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Impact of primitive cells in intracoronary thrombi on lesion prognosis: temporal analysis of cellular constituents of thrombotic material obtained from patients with acute coronary syndrome

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Impact of primitive cells in intracoronary thrombi on lesion prognosis: temporal analysis of cellular constituents of thrombotic material obtained from patients with acute coronary syndrome

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ABSTRACT

Background Clinical evidence suggests that intracoronary thrombus formation is associated with a high incidence of late restenosis after successful coronary intervention in patients with myocardial infarction (MI). However, little is known about the mechanism by which intracoronary thrombi play pathological roles.

Methods and Results We analysed the cellular constituents of 108 thrombi aspirated from coronary lesions with a thrombectomy device in 62 patients who underwent emergent coronary intervention for the treatment of acute (<24 h) or recent (24–72 h) ST-segment elevation MI (44 men, 18 women, aged 68.0±19.3 years). Immunohistological analysis of aspirated thrombotic materials revealed that the content of platelets, as determined by immunostaining for CD42a, had a negative correlation with the time after the onset of chest pain (correlation coefficient −0.683, $p<0.01$). Immunofluorescent staining for CD34 and breast cancer-resistant protein-1 (bcrp-1) detected primitive cells in intracoronary thrombi. Furthermore, the ratio of CD34-positive cells in intracoronary thrombi had a significant positive correlation with restenosis at follow-up coronary angiography (correlation coefficient 0.76, $p=0.01$).

Conclusions The findings of this study indicate that the early accumulation of primitive cells in platelet aggregates may play a role in neointimal growth after successful coronary intervention in patients with acute coronary syndrome.

It is well known that most of coronary thrombi are precipitated by rupture of soft and vulnerable plaques and platelet aggregation plays an important role initially in their evolution. Thrombus removal using mechanical thrombectomy devices for reducing the thrombotic burden has been thought to be advisable not only for procedural success, but also for better long-term outcome in patients undergoing coronary angioplasty for acute coronary syndromes (ACS).[1] Lesions with a high thrombotic burden are prone to increased procedural risk.[2–4] Furthermore, a number of clinical studies has demonstrated that the presence of intracoronary thrombus detected by angiography and/or intravascular ultrasonography increases the risk of long-term restenosis after angioplasty.[5] Autopsy studies have revealed that coronary thrombi have a layered structure, with thrombus material of differing ages, indicating that they are formed successively from repeated mural deposits that cause progressive luminal narrowing over an extended period of time.[6] However, it remains unclear how intracoronary thrombi promote restenosis after successful intervention in patients with ACS.

Evaluation of intracoronary thrombi in ACS patients had been relatively difficult because only post-mortem specimens were available. Recent progress in mechanical thrombectomy and distal protection devices[3 4 7] has made it possible to aspirate fresh intracoronary thrombotic material for histological analysis.[8]

In the present study, the cellular constituents of intracoronary thrombotic material aspirated from patients with acute or recent ST-elevation myocardial infarction (MI) were analysed in accordance with the clinical time course. Our findings suggested that the accumulation of primitive cells in the thrombotic material may play a role in the pathogenesis of lesion progression after successful coronary intervention for ACS.

MATERIALS AND METHODS

Patient population

One hundred and eight thrombus samples from 62 patients were successfully obtained and analysed. The subjects were patients hospitalised at the University of Tokyo Hospital with the diagnosis of acute or recent ST-segment elevation MI who underwent percutaneous coronary intervention including thrombectomy. They were diagnosed according to their symptoms accompanied by ST-segment elevation on the ECG and/or a positive result of qualitative analysis of cardiac troponin T. After diagnosis, all patients received intravenous administration of 130 units/kg of unfractionated heparin in addition to oral administration of 200 mg aspirin if they did not have any contraindication.

Procedures and devices

The femoral artery approach with a 7 or 8 French sheath was selected in all patients. After engaging the guiding catheter into the coronary artery, a conventional 0.014-inch guide wire was employed to cross the target lesion. After morphological lesion examination with intravascular ultrasound, a thrombectomy device, such as the Thrombuster

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(n=32; Kaneka Medical, Osaka, Japan), TVAC (n=1; Nipro Co, Osaka, Japan) or Eliminate (n=25; Clinical Supply Co, Gifu, Japan) was used to aspirate thrombi in the case of visible mural thrombi as observed by angiography or intravascular ultrasound. After aspirating thrombotic material, if necessary, conventional procedures such as plain old balloon angioplasty and/or stent implantation were performed. In most of the cases (58/62, 93.5%), a distal protection device was used to avoid slow flow, no-reflow phenomenon and distal embolisation.

Immunohistochemical analyses

The thrombotic material was frozen with liquid nitrogen or fixed in methanol as quickly as possible after aspiration. Then, 5 μm frozen or paraffin-embedded sections were examined with H&E staining. Oil-red-O staining was performed only on frozen sections. Immunohistochemical analysis was performed with antibodies against α-smooth muscle (SMα) actin (clone 1A4; Sigma St Louis, MO, USA), CD42a (clone ALMA.16; Pharmingen San Diego, CA, USA) for platelets, CD45 (clone 2B11 +PD7/26; DAKO, Copenhagen, Denmark) for white blood cells, HAM56 for macrophages (clone HAM56; DAKO), CD34 (clone QBEND10; Immunotech, Marseille, France) and bcrp-1/ABCG2 (clone 5D3; Pharmingen) for primitive cells. After blocking non-specific reactions with 1% horse serum, sections were incubated with primary antibodies at 4°C overnight. Then they were incubated with biotinylated secondary antibody at room temperature for 1 h. The reaction product was visualised with streptoavidin–biotin complex with horseradish peroxidase. Double immunofluorescent staining was performed in combination with Cy3-conjugated anti-SMα actin and HAM56 antibody,[9] FITC or Alexa488-conjugated anti-CD34, CD42a, CD45 and bcrp1/ABCG2 antibodies. After nuclear counterstaining with Hoechst 33 253, signals were examined by confocal microscopy (FV1000; Olympus Co, Tokyo, Japan). The areas stained by specific antibodies were quantitatively measured graphically using Scion image soft (Scion Corporation, Washington, DC, USA). Cell numbers were counted in at least 10 visual fields at ×200 magnification.

Flow cytometric analysis of occluded coronary artery blood

Blood drawn from the occluded coronary artery was mixed with EDTA at a final concentration of 10 mmol/l and incubated on ice immediately until flow cytometric analysis. After haemolytic processing, blood was incubated with FITC-conjugated anti-CD34 antibody for 1 h. Samples were analysed with an EPICS-ALTRA cell sorting system (Beckman-Coulter). One hundred thousand (100 000) nucleated alive cells in each patient were analysed.

Quantitative coronary analysis

All coronary angiograms were analysed using a Clinical Measurements Solutions system (QCA-CMS, version 5.1; MEDIS Imaging Systems, Leiden, The Netherlands). The minimal lumen diameter was measured, and percentage diameter stenosis (%DS) was calculated in comparison with the reference diameter before and after the initial intervention and at follow-up studies at 3 months or later. %DS over 60 was considered to be significant stenosis.

Statistical analysis

Differences in clinical variables were analysed by analysis of variance for parametric data. Comparison of allelic frequencies between groups was performed using Fisher's exact test or the non-parametric unpaired Student's t test or χ^2 test as appropriate and corrected for inequality of variances (Levene's test). Correlations were evaluated using Spearman's rank correlation coefficient and linear regression was calculated using the least squares method. Quantitative data were expressed as mean±SEM, and a p value less than 0.05 was considered statistically significant.

Table 1 Patients' characteristics

Female/male (number)		18/44
Age (years)		68.0±19.3
Body mass index		23.6±3.5
Hypertension, n (%)		49 (79.0)
Diabetes, n (%)		20 (31.5)
Lipid disorder, n (%)		46 (74.2)
Triglycerides (mg/dl)		117.2±75.4
Low-density lipoprotein cholesterol (mg/dl)		114.2±33.7
Smoking history, n (%)		43 (69.4)
Diagnosis, n (%)	AMI (<24 h)	48 (77.5)
	RMI (24–72 h)	14 (22.5)
Target vessel, n (%)	LAD (including LMCA)	26(41.9)
	LCx	11 (17.7)
	RCA	25 (40.3)
Procedures, n (%)	POBA+ stenting§	24(38.7)
	Direct stenting§	35 (56.5)
	Only thrombectomy	3 (4.8)
Mean time between onset and thrombectomy (h)		17.8 (0.5-72)
Follow-up coronary angiography, n (%)		57 (96.6)
Major adverse cardiac events, n (%)		11 (18.6)
	Cardiac death, n (%)†	1 (1.7)
	Myocardial infarction, n (%)	0 (0)
	Target lesion revascularisation, n (%)	10(16.9)

AMI, acute myocardial infarction; LAD, left anterior descending artery; LCx, left circumflex branch; LMCA, left main coronary artery; POBA, plain old balloon angioplasty; RCA, right coronary artery; RMI, recent myocardial infarction.
†One patient died due to uncontrollable congestive heart failure.
§All implanted stents were bare-metal stents.

RESULTS

Characteristics of patients and procedures

The patients' characteristics are summarised in table 1. Forty-four of 62 patients were men. The mean age was 68.0±19.3 years; 31.5% of patients had diabetes, 79.0% had hypertension and 74.8% had dyslipidaemia. Of the affected vessels, 41.9% were the left anterior descending artery, 17.7% the left circumflex branch and 40.3% the right coronary artery. In 35 patients (56.5%), stents were directly implanted. All patients were implanted with bare metal stents except three patients who archived good re-flow by thrombectomy alone without any additional intervention. The mean time between the onset of symptoms and thrombectomy in this study was 17.8±18.9 h, which widely ranged from 0.5 to 72 h.

Major adverse cardiac events occurred in 11 of 59 patients. One patient who presented with cardiogenic shock due to left main coronary artery occlusion died of uncontrollable heart failure. Ten patients needed target lesion revascularisation.

Immunohistochemical analysis of thrombotic material

The macroscopic findings of the aspirated thrombotic material are shown in figure 1. These were highly variable in colour, size, configuration and quantity among patients (figure 1A), and even among aspirates from one patient (figure 1B(1)–(3)). H&E staining of thrombotic material demonstrated the structure of thrombi (figure 2). They were generally composed of three parts;

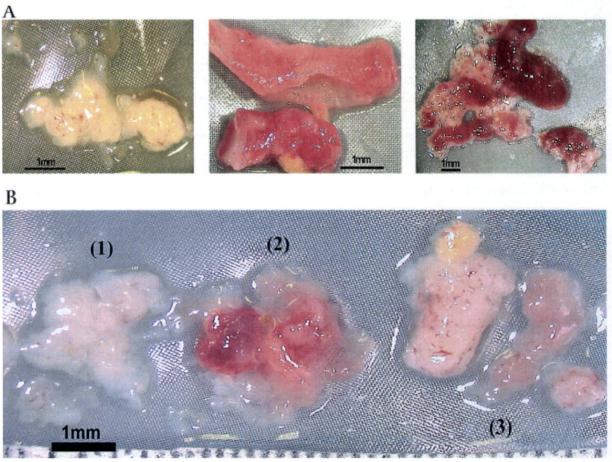

Figure 1 Macroscopic views of aspirated material obtained from the coronary arteries of patients with acute coronary syndrome. These samples were distinctive in colour, size, configuration and quantity among the patients (A). The thrombotic material was also different at each time of aspiration (B). Sample 1 was first aspirated, 2 was second, and 3 was obtained from the distal protection device.

nucleated cell clusters (figure 2A), organised fibrin with infiltration of a few nucleated cells (figure 2B) and clusters of erythrocytes (figure 2C, arrows). The proportion of each component was related to the colour and shape of the sample. There was no significant correlation among the numbers of CD34, HAM56, CD45-positive cells. Immunofluorescent staining (figure 3) revealed that the infiltrated cells were mostly white blood cells expressing CD45 and/or HAM56, a marker for macrophages. Although the thrombotic material included various amounts of lipid detected by Oil-red-O staining (figure 4), the content of triglyceride showed no relationship with the serum triglyceride/cholesterol levels or body mass index.

Figure 5 shows the results of immunofluorescent and immunohistochemical studies of SMα-actin and platelets (CD42a). The areas positive for each antibody were basically distinctive. CD42a was mainly expressed in organised fibrin, whereas SMα-actin-positive cells were mainly located in the area of clusters of nucleated cells (figure 5A). Notably, the proportion of the CD42a-positive area had a significant negative correlation with the time passed between the onset of symptoms and

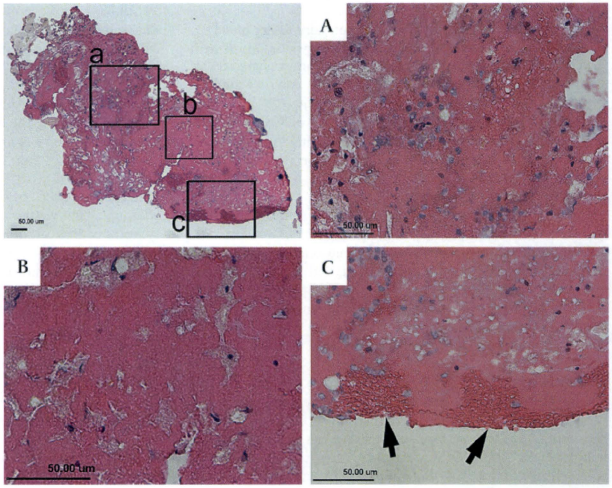

Figure 2 H&E staining of thrombotic material. Frozen sections (4 μm) were fixed in methanol and stained with H&E. Most of the thrombotic material was mainly composed of erythrocytes (C, arrows), organised fibrin with abundant platelets with a few nucleated cells (B), or a cluster of nucleated cells (A).

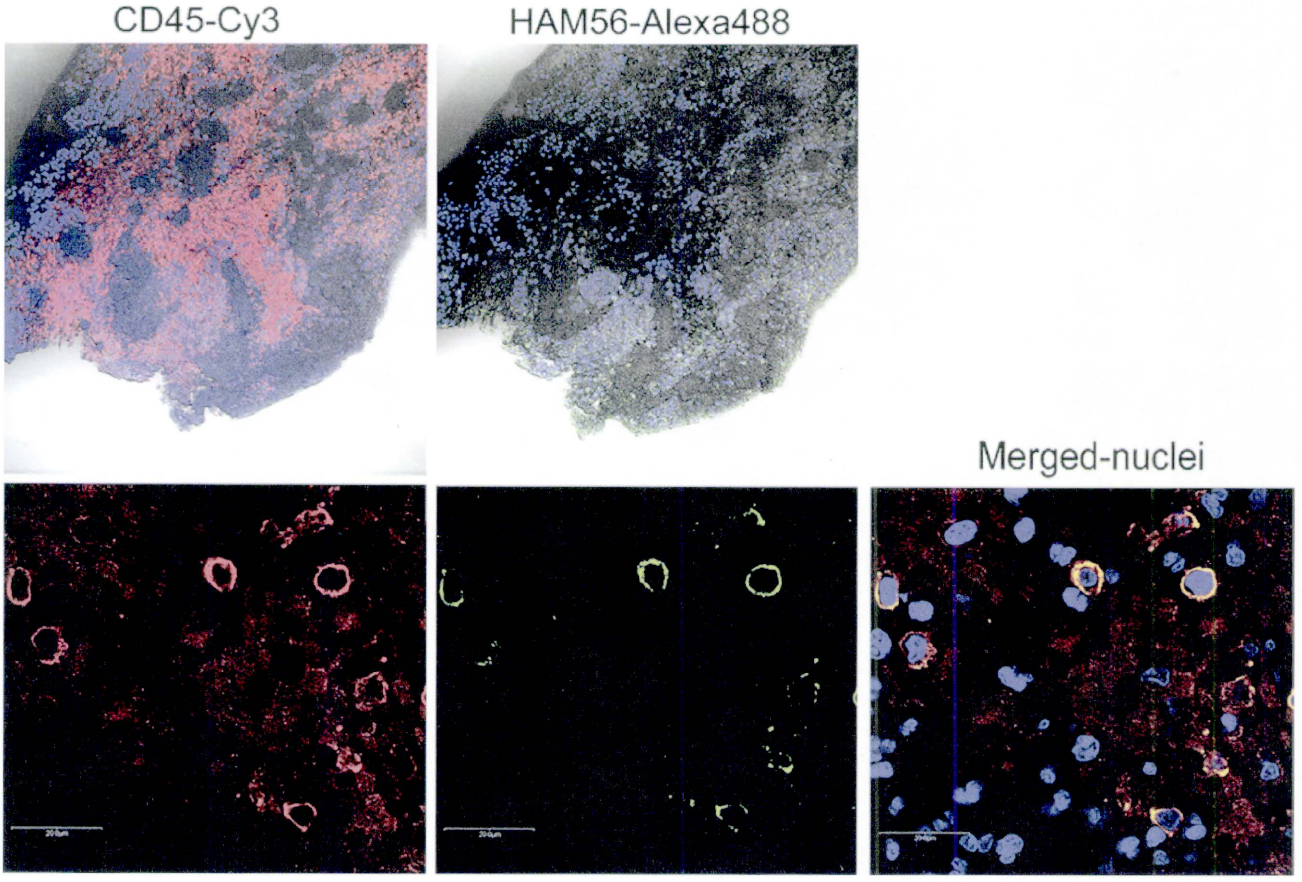

Figure 3 Cell accumulation detected in thrombotic material. Double immunofluorescent study of CD45 (Alexa488, green) and HAM 56 (Cy3, red) in thrombotic material. Most of the nucleated cells were positive for CD45 or HAM56. At greater magnification, there were some cells that were positive for both CD45 and HAM56.

thrombectomy (correlation coefficient: −0.59, $p<0.01$) (figure 5B). The proportion of SMα-actin-positive area tended to have a positive correlation with the time after onset (correlation coefficient: 0.29, $p=0.025$) (data not shown).

Moreover, immunostaining with antibodies against smooth muscle cell (SMC) lineage markers demonstrated that a very limited number of nucleated cells expressed highly differentiation markers of SMC, such as smooth muscle myosin heavy chain isoform 1 (SM1), calponin and caldesmon (see supplementary figure 1a, available online only). Conversely, considerable number of cells expressed cytokines that are known as promoting neointima hyperplasia, such as tumour necrosis factor alpha, platelet-derived growth factor B and matrix metalloproteinase 2 (see supplementary figure 1b, available online only).

To characterise further the cellular constituents in thrombi, histological evaluation was performed focussing on primitive stem cells. Among the nucleated cells in the thrombus samples, some cells expressed stem cell markers, such as CD34 and bcrp1/ABCG2, which is known to be an essential cell surface co-transporter of side-population cells[10] (figure 6A). The number of CD34-positive cells in the blood was compared with that in intracoronary thrombi in five patients. The mean proportion of CD34-expressing cells in 100 000 alive nucleated cells was 0.165±0.034% in the blood aspirated from the occluded coronary artery. In comparison, it was significantly greater in thrombus samples from the same patients (2.67±0.687%, $p=0.019$), although different assays for the detection of CD34-positive cells were employed. Regarding the correlation between the proportion of CD34-positive cells and clinical outcomes, the proportion of CD34-positive cells (2.58±0.35%, range 0.05–8.5%) showed a significant correlation with percentage diameter stenosis at follow-up coronary angiography calculated by quantitative coronary analysis (correlation coefficient 0.57, $p<0.01$) (figure 6B). On the other hand, no significant correlation was found with the number of CD45 and HAM56-positive cells. Similarly, analysis of the two patient groups 'restenosis +' (≥60% diameter stenosis at follow-up angiography) and 'restenosis−' (<60%) showed that the proportion of CD34-positive cells was significantly greater in the restenosis+ group than in the restenosis− group (5.10±0.66% vs 1.88±0.24%, $p<0.01$). No significant difference in the mean CD45 and HAM56-positive ratio was observed between the two groups (figure 6C). Conversely, when the patients were divided into two groups, low CD34 (<2.5%, n=34) group and high CD34 (≥2.5%, n=23) group, percentage diameter stenosis at follow-up angiography was significantly greater in the high CD34 group, despite there being no significant difference in clinical, procedural and angiographical characteristics. The proportion of CD34 cells showed no relation with pre and post-procedural percentage diameter stenosis (figure 6D).

DISCUSSION

Our study demonstrated that: (1) the cellular constituents of thrombotic material in patients with ST-elevation acute MI or recent MI varied according to the time since the onset of

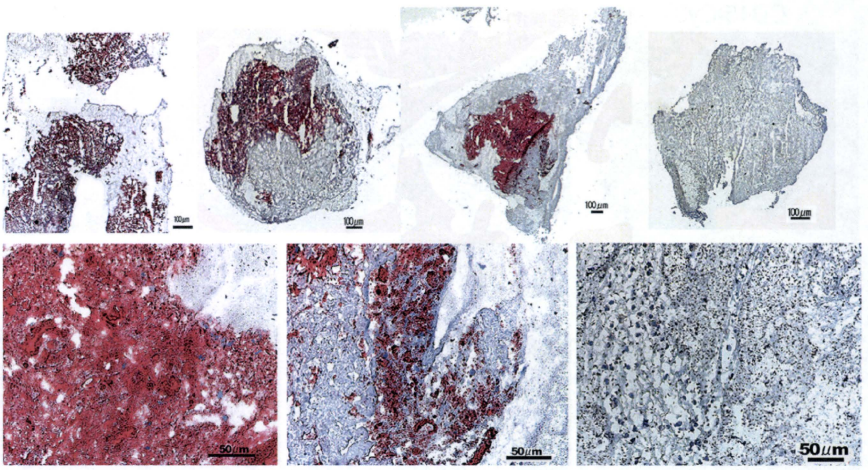

Figure 4 Oil-red-O staining of thrombotic material. Oil-red-O staining revealed that the aspirated materials contained lipid components from the ruptured plaques. Red staining indicates the triglyceride-positive area.

symptoms; (2) thrombotic material included primitive stem cells expressing stem cell markers; (3) the proportion of primitive stem cells was significantly greater in thrombotic material than in peripheral blood; and (4) the number of CD34-positive primitive cells in intracoronary thrombi positively correlated with the degree of lesion progression after coronary intervention, whereas no correlation was found between the number of macrophages/monocytes and lesion prognosis.

It is well known that the presence of intracoronary thrombus increases the risk of long-term restenosis after angioplasty.[5] Moreover, a recent study examining aspirated intracoronary thrombus demonstrated that the prognosis of patients with ST-elevation MI varied in accordance with pathological findings of thrombus.[8] However, the pathophysiological role of the intracoronary thrombi effect on local as well as clinical outcomes remains largely unknown.

There remains a great deal of controversy regarding the origin of cells in vascular remodelling. Although it had been widely believed that intimal SMC are derived from the medial SMC that undergo migration into the intima,[11 12] on the contrary, recent reports suggest that vascular stem cells resident in the circulating blood or local lesions might give rise to cells that express some markers of SMC in both animal models[13] and humans.[14] In addition, haematopoietic stem cells are known to have paracrine and autocrine properties in conditions promoting intimal cell proliferation and differentiation.[15 16]

The present study demonstrates primitive stem cells in thrombotic material in patients with ACS. In addition to CD34-positive cells, Bcrp1/ABCG2-positive cells indicating very primitive cells were found (side-population cells).[10 17] Furthermore, flow cytometric and histological analyses showed that the proportion of CD34-positive cells within thrombi was siginificantly greater than that in blood drawn from the occluded coronary artery. These findings indicate that primitive cells expressing stem cell markers greatly accumulate into intracoronary thrombi.

Although a recent trial with intracoronary infusion of primitive bone marrow cells for patients with ST-elevation MI showed beneficial effects including the prevention of cardiac remodelling,[18] there remains concern that these cells might promote neointimal proliferation. Bartunek *et al*[19] reported a high rate of in-stent restenosis or re-occlusion after intracoronary injection of CD133-positive cells in ACS patients. Kang *et al*[20] reported that more than half of MI patients who were administered granulocyte colony-stimulating factor alone or purified CD34-positive cells mobilised by granulocyte colony-stimulating factor showed restenosis. Moreover, the CD34-positive cell-capture stent trial indeed showed long-term safety and efficacy in patients with stable and unstable angina; however, to date, the efficacy of that CD34-capture stent in MI patients is still unknown.[21 22] Furthermore, we previously showed a significantly greater elevation in the number of peripheral CD34-positive cells in patients with restenosis at chronic time points after coronary stenting with bare metal stents than in patients without stenosis.[23] Taken together, these data indicate that circulating or local CD34-expressing primitive cells might play a role in neointimal hyperplasia. The results of the present study suggest that the infiltration of a greater number of CD34-positive cells is an indicator of excessive neointima formation. Although the precise roles of these cells remain unclear, it is possible that the primitive cells observed in intracoronary thrombi may play a role in the pathogenesis of restenosis.

Previous reports suggested that enhanced infiltration of macrophages in atherosclerotic lesions was associated with a high incidence of restenosis after angioplasty.[24 25] In contrast, no significant correlation was observed between the number of macrophages/monocytes and lesion progression in this study. This discrepancy apparently results from the difference in the lesions analysed. We

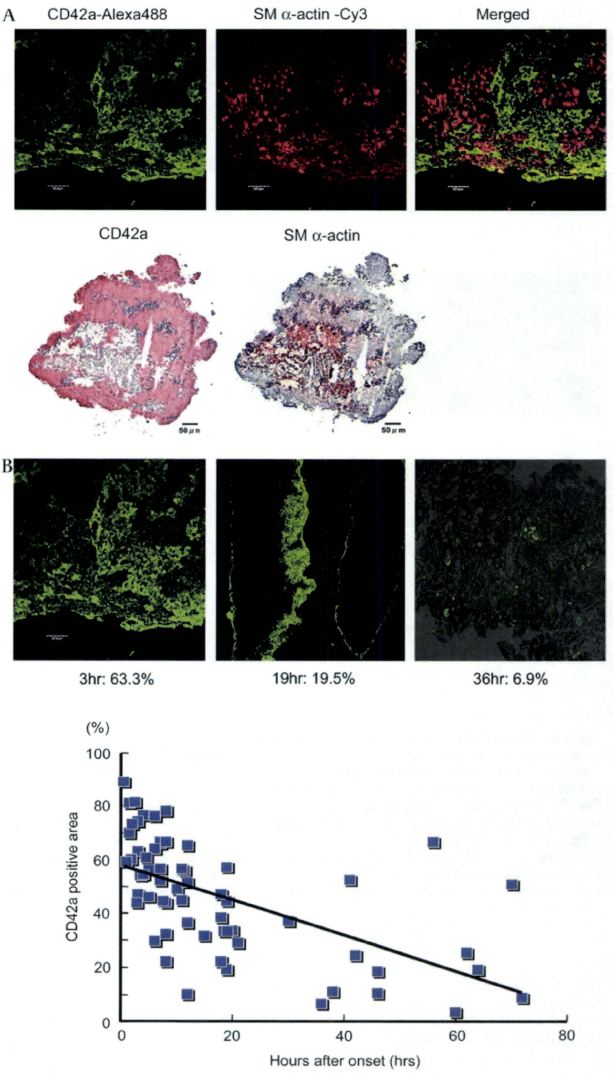

Figure 5 Characterisation of cells observed in thrombotic material. (A) Immunostaining for CD42a (green) and α-smooth muscle actin (SMα-actin, red). Immunostaining with anti-CD42a and SMα-actin antibody shows that the expression of these two molecules was generally distinct. CD42a was mainly expressed in the area of organised fibrin as determined by H&E staining. On the other hand, a part of the nucleated cells expressed SMα-actin in the area of cell infiltration. The co-expression of SMα-actin and CD42a was seldom observed. (B) Negative correlation between time passed since onset to thrombectomy and the proportion of the CD42a-positive area. There is a significant negative correlation between the time since onset and the proportion of the CD42a-positive area. The longer the time passed after the onset until thrombectomy, the fewer platelets and fibrin were observed.

could count the macrophages only within the aspirated intracoronary thrombi, whereas most of the previous studies performed immunohistochemical analysis on the cross-sections of the coronary arteries obtained during atherectomy. Moreover, recent evidence suggests that macrophages/monocytes consist of heterogeneous subpopulations with different immunological functions.[26] The subpopulation of macrophages in thrombotic materials might differ from that in atherosclerotic plaques.

Thereafore, this study might at least partly indicate that in patients with MI, immunohistological analysis of intracoronary

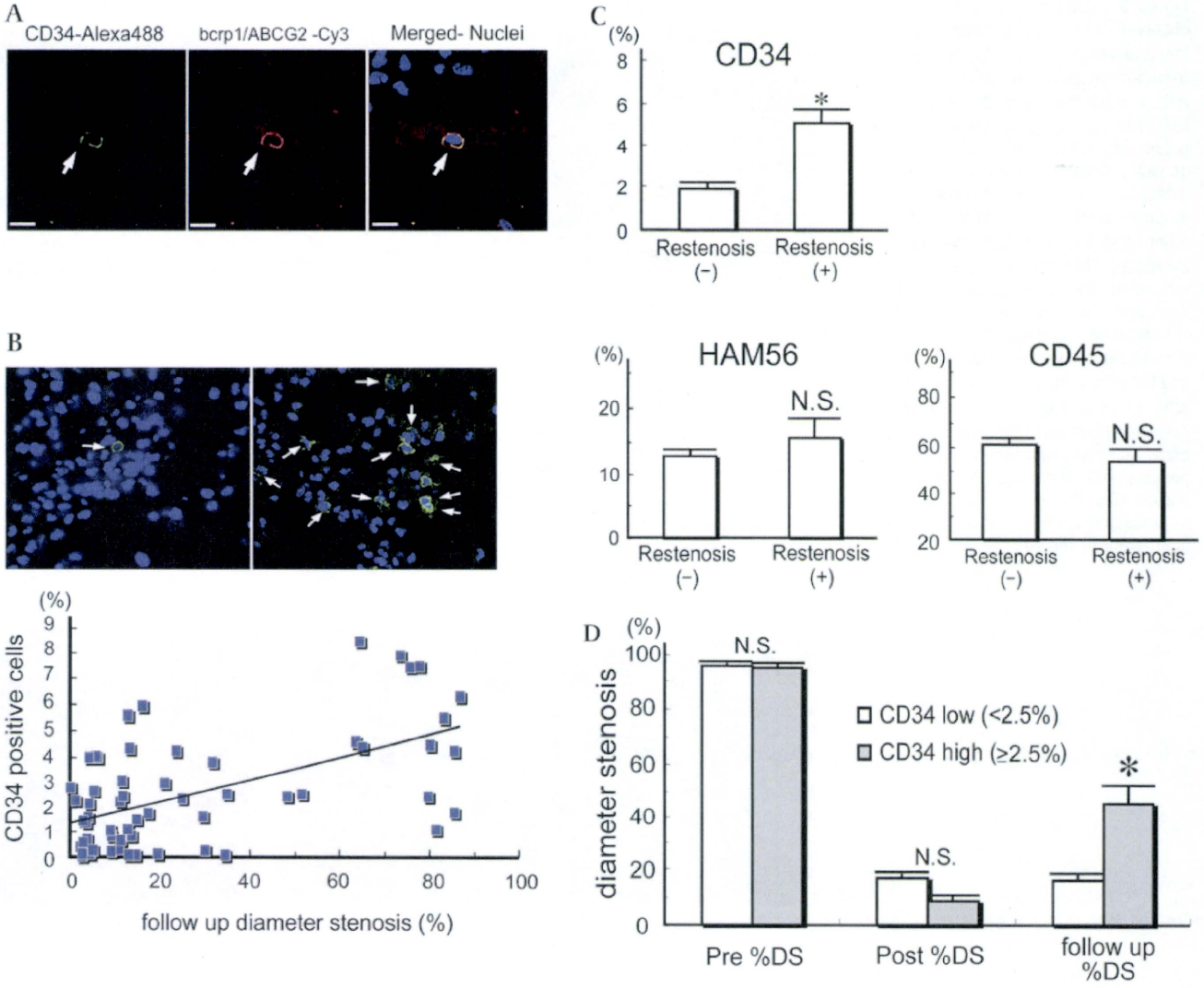

Figure 6 Primitive cells observed in thrombotic material. (A) Immunofluorescent images of thrombotic material stained for markers of primitive cells. In the clusters of nucleated cells, there was a cell that was positive for both CD34 and Bcrp1/ABCG2. (B,C) Positive correlation between the CD34-positive ratio in thrombotic material and lesion progression (restenosis) after coronary intervention. As shown in the upper panel, the number of CD34-positive cells varied among samples. A significant positive correlation was observed between the proportion of CD34-positive cells and the percentage diameter stenosis calculated by quantitative coronary analysis at follow-up coronary angiography (correlation coefficient 0.57, $p<0.01$). (C,D) The proportion of CD34-positive cells was significantly greater in patients with restenosis (percentage diameter stenosis (%DS) ≥60) than in patients without restenosis. There was no significant difference between the two groups in the proportion of CD45 or HAM-positive cells. (D,E) Patients were divided into a 'low CD34 group' (<2.5%) and 'high CD34 group' (≥2.5%) according to the proportion of CD34-positive cells. Percentage diameter stenosis was compared between the groups before intervention (pre %DS), after intervention (after %DS), and at follow-up coronary angiography (follow-up %DS). Percentage diameter stenosis at follow-up angiography was significantly greater in the high CD34 group than in the low CD34 group (45.3±7.4 vs 16.0±2.2%).

thrombi focussing on primitive cells might be an attractive tool for the prediction of lesion prognosis.

POTENTIAL STUDY LIMITATIONS

As thrombectomy devices always indiscriminately aspirate intracoronary material, the possibility cannot be excluded that the material aspirated through these devices includes other components, such as ruptured vessel wall, the content in lipid cores and thrombi that are thought to be present for an extended time.[27 28] In that respect, studies examining material aspirated through thrombectomy devices may be more imprecise than autopsy-based studies for examining 'intracoronary thrombus' itself. Moreover, as aspirated samples were highly variable even within the same patient, potential sampling error could not be excluded. However, thrombectomy devices enable us to examine samples by real-time analysis. Therefore, this method could be considered suitable for evaluating events that change dramatically with the time course, such as evolving thrombi with the recruitment of cells with primitive cell phenotypes. Larger scale clinical studies as well as detailed and quantitative evaluation of expressions of inflammatory cytokines/growth factors are required to confirm the precise role of primitive cells observed in coronary thrombi in lesion progression after successful intervention in patients with ACS.

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Competing interests None.

Ethics approval This study was conducted with the approval of the ethics committee of the University of Tokyo.

Provenance and peer review Not commissioned; externally peer reviewed

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Demographics and Changes in Medical/Interventional Treatment of Coronary Artery Disease Patients Over a 3.5-Year Period in Japan

—— The Japanese Coronary Artery Disease Study: Trend Examination ——

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Background Cardiovascular medicine has undergone rapid changes in recent years, but there are insufficient reports using large cohorts regarding these changes for Japanese coronary artery disease (CAD) patients. Hence, a large-scale prospective observational study was needed.

Methods and Results A total of 36,298 patients were registered over 6 periods. Patients with hypertension, hyperlipidemia, obesity, and impaired glucose tolerance increased in number, while those with old myocardial infarction (MI), smoking habit, and family history of CAD decreased. Regarding the trends in interventional procedures, stent use increased in both the whole cohort and the acute MI subgroup, while the use of only medical control decreased. Regarding prescription trends, angiotensin-receptor blockers increased while nitrates decreased.

Conclusions In a period of 3.5 years, significant changes were observed for both interventional procedures and medication, which might be related to the well-timed compliance of physicians with published evidence. However, these changes were not related to changes in the event rates, at least over the short term. Although careful attention should be paid in interpreting the results, because this is an observational study and the background of patients in each cohort might have been heterogeneous, such investigations should be constantly conducted for evidence-based practice. (*Circ J* 2008; **72:** 1397 - 1402)

Key Words: Coronary artery disease; Evidence-based practice; Medicine; Percutaneous intervention; Trends

Among the vascular-related diseases in Japanese, cerebrovascular diseases have demonstrated a constant decline[1,2] partly because of the decrease in sodium intake[3] and the resultant decrease in blood pressure.[4] However, cardiovascular diseases in Japanese have not decreased substantially over several decades;[5] so they are of relatively greater clinical concern. In general, interventional cardiology has progressed rapidly over the past decades[6,7] and ample scientific evidence with regard to the appropriate medication to be administered in various situations has also accumulated. This evidence has been generated through a number of clinical researches, and many clinical guidelines are based on these studies; however, there are insufficient reports regarding the actual practice of cardiovascular medicine in Japan, which prompted us to conduct a large-scale observational study with patients suffering from significant coronary artery disease (CAD, Japanese coronary artery disease (JCAD) study).[8] The JCAD study has 2 arms: a follow-up arm and a trend-only arm. We previously reported the results of the follow-up arm, in which patients were followed-up for a mean of 2.7 years.[9]

In order to elucidate the changes in medication or interventional procedures in Japanese cardiology practice, as well as the angiographic findings in JCAD patients, we analyzed the data of the trend-only group, together with that of the follow-up group, at the time of registration.

Methods

Patients

The protocol of this study has been published elsewhere.[8] Briefly, consecutive patients who underwent coronary angiography (CAG) and who were diagnosed as having 75% or higher stenosis, based on the classification of the American Heart Association (AHA),[10] in at least 1 branch of a coronary artery were registered for the study. All CAG were performed after obtaining written informed consent from the patients. Patients in the first cohort were enrolled from April 2000 until March 2001. Initially, 15,628 patients were registered and 13,812 of them were followed up. Subsequently, consecutive patients were enrolled every 6 months over 5 periods until September 2003; 22,486 patients were registered with complete initial data, and 18,641 of them were followed up.

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Table 1 Background Characteristics of Patients at the Time of Registration

Drugs	T1 (n=15,628)	T2 (n=5,277)	T3 (n=4,554)	T4 (n=3,738)	T5 (n=3,664)	T6 (n=3,437)	p value
No. of males and age							
Male	11,979 (76.7%)	4,058 (76.9%)	3,409 (74.9%)	2,834 (75.8%)	2,816 (76.9%)	2,660 (77.4%)	0.891
Age (years)	65.6±9.8	65.9±9.9	66.0±9.8	66.1±10.0	66.5±10.1	66.6±10.0	<0.001
Diagnosis at the time of registration							
AMI	3,274 (20.9%)	1,092 (20.7%)	1,061 (23.3%)	783 (20.9%)	831 (22.7%)	718 (20.9%)	0.145
Old myocardial infarction	4,399 (28.1%)	1,485 (28.1%)	1,194 (26.2%)	992 (26.5%)	877 (23.9%)	885 (25.7%)	<0.001
Unstable AP	2,330 (14.9%)	751 (14.2%)	673 (14.8%)	600 (16.1%)	605 (16.5%)	507 (14.8%)	0.089
Stable AP	4,530 (29.0%)	1,586 (30.1%)	1,312 (28.8%)	1,088 (29.1%)	1,103 (30.1%)	1,036 (30.1%)	0.176
Other	1,095 (7.0%)	363 (6.9%)	314 (6.9%)	275 (7.4%)	248 (6.8%)	291 (8.5%)	0.046
Risk factors							
Hyperlipidemia	8,462 (54.1%)	2,892 (54.8%)	2,506 (55.0%)	2,099 (56.2%)	2,131 (58.2%)	2,021 (58.8%)	<0.001
IGT	6,262 (40.1%)	2,011 (38.1%)	1,789 (39.3%)	1,542 (41.3%)	1,517 (41.4%)	1,531 (44.5%)	<0.001
Hypertension	8,994 (57.6%)	3,064 (58.1%)	2,789 (61.2%)	2,281 (61.0%)	2,306 (62.9%)	2,191 (63.7%)	<0.001
Obesity	5,081 (32.5%)	1,744 (33.0%)	1,579 (34.7%)	1,290 (34.5%)	1,259 (34.4%)	1,143 (33.3%)	0.015
Smoking	6,075 (38.9%)	2,029 (38.4%)	1,645 (36.1%)	1,325 (35.4%)	1,316 (35.9%)	1,273 (37.0%)	<0.001
Family history of CAD	2,563 (16.4%)	748 (14.2%)	758 (16.6%)	560 (15.0%)	542 (14.8%)	449 (13.1%)	<0.001

T1 to T6, 6 cohorts in chronological order.
P value for age was calculated using the Kruskal-Wallis test. All other p values for trend were calculated using the Cochran-Armitage test.
AMI, acute myocardial infarction; AP, angina pectoris; IGT, impaired glucose tolerance; CAD, coronary artery disease.

Data Registration and Accumulation

All data were registered electronically as described previously[8,11] Briefly, a central database server was set up and the clinical information was transmitted to a central computer through a Web-based interface. Diagnosis of CAD at the time of registration was made by the attending physician based on the information provided in a manual that was distributed prior to the start of the study. The trade names and dosages of all the drugs that the patients were taking were registered by the attending physician. Medication data at the time of discharge was considered in the present analysis. The definition of each risk factor was as follows: hyperlipidemia=serum total cholesterol ≥220 mg/dl and/or low-density lipoprotein-cholesterol ≥140 mg/dl and/or triglyceride ≥150 mg/dl; impaired glucose tolerance (IGT), including diabetes mellitus=fasting blood glucose ≥110 mg/dl; hypertension=systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg; obesity=body mass index ≥25 kg/m^2; smoking=at least one episode of smoking in the 2 years before registration; familial history=CAD in any first-degree relative. These data were obtained from each patient by the attending physician. Careful attention was paid to data security.

Angiographic Findings

According to the AHA classification, coronary arteries were classified into 15 segments. When at least 1 segment of an artery (right coronary artery: segments #1–#4; left main trunk (LMT): segment #5; left anterior descending artery (LAD): segments #6–#10; and left circumflex artery: segments #11–#15) had 75% or more stenosis or occlusion, it was classified as diseased. Data were analyzed only for patients with no history of interventional procedures, because previously corrected arteries that did not demonstrate significant restenosis were not registered as diseased. These patients were termed 'de novo' patients.

Investigations

The endpoint was a composite of all-cause death and cardiovascular events and was defined as the occurrence of fatal or nonfatal myocardial infarction (MI), fatal or nonfatal strokes, other cardiovascular events, and death from any cause as the first event. All events were evaluated and registered by the attending physicians. Percutaneous coronary intervention performed against restenosis without clinical symptoms was explicitly excluded as an event.

Ethical Considerations

The institutional review board of each participating institution reviewed and approved the study protocol and other documents. Further, each attending physician explained the study to each candidate patient, who provided voluntary written informed consent prior to enrollment.

Statistical Analysis

Absolute numbers and percentages were computed to describe the patient population. The Kruskal-Wallis test was used to analyze the differences among cohorts with regard to continuous numbers. The Cochran-Armitage test was used to analyze trends over time. P values <0.05 were considered significant. All p values were the result of 2-tailed tests. Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary, NC, USA).

Results

Background Characteristics

The background characteristics of the patients are shown in Table 1. Statistically significant increasing trends were observed for the risk factors hyperlipidemia, IGT, hypertension, and obesity. Significant decreasing trends were observed for old MI (OMI), smoking habit, and family history of CAD.

Angiographic Findings

Table 2 shows the trend in the angiographic findings for patients without prior coronary intervention. No trend of increase or decrease was observed with regard to the site of stenosis or occlusion in the coronary arteries. When examining for single-vessel disease, the LAD artery was the most frequently detected as diseased; 59.4% of the total de novo patients in this study cohort had a diseased LAD (Table 3). LMT involvement was calculated to be 7.6% (n=755).

Table 2 Angiographic Findings in De Novo Patients

LMT	RCA	LAD	LCX	T1 (n=8,878)	T2 (n=3,104)	T3 (n=2,764)	T4 (n=2,196)	T5 (n=2,205)	T6 (n=1,996)	p value for trend
A	P	P	P	1,781 (20.1%)	565 (18.2%)	502 (18.2%)	439 (20.0%)	466 (21.1%)	413 (20.7%)	0.268
A	P	P	A	1,103 (12.4%)	374 (12.0%)	369 (13.4%)	245 (11.2%)	273 (12.4%)	264 (13.2%)	0.716
A	P	A	P	557 (6.3%)	215 (6.9%)	160 (5.8%)	138 (6.3%)	131 (5.9%)	116 (5.8%)	0.281
A	A	P	P	1,061 (12.0%)	336 (10.8%)	338 (12.2%)	268 (12.2%)	250 (11.3%)	235 (11.8%)	0.880
A	P	A	A	1,013 (11.4%)	399 (12.9%)	337 (12.2%)	243 (11.1%)	257 (11.7%)	223 (11.2%)	0.690
A	A	P	A	2,427 (27.3%)	861 (27.7%)	767 (27.7%)	625 (28.5%)	598 (27.1%)	532 (26.7%)	0.815
A	A	A	P	620 (7.0%)	236 (7.6%)	196 (7.1%)	150 (6.8%)	159 (7.2%)	146 (7.3%)	0.769
P	P	P	P	110 (1.2%)	43 (1.4%)	36 (1.3%)	28 (1.3%)	29 (1.3%)	21 (1.1%)	0.734
P	P	P	A	39 (0.4%)	14 (0.5%)	7 (0.3%)	10 (0.5%)	9 (0.4%)	8 (0.4%)	0.712
P	P	A	P	17 (0.2%)	8 (0.3%)	4 (0.1%)	4 (0.2%)	1 (0.0%)	3 (0.2%)	0.237
P	A	P	P	50 (0.6%)	15 (0.5%)	13 (0.5%)	11 (0.5%)	11 (0.5%)	8 (0.4%)	0.383
P	P	A	A	10 (0.1%)	8 (0.3%)	7 (0.3%)	8 (0.4%)	3 (0.1%)	1 (0.1%)	0.744
P	A	P	A	37 (0.4%)	11 (0.4%)	12 (0.4%)	10 (0.5%)	5 (0.2%)	12 (0.6%)	0.758
P	A	A	P	13 (0.1%)	5 (0.2%)	7 (0.3%)	8 (0.4%)	1 (0.0%)	5 (0.3%)	0.396
P	A	A	A	40 (0.5%)	14 (0.5%)	9 (0.3%)	9 (0.4%)	12 (0.5%)	9 (0.5%)	0.888

T1 to T6, 6 cohorts in chronological order.
P values for trend were calculated using the Cochran-Armitage test.
LMT, left main trunk; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; A, lesion absent in the artery; P, lesion present in the artery.

Choice of Treatment

Trends in the choice of treatment for the affected arteries in the whole cohort are shown in Table4. Patients who underwent no interventional procedures were considered to be medically controlled. Plain old balloon angioplasty (POBA) denotes that no interventional procedure other than balloon angioplasty was performed. Statistically significant increasing trends were observed for the use of directional coronary atherectomy and stents. Significant decreasing trends were observed in medical control, POBA, intracoronary thrombolysis (ICT), and intravenous coronary throm-

Table 3 Angiographic Findings of Patients With Single-Vessel Disease

RCA	LAD	LCX	Total (n=9,789)
P	A	A	2,472 (25.3%)
A	P	A	5,810 (59.4%)
A	A	P	1,507 (15.4%)

Abbreviations as in Table 2.

Table 4 Choice of Treatment for the Diseased Artery in Each Cohort

Period	T1 (n=15,628)	T2 (n=5,277)	T3 (n=4,554)	T4 (n=3,738)	T5 (n=3,664)	T6 (n=3,437)	p value
Medicine	5,565 (35.6%)	1,781 (33.8%)	1,479 (32.5%)	1,214 (32.5%)	1,100 (30.0%)	1,006 (29.3%)	<0.001
POBA	1,972 (12.6%)	605 (11.5%)	493 (10.8%)	348 (9.3%)	360 (9.8%)	302 (8.8%)	<0.001
DCA	158 (1.0%)	81 (1.5%)	70 (1.5%)	61 (1.6%)	70 (1.9%)	60 (1.7%)	<0.001
Rotablator	389 (2.5%)	128 (2.4%)	93 (2.0%)	90 (2.4%)	79 (2.2%)	79 (2.3%)	0.215
Stents	6,118 (39.1%)	2,255 (42.7%)	2,026 (44.5%)	1,655 (44.3%)	1,718 (46.9%)	1,680 (48.9%)	<0.001
Cutting balloon	737 (4.7%)	279 (5.3%)	264 (5.8%)	217 (5.8%)	162 (4.4%)	169 (4.9%)	0.423
CABG	1,110 (7.1%)	329 (6.2%)	288 (6.3%)	279 (7.5%)	278 (7.6%)	242 (7.0%)	0.431
ICT	114 (0.7%)	39 (0.7%)	30 (0.7%)	16 (0.4%)	14 (0.4%)	9 (0.3%)	<0.001
IVCT	67 (0.4%)	19 (0.4%)	11 (0.2%)	13 (0.3%)	11 (0.3%)	7 (0.2%)	0.027

T1 to T6, 6 cohorts in chronological order.
P values for trend were calculated using the Cochran-Armitage test.
POBA, plain old balloon angioplasty; DCA, directional coronary atherectomy; CABG, coronary artery bypass graft; ICT, intracoronarythrombolysis; IVCT, intravenous coronarythrombolysis.

Table 5 Choice of Treatment for the Diseased Artery in Patients Initially Admitted for AMI in Each Cohort

Period	T1 (n=3,274)	T2 (n=1,092)	T3 (n=1,061)	T4 (n=783)	T5 (n=831)	T6 (n=718)	p value
Medicine	323 (9.9%)	82 (7.5%)	102 (9.6%)	78 (10.0%)	67 (8.1%)	49 (6.8%)	0.032
POBA	604 (18.4%)	163 (14.9%)	136 (12.8%)	91 (11.6%)	84 (10.1%)	66 (9.2%)	<0.001
Stents	2,099 (64.1%)	781 (71.5%)	749 (70.6%)	571 (72.9%)	619 (74.5%)	559 (77.9%)	<0.001
Cutting balloon	66 (2.0%)	24 (2.2%)	43 (4.1%)	26 (3.3%)	13 (1.6%)	16 (2.2%)	0.454
CABG	137 (4.2%)	31 (2.8%)	40 (3.8%)	26 (3.3%)	37 (4.5%)	23 (3.2%)	0.479
ICT	108 (3.3%)	37 (3.4%)	27 (2.5%)	16 (2.0%)	14 (1.7%)	9 (1.3%)	<0.001
IVCT	64 (2.0%)	19 (1.7%)	9 (0.8%)	12 (1.5%)	11 (1.3%)	7 (1.0%)	0.021

T1 to T6, 6 cohorts in chronological order.
P values for trend were calculated using the Cochran-Armitage test.
Abbreviations as in Tables 1,4.

Table 6 Prescription Trend in the 6 Cohorts

Drugs	T1 (n=13,812)	T2 (n=4,714)	T3 (n=4,113)	T4 (n=3,284)	T5 (n=3,361)	T6 (n=3,188)	p value
ACEI	4,366 (31.6%)	1,570 (33.3%)	1,366 (33.2%)	1,073 (32.7%)	997 (29.7%)	879 (27.6%)	<0.001
ARB	1,868 (13.5%)	836 (17.7%)	869 (21.1%)	779 (23.7%)	917 (27.3%)	930 (29.2%)	<0.001
CCB	6,928 (50.2%)	2,291 (48.6%)	1,936 (47.1%)	1,518 (46.2%)	1,518 (45.2%)	1,382 (43.4%)	<0.001
Statins	5,071 (36.7%)	1,950 (41.4%)	1,723 (41.9%)	1,513 (46.1%)	1,634 (48.6%)	1,600 (50.2%)	<0.001
α-1 blockers	318 (2.3%)	109 (2.3%)	103 (2.5%)	69 (2.1%)	77 (2.3%)	84 (2.6%)	0.547
α-β-blockers	1,479 (10.7%)	661 (14.0%)	666 (16.2%)	536 (16.3%)	634 (18.9%)	581 (18.2%)	<0.001
β-blockers	2,693 (19.5%)	943 (20.0%)	787 (19.1%)	644 (19.6%)	595 (17.7%)	552 (17.3%)	0.001
Fibrates	448 (3.2%)	129 (2.7%)	105 (2.6%)	76 (2.3%)	81 (2.4%)	83 (2.6%)	<0.001
Antithrombotics	12,048 (87.2%)	4,393 (93.2%)	3,824 (93.0%)	3,021 (92.0%)	3,143 (93.5%)	2,975 (93.3%)	<0.001
Nitrates	8,319 (60.2%)	2,778 (58.9%)	2,222 (54.0%)	1,659 (50.5%)	1,528 (45.5%)	1,325 (41.6%)	<0.001
Diuretics	2,155 (15.6%)	765 (16.2%)	686 (16.7%)	550 (16.7%)	614 (18.3%)	586 (18.4%)	<0.001

T1 to T6, 6 cohorts in chronological order. P values were calculated by Cochran-Armitage test for trend.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCB, calcium-channel blocker.

Table 7 Incidence of Events in the Trend-Follow Cohorts

Events	Per 1,000 patients each year				
	T2	T3	T4	T5	T6
All events including death	114.8	127.6	143.0	128.3	110.2
Cardiac events					
AMI	16.2	21.0	16.3	20.5	15.0
Unstable AP	59.1	56.9	80.8	58.8	51.1
Resuscitated cardiac arrest	2.1	0.0	1.2	2.4	3.8
Congestive heart failure	14.5	24.9	18.8	27.7	23.9
Bypass graft surgery	8.7	6.8	12.1	4.8	3.1
CPAOA	3.7	1.0	3.6	5.4	3.1
Cerebral events					
Cerebral infarction or hemorrhage	5.4	13.6	6.0	7.2	5.6
Transient ischemic attack	0.8	0.5	1.2	0.6	0.6
Vascular events					
Aortic dissection	0.8	1.9	0.0	0.0	1.3
Aortic aneurysm rupture	1.2	0.0	0.0	0.6	0.0
Nonvascular deaths	5.8	6.3	6.6	6.6	6.9
All deaths	20.3	18.0	22.3	25.2	24.4
Mean follow up (days)	187.3	183.2	184.3	181.3	183.4

T2 to T6, 5 trend-follow only cohorts in chronological order.
CPAOA, cardiopulmonary arrest on arrival. Other abbreviations as in Table 1.

bolysis (IVCT). Trends in the choice of treatment for the affected arteries in the acute MI (AMI) cohort are shown in Table 5. Statistically significant increasing trends were observed for the use of stents. Significant decreasing trends were observed in medical control, POBA, ICT, and IVCT.

Prescription Trends

The prescription trends at the time of discharge in each group are shown in Table 6. Statistically significant increasing trends were observed for angiotensin-receptor blockers (ARBs), statins, α-β-blockers, antithrombotics, and diuretics. Significant decreasing trends were observed for angiotensin-converting enzyme inhibitors (ACEI), calcium-channel blockers (CCB), β-blockers, fibrates, and nitrates.

Incidence Rate of Events

The incidence rates of events from trend periods 2–5 are shown in Table 7. Mean follow-up of the patients in the trend-only cohort was 184.1 days. The incidence rate of cerebrocardiovascular events, including all-cause deaths, ranged from 110.2 to 143.0 events per 1,000 patients each year. No trend of decrease or increase in events was observed.

Discussion

In this study, we show for the first time the demographics and changes in medical and interventional treatment of JCAD patients in a large cohort over a 3.5-year period.

It is not known, particularly in Japan, which medicines or interventional procedures are used in actual practice and how they are changing according to the evidence provided by clinical studies. Further, the angiographic findings in the JCAD patients have not been reported for a large cohort, which prompted us to conduct a study in which trends in the JCAD patients were followed for approximately 3.5 years. We followed a total of 36,298 patients in 6 periods. For the first cohort of 15,682 patients, 13,812 of them were followed for a mean of 2.7 years. The remaining 5 cohorts were followed for shorter terms, primarily for the purpose of investigating trends in the modes of treatment and angiographic findings. The results will be discussed below.

Although the absolute changes were not very large, statistically significant increasing trends were observed for hyperlipidemia, IGT, hypertension and obesity (Table 1). These changes suggest that either people affected with these conditions are increasing in the general population or that people are better controlled medically before they present with symptoms requiring cardiac catheterization. Direct

evidence that might have contributed to these results was not available from our data. However, it is plausible that each factor played a role in these trends. Obesity is reported to have increased, particularly in Japanese men,[12] and a significant increase in the prevalence of hypercholesterolemia over a 10-year period has been reported.[13] The prevalence of diabetes mellitus is also increasing in the general Japanese population,[14] whereas hypertension is reported to be declining,[4] because of the decreased sodium chloride intake.[3] However, an increasing trend of hypertension was observed among the patients enrolled in this study, despite the decline in the general population and the awareness regarding the Japanese hypertension guidelines among physicians and their improved adherence to them.[15] Statistically decreasing trends were observed for OMI, family history of CAD, and smoking; the decline in smoking is in agreement with reports concerning the general population.[13]

The angiographic findings in patients without prior interventional procedures showed that, when examining for single-vessel disease, LAD involvement was the most frequent (Table 3), possibly because the LAD is most often the dominant artery and so stenosis will typically cause clinical symptoms. Only 7.6% of the patients had LMT involvement. These findings showed similar traits with previous reports.[16,17] There were no statistically increasing or decreasing trends in any of the angiographic patterns, which suggests that the angiographic findings observed in this study may represent those of CAD patients in general.

The trend data for the choice of treatment of the diseased arteries (Tables 4,5) show that there was a significant increasing trend in stent use in both the whole cohort and in the AMI subgroup, which may be considered to reflect the evolution of interventional procedures in general.

Regarding prescription trends, the most notable trends were the substantial increase in the use of ARBs and the decline in the use of nitrates. The increase in the use of ARBs might be a reflection of the positive results reported during the period of this study.[18–20] The gradual decrease in the use of CCBs and ACEIs might be because they are being substituted with ARBs. The decrease in the use of nitrates is thought to be the result of a guideline published in 2000 that contraindicated the long-term use of nitrates in stable patients after MI;[21] however, the evidence used to compile that guideline is not the results of randomized control studies. The most commonly prescribed α-β-blocker was carvedilol (data not shown), the increase in the use of which might be related to the publication of several clinical trials of this drug prior to or during the period of this study.[22,23] Taken together, it might be concluded that doctors participating in the JCAD study modified their practice fairly rapidly to comply with the published evidence.

Event rates for the trend-follow cohort were higher than we had previously reported for the follow-up cohort (Table 7). Events were also clustered in the first 6 months in the follow-up cohort (data not shown), which suggests that secondary events after acute coronary syndromes tend to concentrate in the early period after interventional procedures. No trend of increase or decrease was observed in the event rates despite significant changes in both medical treatment and interventional procedures. The pattern of the incidence rate of AMI and CHF may have reflected seasonal changes,[24] although the data were insufficient to estimate the reasons for the trends in other events.

In conclusion, changes in the background characteristics of patients who underwent cardiac catheterization reflected the trend observed in the general population, except in the case of hypertension. Angiographic findings did not differ greatly from those reported previously in Western populations, and no increasing or decreasing trends were observed. Stent use increased in both the whole cohort and the AMI subgroup. The fairly rapid change in prescription patterns appeared to reflect the results of published evidence and may imply good compliance of the physicians who participated in this study in this regard. However, these changes were not related to the trend in incidence rates of events observed within 6 months after angiography. Although this study used data from a fairly short period, it may be considered to represent cardiovascular practices of Japanese cardiologists fairly well.

Although careful attention should be paid in interpreting the results, because the background of each cohort might have been heterogeneous, the rapid alteration in actual practices observed in this study suggests the need for continuous investigations in the future.

Study Limitations

It must be noted that this was an observational study and is descriptive in nature. Therefore, most of the reasoning as regards the cause of the results is speculative. For example, regarding the reasons for the change in medication and interventions, we did not perform a questionnaire asking physicians for the reason why they opted for the modes of treatment they had chosen.

It should also be noted that the background of the patients in each cohort might have differed significantly, resulting in different treatment strategy among the cohorts. The results and conclusions must be interpreted carefully with these backgrounds in mind.

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ORIGINAL ARTICLE
Ischemic Heart Disease

Beta-Blocker Prescription Among Japanese Cardiologists and Its Effect on Various Outcomes

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Background: Beta-blockers are underprescribed for coronary artery disease (CAD) patients in Japan. Considering the vast amount of evidence showing their benefits in this group of patients, the aim of the present study was to investigate the use of β-blockers in a large cohort of CAD patients.

Methods and Results: The 13,812 patients with angiographically confirmed CAD were followed up for 2.7 years. From this group, 4,160 (30.1%) patients were prescribed β-blockers at the time of discharge. These patients were significantly more likely to have hypertension, hyperlipidemia, obesity, a family history of ischemic diseases and a higher number of diseased arteries. The rate of continuation for β-blockers was 90.8%. A propensity score matching analysis showed no additional benefits of β-blockers in reducing all-cause mortality, cardiac events and cerebrovascular events. Lipophilic β-blockers were significantly more effective than hydrophilic ones in reducing all-cause mortality (hazard ratio 0.467, 95% confidence interval 0.247–0.880, P=0.019).

Conclusions: Despite the low prescription rate of β-blockers for CAD patients among Japanese physicians, the continuation rate was relatively high. Lipophilic β-blockers may be a better choice than hydrophilic β-blockers in terms of mortality risk, although a randomized control study would need to be conducted to verify this assertion. (*Circ J* 2010; **74:** 962–969)

Key Words: Beta-blocker; Coronary artery disease; Observational cohort; Propensity score matching analysis

Beta-blockers are underprescribed by Japanese physicians, possibly because of their deleterious effects on metabolic profiles,[1,2] and patients with bronchial insufficiency,[3] or physicians' high awareness of bradycardia and hypotension induced by the drugs. It has been reported that even for patients with myocardial ischemia, calcium antagonists are preferred over β-blockers for the treatment of angina,[4] maybe from fear of coronary spasm, the rate of which is reported to be higher in the Japanese population than in Westerners.[5] Although β-blockers were being used off-label for congestive heart failure (CHF) in clinical settings, it was only in 2002 that carvedilol was officially approved for the treatment of CHF in Japan. Today, carvedilol remains the only β-blocker approved for the treatment of CHF in Japan. On the other hand, there is ample evidence that β-blockers are beneficial in reducing cardiovascular risks in many conditions.[6–9]

Editorial p 848

We conducted a large observational study (the JCAD study) to investigate the background and treatment of Japanese patients with confirmed coronary artery disease (CAD), defined as ≥75% stenosis in at least 1 branch of the coronary arteries in accordance with the American Heart Association (AHA) classification. We concluded that β-blockers were less likely to be prescribed in Japan than in the West,[10] but considering the enormous evidence of the beneficial effects of β-blockers in patients with cardiovascular diseases, we felt that a more thorough investigation of β-blocker usage was necessary. It has also been reported that different β-blockers produce different outcomes in certain situations,[11] so in the present study we looked at how various classes of β-blockers are used and what effects they had on outcomes.

Methods

Patients

The protocol and major outcomes of this study have been published previously.[12,13] Briefly, patients who underwent coronary angiography (CAG) at each participating institute and who were diagnosed as having ≥75% stenosis according to the AHA classification in at least 1 branch of the coronary arteries were registered. All CAGs were performed with

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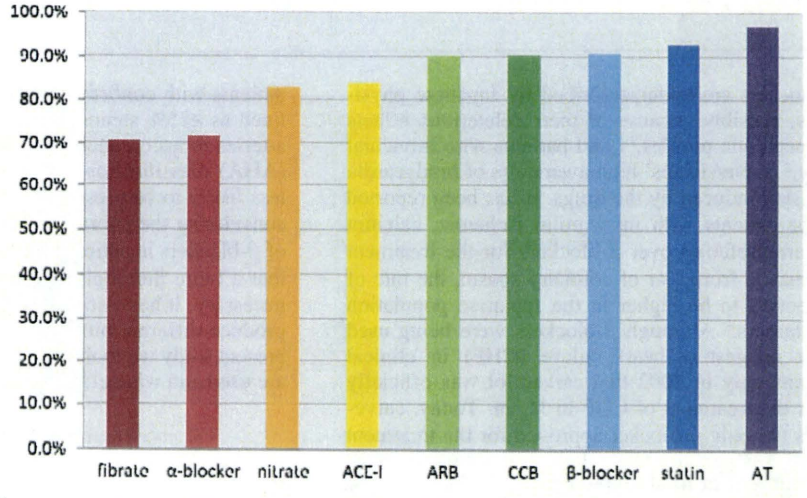
Table 1. Background Characteristics of Patients With or Without β-Blockers

	Without β-blockers (n=9,652)	With β-blockers (n=4,160)	P value
Age	65.53±9.90	65.32±9.63	0.110
Male	7,466 (77.4%)	3,160 (76.0%)	0.075
Hypertension	5,345 (55.4%)	2,606 (62.6%)	<0.001
Hyperlipidemia	5,122 (53.1%)	2,425 (58.3%)	<0.001
IFG	3,857 (40.0%)	1,713 (41.2%)	0.181
Obesity	3,035 (31.4%)	1,407 (33.8%)	0.006
Smoking	3,834 (39.7%)	1,603 (38.5%)	0.190
Drinking	3,625 (37.6%)	1,589 (38.2%)	0.476
Family history	1,533 (15.9%)	748 (18.0%)	0.002
CHF	1,005 (10.4%)	393 (9.4%)	0.128
LMT disease	415 (4.3%)	207 (5.0%)	0.079
No. of affected arteries	1.73±0.79	1.89±0.81	<0.001
Statins	3,207 (33.2%)	1,864 (44.8%)	<0.001
Fibrates	285 (3.0%)	163 (3.9%)	0.003
CCBs	4,913 (50.9%)	2,015 (48.4%)	0.008
ACEIs	2,823 (29.2%)	1,543 (37.1%)	<0.001
ARBs	1,176 (12.2%)	692 (16.6%)	<0.001
α-blockers	187 (1.9%)	131 (3.1%)	<0.001
ATs	8,088 (83.8%)	3,960 (95.2%)	<0.001
Nitrates	5,805 (60.1%)	2,514 (60.4%)	0.750

P values of age and number of affected arteries were calculated by Kruskal-Wallis test. All other P values were calculated by chi-square test.
IFG, impaired fasting glycemia; CHF, congestive heart failure; LMT, left main trunk; CCB, calcium-channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; AT, antithrombotic.



	fibrate	α-blocker	nitrate	ACE-I	ARB	CCB	β-blocker	statin	AT
number at final follow-up	316	228	6919	3678	1683	6249	3777	4716	11707
number at discharge	448	318	8319	4366	1868	6928	4160	5071	12048

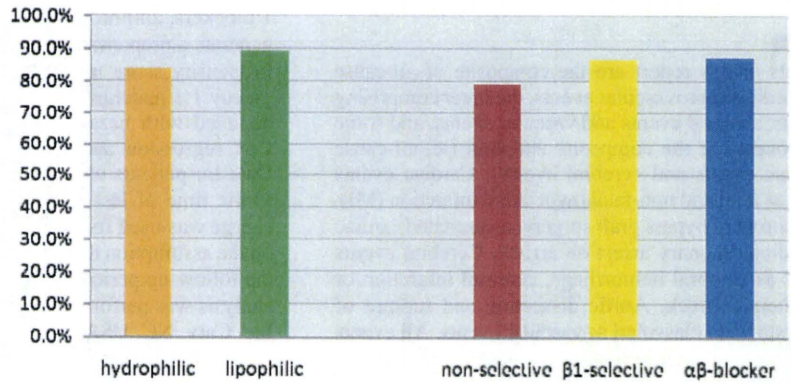
Figure 1. The continuation rate of each class of drug was calculated as the rate of patients who took the medication from the time of discharge through to final follow-up date. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCB, calcium-channel blocker; AT, antithrombotic.

written informed consent. Of the 15,628 patients who were initially registered in the study, 13,812 were followed up and included in the present analysis. Among these, 10,626 of the patients were male and 3,186 were female. Diagnoses at the time of registration included the following: acute myocardial infarction (2,955 patients), history of myocardial infarction (OMI: 3,913 patients), and unstable angina pectoris (UAP: 2,049). Patients were followed up for an average of 2.7 years.

Table 2. Classification of β-Blockers According to Solubility or Receptor Selectivity

Solubility classification			Receptor selectivity classification
Lipophilic β-blockers (n=3,257)	**No. and dosage (mg)***		**β1 selective (n=2,493)**
Amosulalol hydrochloride	2	20.0±14.1	Acebutolol hydrochloride
Arotinolol hydrochloride	53	14.9±6.2	Atenolol
Betaxolol hydrochloride	128	7.5±4.1	Betaxolol hydrochloride
Bevantolol hydrochloride	12	79.2±25.7	Bisoprolol fumarate
Bisoprolol fumarate	574	4.1±2.5	Celiprolol hydrochloride
Bopindolol malonate	5	0.9±0.2	Metoprolol tartrate
Carvedilol	1,421	10.3±5.5	
Metoprolol tartrate	913	49.0±28.6	**αβ-blockers (n=1,491)**
Nipradilol	47	6.2±2.2	Amosulalol hydrochloride
Oxprenolol hydrochloride	1	40	Arotinolol hydrochloride
Pindolol	5	11.0±5.5	Bevantolol hydrochloride
Propranolol hydrochloride	96	32.6±20.5	Carvedilol
			Labetalol hydrochloride
Hydrophilic β-blockers (n=903)			**Non-selective β-blockers (n=176)**
Acebutolol hydrochloride	9	144.4±52.7	Bopindolol malonate
Atenolol	774	34.4±17.0	Bufetolol hydrochloride
Bufetolol hydrochloride	1	10	Bunitrolol hydrochloride
Bunitrolol hydrochloride	1	20	Carteolol hydrochloride
Carteolol hydrochloride	19	12.5±3.7	Nadolol
Celiprolol hydrochloride	95	243.3±403.2	Nipradilol
Labetalol hydrochloride	3	133.3±28.9	Oxprenolol hydrochloride
Nadolol	1	30	Pindolol
			Propranolol hydrochloride
		Total 4,160 (30.1% of all patients included in the analysis)	

*Dosage is represented as mean±1SD.



	hydrophilic	lipophilic	non-selective	β1-selective	αβ-blocker
number at final follow-up	761	2902	136	2174	1297
number at discharge	902	3251	172	2493	1479

Figure 2. The continuation rate of each class of β-blocker was calculated as the rate of patients who took the medication from the time of discharge through to final follow-up date.

Data Registration and Gathering

All follow-up data were gathered electronically over the internet. At the time of registration, a diagnosis of CAD had been given by the attending physician. The brand names and dosages of all the drugs that the patients were taking were registered by the attending physicians. The definition of each risk factor was as follows: smoking, at least 1 incidence of smoking in the 2 years prior to registration; hyperlipidemia, serum total cholesterol ≥220 mg/dl and/or low-density-lipoprotein cholesterol ≥140 mg/dl and/or triglycerides ≥150 mg/dl; impaired fasting glycemia (IFG), defined as fasting blood glucose ≥110 mg/dl (diabetes mellitus was included in this study); hypertension, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg; obesity, body

Table 3. Background Characteristics of Matched Patients With or Without β-Blockers

	Without β-blockers (n=3,892)	With β-blockers (n=3,892)	P value
Age	65.34±9.84	65.34±9.65	0.553
Male	2,965 (76.2%)	2,954 (75.9%)	0.770
Hypertension	2,448 (62.9%)	2,417 (62.1%)	0.468
Hyperlipidemia	2,221 (57.1%)	2,265 (58.2%)	0.313
IFG	1,591 (40.9%)	1,617 (41.5%)	0.549
Obesity	1,306 (33.6%)	1,321 (33.9%)	0.719
Smoking	1,459 (37.5%)	1,488 (38.2%)	0.498
Drinking	1,522 (39.1%)	1,491 (38.3%)	0.471
Family history	671 (17.2%)	683 (17.5%)	0.720
CHF	393 (10.1%)	391 (10.0%)	0.940
LMT disease	200 (5.1%)	191 (4.9%)	0.640
No. of affected arteries	1.88±0.81	1.88±0.81	0.946
Statins	1,703 (43.8%)	1,734 (44.6%)	0.479
Fibrates	159 (4.1%)	151 (3.9%)	0.643
CCBs	1,933 (49.7%)	1,900 (48.8%)	0.454
ACEIs	1,448 (37.2%)	1,444 (37.1%)	0.925
ARBs	657 (16.9%)	641 (16.5%)	0.627
α-blockers	122 (3.1%)	116 (3.0%)	0.693
ATs	3,697 (95.0%)	3,697 (95.0%)	1.000
Nitrates	2,409 (61.9%)	2,390 (61.4%)	0.658

P values of age and number of affected arteries were calculated by Kruskal-Wallis test. All other P values were calculated by chi-square test.
Abbreviations see in Table 1.

mass index ≥25; familial history, first-degree relative with CAD; and drinking, having a habit of alcohol consumption. These data were obtained from each patient by the attending physicians. Careful attention was paid to data security.

Investigations

The endpoints in this report are the composite of all-cause deaths and cardiocerebrovascular events, the latter comprising cardiac events, cerebral events and vascular events, and some of the components of the composite endpoint (ie, all-cause deaths, cardiac events and cerebral events). Cardiac events were defined as fatal and non-fatal myocardial infarction (MI), UAP, CHF, coronary bypass graft surgery, resuscitated cardiac arrest or cardiopulmonary arrest on arrival. Cerebral events were defined as cerebral hemorrhage, cerebral infarction or transient ischemic attack. Aortic dissection and rupture of aortic aneurysm were classified as vascular events. All events were assessed and registered by the attending physicians.

Ethical Considerations

The protocol used in this study was approved by the Central Institutional Review Board of the University of Tokyo. Written informed consent was given by all patients.

Statistical Analyses

For each class of drugs, the continuation rate was defined as the rate of patients who took the medication from the time of discharge through to follow-up date. Because the data for each patient, including prescriptions, were registered by the attending physicians every 6 months, we assumed that a drug was discontinued if a patient continued to be followed up, but the drug that the patient had been prescribed was not registered. The logistic model, which included both patient background characteristics (age, sex, hypertension, hyperlipidemia, IFG, obesity, smoking, drinking of alcohol, family history of CAD, CHF, left main trunk disease, and number of affected arteries) and drug classes (statins, fibrates, calcium-channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blocker (ARBs), α-1 blockers, antithrombotics (ATs), and nitrates) was used to generate a propensity score for each individual in the dataset. Propensity score matching was performed using a 5-digit, greedy 1:1 matching algorithm.[14] Kaplan-Meier curves were depicted with hazard ratios (HR) calculated by univariate Cox regression analysis to examine incidence over time. Data for patients who were lost to follow-up were censored at the time of last contact. Medication at the time of discharge was used for survival analysis, which was performed on the assumption that the medication did not change through the follow-up period (intention-to-treat principle). Statistical analysis was performed with SAS version 9.1 (SAS Institute Inc, Cary, NC, USA).

Results

Patients' Backgrounds

As shown in Table 1, those patients who were given β-blockers had significantly higher rates of hypertension, hyperlipidemia, obesity, family history of ischemic diseases and had a higher number of diseased arteries. With regard to concomitantly prescribed drugs, those patients who were given β-blockers were also significantly more likely to be prescribed statins, fibrates, α-1 blockers, ACEIs, ARBs, and ATs, and were significantly less likely to be prescribed CCBs.

Continuation Rate of Each Class of Drug

Figure 1 shows the continuation rate of several classes of drugs that were prescribed for the patients in this cohort. Fibrates continued to be administered to 70.5% of the patients who were prescribed the medicine at the time of