Serial assessment of endothelial vasomotor function using optimal medical therapy predicts clinical outcomes in patients after complete coronary revascularization

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Abstract

Objective: Previous studies have demonstrated the importance of intensive optimal medical therapy (OMT) in patients with coronary artery disease (CAD). To investigate our hypothesis that patients with and without OMT achievement differed with respect to the risk of future cardiac events, we investigated the endothelial function in patients with CAD who underwent percutaneous coronary intervention (PCI) and contemporary medical therapy.

Methods: We conducted a prospective longitudinal cohort study to evaluate the endothelial function in 96 consecutive patients at 12 h after admission and 3 months at <12 h after admission and at 3 months after discharge by measuring the brachial artery dilatation after 5 min of forearm ischemia flow-mediated dilation (FMD). OMT achievement was defined as systolic blood pressure of ≤130 mm Hg, low-density lipoprotein cholesterol of ≤100 mg/dl, and hemoglobin A1c level of ≤7.0%. The primary endpoint was the incidence of composite major adverse cardiac or cerebrovascular events (MACCE) at 36 months.

Results: Forty-nine (51%) patients achieved all three risk factor targets at 3 months. Although baseline FMD values did not differ between the OMT achievement and non-achievement groups, the 3-month FMD significantly improved in the OMT achievement group (6.6±3.5 vs. 5.2±2.9, p=0.03). Patients with improved FMD at 3 months had a lower rate of 36-month MACCE than those with persistently impaired FMD. A multiple Cox hazards analysis showed that OMT was a protective predictor of MACCE (hazard ratio, 0.19; 95% confidence interval, 0.04–0.88, p=0.03).

Conclusion: This study demonstrated a significant association between the serial measurement of endothelial function with OMT and the clinical outcome in patients after PCI. *(Anatol J Cardiol 2018; 19: 177-83)*

Keywords: endothelial dysfunction, optimal medical therapy, coronary artery disease

Introduction

Coronary artery disease (CAD) is the leading cause of death and poor outcome and is particularly prevalent among patients with diabetes and hypertension. Over the past two decades, percutaneous coronary intervention (PCI) has become a common method used in the initial management of patients with CAD. Although PCI reduces the incidence of death and myocardial infarction in patients with acute coronary syndromes, the risk of major cardiovascular events remains a concern.

Previous studies have reported that PCI in combination with optimal medical therapy (OMT), which includes lifestyle interventions (smoking cessation) and multifaceted pharmacotherapy aimed at controlling dyslipidemia, hypertension, and diabetes mellitus, was superior to OMT alone for angina relief (1). This control of multiple cardiovascular risk factors, which serves as the foundation of OMT, reduces the risk of cardiovascular events among patients with CAD (1). Therefore, achieving target values for multiple risk factors presented a challenge, suggesting that if patients with and without OMT achievement differed with respect to the risk of future cardiac events, then clinicians should more strongly consider the importance of OMT achievement.

The mechanisms underlying OMT achievement in patients with CAD remain unclear. Endothelial dysfunction has been described as a risk factor for cardiovascular events in several clinical settings (2-10). A previous study has shown that improvement in the endothelial function in response to OMT for atherosclerotic burden provides prognostic information on the risk of future cardiovascular events in patients with CAD (10). We hypothesized that endothelial dysfunction correlates with one of the abovementioned mechanisms. Therefore, we investigated the correlation between changes in the endothelial func-

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tion with or without OMT achievement and the clinical outcome. Accordingly, we conducted a serial evaluation of flow-mediated dilation (FMD) in patients receiving modern standard treatments.

Methods

Patient population and classification

We prospectively evaluated 96 consecutive patients with CAD for complete coronary revascularization at our institute between January 2014 and March 2015. This was a prospective longitudinal cohort study.

The inclusion criteria were the presence of an impaired FMD (FMD <5.5%) at enrollment (10). All patients were scheduled the two time points examination with FMD-at baseline (<12 h after admission) and 3 months after discharge. As shown in Figure 1, among the 255 screening for eligible patients with CAD, the exclusion criteria were as follows: (1) patients with FMD values of ≥5.5%; (2) those with acute coronary syndrome; (3) those on hemodialysis; (4) those with other serious systemic diseases, including malignancies; (5) those with FMD values measured after PCI; (6) those who cannot measure first FMD test; and (7) those who were considered difficult for clinical follow-up by the attending physician.

After applying these criteria, a total of 96 patients who underwent revascularization were included.

Clinical data were prospectively entered in the database. Patients were evaluated using drug therapies as prescribed by the attending physicians at admission; at 3 months after discharge, decisions regarding drug therapy usage were made by the clinical physician. The study protocol was approved by the medical ethics committee of the Toho University Ohashi Medical Center. Written informed consent was obtained from all patients for participating in the study.

This investigation conformed to the principles outlined in the Declaration of Helsinki.

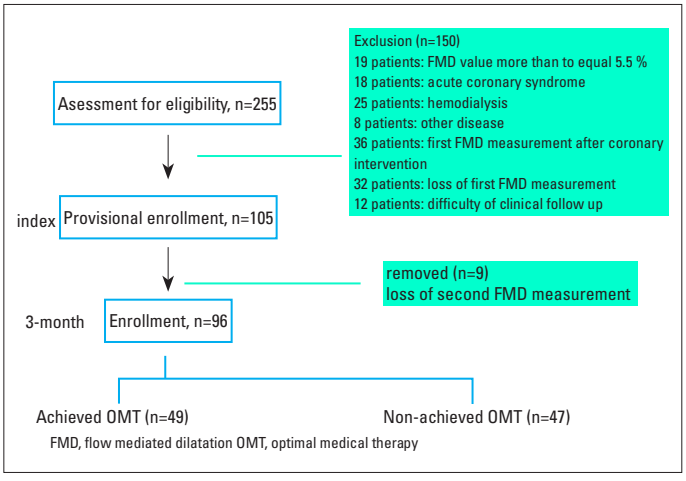

Figure 1. Study flow chart indicates the way to the result. The patients were excluded before enrollment (green)

Follow-up and definitions

Clinical follow-up of patients was performed during concomitant clinical visits. After a 3-month measurement of FMD values, all 96 patients with CAD were prospectively followed up at our institute or in clinical visits for up to 36 months depending on the attending physician. The primary clinical endpoint was the incidence of composite major adverse cardiac or cerebrovascular events (MACCE), including cardiac death, myocardial infarction, heart failure, stroke, and readmission within 12–36 months. Myocardial infarction was diagnosed on the basis of the development of new abnormal Q waves in more than two contiguous precordial or more than two adjacent limb leads or an elevation of creatine kinase (CK)-MB (or total CK if CK-MB was unavailable) level to >3-fold of the upper limit of the normal range (11).

Brachial flow-mediated dilatation measurement

All patients were analyzed <12 h after admission and at 3 months after discharge as described above. Before any invasive procedure, endothelial function was assessed using FMD, which was performed in accordance with the guideline published by the International Brachial Artery Reactivity Task Force (12). The improvement of FMD was defined as an FMD value at 3 months increased to ≥5.5%.

Patients were instructed to abstain from eating, smoking, and consuming caffeine for at least 4 h prior to the initiation of the study and to lie down for 20 min. Brachial artery FMD was measured via an amplitude evaluation and brightness-mode ultrasonography using a linear-array 10-MHz transducer (UNEXEF18G; UNEX Corp., Nagoya, Japan). After obtaining baseline diameter measurements for 30 s, the cuff was inflated to 50 mm Hg above the patient's systolic blood pressure for 5 min and then deflated. The brachial artery diameter was continuously recorded for 2 min after the cuff was deflated. All diameters were measured in the end-diastolic phase, which was defined as the beginning of the R wave on electrocardiography. FMD was calculated as the percentage change in the baseline diameter (before cuff release) to the peak value after cuff release. In this study, the repeated measurement of the baseline arterial diameter had an interobserver variability of 0.05±0.01 mm and an intraobserver variability of 0.02±0.01 mm. These studies were also simultaneously conducted on two separate days in 20 control patients who were initially registered in this study.

Optimal medical therapy

We analyzed OMT achievement both at admission and 3 months after discharge. Medical therapy was largely compared on the basis of OMT achievement or non-achievement for the first 3 months after discharge. All patients were recommended to undergo aggressive medical and lifestyle interventions (e.g., smoking cessation and concomitant exercise) based on secondary prevention guidelines (13). Each patient followed detailed procedures for the secondary prevention of major cardiovascular risk factors. The risk factor goals were based on the findings

Table 1. Baseline characteristics

(n=96)	OMT achievement n=49 (%)	OMT non-achievement n=47 (%)	*P*-value
Age, years	65±10	66±11	0.88
Sex, male	35 (71)	37 (78)	0.55
Hypertension	40 (81)	42 (89)	0.38
Blood pressure, mm Hg	123±17	136±19	0.008
Diabetes mellitus	16 (32)	21 (44)	0.29
Hemoglobin A1c, %	5.9±0.5	6.2±0.7	0.009
Dyslipidemia	38 (77)	40 (85)	0.43
Low-density lipoprotein cholesterol, mg/dL	90±27	111±29	0.08
History of smoking	15 (30)	16 (34)	0.88
Body mass index, kg/m^2	24.1±4	24.1±3	0.97
MDRD GFR, mL/min/1.73 m^2	82±21	80±23	0.65
Antihypertensive agents	35 (71)	37 (78)	0.48
Beta-blockers	19 (38)	19 (40)	1
Calcium antagonists	16 (32)	24 (51)	0.09
Nitrates	7 (14)	7 (14)	1
Statins	42 (89)	33 (75)	0.12
Oral antidiabetic agents	11 (22)	15 (31)	0.41
CAD 1-vessel	23 (46)	24 (51)	0.84
CAD 2-vessel	12 (24)	11 (23)	1
CAD 3-vessel	10 (20)	9 (19)	1
Previous MI	15 (30)	19 (40)	0.88
FMD, %	1.2±1.6	1.8±1.8	0.14
Arterial diameter at rest, mm	4.6±1.3	4.5±0.8	0.52
Polyvascular disease	3 (6)	7 (15)	0.19

Data are presented as the number of patients (%) or mean±SD.
CAD - coronary artery disease; FMD - flow-mediated dilatation; MDRD GFR - modification of diet in renal disease glomerular filtration rate; OMT - optimal medical therapy; SD - standard deviation

of the COURAGE trial as follows: systolic blood pressure ≤130 mm Hg, low-density lipoprotein cholesterol (LDL-C) ≤100 mg/dL, and hemoglobin A1c level ≤7%. OMT achievement was defined as achieving all of the abovementioned conditions, whereas OMT non-achievement was defined as the inability to achieve the abovementioned conditions

Statistical analysis

Data are presented as mean±standard deviation (SD) or numbers with frequencies (%). The normality of the distribution of continuous data was tested using the Kolmogorov–Smirnov test. Normally distributed data are presented as mean±SD, and non-normally distributed data are presented as the median with the interquartile range (IQR). Comparisons between groups were performed using the chi-square test or the Fisher's exact test for categorical data. Continuous variables were compared using the paired Student's t-test or Wilcoxon signed-rank test for the skewed distribution of data. Univariate and multiple logistic regression analyses were used to assess independent correlates of predictors for 12- to 36-month MACCE. The times to event endpoints were compared using Kaplan-Meier survival curves, and the corresponding p-values were obtained using the log rank test. The association of FMD values with future cardio-cerebrovascular events from 12 to 36 months was assessed by a Cox proportional hazard analysis. All variables summarized in Table 1 were entered into the models. All analyses were performed using the IBM-SPSS statistics software program, version 19 (SPSS, Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results

We analyzed data from 96 consecutive patients from January 2014 to March 2015. During a median of 2.7 years of follow-up, 49

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Table 2. Multiple cox proportional hazard analysis for MACCE at 36 month

Variables	Univariate		Multiple	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
OMT	0.18 (0.03-0.88)	0.03	0.19 (0.04-0.88)	0.03
LDL-C mg/dL at index	1.02 (1.08-4.56)	0.06		
A1c % at 3-month	2.22 (1.08-4.56)	0.03		

OMT - optimal medical therapy; CI - confidence interval; HR - hazard ratio

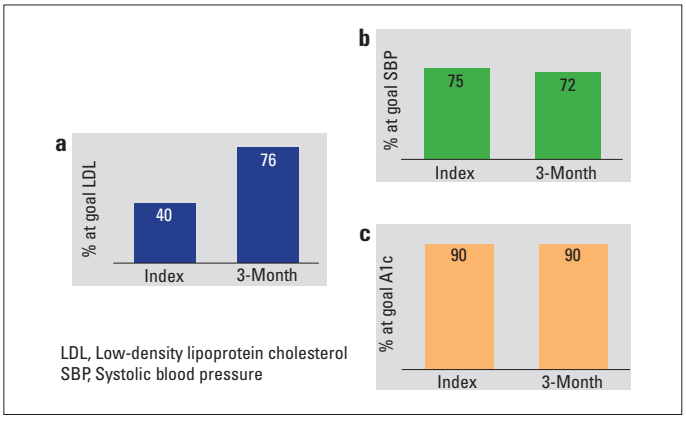

Figure 2. Overall rates of goal achievement for each risk factor. The baseline and 3-month rates were compared. The bar charts in Figure 2A, 2B, and 2C represent the low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (SBP), and hemoglobin A1c (A1c), values, respectively

(51%) patients achieved all three risk factor targets at 3 months (LDL-C ≤100 mg/dL, hemoglobin A1c level ≤7%, and systolic blood pressure ≤130 mm Hg). Target levels were achieved for LDL-C in 76%, for systolic blood pressure in 72% and for hemoglobin A1c in 90% of patients 3 months after PCI (Fig. 2).

Patients were divided into two groups according to OMT achievement (OMT achievement and non-achievement groups). Baseline clinical characteristics of patients of both groups are shown in Table 1. There were no significant differences between the two groups, although the OMT non-achievement group had higher rates of diabetes, hypertension, and polyvascular disease than the OMT achievement group. Proportions of various medications, such as calcium antagonists, statins, and antidiabetic drugs, differed between the groups. The prescription of statins was high in the OMT achievement group, whereas that of calcium antagonists was high in the OMT non-achievement group.

Patients' laboratory data for the targets are listed in Table 1. At admission, patients in the OMT non-achievement group had higher LDL-C and systolic blood pressure than those in the OMT achievement group. Figure 1 shows the achievement rate for each risk factor goal in our trial population at the 3-month follow-up, as prespecified for each respective trial. The LDL-C risk factor achievement rate increased from 40% to 76% at the 3-month follow-up (Fig. 2a). The results for other risk factors [systolic blood pressure (SBP) and hemoglobin A1c] are shown in Figure 2b and Figure 2c.

Baseline FMD values did not significantly differ between the groups (1.2±1.6 vs. 1.8±1.8, p=0.14). However, at the 3-month follow-up, FMD test showed significant difference in the FMD values between the two groups (6.6±3.5 vs. 5.2±2.9, p=0.03; Fig. 3). Moreover, changes in the FMD values (delta FMD %) from baseline to the 3-month follow-up between the two groups also demonstrated significant difference (1.2 → 6.6 vs. 1.8 → 5.2, p=0.03),

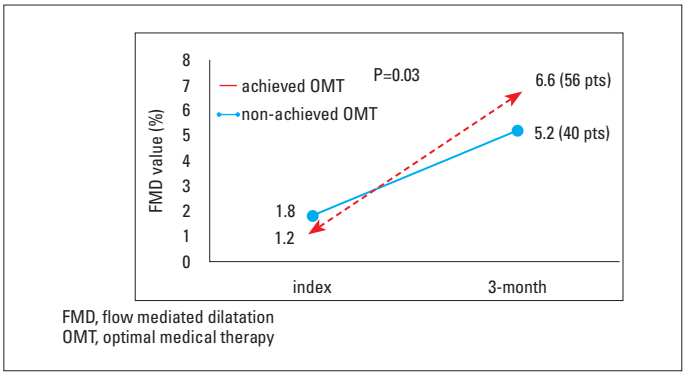

Figure 3. Comparison of changes in FMD values from baseline to the 3-month follow-up between the OMT achievement (dotted line) and non-achievement (solid line) groups. The improved group showed a significantly greater change in FMD values than the impaired group (1.2 → 6.6 vs. 1.8 → 5.2, *P*=0.03). And the each number of patients (pts) at 3-month among 2-groups

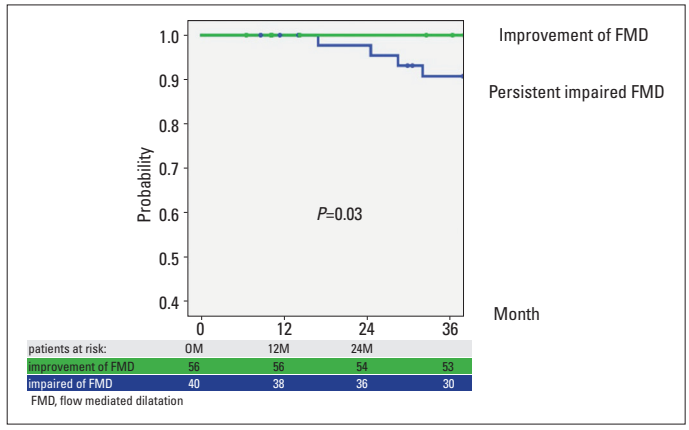

Figure 4. Kaplan–Meier estimates of MACCE at 36 months after coronary revascularization. Improved FMD (≥5.5%) at 3 months (green) versus persistently impaired FMD (<5.5%) at 3 months (blue). The *P*-value was calculated using the log rank test with all available follow-up data

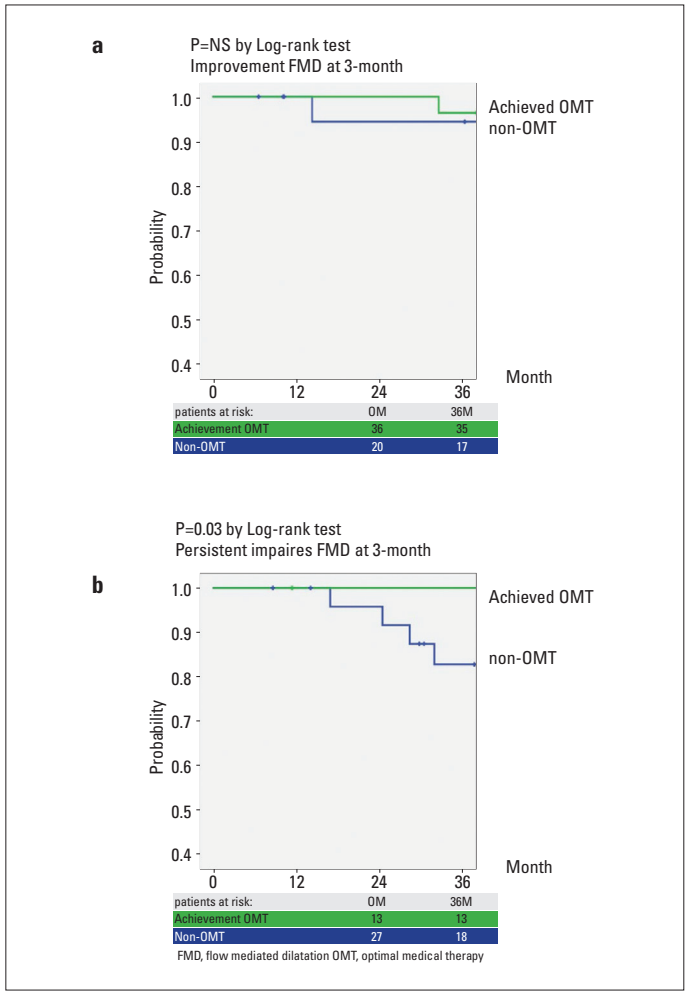

Figure 5. Kaplan–Meier curves for the event-free survival for MACCE between OMT achievement (green) and non-achievement (blue) groups at 36 months. Improved FMD (A) and persistently impaired FMD (B) at 3 months. The p-value was calculated using the log rank test with all available follow-up data

which was observed in 13 patients with MACCE (two cardiac deaths, three heart failures, one stroke, and seven readmissions) between 12 and 36 months. When FMD values at 3 months were analyzed, patients with improved FMD at 3 months had a lower rate of 36-month MACCE than those with persistently impaired FMD (Fig. 4).

Figure 5a shows the Kaplan-Meir curves for MACCE at 36 months in patients with improved FMD values at 3 months. Irrespective of OMT achievement or non-achievement, patients with improved FMD showed good survival rates. Figure 5b shows that in patients without improved FMD value, the two event curves significantly diverged, with a lower survival observed in the OMT non-achievement group at 3 months (p=0.03 by log rank test). A univariate analysis for MACCE at 36-month demonstrated significant difference for the factors of OMT and hemoglobin A1c at 3 months (Table 2).

According to a multiple Cox proportional hazards model analysis, OMT achievement was an independent protective predictor of 36-month for MACCE (HR, 0.19; 95% confidence interval, 0.04-0.88; p=0.03).

Discussion

In the present study, we evaluated improvements in the FMD values, compared the patients with persistently impaired FMD values and those with improved FMD values, and investigated serial measurements of FMD values as risk stratification in the secondary prevention of patients with CAD. The main findings of this study can be summarized as follows: improved FMD value (≥5.5%) at 3 months reduced the incidence of MACCE at 36 months and OMT achievement was a significant independent protective predictive factor for MACCE at 36 months.

Recent randomized controlled trials of management strategies for patients with CAD have incorporated intensive pharmacological and lifestyle interventions that are often termed OMT, either with or without initial revascularization (14, 15). Although the introduction of drug-eluting stent reduced cardiac events in 1 year after PCI, previous studies have demonstrated that cardiac events including additional revascularization in new remoted lesions gradually increase after 1 year (16, 17), which indicates the importance of strict risk factor control with medical or lifestyle interventions for secondary prevention, particularly in patients undergoing stent implantation.

Regarding primary prevention, a previous study has shown that newly diagnosed patients with CAD and a persistently impaired endothelial function were associated with future cardiovascular events (10). The present study focused on patients with established CAD divided into groups based on their achievement of OMT goals. We additionally assessed FMD to determine therapeutic effects of OMT achievement in clinical practice and observed that patients with OMT achievement exhibited improved endothelial function. Several studies have shown that inflammation may impair the endothelial function (17-19) and that increased stress associated with an acute clinical condition may contribute to impaired endothelial function (20).

Currently, there is no consensus regarding the cut-off values for OMT and FMD in the secondary prevention of patients with CAD. In addition, the ideal follow-up period has also not been established. However, a previous study has demonstrated that the assessment of endothelial function is a critical component of therapeutic strategies for preventing future cardiovascular events (10), particularly those that target atherosclerosis (21). In the present study, significantly improved FMD values at the 3-month follow-up were observed in the OMT achievement group, whereas persistently impaired FMD values were observed in the OMT non-achievement group. Persistently impaired FMD resulted in poor outcomes with respect to future cardiovascular events. Serial FMD evaluations may help clarify the optimal therapeutic direction and, thereby, be useful for risk stratification in patients with CAD, although the mechanism to justify the relationship between FMD values and the effect of

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OMT remains unclear. Patients with persistently impaired FMD values at follow-up may require more intensive medical and lifestyle interventions to reduce their risk of future cerebro-cardiovascular events.

Another important aspect is difficulty in achieving each risk factor target goals. Recent pooled analysis from three large trials reported that despite a high usage of medical therapies, 14%–16% of patients achieved treatment targets at 1 year. In contrast, in the present study, 29% of patients achieved all risk factors at baseline compared with 51% following an intensive 3-month intervention, which indicates similar risk factor target achievement rates despite the short duration of our study.

Target criteria for risk factor control have been issued with somewhat different cut-off values in the guidelines of various organizations and societies (22). Although we set an LDL-C target of ≤100 mg/dL, Vytorin Efficiency International Trial (IMPROVE-IT) demonstrated a statistically significant improvement in clinical outcomes when LDL-C level of 53 mg/dL was set as a cut-off point for the secondary prevention of CAD (23). Therefore, further studies discussing the optimal cut-off values and numerous factors, including the inherent challenge of ensuring patient adherence to medication regimens, will likely contribute to the various reports of limited success in composite risk factor goal achievement.

Study limitations

Several limitations associated with the present study warrant mention. This was a single-center study with a small sample size. In addition, confounding factors, such as differences in decisions regarding intensive medical intervention among attending physicians, may have influenced patients' FMD values or other outcomes. Furthermore, patient adherence may have affected the achievement of risk factor goals, particularly among those with OMT non-achievement. The observation period was not long enough to determine the effectiveness of OMT achievement. Further studies are needed to clarify the implications of hidden mechanism-related factors in terms of improvements in FMD values.

Conclusion

Improvements in FMD values may be a direct result of intensive OMT; however, the achievement of multiple risk factor goals widely varies because of several reasons in contemporary clinical practice. The present study suggested that periodic measurements of FMD help guide more intensive interventions and enhance risk stratification.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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