limited payment. If there is any variation in disease management between patients, however, the reasons

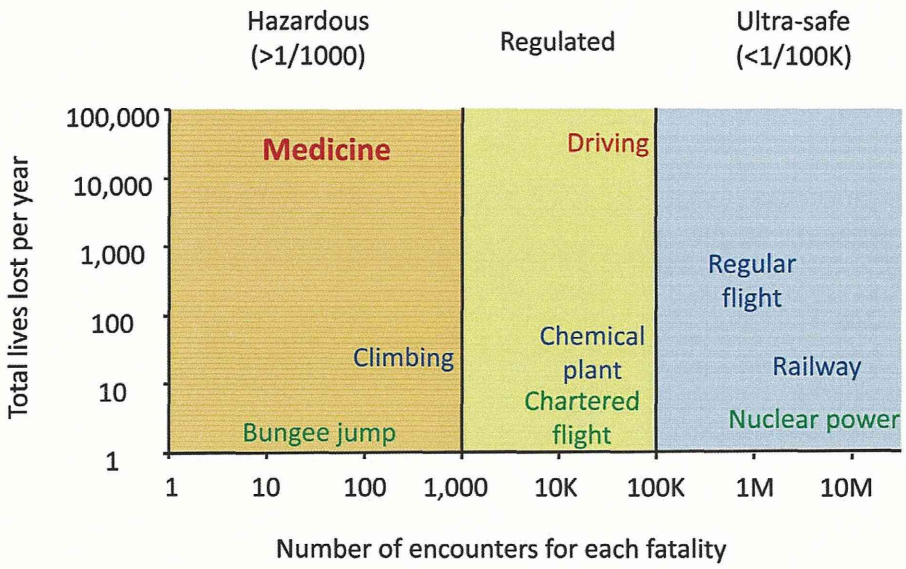

Figure 1. Quality metrics of major industries and human activities. (Adapted with permission from Amalberti R, et al.[2])

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